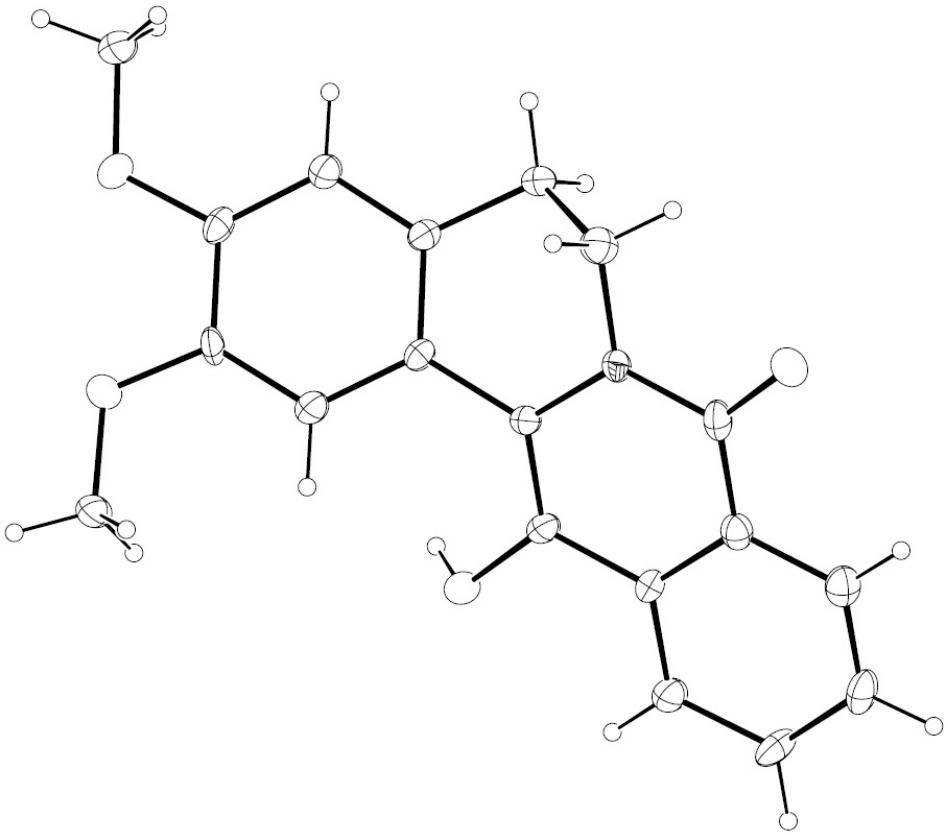
Organic Chemistry

Second Edition



Michael S. Leonard

This book is dedicated to my teachers, Professor David E. Horn and Professor Madeleine M. Joullié, for their tireless dedication to education.

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Preface

Organic chemistry is an important subject because it helps us to better understand biology and biochemistry. We also interact with and consume many organic substances on a daily basis. My goal was to provide you with a text that will make this subject as clear as possible.

Mechanism explains how the reactants (or starting materials) of a reaction are converted into products. To master organic chemistry, it is essential to master mechanism. There are three very common types of questions on organic chemistry exams. You will often be asked to predict the product of a chemical reaction, to draw the reaction mechanism, or to devise a synthesis of an organic molecule. None of these questions can be answered reliably unless you know how the reactions work, and that is what mechanism tells us. This book uses a novel approach to help you better understand the mechanisms of organic transformations.

Many organic chemists use color when teaching reaction mechanism. Color can be used to highlight the reactants and products in such a way that you can follow important features through the reaction. The mechanisms in this book are color coded so that you can clearly see the changes that take place during the reaction. The electrons involved in the mechanism are color coded. The mechanistic arrows originating from those electrons have the same color, as do the bonds or lone pairs formed by them in the intermediates and products. As a result, you can trace specific pairs of electrons through an entire transformation. The description of what each mechanistic arrow means is color coded correspondingly so that it is easy to match up the text with the relevant portion of a reaction diagram. To the best of my knowledge, there is no other introductory organic chemistry textbook that presents reaction mechanism in this way.

Each chapter contains a manageable number of problems. These problems will help you to practice and assess your knowledge of the material. Sometimes you will even learn something new while completing a problem. All of the problems have full solutions in the accompanying *Solutions Manual for Organic Chemistry*. This manual does not merely give you the answers to the questions. There is a written explanation of each question, and when reaction mechanism is a part of the answer, it contains the same color-coded approach described above.

I hope that these features of the textbook will make your introduction to the field of organic chemistry as clear as possible. You might wonder: why an e-book? Textbook costs are extremely high nowadays. In part, this is due to the expense of color printing. In order to provide you with an affordable textbook and solutions manual, I have elected to publish in the e-book format. This also enables you to easily carry your book on one or more of your electronic devices wherever you go.

Good luck with your studies!

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Chapter 1: Introduction to Organic Chemistry

Section 1: Organic chemistry
Section 2: The atomic theory of matter
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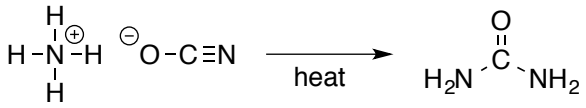
Section 1: Organic chemistry

For quite some time, people have observed a distinction between living things and inanimate objects. A Swedish chemist known as Berzelius formulated a theory called vitalism, in which he proposed that living things possess a "vital force" that is absent in inanimate objects. He defined organic chemistry as the study of compounds derived from living or once-living organisms, and it was thought to be impossible to synthesize (or make) organic compounds from inorganic starting materials, such as minerals.

In 1828, Friedrich Wöhler, a former student of Berzelius, converted ammonium cyanate into urea. This was a significant achievement for two reasons. It was the beginning of the end for the theory of vitalism because ammonium cyanate is an inorganic compound, while urea is an organic molecule isolated from urine. Over the years, as many more organic molecules were prepared from inorganic starting materials, the theory of vitalism crumbled.



ammonium cyanate urea

The second notable feature of Wöhler's synthesis of urea is that it was an illustration of isomerism. Constitutional isomers have the same molecular formula but exhibit differences

in connectivity between their atoms. Ammonium cyanate and urea are isomers. They both have the formula CH_4N_2O but there is a clear difference in how their constituent atoms are connected.

Since the theory of vitalism ultimately proved to be incorrect, organic chemistry is now defined as the study of carbon-containing molecules; whereas, inorganic chemistry is the study of all other compounds. The two fields do overlap in many ways though. You might wonder why an entire field of chemistry focuses on a single element, carbon. It turns out that carbon can bond with itself and with many other elements in ways that lead to tremendous molecular diversity. As a consequence of carbon's bonding patterns, there are millions of organic molecules that are known, and there are millions more that we could make in the laboratory.

Section 2: The atomic theory of matter

Before we delve into the study of organic molecules, we need a firm foundation in their building blocks: atoms. The concept of the atom is quite old. In ancient Greece, Democritus pondered the nature of matter. Imagine having a sample of a pure element and dividing in half time and again. If the sample were divided in half enough times, Democritus proposed that we must eventually arrive at the smallest indivisible particle of that element, and he termed this the atom. While we know nowadays that atoms can actually be further subdivided, it remains true that the atom is the smallest constituent of an element that has the properties of that element.

The British chemist John Dalton made a very important advancement when he proposed the atomic theory of matter in the early 1800s. He stated that elements are composed of atoms and that all atoms of a given element are identical. He also said that compounds consist of atoms of more than one element, which are combined in fixed, precise ratios. Additionally, Dalton noted that, during chemical reactions, atoms may be rearranged but that they are neither created nor destroyed in the process.

This basic understanding of matter continues to guide us today. Atoms are the building blocks of molecules and compounds. As Dalton explained, compounds contain atoms of more than one element. A compound's makeup is often expressed through a formula containing the elements' symbols with whole number subscripts denoting the proportions. For example, the formula for water, H_2O, shows that it has two hydrogen atoms for every oxygen atom. Molecules consist of multiple atoms, but these may or may not include different elements. All compounds may also be called molecules, but there are some molecules, such as H_2, that are not compounds because they contain only a single element.

Atoms themselves consist of subatomic particles: the proton, the neutron, and the electron. Protons have a relative mass of 1 atomic mass unit (amu), as do neutrons. However, protons have a relative charge of +1, while neutrons are neutral (i.e., they have no charge). On the other hand, electrons have a mass that is negligible compared to that of protons and neutrons. Although their mass is negligible, their charge is not. The relative charge of an electron is –1.

Protons and neutrons occupy the nucleus, or center, of an atom, while electrons exist outside the nucleus and define the volume of the atom. Almost all of an atom's mass resides in the nucleus, but the nucleus is tiny compared to the size of the atom as a whole. While greater than 99% of an atom's mass can be found in the protons and the neutrons of the nucleus, the nucleus is about 100,000 times smaller than the atom itself.

Problem 1. What is the mass in amu of the following atoms?

(a) a carbon atom (C) that has six protons, six neutrons, and six electrons

(b) a nitrogen atom (N), which has seven protons, seven neutrons, and seven electrons

(c) a charged oxygen atom (O) that possesses eight protons, eight neutrons, and ten electrons

(d) a charged fluorine atom (F) with nine protons, ten neutrons, and ten electrons

(e) a charged sodium atom (Na) with eleven protons, twelve neutrons, and ten electrons

Atoms can be represented by symbols that have a few components. The element's abbreviation has on its left-hand side superscripted and subscripted numbers. For instance, the most common form of carbon has the atomic symbol ${}^{12}_{6}C$. The subscripted number is the atomic number (Z). The atomic number is the number of protons the atom possesses. The atomic number is the same for all atoms of a given element. The superscripted value is the mass number (A). The mass number is the number of protons and neutrons that the atom has. Therefore, the difference between the mass number and the atomic number provides the number of neutrons. The mass number of 12 provided for this carbon atom shows that it has six neutrons. If an atom happens to be charged due to an imbalance between the protons and electrons, then the charge is a superscript appearing on the right-hand side of the element's symbol.

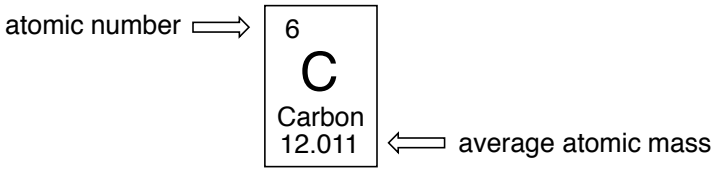
Problem 2. Write the atomic symbol, in the form ${}^{A}_{Z}X$, for the atoms in parts (b) – (e) of Problem 1.

Unlike the atomic number, the mass number can actually differ for atoms of a given element. Isotopes are atoms of a single element that differ in their number of neutrons. Carbon has three naturally occurring isotopes. These are known as carbon-12, carbon-13, and carbon-14, and they have the atomic symbols ${}^{12}_{6}C$, ${}^{13}_{6}C$, and ${}^{14}_{6}C$, respectively. The difference between the mass number and the atomic number gives the number of neutrons each isotope possesses. Carbon-12 has six neutrons. However, carbon-13 and carbon-14 have seven and eight neutrons, respectively. Isotopes usually differ in their natural abundance. Carbon-12 accounts for ~98.9% of carbon; whereas, carbon-13 makes up ~1.1% of carbon. Carbon-14 is present only in trace amounts.

Problem 3. Sulfur (S) has sixteen protons. There are four naturally occurring isotopes having sixteen, seventeen, eighteen, and twenty neutrons. Provide the atomic symbols for these isotopes in their neutral forms.

Section 3: The periodic table

Elements are organized in the periodic table, which was devised by Dmitri Mendeleev in 1869. On the periodic table, information about the element is presented a bit differently. The atomic number is located at the top of the box, and the number underneath the element represents its *average* atomic mass or weight.



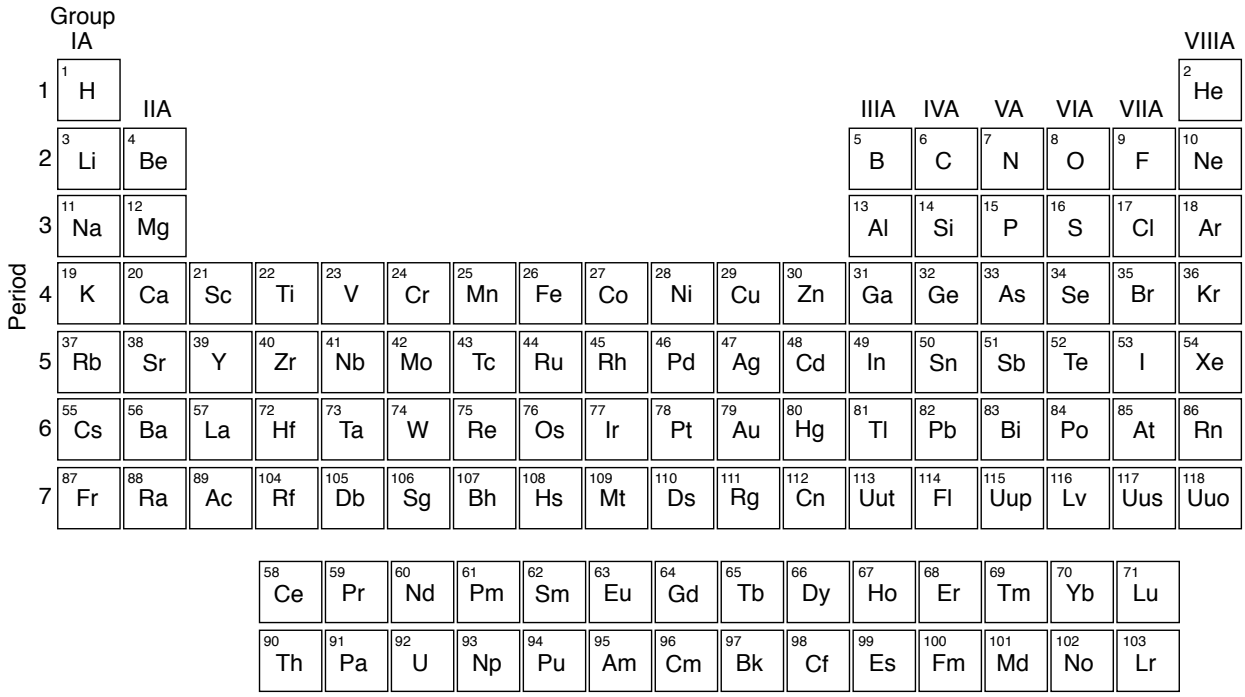
Atomic masses are defined on a carbon-12 scale in which the mass of carbon-12 is said to be exactly 12 amu, and the masses of all other atoms are determined relative to this. The average atomic mass is a weighted average of the masses of each naturally occurring isotope. Each isotope's mass is multiplied by its natural abundance. The calculation is shown below for carbon. Since carbon-14 is only present in trace amounts, it does not affect the calculation with the number of decimal places used here.

$$Ave.\,atomic\ mass\ of\ C = (12.000\ amu)(0.989) + (13.003\ amu)(0.011) = 12.011\ amu$$

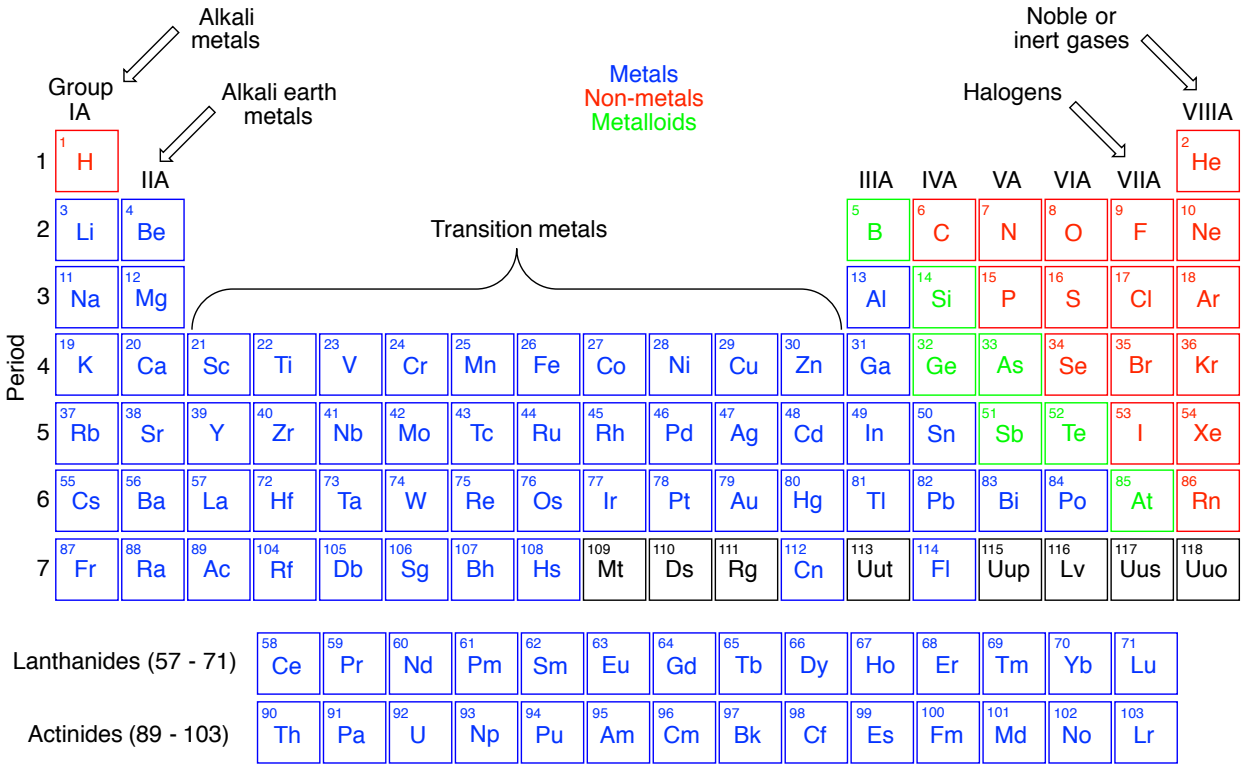
Problem 4. In Problem 3, you wrote the symbols for the four isotopes of sulfur. Now, given their exact masses and relative abundance in nature, calculate the average atomic mass of sulfur.

Isotope	Mass	Relative abundance
$^{32}_{16}S$	31.9721	95.02%
$^{33}_{16}S$	32.9715	0.75%
$^{34}_{16}S$	33.9679	4.21%
$^{36}_{16}S$	35.9671	0.02%

A detailed periodic table can be accessed here: http://www.nist.gov/pml/data/periodic.cfm. A concise version of the periodic table, showing only the elements' symbols and their atomic numbers, is presented below.



One layer of organization is by atomic number. Notice that hydrogen is the first element in the upper left corner, with atomic number 1. The atomic number increases one at a time with each new box on the table. Additional layers of organization are the periods (i.e., rows) and the groups (i.e., columns), which are based on behavior that results from electronic structure. The period numbers are given on the left-hand side of the table. The group numbers are given at the top. Some group names are used fairly frequently. Groups IA and IIA are known as the alkali and alkali earth metals, respectively. Group VIIA is the halogens, and group VIIIA includes the noble gases, which are also known as the inert gases. In general, metals reside on the left side of the periodic table, while nonmetals lie on the right. Metalloids fall at the junction between these two factions.



Section 4: The mole – linking the molecular and the macroscopic level

Chemists often think about substances and reactions at the molecular level. In other words, we may envision a change occurring as two molecules interact. However, when we go into the laboratory to conduct this reaction, we are dealing not with individual molecules but with bulk samples. Since chemists move between the molecular and macroscopic worlds, it is important for us to have a system that enables us to link the two, and it is the mole that fulfills this role.

There are 6.02×10^{23} atoms or molecules in a mole. That may seem like a very strange number, but it comes from a logical deduction. Let's think about carbon and hydrogen, two elements of great importance in organic chemistry. If ^{12}C has an atomic mass of 12.00 amu and ^{1}H has an atomic mass of 1.00 amu, then 12.00 g of ^{12}C must contain the same number of atoms as 1.00 g of ^{1}H. That number of atoms (6.02×10^{23}) is a mole of atoms.

Let's demonstrate that a 12.00 g sample of carbon-12, which is a mole of carbon-12, contains 6.02×10^{23} atoms. To perform this calculation, we need to know that there are $1.66 \times 10^{-24}\ {}^{g}/_{amu}$.

$$\left(\frac{12.00\ g\ {}^{12}C}{1\ mole\ {}^{12}C}\right)\left(\frac{1\ amu}{1.66 \times 10^{-24} g}\right)\left(\frac{1\ atom}{12\ amu}\right) = 6.02 \times 10^{23}\ atoms\ {}^{12}C\Big/_{mole\ {}^{12}C}$$

Now, let's prove that 1.00 g of ^1H (a mole of hydrogen) contains the same number of atoms.

$$\left(\frac{1.00\ g\ {}^1H}{1\ mole\ {}^1H}\right)\left(\frac{1\ amu}{1.66\ \times\ 10^{-24} g}\right)\left(\frac{1\ atom}{1\ amu}\right) = 6.02\ \times\ 10^{23}\ atoms\ {}^1H/_{mole\ {}^1H}$$

This number, $6.02\ \times\ 10^{23}$, is also known as Avogadro's number. It is the number of atoms or molecules in a mole of atoms or molecules. Much as a dozen atoms would be twelve atoms, a mole of atoms is $6.02\ \times\ 10^{23}$ atoms.

Problem 5. Calculate the mass of 1.00 mole of nitrogen-14.

One of the conveniences of the mole is that an atom or a molecule's mass is numerically the same as the mass of a mole of that substance. All that differs is the units. A molecule's mass is determined by simply adding up the masses of the constituent atoms. Therefore, a molecule of methane, which contains one carbon and four hydrogen atoms, has a mass of 16.05 amu.

$$Mass\ of\ methane\ (CH_4)\text{: } 12.01\ amu + 4\ \times\ 1.01\ amu = 16.05\ amu$$

Chemists often use the terms molecular mass and molecular weight interchangeably. The molecular weight can be converted to the molar mass using the conversion factors introduced above. Additional decimal places have been used here to minimize rounding error.

$$\left(\frac{16.05\ amu}{molecule\ CH_4}\right)\left(\frac{1.6605\ \times\ 10^{-24} g}{1\ amu}\right)\left(\frac{6.0221\ \times\ 10^{23}\ molecules\ CH_4}{1\ mole\ CH_4}\right)$$
$$= 16.05\ {}^g/_{mole\ CH_4}$$

Notice that the value is 16.05 either way. If we are talking about one molecule, then the units are amu. On the other hand, if we are considering one mole, the units are grams.

Problem 6. Provide the molecular and molar masses of the following compounds. You can round average atomic masses to two decimal places. Be sure to use the appropriate units in each case.

(a) water (H_2O)

(b) ethanol (C_2H_6O), the alcohol in beer and wine

(c) ibuprofen ($C_{13}H_{18}O_2$), a common pain reliever

(d) adipoyl chloride ($C_6H_8Cl_2O_2$), a building block for nylon

Section 5: Using the mole in calculations

The mole links the molecular and macroscopic realms in multiple ways. We discussed the numerical equivalency of the molecular and molar mass in the preceding section. We can also use the mole in calculations that pose an atomic or molecular-level question about a bulk sample. For instance, we could ask how many carbon atoms are present in a 1.00 g sample of aspirin, which has the molecular formula $C_9H_8O_4$. The sample in question is a macroscopic sample, but we are asking about the number of carbon atoms present, which delves into the atomic realm. The mole allows us to make the connection.

To determine the number of moles in this sample, we need the molar mass of aspirin, which is obtained by adding the molar masses of its constituent atoms.

$$Molar\ mass\ of\ aspirin\ (C_9H_8O_4):$$
$$9\ \times\ 12.01\ g/mole + 8\ \times\ 1.01\ g/mole\ + 4\ \times\ 16.00\ g/mole =\ 180.17\ g/mole$$

We can now convert the mass of the aspirin sample into the corresponding number of moles.

$$1.00\ g\ aspirin\ \left(\frac{1\ mole\ aspirin}{180.17\ g\ aspirin}\right)$$

We don't want to stop here though because the question asks about the number of carbon atoms that are present. The molecular formula, $C_9H_8O_4$, tells us that there are 9 moles of carbon in every mole of aspirin. We can use this to convert the moles of aspirin into moles of carbon, and then Avogadro's number enables us to convert the moles of carbon into atoms of carbon.

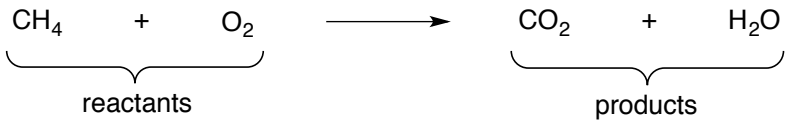
$$1.00\ g\ aspirin\ \left(\frac{1\ mole\ aspirin}{180.17\ g\ aspirin}\right)\left(\frac{9\ moles\ C}{1\ mole\ aspirin}\right)\left(\frac{6.02\ \times\ 10^{23}\ atoms\ C}{1\ mole\ C}\right) = 3.01\ \times\ 10^{22}\ atoms\ C$$

We can also use the mole in calculations involving chemical reactions, but to do so requires *balanced* chemical equations.

Problem 7. Naloxone ($C_{19}H_{21}NO_4$) is a drug that can reverse an overdose caused by heroin or opioid painkillers. Many first responders are now carrying this life-saving medication. How many moles are in a 10.0 mg dosage of naloxone? How many atoms of carbon, hydrogen, nitrogen, and oxygen are contained in this dosage?

Section 6: Balancing chemical reactions

Chemical reactions are portrayed using equations that illustrate the conversion of reactants (i.e., starting materials) into products. Sometimes additional conditions, reagents, catalysts, and/or solvents will be written above or below the reaction arrow. The equation for the combustion of methane (CH_4) is shown below. Oxygen (O_2) is also necessary as a reactant, and the products formed are carbon dioxide (CO_2) and water (H_2O).



A balanced equation has the same number of atoms of each element on both sides of the arrow. It's extremely important to recognize that chemical reactions may not be written in a balanced form, yet before using a reaction equation for any calculations, it absolutely must be balanced. The reaction above is unbalanced as drawn. While it does have one carbon atom on each side of the equation, the numbers of hydrogen and oxygen atoms do not match. To balance an equation, we add whole number coefficients in front of individual chemical species as needed. These are also sometimes called stoichiometric coefficients because stoichiometry entails determination of the relative quantities of reactants and products.

Balancing equations is done by inspection. To balance this combustion reaction, we observe that there are four hydrogen atoms on the reactants side of the equation. To also have four on the products side, we must add a stoichiometric coefficient of 2 in front of water. Now, there are four oxygen atoms on the products side. To obtain an equivalent number on the reactants side, a coefficient of 2 is also placed in front of oxygen. When a substance has no stoichiometric coefficient explicitly written in front of it, the coefficient is assumed to be 1.

When you are balancing chemical equations, the addition of stoichiometric coefficients is the only change that you can make. You *cannot* alter the chemical formulas by changing their subscripts because this would alter the identity of the reactants and products.

Now that the equation is balanced, we can make more specific statements about the reaction. Instead of simply stating that methane reacts with oxygen to yield carbon dioxide and water, we can say that one molecule of methane reacts with two molecules of oxygen to yield one molecule of carbon dioxide and two molecules of water. If we are more interested in the macroscopic level, we can replace the word "molecule" with "mole" throughout this statement. In other words, one mole of methane reacts with two moles of oxygen to yield one mole of carbon dioxide and two moles of water.

Problem 8. Combustion reactions of hydrocarbons (i.e., molecules containing only carbon and hydrogen) always require oxygen (O_2) as a reactant and produce carbon dioxide (CO_2) and water (H_2O) as products. Provide balanced combustion reactions for the following hydrocarbons.

(a) propane (C_3H_8)

(b) ethane (C_2H_6)

(c) octane (C_8H_{18})

(d) acetylene (C_2H_2)

(e) benzene (C_6H_6)

(f) anthracene ($C_{14}H_{10}$)

(g) pyrene ($C_{16}H_{10}$)

Another note on jargon is in order. Chemists often refer to molar equivalents or simply equivalents when discussing stoichiometry. This refers to the stoichiometric coefficients. In other words, when considering the combustion of methane, you can say that two equivalents of oxygen are needed for each equivalent of methane used.

This statement means that twice as many moles of oxygen are needed as moles of methane. If you use 0.5 moles of methane, then 1 mole of oxygen is necessary. If you use 5.6 moles of methane, then 11.2 moles of oxygen are required.

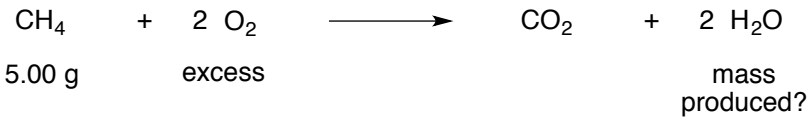
Problem 9. Convert the following statements into balanced reaction equations.

(a) The combustion of heptane (C_7H_{16}) requires 11 equivalents of oxygen and produces 7 equivalents of carbon dioxide along with 8 equivalents of water.

(b) The exhaustive bromination of 1,3-butadiene (C_4H_6) necessitates two equivalents of bromine (Br_2) and yields one equivalent of 1,2,3,4-tetrabromobutane ($C_4H_6Br_4$).

Section 7: Calculations involving reactions

With a balanced chemical equation in hand, it is possible to perform calculations. For instance, we can calculate the mass of water produced if 5.00 g of methane reacts with an excess of oxygen.



By stating that an excess of oxygen is present, we know that there is more than enough oxygen to react with all of the methane that we are using. These calculations always begin with the given quantity, which in this case is 5.00 g CH_4. Since we are interested in the amount of a different substance that is produced, we must utilize moles in the conversion because the reaction equation relates the moles of one substance to the moles of another.

To obtain the moles of methane, we need methane's molar mass, which we calculated to be $16.05\ {}^{g}/_{mole}$ earlier. The reaction equation tells us that one mole of methane yields two moles of water, and this fact can be used to develop a conversion factor that allows moles of methane to be converted into moles of water. Finally, the moles of water can be converted into grams using water's molar mass of $18.02\ {}^{g}/_{mole}$.

$$5.00\ g\ CH_4 \left(\frac{1\ mole\ CH_4}{16.05\ g\ CH_4}\right)\left(\frac{2\ mole\ H_2O}{1\ mole\ CH_4}\right)\left(\frac{18.02\ g\ H_2O}{1\ mole\ H_2O}\right) = 11.2\ g\ H_2O$$

Notice that, with each conversion, both the units and the identity of the substance are written. These two details are essential to ensuring that you know what kind of quantity the number refers to (e.g. grams, milliliters, moles, molecules, etc.) *and* the substance in question. Omitting either detail dramatically increases the odds of making an error. Additionally, scientists never report unitless values because of the ambiguity inherent in such numbers.

Problem 10. When finite quantities of two reactants are used, we will run out of one before the other. The reactant that is consumed first is known as the limiting reactant because it limits how much product can be made. For the reaction equation you drew in Problem 9(b), calculate how much product could be made from 1.75 g of 1,3-butadiene. Then, calculate how much product could be made from 9.50 g of bromine. The smaller of the two values is known as the theoretical yield, and it is the maximum amount of product that can actually be produced during this reaction.

Problem 11. Percent yield provides a way to assess the amount of product obtained from a given reaction. It is defined as:

$$\%\ yield = \frac{amount\ of\ product\ obtained}{theoretical\ yield\ of\ product} \times 100$$

A 100% yield would indicate that you made the maximum amount of product possible. If the reaction described in Problem 10 produces 8.58 g of product when conducted in the laboratory, what is the percent yield?

Section 8: Electronic configuration

Our ultimate goal is to understand the structure, properties, and reactivity of organic molecules. All of this depends upon the electrons in the molecule, which come from the electrons in the constituent atoms. Thus, the electronic structure of atoms is central to our aim.

Our understanding of electronic structure can be traced back to quantum mechanics, which is physics at the atomic and subatomic level. There were a few fundamental insights that set the stage for the development of quantum mechanics in the early 1900s. One of these

was Einstein's observation of the wave-particle duality of light. Prior to this time, there was debate as to whether light consisted of waves or particles. Einstein resolved this by explaining that light has properties of both a wave and a particle. Different types of light have characteristic wavelengths (λ) and frequencies (ν). However, the product of the wavelength and frequency gives the speed of light (c), which is a constant in a given medium.

$$c = \lambda \nu$$

When speaking of the particle nature of light, it may be referred to as a photon.

Another fundamental insight was provided by the French physicist Louis de Broglie, who asserted that particles also have wave-like properties. The wavelength associated with a particle is given by Planck's constant ($6.626 \times 10^{-34}\ Js, where\ J = joule\ and\ s = second$) divided by the particle's momentum, which is the product of its mass and velocity.

$$\lambda = \frac{h}{mv}$$

Although this applies to all particles, the de Broglie wavelength is only large enough to be relevant for particles with extremely small masses, such as electrons.

Finally, the Danish physicist Niels Bohr and the German physicist Max Planck concluded that both photons and subatomic particles, like electrons, have energy related to wavelength and frequency.

$$E = h\nu \quad or \quad E = \frac{hc}{\lambda}$$

Furthermore, this energy is quantized, meaning that it cannot have just any value. The energy of photons and electrons is limited to discrete values, rather than a continuous spectrum of values.

Erwin Schrödinger, an Austrian physicist, formulated the basis of wave mechanics from these fundamental insights. He put forth several postulates, which can be stated simply as:

• Electrons have particle-wave duality.

• The wave nature of an electron can be represented by a wave function, Ψ, which is a mathematical function.

• The probability of finding electron density in a given volume around the nucleus is given by Ψ^2.

• The energy of an electron depends on Ψ.

Although there is an exact solution for Ψ only for the hydrogen atom, a set of quantum numbers is derived from this solution. These quantum numbers can be used to describe electrons in any atom.

The first quantum number is the principal quantum number, n. This quantum number describes the electronic shell and has positive integer values (i.e., 1, 2, 3…). As the value of n increases so does the electron's distance from the nucleus. The value of n also correlates to the row number on the periodic table.

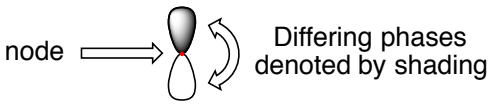
The second quantum number is the angular momentum quantum number, ℓ. It has integer values from 0 to (n–1). For instance, if n is 3, then ℓ can be 0, 1, or 2. This quantum number describes the volume of space, or the orbital, occupied by the electron. The value of ℓ corresponds to a particular orbital as shown below.

ℓ	orbital
0	s
1	p
2	d
3	f

Orbitals have different shapes. An s orbital is spherical, and the nucleus resides in the very center.

s orbital
(nucleus in red)

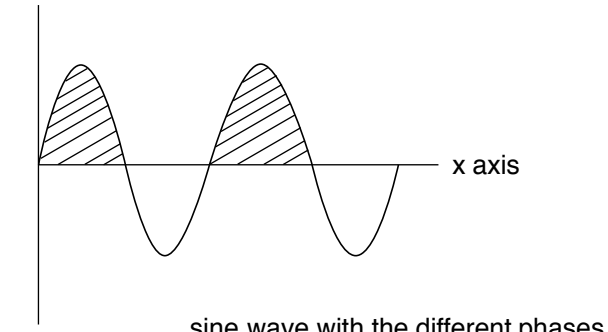
On the other hand, a p orbital has a dumbbell shape. It consists of two lobes with a node (i.e., a point of zero electron density) between them. The nucleus resides at the node. The two lobes of a p orbital have different phases.



p orbital
(nucleus in red)

This is analogous to a sine wave that passes above and below the x-axis. When the wave is above the x-axis, the y values are positive. When it passes below the x-axis, the y values are negative. We'll avoid using the terms positive and negative to describe the phases because, in chemistry, those terms suggest charge, and the lobes of a p orbital are not differently charged. Instead, we'll convey phasing by shading

one lobe and leaving the other unshaded.



sine wave with the different phases highlighted through shading

The shapes of d and f orbitals are more complicated; however, in general, they won't be relevant to the types of molecules we'll be focusing on.

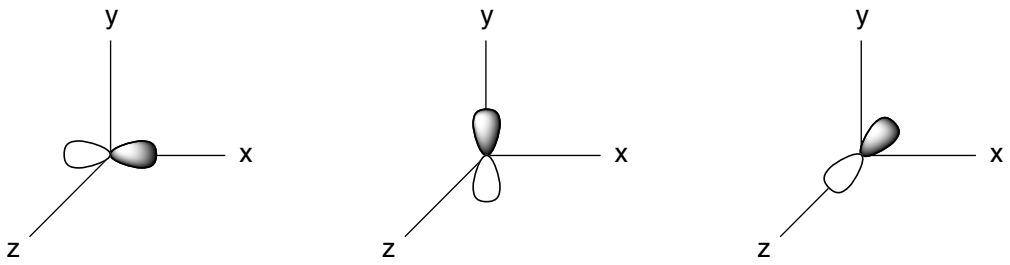
The third quantum number, m_ℓ, is the magnetic quantum number. It tells how many of each type of orbital exist within a given shell. The values of m_ℓ are integers ranging from $-\ell$ to ℓ. The number of values for m_ℓ is equal to the number of orbitals of each type within that shell. The table below expands upon this idea. Let's imagine that n = 4. In this case, we'd be considering an element in the fourth row of the periodic table, the row beginning with potassium. An element in this row can have s, p, d, or f orbitals since ℓ can have values of 0, 1, 2, or 3.

When ℓ is 0 and we are therefore considering an s orbital, the only possible value for m_ℓ is 0. Since there is one value for m_ℓ, there is one type of s orbital within this fourth electronic shell. There are also s orbitals within the first, second, and third shells, but they are closer to the nucleus. There is only one s orbital at the distance from the nucleus that is dictated by being in the fourth shell.

n	**ℓ**	**m_ℓ**	**Meaning of m_ℓ**
4	0 (s)	0	One type of s orbital
	1 (p)	–1	Three types of p orbitals
		0	
		1	
	2 (d)	–2	Five types of d orbitals
		–1	
		0	
		1	
		2	
	3 (f)	–3	Seven types of f orbitals
		–2	
		–1	

		0	
		1	
		2	
		3	

When ℓ is 1, it indicates a p orbital. The values for m_ℓ can be –1, 0, or 1. The fact that there are three possible values for m_ℓ shows that there are three types of p orbitals in this shell. These are known as p_x, p_y, and p_z because they are oriented along different axes.



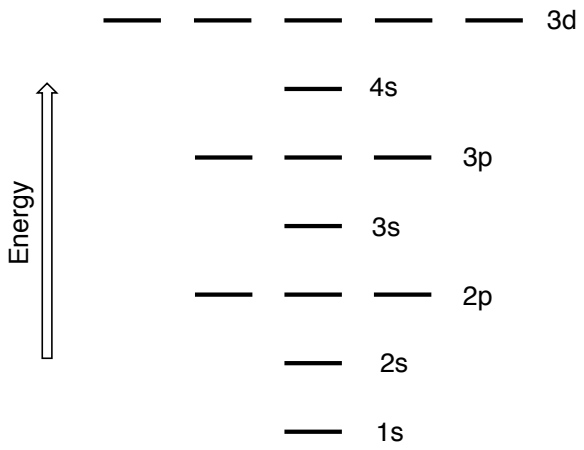
p_x orbital p_y orbital p_z orbital

The table also shows that there are even more types of d and f orbitals: five and seven, respectively. You'll learn their shapes when you study inorganic chemistry.

The fourth quantum number is m_s, the spin quantum number. The spin quantum number has only two possible values, $\pm 1/2$. These represent alignment of the electron with or against an external magnetic field.

The Pauli exclusion principle adds significance to the fourth quantum number. It states that no two of an atom's electrons can have the same four quantum numbers. Since there are only two values of m_s, it follows that an individual orbital can hold a maximum of two electrons. The s orbital can hold two electrons. The p_x, p_y, and p_z orbitals can each hold two electrons for a total of six. Each of the five types of d orbitals can hold two electrons for a total of ten, and each of the seven varieties of f orbitals can hold two electrons, making a total of fourteen.

The energy of orbitals depends upon both n and ℓ. The diagram below shows the relative energies for the first several orbitals. The vertical position denotes energy. Each line represents an orbital capable of holding up to two electrons. The labels give the value of n as a number and the type of orbital. When there is more than one line at the same vertical position, there are degenerate (i.e., equal energy) orbitals. For example, the 2p level has three lines, representing the $2p_x$, $2p_y$, and $2p_z$ orbitals.



Problem 12. What are acceptable quantum numbers for:

(a) an electron in a 4s orbital?

(b) an electron in a 3p orbital?

(c) an electron in a 3d orbital?

(d) an electron in a 2p orbital?

Since the relative energies depend upon both n and ℓ, it is not always obvious which orbital will come next in order of energy. Until you become familiar with the energy levels through practice and experience, there is a mnemonic device to help you remember the energy levels. In a column, write all the s orbitals, 1s through 7s. Then, move to a second column and write all of the p orbitals, but drop down one row so that 2p lines up with 2s. Continue to make new rows like this for the d and f orbitals. Remember to drop down one row each time so that the shell numbers line up.

1s

2s 2p

3s 3p 3d

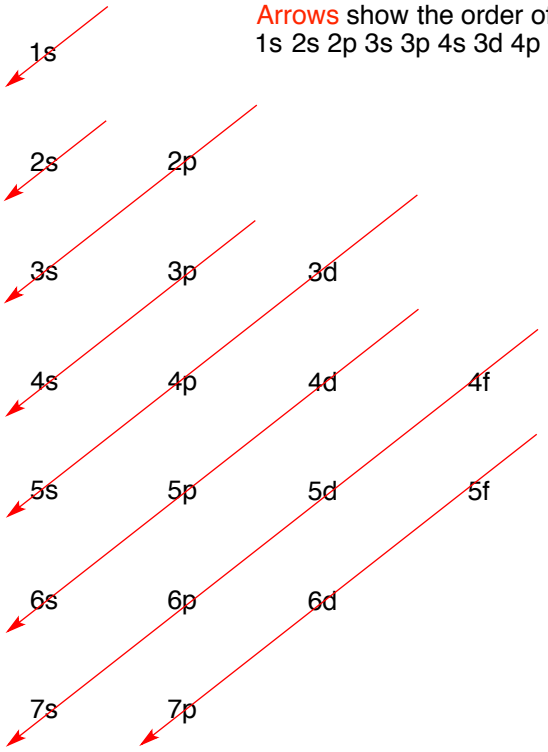
4s 4p 4d 4f

5s 5p 5d 5f

6s 6p 6d

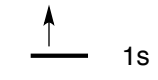
7s 7p

Then, draw a series of diagonal lines as shown below. The order in which the diagonal lines cross the orbitals reveals the order of their relative energies.



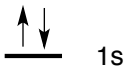
As we begin to consider the specific electronic configurations of particular atoms, we will place the electrons into the lowest energy orbitals available. This is sometimes known as

the aufbau principle from the German for construction. Neutral atoms have the same number of protons and electrons, so the atomic number will tell us how many electrons need to be placed. Let's begin with the first element on the periodic table. Hydrogen has an atomic number of 1, so when neutral, it has one electron as well. This electron is placed into the lowest energy orbital, 1s. The electron is represented by an arrow. If the arrow points up, the m_s value is $^1/_2$. If the arrow points down, the m_s value is $-^1/_2$. The first electron can point up or down.



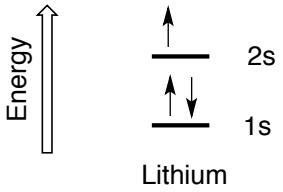
Hydrogen

The next element, helium, has two electrons when neutral. Since no two electrons of any given atom can have the same four quantum numbers, the second electron must be placed in the 1s orbital with an opposite spin.



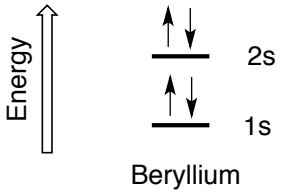
Helium

The element with atomic number 3 is lithium. Due to the Pauli exclusion principle, the third electron must be placed into a different orbital. We have now surpassed the maximum capacity of the 1s orbital, which like any other orbital can hold only two electrons. The third electron is placed into the 2s orbital.



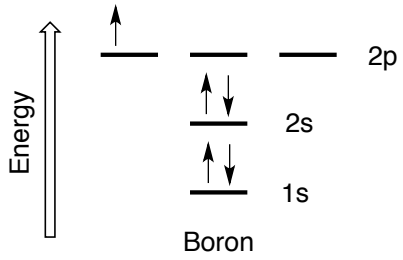
Lithium

With the next element, beryllium, we fill the 2s orbital by adding a fourth electron.

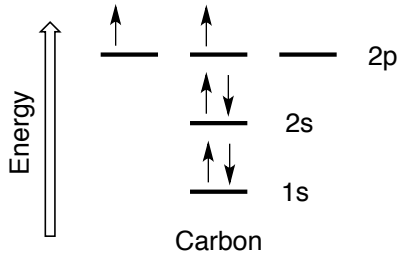


Beryllium

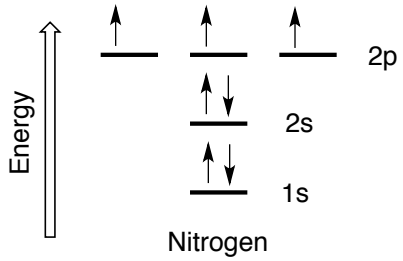
Then, for the subsequent element (boron), we must begin to place electrons into the 2p orbitals. Since the three 2p orbitals are degenerate, the fifth electron can go in any of them.



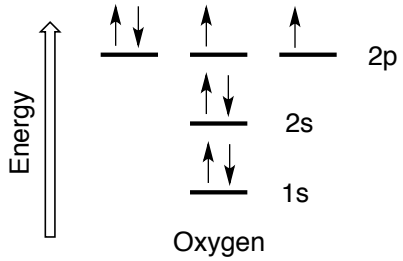
As we move along the second row to carbon, a question arises. We have choices in how the sixth electron is placed. It could go into the same 2p orbital as the fifth electron with an opposite spin, or it could be placed into one of the other two 2p orbitals with either spin. Hund's rule provides guidance in this situation. The German physicist Friedrich Hund determined that the most stable electronic configuration has the greatest number of parallel spins. This shows us that the sixth electron should go into one of the other 2p orbitals and that its spin should be in the same direction as that of the fifth electron.



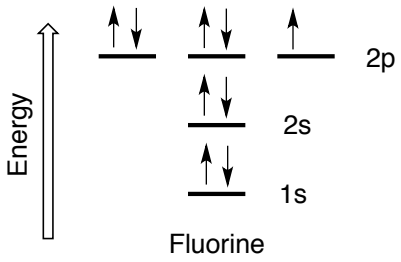
Using Hund's rule again tells us that, for nitrogen, the seventh electron should reside in the last 2p orbital and have a spin parallel to the other 2p electrons.



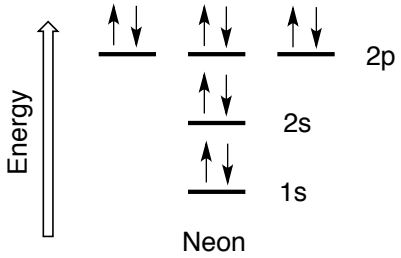
By the time we reach oxygen, we are forced to pair electrons in a 2p orbital.



Fluorine adds one more paired electron.



The second shell is filled when we reach neon.



The process continues in this fashion as we build the electronic configurations of any atom. It is not always necessary to express the configuration in a diagram. We can also concisely report the configuration by writing the shell number, orbital type, and number of electrons in those orbitals as a superscripted value. The configurations of the atoms we've considered thus far are written in this fashion below:

H: $1s^1$
He: $1s^2$
Li: $1s^2 2s^1$
Be: $1s^2 2s^2$
B: $1s^2 2s^2 2p^1$
C: $1s^2 2s^2 2p^2$
N: $1s^2 2s^2 2p^3$
O: $1s^2 2s^2 2p^4$
F: $1s^2 2s^2 2p^5$
Ne: $1s^2 2s^2 2p^6$

As we continue to move through the periodic table, the full configurations can become a bit lengthy, so there is an option to abbreviate electronic configurations. This abbreviation places the symbol of the closest preceding noble gas in brackets to signify its electronic configuration. Then, any additional electrons are described using the method discussed above. For example, sodium's configuration can be written out in its entirety.

Na: $1s^2 2s^2 2p^6 3s^1$

Or, it can be abbreviated as follows, where we simply write the difference from neon's configuration.

Na: [Ne]$3s^1$

Along these lines, calcium's configuration could be rapidly abbreviated as shown below.

Ca: [Ar]$4s^2$

Be careful as you move from calcium to scandium. It may be tempting to proceed from the 4s to the 4p orbitals, but energy depends on both n and ℓ. As we learned previously, the 3d orbitals are next in energy after 4s.

Sc: [Ar]$4s^2 3d^1$

The 3d orbitals would be filled as we proceed through zinc. Then, the 4p orbitals begin to be occupied with gallium.

Ga: [Ar]$4s^2 3d^{10} 4p^1$

There are some idiosyncrasies of filling the d orbitals. Those are more relevant to inorganic chemistry, and you'll learn them when you study this subject.

Problem 13. Provide the electronic configuration for the following elements.

(a) Mg

(b) Al

(c) Si

(d) S

(e) K

(f) As

Elements in the same column of the periodic table share the same valence-electron configuration. The valence electrons are those in the outer shell. For example, compare the halogens. In this case, the electrons in the highest shell follow the pattern s^2p^5. The identical valence-shell configurations account for the similar behavior of elements within a column of the periodic table.

F: [He]$2s^2 2p^5$
Cl: [Ne]$3s^2 3p^5$
Br: [Ar]$4s^2 3d^{10} 4p^5$
I: [Kr]$5s^2 4d^{10} 5p^5$

Problem 14. Which of the following elements have the same valence-shell configuration, and what is that configuration?

H, Be, Ge, S, Cl, Kr, P, Al, Sn

Charged atoms are called ions. When determining the electronic configuration of ions it is important to consider whether electrons have been lost or gained to lead to the charge. For example, Li^+ must have lost an electron. If an electron is lost from a neutral atom, then the protons outnumber the electrons, and a positive charge results. A positively charged ion is called a cation. The highest-energy electron (i.e. the one in the 2s orbital) is lost, and this ion now has no electrons beyond the first shell.

Li^+: $1s^2$

Calcium tends to form a cation with a +2 charge. As a result, we know that it has lost its two highest-energy electrons, and the configuration is as follows.

Ca^{2+}: $1s^2 2s^2 2p^6 3s^2 3p^6$

On the other hand, fluorine will gain an electron to form a negatively charged ion, known as an anion.

F^-: $1s^2 2s^2 2p^6$

Notice how each of these ions has the electronic configuration of a noble gas. The lithium cation has helium's configuration. The calcium cation has argon's configuration, and the anionic form of fluorine has neon's configuration. The noble gases have filled valence shells, and as such they are especially stable. Being particularly stable, they are reluctant to react, hence the alternate name for these elements: *inert* gases. When other elements form ions, they tend to gain or lose electrons so as to attain the same configuration as the nearest noble gas.

Problem 15. What ions would you expect the following elements to make, and what would their electronic configurations be?

(a) Sr

(b) Al

(c) S

(d) K

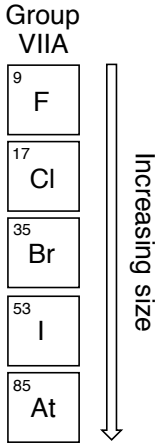
(e) Br

(f) P

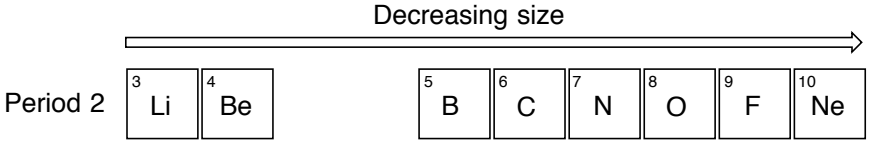
Section 9: Periodic trends

Now that we have a sense of electronic configuration and how the periodic table encodes that information, we can also discuss two important periodic trends: atomic radius and electronegativity.

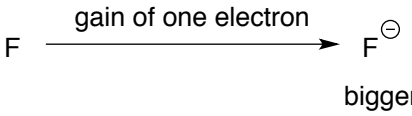
Atomic radius increases as you move down a column of the periodic table. As you move down a column, the values for the principal quantum number (n) increase, which means that the electronic shell is getting larger.



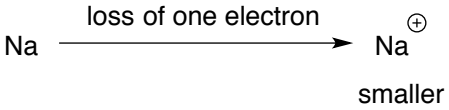
Within a row of the periodic table, atomic radius decreases as you move from left to right. The rationale for this trend is that, while the electronic shell remains the same within a row, there are more protons in the nucleus as we move to the right. The increasing number of protons pulls the electrons in that shell closer to the nucleus, thereby decreasing the atomic radius.



We can also compare the size of a neutral atom to that of an ion derived from it. If an atom gains electrons to form an ion, then the atomic radius will be increased.

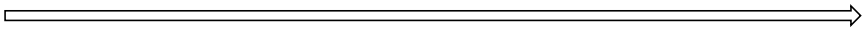


Conversely, if an ion is formed through the loss of electrons, the atomic radius decreases.



An isoelectronic series is a group of atoms and ions that have the same electronic configuration. Since each of the species in an isoelectronic series has the exact same number of electrons, the one with the most protons will be the smallest because a larger number of protons attracts the electrons closer to the nucleus.

	O^{2-}	F^-	Ne	Na^+	Mg^{2+}
# electrons	10	10	10	10	10
# protons	8	9	10	11	12



Decreasing size

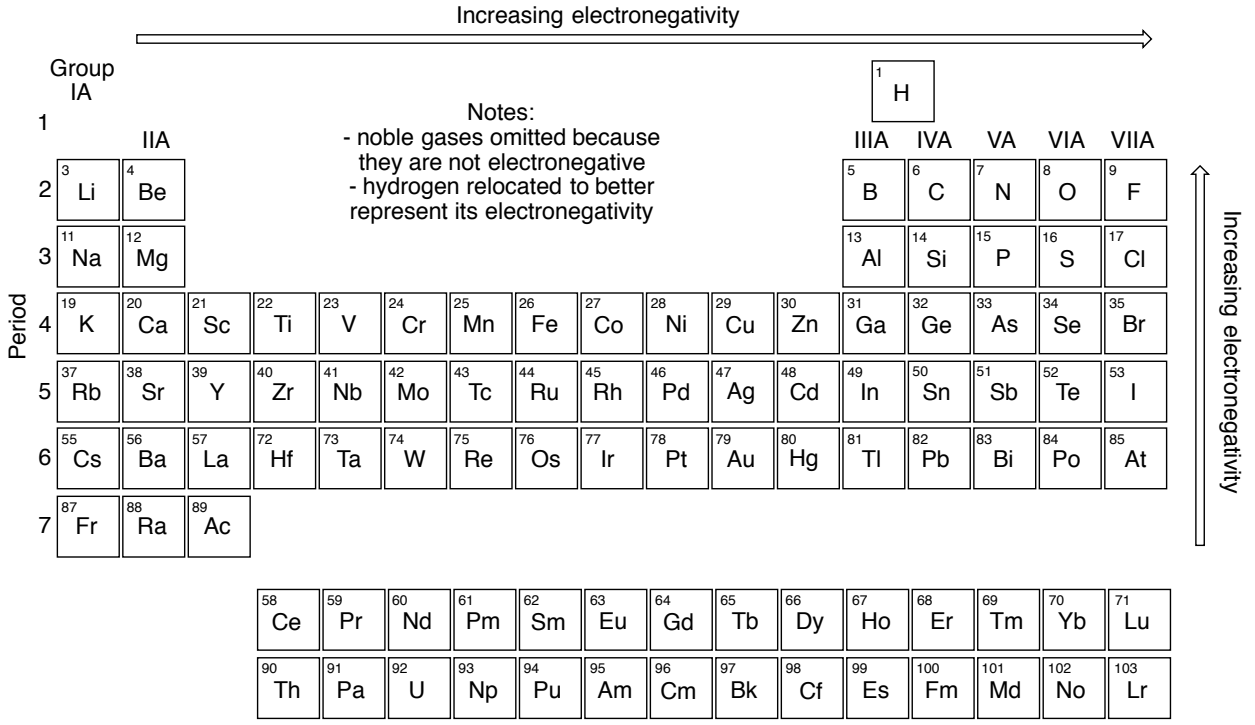
Problem 16. Identify the largest species in each of the following lists.

(a) germanium, silicon, tin, carbon, lead

(b) sulfur, sodium, aluminum, magnesium, silicon, phosphorus, chlorine

(c) P^{3-}, Ar, Ca^{2+}, Cl^-, K^+, S^{2-}

A second important periodic trend is electronegativity. Electronegativity is the tendency of an element to pull electron density toward itself. This tendency increases as you move up and to the right in the periodic table; however, the noble gases are not electronegative because they already have filled valence shells. As a consequence, fluorine is the most electronegative element on the periodic table. As you move closer to fluorine, electronegativity increases. Although hydrogen resides on the far left of the periodic table, it actually has an electronegativity between that of boron and carbon, so it is relocated in the following diagram to reflect this.

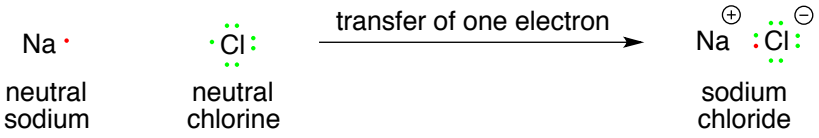


Problem 17. Identify the most electronegative element in this list: cesium, ruthenium, gallium, arsenic, phosphorus, sulfur.

Section 10: Bonding and Lewis structures

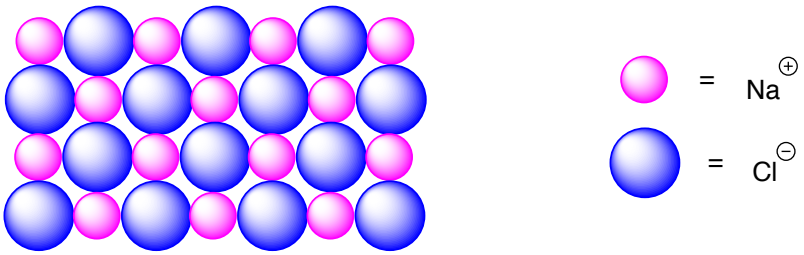
When two atoms bond, they transfer or share electrons so as to attain filled valence shells. This results in a lower energy state because atoms with filled valence shells have noble gas configurations, which are especially stable. For second-row elements, a filled valence shell necessitates eight electrons, so this tendency is referred to as the octet rule.

There are two types of bonds: ionic and covalent. Ionic bonds result from the transfer of electrons between two atoms. This transfer leads to the formation of ions. Sodium chloride (NaCl) is table salt, and it provides an example of an ionic substance. To describe the bonding in sodium chloride, we can use Lewis dot structures, in which the valence electrons are represented by dots surrounding the element's symbol. Only the valence electrons are shown because it is just the electrons in the outermost shell that are available for interaction with other species. When sodium is neutral, it has a single electron in the third shell, which is its valence shell. When chlorine is neutral, it possesses seven electrons in its outer shell, which is also the third shell. As we learned in Section 8, atoms tend to gain or lose electrons so as to attain the same configuration as the nearest noble gas. For sodium, this means losing one electron to obtain neon's electronic configuration; whereas, chlorine will gain one electron to have the same configuration as argon. These two elements are ideally matched, so sodium transfers an electron to chlorine. As these elements become ions, the attraction between their opposite charges (sometimes called electrostatic attraction) is the source of the ionic bond.



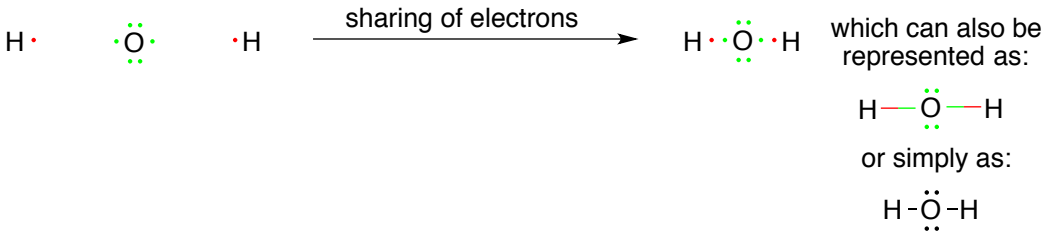
Ionic bonds are formed between elements that have large differences in electronegativity. Notice that sodium and chlorine exist on opposite sides of the periodic table. Since one element is very close to fluorine while the other is very far from it, there is clearly a substantial difference between these two elements in their desire for electrons. The more electronegative element acquires an electron, and the less electronegative element relinquishes an electron. Also, take note that even though sodium chloride may be written as NaCl, where it is not obvious that there are charges, those charges exist nevertheless.

Sodium chloride, like other ionic substances, does not consist of discrete molecules of NaCl. Instead there is a crystal lattice containing one sodium cation for every chloride. Chloride is the name for Cl^-.

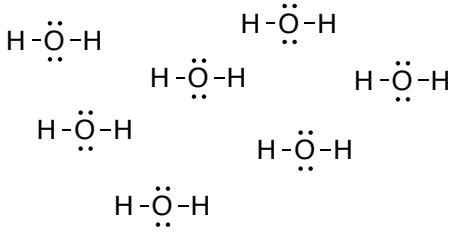


Problem 18. Draw Lewis dot structures for magnesium and oxygen. Then, draw a Lewis dot structure for the ionic species formed from the two.

The other type of bond between atoms is covalent and results from sharing, rather than transfer, of electrons. Water (H_2O) provides an illustrative example. Each neutral hydrogen atom has one electron in its valence shell, and oxygen has six electrons in its. Although there is certainly an electronegativity difference between hydrogen and oxygen, it is not as pronounced as that between sodium and chloride. Elements having smaller electronegativity differences will share electrons. When both hydrogens share their single electrons with oxygen, the result is the water molecule. Each of the atoms now has a filled valence shell. Hydrogen only needs two electrons to fill its outermost shell (n = 1), and the two electrons it shares with oxygen serve that purpose. Oxygen needs an octet, which it attains through its two unshared and two shared pairs. Shared pairs of electrons are often represented as lines between the atoms instead of dots. When this is done, the diagrams are sometimes called Kekulé formulas.



Unlike ionic materials, covalent substances do consist of discrete groups of atoms that have formed bonds to make a single entity known as a molecule. So, a sample of water contains many, many individual water molecules that are distinct from one another.

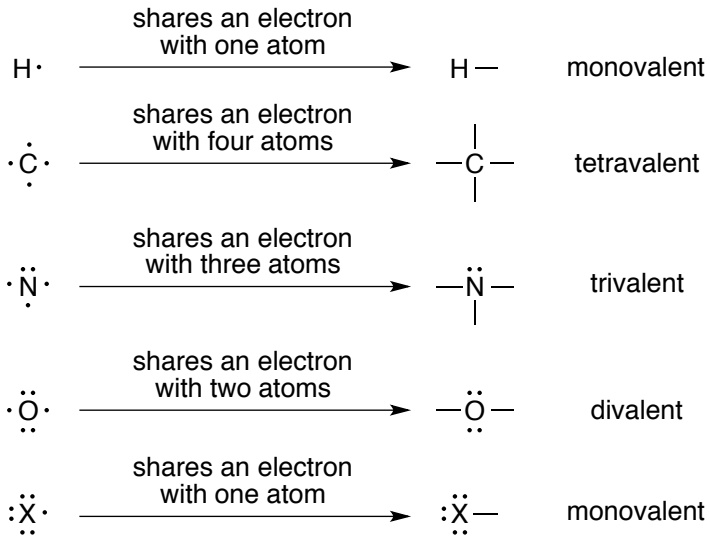


Carbon's principal mode of bonding is covalent. Since it is in the middle of a row, carbon would have to gain or lose a large number of electrons to form an ion with a noble gas configuration, making this improbable. Additionally, carbon's intermediate electronegativity causes it to be more inclined to share electrons than to transfer them.

Based on the number of valence electrons they have, elements make different numbers of bonds to fill their valence shells.

Element	Valence electrons	Number of bonds	Filled valence shell
H	1	1	2 electrons
C	4	4	8 electrons
N	5	3	8 electrons
O	6	2	8 electrons
Halogens (F, Cl, Br, I)	7	1	8 electrons

Hydrogen makes one bond to fill its outer shell with two electrons. An element that makes one bond can be called monovalent. Carbon makes four bonds to complete its octet, so it is tetravalent. Nitrogen engages in three bonds, making it trivalent. Oxygen needs only two bonds to fill the octet and is therefore divalent. The halogens need just one bond to attain an octet and are monovalent, like hydrogen, as a result.



Atoms will sometimes deviate from their normal valence (i.e., their normal number of bonds). When this occurs, the atom will usually have a charge or an unpaired electron.

We can use our knowledge of the elements' valences to build Lewis structures for molecules. There are a few simple guidelines that will help us through this process:

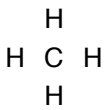
(1) Begin by tallying the valence electrons for each atom in the molecule. If the molecule is charged, add one electron for each negative charge, or subtract one electron for each positive charge.

(2) Arrange the atoms in a way that maximizes the chance of satisfying their normal valences. Atoms that make more than one bond should occupy the central positions, while the monovalent elements should reside on the periphery of the molecule.

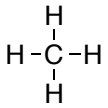
(3) Place electrons so as to form bonds between all of the atoms. If electrons remain, place them as unshared pairs to complete the octet as needed. If all of the electrons have been used and some elements have incomplete octets, consider the use of double or triple bonds.

(4) Assign charges for elements that deviate from their normal valence as appropriate.

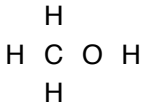
Let's consider some examples that will give us an opportunity to expand upon these guidelines. We'll start with the simplest organic molecule: methane. Methane has the molecular formula CH_4. The first step is to determine the total number of valence electrons that we have to work with. Carbon has four valence electrons, and each hydrogen contributes one, for a total of eight. Then, we place the atoms in a way that makes sense based on their preferred number of bonds. Since carbon is the only element in this molecule that makes more than one bond, it must reside at the middle and be surrounded by hydrogens.



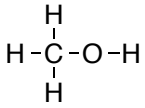
As we place electrons to create bonds, we consume all eight electrons available. None of the elements deviate from their normal valence, so we don't expect to find any charges in this molecule.



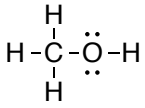
Now, let's consider methanol, which has the molecular formula CH_4O. Carbon has four valence electrons, oxygen has six, and each hydrogen contributes one. This gives a total of fourteen electrons that we can use to build the molecule. In this case, there are two atoms that make more than one bond. Carbon and oxygen therefore occupy the center of the molecule and are surrounded by hydrogens. Since oxygen only makes two bonds, we'll only put one hydrogen near it. The remainder of the hydrogen atoms surround carbon.



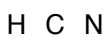
By placing electrons to form bonds, we consume ten of the fourteen available.



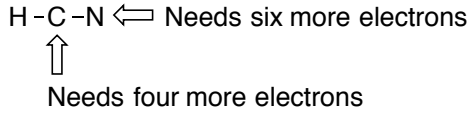
At this point, carbon and all of the hydrogens have filled valence shells, but oxygen does not. This causes us to place the remaining four electrons on oxygen as two unshared (a.k.a. lone) pairs. Now, we have used all of the electrons, and all atoms have a filled outer shell.



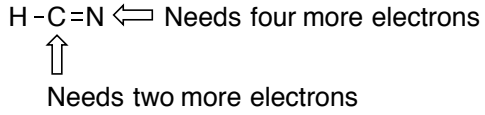
For our next example, let's consider hydrogen cyanide (HCN). Nitrogen has five valence electrons. Added to carbon's four and hydrogen's one, this gives us a total of ten electrons to use when constructing this molecule. Carbon and nitrogen occupy the core of the molecule because they can each make more than one bond. There is only one hydrogen to place, and we have to decide whether it should be close to carbon or nitrogen. Since carbon makes more bonds than nitrogen, it is more likely to need the hydrogen atom, so we place it near carbon.



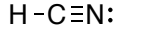
It only takes four electrons to bond the elements to one another. And, we quickly realize that the remaining six electrons are insufficient to fill the octet for both carbon and nitrogen. Ten additional electrons would be required, and we simply don't have that many.



We noted earlier in step 3 that, if all of the electrons have been used and some elements have incomplete octets, it may be necessary to consider the use of double or triple bonds. So, we can try to place a double bond between carbon and nitrogen. In doing so, we have placed a total of six electrons, leaving us with four more, but that number falls short of what is needed to fill the octet for carbon and nitrogen.

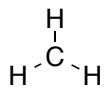


As a result, we place a triple bond between carbon and nitrogen. With eight electrons in bonds, we are left with only two more to place. Nitrogen needs one lone pair of electrons to fill its octet. We have attained every element's normal valence using the available quantity of electrons.



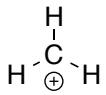
Notice that the normal valence denotes the number of bonds an element makes when neutral. These bonds do not have to be to separate atoms. Carbon tends to make four bonds, and it does so in this structure. It is irrelevant whether those four bonds come in the form of four single bonds or one single and one triple bond.

Now, let's turn our attention to some examples in which elements deviate from their normal valence. Consider the methyl carbocation, which has the formula CH_3^+. Carbon contributes four valence electrons and each hydrogen contributes one. Remember that we have to make an adjustment because of the charge. A positive charge indicates that there is one fewer electron than expected, so the total number of electrons is six. Carbon is placed in the middle and surrounded by hydrogens. Making the three required bonds consumes all six electrons. We have no more electrons with which to complete the octet for carbon.



Incomplete drawing:
Where does the positive charge reside?

This drawing is not complete until we add the charge, which can also be referred to as a formal charge. One of the atoms in the structure carries the positive charge indicated by the molecular formula. When an atom deviates from its normal valence, it usually has a charge or an unpaired electron. Carbon is the atom with an unusual valence; it has only three, rather than its usual four, bonds. We can therefore anticipate that carbon will have the positive charge.



We need to understand why carbon has a positive charge though. There is a simple way of calculating formal charge, and it entails comparing the number of electrons that an element "owns" to the number it should possess, which is its number of valence electrons. We already know how to count the valence electrons for an atom. The number of electrons that an atom "owns" includes any in unshared pairs and half of those in shared pairs. Carbons have four valence electrons, but this carbon atom only "owns" three electrons (half of the six shared electrons in its bonds). Since carbon "owns" one fewer electron than it should, its protons outweigh its electrons by one, and a positive one charge results. This way of thinking about formal charge can be expressed in the formula shown below.

$$Formal\ charge = Valence\ electrons - [unshared\ electrons + {}^{1}/_{2}\ shared\ electrons]$$

$$Formal\ charge\ on\ carbon = 4 - \left[0 + {}^{1}/_{2}\ (6)\right] = 4 - 3 = +1$$

Let's also examine a negatively charged species: hydroxide ($^{-}$OH). Oxygen has six valence electrons, and hydrogen has one. The negative charge indicates that the molecule has one more electron than anticipated, and this must be added to our tally, giving a total of eight electrons. After filling in the two needed for the bond, six are placed as lone pairs on oxygen to complete its octet.

Incomplete drawing:
Where does the negative charge reside?

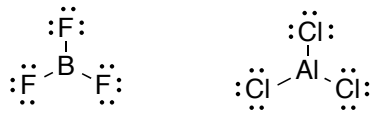
One of the two atoms is negatively charged, and we know that oxygen is the most likely candidate since it deviates from its normal valence. Nevertheless, let's do the formal charge calculation to convince ourselves.

$$Formal\ charge = Valence\ electrons - [unshared\ electrons + {}^{1}/_{2}\ shared\ electrons]$$

$$Formal\ charge\ on\ oxygen = 6 - \left[6 + {}^{1}/_{2}\ (2)\right] = 6 - 7 = -1$$

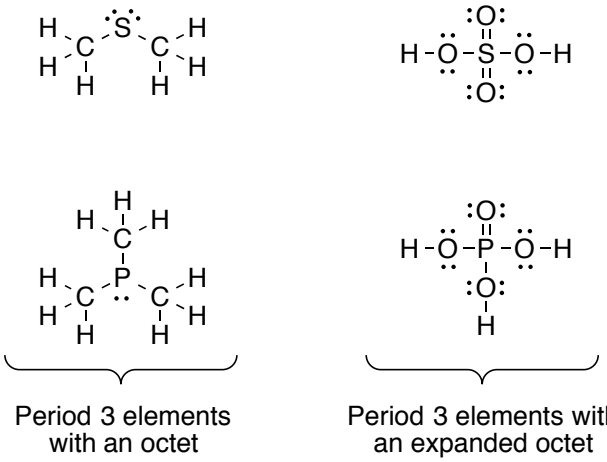
Thus, the complete Lewis structure for hydroxide has a negative charge on oxygen.

Before we proceed further, it is important to note that there are some notable exceptions to the octet rule. In fact, we've already encountered one. Hydrogen needs only two electrons to fill its valence shell. The Group IIIA elements, such as boron and aluminum, are another exception. When these atoms are neutral, they make three bonds and have no unshared electrons. As a result, they only have a sextet of electrons.



Group IIIA elements have a sextet of electrons when neutral.

Another exception to the octet rule comes from elements in Period 3 or greater. Second-row elements (i.e., those in Period 2) can never exceed an octet of electrons. Quantum mechanics shows us that they simply don't have access to enough orbitals to hold more than eight electrons in their valence shells. However, in Period 3 when n = 3, ℓ can be 0, 1, or 2, meaning that there are *s*, p, and d orbitals. With d orbitals, these elements can hold more than an octet of electrons, so elements in Period 3 or greater may have an octet or an expanded octet, which means more than eight electrons.



Period 3 elements with an octet

Period 3 elements with an expanded octet

Problem 19. Draw Lewis structures for the following molecules.

(a) $CHCl_3$

(b) CH_2O

(c) CH_2O_2

(d) C_2H_2

Section 11: Other molecular representations

Lewis structures are very useful representations, but they can be tedious to draw for even moderately sized organic molecules. As a result, there are some alternatives that allow us to convey organic structure more rapidly. One such alternative is the condensed formula, which is prepared according to the following guidelines.

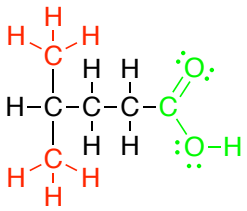
(1) Single bonds are omitted from condensed structural formulas, and atoms are simply drawn next to other atoms to which they are bonded.

(2) Carbon-carbon double and triple bonds are drawn, but double and triple bonds involving other elements may or may not be drawn.

(3) When one atom is bonded to multiple identical groups, those groups are clustered together in parentheses and a subscript is used to denote the number that are present.

(4) While formal charges and unpaired electrons must be drawn, lone pairs may or may not be drawn.

Let's practice this by converting the molecule shown below as a Lewis structure into a condensed formula. As we move along the molecule from left to right, we first notice that two identical CH_3 groups are bonded to the same carbon. These are grouped in parentheses and drawn next to the CH group to which they are attached. This is followed by two CH_2 groups. The molecule terminates on the right-hand side with a carbon bonded to two oxygens, one of which has a hydrogen. This grouping of atoms can be represented as CO_2H or COOH. In either case, the double bond between carbon and oxygen is implied by the fact that carbon has four bonds when neutral but is bonded to only three atoms.



Lewis structure

can also be drawn as:

$(CH_3)_2CHCH_2CH_2CO_2H$

or

$(CH_3)_2CHCH_2CH_2COOH$

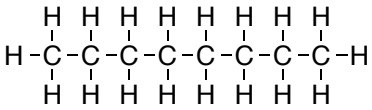
Condensed formulas

We can condense these structures even further if desired by grouping the two sequential CH_2 groups in parentheses. This highlights the fact that different levels of compression are acceptable. Molecules will be drawn in whichever fashion best showcases the features important at the moment. You may find it useful to condense the two CH_2 groups if they aren't the focus. On the other hand, if you want to consider one or both of them in more detail, you may prefer to draw them individually.

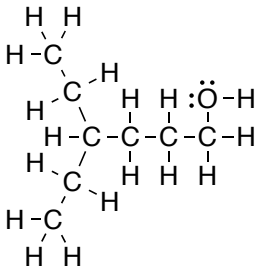
$(CH_3)_2CHCH_2CH_2CO_2H$ or $(CH_3)_2CHCH_2CH_2COOH$ can also be drawn as: $(CH_3)_2CH(CH_2)_2CO_2H$ or $(CH_3)_2CH(CH_2)_2COOH$

Problem 20. Convert the following Lewis structures into condensed formulas.

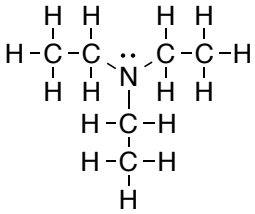
(a)



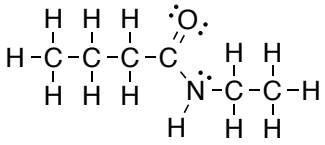
(b)



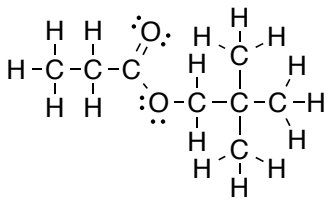
(c)



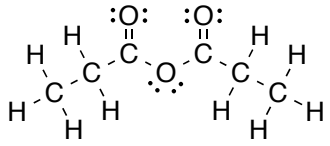
(d)



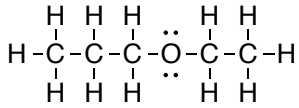
(e)



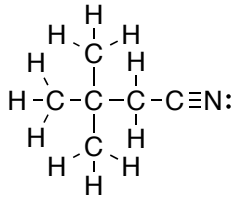
(f)



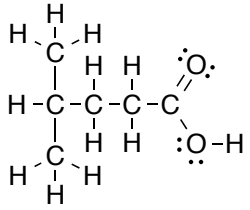
(g)



(h)



In a related vein, chemists will sometimes mix different structural representations to suit their needs. Maybe the right-hand side of the molecule is important (as it will be in our next chapter on acids and bases). In this case, you could leave that portion of the Lewis structure intact and condense only the remainder of the molecule.



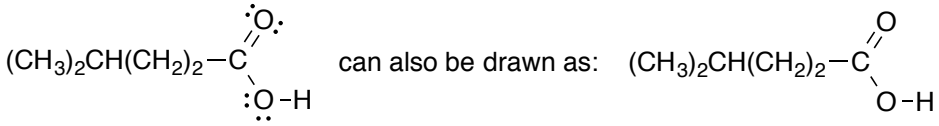
Lewis structure

can also be drawn as: $(CH_3)_2CH(CH_2)_2$—C(=O)–O–H

A partially condensed formula

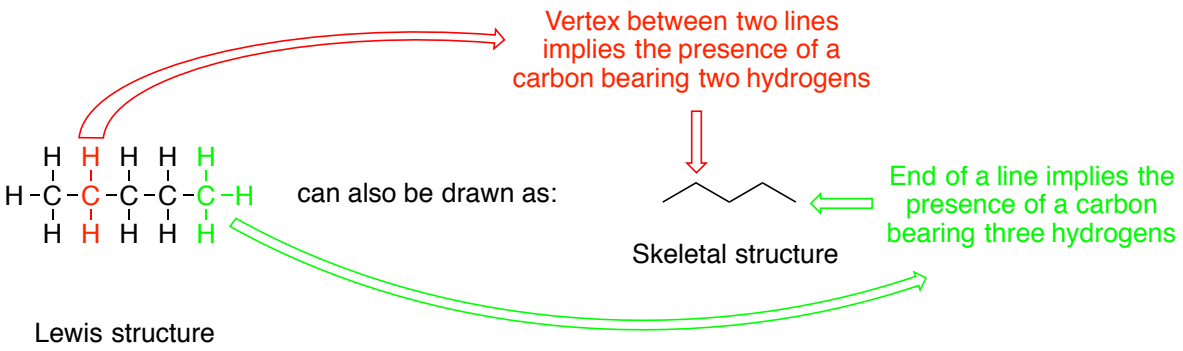
If it is not necessary to emphasize the lone pairs of electrons, they may be omitted to speed the drawing. It may seem like there are a lot of choices, but the bottom line is simple: emphasize those structural features that are under consideration using whatever level of

detail is appropriate. We'll quickly get a feel for this as we move through the chapters in this book.

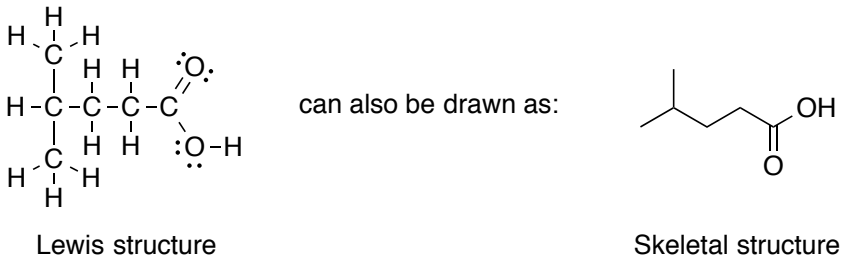


An even greater abbreviation is achieved using skeletal structures, which are also called bond-line or line-angle formulas. In these formulas, the carbons and hydrogens themselves are omitted and their presence is merely implied. As before, a line is used to represent a shared pair of electrons in a bond. Adjacent bonds are drawn in a zigzagged fashion so that the vertices between them are readily apparent. The end of a bond or a vertex between two bonds indicate the presence of a carbon atom. Unless a charge or an unpaired electron is present, we assume that there are enough hydrogens on each carbon to complete its octet.

For instance, the following five-carbon molecule can be quickly represented as a skeletal structure. Two carbons in the molecule are highlighted. One appears at the intersection between two lines representing bonds. This carbon needs two hydrogens to complete its octet. The other indicated carbon is at the end of a line. This carbon needs three bonds to hydrogens to fill its valence shell.



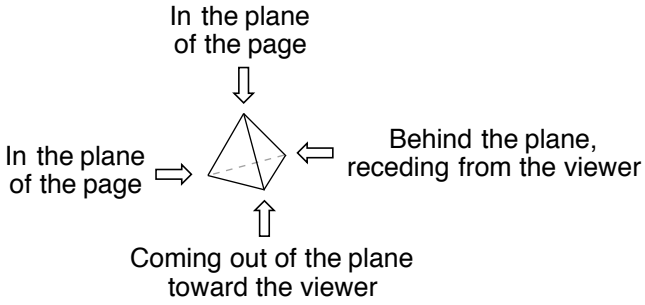
Any atoms other than carbon and hydrogen must be drawn in skeletal structures. Such atoms are sometimes called heteroatoms to accentuate their difference from carbon and hydrogen. If a heteroatom's symbol appears at the end of a line or at a vertex, it replaces the carbon that would otherwise have been implied at that location. Any hydrogens bonded to heteroatoms must be explicitly drawn; they cannot be implied. In the following molecule, the two oxygens are clearly shown in the skeletal structure, and the hydrogen bonded to oxygen is also drawn out.



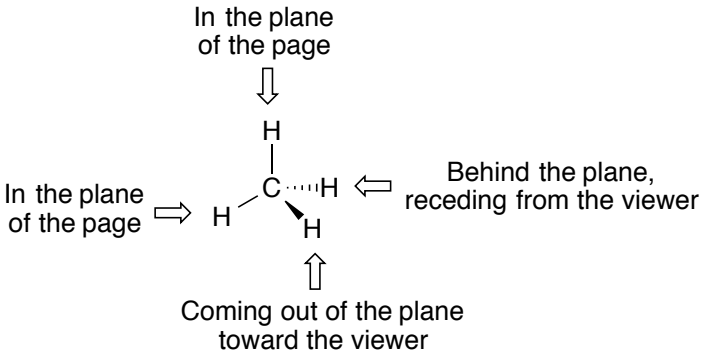
Lewis structure Skeletal structure

Problem 21. Convert the Lewis structures in Problem 20 into skeletal structures.

Finally, wedges and dashes can be used with any structural formula to depict shape. For reasons we'll learn in Section 15, the four bonds of methane (CH_4) point to the four corners of a regular tetrahedron. We can orient a tetrahedron so that two of its corners are in the plane of the page. When we do so, one corner comes out of the plane of the page and approaches the viewer, while the other is behind the plane of the page and recedes from the viewer.



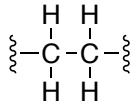
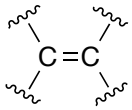
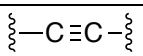
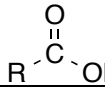
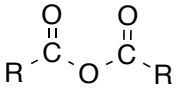
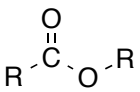
Methane can be situated in the same fashion. To better highlight its shape, we use regular lines for bonds that are in the plane of the page. A bond that extends out of the plane toward the viewer is drawn as a wedge, and a bond that falls behind the plane of the page is dashed.

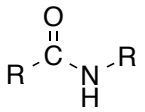


Section 12: Functional groups

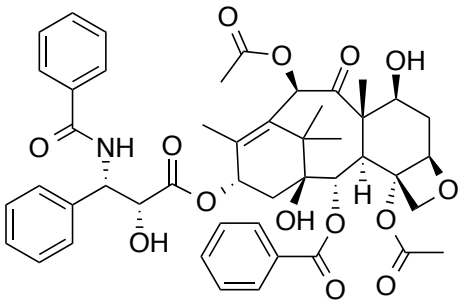
The portions of a molecule that contain only carbons, hydrogens, and single bonds are not very reactive. In contrast, when heteroatoms and/or double or triple bonds are present,

these structural features tend to dictate the properties and reactivity of a molecule. Functional groups are particular arrays of atoms within a molecule that give rise to many of its attributes. They are commonly occurring structural motifs within organic compounds, so it is important to learn the functional groups early in our study of organic chemistry. A table of some of the most common functional groups is provided below. The squiggly lines are used to cut out a fragment of a molecule. In some entries, an R group is used. R denotes an alkyl group, which is a cluster of carbons and hydrogens containing only single bonds. R is often used as a shorthand for the rest of the molecule when we don't necessarily care about its exact structure.

Functional group	**Structure**	**Condensed formula**	**Key component**
Alkane			Single bonds
Alkene			Double bond
Alkyne			Triple bond
Aromatic ring			Benzene ring
Alkyl halide			
Alcohol			Hydroxyl group (OH)
Ether			Alkoxy group (OR)
Epoxide			Three-membered ring containing oxygen
Amine	 (N can have 1 – 4 R groups)		Amino group (N with any Hs it may bear)
Aldehyde		RCHO	Carbonyl (C=O)
Ketone		RC(O)R	Carbonyl (C=O)
Carboxylic acid		RCO_2H or RCOOH	Carboxyl group (CO_2H)
Acid chloride		RC(O)Cl	
Anhydride		$(RCO)_2O$	
Ester		RCO_2R	

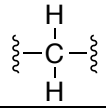
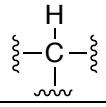
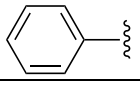
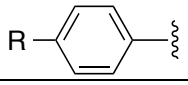
Amide	 (N can have 0 – 2 R groups)	RC(O)NHR	
Nitrile	R–C≡N	RCN	Cyano group (CN)

Problem 22. Paclitaxel, also known as taxol, was isolated from a yew tree and is now used in the treatment of certain forms of cancer. Identify the functional groups in taxol.

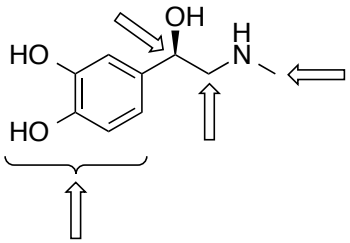


Section 13: Commonly occurring fragments and reactive intermediates

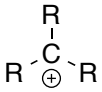
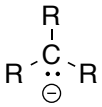
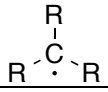
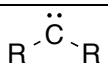
There are a few molecular fragments that have commonly used names. Within an alkyl group, we may encounter CH_3, CH_2, and CH groups. These are known as methyl, methylene, and methine groups, respectively. Also, the benzene ring may sometimes be found as a group attached to a more complex molecule. In such cases, it can be called a phenyl group and abbreviated as Ph. Substituted aromatic rings are known as aryl groups.

Group	Structure	Abbreviation
Methyl		Me
Methylene		
Methine		
Phenyl		Ph
Aryl		Ar
The aryl moiety can have any number or kind of groups attached to it.		

Problem 23. Name the indicated groups in the structure of epinephrine, which is also known as adrenaline.



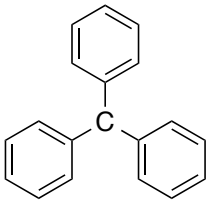
Additionally, when carbon deviates from its normal valence, it is often quite reactive. As a result, such species are intermediates in chemical reactions. In other words, they appear transiently between the reactants and the products and are implicated in the reaction mechanism, which explains how the reactants become the products. These reactive intermediates are shown below.

Reactive intermediate	Structure	Number of electrons
Carbocation		6
Carbanion		8
Radical		7
Carbene		6
In each case, the number of R groups may vary.		

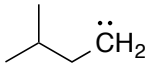
A carbocation (i.e., a cation on carbon) has three bonds and no unshared electrons. Such a carbon has six electrons in its valence shell and a formal positive charge, so it is electron deficient. Conversely, a carbanion (i.e., an anion on carbon) has three bonds and a lone pair. It has a complete octet and a formal negative charge, making it electron rich. A carbon radical has three bonds and a single unshared electron. This can also be called an unpaired electron. While the carbon has no formal charge, it is still electron deficient because it has only a septet of electrons, rather than the desired octet. Finally, a carbene has two bonds and a lone pair. Like a radical, it has no formal charge but is nevertheless electron deficient because it has only a sextet of electrons.

Problem 24. In the following structures, all of the lone pairs are shown, but formal charges are missing. Identify the atoms (if any) bearing formal charges, and place the correct formal charge on them.

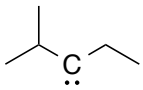
(a)



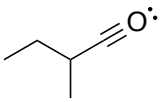
(b)



(c)

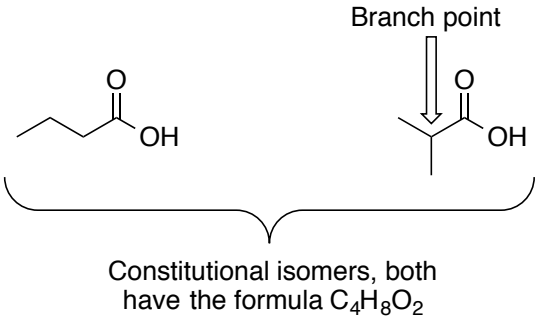


(d)

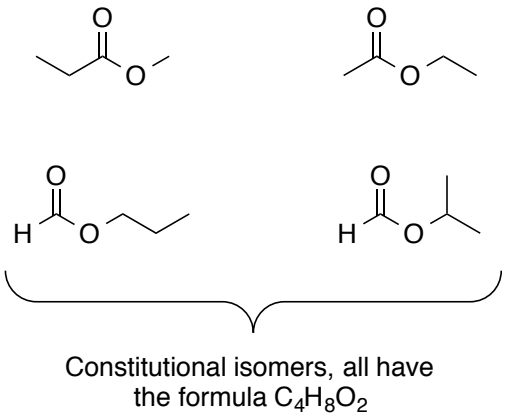


Section 14: Constitutional isomers

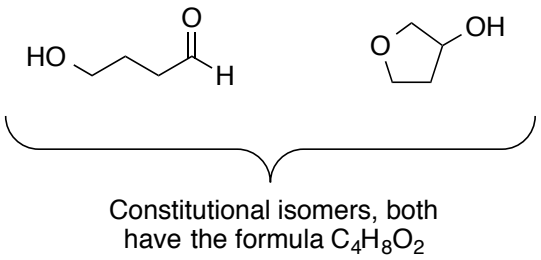
As molecular formulas become more complex, there are frequently multiple structures with the same composition. This phenomenon is known as isomerism. Constitutional isomers are molecules with the same molecular formula but differing connectivity between the constituent atoms. For example, we can draw two carboxylic acids with the molecular formula $C_4H_8O_2$. In the first, all of the carbons are connected end to end. In the second, there is a branch point where the carbon chain diverges.



The isomers above have the same functional group and merely differ in the specific structure of their R groups. However, it is also possible to draw isomers with different functional groups. For example, the following isomers contain esters.



It is also sometimes possible to draw isomers with a different number of functional groups. In the following two examples, the first compound contains an alcohol and an aldehyde, while the second has an ether and an alcohol.



Constitutional isomers have different properties and reactivity. The extent of the differences depends on the extent of the structural deviation between them. For instance, the two isomeric carboxylic acids both contain the same functional group; since the functional group largely dictates the characteristics of a molecule, we can expect these two compounds to behave similarly. However, constitutional isomers containing altogether different functional groups will likely have vastly divergent chemical behavior.

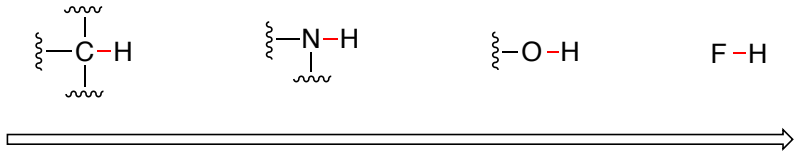
Problem 25. Draw all the constitutional isomers of $C_4H_{10}O$.

Section 15: Hybridization and molecular shape

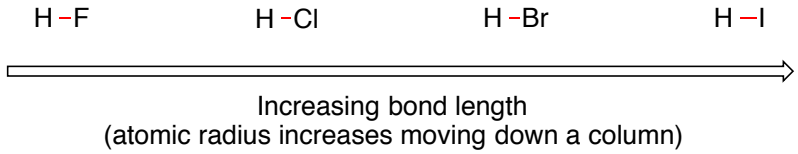
At a basic level, molecular shape is described using bond length and bond angle. We'll learn about another important facet of molecular shape known as dihedral angle in the chapter on alkanes. Bond length is simply the distance between the nuclei of two bonded atoms. Since this is a very small distance, it tends to be measured using small units, such as angstroms (Å). One angstrom is 1×10^{-10} meters. Carbon-carbon bonds are approximately 1.5 Å in length, while carbon-hydrogen bonds are about 1.1 Å long.

Bond length is the sum of the atomic radii, so it follows the periodic trend that we learned for atomic radius. A smaller atom leads to a shorter bond. In the series below, there are bonds between hydrogen and a second-row element. Moving left to right across a row, the

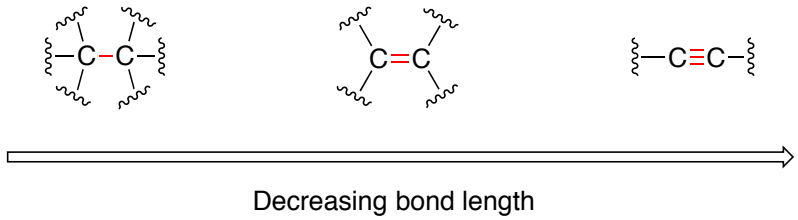
atomic radius decrease because there are more protons to pull in the electrons in the same valence shell. As a result, the bond length diminishes accordingly.



In the next series, a group of hydrogen-to-halogen bonds are given. As we move down a column of the periodic table, the valence shell increases in size, and the bond length increases as a result.



Additionally, multiple bonds are shorter than single bonds of the same type because the nuclei are held more tightly by the greater number of electrons shared between them. It is also worth noting that single, double, and triple bonds are said to have bond orders of 1, 2, and 3, respectively.

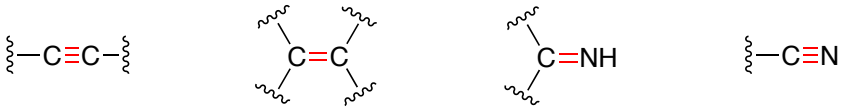


Problem 26. In each of the following sets, identify the shortest bond.

(a)

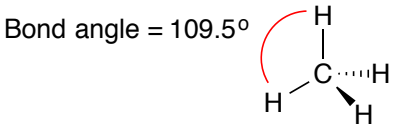
(b)

(c)

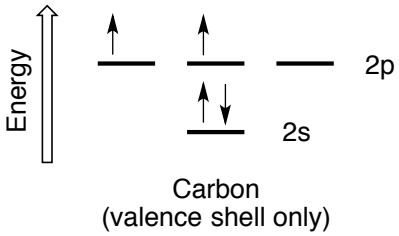


(d)

A bond angle is defined by any three contiguous nuclei. For example, in methane a bond angle can be defined as the angle between any H-C-H. All of the bond angles in methane are identical. They are 109.5˚.



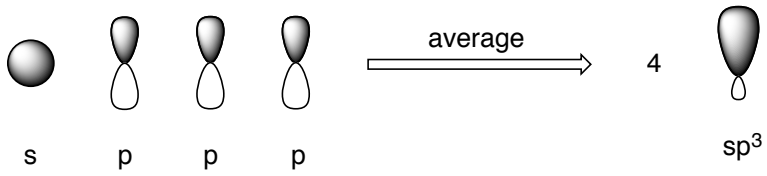
Not only are all of the bond angles in methane identical, but all of the C-H bonds are of the same length as well. This presents a conundrum when we attempt to reconcile this fact with the valence shell electronic configuration of carbon.



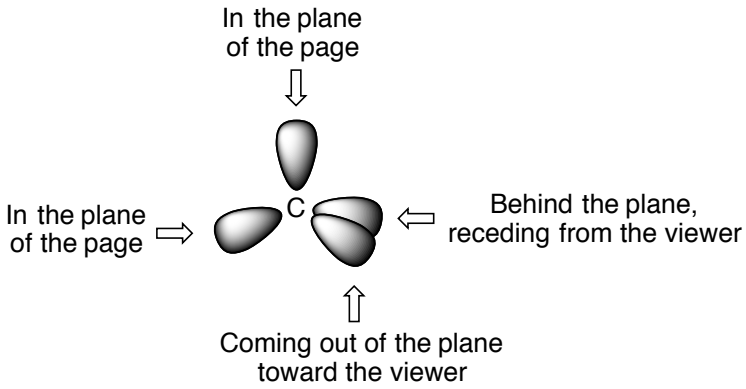
If carbon makes four bonds and the four orbitals in its valence shell are an s orbital and three p orbitals, how could all of the bond lengths be identical? Since s and p orbitals differ in shape, we would expect them to yield bonds of differing lengths. Additionally, it is not clear why the bond angles are 109.5˚. The p orbitals, for instance, are mutually orthogonal, meaning that they have 90˚ angles between them.

It was Linus Pauling who provided the solution to this puzzle when he proposed the hybridization of atomic orbitals. Pauling proposed that the wave functions for the valence-shell orbitals could be averaged to explain the observed geometry. This averaging of wave functions yields orbitals that have a mixture of s and p character; hence they are hybrids. A carbon that needs to make four single bonds will average its s and three p orbitals to yield a hybrid orbital that has one part s character and three parts p character. This is known as an sp^3 hybrid orbital. The shaded lobes of the p orbitals are augmented by the s orbital because there is constructive interference between these parts of the wave functions. However, the unshaded lobes of the p orbitals are diminished by the s orbital because of

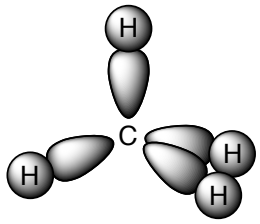
the destructive interference between them. The number of orbitals is conserved in this process. Since four atomic orbitals were averaged, four sp^3 hybrid orbitals result.



Valence shell electron pair repulsion (VSEPR) theory helps us to predict the molecular geometry for methane. VSEPR is based on the fact that electron pairs repel each other. Therefore, they should be distributed around the atoms within a molecule so as to minimize this repulsion. Since the four hybrid orbitals are completely identical, they can be distributed evenly in space. This happens to place them at 109.5° angles. In diagrams using hybrid orbitals, the small back lobes tend to be omitted for clarity.

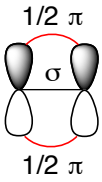


To depict methane, we can use valence bond theory, which is an approximation in which atomic orbitals overlap to give the bonds found in a molecule. Each of carbon's sp^3 hybrid orbitals overlaps with a hydrogen s orbital to make the four C-H bonds.

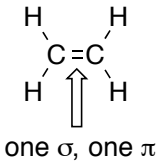


This direct head-to-head overlap of orbitals yields a sigma (σ) bond. A σ bond is always the first connection between any two nuclei. However, any additional bonds are pi (π) bonds. π bonds are very different from σ bonds because they result from the side-to-side overlap of parallel p orbitals on adjacent atoms. In the diagram below, the σ bond is represented simply as a line between the two nuclei, and the orbitals overlapping to form this σ bond have not been shown. Instead, the π bond is emphasized. It requires one p orbital on each of these adjacent atoms. The p orbitals must be parallel and in phase with one another. The

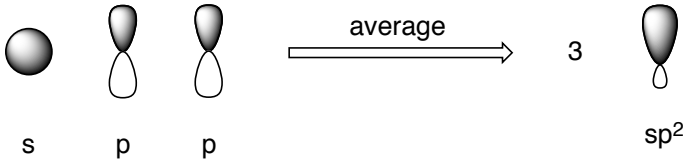
side-to-side overlap of the shaded lobes gives half of the π bond, and the analogous overlap of the unshaded lobes provides the other half of this π bond. The electron density in π bonds is further from the nuclei than it is in σ bonds, and as a result, π bonds are weaker.



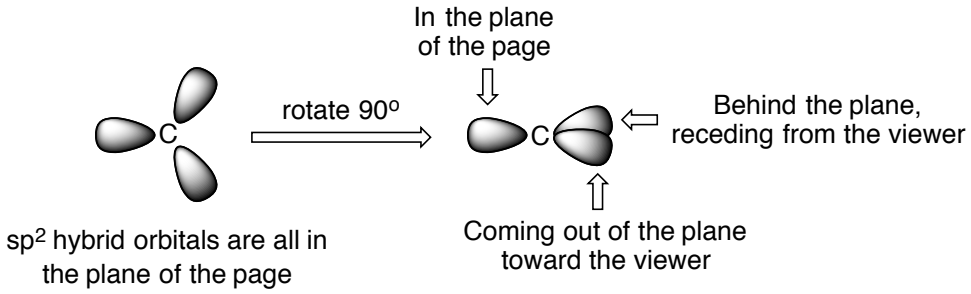
Due to the fact that π bonds are only formed using p orbitals, any atoms participating in a π bond must reserve one unhybridized p orbital. This changes the element's hybridization. Let's consider ethylene—a plant hormone responsible for fruit ripening—as an illustrative example. All of the carbon-hydrogen bonds are σ bonds. The carbon-carbon double bond consists of one σ and one π bond. Remember that the first connection between any two nuclei will be a σ bond, and any additional bond between them is π.



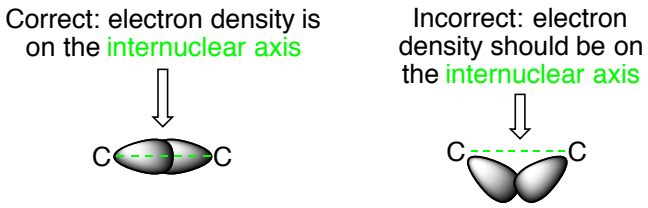
Each carbon must reserve one unhybridized p orbital for the π bond. As a result, the hybridization averages the s and only two p orbitals. The result is three sp^2 hybrid orbitals. Since these hybrids have one-third s character, they are slightly shorter than sp^3 hybrids, which have only one-quarter s character.



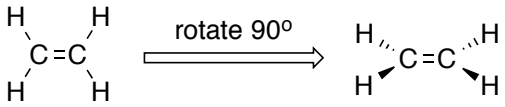
The three sp^2 hybrids are situated as far apart from one another and from the π bond as possible, as dictated by VSEPR theory. They lie in the same plane and have 120° angles between them. The orbitals may be drawn so that they all fall in the plane of the page. Alternatively, in some situations it will be convenient to rotate the whole system by 90° so that it is perpendicular to the plane of the page. This does not alter the 120° angles between the orbitals; it is merely a different viewpoint.



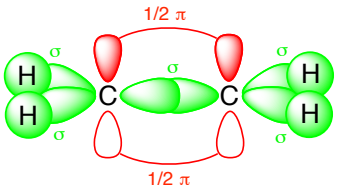
The three sp^2 hybrid orbitals are used to make the three σ bonds that each carbon of ethylene has. The C-H σ bonds are easy to draw because there is only one way to overlap the spherical s orbital of hydrogen with carbon's hybrid orbital. However, when drawing the C-C σ bond, it is important to be mindful of the fact that the electron density of a σ bond falls on the internuclear axis. In other words, if you draw a straight line between the two nuclei, the overlapping orbitals of a σ bond must reside on this axis.



It will be easiest to draw the orbital overlap if we begin by rotating the structure 90° so that the σ framework of the molecule is perpendicular to the plane of the page.

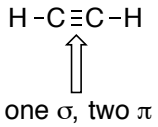


Doing so enables us to draw the π bond in the plane of the page, which provides the maximum separation of the electrons in the π bond from those in the σ bonds. Notice that, while π bonds are always made from the overlap of parallel p orbitals, σ bonds can be formed by overlapping different types of orbitals. There are two types of σ bonds in this molecule. The C-H σ bonds are made by the overlap of carbon's sp^2 hybrid with hydrogen's s orbital. On the other hand, the C-C σ bond results from the overlap of sp^2 hybrid orbitals from two carbons.

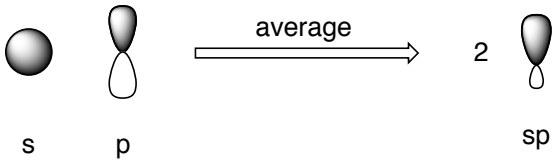


When a triple bond is present, the hybridization changes once again. Acetylene is a fuel used in welding torches. It is the smallest alkyne. Its carbon-hydrogen bonds are σ bonds.

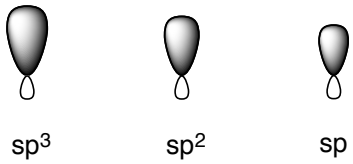
The triple bond consists of one σ bond and two π bonds. Recall that the first connection between any two atoms is a σ bond. The electron density in σ bonds falls on the internuclear axis. Once that space is occupied by an electron pair, it cannot be occupied by any more. Thus, the remaining two bonds must both be π bonds.



Since each carbon must reserve two unhybridized p orbitals (one for each of its π bonds), there is only one s and one p orbital remaining to hybridize.

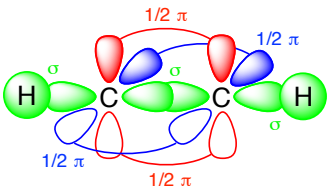


The two sp hybrids that result have one-half s character, so they are even shorter than the sp^2 hybrids.

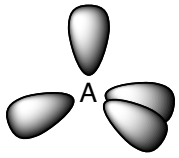
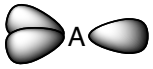


As VSEPR theory dictates, the two sp hybrids are separated by 180° so that the repulsion between the electrons occupying them is minimized.

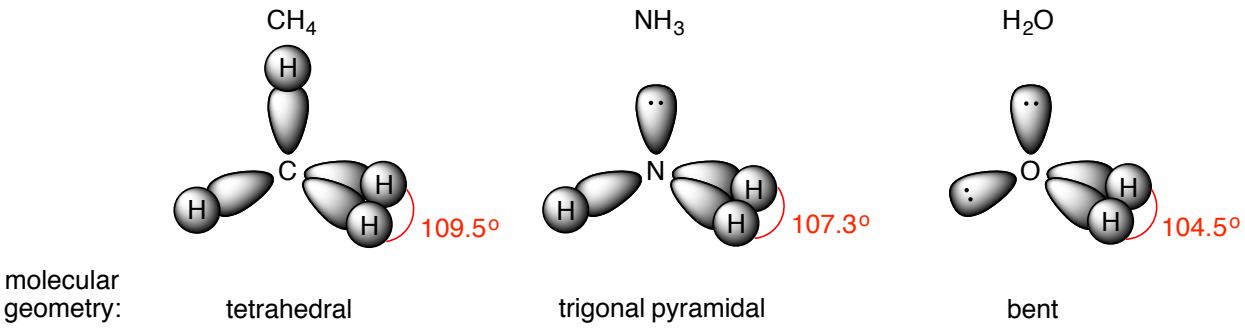
These sp hybrid orbitals are used to make each carbon's σ bonds. The C-H σ bonds are formed by overlapping carbon's sp hybrid with hydrogen's s orbital. The C-C σ bond results from the overlap of each carbon's sp hybrid. Both of the π bonds are made from p orbitals that are orthogonal to (i.e., 90° from) the σ framework. The red π bond is in the plane of the page but perpendicular to the σ bonds. The blue π bond is perpendicular to both the σ bonds and the red π bond. This means that the blue p orbitals come in and out of the plane of the page. This is represented graphically by drawing the blue p orbitals on an angle so that both lobes can still be seen.



Having completed these three examples, we are now in a position to make some generalizations about hybridization. Hybridization can be predicted by the number of atoms and/or lone pairs around a central element. The only caveat is that hydrogen and the halogens do not hybridize. Other elements will hybridize enough atomic orbitals to accommodate the atoms and lone pairs surrounding them. Any combination of atoms and lone pairs that totals four leads to sp^3 hybridization and a tetrahedral arrangement of the orbitals. Any combination totaling three results in sp^2 hybridization. Since these hybrids point to the corners of a triangle and reside in the same plane, their arrangement is termed trigonal planar. Lastly, any combination of atoms and lone pairs equaling two gives sp hybridization. These hybrid orbitals are arranged linearly.

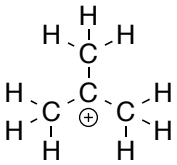
Number of atoms and/or lone pairs around central atom	**Hybridization**	**Hybrid orbital arrangement**	**Bond angle**
4	sp^3	 tetrahedral	~109.5˚
3	sp^2	 trigonal planar	120˚
2	sp	 linear	180˚
"A" stands for atom.			

There are some finer distinctions between sp^3 hybridized atoms that are based on the number of lone pairs. Lone pairs are more diffuse than electrons in σ bonds. This is due to the fact that lone pairs are only attracted to one nucleus; whereas, electrons in σ bonds are reined in more tightly by their attraction to two nuclei. Since lone pairs are more diffuse, they repel the electrons in bonds, thereby compressing bond angles slightly. Methane (CH_4) has no lone pairs, so it has perfectly tetrahedral bond angles of 109.5˚. Ammonia (NH_3) has one lone pair, which compresses the H-N-H bond angles slightly to 107.3˚. Water has two lone pairs; therefore, the compression is a bit more pronounced, and the H-O-H bond angle is 104.5˚. In molecules with atoms larger than hydrogen surrounding the central atom, we can expect less bond-angle compression because larger groups resist being pushed closer together.

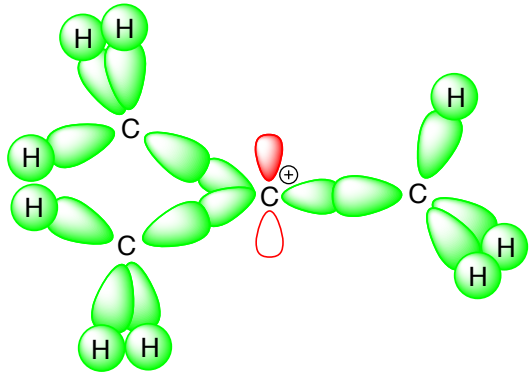


The molecular geometry is defined by where atoms reside. In methane, there are hydrogen atoms at the four corners of a tetrahedron, so the geometry is called tetrahedral. In ammonia, however, one of those corners is not occupied by an atom. Ammonia's geometry is termed trigonal pyramidal because the nitrogen and three hydrogens form a pyramid shape with a triangular base. In water, the oxygen and two hydrogens reside on a bent line, so the geometry is simply called bent.

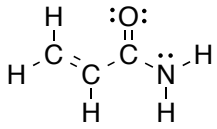
Orbital overlap diagrams can be derived for all sorts of molecules using the basic information given above. Let's try two additional examples together. For the first, we'll examine the *tert*-butyl carbocation, which has the formula $(CH_3)_3C^+$. Our task will be easier if we convert the condensed formula into a Lewis structure. There are three methyl groups bonded to a central carbocation in this molecule.



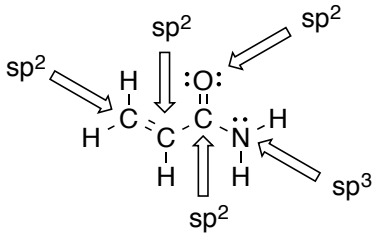
The central carbon is surrounded by three atoms and no lone pairs, so it is sp^2 hybridized. The methyl group carbons are sp^3 hybridized because they are surrounded by four atoms. The central carbon has the trigonal planar shape, while the peripheral carbons are tetrahedral. The central carbon also has one unhybridized p orbital that is empty due to the atom's formal positive charge. All of the bonds in the molecule are σ bonds. The bond angles around the central carbon are 120˚, and the angles around the carbons of the methyl groups are 109.5˚.



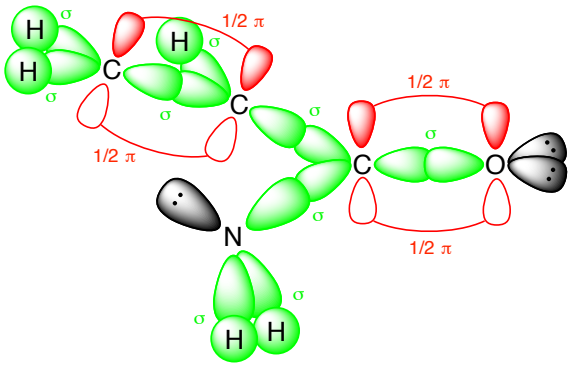
Let's also consider acrylamide, which is polymerized to yield polyacrylamide that is used in gel electrophoresis (a common technique in biochemistry and molecular biology). Acrylamide is $H_2C{=}CHC(O)NH_2$. Once again, we'll begin by converting the condensed formula into a Lewis structure.



Next, we need to determine the hybridization of each atom other than hydrogen. The leftmost carbon is surrounded by three atoms, so it is sp^2 hybridized. The same can be said of the other alkene carbon and the carbonyl carbon. Oxygen arrives at the same hybridization via a different route: It has one atom and two lone pairs around it. Nitrogen is sp^3 hybridized because it is surrounded by three atoms and one lone pair.



We now assemble the diagram using the basic shapes of sp^2 and sp^3 hybridized atoms. It will be easiest if the π bonds are drawn in the plane of the page. The molecule's σ bonds are shown in green. The two π bonds are labeled in red, and the lone pairs are in black orbitals.

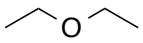


Problem 27. Draw orbital overlap diagrams for the following molecules.

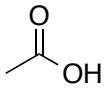
(a) CH_3CH_3

(b) $CH_3CH_2CH_2CH_3$

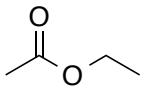
(c)



(d)



(e)

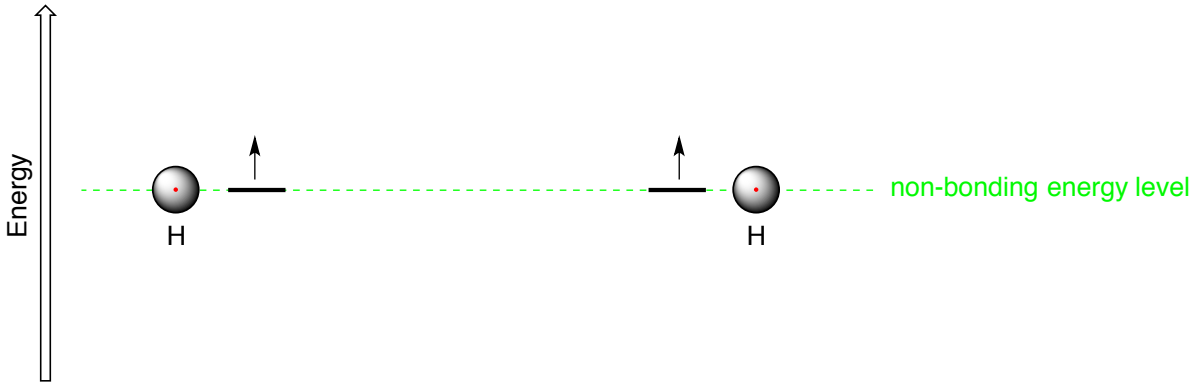


(f)

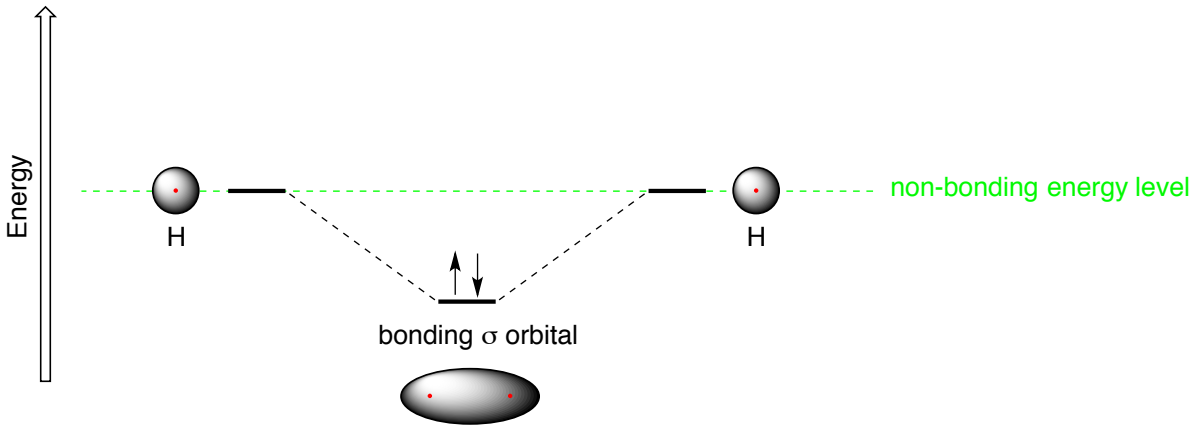
Section 16: Molecular orbitals

In the previous section, we developed orbital diagrams for molecules using valence bond theory in which the overlap of atomic orbitals gives a reasonable representation of a molecule's shape. Valence bond theory assumes that the electrons are localized between the bonded nuclei, but this is not always the case, as we'll see in Chapter 12. Molecular orbital theory considers how atomic orbitals combine to form orbitals that apply to the molecule as a whole; these are known as molecular orbitals.

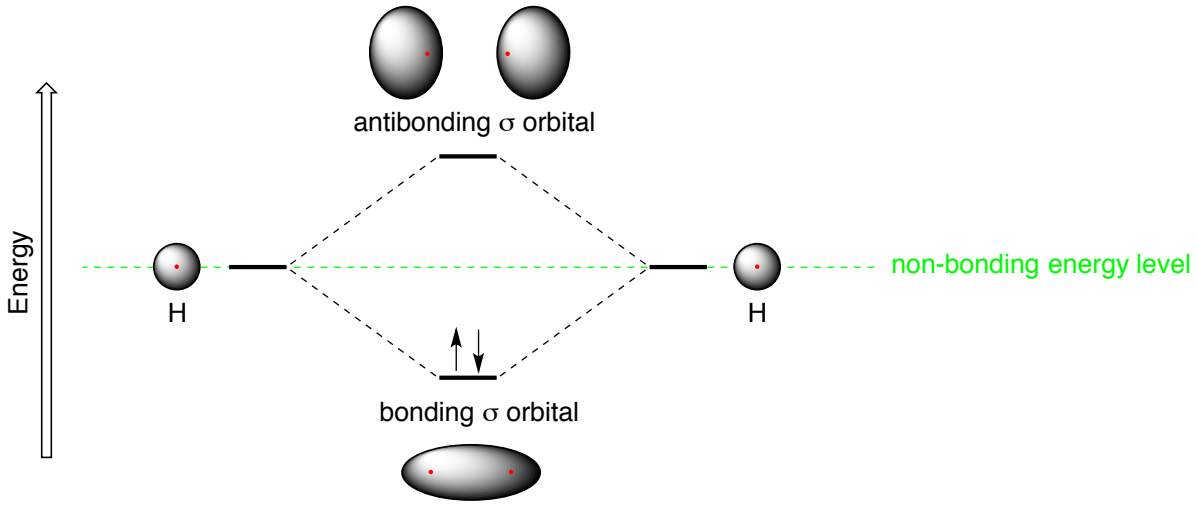
Molecular orbital (MO) theory is more complex, and we'll consider it only at a basic level in this text. Even at a simplistic level though, it does help us to better understand the process of bonding. As an example, let's imagine the combination of two hydrogen atoms to yield molecular hydrogen (H_2). The diagram below shows two hydrogen atoms, each with a single electron in its 1s orbital. These orbitals reside at the non-bonding energy level because the atoms currently exist as independent species.



As the nuclei approach one another and come to bonding distance, a σ-bonding molecular orbital is created. Both electrons can occupy this orbital, and they are now lower in energy because they are attracted to two nuclei, rather than just one. The electron density falls between the two nuclei, so this represents a bond.



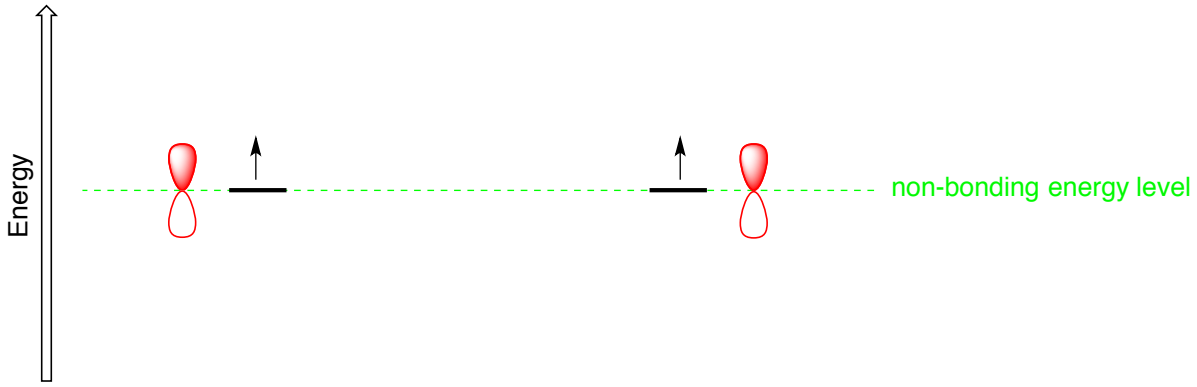
However, we must conserve energy and the number of orbitals. As the two atomic s orbitals combine to generate a lower-energy, σ-bonding molecular orbital, they must also produce a second orbital that is destabilized to the same extent. The destabilization stems from the fact that the electron density is not between the two nuclei in this higher-energy molecular orbital, which is called an antibonding orbital.



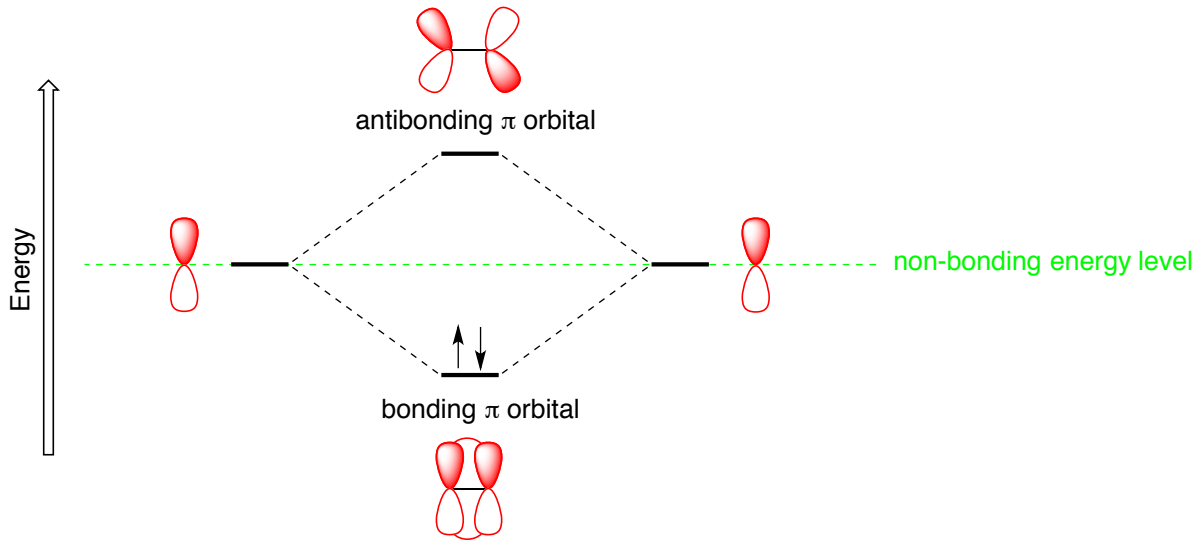
Molecular orbital theory helps to explain the process of bonding. Although the net energy of the bonding and antibonding orbitals is the same as the energy of the two atomic orbitals at the non-bonding level, it is only the bonding orbital that is occupied. Thus, the electrons are stabilized through bond formation.

Problem 28. Use a molecular orbital diagram to explain why diatomic helium (He_2) is not nearly as favorable as diatomic hydrogen (H_2).

We can also look at a π bond through the lens of molecular orbital theory. The identity of the atoms is not important. We begin with two p orbitals on unspecified atoms at the non-bonding energy level.



When the two atoms are in bonding distance (and already have a σ bond between them), the p orbitals can be aligned in phase with one another. This allows for the formation of a bonding π orbital. The electrons occupy this molecular orbital and are stabilized by their attraction to two nuclei. However, to conserve energy and orbitals, an antibonding π orbital is also created. In this molecular orbital, the p orbitals are aligned out of phase with one another and the electron density is splayed away from the space between the nuclei.

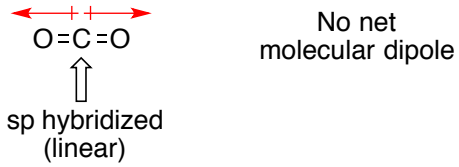


Section 17: Polarity

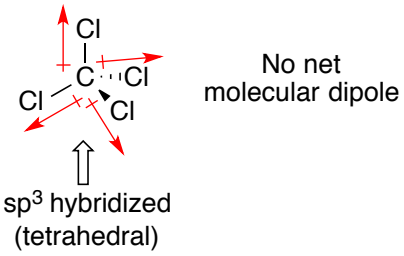
In Section 9, we defined electronegativity as the tendency of an element to pull electron density toward itself. When elements with differing electronegativities are covalently bonded, the more electronegative element pulls electron density from the shared pair closer to itself. This creates a dipole in which the unequal sharing of electrons causes one element to have a partial positive charge (δ^+) and the other to have a partial negative charge (δ^-).

A dipole can be represented by an arrow with a vertical line near the tail. The arrow points toward the more electronegative element and shows the direction that electron density is being pulled. A bond with a dipole is said to be polarized.

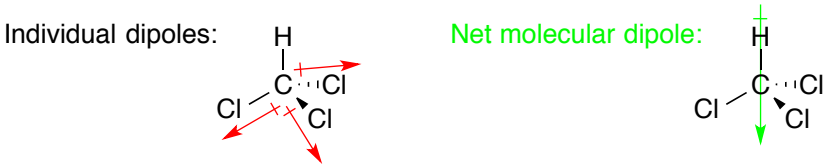
A molecule containing polarized bonds may or may not be polar. The outcome depends on the molecule's geometry. Carbon dioxide is a non-polar molecule despite the fact that it contains individual bond dipoles. Each of the carbon-oxygen bonds is polarized toward the more electronegative oxygen atom. However, because the central carbon is sp hybridized and therefore has linear geometry, these dipoles directly oppose one another and cancel each other out. As a result, there is no net molecular dipole.



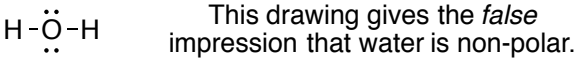
Carbon tetrachloride (CCl_4) is another molecule that contains polarized bonds but is overall non-polar. Each of the bonds between carbon and chlorine is polarized toward the more electronegative chlorine atom. The central carbon's sp^3 hybridization causes these four dipoles to be completely evenly distributed in space. Consequently, they cancel each other yielding a non-polar molecule.



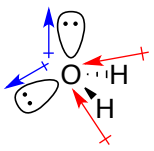
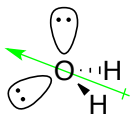
Any change that breaks this symmetry will yield a polar molecule. For instance, if one of the chlorine atoms is replaced by hydrogen, the molecule becomes chloroform ($CHCl_3$). Carbon and hydrogen have such similar electronegativities that bonds between them are considered non-polar. The three remaining dipoles have horizontal components that cancel because they are evenly distributed around the central C-H bond. However, all of these dipoles point slightly downward, so their vertical components are additive. This yields a net molecular dipole pointing down through the center of the molecule.



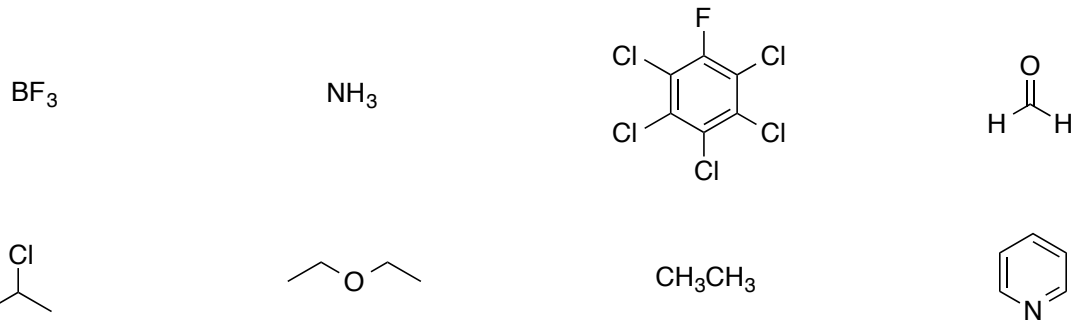
It is always necessary to consider a molecule's geometry before making assumptions about its polarity. For instance, if water is drawn without regard to geometry, it may *incorrectly* appear to be non-polar.



However, when we account for the central atom's sp^3 hybridization, water's polarity becomes evident. The two O-H bonds are polarized toward oxygen. Lone pairs are considered to have a dipole pointing toward the electrons because there is a δ^- at the periphery of a lone pair where only electrons (and no nucleus) reside. These two types of dipoles differ in magnitude. Although a component of both the red and the blue dipoles cancels, a component is also additive, so there is a net molecular dipole.

Individual dipoles:  Net molecular dipole: 

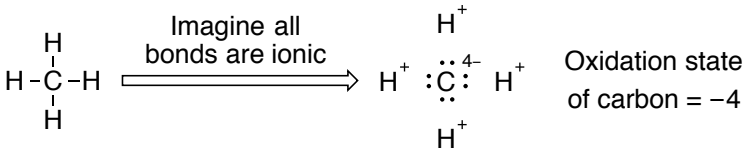
Problem 29. Which of the following molecules have no net molecular dipole? Which have a net molecular dipole?



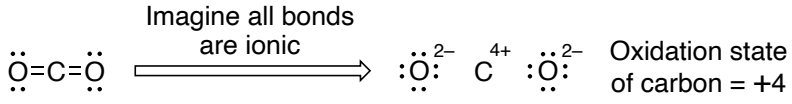
Section 18: Oxidation state

Organic molecules are sometimes described according to their oxidation state. Oxidation is the loss of electrons, and reduction is the gain of electrons. Oxidation state is a numerical expression of the extent of oxidation or reduction. It is determined quite simply. Imagine that all of the bonds in the molecule were purely ionic. This necessitates giving any shared pairs of electrons to the more electronegative element. If the elements are identical, then one electron is given to each. The hypothetical charge on each atom that results from cleaving the bonds in this fashion is its oxidation state. While we can calculate an oxidation state for any atom, we are typically most interested in carbon's oxidation state.

To determine the oxidation state of the carbon of methane, we envision converting all of its covalent bonds to ionic bonds. Although their electronegativity is similar, carbon is slightly more electronegative than hydrogen, so we give both of the electrons in each bond to carbon. This would result in a –4 charge on the carbon, so its oxidation state is –4.



When the same is done for carbon dioxide, the four electrons in each carbon-oxygen double bond are awarded to the more electronegative oxygen atoms. This results in a hypothetical charge of +4 on carbon, so it has an oxidation state of +4.



These molecules define the boundaries of carbon's possible oxidation states. They range from –4 to +4. The lower the value, the more reduced carbon is. The higher the value, the more oxidized it is. Methane is a highly reduced form of carbon, while carbon dioxide is a highly oxidized form.

Problem 30. Provide the oxidation state of the indicated carbon in each of the following molecules.

(a) $(CH_3)_3\underline{C}OH$

(b) $CH_3\underline{C}O_2H$

(c) $H\underline{C}O_2H$

(d) $\underline{C}H_2O$

(e) $\underline{C}H_3CH_3$

(f) $H\underline{C}(CH_3)_3$

(g) $\underline{C}H_3OH$

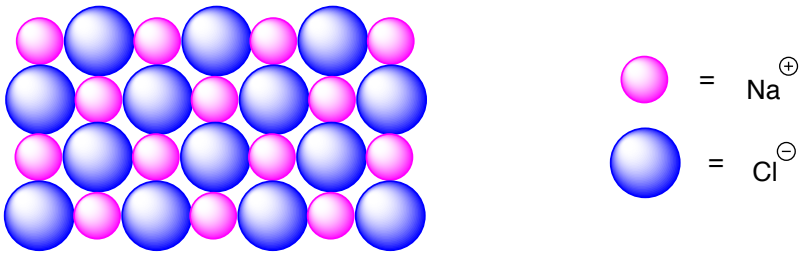
Section 19: Intermolecular forces

The attractive forces between molecules impact a substance's properties. Let's begin by outlining these intermolecular forces, and then we'll consider how they impact properties.

There are four types of intermolecular forces, and they are listed below from strongest to weakest.

(1) electrostatic forces
(2) hydrogen bonding
(3) dipole-dipole interactions
(4) van der Waals forces

Electrostatic forces are the attractions between positive and negative charges. These are extremely strong attractive forces, and they play a role in ionic substances.

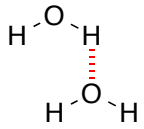


Electrostatic forces are the root of the attraction between Na^+ and Cl^-.

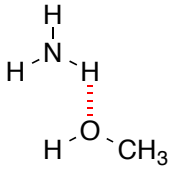
Hydrogen bonding is the attraction between a hydrogen on nitrogen, oxygen, or fluorine and another nitrogen, oxygen, or fluorine. The species with a hydrogen is called the hydrogen-bond donor. The other site is called the hydrogen-bond acceptor. Any combination of hydrogen-bond donor and acceptor is suitable.

Hydrogen-bond donors	Hydrogen-bond acceptors
N-H	N
O-H	O
F-H	F

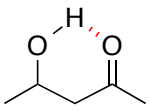
The interaction between a hydrogen-bond donor and acceptor can be thought of as a partial covalent bond. It can occur between identical molecules or different substances. Hydrogen bonding can also take place intramolecularly (i.e., within a single molecule) if a molecule contains both a donor and an acceptor.



Hydrogen bond between two water molecules

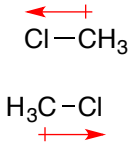


Hydrogen bond between different molecules

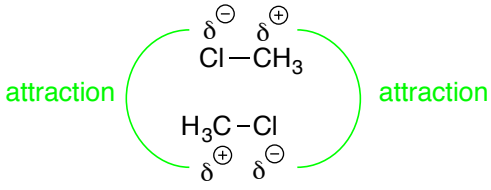


Hydrogen bond within a single molecule

Dipole-dipole interactions are attractive forces between molecules containing permanent dipoles. When these dipoles are oriented in a complementary fashion, there is an attraction between the δ^+ and δ^- ends.

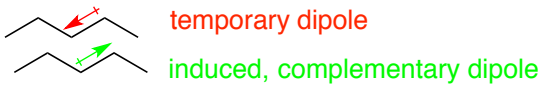


can also be drawn as:



Van der Waals forces are also called London dispersion forces. They are the attraction between temporary, induced dipoles. Even a non-polar molecule can have fleeting dipoles. These temporary dipoles induce complementary ones in adjacent molecules. Although

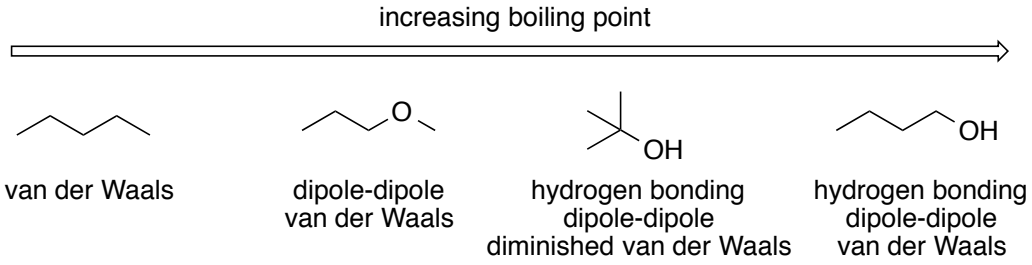
these dipoles vanish in an instant, they cause an attraction between neighboring molecules during their brief existence.



Van der Waals forces increase with surface area because they occur at places where molecules can approach each other closely. Additionally, larger atoms have sizable electron clouds that are relatively easy to distort. This is known as polarizability. Since van der Waals forces rely upon the distortion of electron density to induce temporary dipoles, larger atoms result in increased van der Waals attractions.

Now that we know about the various types of intermolecular forces, we can consider their impact on physical properties. The boiling point of a substance is the temperature at which the attractive forces between molecules in the liquid state are overcome. This allows them to move further apart as they enter the gas phase. Increased intermolecular forces therefore result in higher boiling points. Ionic substances have extremely high boiling points because of their powerful electrostatic attractions. Among covalent species, hydrogen bonding, dipole-dipole interactions, and van der Waals forces all exert an influence on boiling point, but hydrogen bonding holds the most sway, while van der Waals forces are the least significant.

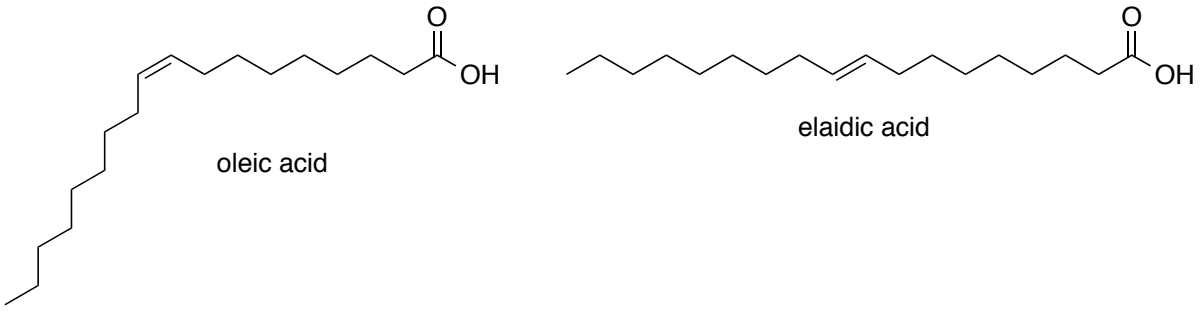
Consider the following series of comparably sized molecules. The alkane has only the weakest intermolecular force: van der Waals forces. As a result, it will have the lowest boiling point. The ether has stronger dipole-dipole interactions, as well as van der Waals forces. Due to its increased intermolecular forces, its boiling point is elevated. The alcohols have the even stronger force hydrogen bonding, as well as dipole-dipole and van der Waals interactions, so they will have the highest boiling points. The unbranched alcohol has a greater surface area than the branched one, so it has more van der Waals interactions and the highest boiling point.



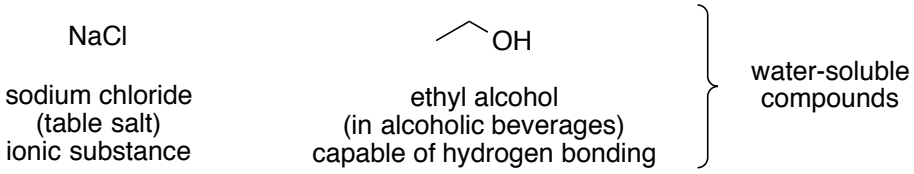
Melting point is affected similarly by intermolecular forces. Since molecules are quite close in the solid state, symmetry is also a consideration. All things being equal, a more symmetrical molecule will pack more efficiently in the solid state, thereby leading to a higher melting point. Consider the two alcohols in the preceding series of compounds. The branched alcohol has a *lower* boiling point than its unbranched counterpart. However, it

has a *higher* melting point. This is due to the increased symmetry of the branched molecule, which leads to more efficient packing in the crystal lattice of the solid state.

Problem 31. Oleic acid is found in vegetable oils; whereas, elaidic acid can be found in hydrogenated vegetable oils. *Trans* fatty acids, like elaidic acid, can raise "bad cholesterol" levels. Which of these compounds has a higher melting point and why?

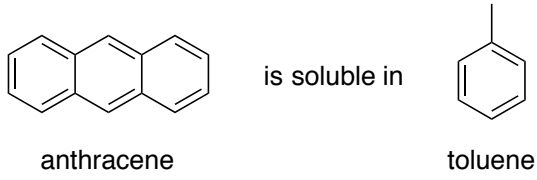


Solubility is impacted by the intermolecular forces between the solute (i.e., the molecule that is dissolved) and the solvent (i.e., the substance that does the dissolving). As a general rule, like dissolves like. This means that a polar solvent will dissolve polar solutes, while a non-polar solvent will dissolve non-polar solutes. Water is very polar, so it will dissolve highly polar solutes, like ionic substances including table salt. Additionally, water dissolves solutes that have the potential to hydrogen bond with it extensively. For instance, ethyl alcohol is found in alcoholic beverages. It can hydrogen bond quite effectively with water. In fact, ethyl alcohol is actually miscible with water, which means that they will mix in any proportions to give a solution.



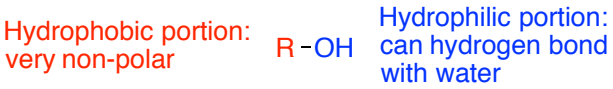
Substances like salt and ethyl alcohol can be called hydrophilic, which means water loving.

Organic solvents are less polar than water, but they still have a wide range of polarities. Those molecules with limited potential to interact with water are likely to be more soluble in organic solvents. For instance, anthracene in quite non-polar, so it has very low water solubility. But, anthracene dissolves much more readily in toluene, a non-polar organic solvent.

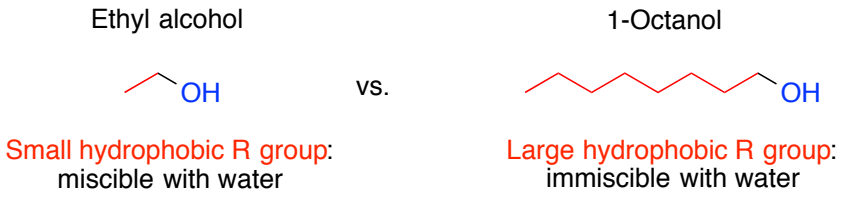


A substance like anthracene can be called hydrophobic, which means water fearing.

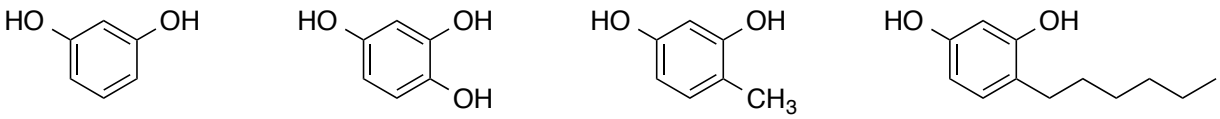
There are some compounds with a dual nature. Part of the molecule can be hydrophilic, while another part is hydrophobic. Such substances are called amphipathic. In these molecules, we must weigh the relative impact of the two segments of the molecule to predict its solubility. For instance, alcohols are amphipathic molecules. The hydroxyl (OH) group can hydrogen bond with water, so it is the hydrophilic portion of the molecule. However, the R group, which contains only carbons, hydrogens, and single bonds, is quite non-polar, so it is hydrophobic.



When the R group is small, the alcohol will be highly water soluble. As we saw with ethyl alcohol, it is so water soluble that it is actually miscible with water. As the R group grows in size, the water solubility diminishes. 1-Octanol, an eight-carbon alcohol, has such low water solubility that the two liquids are immiscible. This means that they actually form two separate layers when combined, much like oil and water do.



Problem 32. Antimicrobial agents can be more effective if they are better able to penetrate the microbial membrane, which is a phospholipid bilayer with a hydrophobic interior. Which of the compounds below stands the greatest chance of passing through the hydrophobic interior of the microbial membrane and why?



End-of-the-Chapter problems

Problem 33. Provide the requested information about each of the following atoms or ions.

(a) Provide the complete symbol for an element with 53 protons, 74 neutrons, and 54 electrons.

(b) Provide the complete symbol for an element with 56 protons, 82 neutrons, and 54 electrons.

(c) An element has 86 electrons and a +1 charge. It also has a mass number of 223. What is the element's symbol, and how many neutrons does it possess?

(d) An element has 13 protons, 14 neutrons, and a +3 charge. What is its symbol, and how many electrons does it have?

(e) How many protons, neutrons, and electrons does $^{31}P^{3-}$ have?

(f) Which alkali earth metal would readily form a cation with 18 electrons?

(g) Which Period 4 element would preferentially form a –2 ion?

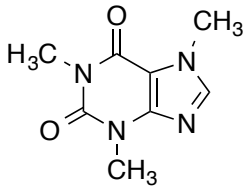
(h) Which noble gas has an isotope with 77 neutrons?

Problem 34.

(a) Chlorine has two principal isotopes, ^{35}Cl and ^{37}Cl, which have masses of 34.9689 amu and 36.9659 amu, respectively. Chlorine's average atomic mass is 35.453 amu. What is the relative abundance of chlorine-35 and chlorine-37?

(b) Bromine has an average atomic weight of 79.904 amu. It has two isotopes. ^{79}Br has a mass of 78.9183 amu, and ^{81}Br has a mass of 80.9163 amu. What are their relative abundances?

Problem 35. Caffeine is a well-known component of coffee.



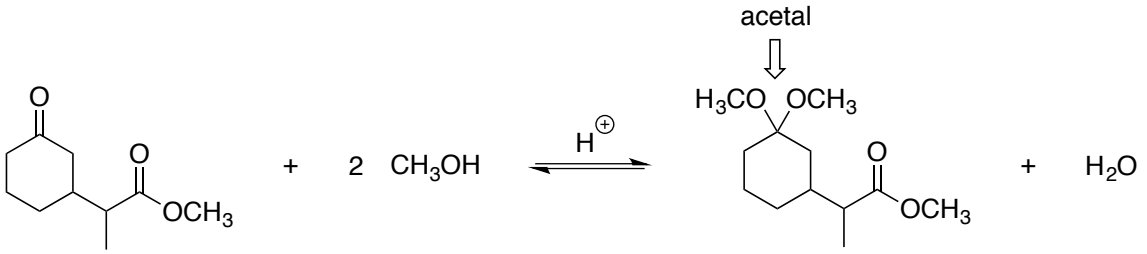
(a) What is the mass of a sample of caffeine containing 3.10×10^{21} carbon atoms?

(b) How many moles of oxygen are in this sample of caffeine?

(c) How many atoms of hydrogen does this sample of caffeine contain?

(d) What is the mass of nitrogen in this sample of caffeine?

Problem 36. In Chapter 15, we'll learn about acetal formation, an example of which is shown below. An investigator begins with 5.00 g of the ketone-containing reactant and 2.00 mL of methanol (CH_3OH), which has a density of 0.792 g/mL.



(a) What is the theoretical yield of the acetal?

(b) If the investigator isolates 5.25 g of the acetal, what is the percent yield for this reaction?

(c) What volume of water will be produced during this transformation? Note that water has a density of 1.00 g/mL.

Problem 37.

(a) How many of magnesium's electrons have an angular momentum quantum number, ℓ, of 0?

(b) How many electrons does silicon have with $\ell = 1$?

(c) How many electrons does bromine have with a ℓ value of 2?

(d) What is wrong with the following set of quantum numbers: n = 1, $\ell = 1$, $m_\ell = 0$, $m_s = {}^1/_2$?

(e) How many electrons can have the quantum numbers n = 2 and $\ell = 1$?

(f) How many electrons can have the quantum numbers n = 4 and $\ell = 2$?

(g) What is wrong with the following set of quantum numbers: n = 2, $\ell = 1$, $m_\ell = -2$, $m_s = 1$?

(h) Give an acceptable set of quantum numbers for phosphorus' fifteenth electron.

Problem 38.

(a) Provide the electronic configuration for xenon.

(b) Provide the electronic configuration for In^{3+}.

(c) How many unpaired electrons does selenium have?

(d) How many unpaired electrons does tin have?

(e) What neutral element is denoted by this electronic configuration:

$1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6 5s^2 4d^{10} 5p^4$?

(f) What –2 ion is denoted by this electronic configuration:
$1s^2 2s^2 2p^6 3s^2 3p^6$?

(g) There is an error in the following electronic configuration. What is the error?
N^{3-}: $1s^2 2s^2 2p^3$

(h) There is an error in the following electronic configuration. What is the error?
S: $1s^2 2s^2 2p^6 3s^1 3p^5$

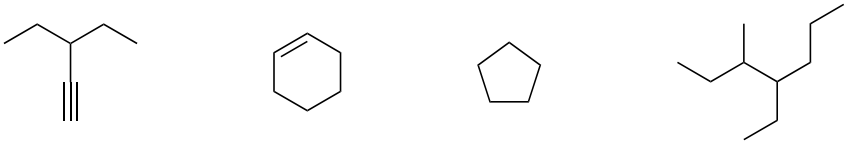
Problem 39.

(a) Which ion is the largest: Rb^+, K^+, Li^+, Cs^+, or Na^+?

(b) Which bond is the shortest: C-F, C-Si, C-C, C-B, C-S, C-O, C-P, C-Br?

(c) Which element is least electronegative: F, C, Si, S, I, K, Mg?

(d) Which molecule contains the shortest carbon-carbon bond?



(e) Which ion is the smallest: Si^{4-}, Al^{3+}, Cl^-, Na^+, P^{3-}, Mg^{2+}, S^{2-}?

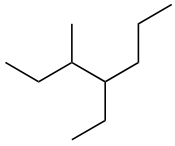
(f) Which of the following is the biggest: As^{3-}, Br^-, Sr^{2+}, Kr, Se^{2-}, Rb^+?

(g) Which bond has the largest dipole: C-F, C-Si, C-C, C-B, C-S, C-O, C-P, C-Br?

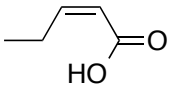
(h) Which of the following is smaller: H^- or He?

Problem 40.

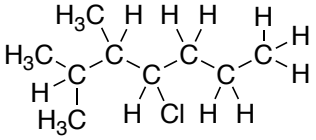
(a) Convert the following molecular representations to Lewis structures.



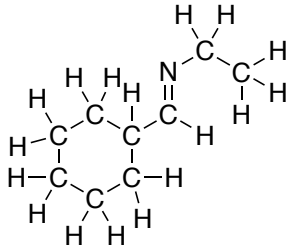
$(CH_3)_2CHCH_2CH(CH_2CH_3)OCH_2CO_2CH_3$



(b) Convert the following diagrams to skeletal structures.

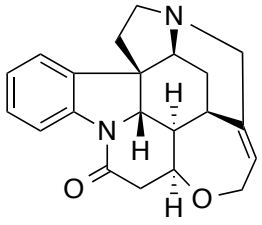


$(CH_3)_2CHCH_2CH(CH_2CH_3)OCH_2CO_2CH_3$



Problem 41.

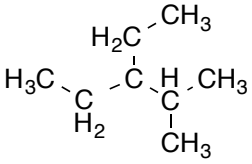
(a) Strychnine is a naturally occurring molecule that is a well-known poison. Name the functional groups in strychnine.

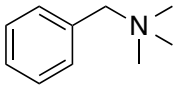


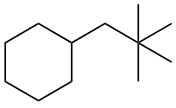
(b) Draw four constitutional isomers of $C_6H_{10}O_4$: one containing esters as the only functional groups; one containing carboxylic acids as the only functional groups; one containing ethers as the only functional groups; and one containing alcohols as the only functional groups.

Problem 42.

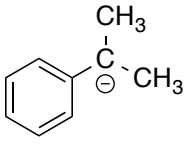
(a) In the following compounds, all bonds and lone pairs have been drawn. Point out the errors in these structures.

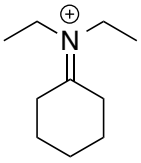


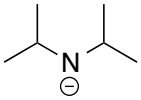




(b) In the following compounds, lone pairs have not been drawn, but all bonds and charges are shown. Fill in any missing lone pairs.







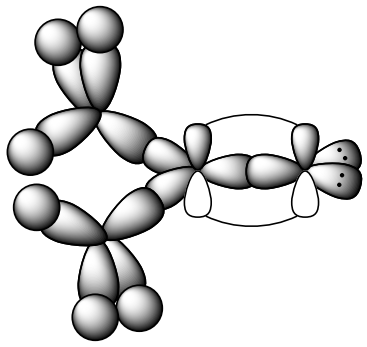
Problem 43.

(a) Draw all of the isomers of C_6H_{14}.

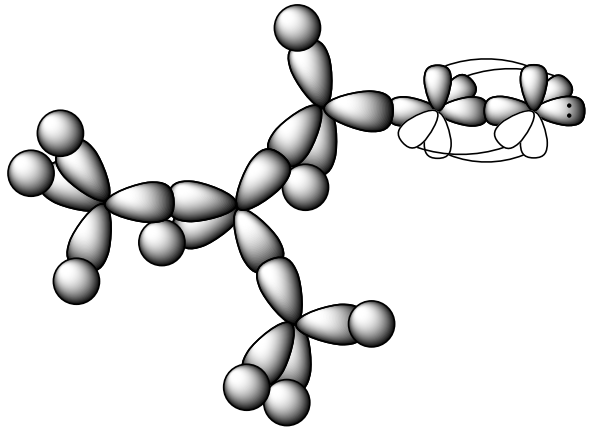
(b) Draw all of the isomers of C_7H_{16}.

Problem 44. In the following orbital overlap diagrams, the atom labels have been omitted. Deduce the identity of the molecule from the diagram, and draw the molecule's structure.

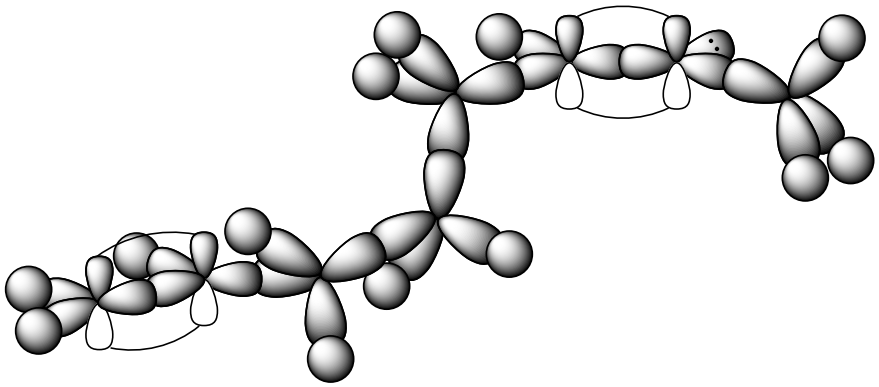
(a)



(b)



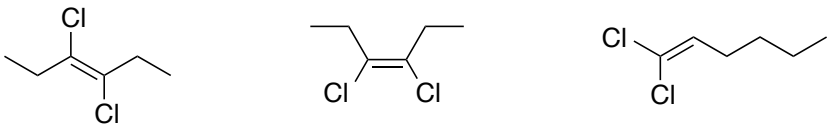
(c)



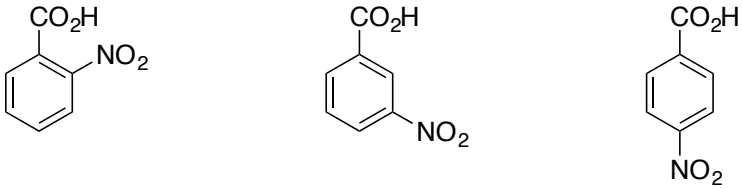
Problem 45. Draw a molecular orbital diagram that explains the π bonding in ethylene ($H_2C=CH_2$), which is a fruit-ripening hormone in plants.

Problem 46. Identify the least polar molecule in each of the following sets.

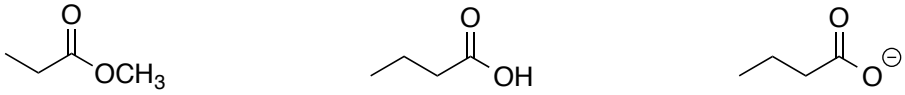
(a)



(b)



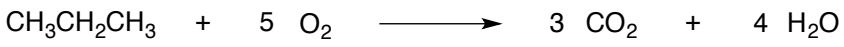
(c)



Problem 47. Organic reactions can be classified as oxidations or reductions by following the fate of the carbon(s) undergoing a chemical change. If there is a net oxidation state increase, the reaction is an oxidation. On the other hand, if there is a net oxidation state decrease, the reaction is a reduction. A reagent that causes an organic compound to be oxidized is an oxidizing agent, and a reagent that causes an organic compound to be reduced is a reducing agent.

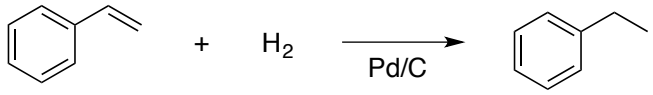
For the following reactions, describe them as an oxidation, a reduction, or neither. Also, classify the reagent used as an oxidizing agent, a reducing agent, or neither.

(a)

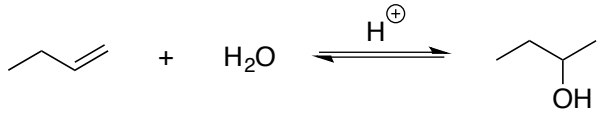


(b)

(c)

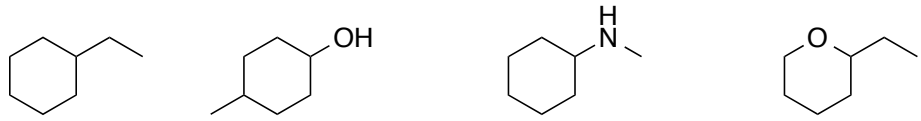


(d)

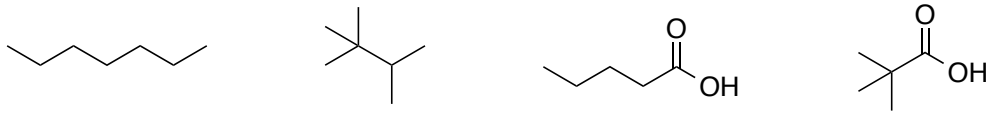


Problem 48.

(a) Which of the following compounds has the highest boiling point?



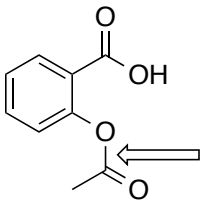
(b) Which of the following compounds has the highest melting point?



(c) Which of the following compounds has the greatest water solubility?

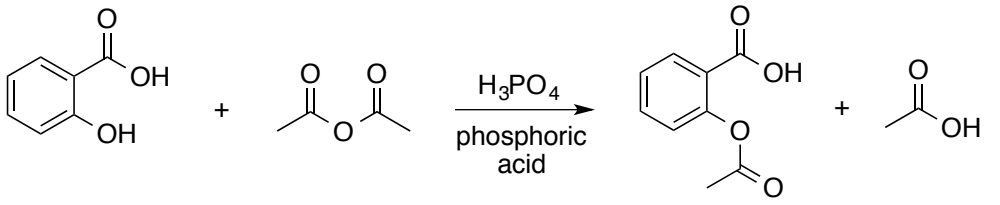
Problem 49. Fill in the blanks in the following paragraphs.

Aspirin is shown below. It is made from three _____: carbon, hydrogen, and oxygen. Specifically, it contains ___ carbon, ___ hydrogen, and ___ oxygen _____. Since it consists of multiple atoms held together by bonds, it can be called a _____. Alternatively, it may also be called a _____ because it contains atoms of more than one element combined in a fixed, precise ratio.



Since the bonds in aspirin result from the sharing of electrons, they are _____. Aspirin contains ___ σ and ___ π bonds, along with eight _____. The functional groups in aspirin include an _____, a _____, and an _____. ___ of its atoms are sp^3 hybridized, while ___ are sp^2 hybridized and ___ are unhybridized. The bond indicated by the arrow is formed from the overlap of carbon's ___ orbital with oxygen's ___ orbital.

Based on the following reaction equation, aspirin can be prepared by the treatment of _____ with ___ equivalent of _____. The reaction yields ___ _____ of aspirin and ___ _____ of acetic acid as a byproduct. A minimum of ___ mL of acetic anhydride would be needed to react completely with 8.00 g of salicylic acid to yield up to ___ g of aspirin and ___ mL of acetic acid. _____, the only substance not included in the calculations, is a catalyst and is therefore neither created not destroyed in the reaction. If an experimenter actually obtains ___ g of aspirin from this reaction, the _____ is 82.0%.



salicylic acid | acetic anhydride density: 1.082 g/mL | aspirin | acetic acid density: 1.049 g/mL

Problem 50. A hydrocarbon is combusted in the presence of eight equivalents of oxygen (O_2) to yield five equivalents of carbon dioxide (CO_2) and six equivalents of water (H_2O). The hydrocarbon used in this combustion reaction has a higher melting point than any of its isomers. Draw the structure of this hydrocarbon.

Chapter 2: Acid-Base Chemistry

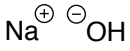
Section 1: The Brønsted-Lowry definition of acids and bases
Section 2: Drawing the mechanism for a Brønsted-Lowry acid-base reaction
Section 3: The conjugate acid and base
Section 4: Structural factors affecting acidity
Section 5: Determining which side of the reaction is favored at equilibrium – Part I
Section 6: Acidity and the pK_a value
Section 7: Determining which side of the reaction is favored at equilibrium – Part II
Section 8: The importance of solvent
Section 9: The Lewis definition of acids and bases

Section 1: The Brønsted-Lowry definition of acids and bases

The Brønsted-Lowry definition of acids and bases focuses on the transfer of a proton (i.e., H^+). A Brønsted-Lowry acid is a proton donor. If you've learned a bit about acids previously, you may have talked about hydrochloric acid (HCl) or sulfuric acid (H_2SO_4), both of which are common inorganic acids.

hydrochloric acid sulfuric acid

On the other hand, a Brønsted-Lowry base is a proton acceptor. You may have heard of sodium hydroxide (NaOH), which is a common inorganic base.

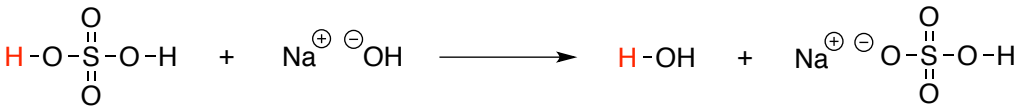


sodium hydroxide

In a Brønsted-Lowry acid-base reaction, a proton is transferred from an acid to a base. For example, hydrochloric acid can donate a proton to sodium hydroxide.

acid base

Or, in another example, a proton can be transferred from sulfuric acid to sodium hydroxide.



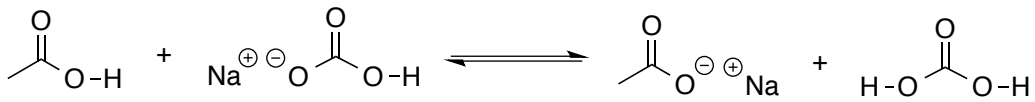
acid base

In acid-base reactions where the products are highly favored (such as those shown above), you may see a reaction arrow drawn between the reactants and products. However, acid-base reactions also frequently employ equilibrium arrows. The equilibrium arrows draw attention to the reversibility of a reaction. One of the equilibrium arrows can be elongated to show that either the reactants or products are favored. Later in this chapter, we'll learn how to decide whether the reactants or products predominate when the system reaches equilibrium.

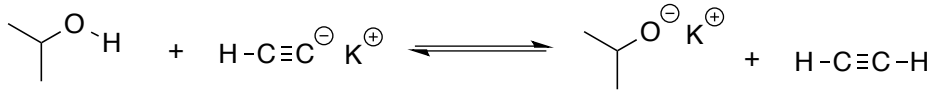
Problem 1. Identify the acid and the base in each of the following reactions.

(a)

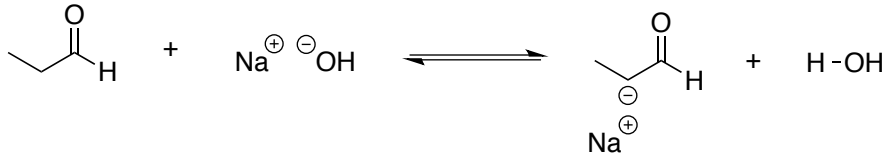
(b)



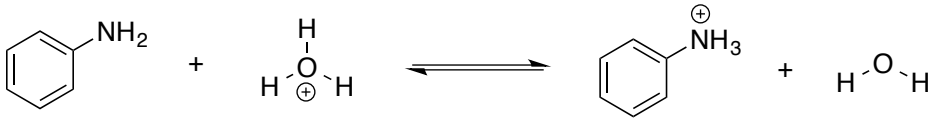
(c)



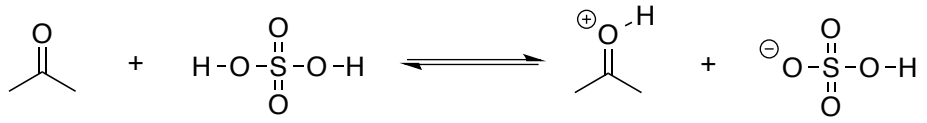
(d)



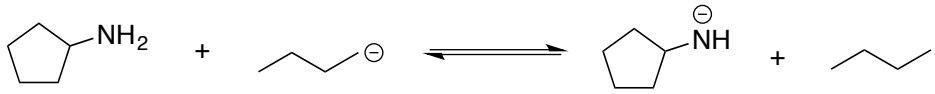
(e)



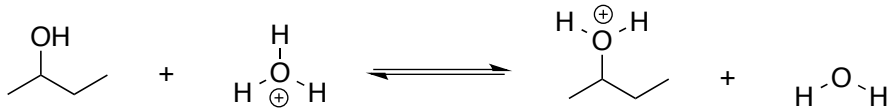
(f)



(g)



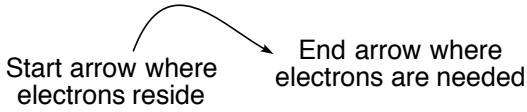
(h)



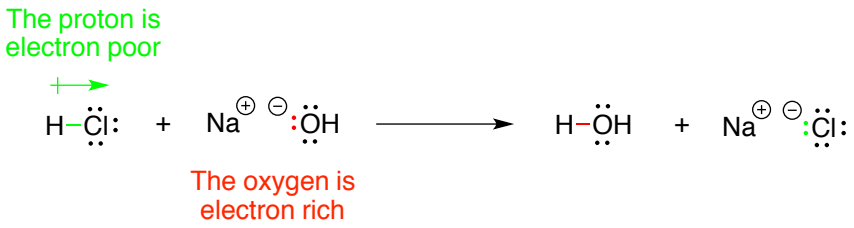
To better understand these reactions, we need to consider the electrons that make them possible.

Section 2: Drawing the mechanism for a Brønsted-Lowry acid-base reaction

The mechanism for a reaction shows the flow of electrons that explains how bonds are made and broken. To do this, curved arrows are used to represent the flow of two electrons. By convention, the arrow begins where electrons are present and ends at the site to which they are attracted.

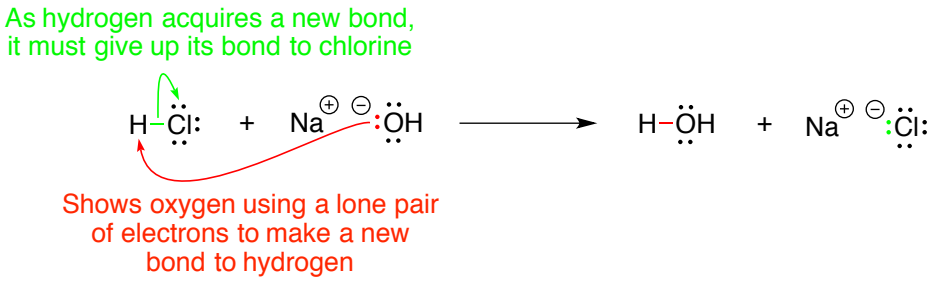


Let's reconsider the reaction of hydrochloric acid with sodium hydroxide. The oxygen is the most electron-rich atom among the reactants because of its three lone pairs and negative charge. The proton of hydrochloric acid is electron poor because the H-Cl bond is polarized toward chlorine due to its greater electronegativity. This leaves a δ^+ on the hydrogen atom.



We now draw an arrow from the electron-rich site (i.e., the oxygen of hydroxide) to the electron-poor site (i.e., the proton of HCl). This signifies that oxygen is using one of its lone

pairs to form a new bond to the proton of HCl. Since hydrogen is monovalent, it must relinquish a bond as it gains a new one. Therefore, a second arrow is needed to describe the cleavage of the H-Cl bond. The electrons in that σ bond must flow to one of the two atoms involved the bond, so they flow onto the more electronegative chlorine atom. This arrow begins on the σ bond itself where the electrons reside and ends on the chlorine atom.



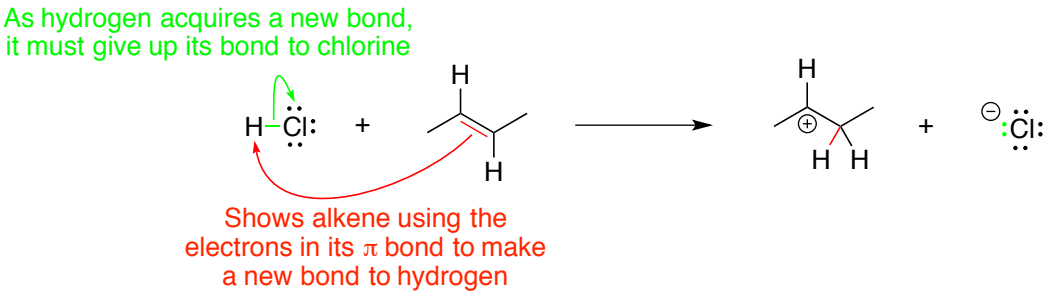
Notice that the red lone pair of hydroxide becomes the σ bond of water, while the green σ bond of H-Cl becomes a lone pair on chloride. The arrows tell us the fate of the electrons so that we can deduce what the products should be simply by considering how the reactants behave. **This is the value of mechanism: It allows us to predict reaction products based on an understanding of the behavior of the reactants.** Mechanism is what makes organic chemistry rational. It provides an explanation for reactions that occur, so that you can understand them, as opposed to merely memorizing them. In order to master organic chemistry, it is essential to master mechanism because it is impossible to memorize every conceivable reaction. Instead of attempting to memorize your way through the course, you want to invest the time now to learn how to properly draw mechanisms. Doing so will pay huge dividends later in the course.

Problem 2. Draw the mechanism for each of the Brønsted-Lowry acid-base reactions shown in Problem 1.

Based on the electronic description of a Brønsted-Lowry acid-base reaction, it becomes apparent that there are structural requirements for both an acid and a base. An acid must have a reasonably acidic proton to donate. Later in this chapter, we'll learn how to judge the acidity of protons within a molecule. On the other hand, a base must have a pair of electrons that can be used to form a bond to that proton. These electrons can be a lone pair or a π bond. In general, the electrons in σ bonds cannot be used for this purpose except in very special circumstances.

Problem 3. Which of the following compounds is incapable of serving as a Brønsted-Lowry acid?

When we considered the reaction between HCl and NaOH, we saw a base that uses a lone pair of electrons to accept a proton. In the following example, the base is an alkene that uses a π bond to create the new bond to a proton. Notice that the red arrow begins at the center of the π bond. The π electrons do not reside on either of the alkene carbons. Instead, they are shared between the alkene carbons. This is why the arrow begins between the two carbons rather than on either of them. Since the alkene is symmetrical, it does not matter which carbon of the double bond acquires the new proton. The alkene carbon that does not get the proton ends up with only three bonds and therefore has a formal positive charge.

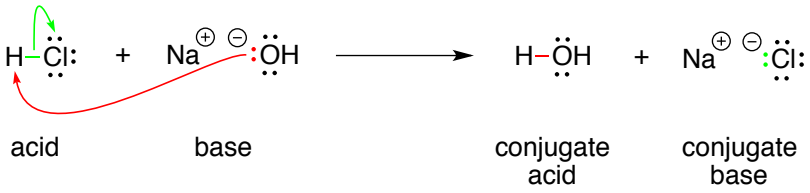


Problem 4. Which of the following compounds is incapable of acting as a Brønsted-Lowry base?

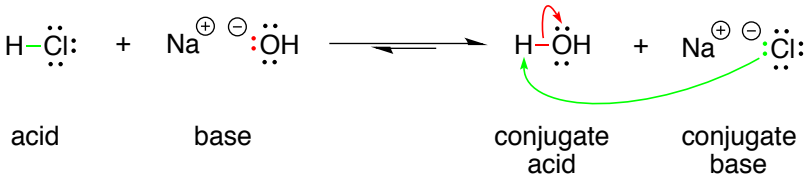
Section 3: The conjugate acid and base

Now we can identify the acid and the base and draw a mechanism for the reaction between them. The products of a Brønsted-Lowry acid-base reaction are often called the conjugate acid and conjugate base. Assigning these labels is very straightforward.

We begin by determining which reactant is the acid and which is the base. For instance, as we saw previously, hydrochloric acid is an acid, and sodium hydroxide is a base. After the loss of a proton, what is left of the reactant acid is known as its conjugate base. Once it loses its proton, all that is left of hydrochloric acid is chloride (Cl^-). Chloride is therefore the conjugate base of hydrochloric acid. Similarly, after acquiring a proton, the base becomes its conjugate acid. Upon receiving a proton, hydroxide is transformed into water. Consequently, water is the conjugate acid of hydroxide.

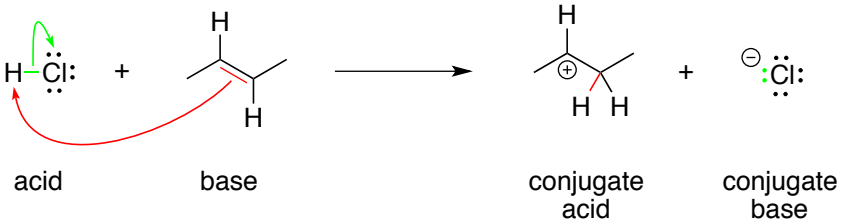


These labels make sense when you think of the products' roles if the reaction were to proceed in the reverse direction. To return to reactants, chloride would need to function as a base and remove a proton from water. As a proton donor, water would play the role of an acid. So, we are merely describing the roles of the products in the reverse reaction, and we are designating these substances as products of the original acid and base by using the prefix "conjugate."



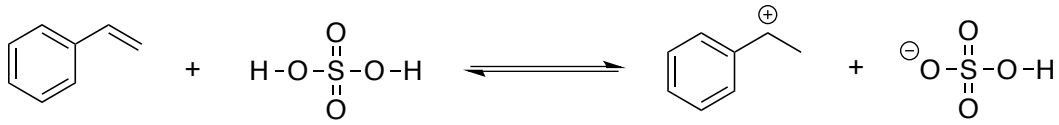
Problem 5. For the reactions shown in Problems 1 and 2, label the conjugate acid and base.

Let's consider the other reaction whose mechanism we discussed in the preceding section. Hydrochloric acid, being the proton donor, is the acid. After losing its proton, all that remains of hydrochloric acid is chloride, so chloride is the conjugate base. The alkene accepts the proton and is therefore the base. Upon adding a proton, it yields a carbocation, which is its conjugate acid.

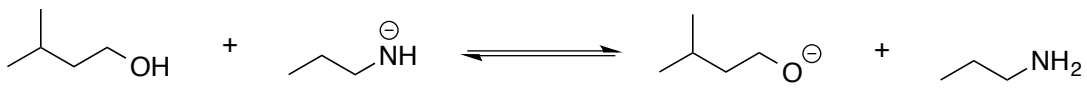


Problem 6. For the reactions shown below, label the acid, the base, the conjugate acid, and the conjugate base.

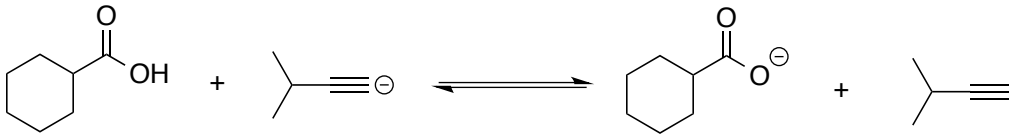
(a)



(b)



(c)



(d)

Section 4: Structural factors affecting acidity

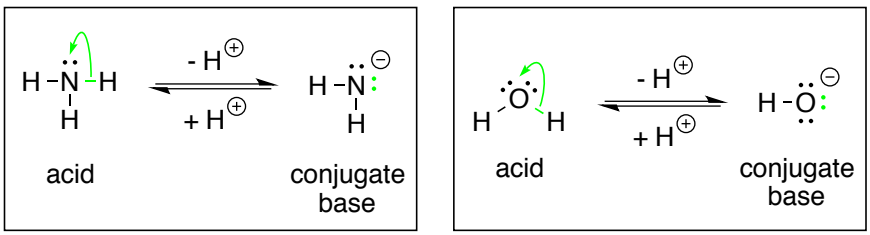
In this chapter, our goal is to develop an in-depth understanding of acids and bases. If we understand them well enough, then when given a pair of reactants we can not only predict the products but also determine which side of the reaction is favored at equilibrium. In other words, we can say whether or not the reaction will actually yield an appreciable quantity of products.

To get to this point, we have to be able to evaluate the relative strength of acids on both a qualitative and quantitative scale. In this section, we'll discuss factors that enable us to assess the relative strength of acids qualitatively based on their structures. Stated differently, by evaluating the structures of two acids, we can determine which one is stronger.

There are multiple structural factors that affect acidity. These include: (1) element effects, (2) resonance, (3) induction, and (4) hybridization.

(1) Element effects

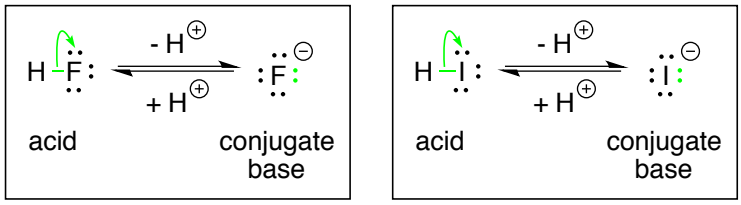
Perhaps the most obvious structural factor affecting acidity is the element that bears the proton. We'll consider two types of comparisons: elements in the same row and elements in the same column of the periodic table. Let's begin with a same-row comparison. Ammonia (NH_3) and water can both serve as acids. To determine which one is the stronger acid, let's consider their charged conjugate bases: H_2N^- and HO^-.



In this case, the element bearing the charge differs. Nitrogen and oxygen reside the same row (i.e., period) of the periodic table. Within a row, the most significant difference between elements is electronegativity. Oxygen is the more electronegative element, so it is

more stable as an anion. We have easily identified that hydroxide (HO^-) is the more stable conjugate base, and there is a guideline that **the more stable conjugate base comes from the stronger acid.** If you ponder this guideline for a moment, you'll see that it makes complete sense. A strong acid gives up a proton easily, and it would only do so if the conjugate base that is left behind will be stable. Since hydroxide is the more stable conjugate base, water is the stronger acid.

We may also encounter same-column comparisons. To illustrate this point, let's compare the acidity of HF and HI. Once again, it is easiest to consider the charged conjugate bases: fluoride (F^-) and iodide (I^-).

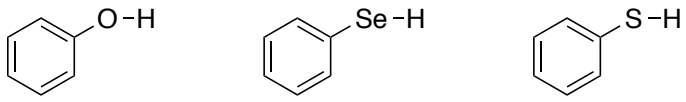


The element bearing the negative charge differs. Fluorine and iodine reside within the same column (i.e., group) of the periodic table. While there are electronegativity differences within a column, these are not as significant as the size differences between elements in the same column. Iodine is much larger than fluorine. Therefore, in iodide the negative charge is dispersed over a much larger area. Spreading out the burden of charge increases stability, so iodide is more stable than fluoride. Since iodide is the more stable conjugate base, HI is stronger acid.

Problem 7. Rank the following acids from strongest to weakest. The protons to consider have been drawn.

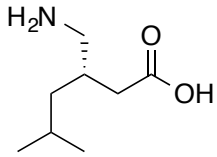
(a)

(b)

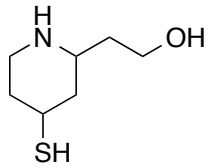


Problem 8. Rank the acidity of the protons drawn in the following molecules.

(a) This compound is pregabalin. It has been marketed by Pfizer as Lyrica for the treatment of epilepsy and fibromyalgia, among other conditions.

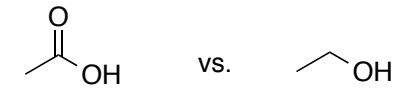


(b)



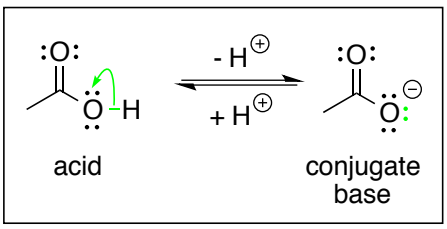
(2) Resonance

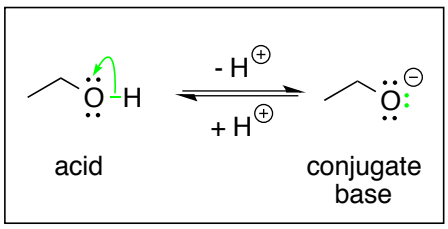
Sometimes the atoms bearing the acidic proton(s) are equivalent. In these cases, we have to look more deeply to explain differences in acidity. For instance, consider acetic acid and ethanol.



acetic acid ethanol

In each molecule, the most acidic proton is the one bonded to oxygen. When these protons are lost, conjugate bases are produced that both have a negatively charged oxygen atom. The elements bearing the charges in the conjugate bases are identical; nevertheless, one of these molecules is much more stable than the other.





The reason for the difference in stability is that the charge is spread out, or delocalized, in the conjugate base of acetic acid. Our system of drawing Lewis structures is an imperfect representation of the real molecules. Occasionally, it is necessary to draw more than one Lewis structure to get a true sense of the actual molecule. For instance, there are two Lewis structures that can be drawn for the conjugate base of acetic acid.

These two Lewis structures show that either oxygen atom can bear the negative charge. The charge is therefore delocalized, or spread out, over multiple nuclei, and this exerts a stabilizing influence.

Ethanol's conjugate base has no alternative Lewis structures. Since the negative charge is spread out over two oxygen atoms in acetic acid's conjugate base, this anion is more stable, and as a result, acetic acid is a stronger acid than ethanol.

When multiple Lewis structures can be drawn for a single molecule, they are known as resonance forms or resonance structures. Additional resonance forms can be derived from a single resonance structure using the same curved-arrow notation that we used to depict mechanism earlier. There are just a couple of rules for drawing resonance structures:

(1) Lone pair electrons may be moved to an adjacent bond. In other words, an atom can share a lone pair of electrons with an adjacent atom.

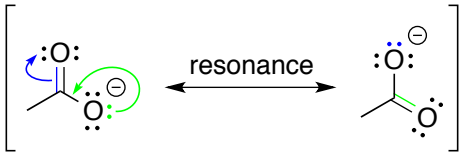
(2) π-bonding electrons may be moved to an adjacent atom. This is to say that a shared pair of π electrons may be relocated onto one of the atoms involved in the π bond.

(3) π-bonding electrons may be moved to an adjacent bond. In other words, an atom that was sharing π electrons with one neighboring atom may share them with its other neighbor instead.

(4) As you make the modifications described above, you must never exceed a filled valence shell for any atom (i.e., two electrons for hydrogen or an octet for second-row elements).

(5) σ bonds are neither created nor broken when drawing resonance forms.

Using these guidelines, we can start with one resonance structure of acetic acid's conjugate base and derive the other. As always, when drawing arrows, we must remember that these represent the flow of electrons. This flow begins at an electron-rich site, and the most electron-rich site in the molecule is the negatively charged oxygen. A lone pair of electrons from this oxygen can be shared with the neighboring carbon, so we draw the arrow ending between oxygen and carbon to denote the sharing that will take place. As carbon acquires a new bond, it must relinquish a preexisting bond. Since we cannot break σ bonds, our only option is to move the π-bonding electrons onto the adjacent oxygen atom. This indicates that the pair of electrons that was shared between carbon and oxygen will now reside solely on oxygen.



A special double-headed arrow is placed between resonance forms. This arrow differs from reaction arrows or equilibrium arrows because, in resonance, no reaction is taking place. We are simply indicating that the electrons can be distributed differently within a molecule without any chemical change taking place. Resonance forms are also sometimes enclosed in brackets to set them apart and highlight the fact that they are related to one another.

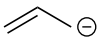
A reaction arrow shows that a chemical reaction is taking place. It is usually used when the products are highly favored.

Equilibrium arrows show that a chemical reaction is taking place. They are used to highlight the reversibility of a reaction.

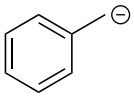
A resonance arrow shows that no chemical reaction is taking place. It merely separates resonance forms, which are different depictions of the exact same molecule.

Problem 9. Draw the indicated number of resonance forms for the following molecules.

(a) Draw one resonance form.

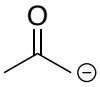


(b) Draw four resonance forms.

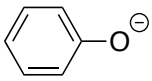


Problem 10. Sometimes resonance structures differ in stability. For the following anions, draw the indicated number of resonance forms, and identify the most stable one(s).

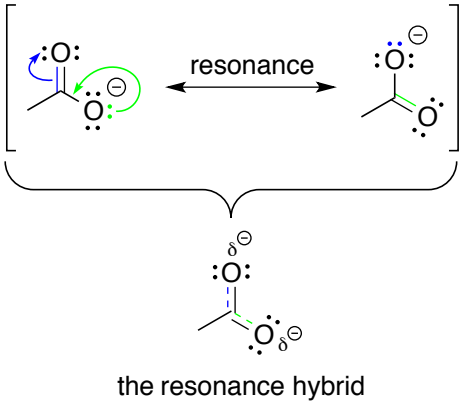
(a) Draw one resonance form.



(b) Draw four resonance forms.



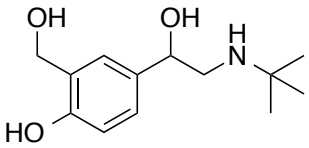
None of the individual Lewis structures accurately represent the actual molecule. Instead, the actual molecule is a hybrid, or a combination, of all of the resonance forms. In the case of acetic acid's conjugate base, the resonance hybrid has a partial negative charge on each of the oxygen atoms and partial double bond character in each carbon-oxygen bond. This partial double bond character is represented by dashed lines. The electrons that are delocalized through resonance are said to be in conjugation.



Problem 11. Draw the resonance hybrid for the molecules in Problems 9 and 10.

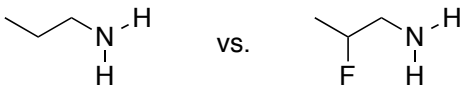
Although the resonance hybrid is a more accurate depiction of the real molecule, we will often use an individual resonance form when drawing reaction mechanisms. The reason is that it is easier to keep track of the electrons in an individual resonance structure where the delocalization is not overtly shown.

Problem 12. Salbutamol is used in the treatment of asthma and chronic obstructive pulmonary disease. Identify the most acidic proton in this molecule.

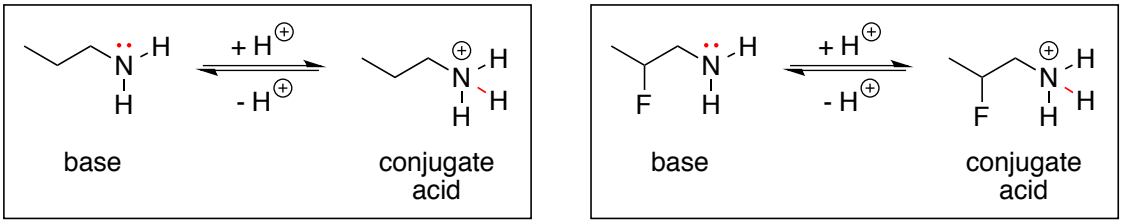


(3) Induction

Induction is the redistribution of electron density through σ bonds. It is relevant when electronegative atoms are present within the structure of an acid or base. Let's compare the basicity of the following amines.



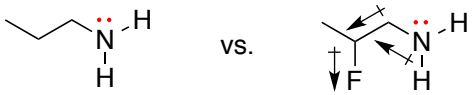
Since the amines possess lone pairs, they can accept a proton and function as a Brønsted-Lowry base. We can compare the charged conjugate acids in order to determine which amine is more basic.



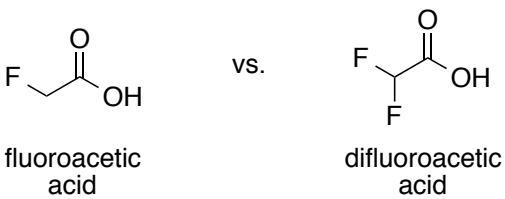
The fluorine atom is the glaring difference between the two conjugate acids, so we need to consider its impact. Being an electronegative element, its bond to carbon is polarized. As the carbon is rendered electron poor by its connection to the electronegative fluorine, the carbon pulls electron density from its neighbors. This, in turn, induces additional dipoles. The chain of dipoles shows that the electronegative fluorine atom pulls electron density toward itself through the molecule's σ bonds, which is known as induction.

The effect of this series of dipoles is to intensify the positive charge on nitrogen. This is destabilizing. If the conjugate acid is unstable, the base is less likely to acquire a proton to form this species. We can therefore say that the amine bearing fluorine is a weaker base.

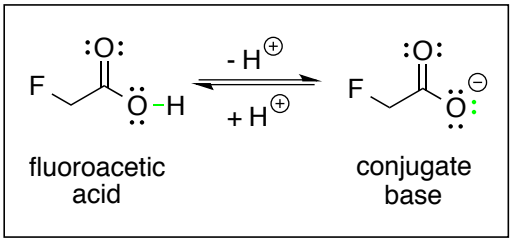
It is worth noting that sometimes we can formulate our argument using either the compounds or their conjugates. We would have arrived at the same answer by comparing the two amines. The same series of dipoles in the fluorinated amine reduces the electron density on nitrogen. Since there is less electron density on nitrogen, this amine is less basic.

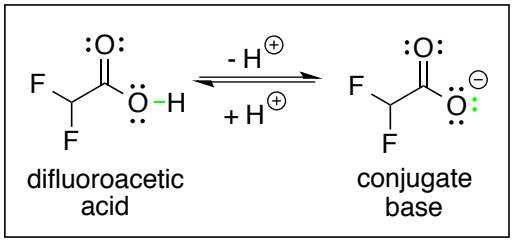


There can be a cumulative effect of multiple electron-withdrawing elements. For example, compare the relative acidity of fluoroacetic acid and difluoroacetic acid.

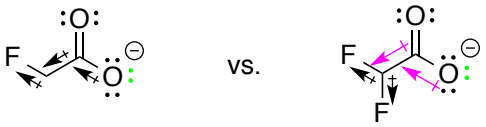


We can rank the acidity of these carboxylic acids by comparing the stability of their conjugate bases.



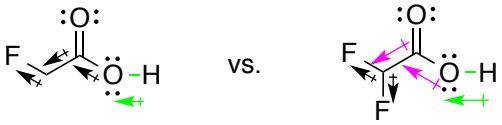


The one with two electronegative fluorine atoms will exhibit a more significant inductive electron withdrawal that will reduce the intensity of oxygen's negative charge to a greater extent. Since the conjugate base of difluoroacetic acid has a less intense charge on oxygen, it is more stable. Therefore, difluoroacetic acid is the stronger acid.



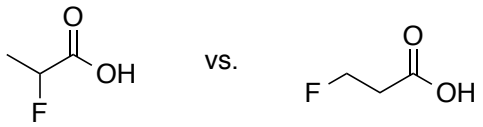
More stable: larger dipoles result from the cumulative electron withdraw of two fluorines

Once again, we could have arrived at the same conclusion by examining the carboxylic acids themselves. Difluoroacetic acid's two fluorines pull a great deal of electron density toward themselves. Through induction, a significant amount of electron density is pulled out of the O-H bond of the carboxylic acid. This weakens the bond, meaning that the proton will be lost more easily. So, difluoroacetic acid is a stronger acid than its counterpart having only one fluorine atom.



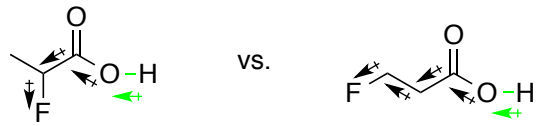
Stronger acid: O-H bond weakened to a greater extent

Another nuance of the inductive effect is that it diminishes quickly with increasing distance between the acidic or basic site and the electronegative element. Compare 2- and 3-fluoropropionic acid.



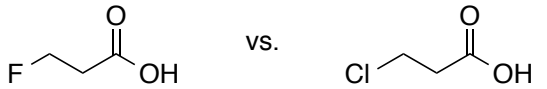
2-fluoropropionic acid | 3-fluoropropionic acid

In both of these carboxylic acids, the electronegative fluorine will pull electron density toward itself. As a result, the O-H bond of the carboxylic acid will be weakened. However, in 2-fluoropropionic acid, fluorine is closer to the carboxylic acid and therefore weakens the O-H bond to a greater extent, making this the stronger acid. In 3-fluoropropionic acid, the fluorine must pull through one additional σ bond before exerting any influence on the O-H bond of the carboxylic acid. As a result, it has less influence on the molecule's acidity.



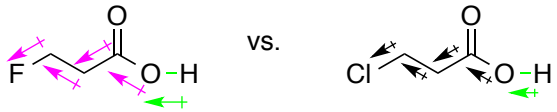
Stronger acid: must pull electron density through only three bonds before weakening O-H bond | Weaker acid: must pull electron density through four bonds before weakening O-H bond

Lastly, we must always be mindful of the fact that the inductive effect relies upon electronegativity. For example, if we compare 3-fluoropropionic acid to 3-chloropropionic acid, it is the former compound that is the stronger acid.



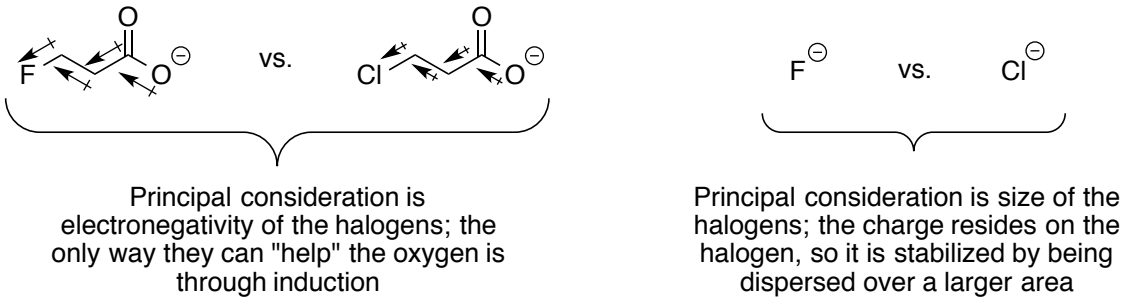
3-fluoropropionic acid | 3-chloropropionic acid

Fluorine is more electronegative than chlorine so it creates larger dipoles within the molecule, thereby removing more electron density from the carboxylic acid's O-H bond. This weakens the bond significantly. Since 3-fluoropropionic acid will therefore lose its proton more easily, it is a stronger acid.

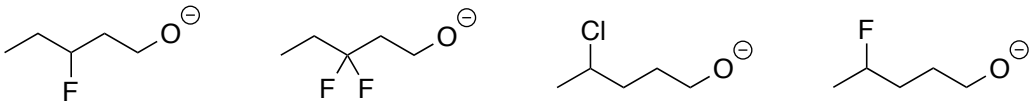


Stronger acid: larger dipoles due to more electronegative fluorine ultimately weaken the O-H bond to a greater extent

This type of comparison can be confusing because, when we studied element effects earlier, a comparison between two atoms in the same column of the periodic table would have been based on size. The difference is that in such examples (e.g., HF vs. HCl) the charge in the conjugate base will reside on the halide. The halide's size matters as a result because a charge spread out over a larger area is more stable. However, in the comparison of 3-fluoropropionic acid to 3-chloropropionic acid, the negative charge resides on oxygen in each of the conjugate bases. The size of the halogen is irrelevant in this case because the only way that the halogen can "help" oxygen is through induction, which is based on electronegativity.

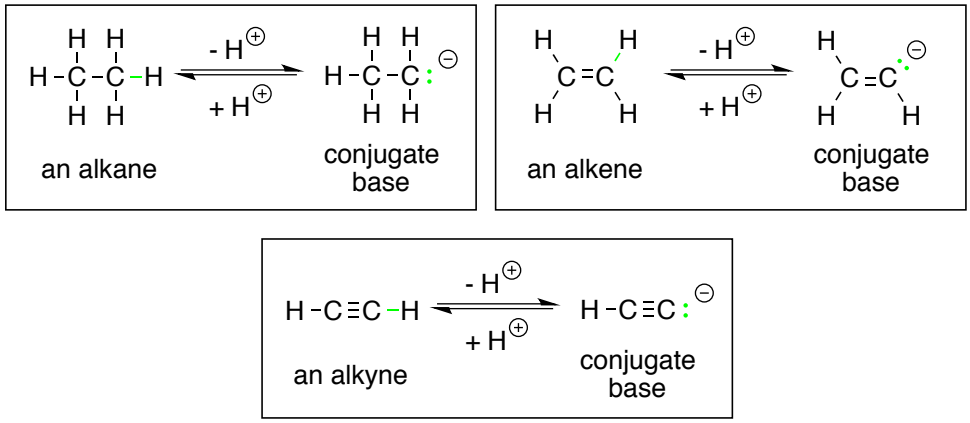


Problem 13. Rank the following bases from weakest to strongest.



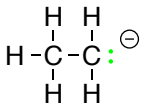
(4) Hybridization

Sometimes the principal difference between acids or bases is the hybridization of the reactive atom. Consider the relative acidity of an alkane, an alkene, and an alkyne.

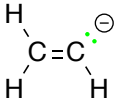


In each of the conjugate bases, the negative charge resides on carbon, so there are no element effects. There is no resonance that can help to stabilize any of the conjugate bases, and none of the conjugate bases contain electronegative elements that would provide

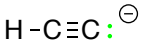
inductive stabilization. However, there is a difference in the hybridization of the carbons bearing the charge in the three conjugate bases. The alkane's conjugate base has the charge on an sp^3 hybridized carbon. The carbon of the alkene's conjugate base that bears the charge is sp^2 hybridized, and the corresponding carbon in the alkyne's conjugate base is sp hybridized.



sp^3
25% s character



sp^2
33% s character

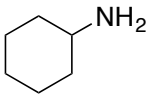


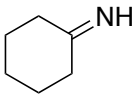
sp
50% s character

Each of these different hybrid orbitals contains a unique percentage of s character. When carbon is sp^3 hybridized, each hybrid orbital is one part s and three parts p. Another way of phrasing this is that the sp^3 hybrid has 25% s orbital character. The sp^2 hybrid orbitals are one part s and two parts p. In other words, they have 33% s character. The sp hybrids are one part s and one part p, or have 50% s character.

When the lone pair is held in an orbital with more s character, it is more stable. This is because s orbitals are closer to the nucleus than p orbitals in the same shell, and electrons closer to the nucleus are lower in energy. Therefore, the alkyne's conjugate base is the most stable of the three. This means that the alkyne is the strong acid of this group.

Problem 14. Which of the following molecules is expected to be more acidic?





When comparing any set of acids or bases, the order in which these effects were covered is also typically their order of importance:

(1) element effects (most important)
(2) resonance
(3) induction
(4) hybridization (least important)

There are some exceptions to this general guideline. When we take a more quantitative look at acidity and basicity using pK_a values, we'll gain insight into dealing with those situations.

Problem 15. In each pair below, identify the weaker acid.

(a)

(b)

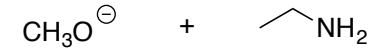
(c)

(d)

Section 5: Determining which side of the reaction is favored at equilibrium – Part I

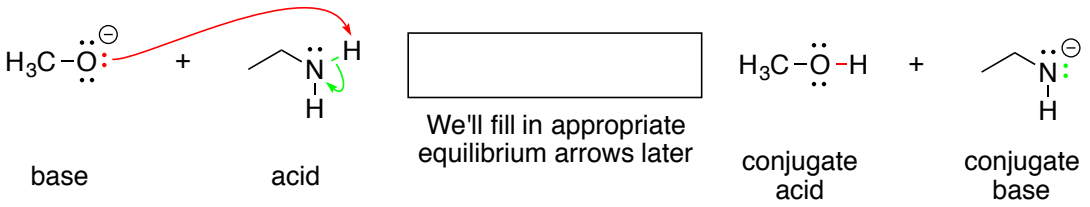
We can draw a mechanism for a reaction between any acid and base, and we can predict the products of that reaction. But, this doesn't necessarily mean that the products will be favored at equilibrium. Once we've drawn the complete acid-base reaction, we have to consciously evaluate which side of the reaction (reactants or products) will be favored when the system reaches equilibrium. In any reaction, the more stable species are favored at equilibrium, so to decide whether the reactants or products are favored, we'll be comparing their relative stabilities.

Let's consider the reaction between methoxide and ethylamine.

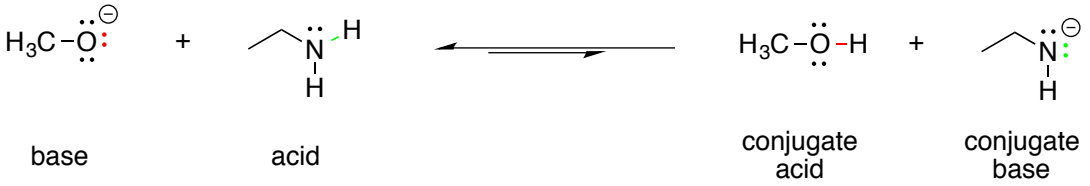


methoxide ethylamine

Both oxygen and nitrogen have lone pairs that could be used to acquire a new proton; however, the oxygen is clearly more electron rich since it possesses a negative charge. Methoxide is therefore the base. The most acidic protons in ethylamine are those on the nitrogen atom. This is explained by element effects: We would rather place a negative charge on nitrogen than on carbon because nitrogen is more electronegative. Methoxide uses a lone pair of electrons to make a bond to a proton of the amine. As this proton gets a new bond, it must give up its bond to nitrogen.

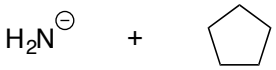


With the full acid-base reaction before us, we can now determine which side of the reaction is favored at equilibrium. The charges are obvious points of instability, so we should focus on the charged species. The reactant anion has a negative charge on oxygen, while the negative charge resides on nitrogen in the product anion. Element effects allow us to decide which is more stable. Oxygen and nitrogen reside in the same row of the periodic table, so the most pronounced difference between them is in their electronegativity. The negative charge is more stable on the more electronegative oxygen atom. It is therefore the reactants that are favored at equilibrium in this case. We can represent this by drawing equilibrium arrows in which the one pointing toward the reactants is larger.



Problem 16. Draw the products of the following acid-base reactions, as well as mechanisms to explain their formation. Then, determine which side of the reaction is favored at equilibrium.

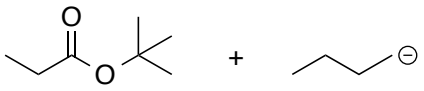
(a)



(b)

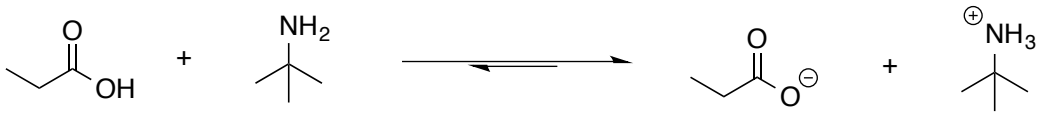
(c)

(d)



Section 6: Acidity and the pK_a value

To this point, we've assessed acidity qualitatively by considering element effects, resonance, induction, and hybridization. We can address many acid-base questions using this method, but there are some situations that present difficulties unless we have a more quantitative assessment of acidity. For instance, what if there aren't charged species on both sides of the reaction? The following reaction has neutral reactants and charged products. Without any additional information, we might be tempted to suggest that the reactants would be favored at equilibrium due to the absence of charges, but this is not the case. In fact, the products are favored at equilibrium, and we'll understand why once we've discussed pK_a values.



To understand what a pK_a value is, you first need to know about equilibrium constants. The equilibrium constant (K_{eq}) for any reaction is the ratio of the concentrations of the products to those of the reactants. Concentration is often denoted by brackets. Additionally, each term is raised to the power of its stoichiometric coefficient. In the following reaction, A and B are converted to C and D, and the lowercase letters represent the stoichiometric coefficients.

$$a\,A + b\,B \rightarrow c\,C + d\,D$$

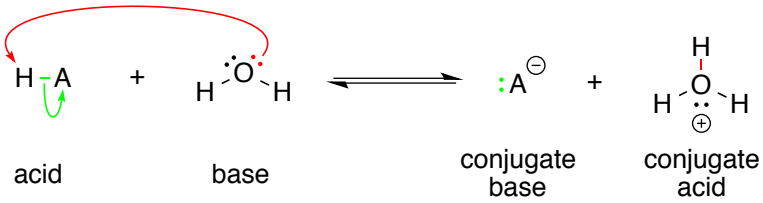
$$K_{eq} = \frac{[C]^c\,[D]^d}{[A]^a\,[B]^b}$$

In organic acid-base reactions, the stoichiometry is usually 1 : 1 : 1 : 1, so the equilibrium constant simplifies.

$$acid + base \rightarrow conjugate\ base + conjugate\ acid$$

$$K_{eq} = \frac{[conjugate\ base]\,[conjugate\ acid]}{[acid]\,[base]}$$

It is common to measure equilibrium constants for acids in water. HA is a commonly used generic representation of an acid, in which H is the acidic proton and A is the rest of the acid's structure. The acid-base reaction of HA with water is as follows.



The equilibrium constant for this reaction is:

$$K_{eq} = \frac{[A^-]\,[H_3O^+]}{[HA]\,[H_2O]}$$

When making measurements of this type, it is common to use water as the solvent, in which case it is present in much greater abundance than the other substances. While the concentration of water will change during the reaction, that change is negligible. Since the concentration of water is therefore effectively constant, we would like to eliminate the water term from the equation. To do so, the acid dissociation constant (K_a) is defined as:

$$K_a = K_{eq}\,[H_2O]$$

This cancels the water term, giving:

$$K_a = \frac{[A^-]\,[H_3O^+]}{[HA]}$$

K_a is useful because it provides a measure of whether the reactants or products are favored at equilibrium. A K_a greater than 1 signifies that the products are favored, while a K_a less than 1 denotes that the reactants are favored.

There is a huge range of K_a values for various acids. For instance, sulfuric acid has a K_a of about 10^{10}. This reveals just how strong of an acid it is; for every one molecule of sulfuric acid remaining at equilibrium, ten billion have dissociated. On the other hand, an alkane has a K_a of 10^{-50}. It is an exceedingly weak acid. For every molecule that dissociates, 10^{50} unreacted molecules remain. This essentially means that alkanes don't dissociate at all in water.

There is a range of sixty orders of magnitude (i.e., sixty powers of 10) in the K_a values of sulfuric acid and an alkane! When such a tremendous range exists, it is convenient to use a logarithmic scale to make the numbers more manageable. To that end, pK_a is commonly used.

$$pK_a = -log\,K_a$$

The pK_a values of sulfuric acid and an alkane are –10 and 50, respectively. These two substances mark the boundaries of the range in pK_a values that are commonly encountered. *It is important to recognize that a strong acid has a large K_a but a small pK_a value.* For

instance, sulfuric acid is an extremely strong acid. Its K_a (10^{10}) is very big, but its pK_a (–10) is small. On the other hand, an alkane is an exceedingly weak acid. Its K_a of 10^{-50} is miniscule, but its pK_a of 50 is large.

Since pK_a utilizes a logarithmic scale, each pK_a unit is an order of magnitude (or a power of ten). To underscore this, compare HCl, which has a pK_a of –7, to HI, which has a pK_a of -9. There is a difference of 2 pK_a units between these two acids. However, HI is <u>not</u> twice as strong of an acid as HCl. It is 10^2 (or 100) times stronger!

HCl vs. HI

pK_a -7 pK_a -9

100x stronger acid

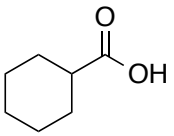
Problem 17. Using the information given below, determine which is the stronger acid in each pairing.

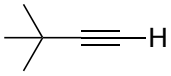
(a)

H_3O^+ H_2SO_4

$K_a = 10^{1.7}$ $K_a = 10^{10}$

(b)



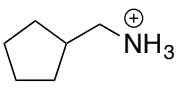


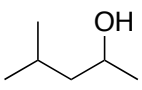
$pK_a \sim 5$ $pK_a \sim 25$

(c)

$K_a \sim 10^{-35}$ $K_a \sim 10^{-45}$

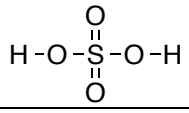
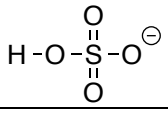
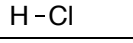
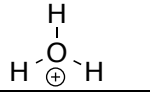
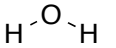
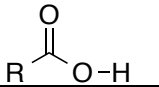
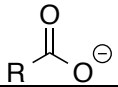
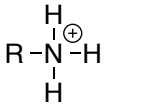
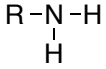
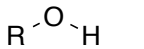
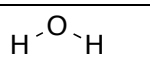
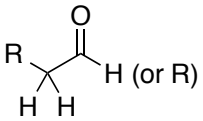
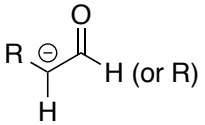
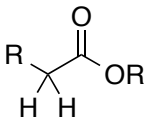
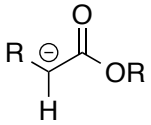
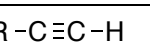
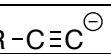
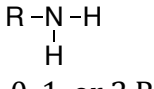
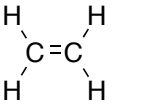
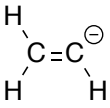
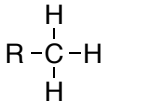
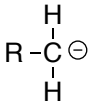
(d)





$pK_a \sim 10$ $pK_a \sim 15$

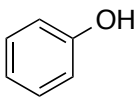
The pK_a values have been measured for many compounds. The table below has a representative listing of those that are frequently used. The strongest acids are at the top of this table, and the weakest appear at the bottom.

Acid	Acid's pK_a value	Conjugate base
	–10	
	–7	
	–1.7	
	~5	
 (N can have 0, 1, 2, or 3 R groups)	~10	
	~15	
	15.7	
	~20	
	~25	
	~25	
 (N can have 0, 1, or 2 R groups)	~35	
 (the alkene can have up to 3 R groups)	~45	
 (C have 0, 1, 2, or 3 R groups)	~50	

Problem 18. Explain the following pK_a values.

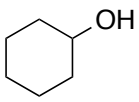
(a) A phenol has a pK_a of about 10, but an alcohol has a pK_a value of around 15.

phenol



$pK_a \sim 10$

an alcohol



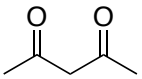
$pK_a \sim 15$

(b) A ketone has a pK_a value of around 20, but a β-diketone has a pK_a of about 9.

a ketone

$pK_a \sim 20$

a β-diketone



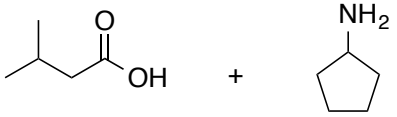
$pK_a \sim 9$

Notice that some species appear twice on the table. For instance, water appears as the conjugate base of the hydronium ion (H_3O^+) and as an acid capable of losing a proton to form hydroxide (HO^-). Such species are known as amphoteric. An amphoteric compound like water can act as an acid or as a base, depending on the circumstances. It is especially important with such substances to remember that a pK_a value is associated with an acid. When selecting the relevant pK_a value you have to carefully assess how the molecule is behaving in the context of the reaction under consideration.

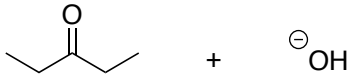
Problem 19. Identify a second amphoteric compound in the table of pK_a values.

Problem 20. Assign the relevant pK_a values to the acid and the conjugate acid in each of the following reactions.

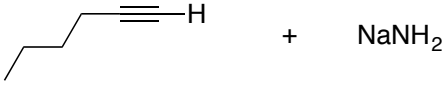
(a)



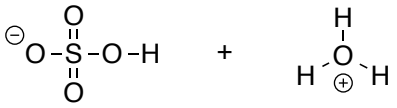
(b)



(c)



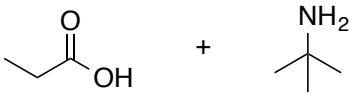
(d)



Section 7: Determining which side of the reaction is favored at equilibrium – Part II

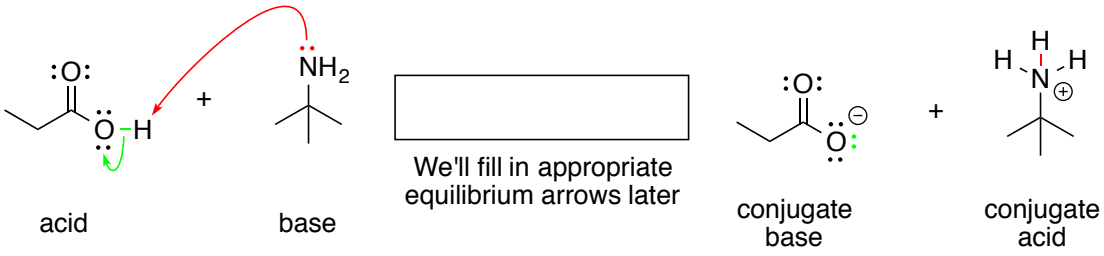
Now that we know about pK_a values, we can use these quantitative measures of acidity to predict the outcome of acid-base reactions, even if there are not charged species on both sides of the reaction. It is still the case that the more stable species are favored at equilibrium, and this will always be true. We can tailor this guideline to acid-base reactions by stating that equilibrium favors the side with the weaker acid, which has the higher pK_a. Rather than memorizing this guideline, it is preferable to understand it. Substances that are very reactive have a tendency to undergo a change and become less reactive species in the process. Thus, strong acids react readily to make weaker ones. This is the rationale behind the guideline.

Let's reconsider the reaction between a carboxylic acid and an amine, which was introduced in the last section.

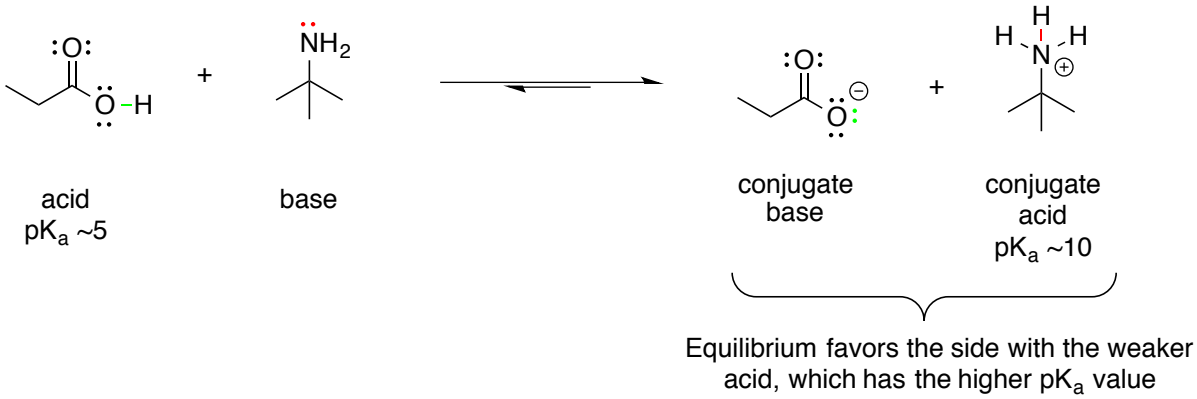


The most acidic proton in the system is on the carboxylic acid. We know this to be the case for two reasons. Removing this proton leaves a negative charge on oxygen, which is a fairly electronegative element. Element effects therefore suggest that the carboxylic acid proton is fairly acidic. Additionally, the conjugate base of a carboxylic acid has resonance stabilization.

Now that we've identified the most acidic proton in the system, we need only draw a mechanism to explain its transfer to the amine, which must serve as the base since it is the only other component present. The lone pair of electrons on nitrogen is used to form the new N-H bond. As the proton acquires a new bond, it must relinquish the preexisting bond to oxygen.



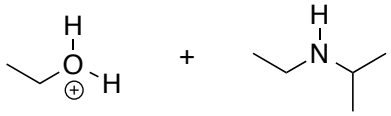
With the complete reaction before us, we can now determine which side is favored at equilibrium. To do so, we'll assign a pK_a value to the acid on each side of the reaction. A carboxylic acid has a pK_a of approximately 5. A protonated amine has a pK_a of about 10. At equilibrium, the side with the weaker acid (i.e., the higher pK_a value) is favored. So, in this case, the products are favored.



Furthermore, we can specify the extent to which the products are favored. There is a difference of 5 in the pK_a values of the two acids in this reaction. Since pK_a values are on a logarithmic scale, this means a difference of 5 orders of magnitude (or 10^5). The products are therefore favored by 10^5, or 100,000.

Problem 21. Revisit the reactions shown in Problem 20, and determine whether the reactants or products are favored at equilibrium and by how much.

Problem 22. Sometimes you will encounter acids that do not appear in the pK_a table, and you may have to make an informed judgment about their acidity based on the structural similarities with acids whose pK_a values you do know. Keeping this in mind, determine the products of the following reaction, and decide which side is favored and by how much.

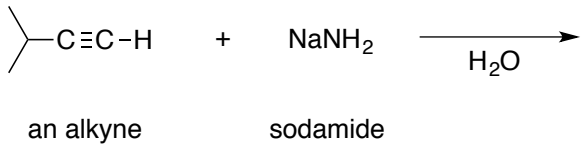


Section 8: The importance of solvent

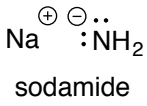
Most reactions are conducted in a solvent. In other words, the reactants are not simply mixed together. They are dissolved in a solvent, and the acid-base reaction takes place in this solution. When choosing a solvent for an acid-base reaction, it is critical to ensure that the solvent will not disrupt the reaction.

For example, water can be used as a solvent for some reactions, but it is not an appropriate solvent for all reactions because of its ability to behave as an acid or a base. Imagine trying

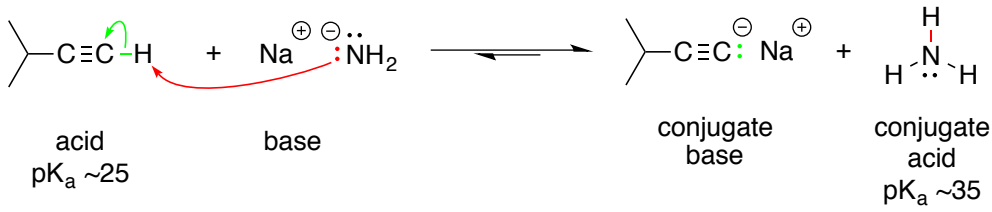
to conduct a reaction between sodium amide (also known as sodamide) and an alkyne using water as the solvent. The solvent is often written below the reaction arrow.



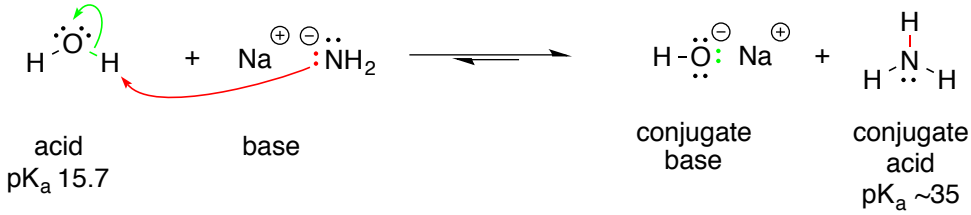
We must first identify the acid and the base. In this instance, a spectator ion has been shown. When a metal is part of a molecular formula, it is present as a cation. Thus, sodamide, while net neutral, contains formal charges. The sodium cation is not a meaningful participant in the reaction. It merely associates with whatever species happens to be anionic; as such, it is called a spectator ion. Spectator ions are sometimes shown and sometimes omitted.



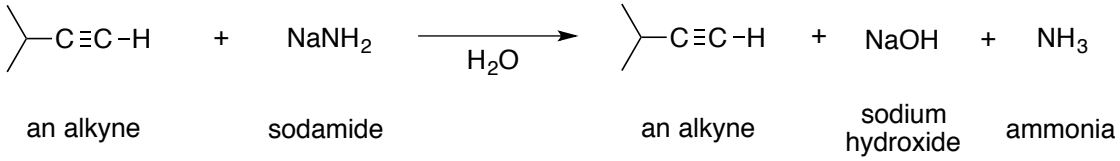
The amide ion is clearly electron rich, so it serves as the base. In this reaction, we are probably *hoping* that sodamide will remove a proton from the alkyne as shown below. If this were to occur, the alkyne's conjugate base would be produced and the products would be favored by 10^{10}.



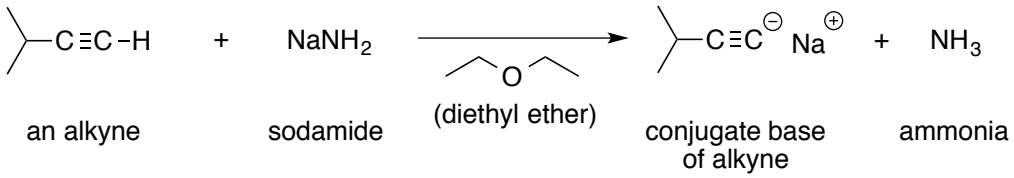
However, this reaction fails to produce the desired product because water has been used as the solvent, and *water is a stronger acid than the alkyne*. Sodamide reacts with the stronger acid, water, to yield sodium hydroxide and ammonia (NH_3). These products are favored by more than 10^{19}.



The net result of this reaction is that the alkyne is left unchanged, while sodamide reacts with the solvent to yield sodium hydroxide and ammonia. Since the intention was for sodamide to react with the alkyne, this is considered a failed reaction.

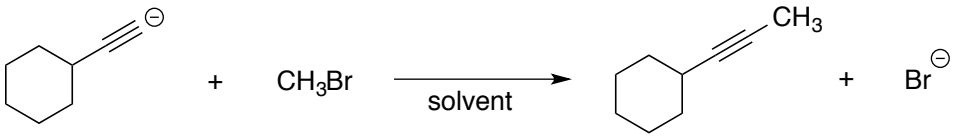


To obtain the desired reaction, we must use a solvent without acidic protons, such as diethyl ether. When sodamide cannot react with the solvent, it will deprotonate (i.e., remove the proton from) the alkyne.



The role of solvent in acid-base chemistry is sometimes referred to as the leveling effect, or as solvent leveling. As we saw in the preceding example, the strongest base that can exist in a solution is the conjugate base of the solvent. If a stronger base is added to the medium, it deprotonates the solvent to yield the solvent's conjugate base. The same principle applies to acids; the strongest acid that can exist in a solution is the solvent's conjugate acid. If a stronger acid is introduced, it merely protonates the solvent.

Problem 23. In Chapter 7, you'll learn about the S_N2 reaction, an example of which follows.

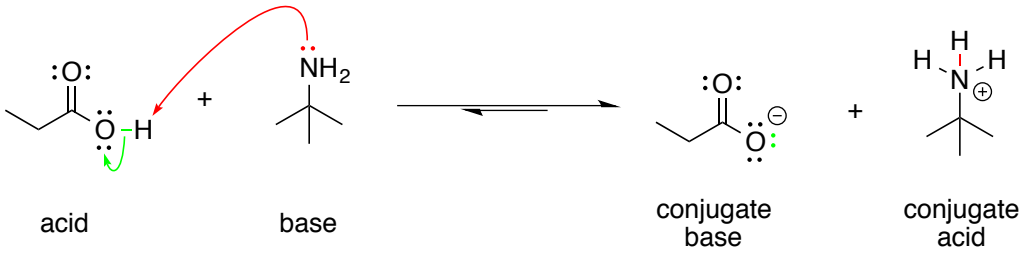


Which of the following solvents could be used for this reaction?

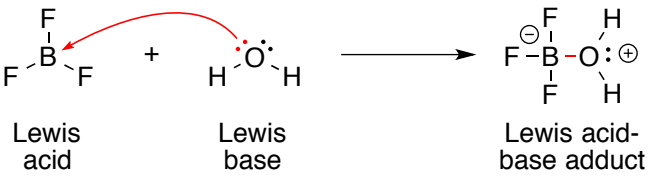
Section 9: The Lewis definition of acids and bases

Every acid-base reaction we've considered so far involves the transfer of a proton. There are, however, some acid-base reactions in which no proton is involved. The Lewis definition of acids and bases is broader and more inclusive than the Brønsted-Lowry definition and allows us to deal with such situations. A Lewis acid is an electron-pair acceptor, while a Lewis base is an electron-pair donor. Anything that was classified as a Brønsted-Lowry acid will still be termed an acid under the Lewis definition, and the same applies for bases.

For instance, let's reexamine the reaction between a carboxylic acid and an amine that we encountered in Section 7. Under the Brønsted-Lowry definition, the carboxylic acid is an acid because it is a proton donor. The carboxylic acid is still classified as an acid under the Lewis definition because its proton is accepting electrons from the amine as a new bond is formed. The amine was assigned the role of the base under the Brønsted-Lowry paradigm because it accepts the proton donated by the carboxylic acid. The amine is still a base when we look through the lens of the Lewis definition because it donates the electron pair needed to form the new N-H σ bond.



The utility of the Lewis definition is that it enables us to address transformations that would not otherwise be classified as acid-base reactions. Consider the reaction between water and boron trifluoride. Boron trifluoride lacks an octet, so it is electron deficient despite the fact that it has no formal charge. Consequently, it attracts the oxygen atom of water, which is electron rich due to the presence of two unshared pairs of electrons.

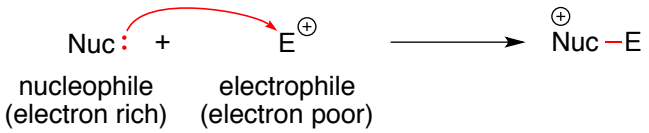


In this reaction, no proton is transferred, so there are no Brønsted-Lowry acids or bases at play. However, boron trifluoride acts as an electron pair acceptor, making it a Lewis acid. It is accepting electrons from water as the new boron-oxygen σ bond is formed. Conversely, water is an electron-pair donor, so it is a Lewis base. It is contributing the electrons needed for the new σ bond.

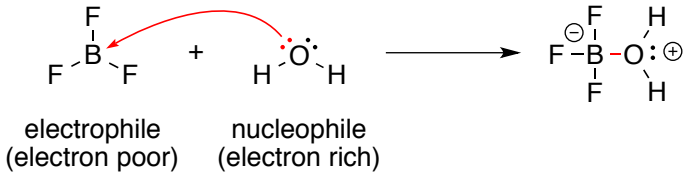
There are two additional terms that we can use to describe reactants like Lewis acids and bases. These terms will be used a great deal throughout the remainder of the text beginning in Chapter 7. Nucleophiles (literally "nucleus-loving" entities) are species that are electron rich, and as such, they are attracted to electron-poor nuclei. Conversely, electrophiles (literally "electron-loving" species) are electron poor and are therefore attracted to electron-rich sites.

The reaction between a nucleophile and an electrophile is shown generically below. The nucleophile has a lone pair of electrons (although a π bond would also suffice) and is therefore electron rich. Nucleophiles will sometimes be neutral and sometimes negative. The electrophile has a positive charge, making it electron poor, but this electron deficiency

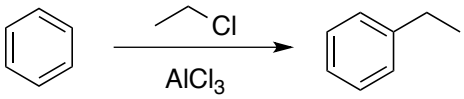
could also be due to a δ^+ instead of a full positive charge. The nucleophile shares its electron pair with the electrophile. Since the nucleophile is donating an electron pair for the reaction, it can also be described as a Lewis base. On the other hand, the electrophile accepts the electron pair, making it a Lewis acid.



If we revisit the reaction between boron trifluoride and water, we can label water as the nucleophile. It is reasonably electron rich because of its two lone pairs of electrons. As a result, it is attracted to the electron-poor boron nucleus. BF_3 is the electrophile. Boron is electron poor because it lacks a complete octet, and this causes it to be attracted to the electron-rich oxygen of water.



Problem 24. In Chapter 14, you'll learn about the Friedel-Crafts alkylation, which is a reaction of benzene and related aromatic molecules. An example of a Friedel-Crafts alkylation is shown below.

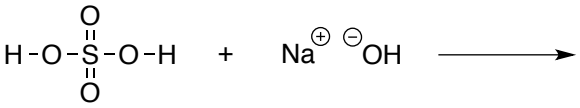


The transformation begins with a Lewis acid-base reaction between the alkyl chloride and aluminum trichloride ($AlCl_3$). Provide a mechanism for just this one step, and show the resultant Lewis acid-base adduct. Finally, label the $AlCl_3$ and alkyl chloride appropriately using the terms nucleophile and electrophile.

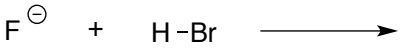
End-of-the-Chapter problems

Problem 25. Draw mechanisms and products for the following Brønsted-Lowry acid-base reactions. Also label the acid, the base, the conjugate acid, and the conjugate base.

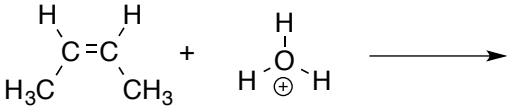
(a)



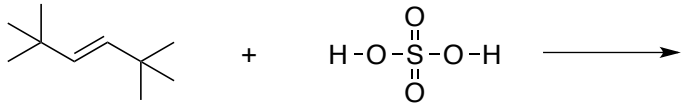
(b)



(c)



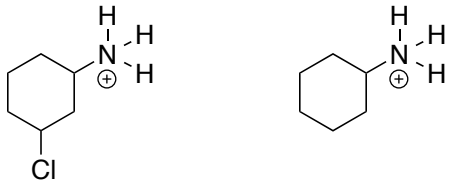
(d)



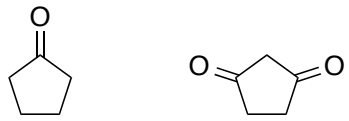
Problem 26. In each of the following pairs, identify the stronger acid.

(a)

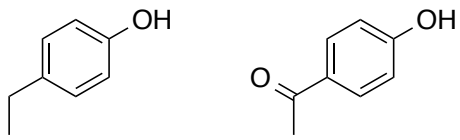
(b)



(c)



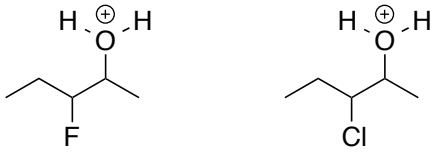
(d)



(e)

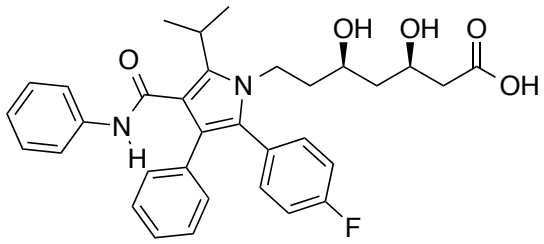
(f)

(g)



(h)

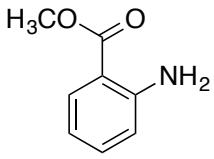
Problem 27. Identify the most acidic proton(s) in the cholesterol-lowering agent Lipitor.

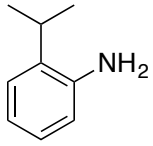


Problem 28. In Chapter 16, we'll learn about a way to produce amides through the reaction of an acid chloride with an amine. This reaction produces hydrochloric acid as a byproduct. As a result, a second molar equivalent of the amine must be used. Show the reaction of this second equivalent of amine with HCl, and provide a balanced equation for the overall reaction of the acid chloride with two equivalents of the amine.

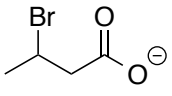
Problem 29. In each of the following pairs, identify the stronger base.

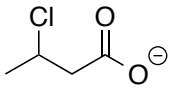
(a)



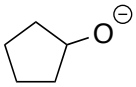


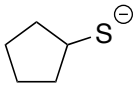
(b)



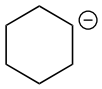


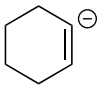
(c)



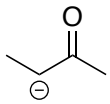


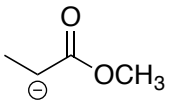
(d)



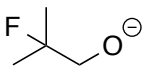


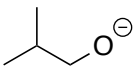
(e)



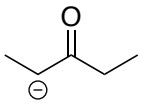


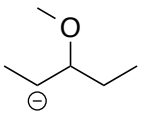
(f)



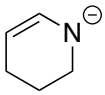


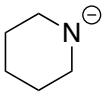
(g)





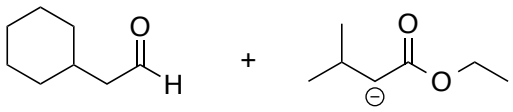
(h)





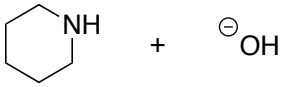
Problem 30. For each of the following reactions, predict the products, and then decide which side of the reaction is favored at equilibrium and by how much.

(a)

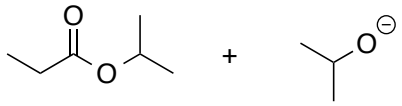


(b)

(c)

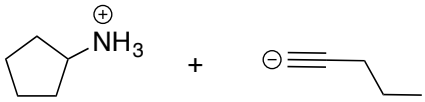


(d)



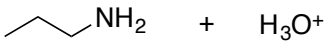
(e)

(f)



(g)

(h)



Problem 31. Based on the solvent leveling effect, what acid is present in each of the following cases?

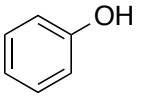
(a)

H_2SO_4 is mixed with H_2O

(b)

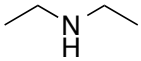
HCl is mixed with CH_3CH_2OH

(c)



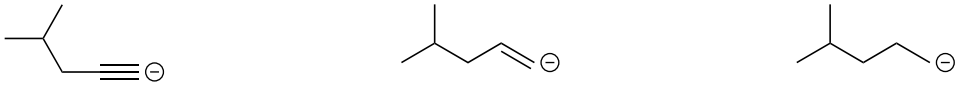
is mixed with H_2O

(d)

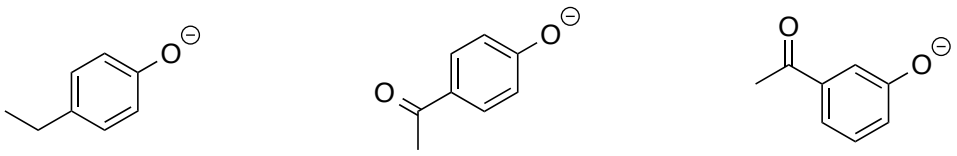
H_2SO_4 is mixed with 

Problem 32. In each of the following groups, identify the compound with the strongest conjugate acid.

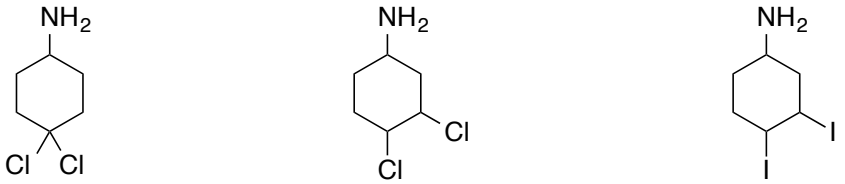
(a)



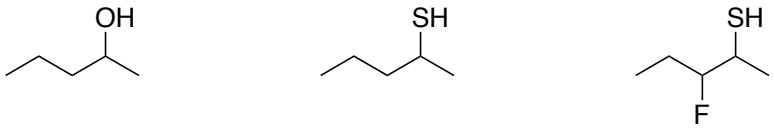
(b)



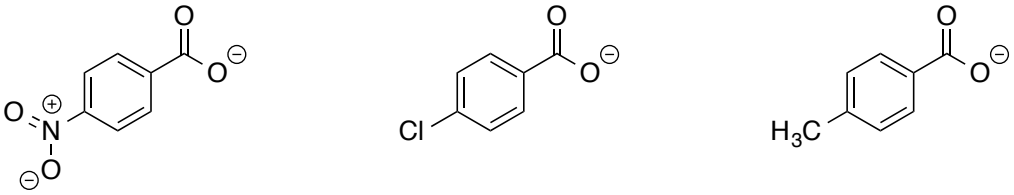
(c)



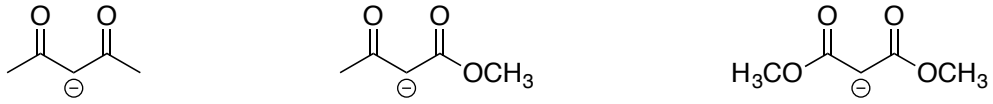
(d)



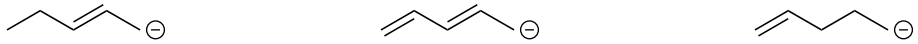
(e)



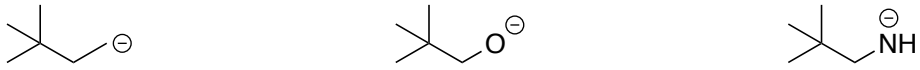
(f)



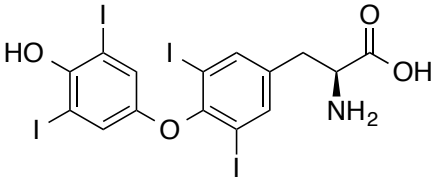
(g)



(h)

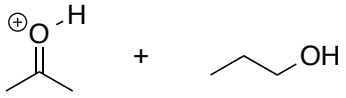


Problem 33. Identify the most acidic proton(s) in Synthroid, a compound used to treat thyroid hormone deficiency. Synthroid's structure is identical to that of thyroxine, which is produced by the thyroid gland.

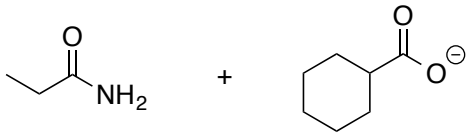


Problem 34. Predict the products of the following reactions, and then decide which side is favored at equilibrium. Note that we have not yet seen all of the pK_a values relevant to these questions, so your decision may have to be a qualitative one based on the structural factors that affect acidity.

(a)

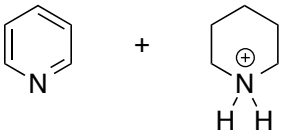


(b)

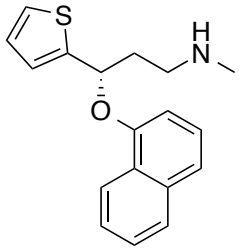


(c)

(d)

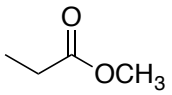
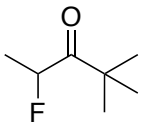
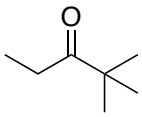


Problem 35. Identify the most basic site in Cymbalta, which is used in the treatment of depression.

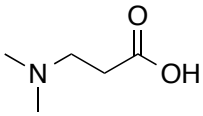
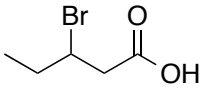
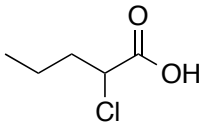


Problem 36. In each of the following groups, identify the compound with the weakest conjugate base.

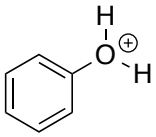
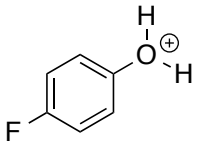
(a)


O
OCH3

O
F

O

(b)


O
N
OH

Br
O
OH

O
OH
Cl

(c)


H
O
H

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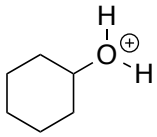
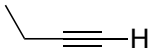
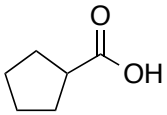
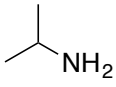
O
H
F

H
O
H

(d)


H

O
OH

OH

(e)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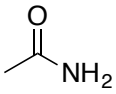
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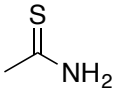
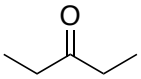
NH2

S
NH2

(f)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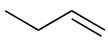
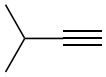
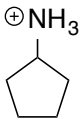



(g)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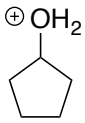
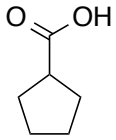
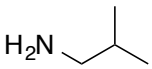

OH2

O
OH

(h)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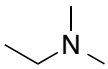
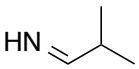
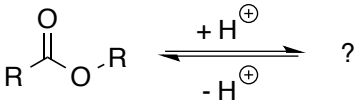
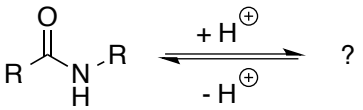

N

HN

Problem 37. When esters and amides act as bases, where should they be protonated? Are they protonated on the sp^3 hybridized oxygen/nitrogen or on the carbonyl oxygen? Why?



ester

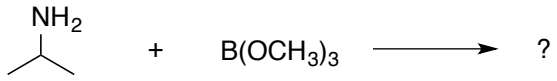


amide

Problem 38. Show the missing components of the following Lewis acid-base reactions. Then, draw each reaction's mechanism. Label the reactants as Lewis acid or Lewis base, and as nucleophile or electrophile.

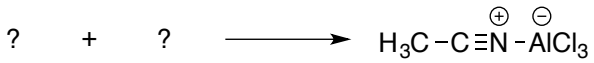
(a)

(b)



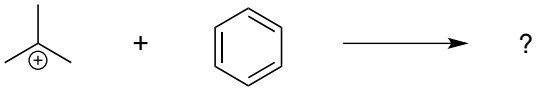
(c)

(d)

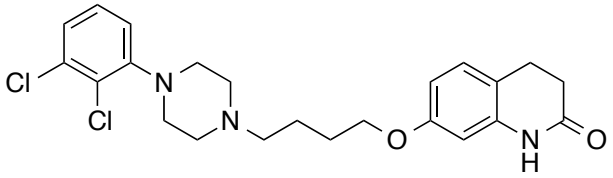


(e)

(f)

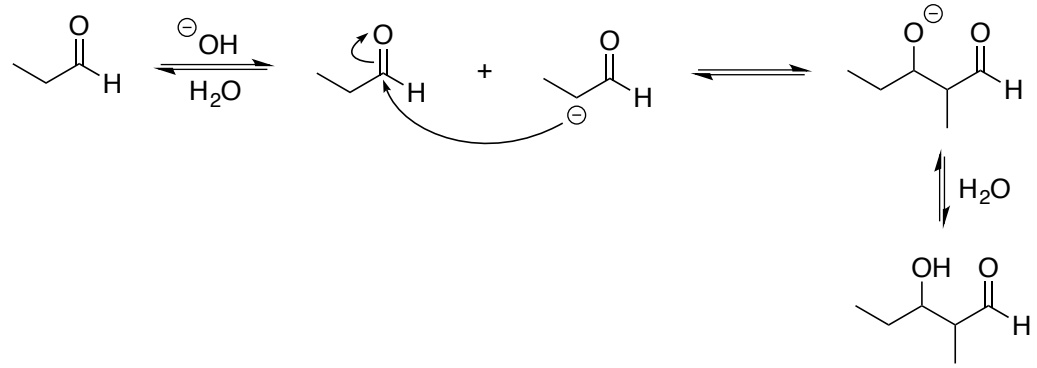


Problem 39. Abilify is used in the treatment of schizophrenia and bipolar disorder, among other conditions. Identify the most basic site in this molecule.

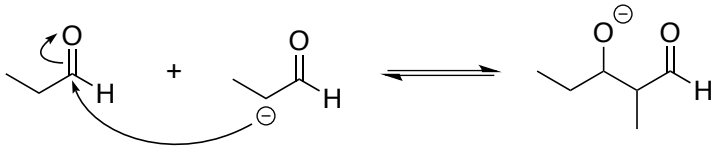


Problem 40.

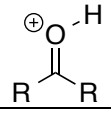
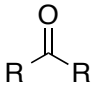
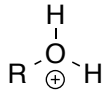
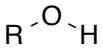
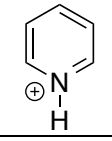
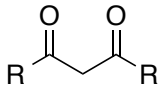
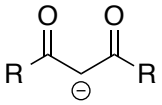
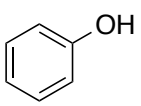
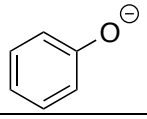
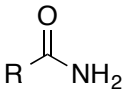
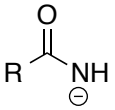
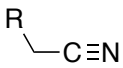
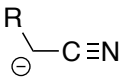
(a) In Chapter 17, we will learn about the aldol reaction, an example of which is shown below. The aldol reaction relies upon the coexistence of an aldehyde (or ketone) and its conjugate base. Using pK_a values, explain why hydroxide is a suitable base for this reaction but sodamide ($NaNH_2$) is not.



(b) For the second step of the aldol reaction, label the reactants as nucleophile and electrophile as appropriate.



Throughout the problems, several additional pK_a values have been introduced. They are summarized in the following table.

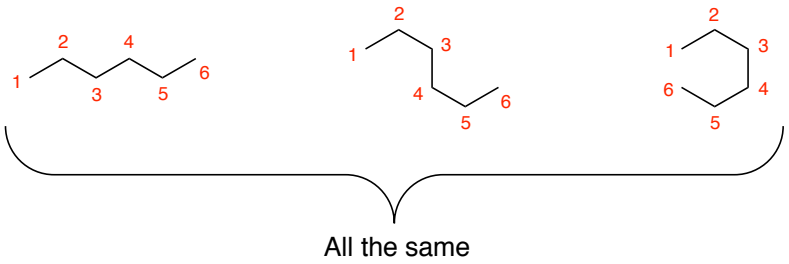
Acid	Acid's pK_a value	Conjugate base
HI	–9	
	–6 to –7	
	~ –2	
	~5	
	~9	
	~10	
	~15	
	~25	

Chapter 3: Alkanes

Section 1: Types of alkanes
Section 2: Classification of carbons and hydrogens
Section 3: Nomenclature
Section 4: Conformational analysis of acyclic alkanes
Section 5: Conformational analysis of cyclic alkanes
Section 6: Combustion

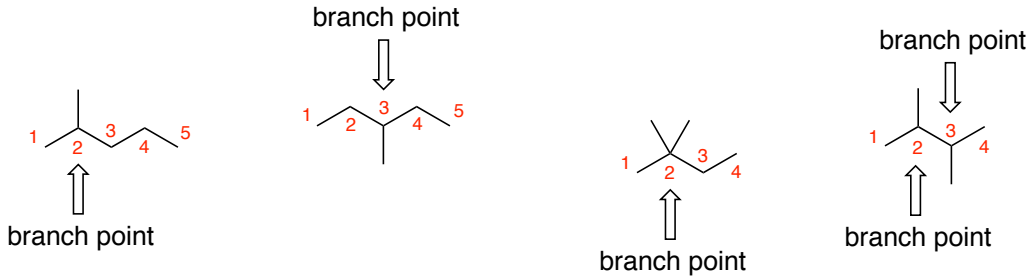
Section 1: Types of alkanes

As we learned in Chapter 1, alkanes are hydrocarbons containing only single bonds. Though even in the absence of other functionality, there is still a great deal of structural variation possible. Alkanes can be further subdivided into linear, branched, and cyclic molecules. Linear alkanes have all of the carbons connected in a single chain with no branch points. Three representations of the exact same linear alkane are shown below. In each instance, there are six carbon atoms in a chain with no branch points. These three drawings highlight the fact that a molecule may be portrayed in a number of different ways, but if the connectivity between its elements is unchanged, then it is still the same molecule.



This linear alkane has the molecular formula C_6H_{14}, and it is saturated with hydrogens. In other words, there is no way that a six-carbon molecule can contain more than 14 hydrogens. Linear alkanes are always saturated with hydrogens (or simply "saturated"), and therefore have molecular formulas of the type C_nH_{2n+2}.

In a branched alkane, the carbon chain splits at least once. The following compounds all contain six carbons, just like the linear alkane we saw above. However, in these molecules, there are places where the carbon chain divides. In the first structure, C2 is a branch point that leads to C3 as well as a one-carbon group. In the second molecule, C3 is the branch point. In the third molecule, C2 is a point at which the carbon chain divides into three paths: C3 and two one-carbon groups. Finally, the last structure has two branch points. These occur at C2 and C3.



Notice though that all of these molecules have the same molecular formula: C_6H_{14}. They are therefore saturated, like the linear alkane, and these molecules are constitutional isomers of each other and of the linear six-carbon alkane.

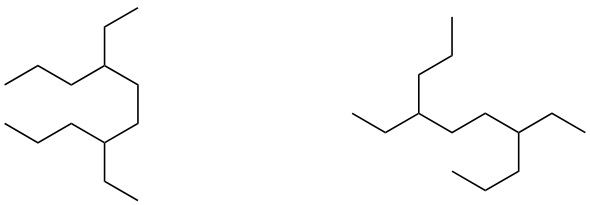
Problem 1. Are the following pairs of molecules the same, or are they isomers?

(a)

(b)

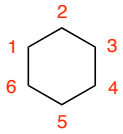
(c)

(d)



Problem 2. Draw all of the isomers for C_5H_{12}.

It is also possible for alkanes to be cyclic. In other words, the carbon chain of an alkane can contain a ring. For instance, the following molecule contains a six-carbon ring.

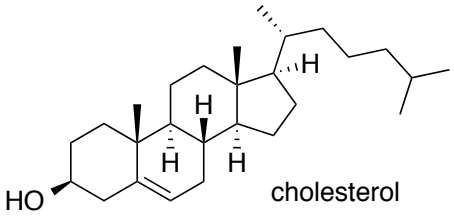


This structural feature alters the molecular formula. While this compound contains six carbons, like the linear and branched alkanes above, it has only 12 hydrogens. The ring causes the molecule to have less than the maximum number of hydrogens. This compound is therefore unsaturated, and the ring can be thought of as "a degree of unsaturation." Cyclic alkanes containing a single ring have the formula C_nH_{2n}, but if there are additional rings, the hydrogen count will be further reduced. Notice that one ring reduces the hydrogen count by two because the two carbons to be joined into a ring must each have one open valence.

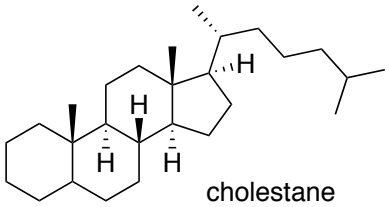
Problem 3. Draw all of the isomers of this cyclic alkane that also contain one ring.

Section 2. Classification of carbons and hydrogens

Carbons are classified as primary (1°), secondary (2°), tertiary (3°), or quaternary (4°) based on the number of other carbon atoms to which they are bonded. This can be illustrated with an example. Cholesterol is an important biologically relevant molecule, but it is not an alkane. However, cholestane (a steroid precursor) is an alkane with the same carbon framework as cholesterol.

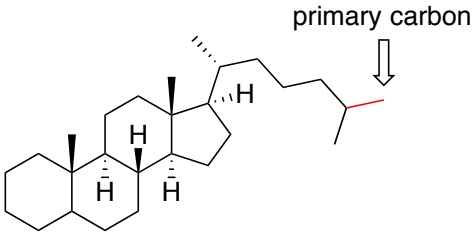


cholesterol

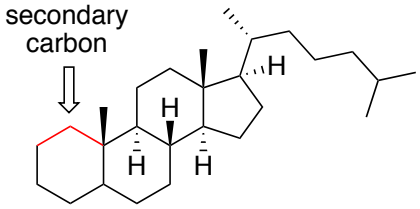


cholestane

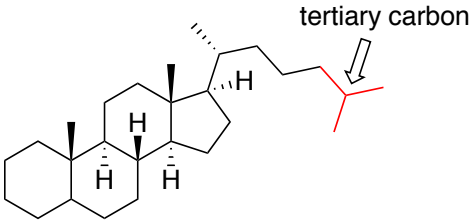
Cholestane contains within it primary, secondary, tertiary, and quaternary carbon atoms. The primary carbons, like the one highlighted in the structure below, are bonded to one and only one other carbon atom.



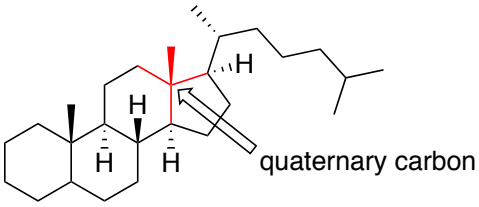
Secondary carbons are bonded to exactly two other carbon atoms. One of the secondary carbons in cholestane is shown below.



Tertiary carbons are bonded to three other carbons.



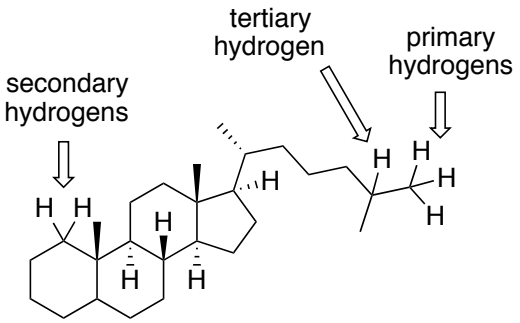
Finally, quaternary carbons are bonded to four other carbons.



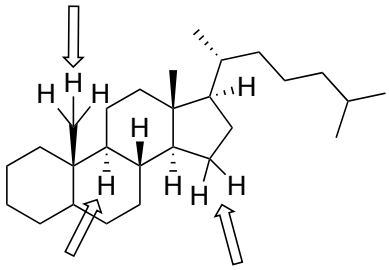
Problem 4. In the discussion above, one illustrative example of each type of carbon was shown. Now, classify each carbon in cholestane as primary, secondary, tertiary, or quaternary.

Hydrogens are only ever connected to a maximum of one carbon atom, so we cannot classify a hydrogen based on the number of carbons to which it is bonded. Instead, we classify a hydrogen based on the type of carbon to which it is bonded. For example, a primary hydrogen is bonded to a primary carbon.

In the diagram below, one set of primary, secondary, and tertiary hydrogens is shown. It is impossible to have a quaternary hydrogen atom because a quaternary carbon has four bonds to other carbons, leaving no open valences for hydrogen.

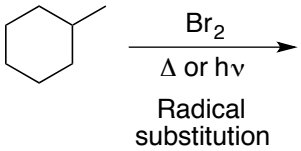


Problem 5. Label the indicated hydrogens in cholestane as primary, secondary, or tertiary.



These classifications are useful in describing groups within molecules, but as we'll see in the chapters to come, they are also important when discussing reactions. Different types of carbons and hydrogens have differing levels of reactivity in particular transformations.

Problem 6. In Chapter 6, we'll learn about radical substitution reactions. It turns out that tertiary hydrogens are the most reactive in this process, which ultimately replaces a tertiary hydrogen with a bromine atom. Using this information, show the radical substitution product of the following reaction.



Section 3: Nomenclature

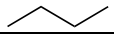
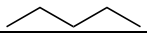
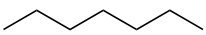
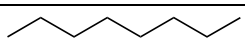
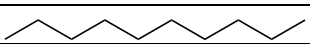
Linear alkanes

Nomenclature is the system of naming molecules that is utilized in organic chemistry. Some of the problems above have illustrated that there are at least several possible isomers for most molecular formulas. As formulas include more and more atoms, the number of possible isomers increases dramatically. In fact, there are millions of known organic

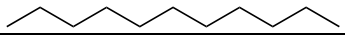
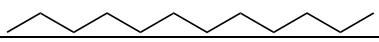
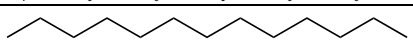
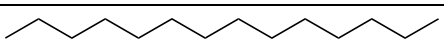
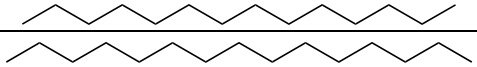
molecules, and there are millions more that we could draw on paper and make in the laboratory. Some have been named arbitrarily. We'll see examples of these so-called common names throughout the chapters to come. But, with such a vast number of molecules both known and as-of-yet unknown, it would be impossible to memorize names for all of them.

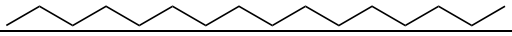
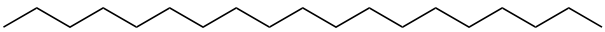
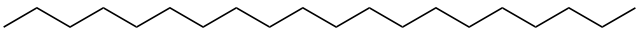
Consequently, the International Union of Pure and Applied Chemistry (IUPAC) devised a systematic method for naming molecules. Systematic or IUPAC names are derived using a handful of basic nomenclature rules that can be applied to any compound. In this chapter, we'll learn the rules for alkanes, and in subsequent chapters, we'll add rules as needed to name new functional groups. One of the beauties of the IUPAC system is that the guidelines we learn now will still apply to other types of functionalities. We'll simply see the addition of new rules to deal with new structural features.

The systematic nomenclature of alkanes begins with the homologous series. Homologues are molecules that are similar in nature but differ in their carbon count. The homologous series is a set of linear alkanes that grow in size one carbon at a time. The first ten alkanes in the homologous series are included in the following table. These are by far the most commonly used building blocks in naming other compounds in this book. Notice that all of the names end with "ane" just like alkane. This "ane" suffix therefore denotes the functional group present in the molecule. In the chapters to follow, when new functional groups are introduced, the suffix will change to reflect that.

Carbon count	Structure	Name
1	CH_4	methane
2		ethane
3		propane
4		butane
5		pentane
6		hexane
7		heptane
8		octane
9		nonane
10		decane

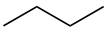
The homologous series doesn't end with decane though. It continues in increments of one carbon. Although they are less commonly used, the next ten alkanes in the homologous series are shown below.

Carbon count	Structure	Name
11		undecane
12		dodecane
13		tridecane
14		tetradecane
15		pentadecane

16		hexadecane
17		heptadecane
18		octadecane
19		nonadecane
20		icosane (also eicosane)

Of course, the homologous series continues further, but the subsequent names are used even less frequently. For the time being, the linear alkanes we've seen thus far will suffice.

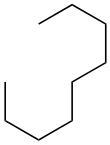
Sometimes the names of linear alkanes four carbons or larger are preceded by the prefix "*n*-". This prefix underscores the fact that the alkane is linear. It is not necessary to use this prefix, but it is sometimes used to draw special attention to an alkane's linear structure in contrast to that of a branched isomer.



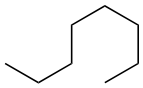
may be called
butane or *n*-butane

Problem 7. Identify each of the following linear alkanes.

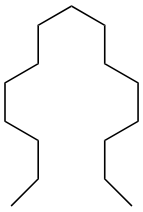
(a)



(b)

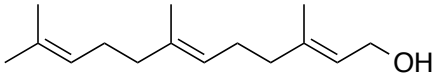


(c)



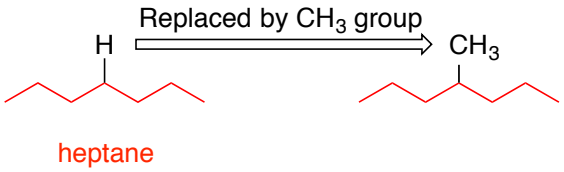
(d) Farnesol contains both alkenes and an alcohol. It is a precursor to many naturally occurring molecules, including cholesterol. As we'll learn in the chapters to come, more complex molecules, such as this one, are given IUPAC names by first finding the longest, continuous carbon chain and then modifying the name of the parent alkane so as to

communicate the presence of functional groups. Identify the longest, continuous carbon chain in farnesol and provide the name of the corresponding alkane.



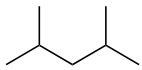
Branched alkanes

If we only needed to name linear alkanes, the homologous series would suffice. However, we also need to be able to apply names to branched alkanes. Branched alkanes can be thought of as containing a parent carbon chain, which is the longest, continuous linear alkane that can be found in the structure. The groups branching off of the parent chain are known as substituents. Substituents are groups that take the place of a hydrogen atom on the parent alkane. In the diagram below, a hydrogen of heptane is replaced by a CH_3 group, which is a substituent on the heptane parent.

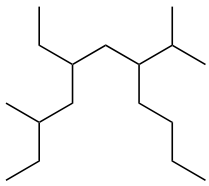


Problem 8. Identify the parent chain in each of the following molecules.

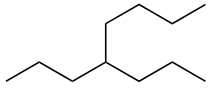
(a)



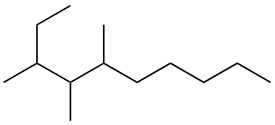
(b)



(c)



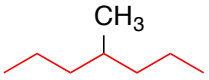
(d)



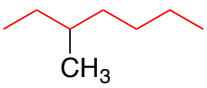
When substituents consist of only carbon, hydrogen, and single bonds, they are known as alkyl groups to denote their similarity to alkanes. The names of linear alkyl groups are derived from the names of the corresponding linear alkanes. This is done by removing the "ane" suffix and replacing it with "yl" to denote that the chain of carbons is now a substituent rather than a stand-alone molecule.

Carbon count	Structure	Name
1	Parent $-CH_3$	methyl
2	Parent $-CH_2CH_3$	ethyl
3	Parent $-CH_2CH_2CH_3$	propyl
4	Parent $-CH_2CH_2CH_2CH_3$	butyl
5	Parent $-(CH_2)_4CH_3$	pentyl
6	Parent $-(CH_2)_5CH_3$	hexyl
7	Parent $-(CH_2)_6CH_3$	heptyl
8	Parent $-(CH_2)_7CH_3$	octyl
9	Parent $-(CH_2)_8CH_3$	nonyl
10	Parent $-(CH_2)_9CH_3$	decyl

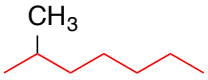
We can now identify the substituted heptane that we saw previously as a methylheptane. But, it turns out that this is insufficient to name the molecule completely. Each molecule must have a name that clearly differentiates it from its isomers. There is more than one location on the parent chain where a substituent can reside, so the name methylheptane does not differentiate the following three isomers.



a methylheptane

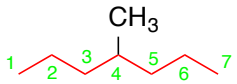


also a methylheptane

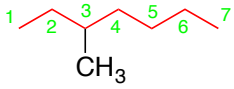


also a methylheptane

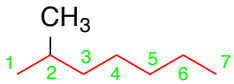
To distinguish these constitutional isomers, we must indicate where on the parent alkane the substituent lies. This is done by assigning numbers (or locants) to each carbon of the parent beginning at one terminus and ending at the other. The parent is numbered so as to give the substituent the lowest possible number, and that number is placed before the substituent name. A hyphen is used to separate the number from the letters that follow. Notice that each of the three isomers now receives a unique name.



4-methylheptane



3-methylheptane



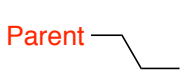
2-methylheptane

Problem 9. Identify the error in the following names, and then provide the correct name.

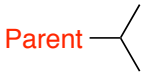
(a) 1-methylheptane

(b) 6-methylheptane

Substituents need not necessarily have linear carbon chains, and this has an impact on nomenclature. The propyl group is the first substituent that has an isomer. While a linear propyl group is connected to the parent through a terminal carbon, it is also possible to connect a three-carbon substituent to the parent through the central carbon. This isomer of the propyl group is called the isopropyl group.

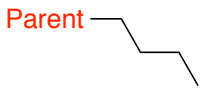


propyl group

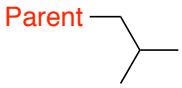


isopropyl group

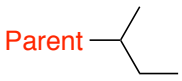
The butyl group has even more isomers. The four possibilities are shown below. The butyl (or *n*-butyl) group is linear. The isobutyl group branches into two methyls at the end of the substituent, much like isopropyl does. The remaining two isomers are named based on the classification of the carbon bonded to the parent. The *sec*-butyl group has a secondary carbon attached to the parent, while the *tert*-butyl group has a tertiary carbon at the point of connection to the parent.



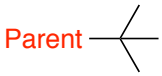
butyl group



isobutyl group

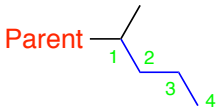


sec-butyl group



tert-butyl group

With an increasing number of carbons in the substituent, the number of isomers also increases. As a result, larger substituents that contain branching are named in a systematic fashion. The longest chain within the substituent is the parent alkyl group. It is numbered so that C1 is the carbon bonded to the parent alkane. The names of substituents on the alkyl group itself are placed before the parent alkyl group, along with a locant to indicate each group's placement. The entire substituent's name is placed inside parentheses to highlight the fact that it is a single group.

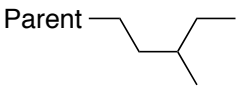


a (1-methylbutyl) group

Problem 10. Name the following substituents using the systematic approach described above.

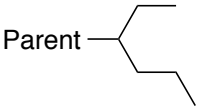
(a) the *sec*-butyl group

(b)



(c) the isobutyl group

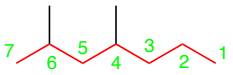
(d)



Branched alkanes with multiple substituents

An alkane could, of course, have multiple substituents. When this is the case, the parent is numbered so as to give the first substituent the lowest possible number.

Correct numbering:
first substituent at C2

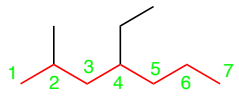


Incorrect numbering:
first substituent at C4

If the substituents are identical (as they are in the molecule above), a prefix (e.g., di, tri, tetra) is used to indicate the number of this type of substituent. This helps to keep the name as concise as possible. For instance, the above compound is a dimethylheptane. However, we also need locants for the two methyl groups. Numbers are separated by commas, while numbers are separated from letters by hyphens. So, the full name is 2,4-dimethylheptane.

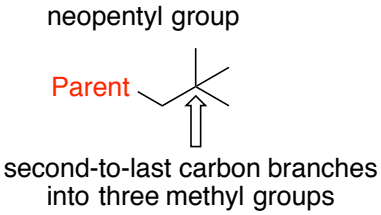
When the substituents are not identical, their names are alphabetized before the parent's name. Each substituent name is immediately preceded by its locant. For example, the following heptane bears both a methyl and an ethyl substituent. Numbering from the left gives the first substituent the number 2, which is a lower value than numbering from the

right gives. “Ethyl” appears before “methyl” in alphabetical order, and each locant is placed with its corresponding substituent.

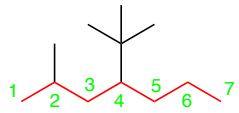


4-ethyl-2-methylheptane

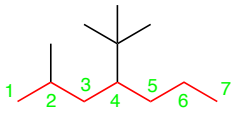
There is one subtlety for alphabetizing substituent names. Substituent names may include prefixes that denote structure, such as iso, *sec*, or *tert*. They may also include prefixes that indicate the number of a particular substituent present in the molecule (e.g., di, tri, tetra). The *only* prefixes that are counted in alphabetization are cyclo, iso, and neo. We haven’t used “cyclo” yet, but we will soon. We’ve seen “iso” in the context of isopropyl and isobutyl groups. “Neo” is used when the penultimate carbon of the substituent branches into three methyl groups.



Any prefix other than cyclo, iso, or neo is ignored when alphabetizing substituents. The following molecule provides an illustrative example. This heptane bears a methyl and *tert*-butyl group. Since *tert* is not among the prefixes that count for alphabetization, *tert*-butyl comes before methyl.



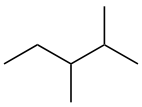
4-*tert*-butyl-2-methylheptane
(**Correct**)



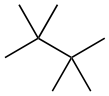
2-methyl-4-*tert*-butylheptane
(**Incorrect**)

Problem 11. Provide IUPAC names for the following branched alkanes.

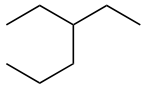
(a)



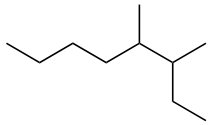
(b)



(c)



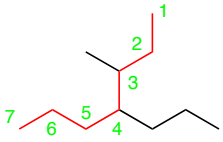
(d)



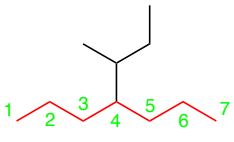
Tiebreaker rules

When naming molecules, you will sometimes encounter situations in which more than one option seems viable. In such cases, you'll need a tiebreaker to select the correct choice. Let's consider some examples that illustrate these conundrums and the rules that help us to resolve them.

Occasionally, you may find that there is more than one parent carbon chain of the same length. When this occurs, the correct parent is the one with more substituents. The rationale is simple; if there are more substituents, they will be smaller and therefore easier to name. Consider the following example. There are two seven-carbon chains within this molecule. The one highlighted in the left-hand structure has two substituents, while the one highlighted in the right-hand structure has only one substituent. The correct seven-carbon parent has two substituents, making the name of this molecule 3-methyl-4-propylheptane.

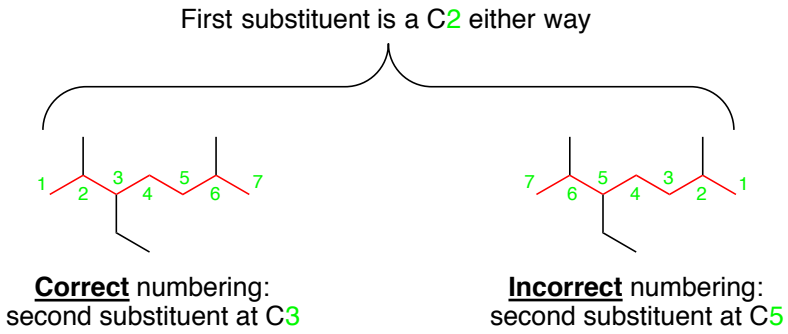


Correct parent:
more substituents

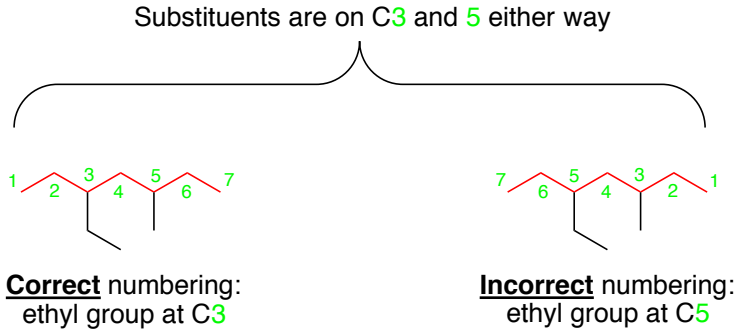


Incorrect parent:
fewer substituents

Sometimes the first substituent will receive the same number regardless of the direction of numbering. For instance, in the following molecule the first substituent will be located at C2 regardless of the direction of numbering. Since the two numbering schemes appear to be tied from this perspective, we resort to a tiebreaker in which the correct scheme gives the second substituent the lower number. This allows us to choose the accepted numbering of the parent, and we can now conclude that the compound is 3-ethyl-2,6-dimethylheptane. Remember that "di" is not counted in alphabetization, so ethyl appears before dimethyl in the name.

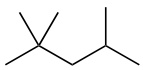


Sometimes you may find that the substituents will receive the same locants regardless of the direction of numbering. In this instance, the tiebreaker of last resort is to give the alphabetically first substituent the lowest number possible. In the following example, the locants will be 3 and 5 regardless of how we number the parent. Since ethyl appears before methyl in alphabetical order, we choose the numbering scheme that gives it the lower number to break the tie. Doing so makes the name for this compound 3-ethyl-5-methylheptane.

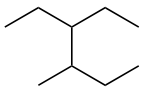


Problem 12. Name the following alkanes.

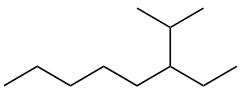
(a)



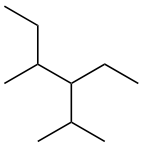
(b)



(c)

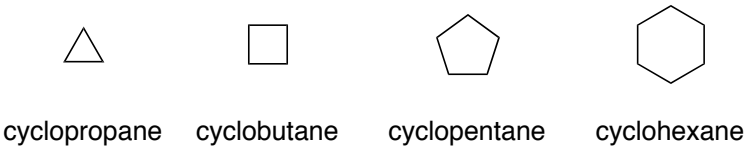


(d)

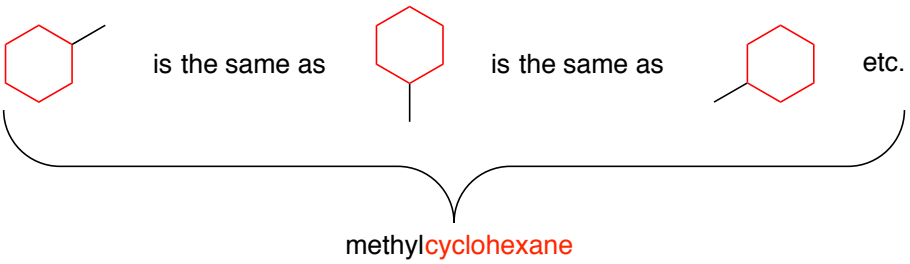


Cycloalkanes

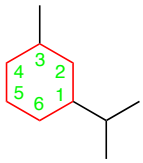
Simple, unsubstituted cycloalkanes are named by adding the prefix "cyclo" to the corresponding linear alkane. For instance, rings of three, four, five, and six carbons are known as cyclopropane, cyclobutane, cyclopentane, and cyclohexane, respectively.



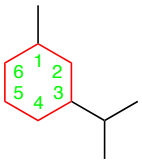
When a ring bears a substituent, the ring will be the parent provided that no single substituent contains a chain with more carbons than the ring. When only one substituent is present on the ring, no locant is needed because all of the ring atoms are equivalent until the first substituent is placed. This is illustrated by drawing methylcyclohexane in a variety of different ways below. Regardless of where the methyl group is placed, the same molecule is produced.



However, when there are multiple substituents on the ring, locants must be used to communicate their relative position. One of the substituents will appear at C1, and the ring is numbered so as to give the lowest possible number to the next substituent. In the following molecule, the cyclohexane ring bears an isopropyl and a methyl group. There are two ways to number the ring so that these will appear at C1 and C3. Our last resort tiebreaker is used to decide between the two: Recall that, when the same set of numbers are obtained in two ways, the numbering scheme that gives the lowest locant to the alphabetically first substituent is the correct one. "Iso" is one of the prefixes that counts in alphabetization. Therefore, the ring is numbered so as to place it at C1 and the methyl group at C3, making the complete name 1-isopropyl-3-methylcyclohexane.



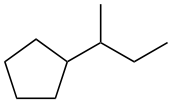
Correct numbering:
isopropyl group at C1



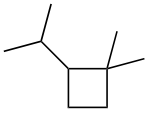
Incorrect numbering:
isopropyl group at C3

Problem 13. Provide systematic names for the following cycloalkanes.

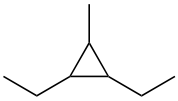
(a)



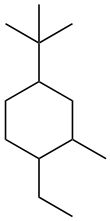
(b)



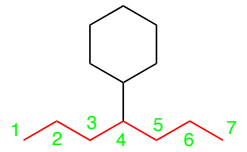
(c)



(d)



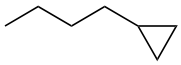
If the ring is smaller than the longest chain in a group pendent to it, then the ring will be treated as a substituent on a linear alkane. In such cases, the ring is a cycloalkyl group. In the following compound, the ring contains six carbons, but a seven-carbon chain is bonded to it. The longer seven-carbon chain is therefore the parent, and the ring is a cyclohexyl substituent. Since there are differing locations on the heptane parent where the cyclohexyl group could be placed, a number is needed to denote its position. This is therefore 4-cyclohexylheptane.



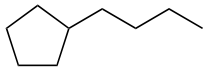
4-cyclohexylheptane

Problem 14. Name the following alkanes.

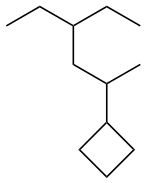
(a)



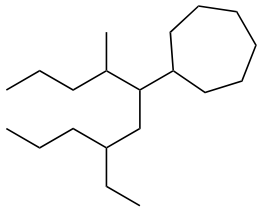
(b)



(c)

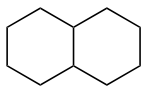


(d)



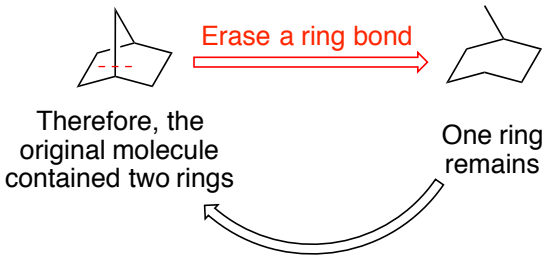
Bicyclic alkanes

Bicyclic alkanes contain two fused rings. In some instances, the fusion is readily apparent, as in the following molecule, which has two six-membered rings that happen to share a bond.

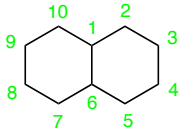


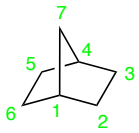
In other instances, the number of rings present is a bit less clear. Consider the following molecule, which looks a bit unusual relative to the structures we've encountered thus far. Its unique appearance may obscure the actual number of rings present within the molecule.

Fortunately, there is a straightforward method to ascertain how many rings are present. Simply imagine erasing one ring bond. You can pick any bond to erase as long as it is part of a ring. After erasing this bond, it is easy to see that a single ring remains. This means that, before we erased a ring bond, there was an additional ring. Hence, the molecule is bicyclic.

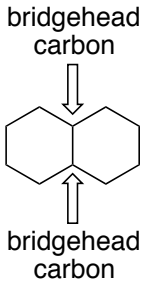


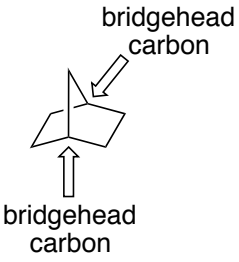
To name bicyclic alkanes, we add the prefix "bicyclo" to the name of the linear alkane with the same number of carbons. The two bicyclic molecules we've considered contain ten and seven carbons, so they are examples of a bicyclodecane and a bicycloheptane, respectively.





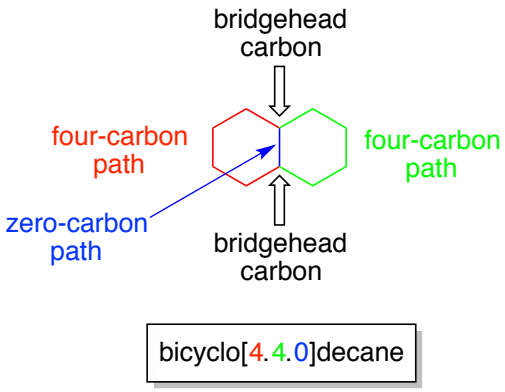
The two carbons that are shared by both rings are known as the bridgehead positions.



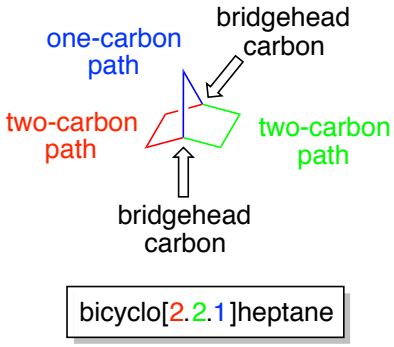


Between the "bicyclo" prefix and the linear alkane name, we insert three numbers inside the brackets and separated by periods. These numbers indicate the number of carbons on the paths between the bridgehead positions. The numbers are listed in order of decreasing magnitude. In the ten-carbon bicycle, you can get from one bridgehead carbon to the other

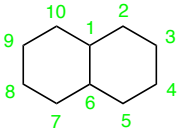
through one of two four-carbon paths or a zero-carbon path. Therefore, its complete name is bicyclo[4.4.0]decane.

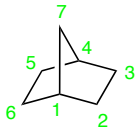


In the seven-carbon bicycle, the bridgehead carbons are joined by two two-carbon paths and a one-carbon path, making its complete name bicyclo[2.2.1]heptane.

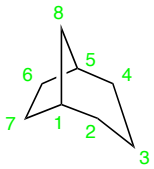


When substituents are present, we need to be able to number the bicyclic molecule in order to provide locants for the substituents. The numbering begins at either of the two bridgehead carbons and proceeds along the longest bridge first. Then, the numbering continues along the second-longest bridge, and finally the shortest bridge is numbered. In the two examples that we've considered thus far, there are two bridges of identical length followed by a shorter bridge. Numbering starts at a bridgehead carbon and moves along either of the long bridges first. After reaching the second bridgehead carbon, the numbering continues along the second long bridge. Finally, if any carbons remain, the short bridge is numbered.

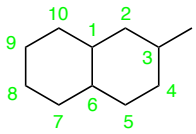




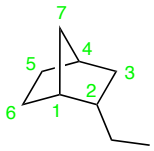
In the following bicyclo[3.2.1]octane, all of the bridges are of differing lengths. Here, the numbering starts at a bridgehead position, proceeds along the longest bridge, continues on the second-longest bridge, and then concludes on the short bridge.



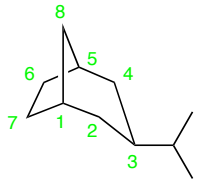
These numbers are used exactly as you would expect when naming a substituted bicyclic alkane.



3-methylbicyclo[4.4.0]decane



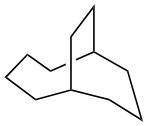
2-ethylbicyclo[2.2.1]heptane



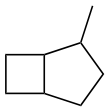
3-isopropylbicyclo[3.2.1]octane

Problem 15. Name the following bicyclic alkanes.

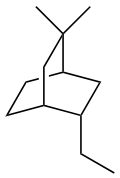
(a)



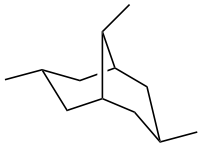
(b)



(c)



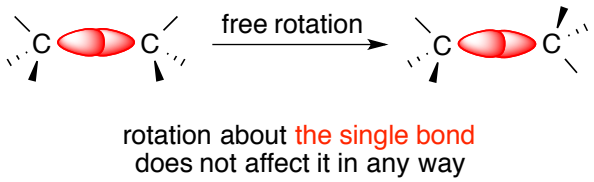
(d)



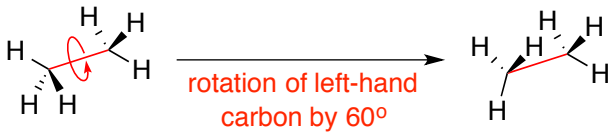
Section 4: Conformational analysis of acyclic alkanes

Newman projections

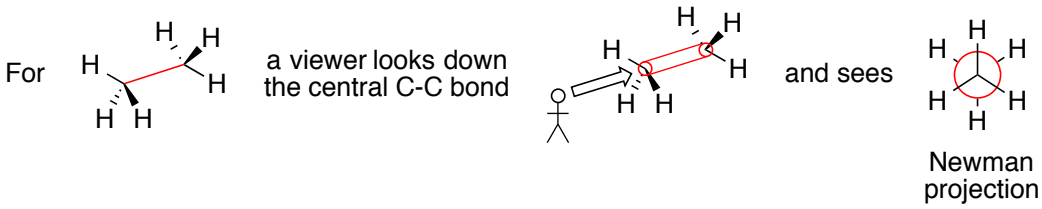
Although we draw molecules in fixed shapes on the page, they are in reality quite dynamic. Single bonds are cylindrically symmetrical, so there is free rotation about any single bond in an acyclic alkane.



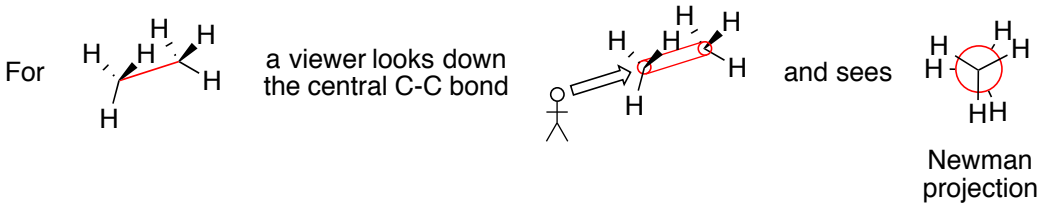
Different shapes that are derived by rotation around single bonds are known as conformations. Structures that differ in conformation, or shape, can be called conformers. Ethane is the smallest alkane in which we observe this phenomenon. Rotation about the central carbon-carbon single bond places the hydrogens in different spatial orientations relative to each other.



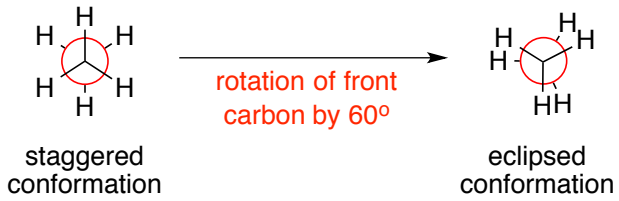
There are also other options for viewing the molecule, which may make the change in shape easier to see. The most popular of these perspective drawings is known as a Newman projection. A Newman projection is derived by looking down the "barrel" of a single bond of interest, which is represented as a circle. There is a carbon at the front of this barrel and at the back. The bonds to the front carbon pass all the way into the center of the circle, while those in the back (which are slightly obscured from our view) stop at the edge of the circle.



We can similarly derive a Newman projection for the other conformation of ethane.



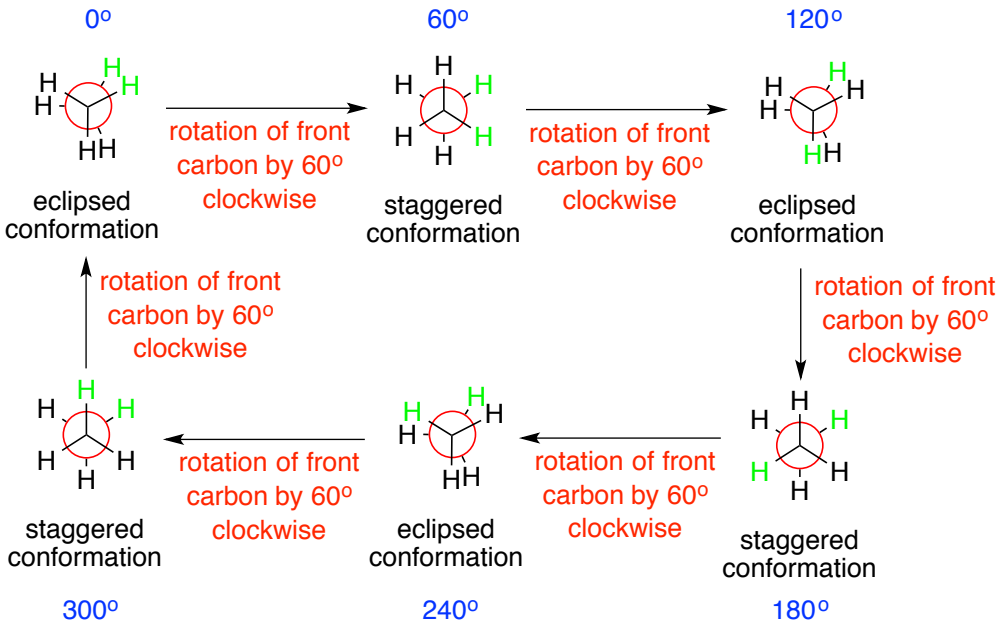
A comparison of the two conformers very clearly shows a difference in how the hydrogens are oriented relative to each other. In the first conformation, the hydrogen atoms are nicely distributed in space. They could be said to be staggered, so this is known as the staggered conformation. In the second conformation, the hydrogens in the front eclipse those in the back, so this is known as the eclipsed conformation. A 60˚ rotation of one carbon relative to the other converts a staggered to an eclipsed conformer and vice versa.



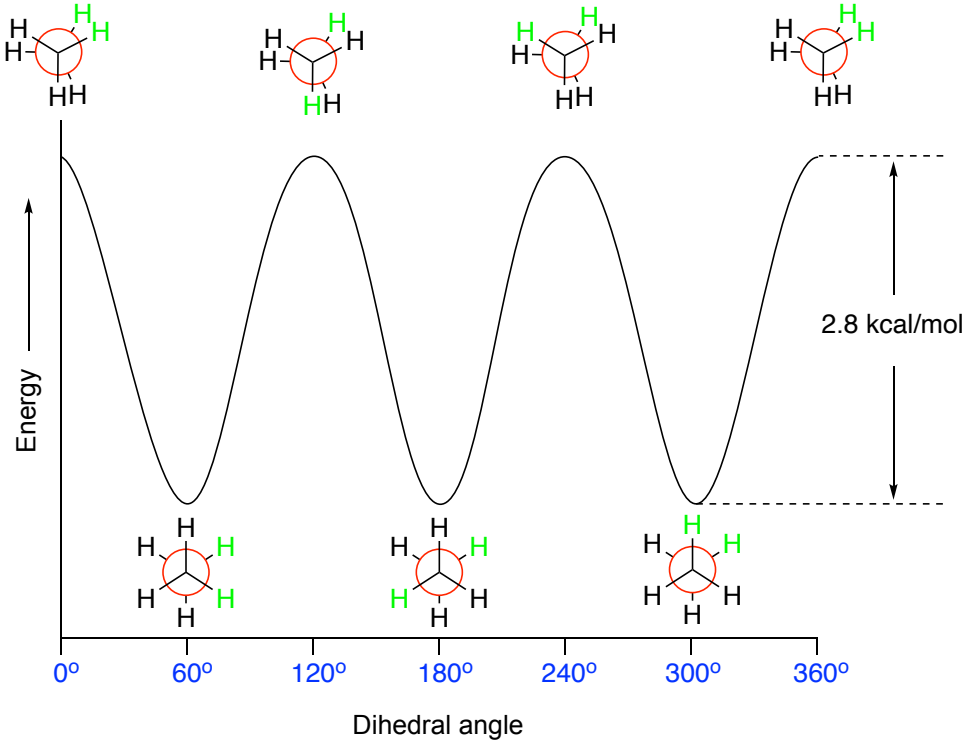
Conformational analysis of ethane

Staggered and eclipsed forms are the extremes of conformation. There are, of course, a multitude of conformations between staggered and eclipsed, but it is most convenient to limit our discussion to these two conformers. Let's rotate ethane through a full 360˚. By examining all of its extreme conformations, we will conduct a "conformational analysis" of the molecule. As we do so, it will help to refer to the dihedral angle between hydrogen atoms. While a bond angle is defined by three contiguous atoms, a dihedral angle is the angle between the termini of a sequence of four contiguous atoms.

We can begin with any conformation of ethane. In the diagram below, an eclipsed conformation was designated as the starting point. There is a 0˚ dihedral angle between the two highlighted hydrogens. One of the carbons (in this case, the front carbon) is then incrementally rotated by 60˚ at a time. Notice that every 60˚ rotation converts an eclipsed to a staggered conformer or vice versa. In this simple molecule, all staggered conformations are identical, as are all eclipsed conformations.



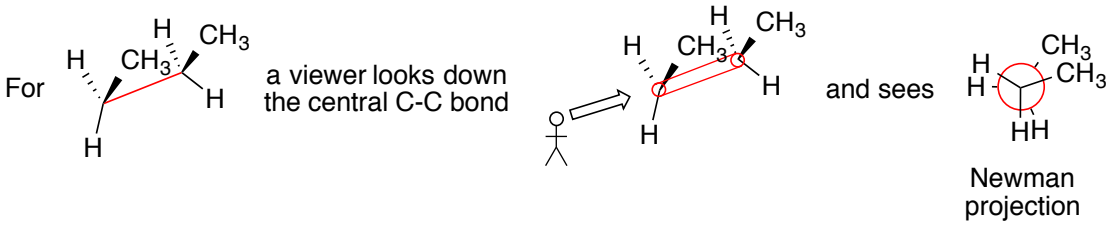
In the eclipsed conformation, the C-H σ bonding electrons are closer to each other than in the staggered conformation. There is repulsion between these electron pairs that is referred to as torsional strain, and it elevates the energy of the eclipsed conformer relative to that of its staggered counterpart. The eclipsed conformer is about 2.8 kcal/mole higher in energy. All of this information can be depicted in an energy diagram (also known as an energy profile) that shows the energy of the molecule as a function of the dihedral angle.



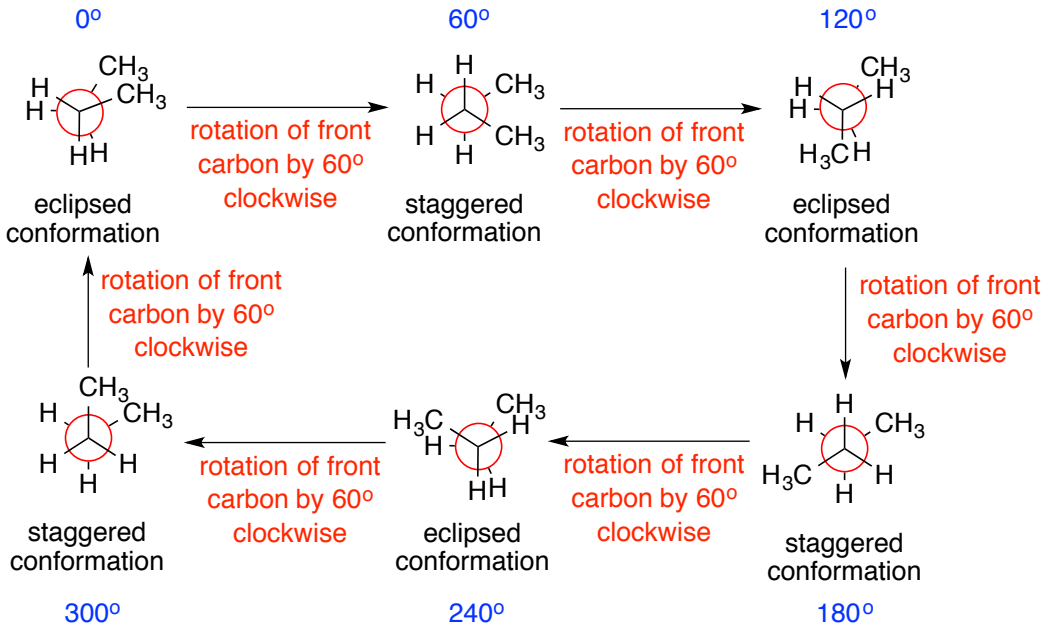
Problem 16. Beginning with an eclipsed conformation, draw Newman projections for propane through 360˚ of rotation in 60˚ increments. Then, show the relative energies in an energy profile.

Conformational analysis of butane

Conformational analysis becomes more nuanced with increasingly complex molecules. For instance, if we look down the central C-C bond of butane, we'll observe more unique conformations because of the methyl groups on C2 and C3.

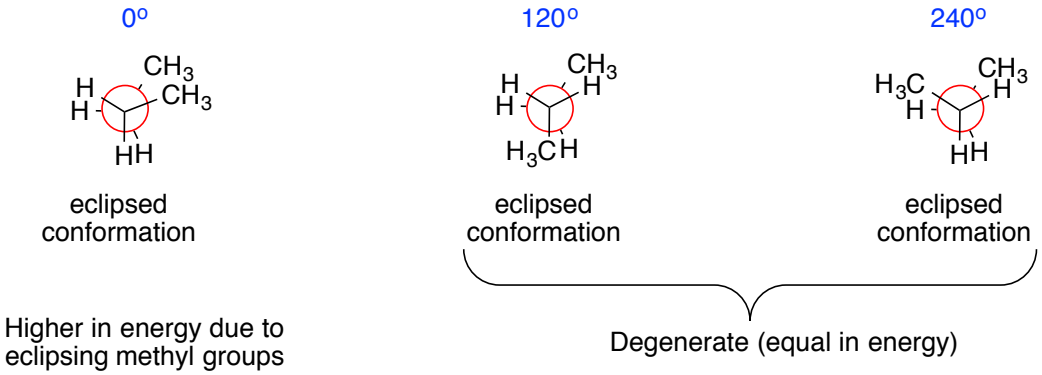


Once again, we can begin with any conformer. In the diagram below, the starting point is the conformation with eclipsing methyl groups, which have a 0˚ dihedral angle between them. Cycling through 60˚ clockwise rotations of the front carbon, the same general pattern emerges in that eclipsed and staggered conformations alternate. What differs in this example is that the eclipsed conformations are not all identical. Similarly, there are unique staggered conformations as well.

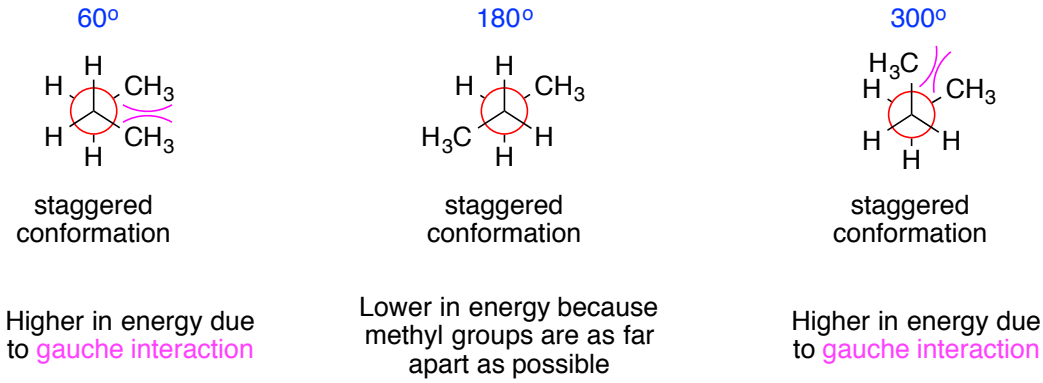


Let's compare the eclipsed conformations first. One eclipsed conformer (0˚) has the large methyl groups eclipsing one another. As these groups are brought close together, there is repulsion between them due to their size. This is known as steric strain, and it raises the

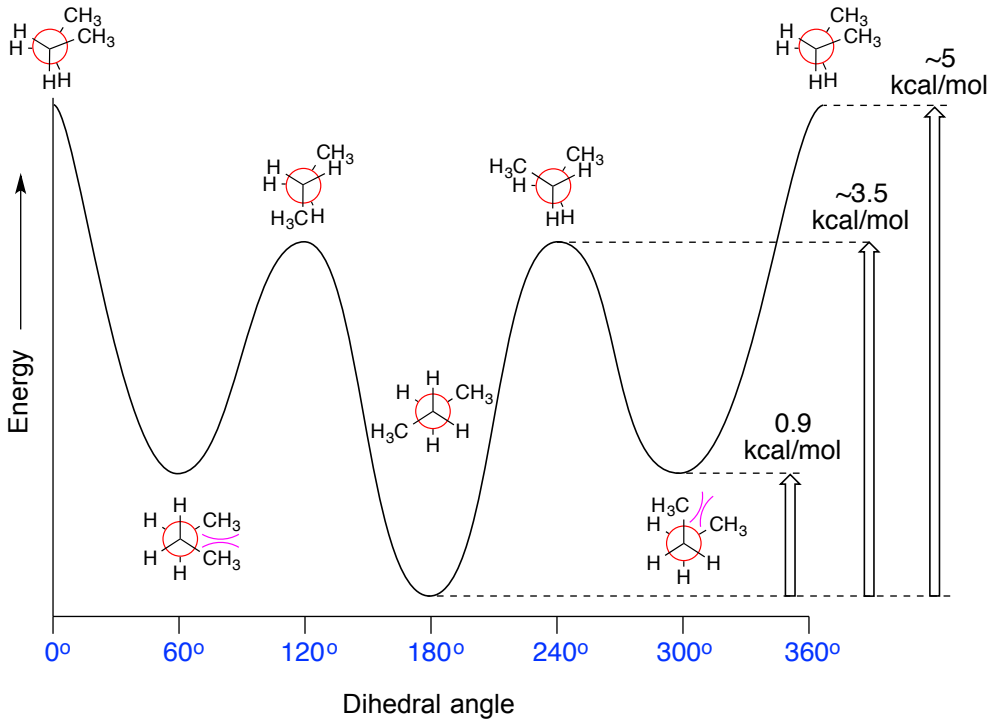
energy of this conformation above that of the other eclipsed conformers. The remaining eclipsed conformations (120° and 240°) are equal in energy, or degenerate. They suffer from torsional strain, and the repulsion between their eclipsing methyl groups and hydrogens will be slightly larger than that of the eclipsing hydrogens in ethane. However, they don't experience the more significant steric strain of eclipsing methyl groups found in the 0° conformer.



Now, let's examine the staggered conformations. Two of these (60° and 300°) experience steric strain because the methyl groups are relatively close to one another. When alkyl groups are adjacent to one another in a staggered conformation, the steric repulsion between them is known as a gauche interaction, and it raises the energy of these conformers. On the other hand, the remaining staggered conformation (180°) has the methyl groups as far apart as they can possibly be. They are on opposite sides of the central C-C bond, and are therefore said to be anti. This conformer therefore has no torsional nor steric strain.



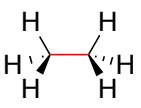
This information can be compiled into a single energy diagram. All of the staggered conformations are lower in energy than the eclipsed. However, the staggered conformer with anti methyl groups is the absolute lowest in energy, and the conformer with eclipsing methyl groups is the overall highest in energy. A gauche conformer is 0.9 kcal/mole higher in energy than its anti counterpart. An eclipsed conformer is raised by around 3.5 kcal/mole relative to anti, and eclipsing methyl groups elevate the energy by about 5 kcal/mole above the anti conformer.



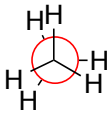
Problem 17. Consider pentane. Looking down the C2-C3 bond, draw the conformation in which the alkyl groups are eclipsing. Then, rotate about the C2-C3 bond in 60˚ increments, showing all staggered and eclipsed conformations. Finally, show the relative energies of the conformers in an energy profile.

Sawhorse projections

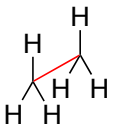
We've used Newman projections throughout our discussion of conformational analysis, but there are other perspective drawings that can helpful in visualizing molecules. While a skeletal structure is a view of a molecule from the side and a Newman projection is a view of the molecule down a particular bond, the sawhorse projection is a view of a molecule from an oblique angle.



Skeletal structure: view from the side

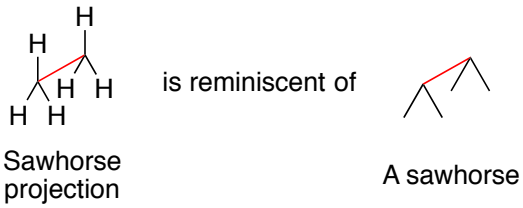


Newman projection: view down a C-C bond

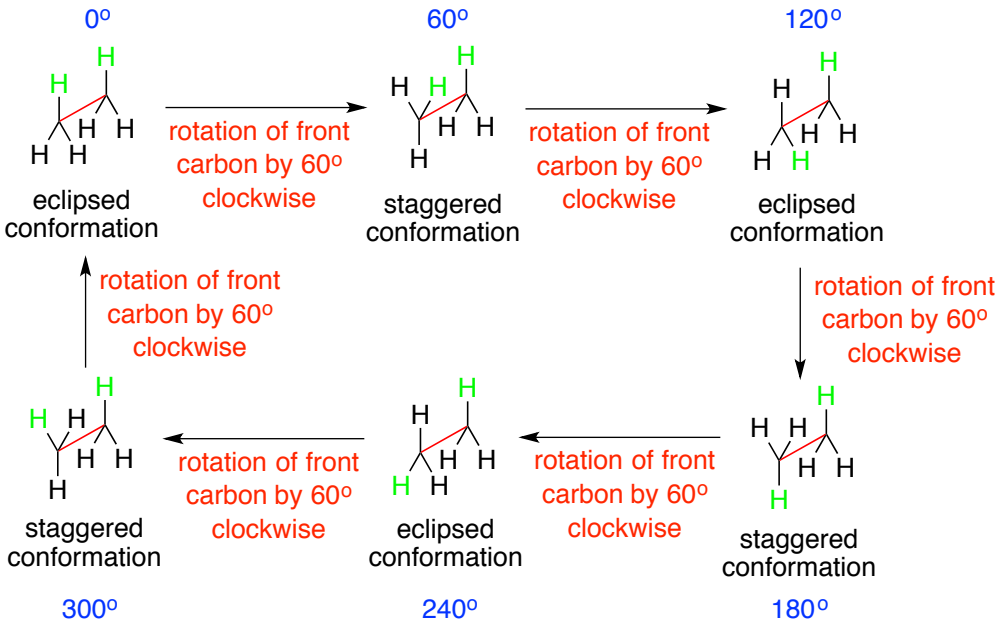


Sawhorse projection: view from an oblique angle

The sawhorse projection derives its name from the fact that the conformer shown above looks like a sawhorse if we ignore the two hydrogens pointing directly upward.



The sawhorse projection can be used in conformational analysis, much like the Newman projection. Ethane's staggered and eclipsed conformers are shown below in sawhorse projections. Two hydrogens have been highlighted to emphasize the 360° rotation taking place in 60° increments.



Problem 18. Starting with the conformer that has eclipsing ethyl groups, draw the conformations of hexane that result from successive 60° rotations about the C3-C4 bond. Draw an energy profile showing the relative energies of these conformations.

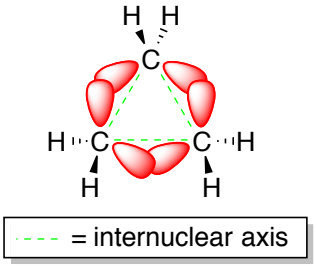
Section 5: Conformational analysis of cyclic alkanes

Although we often draw rings as though they exist in a single plane, those drawings can be misleading. Cyclic alkanes are also capable of adopting various conformations. These shapes can help to alleviate a type of strain that we didn't encounter with acyclic alkanes: bond-angle strain. In the diagram below, cyclopropane, cyclobutane, cyclopentane, and cyclohexane are drawn as planar, and their bond angles are given for this specific conformation. The angles inside a regular polygon can be derived using the formula: $180° - \frac{360°}{n}$, where n is the number of sides.

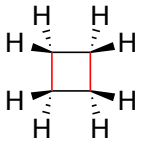
Bond angles if rings were planar: 60° 90° 108° 120°

Notice that most of these bond angles represent a significant deviation from the ideal bond angle of 109.5° for an sp^3 carbon. This deviation would result in bond-angle strain, and in some instances, it can be reduced or eliminated if the ring exists in a non-planar conformation.

Cyclopropane does not have this option though because three points—or in the case of a molecule, three atoms—define a plane. Its three carbon atoms must all reside in the same plane, so it experiences a significant amount of bond-angle strain. That strain is ameliorated to some extent by an unusual type of bonding that takes place within this particular ring. In Chapter 1, we learned that σ bonds have orbital overlap on the internuclear axis, but due to the extreme bond-angle deformation in cyclopropane, the orbital overlap is actually slightly outside the internuclear axis. This widens the bond angle a bit and alleviates some of the strain. The carbon-carbon bonds in cyclopropane are sometimes referred to as banana bonds due to the curvature of the orbital overlap.

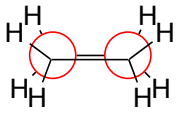


Cyclobutane is the smallest cycloalkane capable of bending out of planarity, and it does do so. Cyclobutane adopts a "puckered" conformation, which actually reduces the bond angle slightly from 90° (for a planar conformer) to 88°. However, the small accompanying increase in bond-angle strain is offset by a sizeable reduction in torsional strain. If cyclobutane were planar, all of its hydrogens would necessarily eclipse one another.

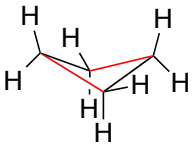


Planar conformation

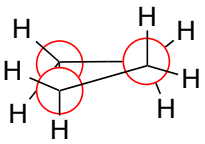
when viewed down two C-C bonds:



However, in the puckered conformation, these eclipsing interactions are minimized, which reduces the overall energy of the molecule.

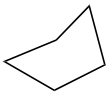


when viewed down two C-C bonds:

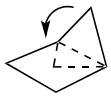


Puckered conformation

Cyclopentane also bends out of planarity, adopting what is known as the envelope conformation to minimize its torsional and bond-angle strain.



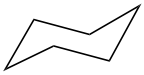
is reminiscent of



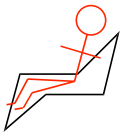
an envelope that is about to be sealed

Cyclohexane and the chair conformation

Cyclohexane rings are capable of adopting a conformation that is essentially strain free. As a result, cyclohexane rings are extremely common structural motifs that occur frequently in nature. The low-energy conformation of cyclohexane is known as the chair conformation.

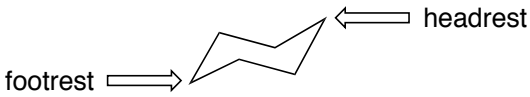


is reminiscent of

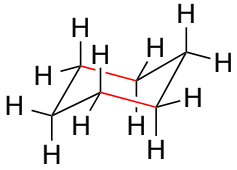


a chair

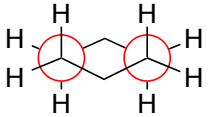
This analogy allows us to designate the extreme right- and left-hand carbons as the headrest and footrest, respectively.



The chair conformation is low in energy because it exhibits nearly ideal bond angles for sp^3 carbons and has completely staggered hydrogens.

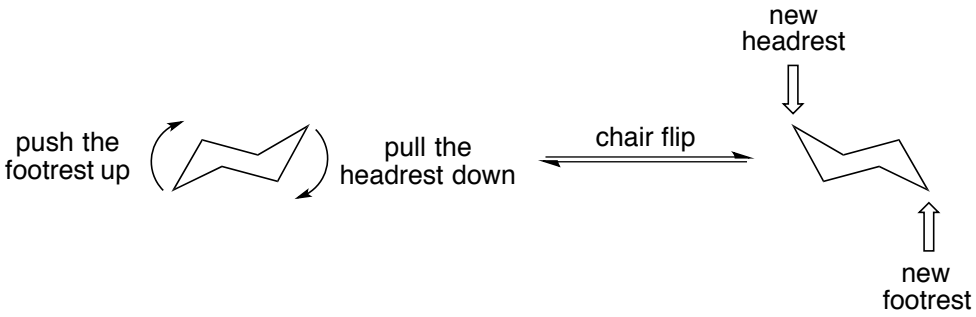


when viewed down two C-C bonds:



entirely staggered

A single cyclohexane ring can access two chair conformations. The second chair conformation is accessed by pulling the headrest down and pushing the footrest up. It is very helpful to see this in a model. Use your molecular model kit to build a chair conformation. Then, holding onto the headrest and footrest only, twist these carbons as indicated. You'll find that a second chair conformation is produced as a result.

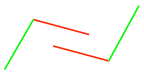


Because it is so prevalent, it is important to be able to draw cyclohexane in its chair conformation with the bonds emanating from each carbon in their proper positions. There are a few short steps that make this process straightforward. They begin with construction of the ring itself. The ring is composed of three sets of parallel lines. Begin by drawing one set of parallel lines that are angled slightly and offset relative to one another.

Step 1: Draw a pair of parallel lines that are slightly angled and offset

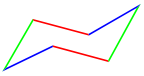
Next, add a second set of parallel lines that are perpendicular to the first set.

Step 2: Add a second set of parallel lines that are perpendicular to the first set



Finally, close the ring with a third and final set of parallel lines.

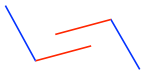
Step 3: Close the ring with a third set of parallel lines



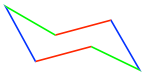
To draw the other chair conformation, simply begin in step 1 with a pair of parallel lines that are offset and angled slightly in the *opposite* directions.

Step 1: Draw a pair of parallel lines that are slightly angled and offset

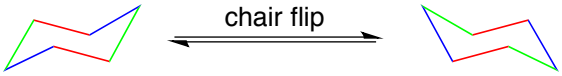
Step 2: Add a second set of parallel lines that are perpendicular to the first set



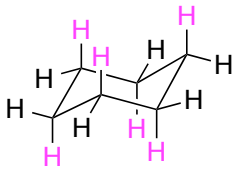
Step 3: Close the ring with a third set of parallel lines



These two chair conformations are in equilibrium with one another. As with any other conformational change, they interconvert through rotation about single bonds.

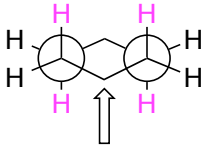


Cyclohexane's hydrogens reside on two distinct types of bonds. There is a set of six bonds that point directly up or directly down. These bonds are perpendicular to a plane passing through the ring laterally, and they are called axial bonds.



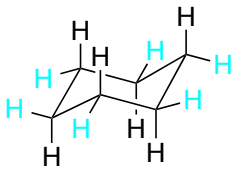
Axial hydrogens

when viewed down two C-C bonds:



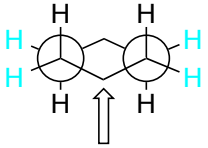
Note that, in the Newman projection, the axial hydrogens on the methylenes joining the two barrels are not drawn

There is another set of six bonds that are angled slightly upward or downward but that reside more-or-less on the ring's equator. These are known as equatorial bonds.



Equatorial hydrogens

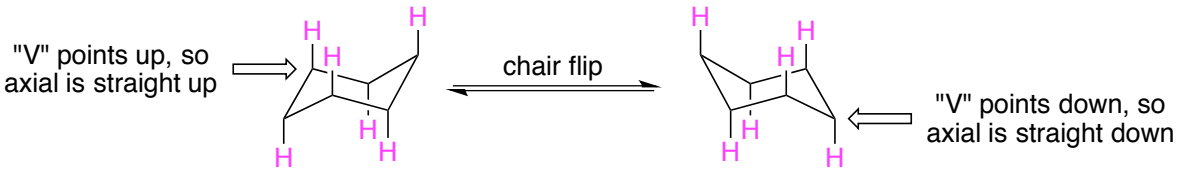
when viewed down two C-C bonds:



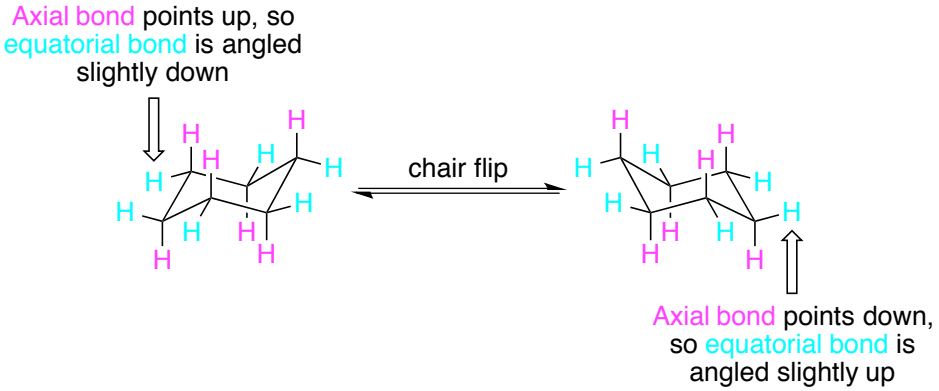
Note that, in the Newman projection, the equatorial hydrogens on the methylenes joining the two barrels are not drawn

When you are drawing a chair conformation, there are some simple guidelines that will enable you to accurately fill in the axial and equatorial bonds. Each vertex of the ring makes

a sort of "V". The point of the V faces either upward or downward. If the point of the V faces upward, the axial bond at that center is straight up. If the point of the V faces downward, the axial bond at that center is straight down. In the diagram below, only the axial bonds are shown, and two sites are labeled as examples.



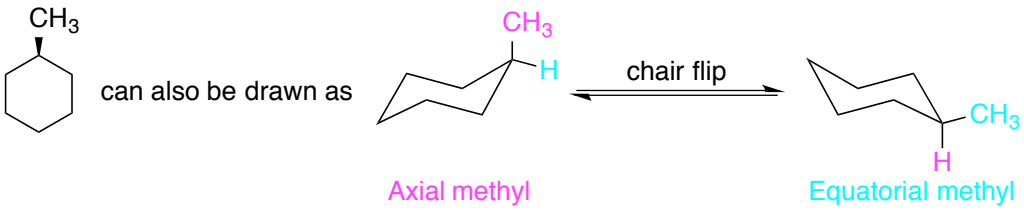
Then, at each center the equatorial bond is angled a little bit in the direction *opposite* the axial bond.



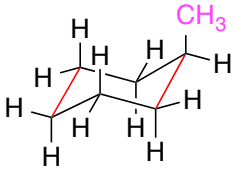
With cyclohexane itself, the two chair conformations are equal in energy.

Monosubstituted cyclohexane derivatives

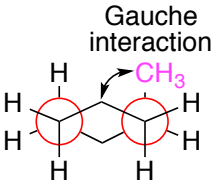
When a substituent is placed on the ring, the two chair conformations will no longer be equal in energy. Consider methylcyclohexane. When it is drawn in a chair conformation, the methyl group may be either axial or equatorial. In fact, we find that when the chair flip occurs the axial methyl group is converted to equatorial and vice versa.



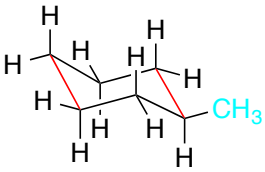
These two conformations are not equal in energy. When the methyl group is in the axial position, it experiences gauche interactions with methylene groups of the ring, one of which is shown in the Newman projection below.



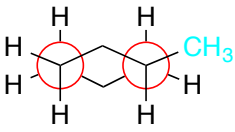
when viewed down two C-C bonds:



On the other hand, when the methyl group is equatorial, it experiences no such gauche interactions. The conformation with the equatorial methyl group is therefore favored.



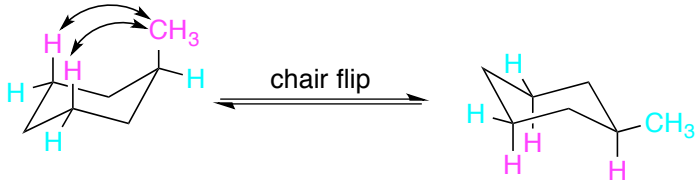
when viewed down two C-C bonds:



No gauche interactions

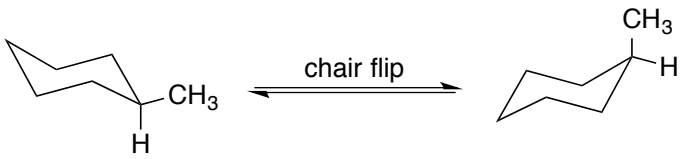
Another way of illustrating the same factor that destabilizes the axial conformer is shown below. When the methyl group is axial, it experiences a steric clash with the other axial groups on the same side of the ring. These are known as 1,3-diaxial interactions because, if the methyl group is said to be on C1, the groups with which it clashes are found three carbons away. This steric strain is not present in the equatorial conformer.

1,3-diaxial interactions



The energetic cost of the two 1,3-diaxial interactions is termed an A value. The A value for a methyl group is 1.8 kcal/mole. This is twice the energetic cost of a gauche interaction, which we saw to be 0.9 kcal/mole when we considered the conformational analysis of butane. The A value tells us that the axial conformer of methylcyclohexane is 1.8 kcal/mole higher in energy than its equatorial counterpart.

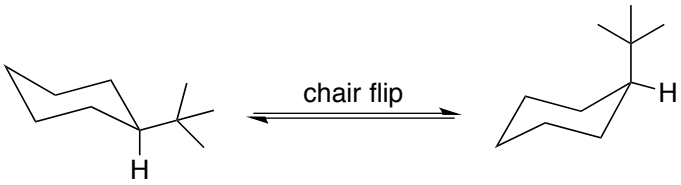
Problem 19. The change in Gibbs free energy for a process is related to the equilibrium constant through the following equation: $\Delta G^\circ = -RT \ln K_{eq}$. Using the methyl group's A value, predict the K_{eq} for the following conformational change at room temperature (298 K). Note that R = 1.987 x 10^{-3} kcal/K mol.



A values for a few different substituents are provided in the table below. As the steric demand of a group increases so does the energetic cost associated with placing it axially.

Substituent	A value (kcal/mole)
$-CH_3$	1.8
$-CH_2CH_3$	1.8
$-CH(CH_3)_2$	2.1
$-C(CH_3)_3$	4.9
-Ph	2.7
-Cl, -Br, -I	~0.5
-OH	0.94
-OMe	0.75

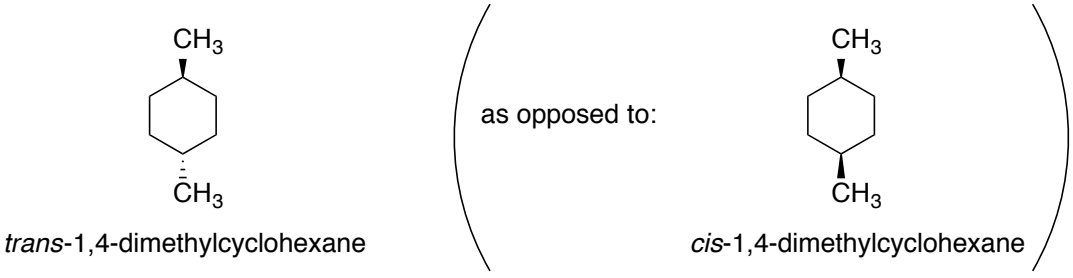
Problem 20. Using the table of A values above, predict the K_{eq} for the following conformational change at room temperature. Compare the preference for the equatorial conformer in this problem to that obtained for methylcyclohexane in Problem 19.



Disubstituted cyclohexane derivatives

We've established that a lower energy conformer results from substituents placed equatorially. However, it is important to recognize that it may not always be possible for all substituents to reside on equatorial bonds. Let's compare a few examples to illustrate this point.

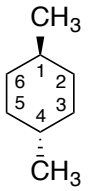
For our first example, we'll use *trans*-1,4-dimethylcyclohexane. A brief note on the nomenclature is in order. When two groups are on the same side of a ring, the arrangement is termed *cis*. However, when they are on opposite sides of the ring, as in this example, the configuration is called *trans*.



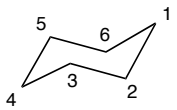
trans-1,4-dimethylcyclohexane

cis-1,4-dimethylcyclohexane

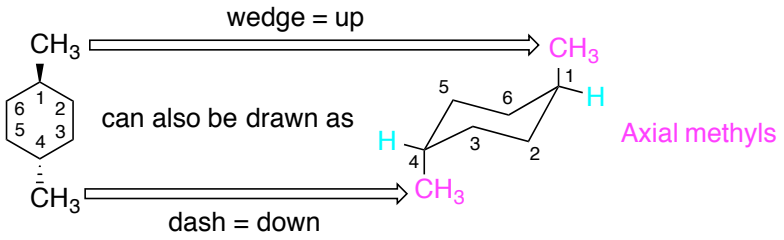
Successfully converting the skeletal structure to a chair conformation is critical for proper conformational analysis. It is helpful to number the skeletal structure. This numbering need not relate to IUPAC nomenclature. Its sole purpose is for tracking the carbons.



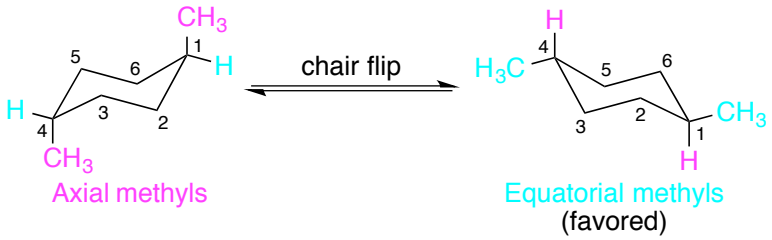
You can apply the label "1" to any of the carbons in the first chair conformation. It is typically easiest to locate and follow the headrest and the footrest, so either of these is a good choice for C1. Then, the other ring carbons must be labeled in the clockwise direction because we numbered the skeletal structure in the clockwise direction. *Once you set that initial labeling, it must be applied consistently throughout.*



Having labeled the first chair conformation, we know that methyl groups must be placed on C1 and C4. Furthermore, in the skeletal structure, the C1 methyl group is pointing up out of the page, so the methyl group must be placed on the more upward bond in the chair conformation, which happens to be the axial bond. The C4 methyl group points down behind the page in the skeletal structure, so we place it on the more downward bond at C4 in the chair conformation, which happens to be axial as well.

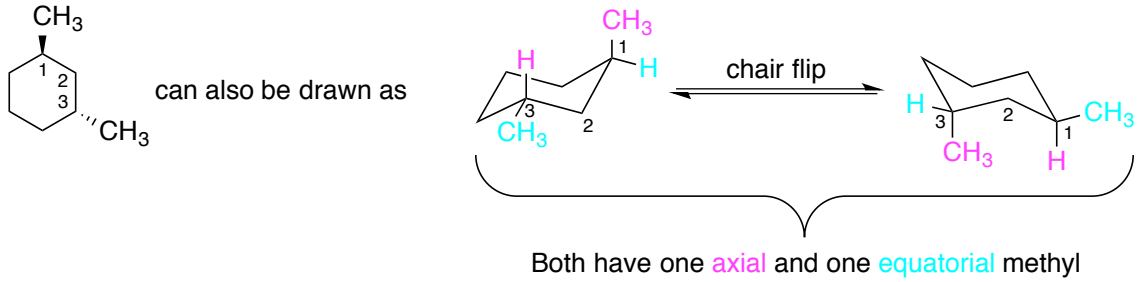


Then, the other chair conformation can be derived through a chair flip. The ring itself is not rotated during the chair flip, so C1, which was the far right-hand carbon in the first chair conformer, is still the far right-hand carbon in the second chair conformer. When the chair flip occurs, axial substituents become equatorial (and vice versa). Notice though that the C1 methyl group is on the more upward bond in both conformations, and the C4 methyl group is on the more downward bond in both conformations.

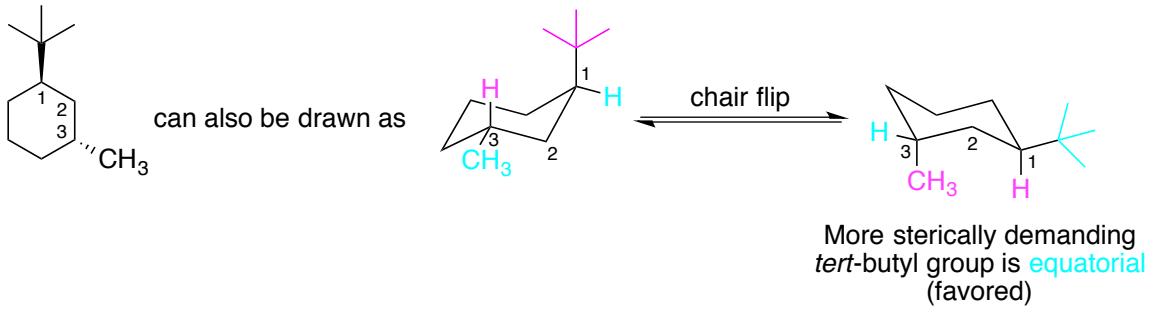


It just so happens that, in this case, one conformation has both methyl groups axial, while the other has both methyl groups equatorial. The conformer with equatorial methyl groups is clearly the more stable of the two.

For our second example, consider *trans*-1,3-dimethylcyclohexane. Due to the stereochemistry of C1 and C3, it is not possible to place both methyl groups on equatorial bonds of a single chair conformation. Each chair conformer possesses one axial and one equatorial methyl group, so in this case, the two conformers are equal in energy.

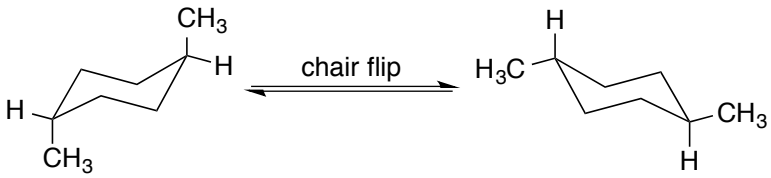


Now, let's change one of the methyl groups to a *tert*-butyl group as we consider 1-*tert*-butyl-3-methylcyclohexane. Much like the previous example, it is impossible to have both substituents simultaneously equatorial due to the stereochemistry. However, since the groups now differ in size, the chair conformations differ in energy. The *tert*-butyl group is much more sterically demanding than a methyl group, so the conformer with an equatorial *tert*-butyl group is favored.

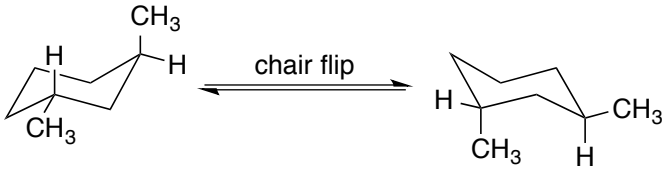


Problem 21. Using the A values, assign relative energies to the following pairs of chair conformations, which we examined in the preceding discussion.

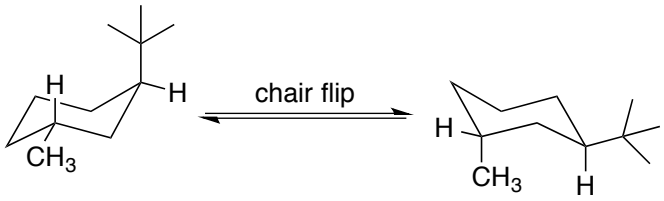
(a)



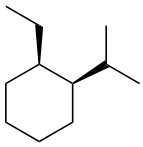
(b)



(c)

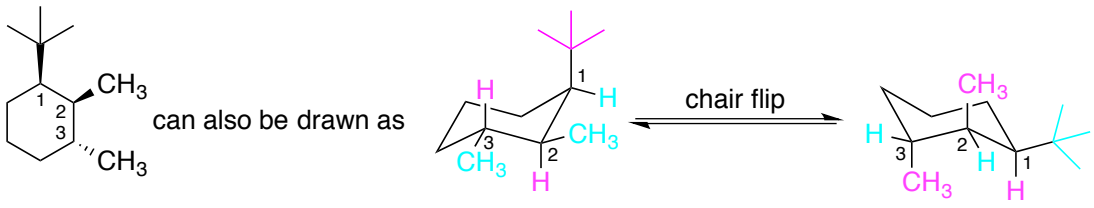


Problem 22. Draw both chair conformations of *cis*-1-ethyl-2-isopropylcyclohexane, which is shown below. Which conformation is favored at equilibrium? Determine the K_{eq} for this conformational change at room temperature.



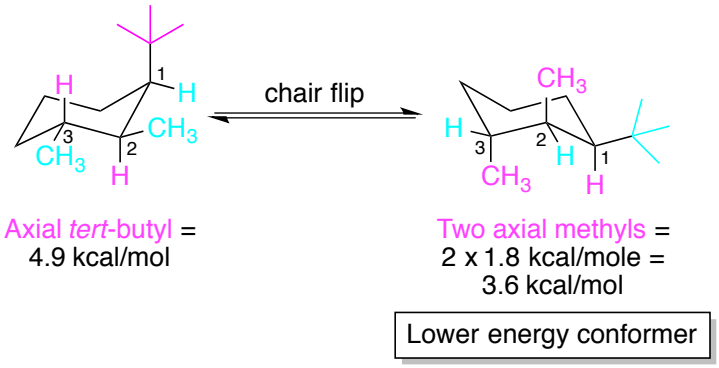
Polysubstituted cyclohexane derivatives

When a cyclohexane derivative has multiple substituents, the conformational analysis does not change in any fundamental way. We begin by drawing both chair conformations.

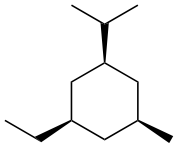


With polysubstituted rings, such as this one, it is less obvious which chair conformation is more stable. To make the determination, we must calculate the relative energies of the two

conformers using A values. Even though it has two axial groups, the second chair conformation is still lower in energy because those groups are less sterically demanding. Consequently, this is the favored conformer.

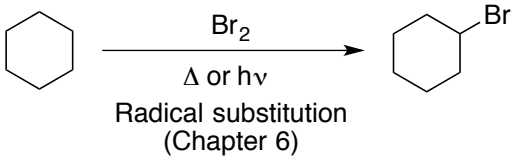


Problem 23. Draw both chair conformations of the following molecule. Which one is favored at equilibrium and by how much?

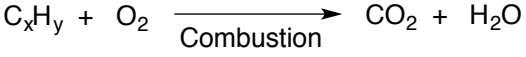


Section 6: Combustion

Since they contain only strong carbon-carbon and carbon-hydrogen σ bonds, alkanes are fairly unreactive. In Chapter 6, we'll learn about their halogenation, which takes place under radical conditions.



Aside from radical substitution, combustion is one of the few other reactions of alkanes. Any time you burn a hydrocarbon fuel, you are unleashing the energy in carbon-carbon and carbon-hydrogen σ bonds for some application, be it cooking on a gas stove, heating your home with a gas furnace, or driving an automobile that utilizes a combustion engine. Combustion releases an enormous amount of energy as a hydrocarbon in the presence of oxygen is converted to carbon dioxide and water. A generic, unbalanced combustion reaction is shown below for a hydrocarbon (C_xH_y).



Petroleum is the principal source for these important fuels. Crude oil is refined through fractional distillation into a series of fractions having different uses. The smallest alkanes (C_1 – C_4) are gases. Hydrocarbons containing between five and twelve carbons are used for gasoline. Alkanes of twelve to sixteen carbons find utility in kerosene, while diesel fuels include those having fourteen to twenty carbons. Larger alkanes are used for lubricating and fuel oils; they are also sometimes "cracked" into smaller hydrocarbons.

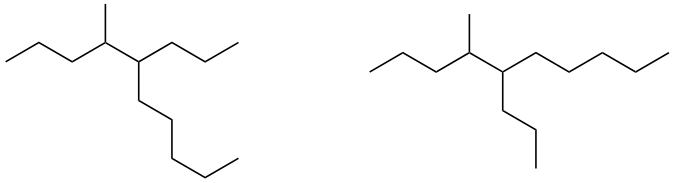
Problem 24. When you think of gasoline, you might think of its octane rating, which is a measure of the fuel's compressibility. Write a balanced chemical equation for the combustion of octane.

End-of-the-Chapter problems

Problem 25. In each of the following pairs, are the molecules identical, constitutional isomers, or unrelated compounds with different molecular formulas?

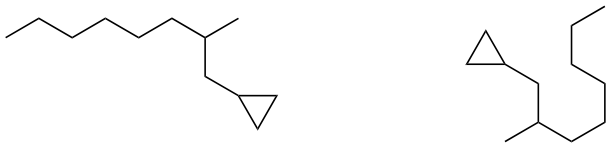
(a)

(b)

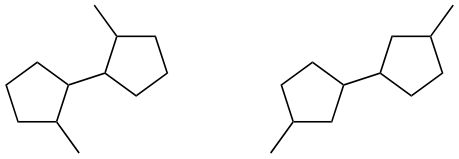


(c)

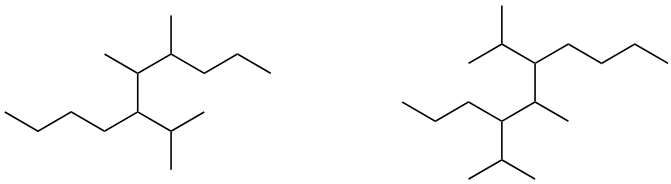
(d)



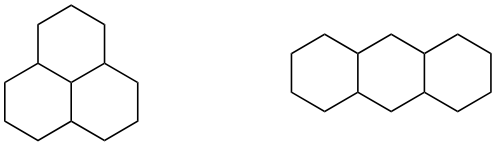
(e)



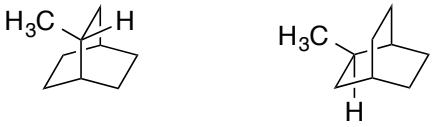
(f)



(g)



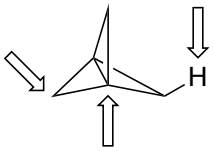
(h)



Problem 26. Draw all of the isomers of C_7H_{16} and name them.

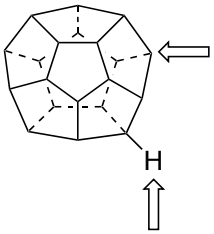
Problem 27. Classify the indicated atoms in the following structures as primary, secondary, tertiary, or quaternary.

(a) This molecule is known as [1.1.1]propellane because of its resemblance to a propeller. Its bridgehead carbons have a nearly inverted tetrahedral geometry, so it is quite strained.

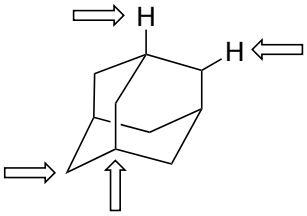


(b) This molecule is called prismane because it has the shape of a prism.

(c) This molecule is dodecahedrane because it has twelve sides like a dodecahedron.

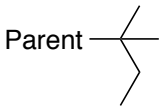


(d) This molecule is adamantane. It is a tricyclic ring system, in which all of its six-membered rings exist in chair conformations.

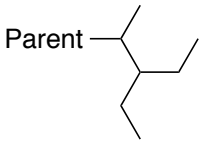


Problem 28. Provide systematic names for the following complex substituents.

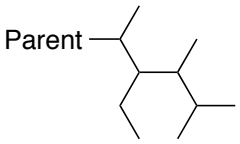
(a)



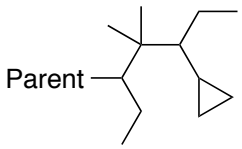
(b)



(c)



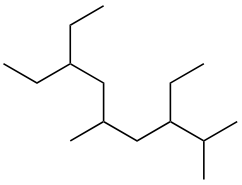
(d)



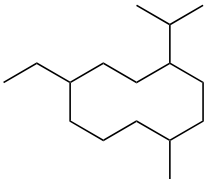
Problem 29. We've seen the formulas for linear, branched, and cyclic alkanes, but what about bicyclic alkanes? What form does their molecular formula take?

Problem 30. Provide systematic names for the following molecules.

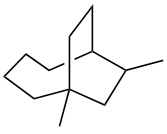
(a)



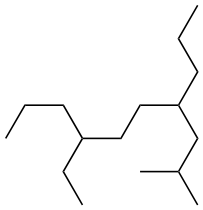
(b)



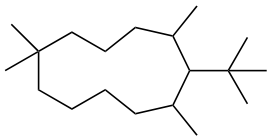
(c)



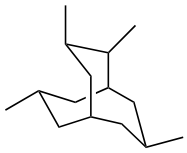
(d)



(e)



(f)



Problem 31. Draw the structures of the molecules having the following names.

(a) 2,2,3,3,4,4-hexamethylpentane

(b) 2-cyclobutyl-4-ethyl-1-isopropylcyclohexane

(c) 5-*sec*-butyl-6-cyclohexyl-2,6-dimethylnonane

(d) 1-cyclopropyl-2-methylpentane

(e) 5-*tert*-butyl-1,2-dimethylcycloheptane

(f) 3,5-diethyl-4-isopropylheptane

Problem 32. Each of the following names contains at least one error. In each case, determine the molecule suggested by the name, and then provide the correct IUPAC name for it.

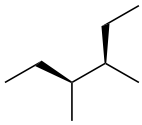
(a) 1,1,1-trimethylbutane

(b) 1-cyclopropyl-4,4-dimethyl-2-*sec*-butylcyclohexane

(c) 3,3,8-trimethyl-5-isopropylnonane

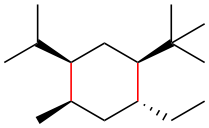
(d) 3-isobutylheptane

Problem 33. Using a Newman projection, draw the most stable conformation of 3,4-dimethylhexane when viewed down the C3-C4 bond.

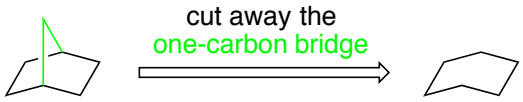


Problem 34. Starting with a conformation that has eclipsing methyl groups, show all of the staggered and eclipsed conformers of 2-methylbutane in sawhorse projections. Illustrate the relative energies of the conformers using an energy profile.

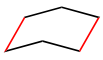
Problem 35. Draw the most stable conformation of the following molecule. Then, looking down the red C-C bonds, draw this conformation in a Newman projection.



Problem 36. Although the chair conformations are typically the most stable, other conformations of cyclohexane do exist. One such conformation is present in the bicyclic molecule shown below. The one-carbon bridge is a conformational constraint that holds the six-membered ring in a conformer other than the chair. This can be seen more clearly if we imagine erasing the one-carbon bridge.

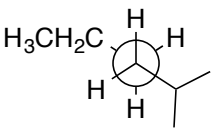


Draw this conformation of cyclohexane in a Newman projection, looking down the red C-C bonds from the front, and then explain why this is not typically a favored conformation.

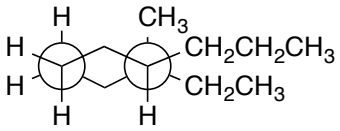


Problem 37. Convert the following Newman projections into skeletal structures. For the cyclohexane derivatives, also draw the corresponding chair conformation.

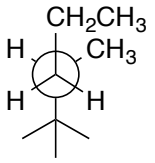
(a)



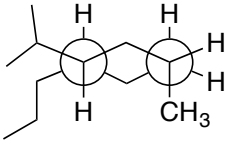
(b)



(c)



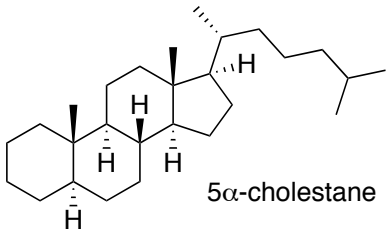
(d)



Problem 38. For the cyclohexane derivatives in Problem 37 [parts (b) and (d)], draw both chair conformations. Indicate which is favored at equilibrium and by how much.

Problem 39. In a combustion reaction, one mole of an alkane reacts with 10 moles of oxygen to yield 7 moles of carbon dioxide and 6 moles of water. What is the alkane's molecular formula? Provide two structures consistent with this formula.

Problem 40. Conformational analysis can be applied to polycyclic systems, such as cholestane, which we first encountered in Section 2. An isomer known as 5α-cholestane is shown below. All three of its six-membered rings exist in the chair conformation. Draw this molecule so as to show the conformations of its rings.



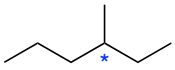
Chapter 4: Stereochemistry

Section 1: Chirality
Section 2: Enantiomers
Section 3: Nomenclature
Section 4: Physical and chemical properties of enantiomers
Section 5: Diastereomers
Section 6: Internal symmetry
Section 7: Fischer projections
Section 8: Resolution

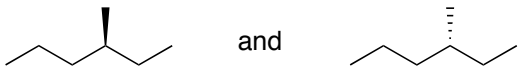
Section 1: Chirality

In the previous chapter, we began to explore the three-dimensionality of molecules through conformational analysis, in which we examined shapes that interconvert through rotation about single bonds. Stereochemistry is another aspect of molecular shape, and it deals with forms—known as configurations—that cannot be interconverted without a chemical reaction taking place.

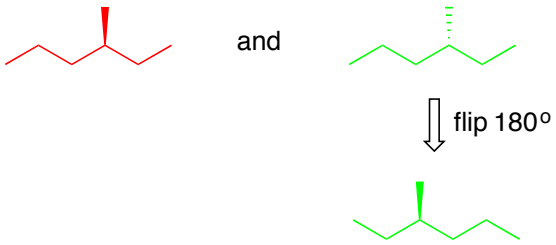
Consider the alkane 3-methylhexane. It contains one special carbon (denoted by *) that is known as a chirality center. This carbon bears four different groups: a methyl group, an ethyl group, a propyl group, and a hydrogen atom. Chirality centers are also often referred to as chiral centers, stereocenters, or stereogenic centers.



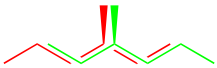
Chirality centers can exist in two different configurations.



The shapes of these molecules differ, and there is no way to convert one to the other without performing a chemical change through a reaction. This differentiates these species from conformers, which are interchanged through simple rotation about single bonds. In the case of the 3-methylhexane isomers shown above, no conformational change can convert one isomer to the other. Furthermore, these species do differ and can be distinguished from one another. At first glance, they may appear to look quite similar, but notice that they differ because there is no way to superimpose one structure on the other. We can attempt to do so by flipping one structure over.

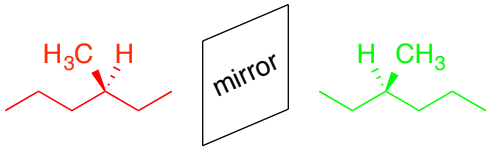


However, upon attempting to superimpose the two molecules, it becomes clear that they differ because the ethyl and propyl groups do not overlay.



not superimposable

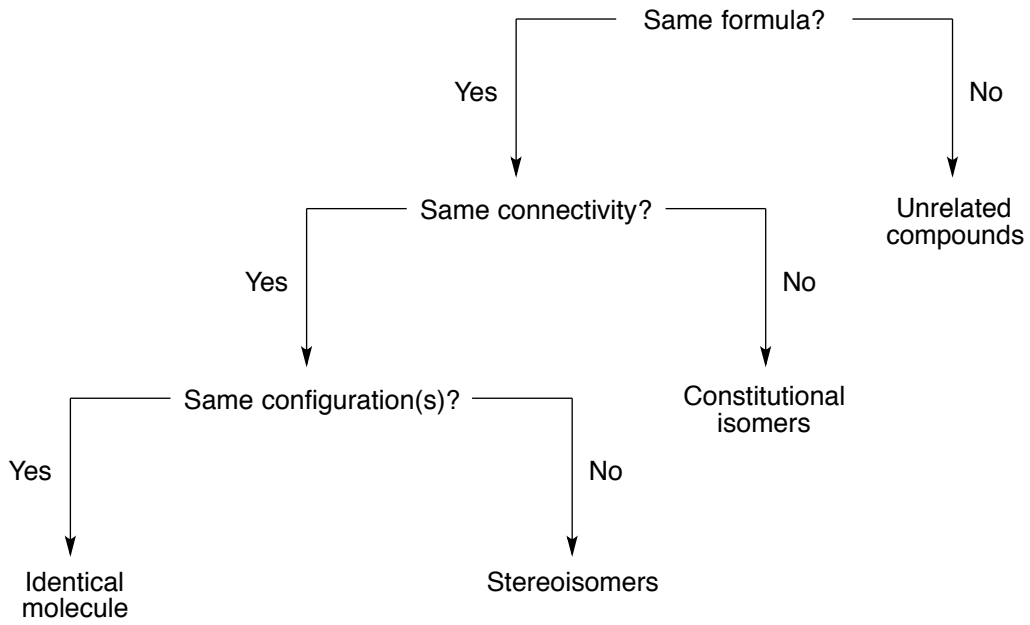
In fact, these two compounds are non-superimposable mirror images. Such species are chiral or can be said to exhibit chirality.



You are already familiar with such objects. Your hands are an excellent example of non-superimposable mirror images. Your left and right hands have all the same parts connected in the same fashion, and they are mirror images of one another. However, they differ. If you try to superimpose them by laying one hand on top of the other, the most obvious difference is that your thumbs point in opposite directions.

Molecules that are non-superimposable mirror images, like your hands, are known as enantiomers. Enantiomers are one type of stereoisomer that we'll discuss in this chapter. Stereoisomers are molecules with the same connectivity but differences in configuration.

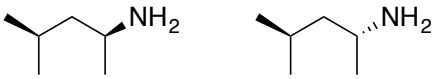
We now know of multiple types of isomerism. Constitutional isomers differ in connectivity, while stereoisomers differ only in configuration. The flow chart below can be helpful when deciding on the relationship between molecules.



Problem 1. In each of the following pairs, are the molecules unrelated, constitutional isomers, stereoisomers, or identical?

(a)

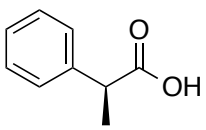
(b)

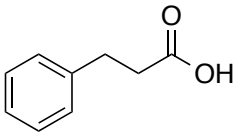


(c)

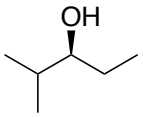
(d)

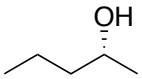
(e)



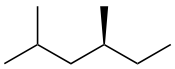


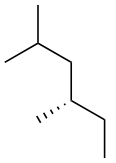
(f)



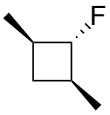


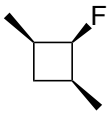
(g)





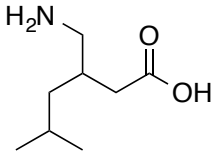
(h)



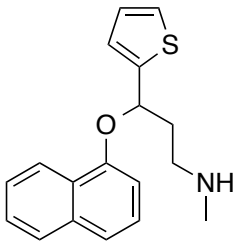


Problem 2. Identify the chirality centers in the following pharmaceuticals by marking them with an asterisk (*).

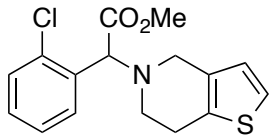
(a) Pfizer's Lyrica is used to treat seizures and some conditions leading to chronic pain, such as fibromyalgia.



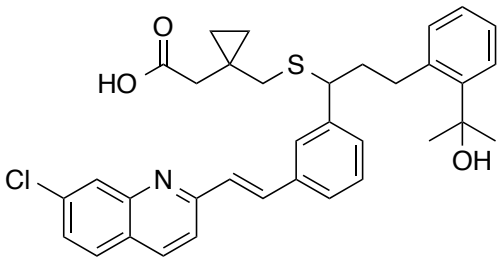
(b) Eli Lilly's Cymbalta is used to treat depression.



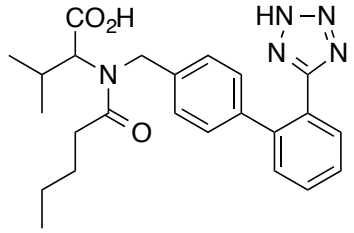
(c) Bristol-Myers Squibb and Sanofi's Plavix is used to inhibit blood clots.



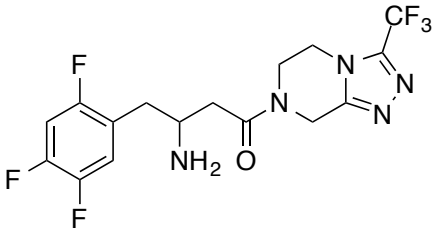
(d) Merck's Singulair is used for the treatment of seasonal allergies.



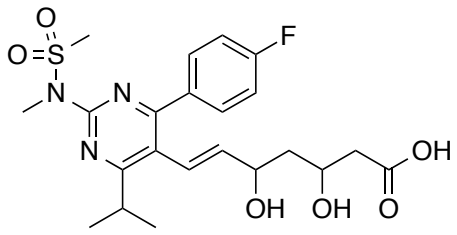
(e) Novartis' Diovan is used to treat high blood pressure.



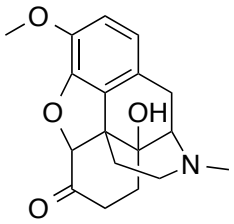
(f) Merck's Januvia is used in the management of type 2 diabetes.



(g) AstraZeneca's statin Crestor is used for the treatment of high cholesterol.



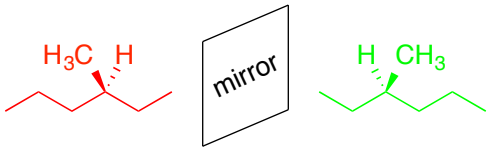
(h) Purdue Pharma's OxyContin contains oxycodone (shown below) and was used in pain management, resulting in great controversy over its addictive nature.



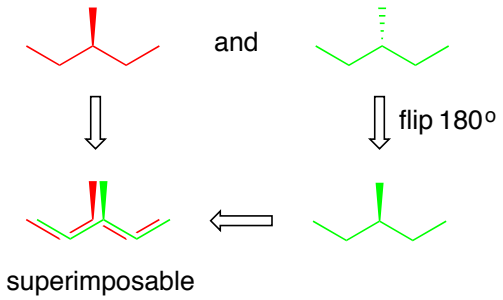
Section 2: Enantiomers

Chirality and enantiomers

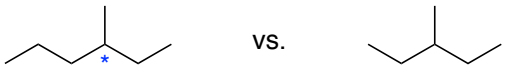
In the last section, we established that the alkane 3-methylhexane has a pair of enantiomers.



It's important to remember that enantiomers are not merely mirror images. All molecules have a mirror image. What is special about enantiomers is that they are *non-superimposable* mirror images. If we merely removed one carbon from 3-methylhexane to make 3-methylpentane, the chirality disappears. We can still draw the methyl group on C3 on a wedge or a dash. However, we find that simply flipping one of the structures allows it to be overlaid on the other. Since these structures are superimposable, they are identical, and there is no difference in configuration.



The difference between 3-methylhexane, which is chiral, and 3-methylpentane, which is not, is the presence of a stereocenter in the former. 3-Methylhexane has one carbon bearing four different groups, but 3-methylpentane does not. C3 of 3-methylpentane bears two identical ethyl groups, and this symmetry renders it achiral (i.e., not chiral).

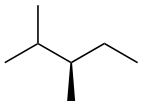


one stereocenter no stereocenters

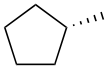
Most molecules without stereocenters are achiral. There are exceptions, but they are comparatively few. On the other hand, molecules that contain a single stereocenter are chiral. In other words, they will have an enantiomer.

Problem 3. Would you expect the following molecules to have an enantiomer? Explain your rationale.

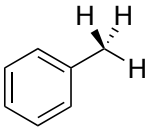
(a)



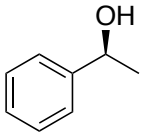
(b)



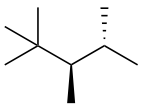
(c)



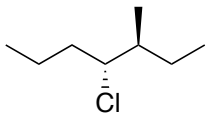
(d)



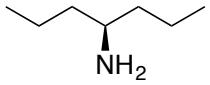
(e)



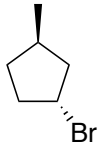
(f)



(g)

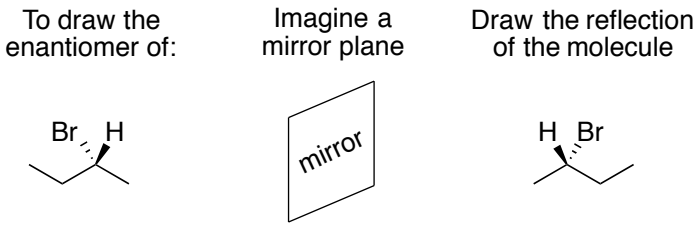


(h)



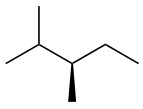
Drawing enantiomers

There are two approaches that can be used to draw the enantiomer of a chiral molecule. One method is to simply draw the reflection of the molecule through a mirror plane. This is illustrated using 2-bromobutane below.

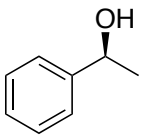


Problem 4. Derive the enantiomer of each of the following molecules by drawing the molecule's reflection through a mirror plane.

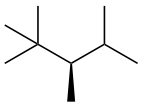
(a)



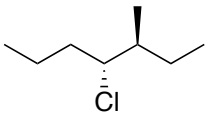
(b)



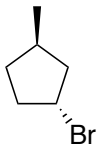
(c)



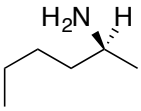
(d)



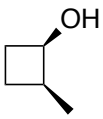
(e)



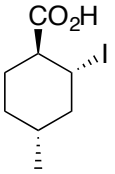
(f)



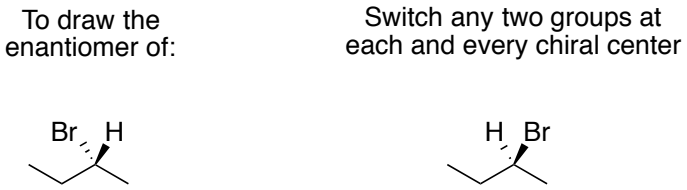
(g)



(h)

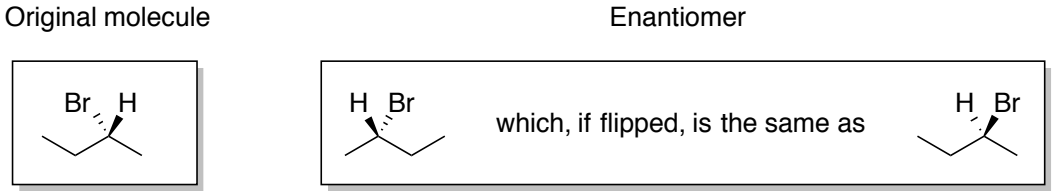


The other option for generating the enantiomer of a chiral molecule is to switch two groups at each and every chiral center. Switching two groups on a chiral center inverts the configuration of that center, and enantiomers have the opposite configuration at all of their stereocenters.



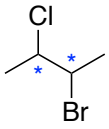
Problem 5. Derive the enantiomer of each of the molecules shown in Problem 4 by switching two groups on each and every chiral center.

The two approaches described above generate the same enantiomer. It is merely oriented differently on the page.

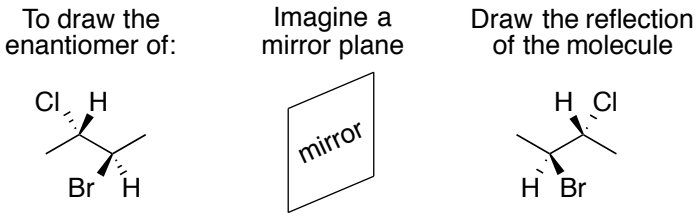


Problem 6. Consider molecules (a), (b), (c), and (f) in Problem 4. Each of these molecules contains a single stereocenter. The enantiomer was drawn by generating the mirror image in Problem 4 and by switching two groups on the chiral center in Problem 5. Compare your answers from Problems 4 and 5 and convince yourself that you have produced the same compound using either method.

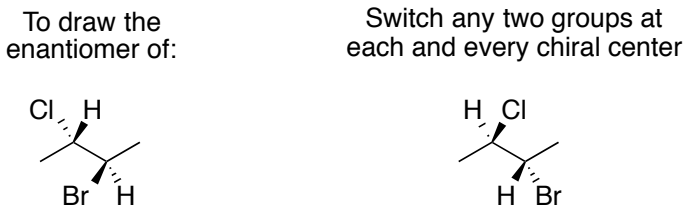
The methods for producing the enantiomer of a chiral molecule do not change if the molecule contains more than one chiral center. Consider 2-bromo-3-chlorobutane. This molecule contains two stereocenters.



When given one stereoisomer, we can derive its enantiomer by drawing the molecule's reflection through a mirror plane.



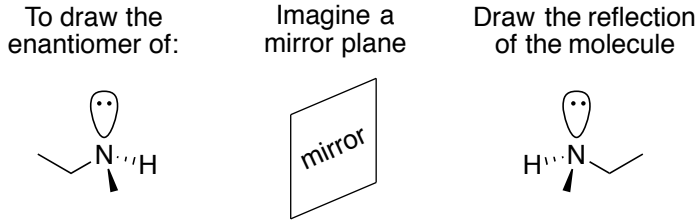
Alternatively, we can switch two groups *at each and every chiral center* to generate the enantiomer.



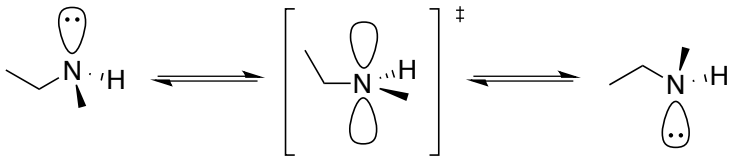
Problem 7. Consider molecules (d), (e), (g), and (h) in Problem 4. Each of these contains multiple stereocenters. You drew the enantiomer by generating the mirror image in Problem 4 and by switching two groups on each and every chiral center in Problem 5. Compare your answers from Problems 4 and 5 and convince yourself that you have produced the same compound using either approach.

Chiral centers other than carbon

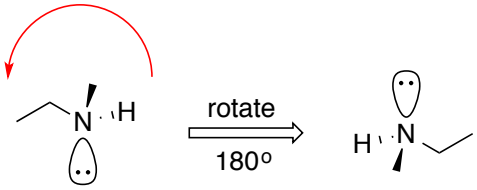
It is possible for an atom other than carbon to be a chirality center. Among the other elements in the second period, nitrogen is of greatest interest in this regard. An amine may contain a nitrogen atom bearing four different groups, which would make it a stereocenter. As a result, the compound has an enantiomer.



However, one of the groups on nitrogen is a lone pair of electrons, and a nitrogen bearing a lone pair undergoes a process known as pyramidal inversion, by which its two configurations interconvert at room temperature. This occurs through transition state in which nitrogen is sp^2 hybridized.

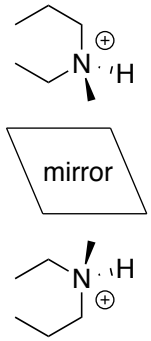


If the product of pyramidal inversion is simply rotated 180˚ counterclockwise, it becomes apparent that this is, in fact, the enantiomer of the original molecule.



Pyramidal inversion makes it challenging to obtain a pure sample of a single enantiomer of an amine with a lone pair of electrons. Such a sample readily equilibrates to form a 50/50 mixture of the two enantiomers, which is called a racemic mixture.

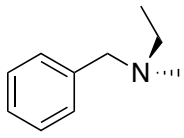
On the other hand, if the nitrogen atom has *bonds* to four unique groups, then it will not undergo pyramidal inversion because it has no lone pair. In this case, a pure sample of a single enantiomer can be obtained.



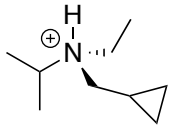
No pyramidal inversion:
enantiomers do **not** interconvert

Problem 8. Draw the enantiomer of each of the following amines. Which pairs of enantiomers interconvert, and which pairs do not?

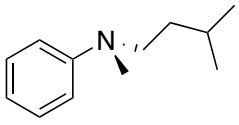
(a)



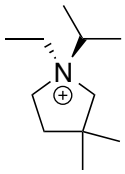
(b)



(c)

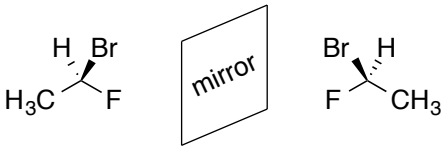


(d)

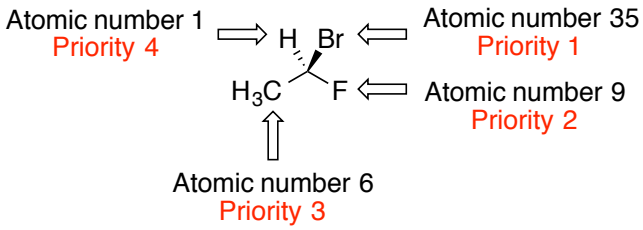


Section 3: Nomenclature

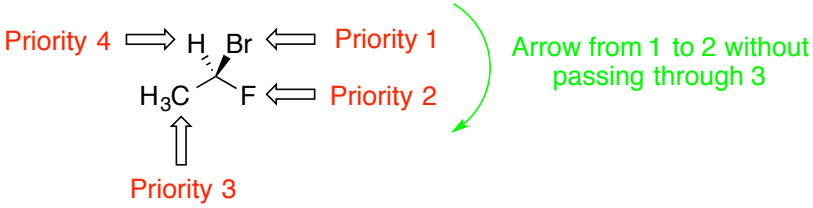
One of the hallmarks of IUPAC nomenclature is that every name denotes one and only one compound. The name 1-bromo-1-fluoroethane could suggest either of the enantiomers shown below and is therefore ambiguous.



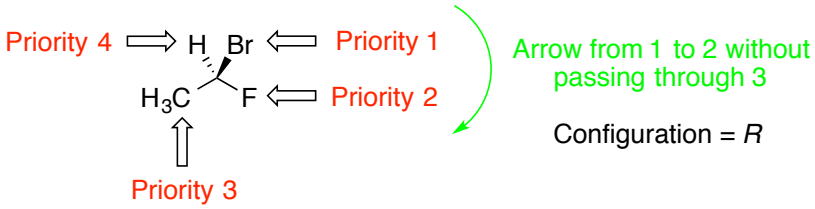
To eliminate that ambiguity, we need a method to convey the configuration of any chiral centers in a molecule. There are a few simple steps that allow us to assign a stereochemical descriptor to a particular configuration. The first step is to assign priorities to the four groups connected to the stereocenter. This is accomplished using the Cahn-Ingold-Prelog priority rules, which are based on atomic number. The higher the atomic number of the atom connected directly to the chiral center, the greater that group's priority will be.



Then, with the molecule oriented so that the lowest priority group faces backward (i.e., on the dash), draw an arrow from priority 1 to 2 without passing through 3.

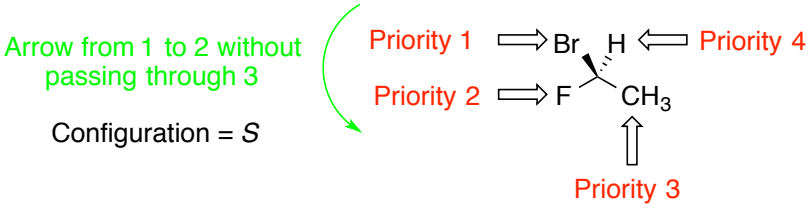


If this arrow goes clockwise (as it does in this instance), the configuration of the chiral center is designated as *R* for the Latin *rectus*, which means "right". When the molecule contains a single chirality center, the designation is simply placed in front of the name in parentheses.



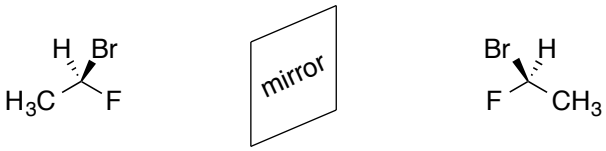
Name: (*R*)-1-bromo-1-fluoroethane

On the other hand, if the arrow goes counterclockwise, the configuration of the chiral center is designated as *S* for the Latin *sinister*, which means "left".



Name: (*S*)-1-bromo-1-fluoroethane

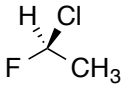
We can now give unique names to each of the enantiomers of 1-bromo-1-fluoroethane.



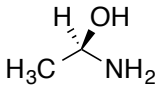
(*R*)-1-bromo-1-fluoroethane (*S*)-1-bromo-1-fluoroethane

Problem 9. Designate the configuration for each of the following molecules.

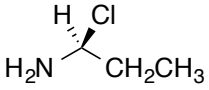
(a)



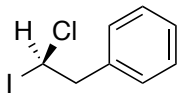
(b)



(c)

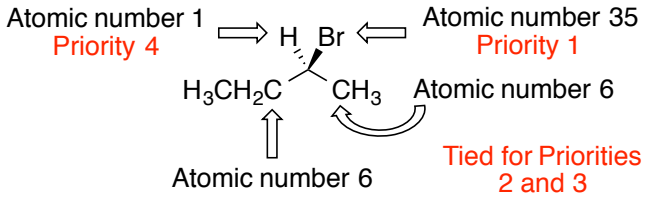


(d)

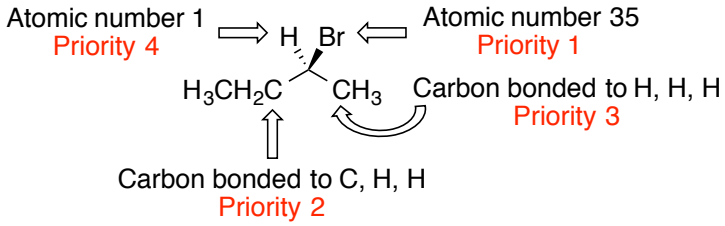


Tiebreaker rules

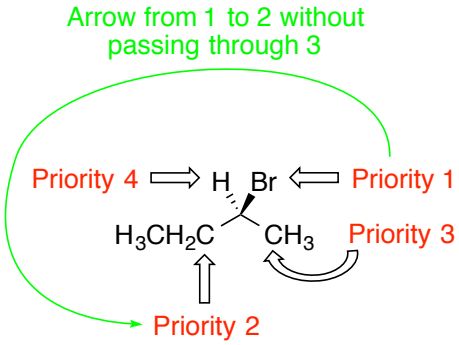
Sometimes the atomic numbers of the atoms directly connected to the chirality center will be identical, and in such cases, tiebreaker rules are needed in order to determine priorities. If the atomic numbers of the atoms directly connected to the stereocenter are the same, then we consider the elements connected to these atoms. For example, a stereoisomer of 2-bromobutane is shown below. The bromine atom has the highest atomic number and therefore has priority 1. Conversely, the hydrogen has the lowest atomic number and is therefore priority 4. However, the carbons of the ethyl and methyl groups both have atomic number 6 and are consequently tied for priorities 2 and 3.



To break the tie, we consider the elements bonded to the tied carbon atoms. The carbon of the methyl group is bonded to three hydrogens (atomic number 1); whereas, the carbon of the ethyl group is bonded to a carbon (atomic number 6) and two hydrogens (atomic number 1). The carbon of the ethyl group is bonded to the higher atomic number element, which makes it the winner of this tiebreaker. As a result, the ethyl group gets priority 2 and the methyl group is assigned priority 3.

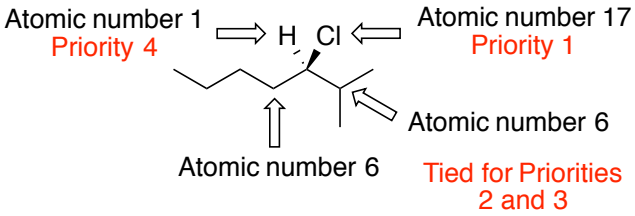


The configuration of this molecule can now be assigned as *S*.

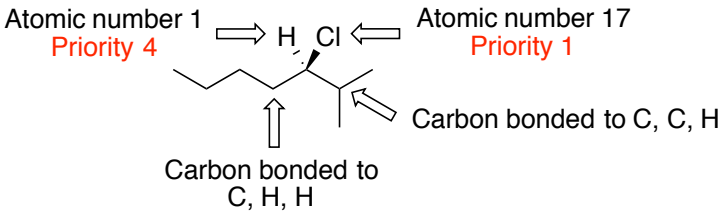


Name: (*S*)-2-bromobutane

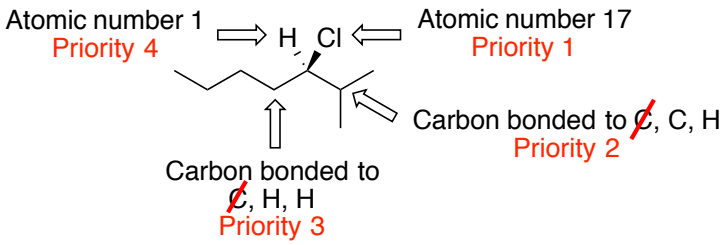
It is important to note that we are not considering the substituents on the chiral center as a whole. We are merely moving away from the stereocenter one atom at a time until we find a point of difference. To illustrate this point, consider the stereoisomer of 3-chloro-2-methylheptane shown below. Chlorine is clearly priority 1, and hydrogen must be priority 4. However, the carbons of the isopropyl and butyl groups are initially tied for priorities 2 and 3.



The tie is broken when we consider the elements bonded to the tied carbons. The carbon of the isopropyl group is bonded to C, C, and H. The carbon of the butyl group is bonded to C, H, and H.



We arrange these elements from highest to lowest atomic number and compare them. Each of the tied carbons is bonded to another carbon, so these cancel. The carbon of the isopropyl group is still bonded to another carbon; whereas, the carbon of the butyl group has only hydrogens left. Therefore, the isopropyl group wins this tiebreaker and is assigned priority 2.

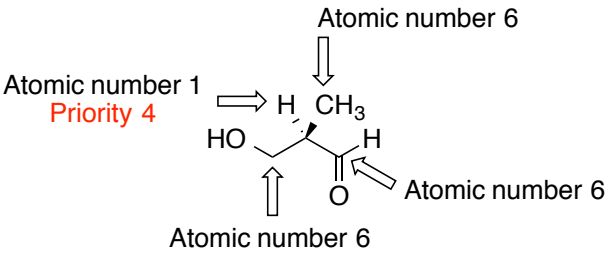


Here's the important point: note that the isopropyl group won the higher priority *despite the fact that the butyl group contains more carbons*. This underscores the fact that we are *not* considering substituents as a whole. Instead, we move away from the stereogenic center one atom at a time until a difference is found, and priorities are assigned on the basis of this first point of difference alone.

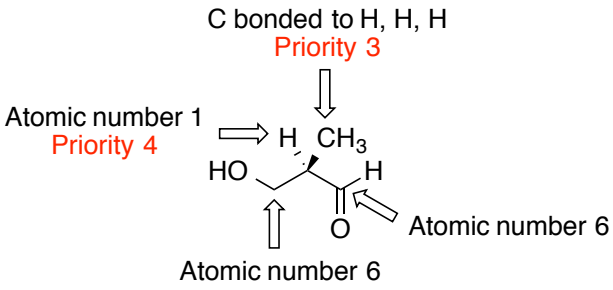
With all of the priorities assigned, we can determine the complete name of the molecule: (*R*)-3-chloro-2-methylheptane.

Name: (*R*)-3-chloro-2-methylheptane

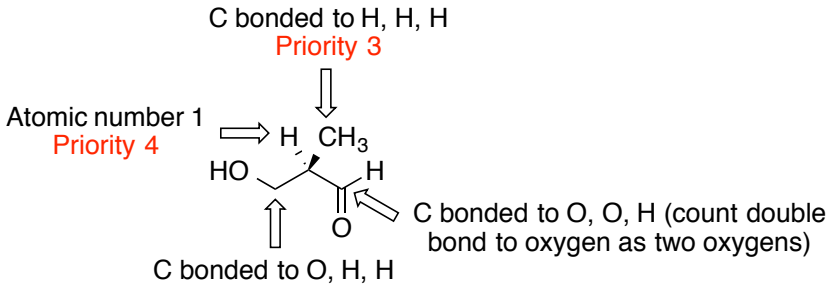
You'll notice from the examples above that each of the tied atoms gets three chances to win the tiebreaker because each of the tied atoms is bonded to three elements in addition to the chiral center itself. When multiple bonds are present, the fairness of this competition appears to be disrupted. In the following example, the stereogenic carbon is bonded to three carbons and a hydrogen. The hydrogen atom is certainly the lowest priority group, but there is a three-way tie between the remaining carbons.



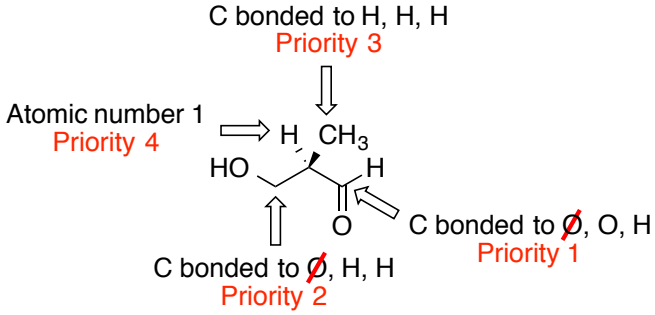
To break the tie, we consider the elements bonded to the tied carbons. The carbon of the methyl group is bonded only to hydrogens. Since these have the lowest possible atomic number, the methyl group receives the lowest of the remaining priorities: priority 3.



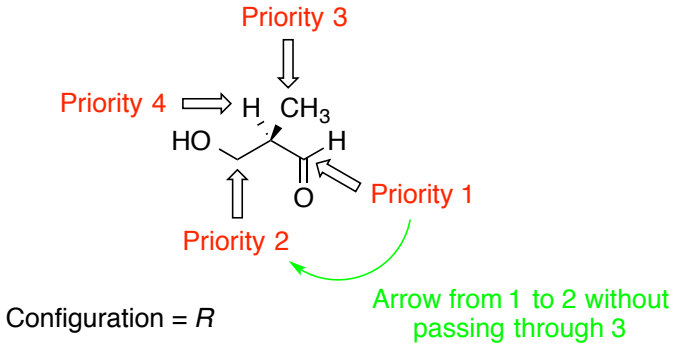
The two remaining carbons are each bonded to oxygen. The alcohol-containing group has a carbon bonded to O, H, and H. The aldehyde group has a carbon bonded only to O and H, but this would give it only two chances to win the tiebreaker. To make the competition fair, each tied atom must have three chances to win, so the double bond to oxygen is counted as two oxygens.



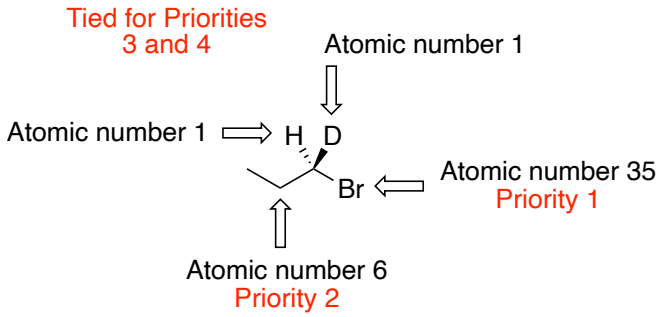
Now that we have established a fair comparison, we can evaluate the remaining groups. The carbons in the alcohol-containing and aldehyde groups are both bonded to an oxygen, so these elements cancel. The carbon of the aldehyde group still has one more bond to oxygen; whereas, the carbon of the alcohol-containing group has only bonds to hydrogen left. As a result, the aldehyde wins the highest priority.



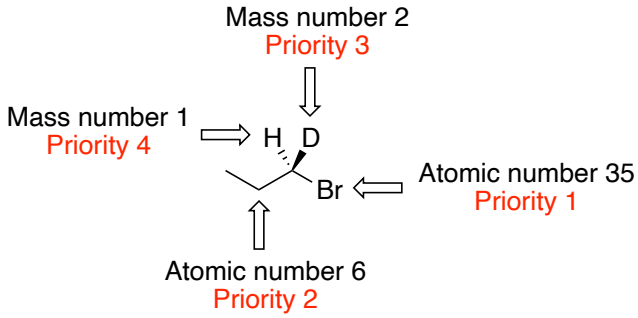
With the priorities in place, we can now determine the configuration, which is *R*.



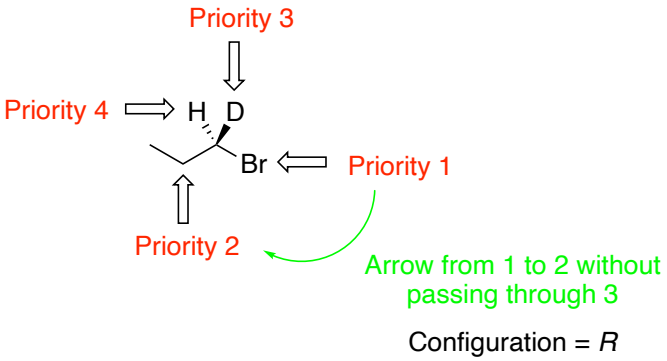
The last type of tiebreaker involves isotopes. Isotopes have the same atomic number because they have the same number of protons in their nuclei. This can result in ties. Consider the following deuterated propyl bromide. It contains deuterium (D), which is an isotope of hydrogen containing one proton and one neutron in its nucleus. Since it is an isotope of hydrogen, they both have an atomic number of 1 and are consequently tied for priorities 3 and 4.



To break this tie, we simply utilize the mass number in the case of isotopes. Recall that this is the number of protons and neutrons in the nucleus. When we account for its neutron, deuterium receives a higher priority than hydrogen.

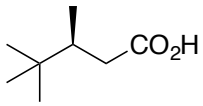


Once all of the priorities have been assigned, we can determine that the stereocenter's configuration is *R*.

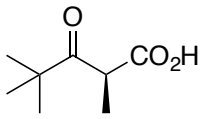


Problem 10. Assign the configurations of the following molecules.

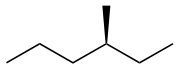
(a)



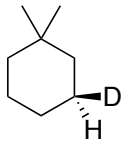
(b)



(c)



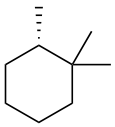
(d)



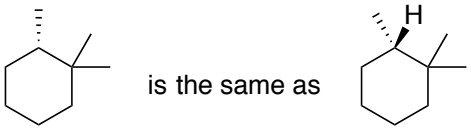
Determining configuration when the low-priority group is not on the dash

The agreed upon perspective when determining configuration is with the low-priority group facing back (i.e., on the dash). In the preceding examples, the low-priority group was fortuitously placed on the dash to begin with. However, you can of course encounter situations in which the low-priority group does not fall on the dash. In such cases, it is imperative to obtain the correct perspective before determining configuration. This can be done in two ways.

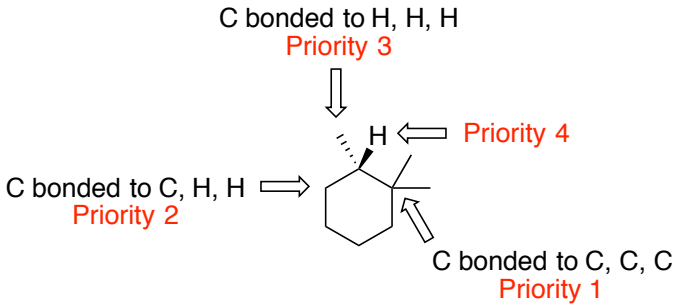
One option is simply to rotate the molecule so that the low-priority group recedes behind the page. Consider the following enantiomer of 1,1,2-trimethylcyclohexane.



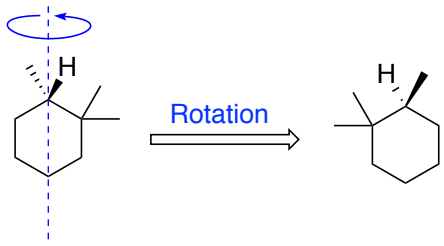
It contains one chiral center. When a hydrogen is implied at the chiral center, it is helpful to draw that hydrogen and indicate its position in space. The chiral carbon has one implied hydrogen. Additionally, it is missing a wedge, so the implied hydrogen must reside on the wedge.



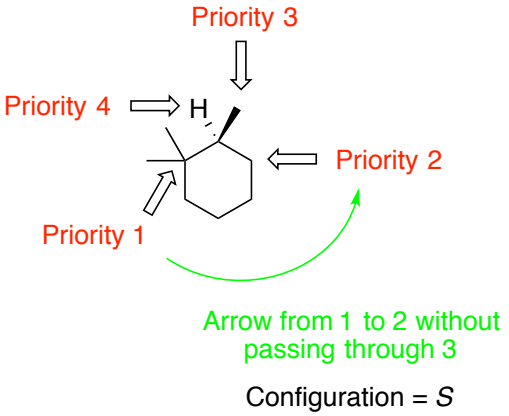
The hydrogen clearly obtains the lowest priority, but there is a three-way tie among the remaining carbons. This tie is readily resolved by considering the elements bonded to the carbon atoms. At this point though, we notice a problem. The low-priority group does not reside on the dash.



To rectify this problem, we can choose to rotate the molecule so as to place the hydrogen on the dash.

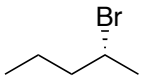


With the proper perspective, we can now draw the arrow from priority 1 to 2 without passing through 3. This reveals the configuration to be *S*, and the complete name of the molecule is therefore (*S*)-1,1,2-trimethylcyclohexane.

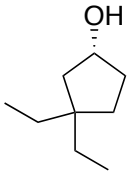


Problem 11. Determine the configuration for each of the following molecules.

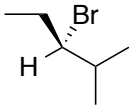
(a)



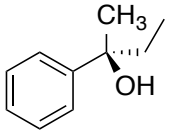
(b)



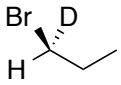
(c)



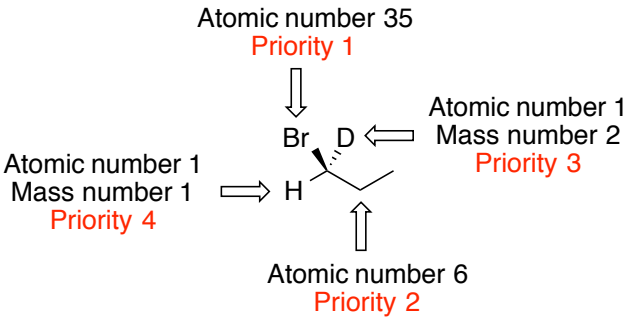
(d)



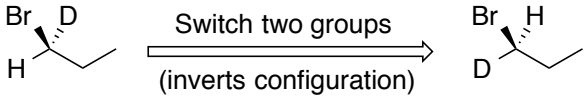
Some people find it cumbersome to rotate molecules because they have trouble visualizing the spatial change. A second option exists for obtaining the proper perspective, and this method does not entail rotation of the compound. It turns out that switching two and only two groups on a chiral center inverts the configuration of that center. We can exploit this fact when the low-priority group resides on a bond other than the dash. Consider the example of the deuterated propyl bromide shown below.



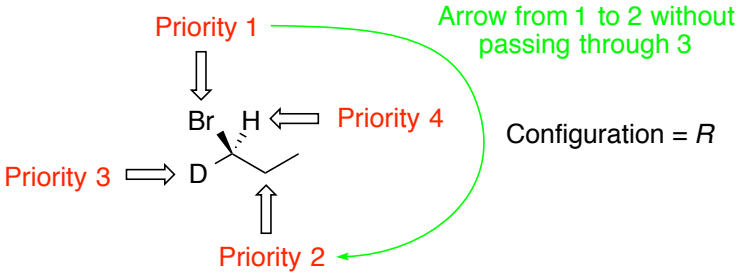
Bromine and carbon take priorities 1 and 2, respectively. Deuterium and hydrogen have the same atomic number, but the mass number of deuterium gives it a higher priority than hydrogen. Consequently, the low-priority group (hydrogen) is not facing back in this example.



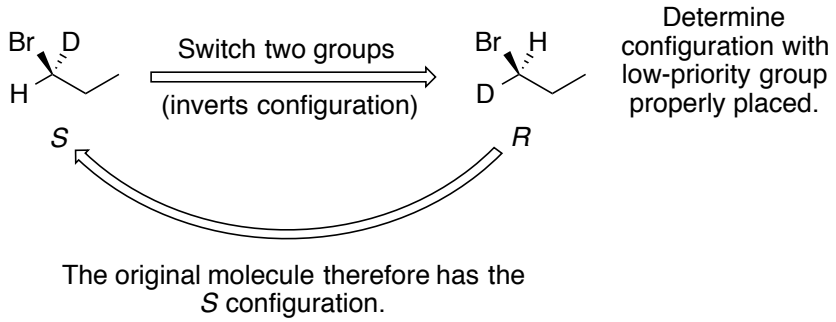
The option to rotate the molecule is still every bit as viable; however, one can also switch two groups on the chiral center so as to place the low-priority group on the dash. When doing this, it is imperative to make a note that the configuration has been inverted through this switch. In other words, we have produced the original compound's enantiomer.



With the hydrogen now facing back, we can determine the configuration. In this case, it is *R*.

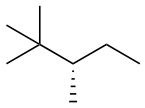


We therefore know that the configuration of the original molecule (prior to switching two groups) was *S*.

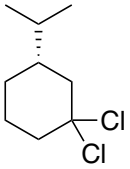


Problem 12. Determine the configuration of the following molecules. Use the method of switching two groups to place the lowest-priority group in the proper location.

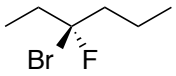
(a)



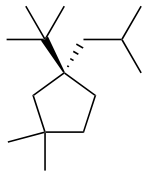
(b)



(c)



(d)

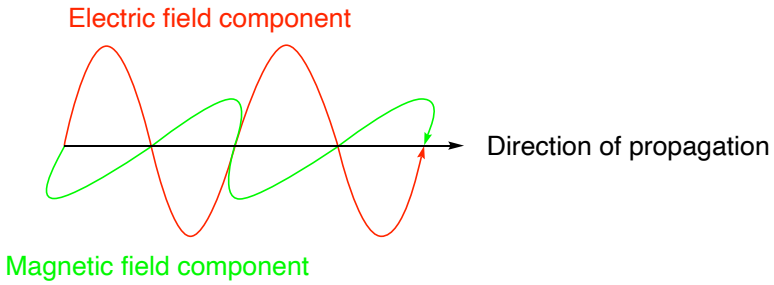


Section 4: Physical and chemical properties of enantiomers

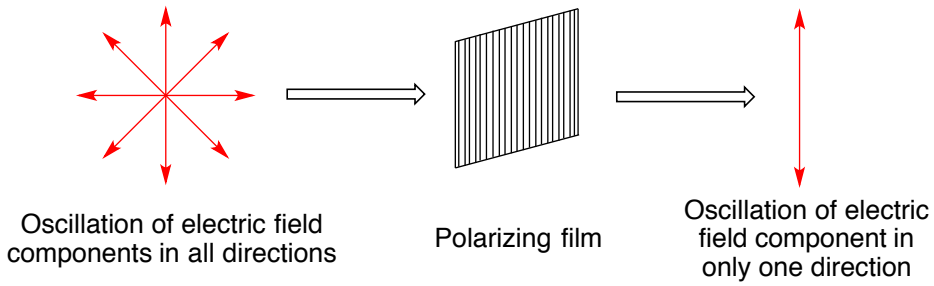
Physical properties

Enantiomers have all of the same physical properties, with only one exception. To name a few, enantiomers have identical melting points, boiling points, densities, and solubility. The only difference between them is in their rotation of plane-polarized light.

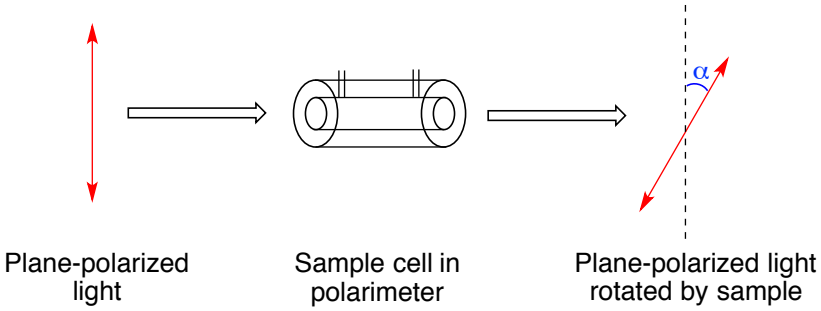
To understand what plane-polarized light is, we should first address the components of a wave of light. Light is composed of electric and magnetic waves that are orthogonal (i.e., 90˚) to each other.



We can focus solely on the electric field component for simplicity's sake. Under normal circumstances, there are light waves with their electric fields oscillating in all possible directions. However, if that light is passed through a polarizing film, what emerges is light with a uniform direction of oscillation. This is plane-polarized light.



If this plane-polarized light passes through a sample cell filled with a solution of a chiral, non-racemic sample, the direction of oscillation will be rotated. The instrument that enables us to make this observation is known as a polarimeter. By convention, we designate a clockwise rotation of plane-polarized light as positive and a counterclockwise rotation as negative. A (+) or (-) can be placed in front of a compound's name to convey its impact on plane-polarized light.



The observed rotation (α) is dependent upon a number of variables, including the wavelength of light used, the temperature, the sample concentration, and the path length of the cell. Specific rotation ([α]) accounts for all of these variables and is defined as follows:

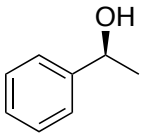
$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{c\,l}$$

T is the temperature in degrees Celsius. The wavelength of light employed is often the D-line of sodium (589 nm), so λ is often simply designated as D. The observed rotation is α. The concentration (c) is expressed as g of solute per mL of solvent. The path length (l) is reported in decimeters because many sample cells are 10 cm (or 1 dm) in length. Specific rotation is treated as unitless by convention.

A compound with a positive specific rotation is known as dextrorotary (*d*), while a compound with a negative specific rotation is termed levorotary (*l*). The designations (+) and *d* are synonymous. Both indicate a clockwise rotation of plane-polarized light. Similarly, the designations (-) and *l* are interchangeable. However, these labels, which convey a property of the molecule, have no connection whatsoever with *R* or *S*, which are based on an arbitrarily system of nomenclature. In other words, a chiral compound with the *R* configuration may be dextro- or levorotary. The same is true of a chiral substance with the *S* configuration. The configuration does *not* allow you to predict the molecule's specific rotation.

We can, however, say one important thing about the specific rotations of enantiomers. They have the exact same magnitude but opposite signs.

Problem 13. A 0.25 g sample of the 1-phenylethanol shown below is dissolved in 5 mL of methanol and placed into a 10 cm sample cell. It has an observed rotation of -2.25° using the D-line of sodium at 20 °C.



(a) Calculate the molecule's specific rotation.

(b) Is the molecule dextro- or levorotary (i.e., *d* or *l*)?

(c) The complete name of a chiral molecule takes the form: (*R* or *S*)-(+ or -)-name. Give the complete name of this molecule.

(d) Give the complete name and specific rotation of its enantiomer.

In unequal mixtures of enantiomers, enantiomeric excess (ee) is the amount by which the major enantiomer exceeds the minor enantiomer:

$$ee = \%\ major\ enantiomer - \%\ minor\ enantiomer$$

We can determine ee from the specific rotation of the mixture ($[\alpha]_{mix}$) as follows.

$$ee = \frac{[\alpha]_{mix}}{[\alpha]_{pure\ enantiomer\ of\ the\ same\ sign}} \times 100$$

Consider a mixture of Compound X ([α] = +16) and its enantiomer with a specific rotation ($[\alpha]_{mix}$) of +4. The ee of this mixture is 25%, and we can determine the percentage of each enantiomer by adding the two following equations.

$$\begin{gathered} 25\% = \%\ major\ enantiomer - \%\ minor\ enantiomer \\ \underline{100\% = \%\ major\ enantiomer + \%\ minor\ enantiomer} \\ 125\% = 2\ (\%\ major\ enantiomer) \\ 62.5\% = \%\ major\ enantiomer \end{gathered}$$

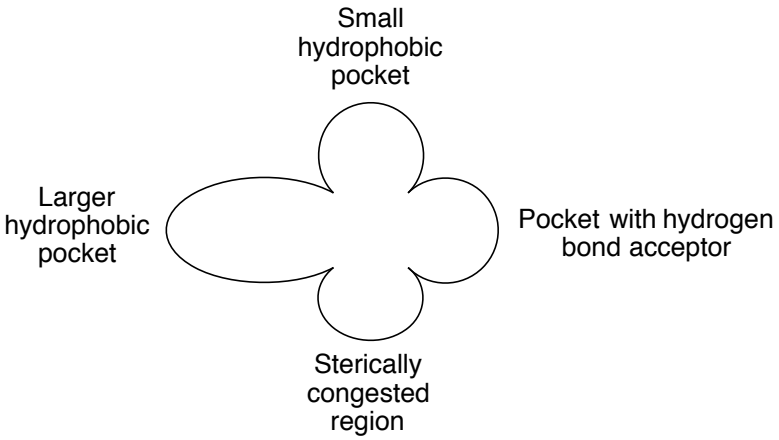
If there is 62.5% of the major enantiomer and therefore 37.5% of the minor enantiomer, then the ee is indeed 25% as we determined above.

Since enantiomers have all of the same physical properties with the sole exception of specific rotation, they cannot be separated using simple laboratory techniques such as distillation, recrystallization, or chromatography. We'll discuss their separation in Section 8.

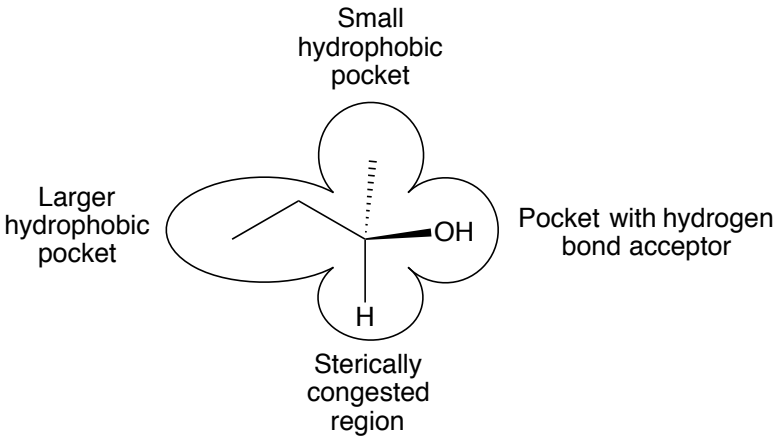
Chemical properties

Enantiomers react identically with achiral reagents and catalysts. However, they can react and interact differently with chiral substances.

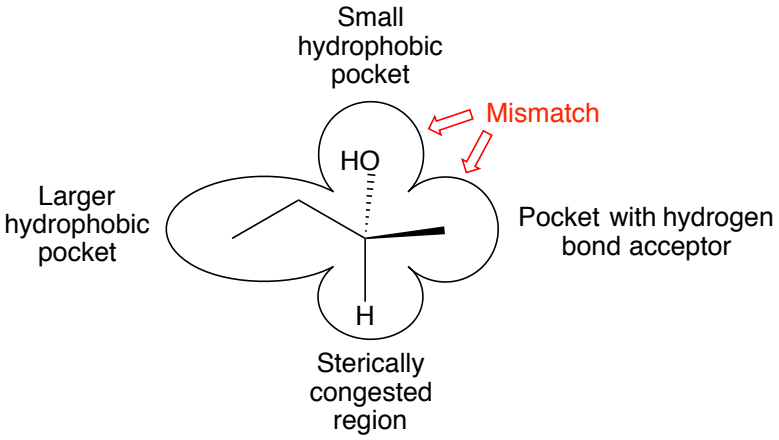
Binding to an enzyme's active site is one example of a molecule entering a chiral environment. Imagine an enzyme with an active site that consists of a small hydrophobic pocket, a slightly larger hydrophobic pocket, a hydrogen bond acceptor, and a sterically congested region.



(*R*)-2-Butanol could fit into this active site, matching each of the groups on its chiral center to a complementary portion of the enzyme.



Its enantiomer, however, cannot fit into the active site without a mismatch.



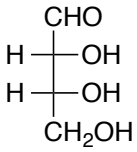
As a result, (*R*)- and (*S*)-2-butanol would interact differently with such an enzyme. (*R*)-2-Butanol would be expected to bind to it readily; whereas; (*S*)-2-butanol would bind sluggishly if at all.

Section 5: Diastereomers

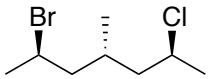
When a molecule contains more than one stereocenter, it will have more than two stereoisomers. The maximum number of stereoisomers that a compound can have is 2^n, where n is the number of stereocenters. For example, a molecule with two chirality centers can have up to four stereoisomers. Enantiomers exist in pairs (think of your left and right hands), so any additional stereoisomers must be of a different type. Stereoisomers that are not mirror images are known as diastereomers.

Problem 14. What is the maximum number of stereoisomers that each of the following compounds could have?

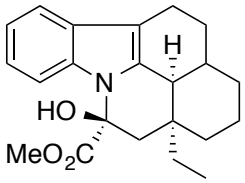
(a) D-erythrose, a carbohydrate



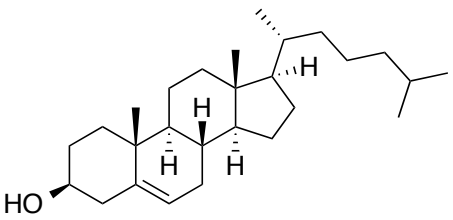
(b)



(c) vincamine, an alkaloid (i.e., a basic compound isolated from a natural source) that is a vasodilator



(d) cholesterol

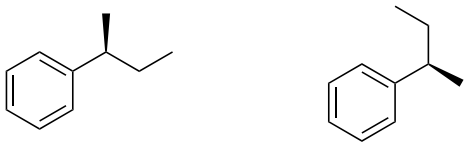


Consider a molecule with two stereoisomers, such as 2-bromo-3-chlorobutane. It has a total of four stereoisomers, which have been labeled A–D below. A and D are mirror images of one another, so they are a pair of enantiomers. The same can be said of B and C. Any other comparison (e.g., A to B) reveals stereoisomers that are not mirror images and are therefore diastereomers.

A B C D

Problem 15. For each of the following pairs, are the compounds unrelated, constitutional isomers, enantiomers, diastereomers, or identical?

(a)

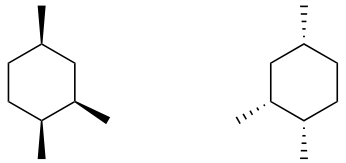


(b)

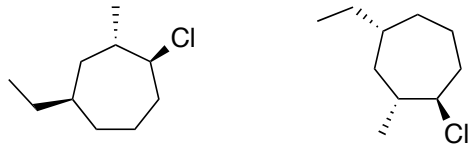
(c)

(d)

(e)

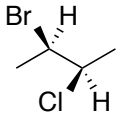


(f)



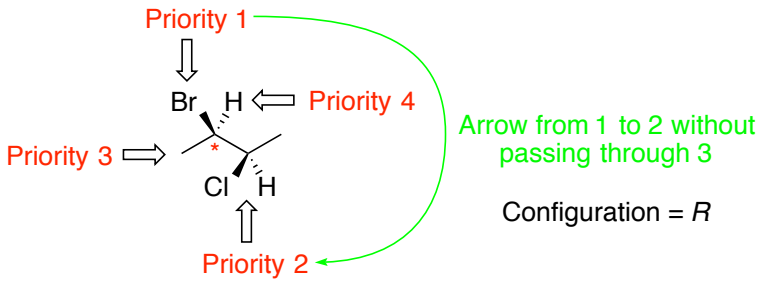
Determining the configurations of compounds A, B, C, and D may seem like a daunting task at first glance, but it can actually be done rather quickly. The most expedient approach is to determine the configuration of each chiral center in one of the compounds. Then, simply by comparing it to the other three stereoisomers, we can rapidly assign their configurations.

While we could use any of the four stereoisomers for determination of configuration, the process will be easier if we choose strategically. Select the stereoisomer that already has the low-priority groups pointing back. This would be stereoisomer A. Each of the stereocenters has an implied hydrogen, and the dash is the only bond not drawn for these centers. Consequently, the hydrogen atoms must reside on dashes.

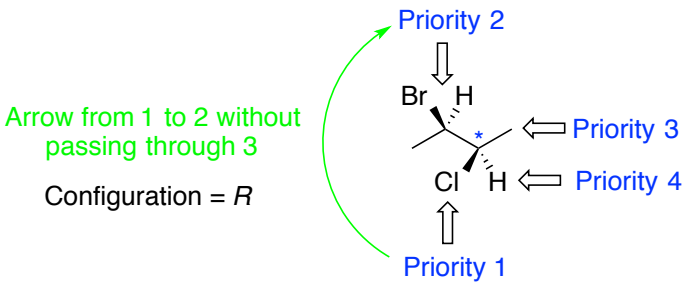


A

When dealing with molecules containing multiple chirality centers, you are best served by using a separate diagram of the molecule for determining the configuration of each chiral center. Focus on one stereocenter per diagram. In the diagram that follows, the configuration of C2 is determined to be *R*.

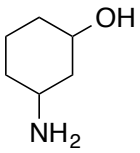


Then, in a separate diagram, the configuration of C3 is assigned as *R*.



Knowing that compound A is (2*R*,3*R*)-2-bromo-3-chlorobutane, we can assign the configurations of the remaining stereoisomers with ease based on whether or not C2 and C3 have the same configuration as in compound A. Compound B has the same configuration at C2 but differs at C3, making it (2*R*,3*S*)-2-bromo-3-chlorobutane. Compound C has a different configuration than compound A at C2 but is the same at C3, so it is (2*S*,3*R*)-2-bromo-3-chlorobutane. Compound D differs from compound A at both stereogenic centers, so it is (2*S*,3*S*)-2-bromo-3-chlorobutane.

Problem 16. Draw all four stereoisomers of the following molecule. Then, assign the configurations for each.



It is also worth noting that *cis* and *trans* alkenes are examples of diastereomers as well. We learned in Chapter 3 that the prefixes *cis* and *trans* can be used to refer to groups on the same side or opposite sides of a ring, respectively. *Cis* and *trans* can also be used to refer to groups on the same side or opposite sides of an alkene. The alkenes shown below are stereoisomers that are not mirror images and are therefore diastereomers.

a *cis* alkene a *trans* alkene

Physical and chemical properties

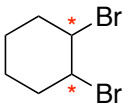
Unlike enantiomers, diastereomers have different physical properties. Their melting points, boiling points, densities, and solubility all differ, as will any other physical properties.

Additionally, diastereomers have different and *unrelated* specific rotations. Furthermore, they react differently, even in achiral environments.

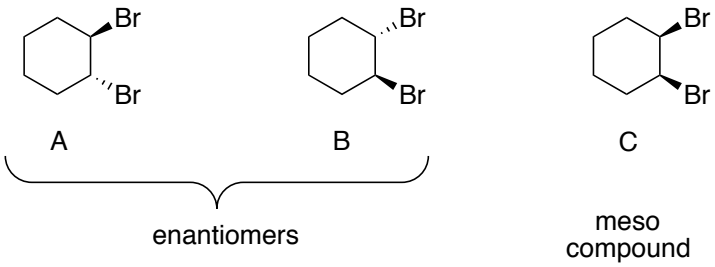
Section 6: Internal symmetry

As we learned in Section 5, the *maximum* number of stereoisomers that a compound can have is 2^n, where n is the number of stereocenters. It is possible for a molecule to have fewer than the maximum number of stereoisomers. This occurs when internal symmetry is present. Internal symmetry precludes chirality. Some molecules with chiral centers also possess an internal plane of symmetry, and such substances are called meso compounds. Due to its internal symmetry, a meso compound is not chiral and does not, therefore, have an enantiomer.

1,2-Dibromocyclohexane has two chirality centers (*).

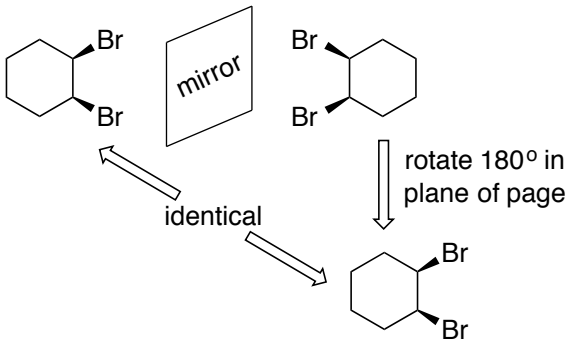


While the maximum number of stereoisomers for this compound is four, it actually has only three. There is a pair of *trans* enantiomers (compounds A and B), as well as a meso compound (compound C).

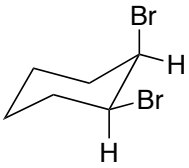


Compound C is said to be meso because of its internal plane of symmetry. An internal plane of symmetry arises when you find all of the same groups in the exact same positions on both sides of the plane. This internal plane of symmetry can pass through bonds and/or atoms.

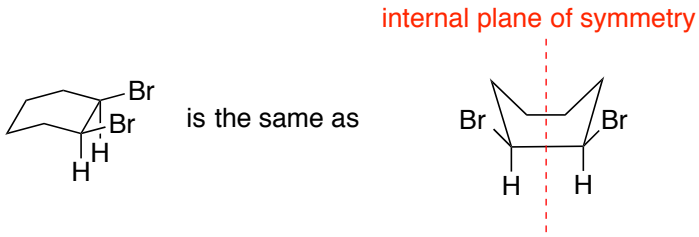
The consequence of this internal symmetry is that the molecule is superimposable on its mirror image. Since compound C is identical to its mirror image, it has no enantiomer.



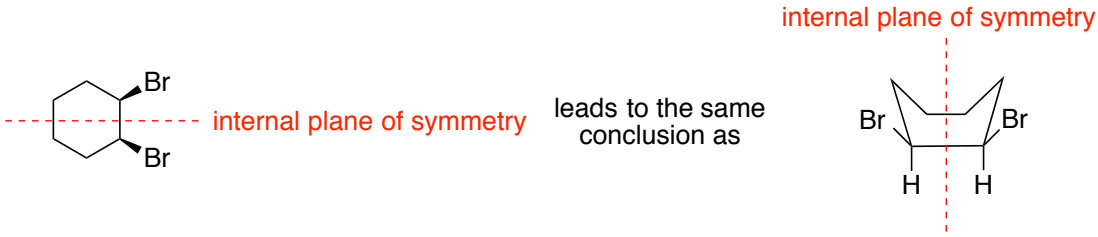
Sometimes a molecule is draw in a particular conformation that may actually obscure the internal plane of symmetry. For example, we could draw compound C in a chair conformation. The internal symmetry is not readily apparent in this conformer.



This reveals an important guiding principle. To find an internal plane of symmetry, the molecule must be drawn in its most highly symmetrical conformation. In other words, you must consider the conformer that has the best chance of achieving internal symmetry. The boat conformation meets this criterion (see Problem 36 in Chapter 3 for a refresher on the boat conformation).

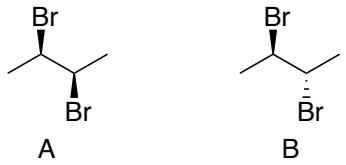


With cyclic compounds, we are able to achieve the same goal simply by treating the ring as though it resides in the plane of the page.

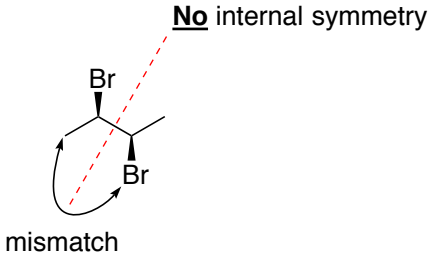


It can be more difficult to spot acyclic meso compounds. Consider the stereoisomers of 2,3-dibromobutane shown below. One is chiral and has an enantiomer. The other is a meso

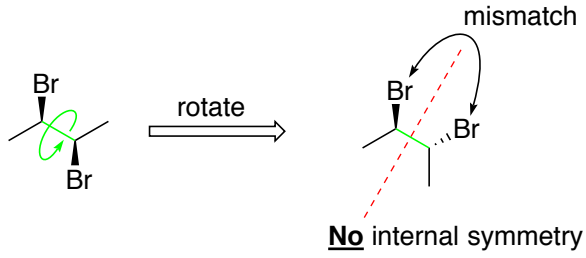
compound, meaning that it is achiral and has no enantiomer. Let's examine them more closely to determine which is which.



Compound A may appear as though it has internal symmetry at first glance, but it does not because there is a mismatch between the methyl and bromo groups on either side of the central axis.

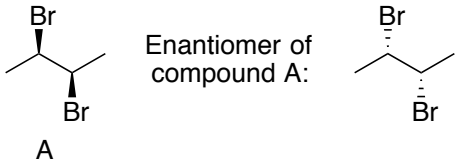


When the molecule is drawn in its most highly symmetrical conformation, the lack of internal symmetry is reinforced. To attain the most highly symmetrical conformer, we can rotate about the central carbon-carbon bond. Doing so places the molecule in an eclipsed conformation in which the methyl groups eclipse one another. Although the same groups reside on each side of the central axis, they are not in the exact same position. A bromine on a wedge does not reflect onto a bromine on a dash.

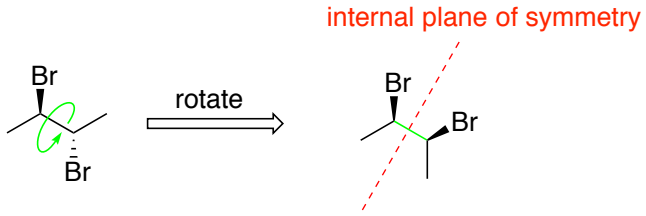


Problem 17. Draw the two conformations above in Newman projections to highlight the eclipsed nature of the latter conformation and the lack of internal symmetry in this molecule.

Since compound A does not have internal symmetry, it is chiral, and it does have an enantiomer.

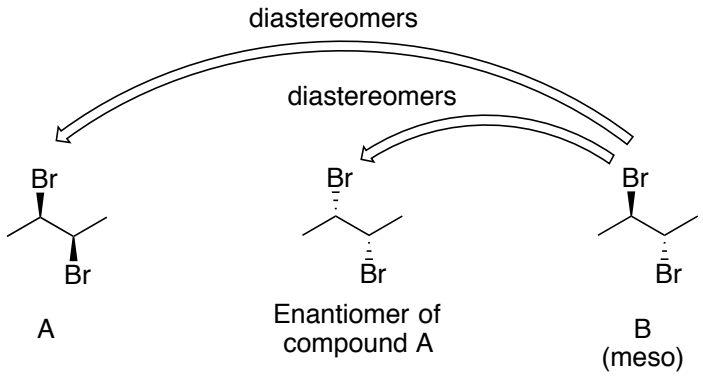


Compound B, on the other hand, proves to be achiral. This is not apparent at first glance because the molecule is not in its most highly symmetrical conformation; however, rotation about the central carbon-carbon bond reveals the internal symmetry. Since compound B is achiral it has no enantiomer.



Problem 18. Draw the two conformations above in Newman projections to highlight the eclipsed nature of the latter conformation and the internal symmetry in this molecule.

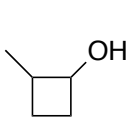
The preceding analysis highlights the fact that there are only three stereoisomers of 2,3-dibromobutane: compound A, its enantiomer, and compound B. Since compound B is a meso form, it has no enantiomer. Nevertheless, it does have diastereomers. Both compound A and its enantiomer are diastereomers of compound B.

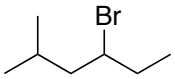


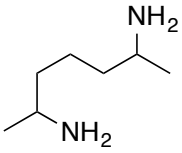
Problem 19. When bromine is a substituent, it is termed a “bromo” group. Knowing this, provide complete IUPAC names for compound A, its enantiomer, and compound B.

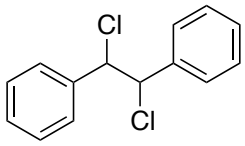
The take home message is that a molecule must be drawn in its most highly symmetrical conformation in order to reveal internal symmetry. For cyclic compounds, the ring can simply be treated as though it resides in the plane of the page. Acyclic compounds must be drawn in an eclipsed conformation to see if internal symmetry exists. A stereoisomer with internal symmetry is a meso form that is by definition achiral and lacks an enantiomer, thereby reducing the total number of stereoisomers compared to the maximum of 2^n.

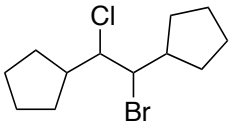
Problem 20. Identify the molecules in the following list that have an internal plane of symmetry in at least one of their stereoisomers.

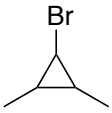


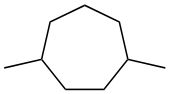


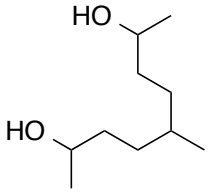






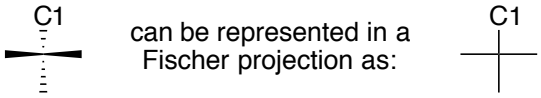






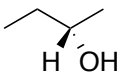
Section 7: Fischer projections

Fischer projections provide us with a shorthand notation for representing chirality using a two-dimensional rendering of a molecule. The convention in a Fischer projection is that the molecule is viewed so that the carbon having the locant 1 is at the top and two substituents at each chiral center are directed toward you (on wedges) in the horizontal plane. When the molecule is held like this, the wedges for the horizontal bonds and the dashes for the vertical bonds can be implied. This implication is the timesaving feature of a Fischer projection: You no longer need to draw all of the wedges and dashes. Each vertex denotes a carbon atom, much as you would expect based on the convention for skeletal structures.

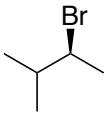


Problem 21. Convert the following structures into Fischer projections.

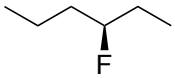
(a) (*S*)-2-butanol



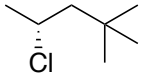
(b) (*S*)-2-bromo-3-methylbutane



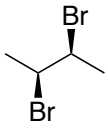
(c) (*R*)-3-fluorohexane



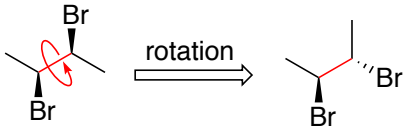
(d) (*R*)-4-chloro-2,2-dimethylpentane



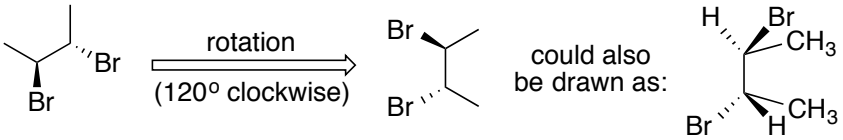
The same convention is utilized for each chirality center in the molecule. If you are converting a skeletal structure to a Fischer projection, it is important to recognize that the molecule is in an eclipsed conformation when represented in a Fischer projection. Therefore, it is likely that the conformation of the skeletal structure will need to be changed in order to convert it to a Fischer projection. Consider (2*S*,3*S*)-2,3-dibromobutane. A typical skeletal structure for this molecule is shown below. This presents the molecule in a staggered conformation.



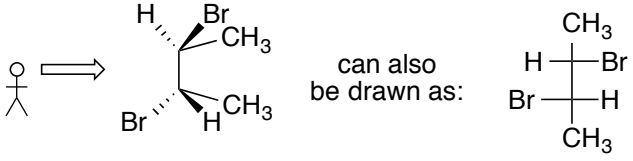
To convert to a Fischer projection, we must rotate about the central carbon-carbon bond so that the molecule adopts an eclipsed conformation.



It is then convenient to rotate the entire molecule to put a terminus of the carbon chain (either of which can be C1 in this case) at the top of the diagram.



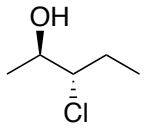
When viewed from the left-hand side, the molecule is observed in a Fischer projection.



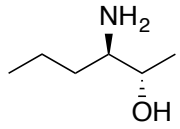
Problem 22. Fischer projections represent eclipsed conformations. Therefore, when internal symmetry is present, it is easy to recognize in a Fischer projection. Draw all of the stereoisomers of (2*S*,3*S*)-2,3-dibromobutane in Fischer projections, and indicate which (if any) possess internal symmetry.

Problem 23. Convert the following drawings into Fischer projections.

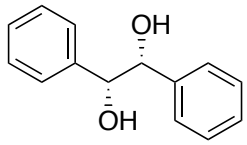
(a)



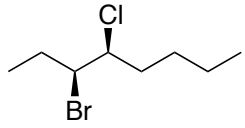
(b)



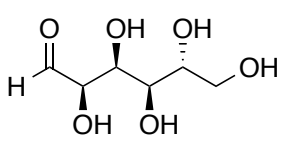
(c)



(d)

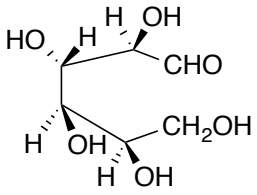


The shorthand notation provided by a Fischer projection is especially convenient when drawing biological molecules, such as carbohydrates, that have a high density of stereocenters. D-Glucose is shown below in a skeletal structure. Rotation about its carbon-carbon bonds can yield an entirely eclipsed conformer.

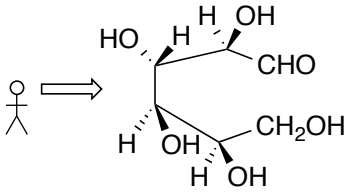


D-glucose

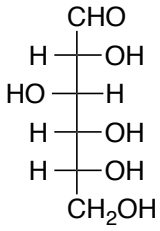
could also be drawn as:



When viewed from the left-hand side, this conformer is presented in a Fischer projection.



can also be drawn as:

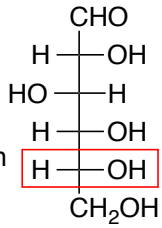


D-glucose

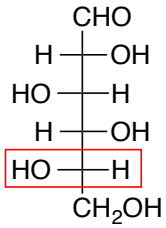
While it can be cumbersome to convert a larger molecule, such as D-glucose, from a skeletal structure to a Fischer projection, you rarely need to do this. Now that you understand the convention of a Fischer projection, you'll find that it is frequently used in certain contexts (such as carbohydrate chemistry) to draw stereoisomers quickly. In fact, it is more common to encounter a drawing of D-glucose in a Fischer projection than in a skeletal structure.

You might be wondering about the "D" in the name D-glucose. This indicates the configuration of the penultimate carbon in the molecule. When the hydroxyl group at that particular center faces to the right in a Fischer projection, it is a D sugar. When the hydroxyl group of the penultimate carbon faces to the left in a Fischer projection, it is an L sugar. The D sugars are naturally occurring in higher organisms.

Hydroxyl on penultimate carbon points to the right in a D sugar



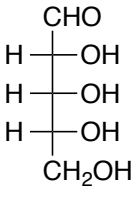
D-glucose



L-glucose

Hydroxyl on penultimate carbon points to the left in a L sugar

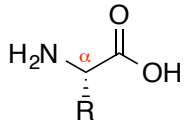
Problem 24. Ribose is a well-known carbohydrate because it is part of the backbone of RNA. D-Ribose is shown below. Using Fischer projections, draw all of its stereoisomers. Label those that are D sugars, as well as those that are L sugars.



D-ribose

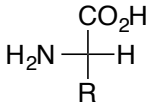
Amino acids are designated as D or L in an analogous fashion. An L amino acid is shown below in a skeletal structure. An amino acid contains a carbon, known as the α carbon, that

bears a carboxylic acid, an amino group, a side chain (R), and a hydrogen. This carbon is often a chirality center.



an L amino acid

When viewed in a Fischer projection with the carbon backbone on the vertical axis, an L amino acid appears as follows. It is deemed L because the amino group faces to the left. The L amino acids are the ones incorporated into proteins.

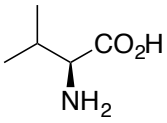


an L amino acid

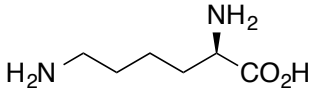
It is important to note that the D and L designations discussed in this section reveal the configuration of a particular chirality center within a molecule. These designations are therefore unrelated to *d* and *l* (dextrorotary and levorotary, respectively), which denote the direction in which the molecule rotates plane-polarized light.

Problem 25. Classify the following amino acids as D or L.

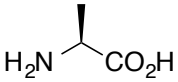
(a) valine



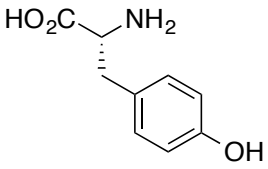
(b) lysine



(c) alanine



(d) tyrosine



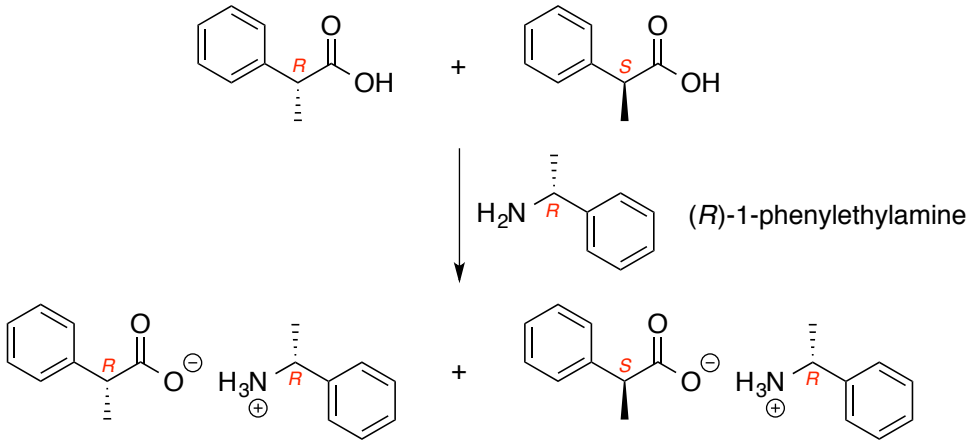
Section 8: Resolution

The fact that enantiomers have identical properties, with the exception of specific rotation, makes them challenging to separate. If they are liquids, a distillation won't separate them because their boiling points are identical. If they are solids, a recrystallization cannot be relied upon to separate them either. Some racemic mixtures do form enantiomerically pure crystals, but this phenomenon is rare. Louis Pasteur observed it with tartaric acid crystals while studying winemaking. The observation of crystals that were non-superimposable mirror images led him to discover and explain enantiomers.

There are processes that allow for the reliable separation of enantiomers, but these hinge upon the formation of diastereomeric compounds or interactions. One method for resolving (or separating) enantiomers exploits acidic or basic functional groups. Consider a pair of enantiomers containing a carboxylic acid functional group, such as (*R*)- and (*S*)-2-phenylpropanoic acid.

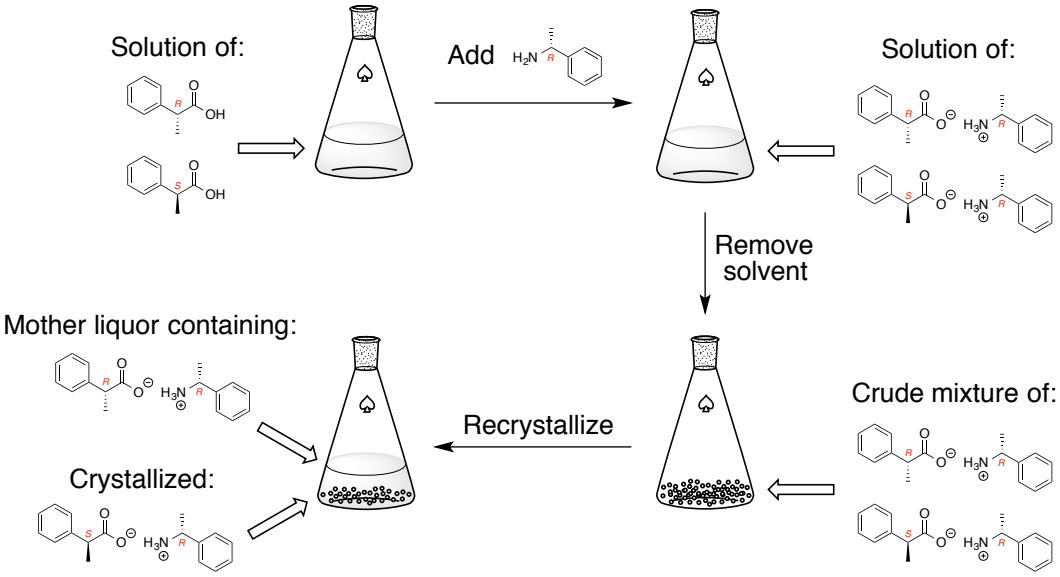
Racemic mixture of (*R*) and (*S*)-2-phenylpropanoic acid

If we add a chiral amine having a single configuration (e.g., *R*) to the mixture, a pair of diastereomeric salts (*R*,*R* and *S*,*R*) are formed through acid-base reaction.

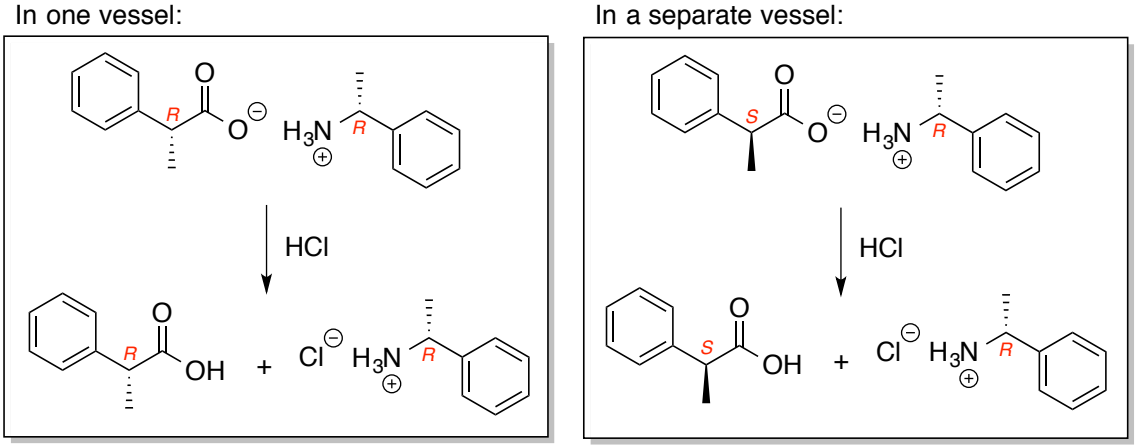


Since these salts are diastereomers, they have differing solubility and can be separated through recrystallization. A schematic of the process is shown below. The chiral, non-racemic amine is added to the racemic mixture of carboxylic acids in solution. This allows

for the acid-base reaction to take place, which yields diastereomeric salts. The solvent can then be removed, giving a crude, solid mixture of the two diastereomeric salts. Upon recrystallization from a suitable solvent, one diastereomer will crystallize preferentially (*S*,*R* in the diagram below), while the other mostly remains in the mother liquor. After filtration, the filter cake will predominantly contain the (*S*,*R*) salt, while the filtrate will be mostly the (*R*,*R*) salt.

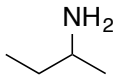


After separation, the salts can be treated with acid to regenerate the carboxylic acids in their original form. The hydrochloride salt of the amine is readily removed from each acid due to its higher water solubility.



Since the chiral, non-racemic amine was used to separate (or resolve) the two enantiomeric carboxylic acids, it is referred to as a resolving agent.

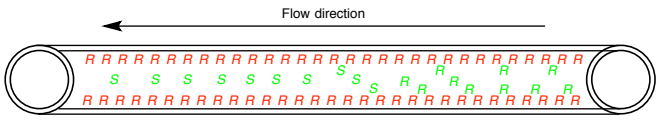
Problem 26. Devise a procedure to resolve a racemic mixture of the following amine. You may use any suitable resolving agent.



A second option for resolution of enantiomers entails chromatography using a chiral, non-racemic stationary phase. In chromatography, compounds of interest (also known as analytes) are separated based on differences in their affinity for a stationary and mobile phase. The analytes pass through a column that is coated with an immobile layer called the stationary phase. There is also some sort of mobile phase (either a gas or a liquid) that moves the sample through the column. Analytes that have a greater affinity for the mobile phase spend more time traveling and elute from (i.e., come off) the column first. Conversely, analytes with a higher affinity for the stationary phase take longer to elute.

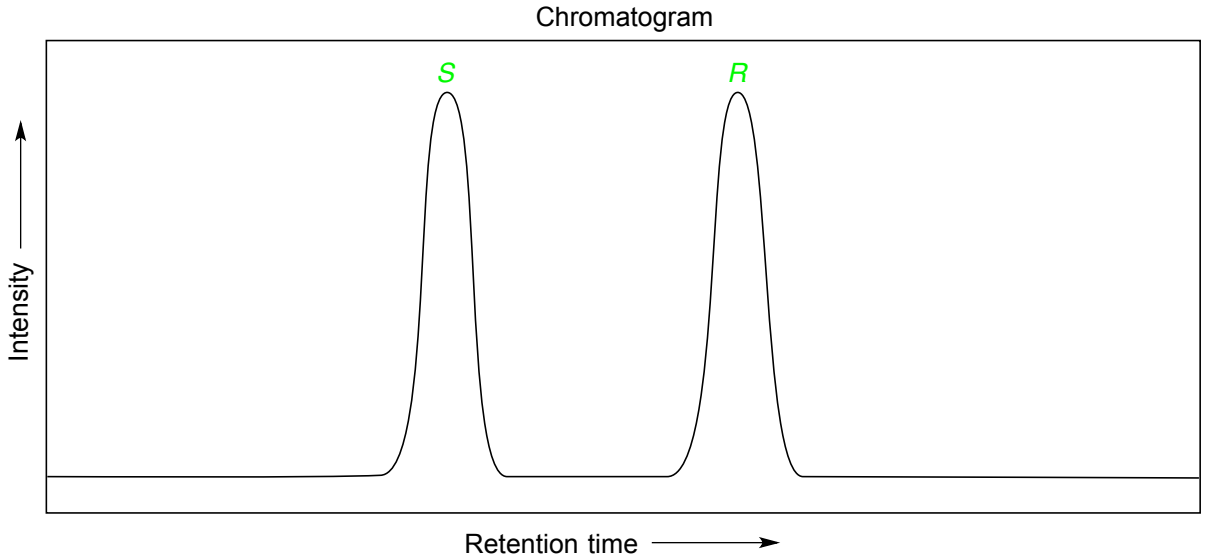
When the stationary phase is achiral, enantiomers will have identical affinities for it, so a separation cannot be achieved. However, if the stationary phase contains a chiral, non-racemic material, the interactions between it and the analytes are diastereomeric. This allows differences to surface. One enantiomer of the analyte may have a higher affinity for the chiral, non-racemic stationary phase. This analyte will be retained on the column longer.

In the schematic below, the chiral, non-racemic coating inside the column is represented by the red *R*s denoting its configuration. The green *R*s and *S*s signify the racemic mixture of analyte molecules. Those that are in the middle of the column are moving with the mobile phase, while those close to the coating are interacting with the stationary phase. The diagram shows that, on average, the *R* enantiomer spends more time interacting with the stationary phase than its *S* counterpart. Note that such a preference is not easily predicted and is much more likely to be determined experimentally.



Cross section of a column containing a chiral, non-racemic stationary phase (*R*)

As a result of the difference in affinity shown above, the *S* enantiomer elutes from the column first and is followed by the *R* enantiomer at a later time.

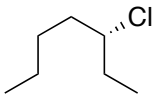


Problem 27. Why are the two peaks in the chromatogram above of equal size?

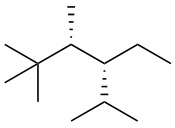
End-of-the-Chapter problems

Problem 28. Draw the enantiomer of each of the following molecules. If the compound does not have an enantiomer, explain why this is the case.

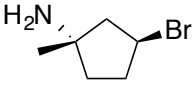
(a)



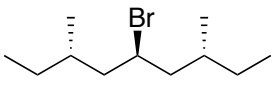
(b)



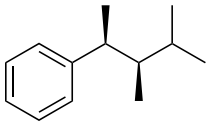
(c)



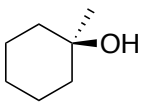
(d)



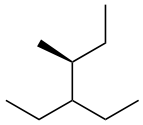
(e)



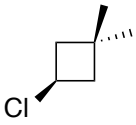
(f)



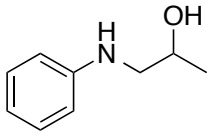
(g)



(h)

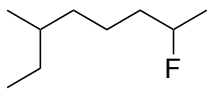


Problem 29. The following molecule has only two stereoisomers at room temperature, despite possessing two chirality centers. Why is this the case?

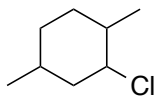


Problem 30. For each of the following molecules, identify the chirality centers and predict the maximum number of stereoisomers possible.

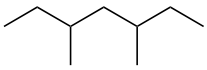
(a)



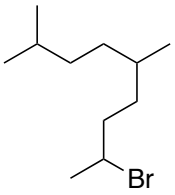
(b)



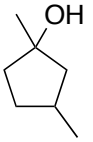
(c)



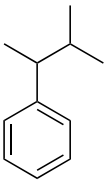
(d)



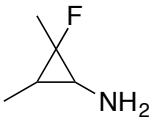
(e)



(f)



(g)



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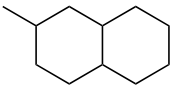
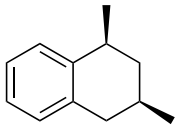
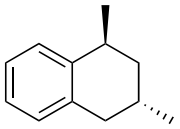


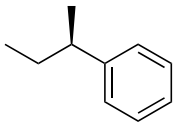
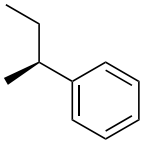
Problem 31. For the molecules in Problem 30, draw all of the stereoisomers that exist.

Problem 32. What is the relationship between the molecules in each of the following pairs?

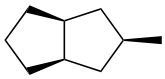
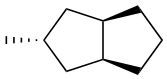
(a)

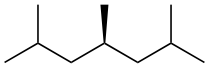
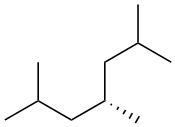
(b)

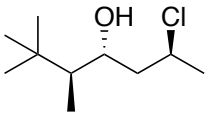
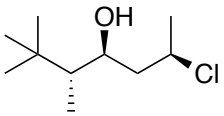
(c)

(d)

(e)

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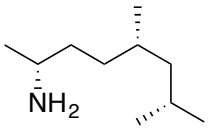
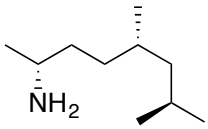
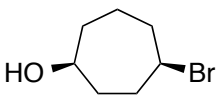
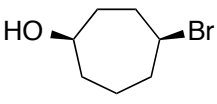
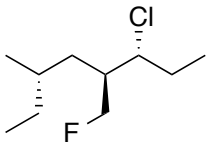
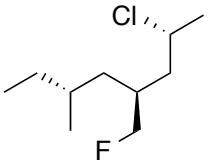



(g)

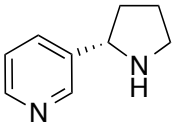
(h)





Problem 33. Assign the configurations for the molecules in Problem 32 (a, b, and e – h).

Problem 34. Nicotine is a well-known alkaloid found in tobacco.



(a) What is its configuration?

(b) The specific rotation of nicotine is -169 at 20 ˚C using the D-line of sodium. What is the concentration (in g of nicotine / mL solvent) if the observed rotation is -21˚ when using a 5 cm sample cell?

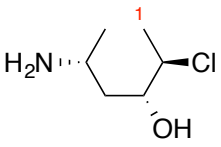
(c) Using the information in parts (a) and (b), provide a complete name for nicotine that designates both its configuration and optical activity.

(d) What would the complete name of nicotine's enantiomer be?

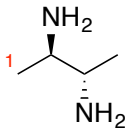
(e) What would the specific rotation be for nicotine's enantiomer under the same conditions described in part (b)?

Problem 35. Convert the following structures into Fischer projections. Note the C1 is indicated in molecules that we have not yet learned how to name.

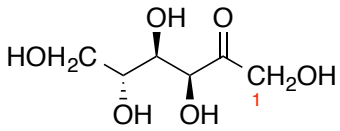
(a)



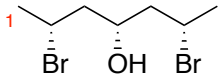
(b)



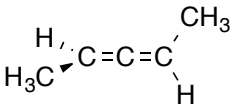
(c) Fructose (shown below) is a component of sucrose, or table sugar.



(d)



Problem 36. There are some unexpected occurrences of chirality in organic molecules. Some compounds without chiral atoms can nevertheless be chiral. Rigidity or restricted rotation is a key feature in such instances. An example is an allene, such as the one shown below.

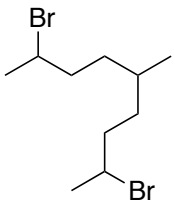


(a) Why are the substituents on one carbon in the plane of the page, while those on the other carbon are perpendicular to the plane of the page?

(b) Draw the mirror image of this allene.

(c) Are the mirror images superimposable? Why or why not?

Problem 37. Draw all of the stereoisomers of the following compound.



Problem 38.

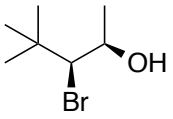
(a) After reading the additional information supplied in the answer to Problem 37, assign the configurations of the molecules shown in Problem 32(c).

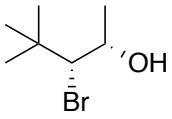
(b) Now that you have drawn fructose in a Fischer projection in Problem 35(c), is it a D or an L sugar?

Problem 39.

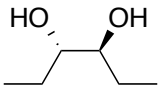
(a) What can you say about the physical properties of the following pairs of compounds?

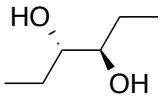
(1)



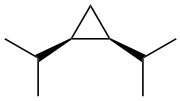


(2)

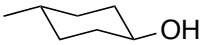


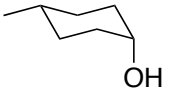


(3)



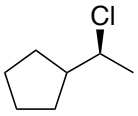
(4)

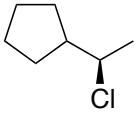




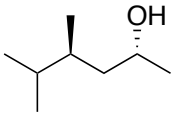
(b) Will the following molecules react the same or differently with achiral reagents? How will they react with chiral reagents?

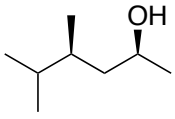
(1)



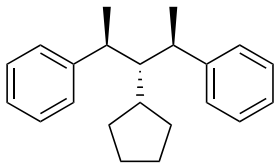


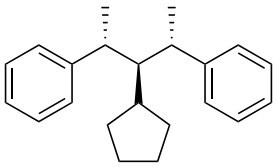
(2)



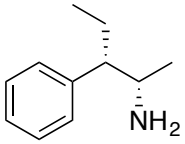


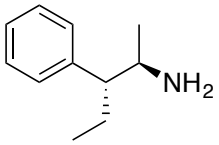
(3)



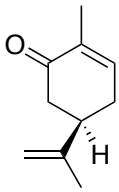


(4)

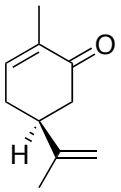




Problem 40. (*R*) and (*S*)-carvone are classic examples of interesting enantiomers because one smells like spearmint and the other has the odor of caraway.



(*R*)-carvone



(*S*)-carvone

The specific rotation of (*R*)-carvone is –61. If the specific rotation of a mixture of the carvone enantiomers is +45, what is the ee of this mixture? What is the major enantiomer and what percentage of the mixture does it account for? What is the minor enantiomer and what percentage of the mixture does it account for?

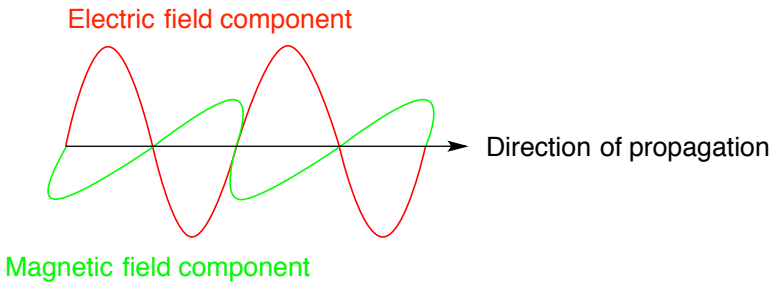
Problem 41. Devise a method for the resolution of a racemic mixture of the following carboxylic acid enantiomers. You may use any suitable resolving agent.

Chapter 5: Infrared Spectroscopy and Nuclear Magnetic Resonance Spectroscopy

Section 1: Spectroscopy Fundamentals
Section 2: Infrared (IR) Spectroscopy
Section 3: Structure Solving Using IR Spectroscopy
Section 4: Nuclear Magnetic Resonance (NMR) Spectroscopy
Section 5: Structure Solving Using NMR Spectroscopy

Section 1: Spectroscopy Fundamentals

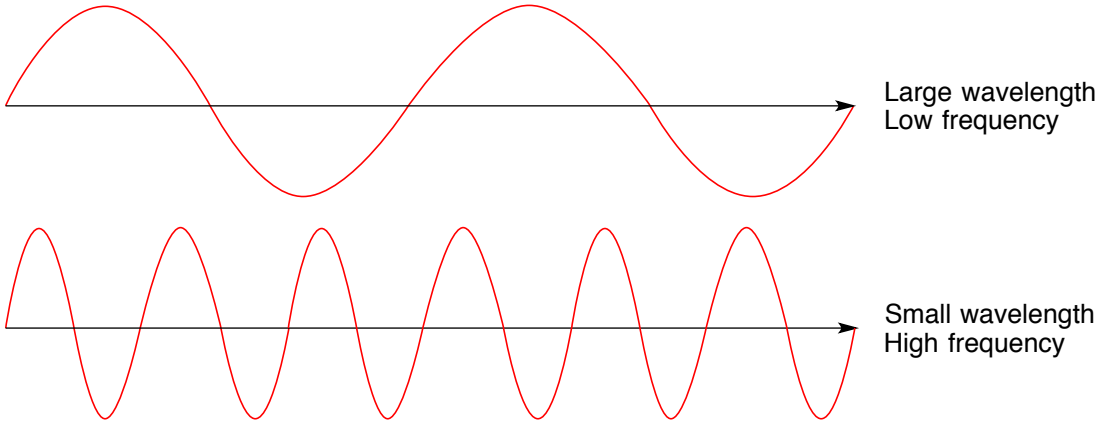
Light can be defined more broadly as electromagnetic radiation. Recall from the previous chapter that a light wave consists of an electric and magnetic field, hence the name electromagnetic radiation.



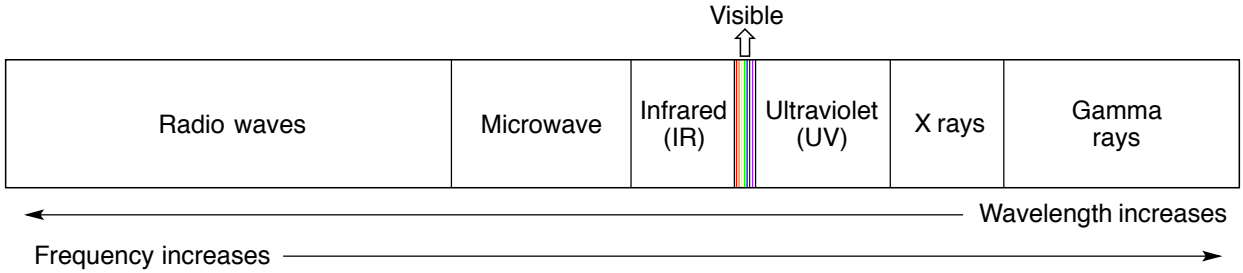
There are various types of electromagnetic radiation, ranging from radio waves to gamma rays, that compose a spectrum of light known as the electromagnetic spectrum. All types of electromagnetic radiation travel at the same speed in a given medium. The speed of light (c) is approximately $3 \times 10^8 \ {}^{m}/_{s}$ in a vacuum. However, different types of light vary in their wavelength (λ) and frequency (ν). The wavelength is the distance from a point on a wave to the identical point on the next wave, and it has units of distance (e.g., m). On the other hand, the frequency is the number of waves passing through a point in space per unit time. Frequency therefore has units of inverse time (e.g., s^{-1}). The product of the wavelength and frequency is the speed of light.

$$c = \lambda \nu$$

Given that the speed of light is a constant in a given medium, wavelength and frequency must be inversely proportion. In other words, if the wavelength is large, then the frequency will be low and vice versa.



The electromagnetic spectrum has low-frequency, large-wavelength radio waves on one end and high-frequency, short-wavelength gamma rays on the other end. In between, we find microwaves, infrared, visible, ultraviolet, and X rays. Notice that, although we tend to think of light as visible, visible light actually composes only a small part of the electromagnetic spectrum.



Light has energy that can be related to its frequency or wavelength. The energy of light is the product of Planck's constant and the frequency.

$$E = h\nu$$

Planck's constant is $6.626 \times 10^{-34}\, Js$, where J represents the unit of energy known as a joule. This equation shows that frequency is directly proportional to energy. Therefore, the *higher* the frequency of light, the *higher* its energy is.

Energy can also be related to wavelength if the equation $c = \lambda\, \nu$ is solved for ν.

$$\frac{c}{\lambda} = \nu$$

Substituting $\frac{c}{\lambda}$ for ν in the equation $E = h\nu$ gives the following relationship.

$$E = \frac{hc}{\lambda}$$

This shows that wavelength is inversely proportional to energy. In other words, the *larger* the wavelength of light, the *lower* its energy is.

The interaction between light and matter is known as spectroscopy. Different portions of the electromagnetic spectrum can excite molecules in different ways. These interactions give us valuable insight into the structure of molecules.

Problem 1. Rank radio waves, microwaves, infrared, visible, ultraviolet, X rays, and gamma rays in order of:

(a) increasing frequency

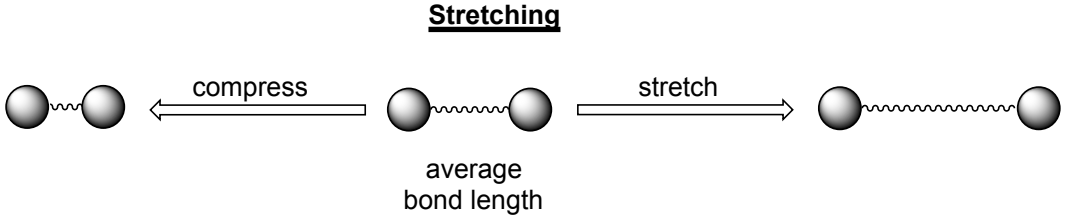
(b) increasing wavelength

(c) increasing energy

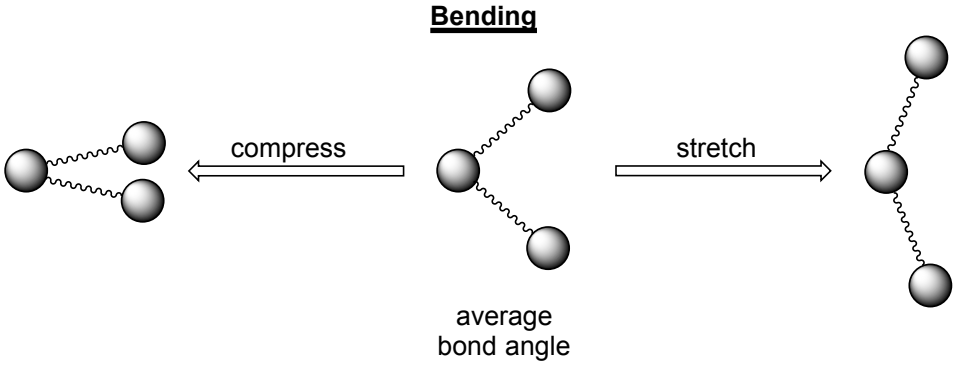
Section 2: Infrared (IR) Spectroscopy

The principles

Molecules have many vibrational modes of motion. These include the stretching and bending of bonds. Bond stretching is shown below. The two atoms are represented as spheres, linked by a bond shown as a spring. Notice that the bond compresses and elongates relative to its average length.



An example of bending is shown below. Here, the bond angle is reduced and widened relative to its average value.



There are additional vibrational modes, such as twisting which would be bending that occurs in and out of the plane of the page.

Each of the molecule's vibrational modes oscillates with a particular frequency. It is convenient to approximate atoms as weights and bonds as springs for this discussion. If we do so, Hooke's law allows us to calculate the frequency of a given vibration:

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

In this equation, k is the force constant of the spring (i.e., a measure of the strength of the bond), and μ represents the reduced mass of the system, which is the product of the two atoms' masses divided by their sum. The mass of atom a is m_a, and the mass of atom b is m_b.

$$\mu = \frac{m_a m_b}{m_a + m_b}$$

We don't need to be particularly concerned with number crunching. It is, however, important to recognize two trends. First, a stronger bond is effectively a tighter spring, and as k increases, so does the frequency of oscillation. This should match your knowledge of the physical world. Imagine a weak spring linking two weights. If you stretch that spring and release it, you expect a modest frequency of oscillation. If you repeat the experiment with the same weights and a stronger spring, you would expect to observe a higher frequency of oscillation.

The second trend is that, as the atoms' masses increase, the frequency of oscillation will decrease. This, too, should match your understanding of the world around you. If you revisit our spring experiment and imagine replacing the weights with heavier ones, then you would anticipate a lower frequency of oscillation. Both of these trends have useful predictive value. In short, we can predict that different sorts of bonds will interact with different frequencies of light.

Problem 2. In each of the following pairs, which bond would be expected to have the higher frequency of vibration?

(a) C=O or C-O

(b) C-F or C-Cl

(c) C=N or C≡N

(d) C-C or C-H

These vibrational modes of molecules tie in with spectroscopy when we consider shining light on a sample. If there are frequencies of light that match the frequencies of oscillation within the molecule, then the compound will absorb those frequencies of light. This leads to an excitation of the vibrational modes that resonated with the light. Infrared (IR) light happens to contain the portion of the electromagnetic spectrum with the proper frequency to excite molecular vibrations.

In IR spectroscopy, frequency is reported in wavenumbers, having units of $\frac{1}{cm}$ (or cm^{-1}). Wavenumber is abbreviated as $\tilde{\nu}$ and is simply the inverse of wavelength.

$$\tilde{\nu} = \frac{1}{\lambda}$$

If we solve $c = \lambda\, \nu$ for wavelength, we obtain $\frac{c}{\nu}$. Substituting this for wavelength in the equation, we'll see that wavenumber is also frequency (ν) divided by the speed of light (c).

$$\tilde{\nu} = \frac{1}{\lambda} = \frac{\nu}{c}$$

Problem 3. For each pair of bonds listed in Problem 2, state which would exhibit a signal at a higher wavenumber.

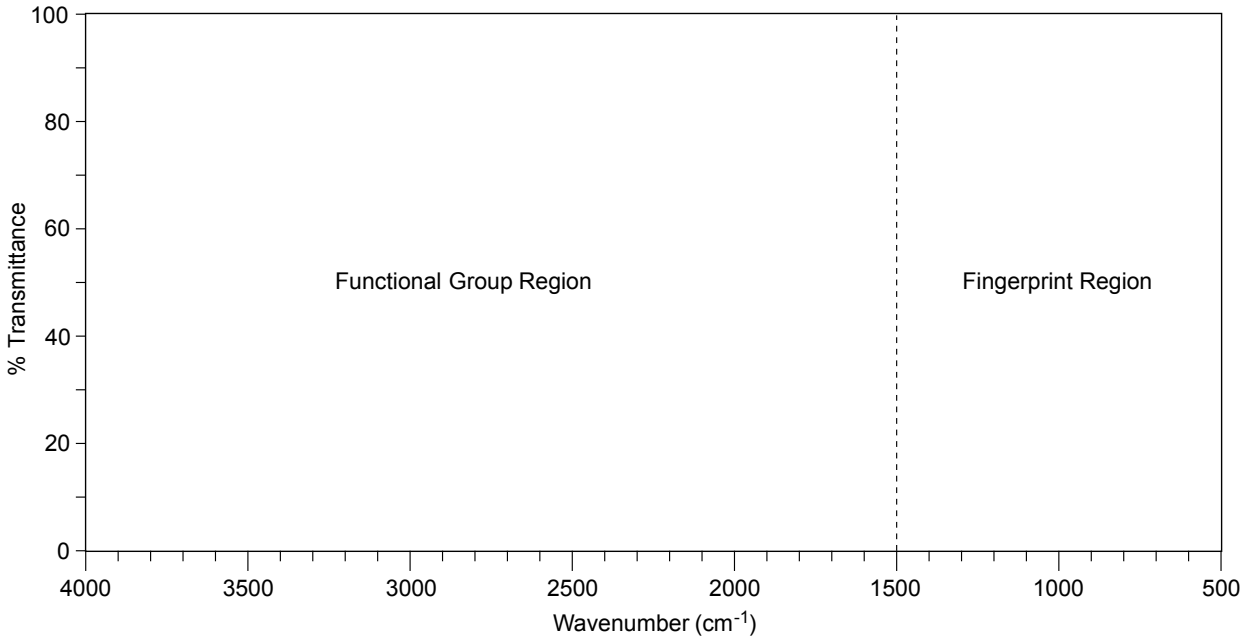
The IR spectrum

An infrared spectrometer allows us to record the interaction between infrared light and matter. A broad spectrum of infrared light is produced by the instrument's light source, and this light shines on a sample of interest. The molecules in the sample will absorb those wavenumbers that excite their vibrations, while the other wavenumbers simply pass through the sample. A detector records the light that passes through the sample. This results in a spectrum showing the wavenumbers that were absorbed and how intensely they were absorbed.

The x-axis shows wavenumbers. The y-axis shows percent transmittance, which is a measure of the percentage of incident light that passed through the sample. A 100% transmittance would indicate that no light of that wavenumber was absorbed, while a 0% transmittance would show that all light was absorbed. Because of the way that the y-axis is defined, peaks in an IR spectrum point downward.

Furthermore, an IR spectrum can be divided into two major segments: the fingerprint region and the functional group region. In general, signals in the fingerprint region have less predictive value. As the name suggests, they are, by and large, a fingerprint of the molecule. Much as you cannot extrapolate what a person looks like from their fingerprints, you cannot easily extrapolate a molecule's structural features from the fingerprint region of the spectrum. Therefore, this information is most useful when comparing a spectrum to entries in a spectral library. In contrast, the functional group region contains peaks that do

have general predictive value. They signify certain types of bonds within a molecule's structure. As a result, the functional group region will be the focus of our discussion.



Functional Group Resonance

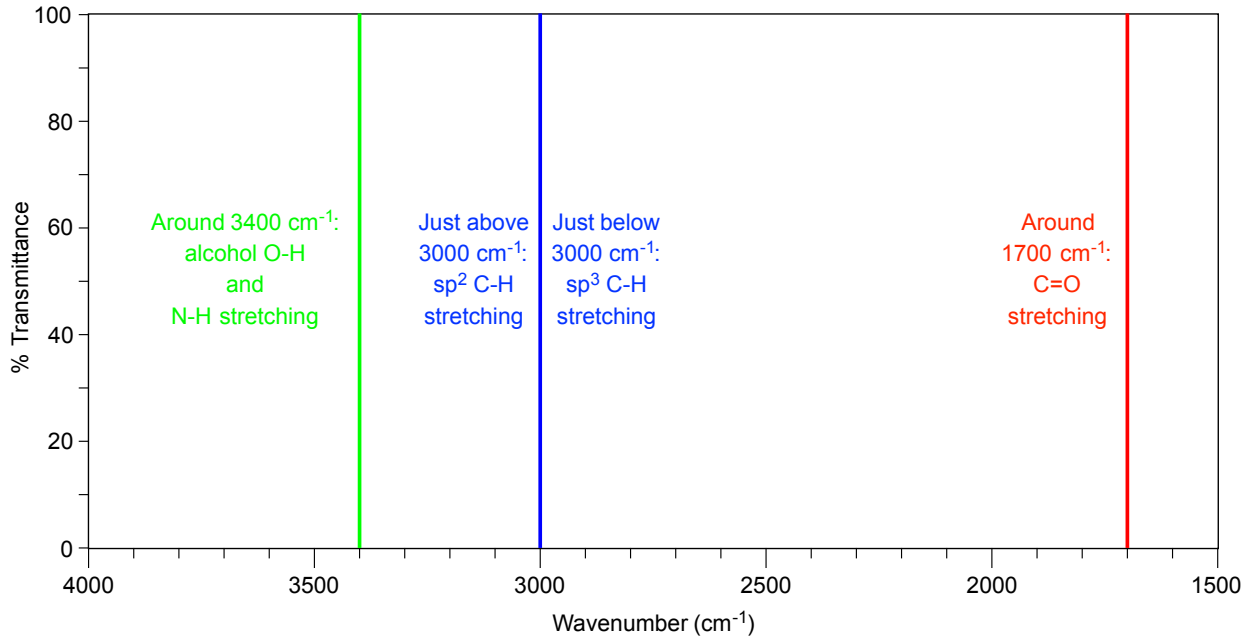
There are many IR correlation tables available. These are tables that enumerate all the many types of bonds and their respective resonances in wavenumbers. However, organic chemists rarely consult a correlation table unless they are studying molecules with unusual types of bonds. It is much more common for an organic chemist to spot-check a few key regions of the IR spectrum. This allows one to very quickly ascertain some key information about the functional group(s) in a molecule. There are three key areas to spot-check:

(a) Carbonyl stretching occurs around 1700 cm^{-1}.

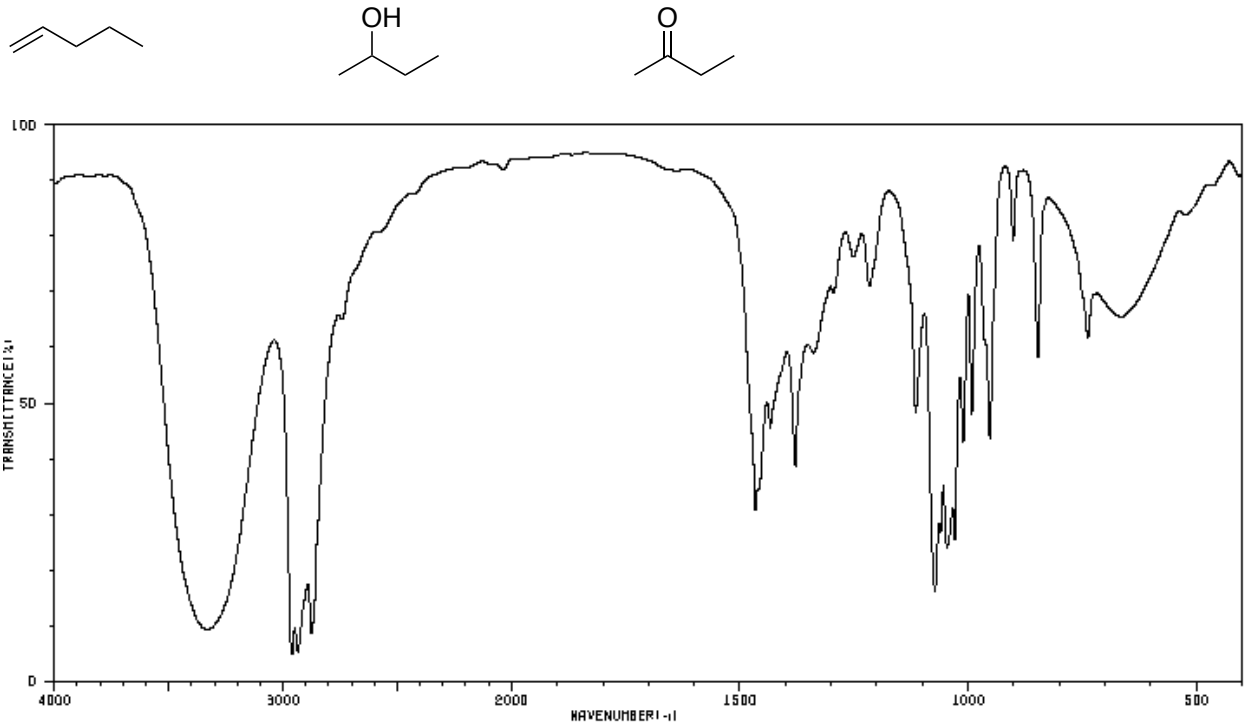
(b) Carbon-to-hydrogen stretching occurs near 3000 cm^{-1}. Importantly, when the carbon is sp^3 hybridized, the stretching occurs just below 3000 cm^{-1}, but when the carbon is sp^2 hybridized and part of an alkene or aromatic ring, the stretching is located just above 3000 cm^{-1}.

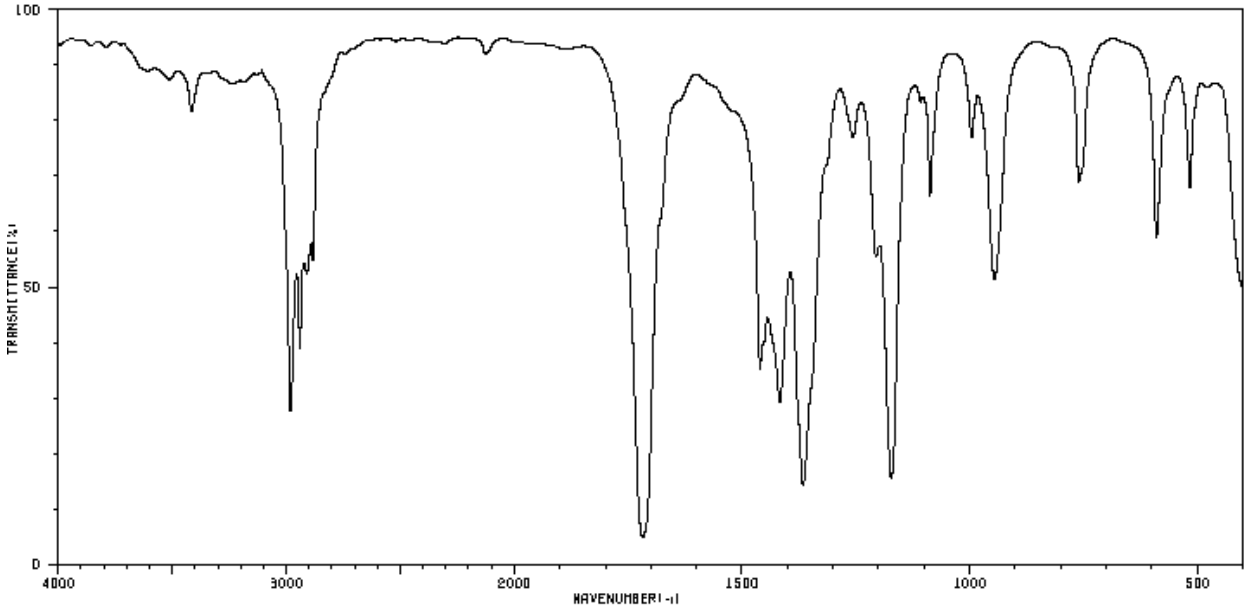
(c) Finally, alcohol O-H stretching and N-H stretching occur around 3400 cm^{-1} ($\pm$ 200 cm^{-1}).

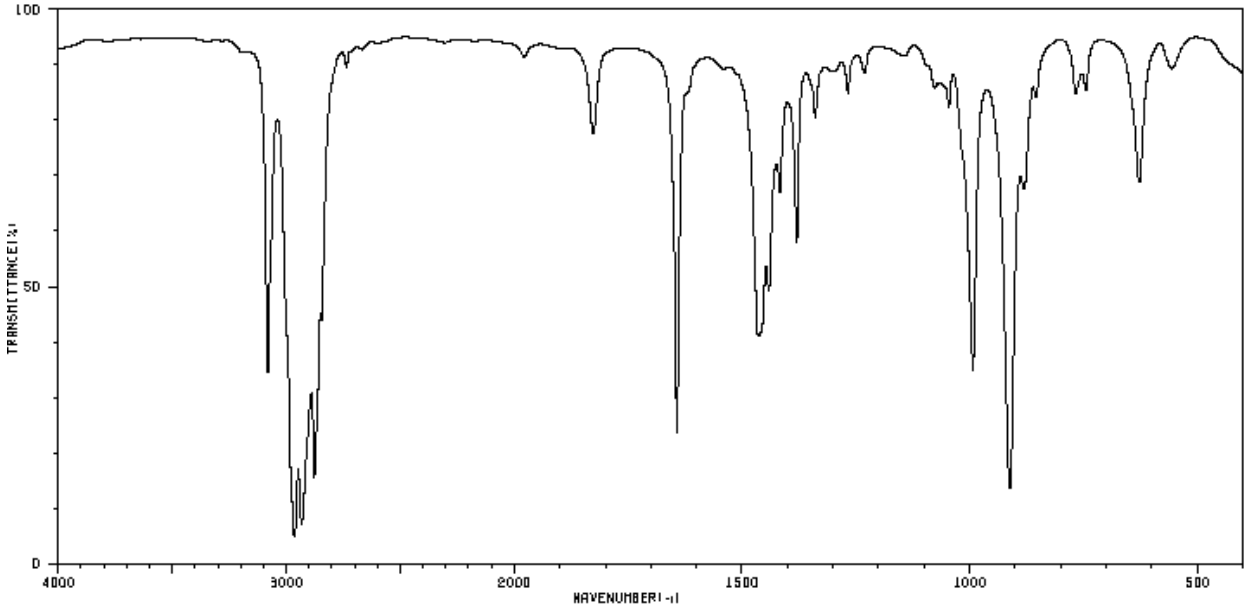
Notice that the spectrum below includes only the functional group region.



Problem 4. Using these three key portions of the functional group region, match the following molecules to their IR spectra.







Any significant peaks outside these three key regions can be compared to the correlation table below.

Correlation Table

Resonance	Bond
3600 – 3200 cm^{-1}	Alcohol or phenol O-H stretch
3500 – 3200 cm^{-1}	N-H stretch
3500 – 2500 cm^{-1}	Carboxylic acid O-H stretch
3300 cm^{-1}	Alkyne (sp) C-H stretch
3100 – 3000 cm^{-1}	Alkene/aromatic (sp^2) C-H stretch
3000 – 2850 cm^{-1}	Alkane (sp^3) C-H stretch

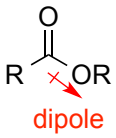
2800 – 2700 cm^{-1}	Aldehyde (sp^2) C-H stretch
2300 – 2200 cm^{-1}	C≡N
2200 – 2100 cm^{-1}	C≡C
1750 – 1650 cm^{-1}	C=O
1650 cm^{-1}	C=C
1600 cm^{-1} and ~1500 cm^{-1}	

Problem 5. Reexamine the IR spectrum of the alkene originally provided in Problem 4. Identify the prominent signal that appears in the correlation table above but was *not* already noted in the answer to Problem 4.

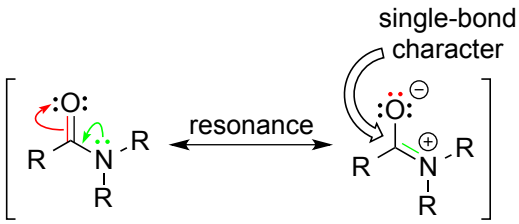
Let's elaborate a bit more on the three key segments of the functional group region.

The carbonyl-stretching region

Simple aldehydes and ketones absorb near 1715 – 1720 cm^{-1}. Esters typically absorb a bit higher, around 1740 cm^{-1}. On the other hand, amides typically absorb a bit lower, around 1650 cm^{-1}. We can explain this by considering the effect of the heteroatom on the carbonyl in each instance. While esters can most certainly experience resonance, the electronegative character of the carboxyl (sp^3) oxygen makes the dipole between the carbonyl carbon and the carboxyl oxygen the predominant influence. The carboxyl oxygen is less inclined to release electron density through resonance than it is to pull electron density toward itself inductively. This has the effect of strengthening "the spring" of the carbonyl. Thus, the frequency of oscillation increases.

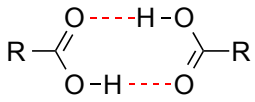


On the other hand, nitrogen is less electronegative than oxygen, so resonance becomes a more significant effect for amides. The resonance of electrons from nitrogen into the carbonyl lends some single-bond character to the carbonyl. Since single bonds are weaker than double bonds, this weakens the spring, resulting in a lower frequency of oscillation.



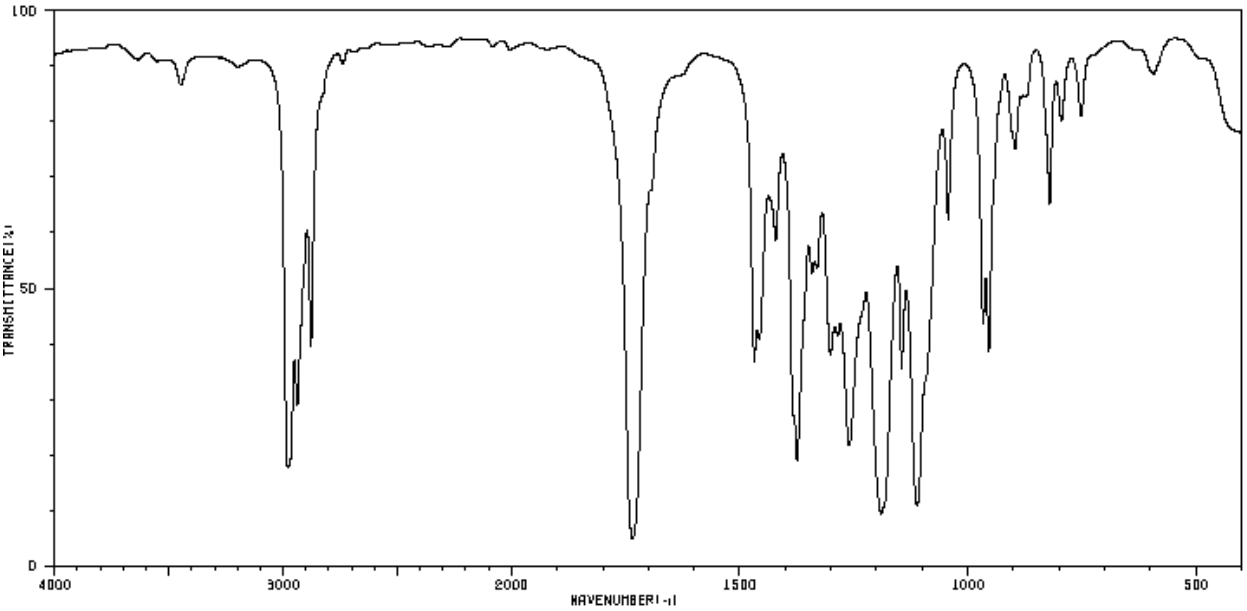
The carbonyl stretch of a carboxylic acid is influenced by hydrogen bonding. A carboxylic acid in isolation will show a carbonyl resonance around 1760 cm^{-1}, not unlike an ester.

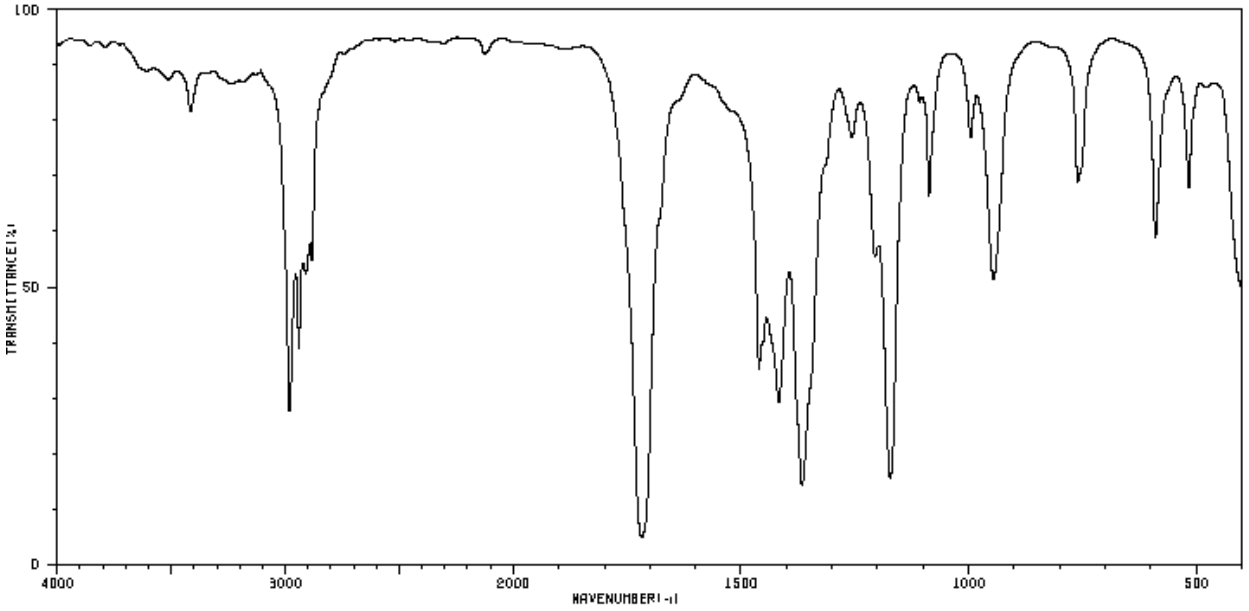
However, if the concentration of the sample is high enough to allow hydrogen bonding (which it usually is), the carbonyl resonance will fall below 1700 cm^{-1}. The hydrogen bonding withdraws some electron density from the carbonyl, weakening the spring constant and reducing the frequency of oscillation.



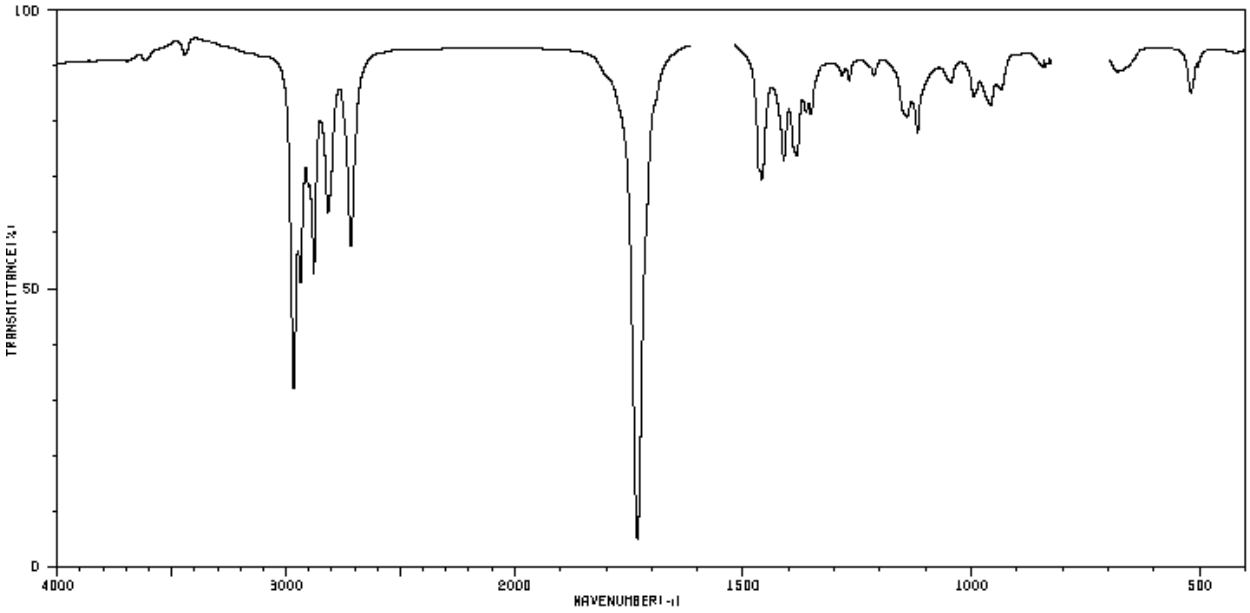
hydrogen bonds

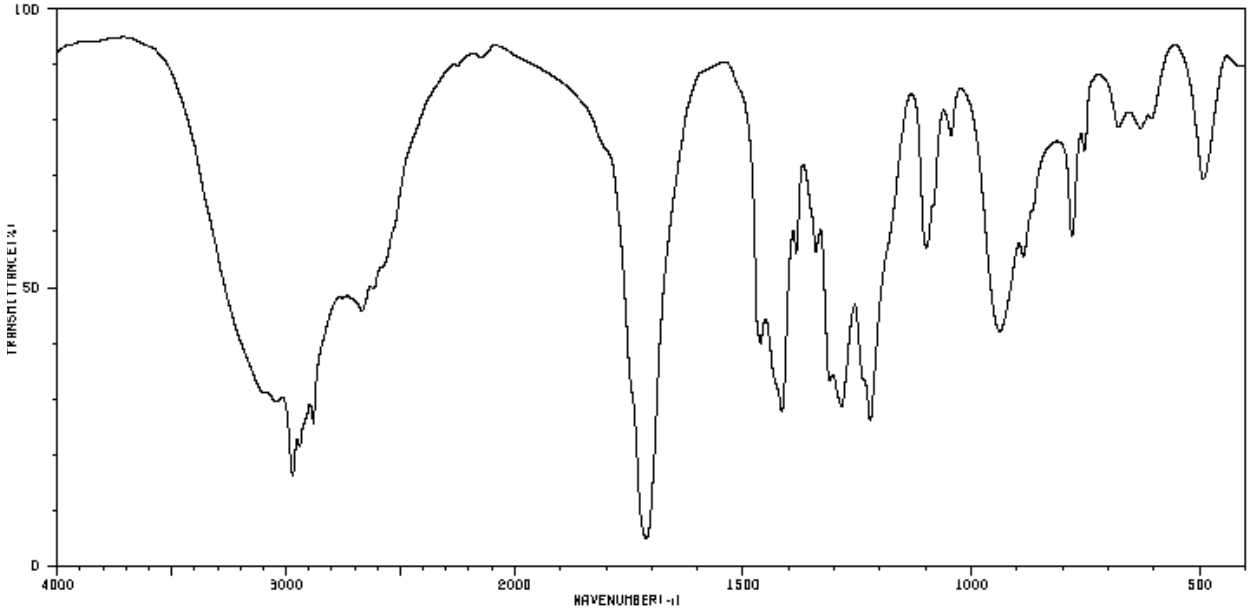
Problem 6. The IR spectra of a ketone and an ester are shown below. Which spectrum is more likely to be that of the ester and why? Hint: You have to look carefully at the carbonyl resonances.





Problem 7. Match the following carbonyl-containing compounds with their IR spectra.

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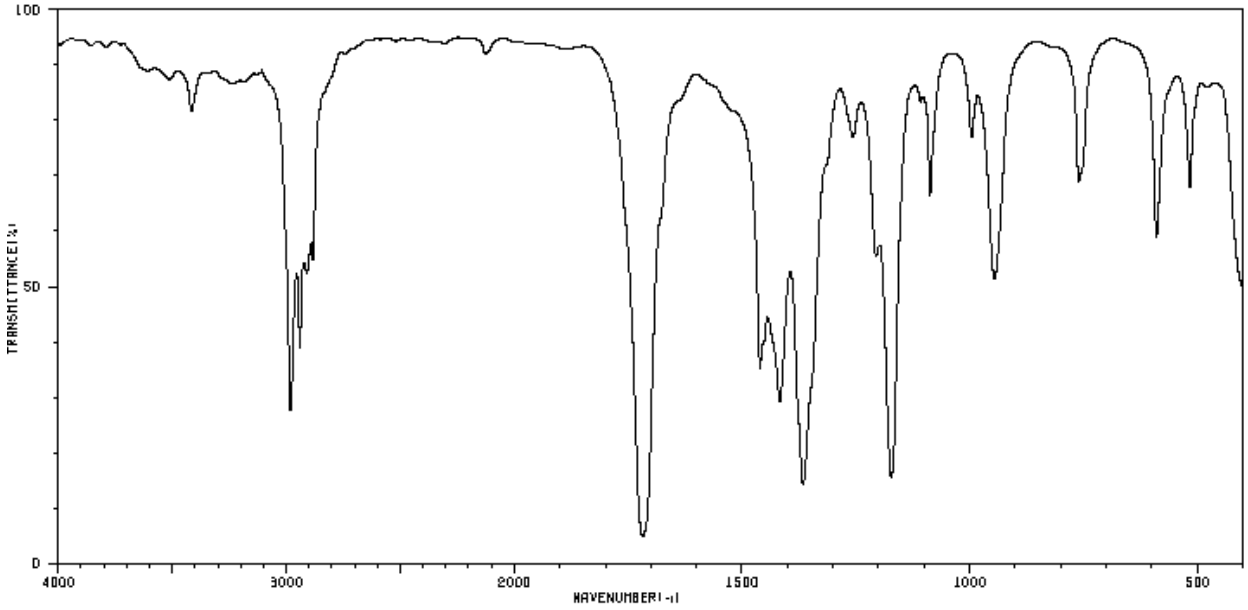
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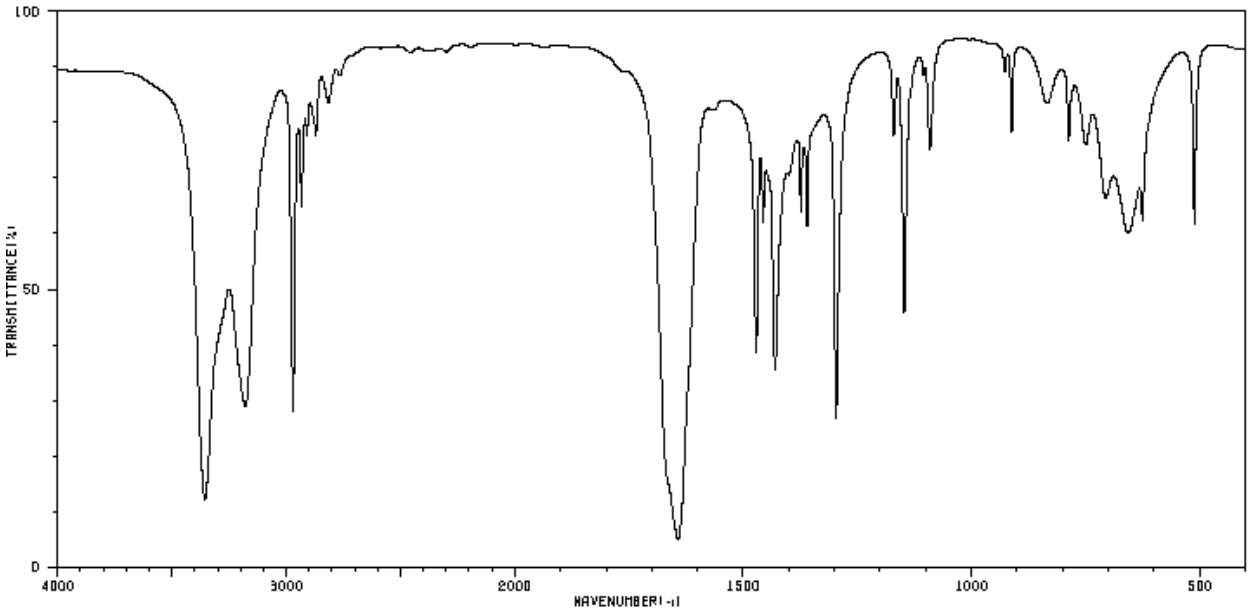
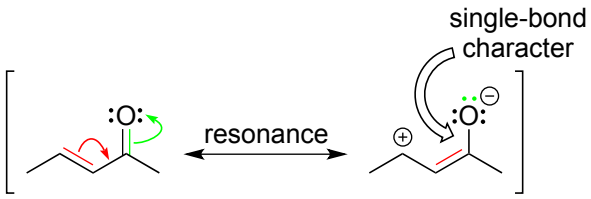
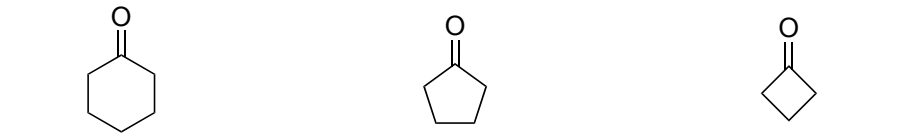


There are two other notable influences on carbonyl stretching: conjugation and ring size. Conjugation lowers the frequency of a carbonyl by about 30 cm^{-1}. Resonance due to conjugation introduces single-bond character to the carbonyl, reducing its spring constant and therefore its frequency.



Ring size also plays a role in adjusting carbonyl frequency. A carbonyl in a six-membered ring is effectively unstrained and will exhibit the expected frequency. However, as the ring size decreases, the bond angle of the carbonyl is constrained, which results in a higher energy absorption.

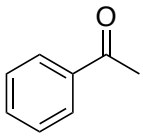


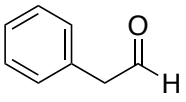
Carbonyl frequency
1715 cm^{-1}

Carbonyl frequency
1750 cm^{-1}

Carbonyl frequency
1775 cm^{-1}

Problem 8. Match the following carbonyl-containing compounds with their IR spectra.


O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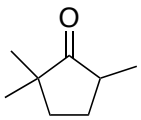
H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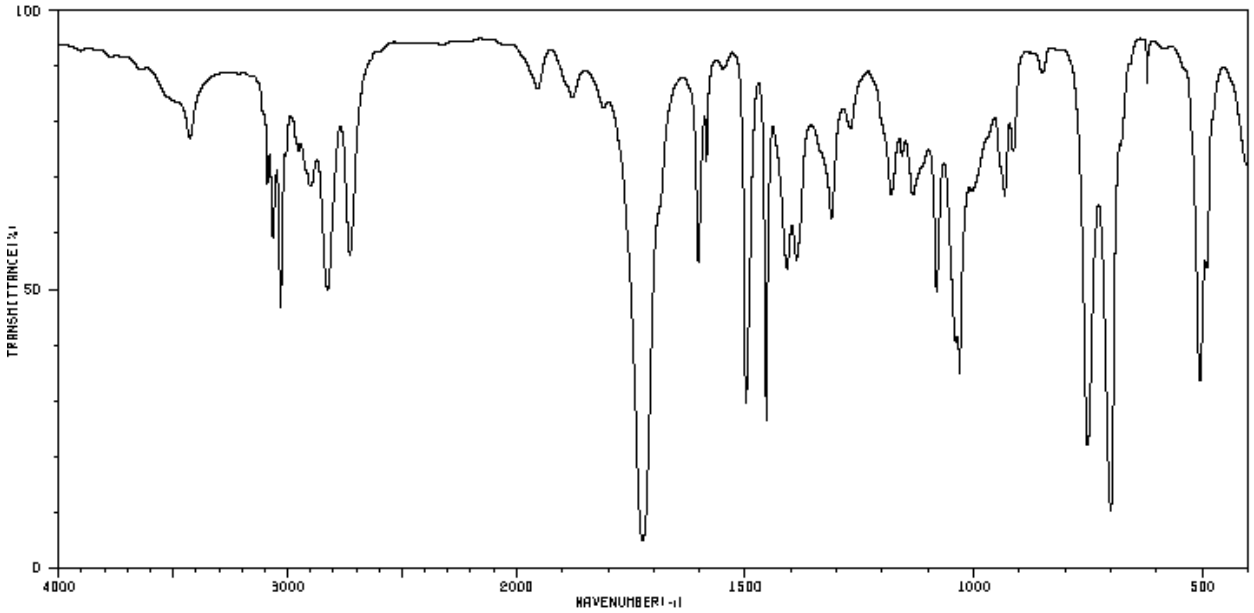
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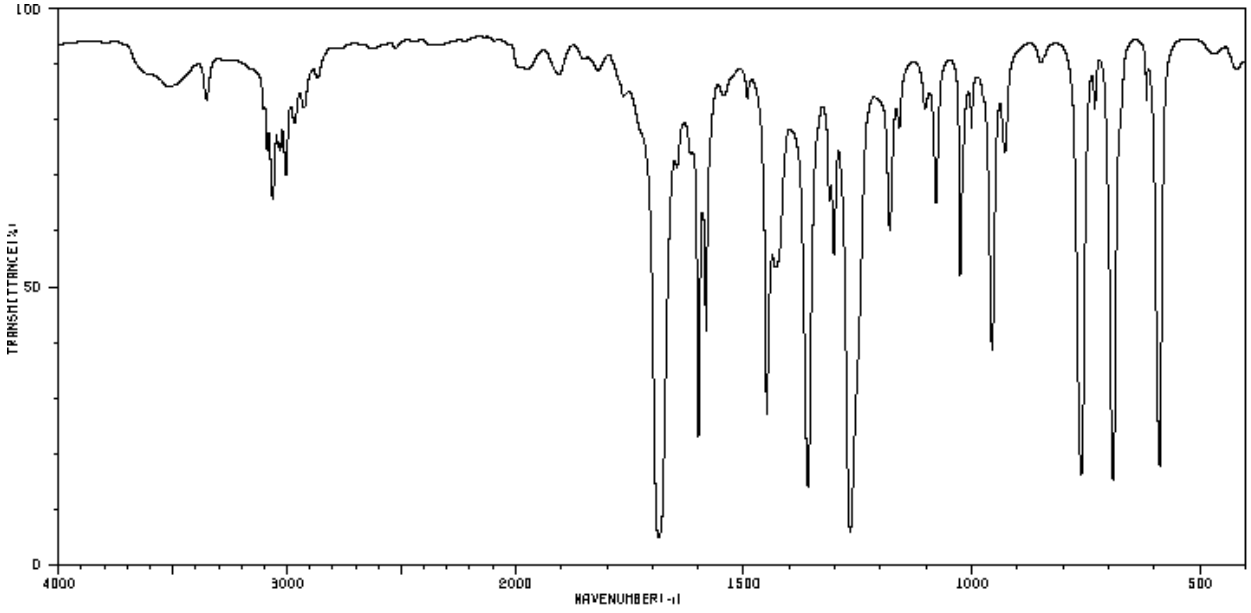
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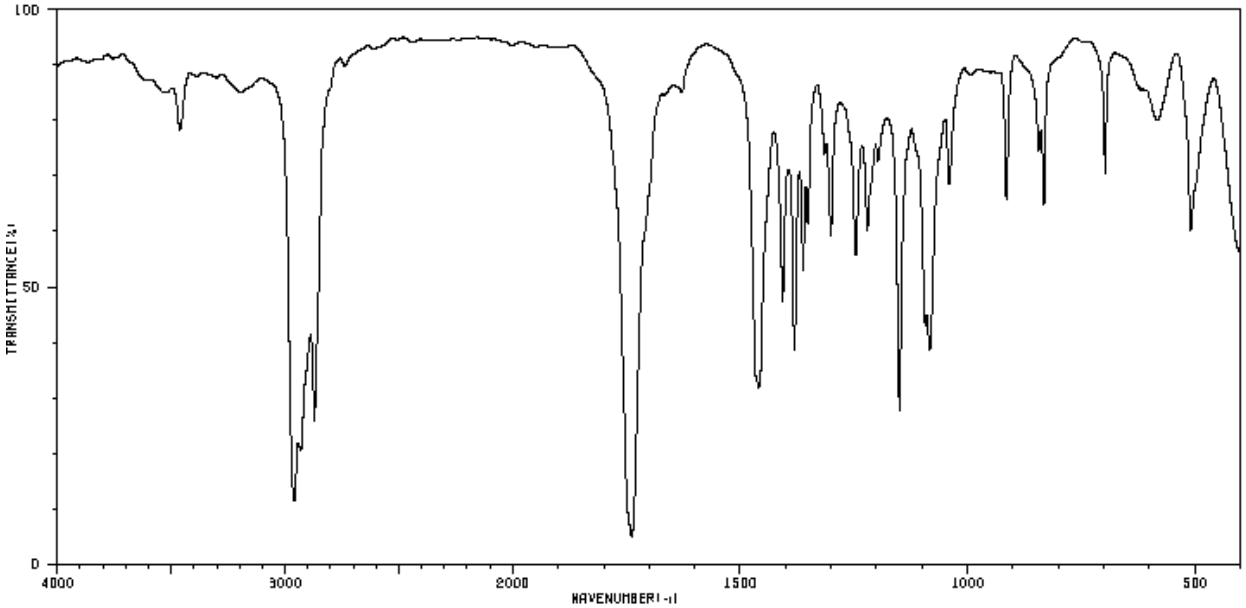
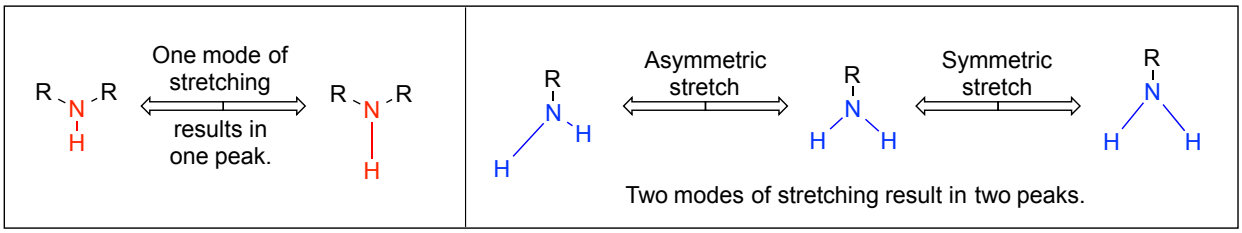


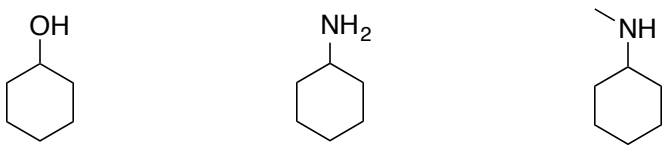
The heteroatom-to-hydrogen stretching region

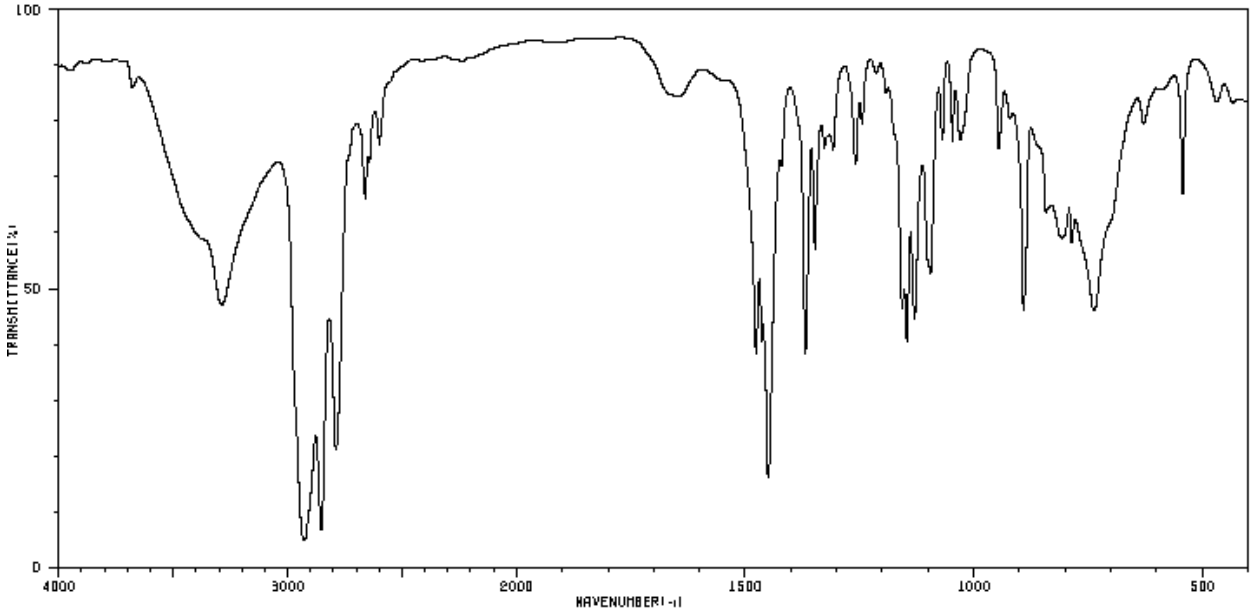
The shape of the peaks in this region of the spectrum (around 3400 cm^{-1}) can provide some excellent structural clues. An alcohol O-H stretch gives a relatively broad signal in this region; whereas, N-H stretching tends to be sharper. It is also worth noting that O-H stretching often yields a more intense signal than N-H stretching. Additionally, while an R_2NH group gives a single sharp peak because it has a single N-H bond, an RNH_2 group displays two peaks due to symmetric and asymmetric stretching.



Carboxylic acid O-H stretching is significantly different from alcohol O-H stretching. The carboxylic acid O-H stretch is much broader, covering a range from 2500 – 3500 cm^{-1} and often obscuring the C-H stretching region.

Problem 9. Match the following compounds with their IR spectra.

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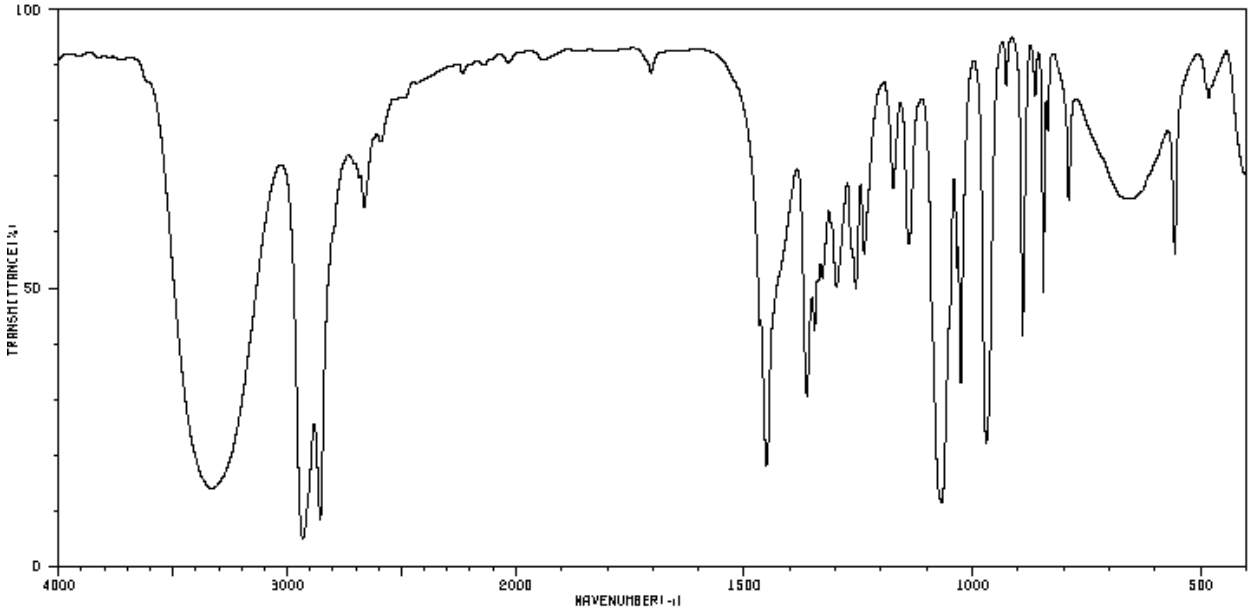
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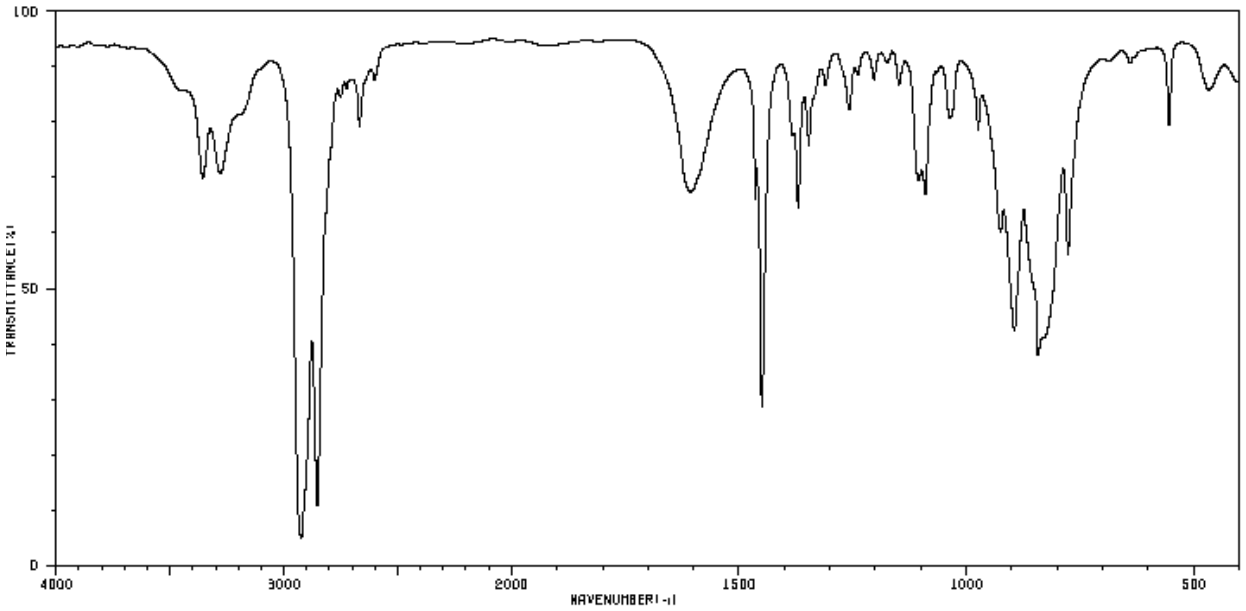
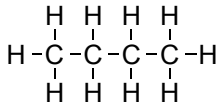


Section 3: Structure Solving Using IR Spectroscopy

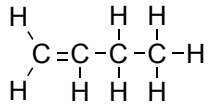
Degrees of unsaturation

In many structure-solving problems, you will have a molecular formula as a guide. The molecular formula alone can give us some structural clues in the form of degrees of unsaturation. We first encountered the notion of a degree of unsaturation in the chapter on alkanes. A molecule that is saturated has the maximum number of hydrogen atoms possible, given the other elements in its formula. For instance, butane is a saturated hydrocarbon. There is no way to put more than ten hydrogens onto four carbons in a single molecule.



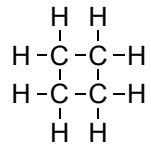
butane
(a saturated hydrocarbon)

In contrast, 1-butene is an *unsaturated* hydrocarbon. This alkene has fewer than the maximum of ten hydrogens that a four-carbon chain could hold.



1-butene
(an unsaturated hydrocarbon)

Similarly, cyclobutane is an unsaturated hydrocarbon. It contains the same number of hydrogens as 1-butene.



cyclobutane
(an unsaturated hydrocarbon)

These two examples show that both a π bond and a ring have the same effect on a molecule's molecular formula: they reduce the hydrogen count by two. Since this results in the molecule being unsaturated, π bonds and rings are referred to as degrees of unsaturation.

When given a molecular formula, the degrees of unsaturation (DOU) can be calculated fairly simply. The maximum number of hydrogens that a given number of carbons (n) can possess is 2n + 2. We subtract from that value the actual number of hydrogen atoms present in the molecular formula. Finally, this difference is divided by two because hydrogen atoms are lost in pairs when a degree of unsaturation is introduced.

$$DOU = \frac{[2n + 2] - hydrogens\ in\ formula}{2}$$

The number of degrees of unsaturation is the total number of rings and/or π bonds in the molecule. We cannot know specifically whether the degrees of unsaturation are due to rings, π bonds, or both without consulting the spectral data.

Problem 10. Calculate the degrees of unsaturation for the following molecular formulas, and propose three structures that are consistent with the given formulas.

(a) C_3H_4

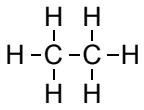
(b) C_5H_{10}

(c) C_6H_6

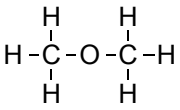
(d) $C_{13}H_{12}$

When a molecule contains atoms other than just carbon and hydrogen, the DOU calculation may be affected. There are three scenarios that we should consider.

(1) When the formula contains oxygen, the DOU calculation is unaltered. There are many examples we could consider to illustrate this point. One is a comparison of ethane to dimethyl ether.



ethane
C_2H_6
(saturated)



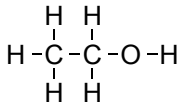
dimethyl ether
C_2H_6O
(saturated)

Ethane is a saturated hydrocarbon. The DOU calculation shows that it has no degrees of unsaturation:

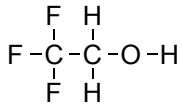
$$DOU = \frac{[2(2) + 2] - 6}{2} = 0$$

Upon adding an oxygen to the formula to make dimethyl ether, the situation has not changed. Therefore, simply ignoring the oxygen in the DOU calculation allows us to reach the correct conclusion, which is that dimethyl ether is also saturated (i.e., it contains no rings or π bonds).

(2) When the formula contains a halogen, the halogen counts as a "hydrogen equivalent." To highlight this point, let's compare ethanol to 2,2,2-trifluoroethanol. Both molecules are clearly saturated since neither contains rings or π bonds.



ethanol
C_2H_6O
(saturated)



2,2,2-trifluoroethanol
$C_2H_3F_3O$
(saturated)

The DOU calculation for ethanol gives us the correct answer without difficulty. Remember that we simply ignore the oxygen atom when performing this calculation:

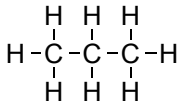
$$DOU = \frac{[2(2) + 2] - 6}{2} = 0$$

However, to reach the correct conclusion for 2,2,2-trifluoroethanol, we need to account for the fact that the fluorine atoms have taken the place of hydrogen atoms. To do so, we count them as "hydrogen equivalents." In other words, we say that the molecule contains a total of six "hydrogens and hydrogen equivalents." By doing so, we reach the correct conclusion that 2,2,2-trifluoroethanol also has zero degrees of unsaturation:

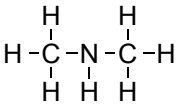
$$DOU = \frac{[2n + 2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(2) + 2] - 6}{2} = 0$$

(3) When the formula contains nitrogen, the nitrogen is counted as one half of a carbon atom in the calculation. An illustrative comparison can be made between propane and dimethylamine, both of which lack π bonds and rings and are therefore saturated molecules.



propane
C_3H_8
(saturated)



dimethylamine
C_2H_7N
(saturated)

The DOU calculation for propane easily shows that it has no degrees of unsaturation:

$$DOU = \frac{[2(3) + 2] - 8}{2} = 0$$

However, to get the correct answer for dimethylamine, we must account for the fact that a nitrogen atom is present and that it carries half as many hydrogen atoms as the central carbon in propane. We can achieve this by counting the nitrogen as one half of a carbon:

$$DOU = \frac{[2(2.5) + 2] - 7}{2} = 0$$

Problem 11. Calculate the degrees of unsaturation for the following molecular formulas, and propose three structures consistent with each formula.

(a) C_4H_8O

(b) C_6H_9F

(c) C_7H_9N

(d) $C_5H_8Br_2$

(e) $C_7H_{14}O_2$

(f) $C_6H_{12}ClN$

An algorithm for structure solving using IR spectra

The general approach for structure solving using infrared spectra is relatively straightforward. It includes only a few steps:

(1) Calculate the degrees of unsaturation.

(2) Spot-check the key portions of the functional group region of the IR spectrum:

(a) the carbonyl-stretching region at 1700 cm^{-1};

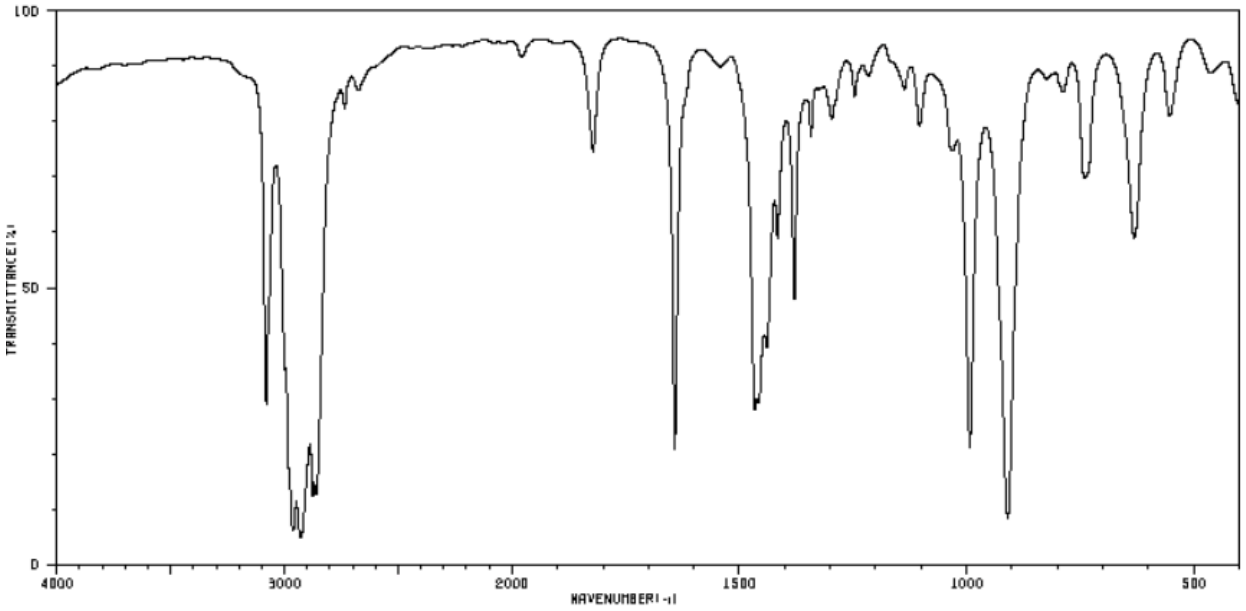
(b) the carbon-hydrogen stretching region (sp^3 C-H: below 3000 cm^{-1}; alkene/aromatic sp^2 C-H: above 3000 cm^{-1});

(c) the heteroatom-hydrogen stretching region at ~3400 cm^{-1}.

(d) Compare any other significant signals to the correlation table.

(3) Propose a structure that is consistent with the available data.

Let's practice this algorithm using some problems. For our first problem, consider a molecule with the formula C_6H_{12} and the following infrared spectrum.



We begin by calculating the degrees of unsaturation as follows:

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(6)+2] - 12}{2} = 1$$

This reveals that the molecule contains one ring or one π bond, but we have to reserve judgment on which of the two is present until we consider the spectral data.

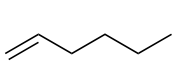
The next step is to spot-check the three key portions of the functional group region. Doing so reveals no carbonyl stretching at 1700 cm^{-1}. Of course, we did not expect to see such a signal since the formula contains no oxygen, which makes it impossible to have a carbonyl. At 3000 cm^{-1}, we see peaks both below and above this dividing line, revealing the presence of sp^3 C-H stretching and alkene/aromatic sp^2 C-H stretching, respectively. Lastly, there is no heteroatom-hydrogen stretching apparent, but we also did not expect to see any due to the absence of heteroatoms in the molecular formula.

There is one significant signal in the functional group region that was not covered by our three spot checks. It appears at ~1650 cm^{-1}. Consulting the correlation table shows that this is C=C stretching.

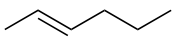
The sp^3 C-H stretching is not especially remarkable. Any molecule that has an alkyl group will have this signal. However, the sp^2 C-H stretching is noteworthy. It reveals the presence of a carbon-carbon double bond bearing at least one hydrogen atom. This tells us that the one degree of unsaturation in the molecule must be a π bond. The presence of C=C stretching at ~1650 cm^{-1} reinforces this conclusion.

We now need to propose a structure that is consistent with the data. It is important to realize that IR spectroscopy often leaves some ambiguity about the molecule's identity. In other words, there can be multiple structures that are consistent with the available data. In this case, we are constrained only by the formula and the fact that one π bond bearing at least one hydrogen must be present. As a result, a number of alkenes are consistent with the data.

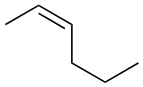
There are five unique straight-chain alkenes having the correct formula.



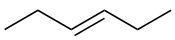
1-hexene



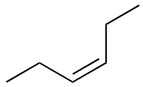
trans-2-hexene



cis-2-hexene

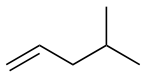


trans-3-hexene



cis-3-hexene

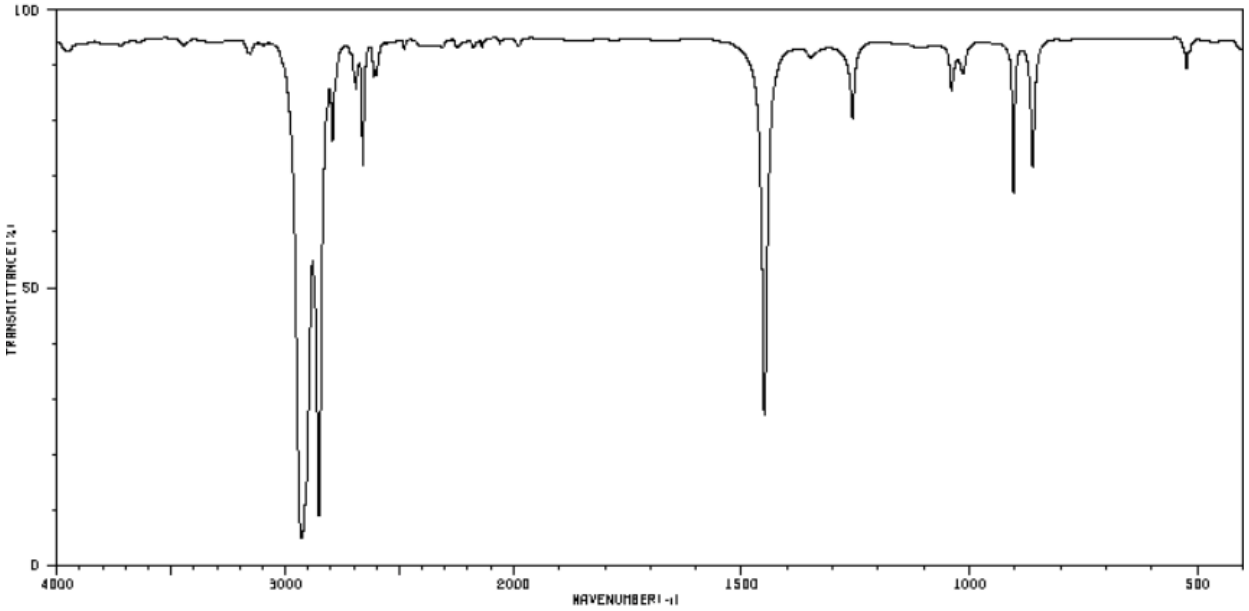
Additionally, we can envision a number of branched isomers as well. One example is shown below.



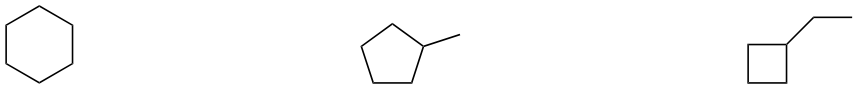
4-methyl-1-pentene

When we incorporate NMR spectroscopy into our structure solving, we'll see that this ambiguity disappears, and we'll be able to specify the exact structure of the molecule with certainty.

Let's consider another example having the same molecular formula: C_6H_{12}. However, this compound has a different IR spectrum, which is shown below.

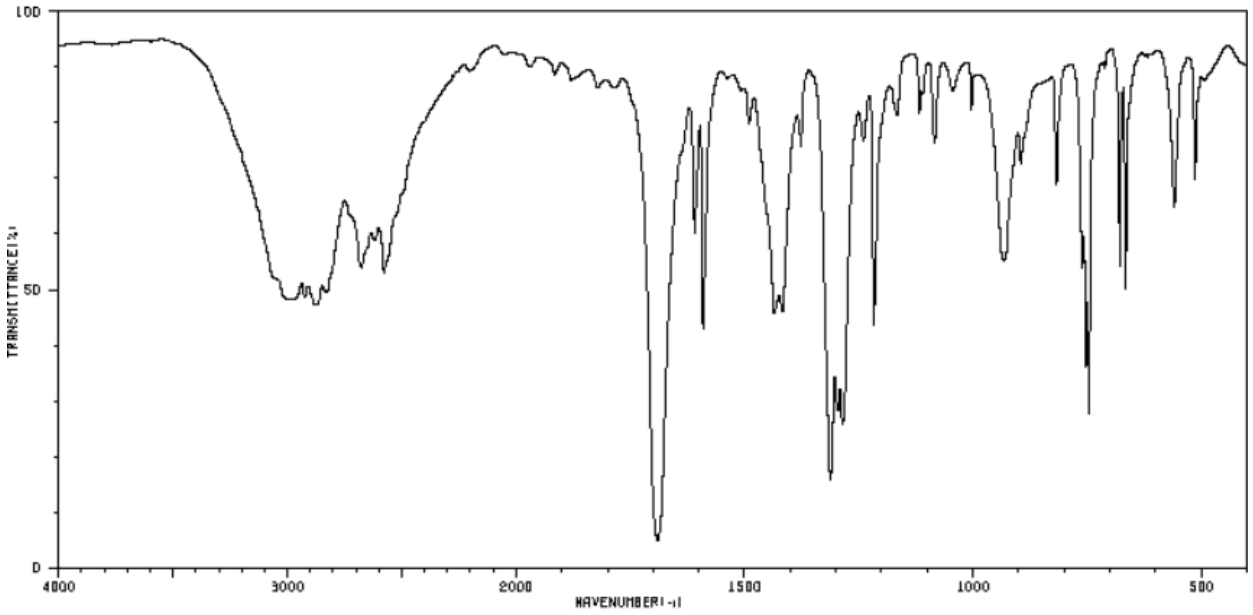


Since this molecule has the same formula as the previous one, we know that it also contains one degree of unsaturation. However, upon completing the spot checks, it becomes clear that the only significant type of signal in the functional group region is the sp^3 C-H stretching just below 3000 cm^{-1}. Consequently, this molecule's degree of unsaturation is *not* a π bond because there is no evidence for one. Although a cycloalkane does not present a specific signal in the IR spectrum, we can conclude that the degree of unsaturation must be a ring based on the absence of evidence for a π bond. There are multiple compounds that are consistent with the given formula and also contain a single ring. A few examples follow.



cyclohexane methylcyclopentane ethylcyclobutane

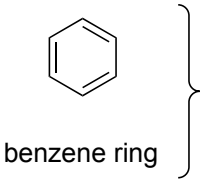
Let's try one more sample problem. This molecule has the formula $C_8H_8O_2$, as well as the IR spectrum shown below.



As always, we should begin by calculating degrees of unsaturation. Recall that oxygen atoms do not impact the calculation.

$$DOU = \frac{[2(8) + 2] - 8}{2} = 5$$

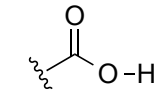
This molecule has a large number of degrees of unsaturation. While it is possible that they could all be unrelated, it is much more likely that a group of them are part of a single structural feature, such as an aromatic ring. The benzene ring has four degrees of unsaturation: three π bonds and one ring. As a general rule, when you encounter highly unsaturated molecules, consider the presence of aromatic rings.



benzene ring

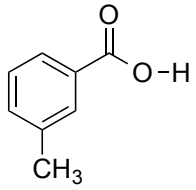
Four degrees of unsaturation:
three π bonds and one ring

In this case, the aromatic ring could account for four of the five degrees of unsaturation. This means that one more ring or π bond remains to be explained. The IR spectrum reveals multiple significant clues. First, we observe a carbonyl resonance around 1700 cm^{-1}. This shows that the remaining DOU is, in fact, a π bond. Additionally, there is a broad peak from approximately 2500 – 3500 cm^{-1} that obscures the carbon-hydrogen stretching region. This extremely broad signal is emblematic of a carboxylic acid's O-H stretch. The carboxylic acid therefore accounts for both of these signals and represents another fragment present in the molecule.



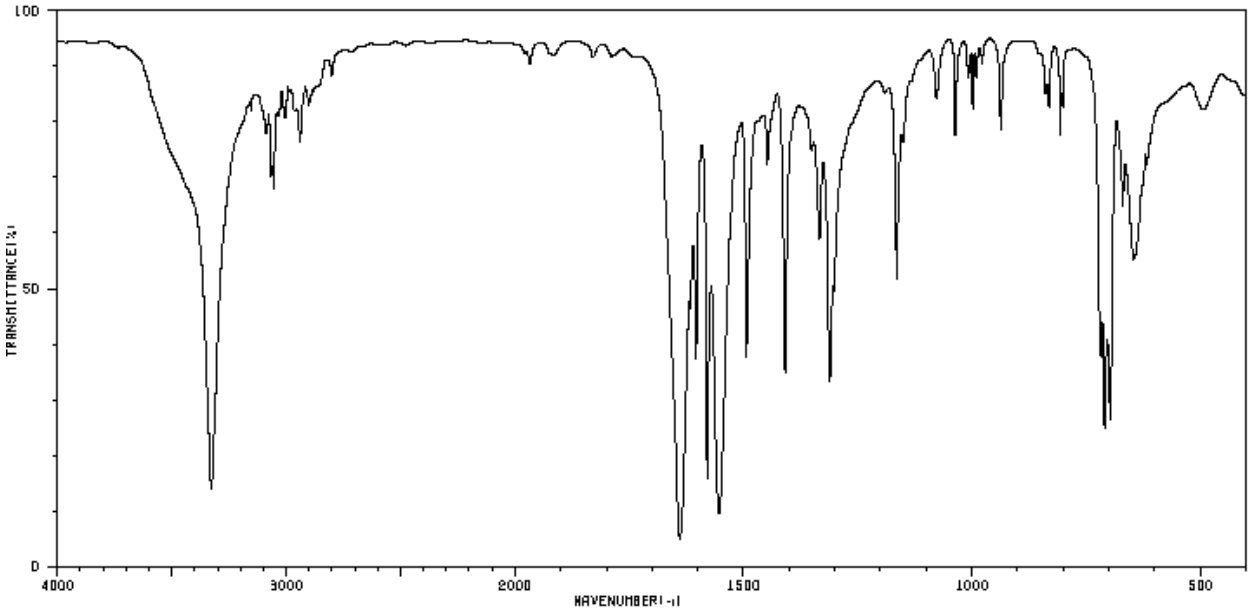
carboxylic acid

One additional carbon remains in the molecular formula. It could be present as a separate substituent on the ring. One of the possible isomers that would be consistent with the data is shown below. It happens to be known as *meta*-toluic acid. Other isomers are also possible.

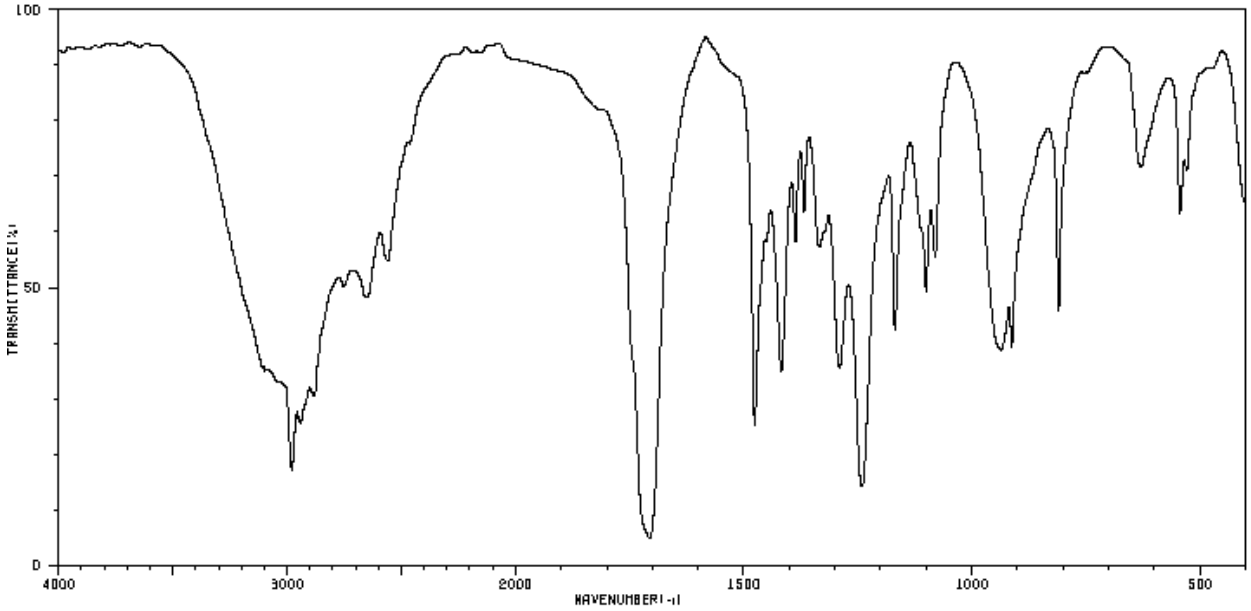


meta-toluic acid

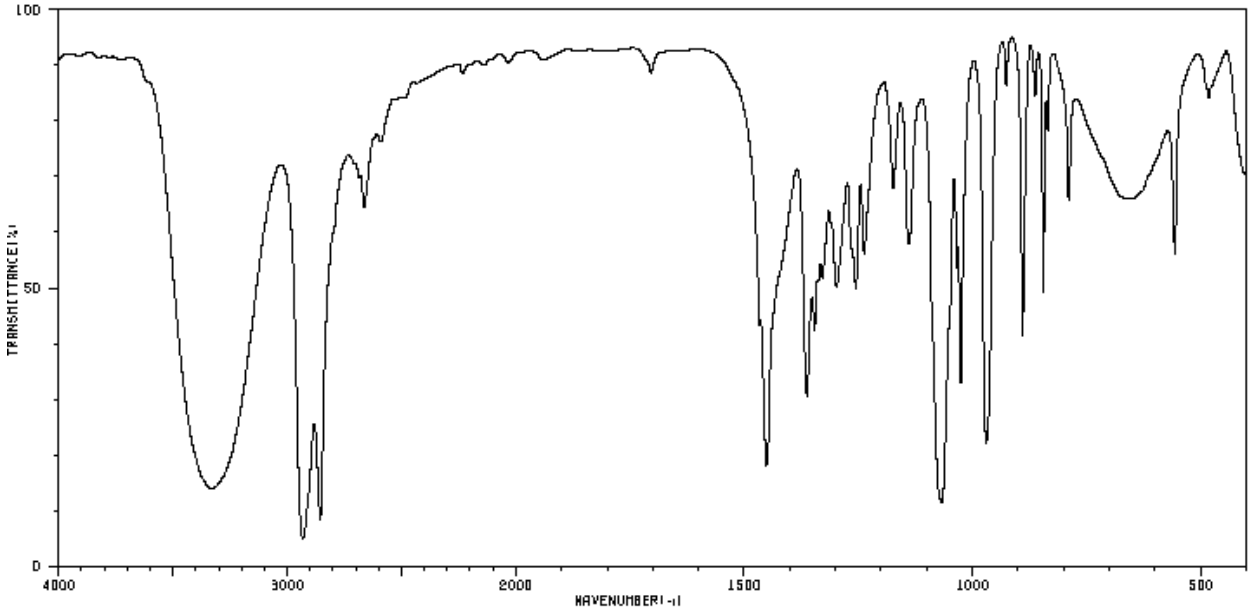
Problem 12. An unknown has the molecular formula C_8H_9NO and the following IR spectrum. Provide a structure consistent with this information.



Problem 13. An unknown having the molecular formula $C_4H_8O_2$ exhibits the following IR spectrum. Provide a structure consistent with this information.



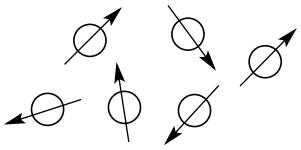
Problem 14. A molecule has the formula $C_6H_{12}O$ and the IR spectrum shown below. Propose a reasonable structure for this molecule.



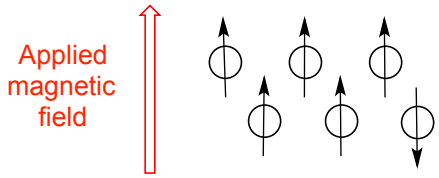
Section 4: Nuclear Magnetic Resonance (NMR) Spectroscopy

The fundamentals

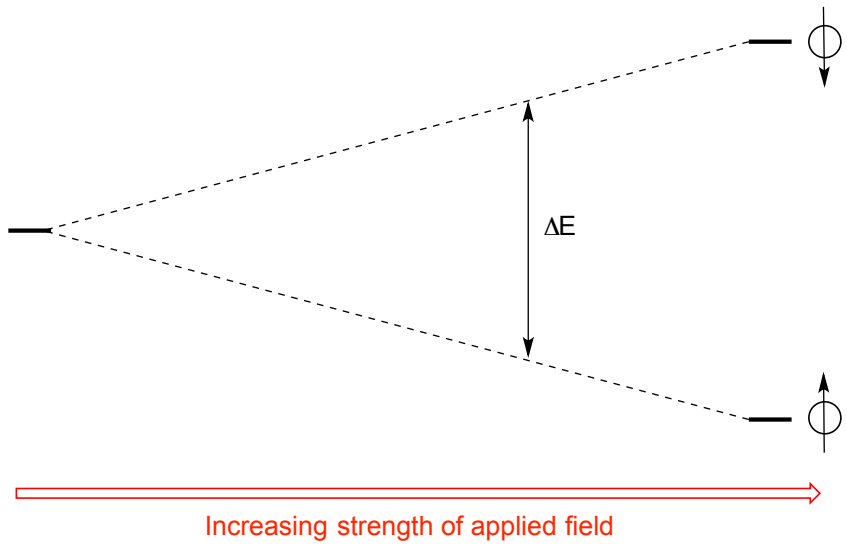
Certain nuclei (e.g., ^{1}H and ^{13}C) have a spin. This is sometimes represented by drawing an arrow through a circle. The circle stands for the nucleus, and the arrow designates the direction of its spin. Ordinarily, these nuclear spins are randomly oriented.



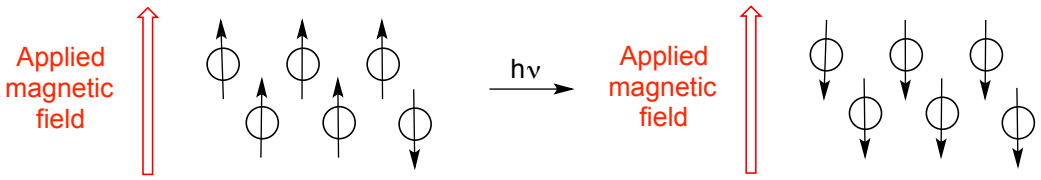
However, when placed in a magnetic field, the orientation of nuclear spins is no longer haphazard. Instead, the spins align in one of two ways: with the external field or against it. Many more nuclei will be aligned with the applied field, since this corresponds to the lower-energy state.



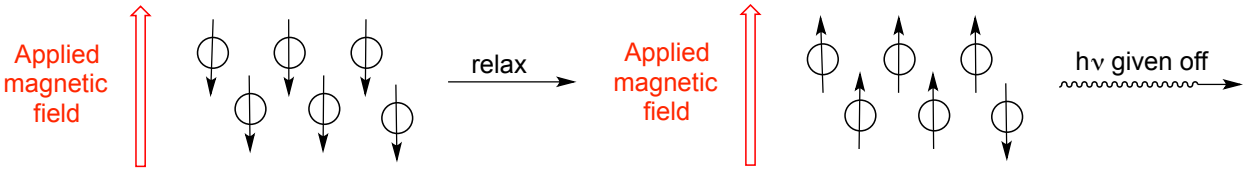
There is an energy difference (ΔE) between these two states, and as you might expect, the energy difference depends upon the strength of the applied field. If the applied field is miniscule, then so is the difference in energy between the two spin states. However, as the field increases in strength, the magnitude of the energy difference between states increases as well. This heightens the probability of finding nuclei in the lower-energy state (i.e., aligned with the applied field).



This phenomenon can be used to probe nuclei and to learn quite a bit about their environment. The process begins with the excitation of nuclear spin. Radio waves are used to promote the nuclei from the lower-energy state, in which they are aligned with the applied field, to the higher-energy state, in which they are opposed to the applied field. The radio waves are abbreviated as hν in the diagram below since this designates the energy carried by electromagnetic radiation.



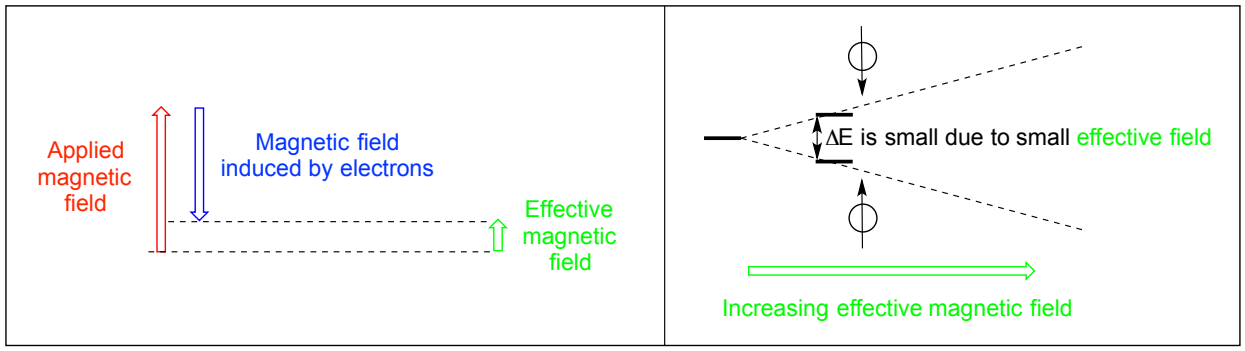
The nuclei are then allowed to relax back to their initial state. When they do so, radiofrequency radiation is emitted. This radiation can be detected, giving us information about the sample.



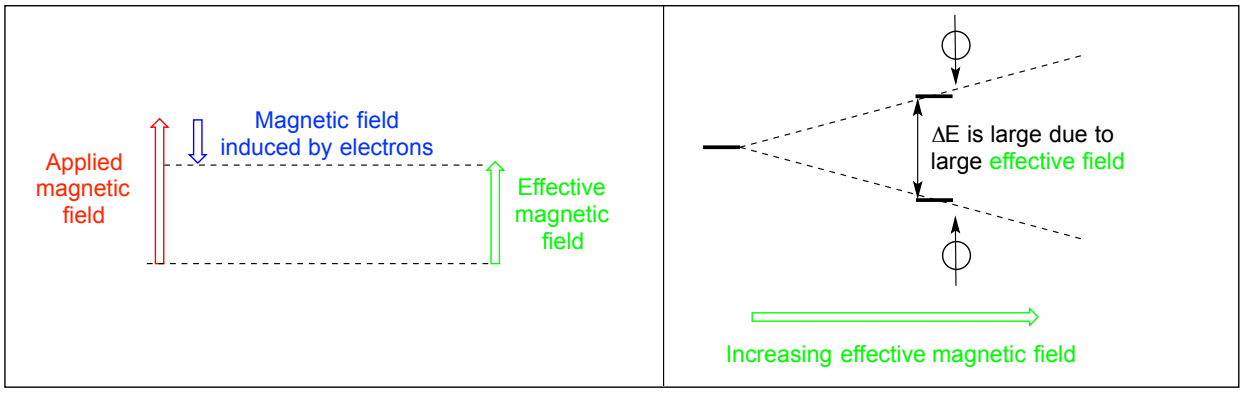
The number of signals in the spectrum

At this point, there is one key detail that is missing. If we are conducting proton NMR, you might expect all protons (i.e., all ^{1}H nuclei) to give off the exact same amount of energy, leading to a single signal. This, however, is not the case. Protons in distinct chemical environments emit unique amounts of energy that reflect the electron density around them. Electrons, being moving charges, generate a magnetic field, and this magnetic field induced by the electrons opposes the external field in most cases.

Let's consider two scenarios. In the first, a nucleus is surrounded by a great deal of electron density. This results in the induction of a prominent field opposed to the applied field. The difference between the applied and induced fields is the effective magnetic field, or the field that the nucleus will actually "feel." In this case, the effective field is small, so the energy difference between spin states is small.

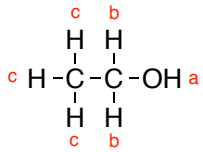


In a second scenario, a nucleus has little electron density in its immediate surroundings. As a result, the induced magnetic field is small and diminishes the applied field to a much lesser extent. In this case, the effective magnetic field is still quite strong, so the energy difference between spin states is large.

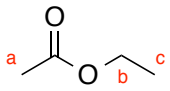


The ultimate take-home message from all of this discussion is that each nucleus in a unique chemical environment will experience a unique effective magnetic field, resulting in a unique ΔE between the two spin states. Consequently, as each chemically distinct type of nucleus relaxes during NMR, it gives off an amount of energy reflective of its surroundings. These emissions translate into the signals observed in the NMR spectrum.

As an example, ethanol (shown below) would be expected to have three signals in its ^1H NMR spectrum. The hydrogen atoms of the CH_3 group (c) are identical to one another because they stem from the same atom. However, they are different from any other type of proton in the molecule because no other protons are part of a CH_3 group. The hydrogens of the CH_2 group (b) are identical to each other, but they too are different from the other protons in the molecule. Lastly, the proton of the hydroxyl group (a) is a third unique type of hydrogen in the molecule.



Ethyl acetate (shown below) also exhibits three signals in its proton NMR spectrum. It contains two methyl groups (a and c), but these methyl groups are different from each other. One is adjacent to a carbonyl, while the other is adjacent to a CH_2 group. As a result, the protons of these methyl groups are in distinct chemical environments and give rise to different signals. Finally, there is a single CH_2 group in the molecule (b), and its protons are therefore different from all of the others.

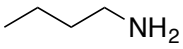


Problem 15. How many signals would you expect to see in the proton NMR spectra of the following molecules?

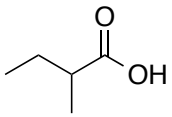
(a)

(b)

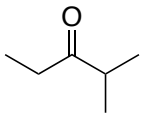
(c)



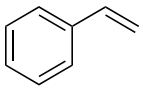
(d)



(e)



(f)



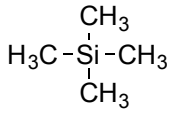
Chemical shift: the x-axis

As we seek to plot signals on an NMR spectrum, we would like to use an x-axis that is directly comparable from one lab to another. As it stands, the ΔE between spin states depends on the effective magnetic field, which in turn depends on the strength of the applied magnetic field. NMR spectrometers can have a wide range of magnetic field strengths. You may have heard your instructor refer to the 60 MHz NMRs of the old days, with permanent magnets. Or perhaps, your instructor has referred to a more modern 300, 400, 500, or 600 MHz instrument in your department.

In order to report signals in such a way that we can make direct comparisons, regardless of the field strength of our individual magnets, chemical shift (δ) is used. Chemical shift measures the ratio of the frequency difference between a signal of interest and that of an internal standard to the operating frequency of the magnet.

$$\delta\ (ppm) = \frac{Frequency\ of\ a\ signal\ (Hz) - Frequency\ of\ internal\ standard\ (Hz)}{Operating\ frequency\ of\ magnet\ (MHz)} \times 10^6$$

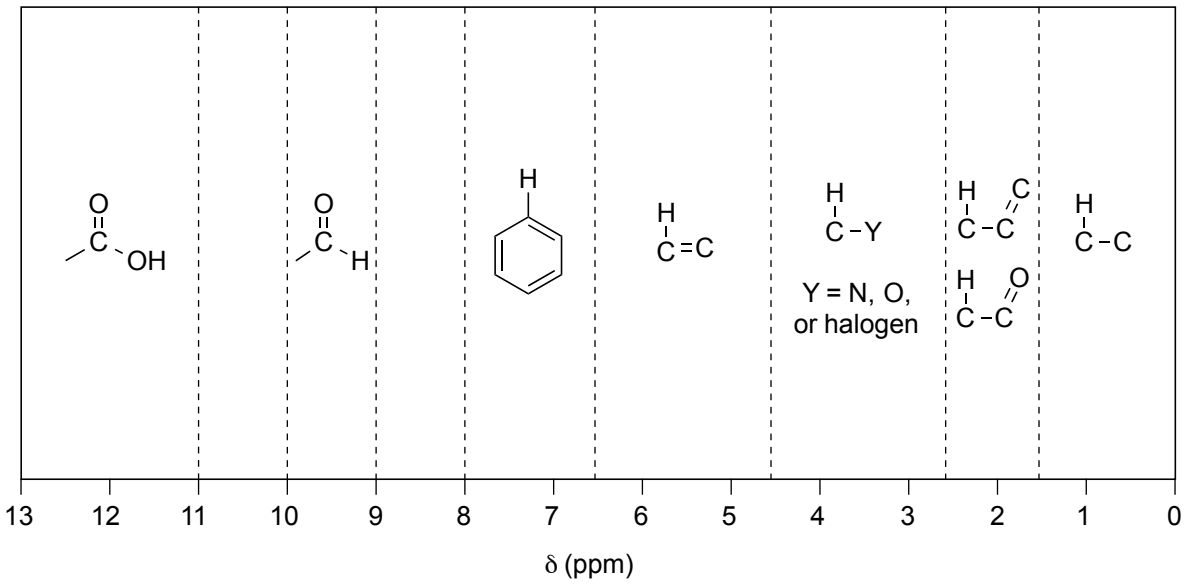
The internal standard is typically tetramethylsilane (TMS), which is the zero-point marker for most NMR spectra. A small quantity of TMS is often introduced into NMR solvents, so that a little bit is present in each NMR sample. It produces one signal that we agree marks 0 ppm.



tetramethylsilane

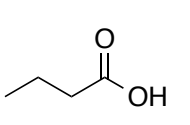
By calculating chemical shift in this way, the dependence upon field strength is removed, and we can directly compare data even if you are using a 500 MHz instrument while I am using a 400 MHz instrument.

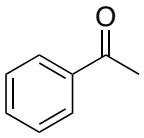
As we've established, chemical shift tells us about the environment in which a nucleus resides. For proton NMR, the correlation between chemical shift and proximity to functionality is shown below. *It is the protons that actually generate the signals, but the local chemical environment affects where these signals fall on the x-axis.*

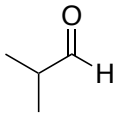


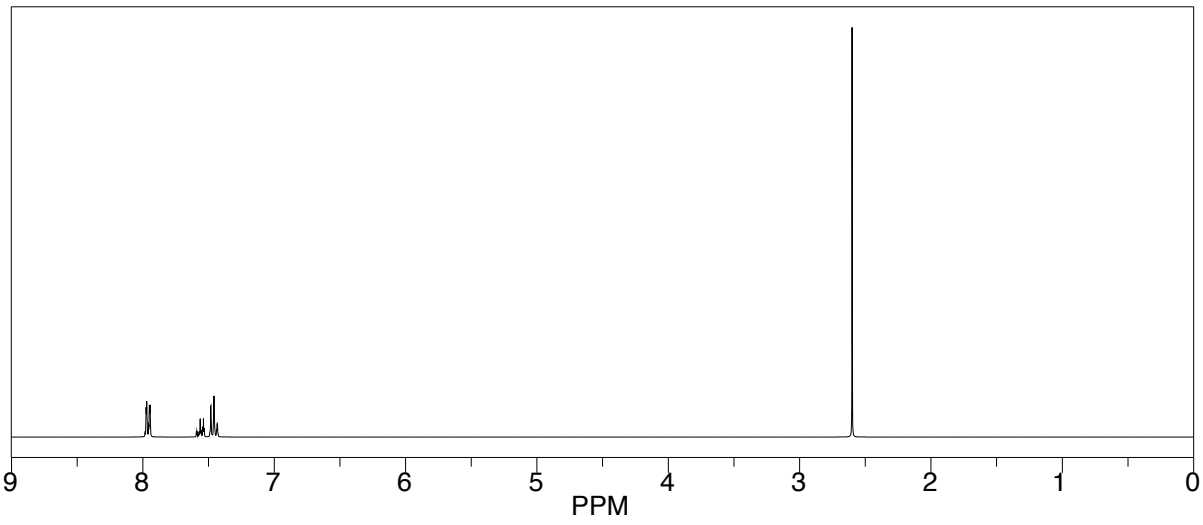
This list is not exhaustive by any means. Notice that there are a couple of glaring omissions, such as the proton of an alcohol's hydroxyl group and amine protons. These protons tend to have widely variable chemical shifts, appearing between 1 and 5 ppm. However, they are usually easy to pick out because they participate in hydrogen bonding, which broadens their signals. *Protons on carbon give sharp signals; whereas, hydrogen-bonding protons (i.e., those bonded to oxygen or nitrogen) typically result in broader peaks.*

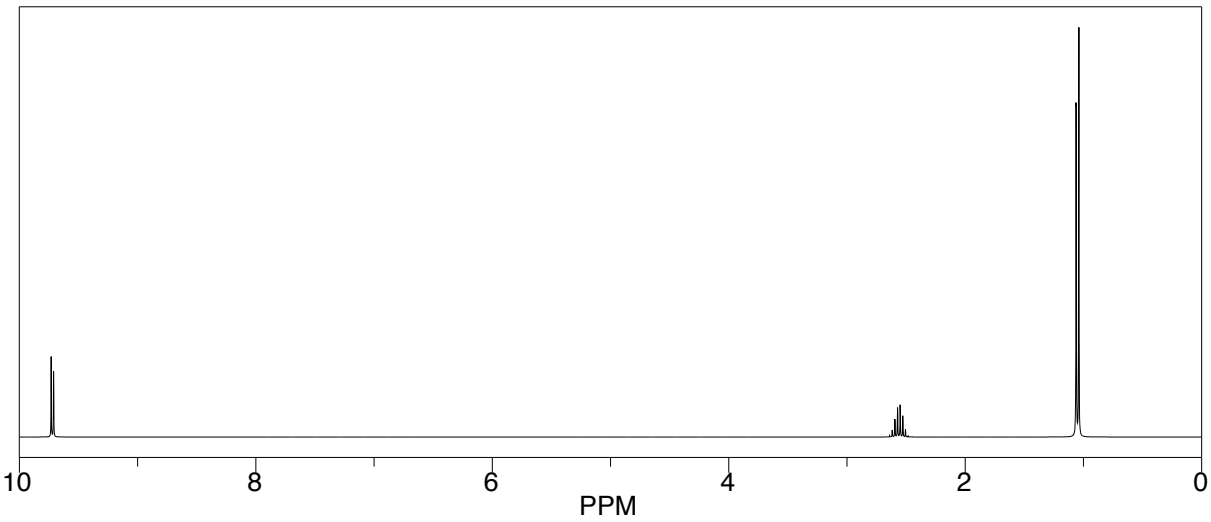
Problem 16. On the basis of the number of signals and their chemical shift values, match the following compounds with their proton NMR spectra.

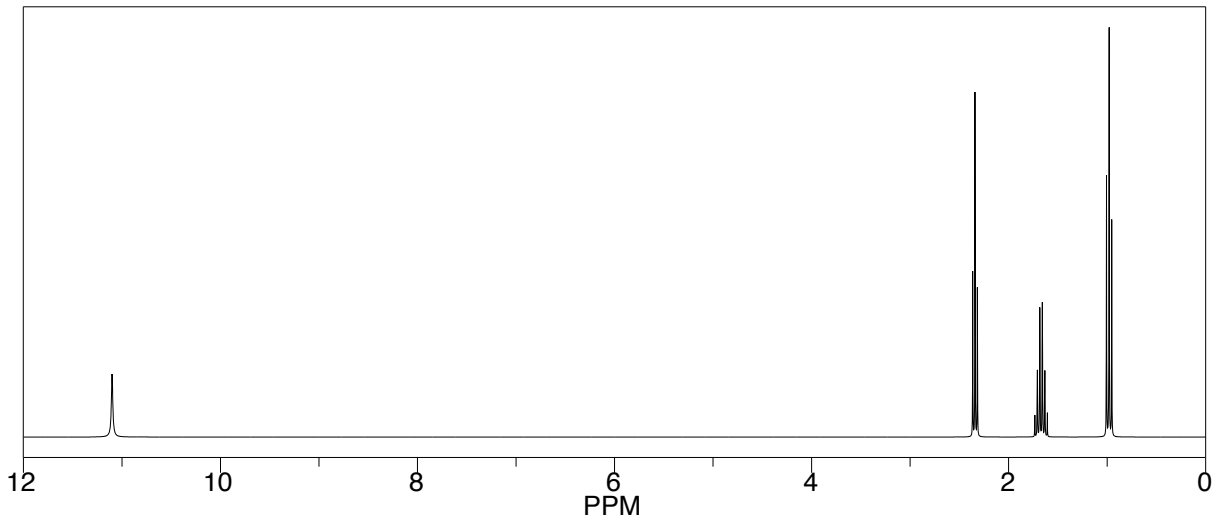




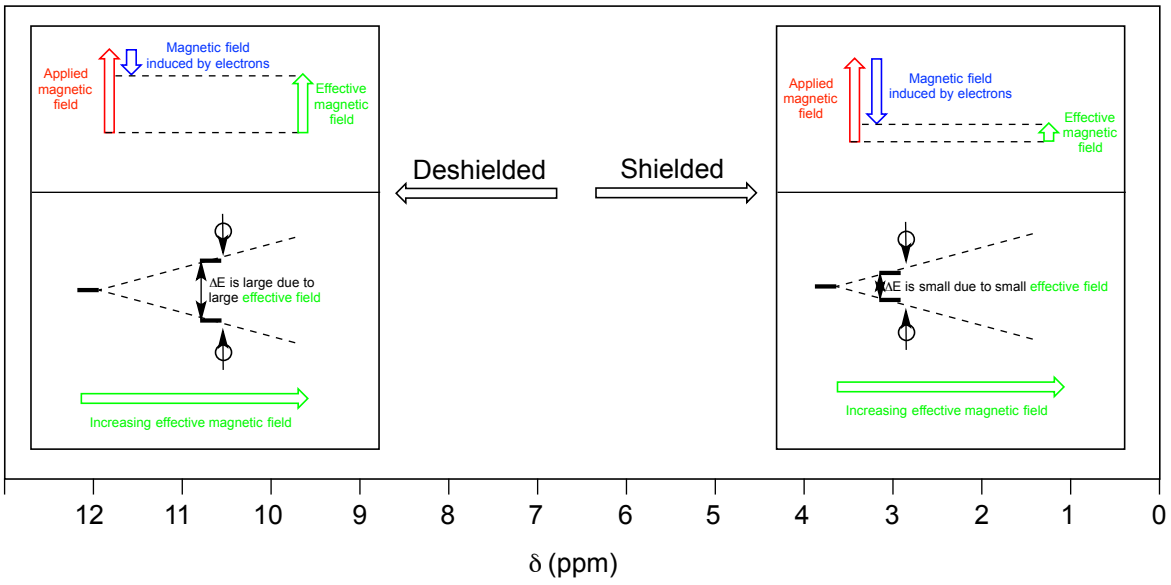




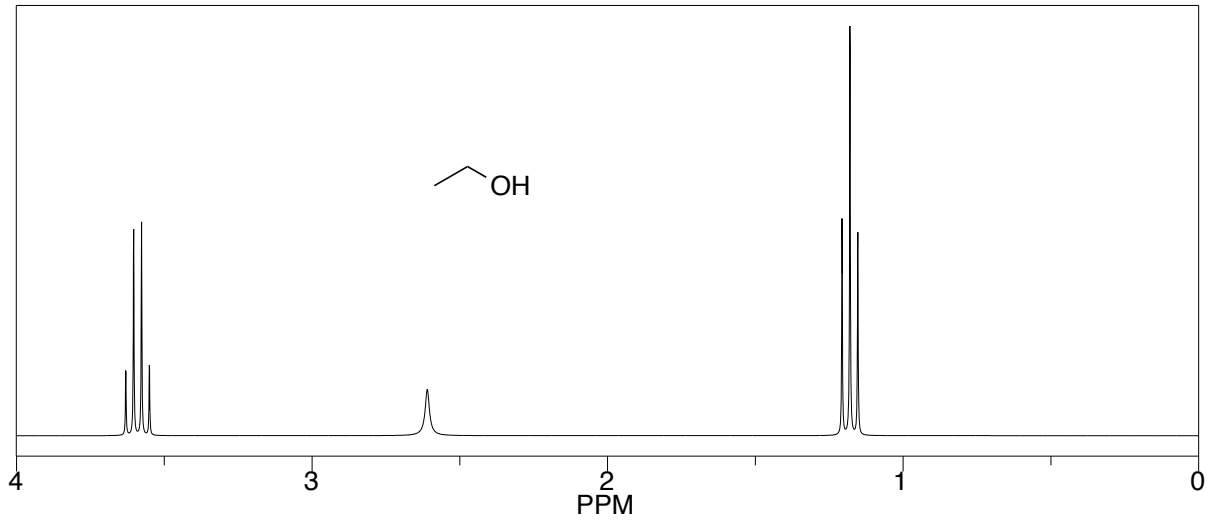




Protons with chemical shift values closer to 0 ppm are referred to a shielded. This stems from the fact that they experience a small effective magnetic field due to the large magnetic field induced by the electrons around them. In other words, the high electron density they possess *shields* them from the applied magnetic field. On the other hand, protons with high chemical shift values are referred to as deshielded since they lack this protection from the applied field and therefore "feel" an effective field that is closer to the full magnitude of that which is applied.

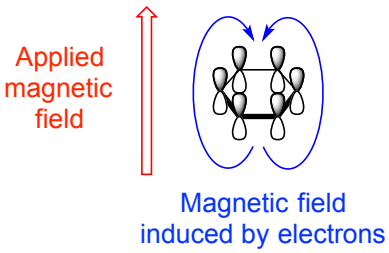


Problem 17. Using what we've learned about NMR thus far, assign the peaks in the proton NMR spectrum of ethanol. In other words, label the types of protons in ethanol with letters and then label each peak with the appropriate letter.

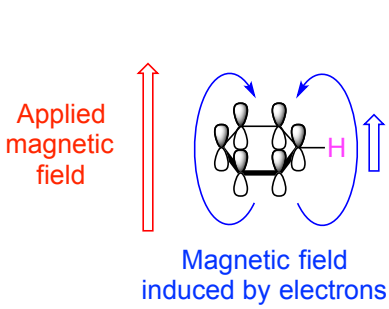


Anisotropy

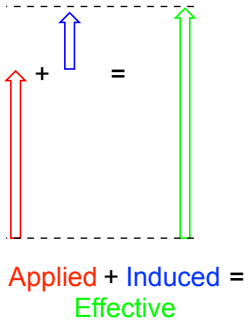
To this point, the shielding we've considered has been isotropic, which means "the same in all directions." However, π clouds are not spherically symmetrical, and as a consequence, the field induced by the electrons depends on the orientation of the protons relative to this π cloud. Benzene is probably the most commonly cited example of this phenomenon. For benzene, the ring current caused by the π electrons generates the magnetic field shown below. As you can see from the diagram, whether the induced field opposes or reinforces the applied field depends on the point in space under consideration.



It is the protons that interest us in proton NMR, and if we consider their location, the induced field reinforces the applied field.

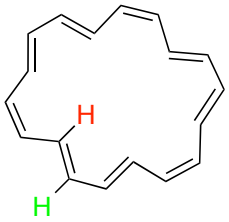


Highlighting one of the aromatic protons, the induced field reinforces the applied field, leading to a large effective field



In benzene itself, all of the protons fall along the outer periphery of the ring, so they all experience this same deshielding. But, if you look at the contour of the induced field, you can see that above or inside the ring the induced field actually opposes the applied field. This seems irrelevant because there are no protons in those locations in benzene, but there are molecules where these points in space could be occupied by protons.

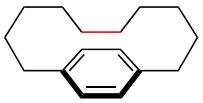
For instance, consider a larger annulene. Annulenes are totally conjugated rings. The name "annulene" is preceded by a number in brackets that tells how many carbons are in the ring. As an example, [18]annulene is a totally conjugated, eighteen-carbon ring. In [18]annulene, there are protons outside the ring that are deshielded (much like those in benzene), and there are protons inside the ring, which are actually shielded.



H inside the ring is shielded by ring current.
It has $\delta < 0$ ppm.

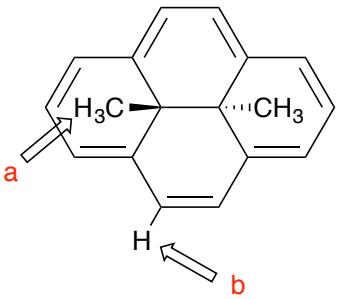
H outside the ring is deshielded by the ring current.
It has $\delta > 9$ ppm.

While [18]annulene illustrates how protons can be inside a ring, cyclophanes illustrate how protons can reside above a ring. Cyclophanes contain a benzene ring with a tether between non-adjacent carbons. In cyclophanes with smaller tethers, some protons may be held above the ring, such as those stemming from the bond highlighted in red in the following diagram. These hydrogens could be expected to exhibit extra shielding.



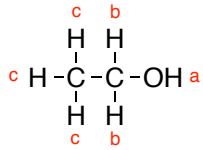
Alkenes and alkynes also have π clouds, which behave in an analogous fashion. In alkenes, deshielding occurs for protons connected to the double bond (i.e., vinyl protons). On the other hand, the orientation of the current for alkynes is such that protons directly connected to the triple bond are more shielded than you would otherwise expect. Their chemical shift typically falls between 2 and 3 ppm.

Problem 18. Rank the indicated protons in order of increasing chemical shift.

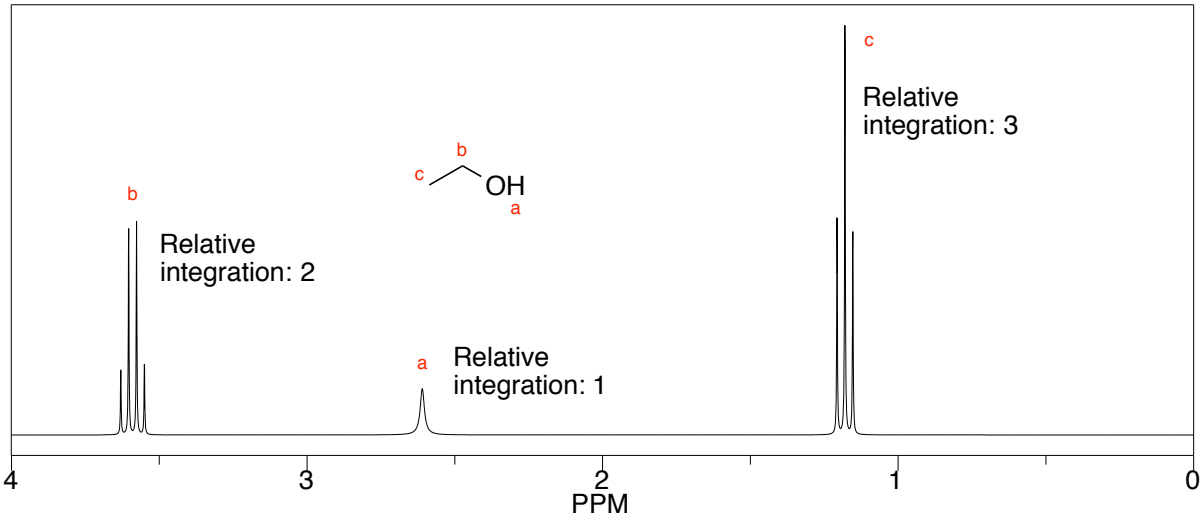


Integration

The signals in an NMR spectrum may differ in size, and this gives us information as well. If you recall our earlier discussion of ethanol, we concluded that it has three signals in its ^1H NMR spectrum for H_a, H_b, and H_c. Yet, each of these signals is due to a different number of hydrogen atoms. There are three protons of type c, two of type b, and one of type a.

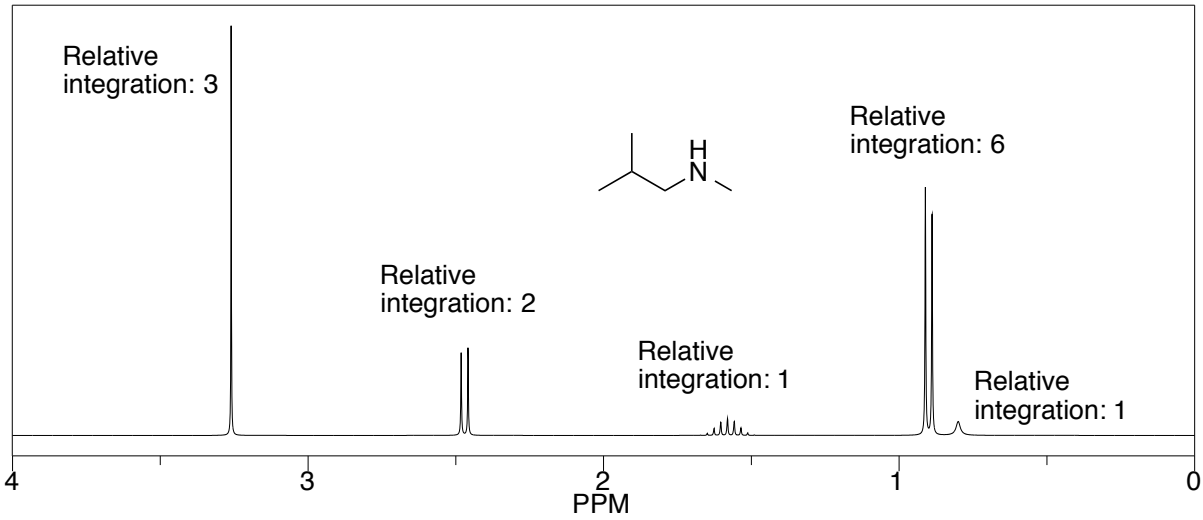


You might consequently expect these three signals to be of different sizes, and in fact, they are. However, we have to be careful how we define size. Height alone does not make for a useful comparison because the peaks differ in shape as well. How can we compare a short, broad signal to a tall, sharp signal? The answer lies in the area under the curve, which is also known as the integration. The integration of signals is directly comparable, regardless of their particular shapes. The ratio of the integration values allows us to assess the number of protons causing each signal. The relative integration values are given in the following spectrum.



The smallest peak with an integration of one hydrogen corresponds to proton a. The signal with a relative integration of two is due to the protons labeled b. Finally, the biggest signal, which has a relative integration of three, results from the hydrogens labeled c.

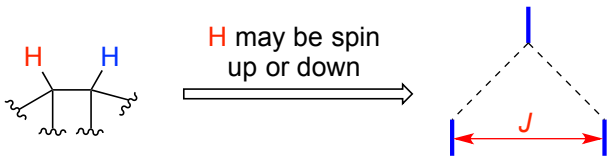
Problem 19. Assign the protons in the following compound to signals in the accompanying NMR spectrum.



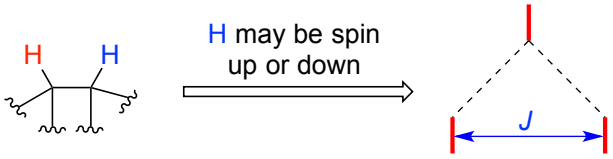
Coupling

As you've seen in some of the sample spectra in this chapter, signals in the proton NMR can differ in shape. This is due to coupling (formally "spin-spin coupling"), which results in splitting. By this we simply mean that a signal can be split into more than one peak, so signals can have complex shapes. The effective field experienced by a proton depends to a small extent on the orientation of the spins of protons on neighboring carbons, and this is the root of coupling.

To expand upon this idea, let's begin by considering a proton with only a single neighbor. A neighbor is defined as a proton on an adjacent carbon. The squiggly lines in the drawing below simply mean that we are cutting out a fragment of a molecule and ignoring the rest of its structure. The blue proton has one (red) neighbor. This red neighbor could have its nuclear spin oriented either up or down (i.e., with or against the applied field). These two possibilities place the blue hydrogen into one of two slightly different energy states, so its signal is split into two peaks, which we call a doublet. The extent of the splitting (i.e., the separation between the two peaks of the doublet) is described by a coupling constant, or *J* value, which is typically expressed in Hz. *J* values usually range from 0 to 20 Hz.



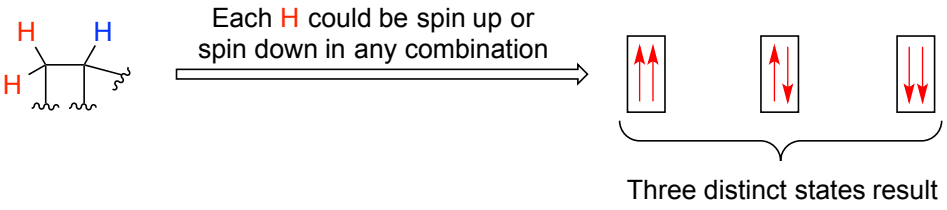
Splitting is reciprocal, so if the red proton splits the blue proton into a doublet, the blue proton will also split the red proton into a doublet with the same *J* value.



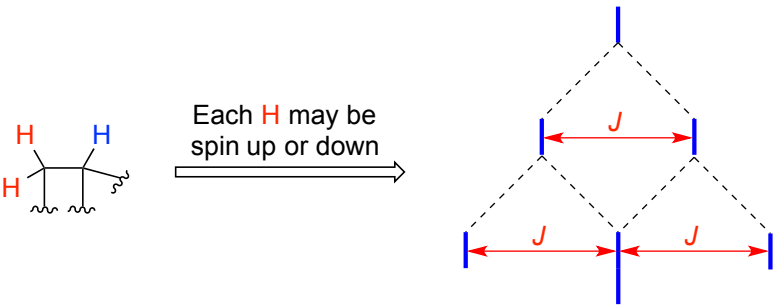
These diagrams, which schematically represent the phenomenon of coupling, are referred to as splitting trees.

It is important to note though that chemically equivalent protons do not split each other. For example, the average methyl group (CH_3) consists of three chemically equivalent hydrogens. While they may be split by protons on neighboring carbons, they do not split each other.

When a proton has two neighbors, there are two broad scenarios. These two neighbors may be equivalent to one another or different. Let's consider both eventualities. First, let's examine a fragment of a molecule in which one proton (blue) has two equivalent neighbors (red). Each of those neighboring protons could be in the spin up or spin down state. Consequently, when all of the possible combinations are considered, there are three states that affect the blue hydrogen differently, meaning that it will absorb energy at three unique frequencies, all of which are in close proximity to one another.

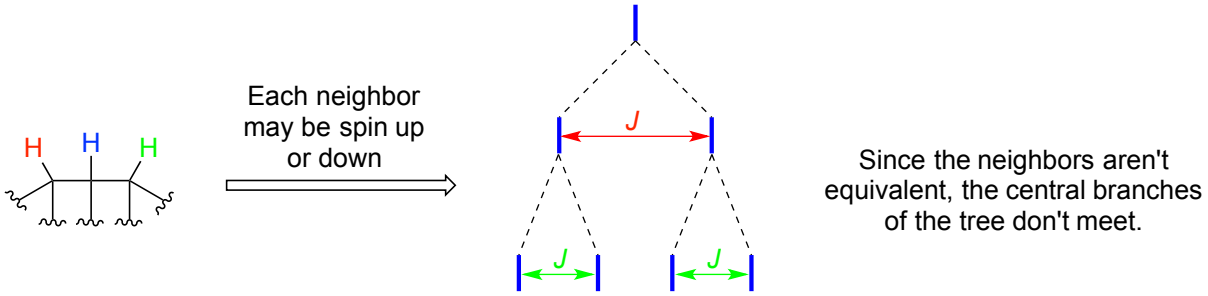


This same concept can be expressed using a splitting tree. The top half of the splitting tree is exactly the same as we saw previously. The blue proton's signal is split into two peaks by a red neighbor. Then, each of those new peaks is split into two by the second red neighbor. Since the red neighboring hydrogens are equivalent, the *J* values for the two splitting events are the same. This means that, during the second splitting, the central branches of the tree meet and overlap, thereby doubling the intensity of the central peak.

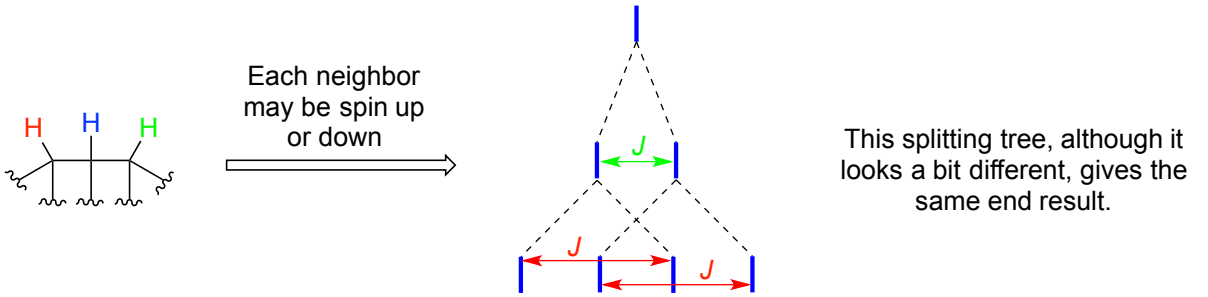


The three peaks are known as a triplet. Their relative intensities are 1:2:1.

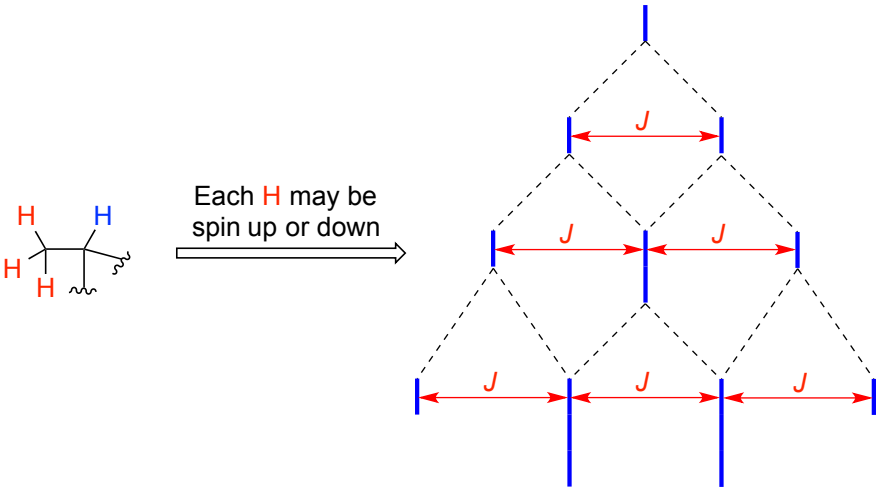
If the two neighbors are inequivalent, the splitting tree looks a bit different. In the fragment below, we'll assume that some asymmetry in the portion of the molecule not shown causes the red and green neighbors to be chemically inequivalent. If that is the case, then each of these neighbors splits the blue hydrogen with its own unique *J* value. As a result, the central branches of the tree may not meet, leading to four peaks of equal intensity. This is known as a "doublet of doublets" since it appears to be two doublets in close proximity to one another.



As it was shown above, the smaller coupling constant was associated with the second splitting event. The same doublet of doublets results regardless of the order in which we consider the splitting events, as shown in the diagram below.



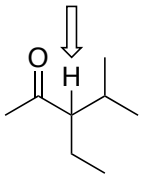
Of course, it is not uncommon for a proton to have three neighbors. Being adjacent to a methyl group will provide three chemically equivalent neighbors. The upper two thirds of the splitting tree matches what we drew for the triplet perfectly. We simply add one more splitting event for the third red neighbor. Every time that branches meet, the intensities of the preceding signals are additive. It follows then that the last splitting event yields a quartet with four peaks having intensities of 1:3:3:1.



If the three neighbors are inequivalent, a much more complex splitting pattern will result.

While you can imagine that a multitude of splitting patterns are possible, the most commonly encountered are singlets, doublets, triplets, and quartets. If more than four peaks are present in a signal, the splitting may be challenging to discern unless the resolution is optimal. In such instances, complex signals are simply referred to as multiplets.

Problem 20. Draw a splitting tree for the indicated proton in the following molecule.



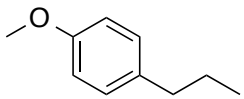
To this point, we have considered situations in which we already knew the number of neighboring hydrogens, and we used that knowledge to predict the splitting by constructing a splitting tree. It would be nice to have a quicker way to determine splitting. Additionally, in laboratory settings, we may obtain an NMR spectrum of an unknown substance. In such a situation, we will be able to observe the splitting in the spectrum, but we won't already know the number of neighbors. We will be interested in determining the number of neighbors because this will help us to figure out the structure of the molecule.

There is one simple guideline that provides easy access to splitting predictions and also allows us to determine the number of neighbors for each signal in a given NMR spectrum. Splitting trees have shown us why a doublet results from a single neighbor, why a triplet results from two neighbors, and why a quartet results from three neighbors. Notice that, in each case, the splitting is the number of neighbors plus one. This gives rise to the n + 1 rule:

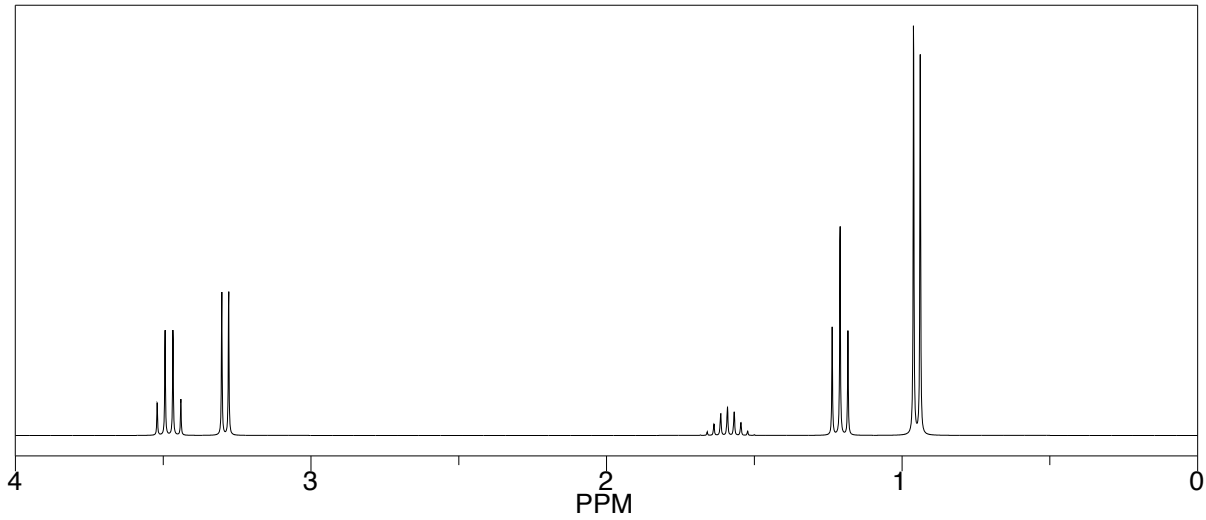
Splitting = n + 1, where n is the number of neighboring protons

This rule allows you to quickly determine the splitting pattern expected for a particular proton. Furthermore, when using a signal's splitting to ascertain the number of neighbors, you need only subtract one from the splitting. A caveat is that the n + 1 rule only works reliably when all of the neighboring protons are equivalent. If there are neighbors of different types, their effects must be considered independently.

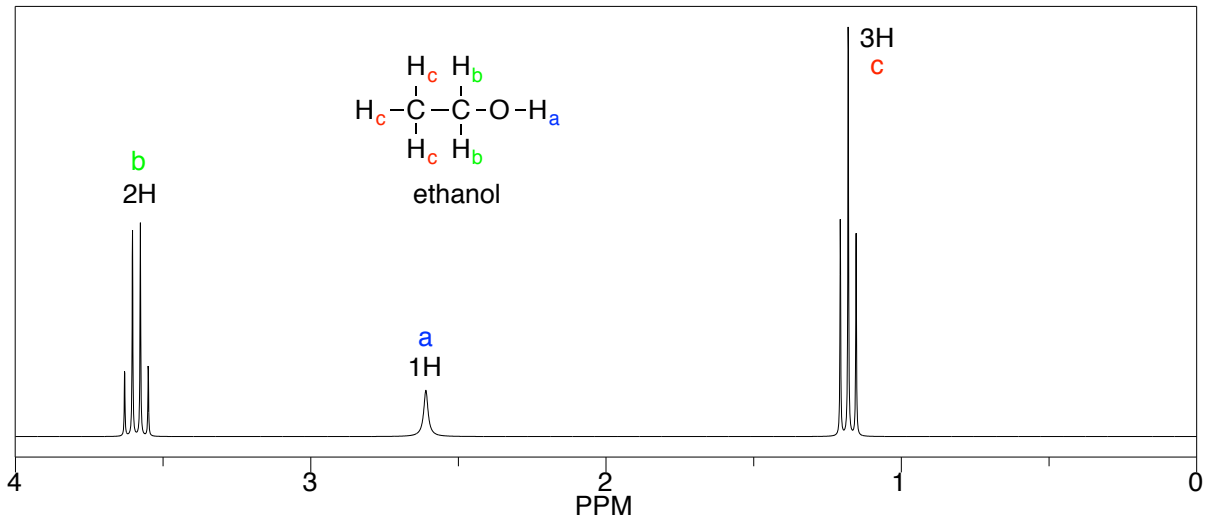
Problem 21. Predict the shape (i.e., the splitting or multiplicity) of each signal in the ^{1}H NMR spectrum of the following compound.



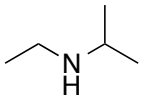
Problem 22. For the signals in the following spectrum, state the number of neighboring protons.

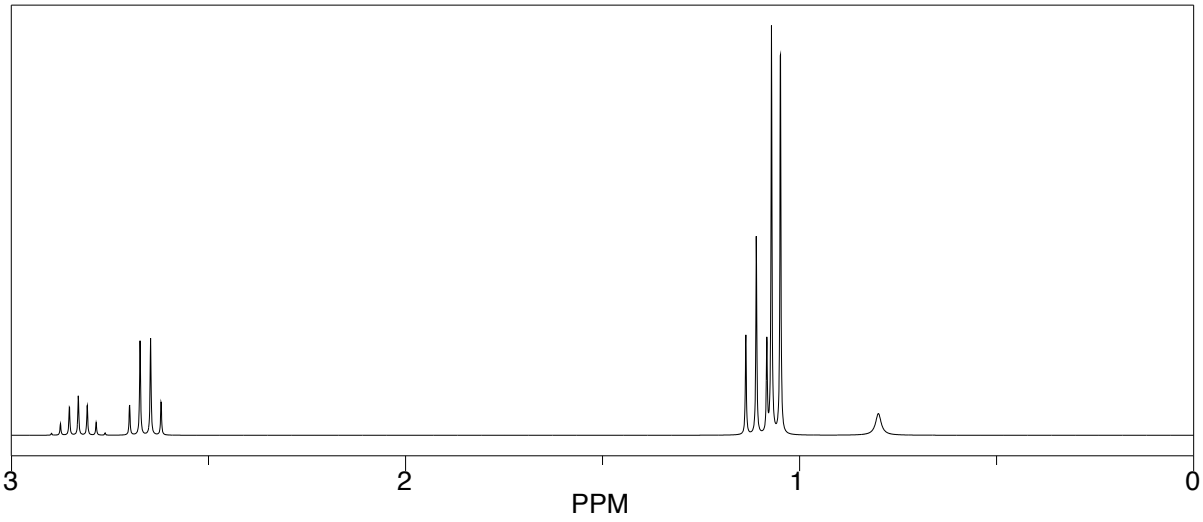


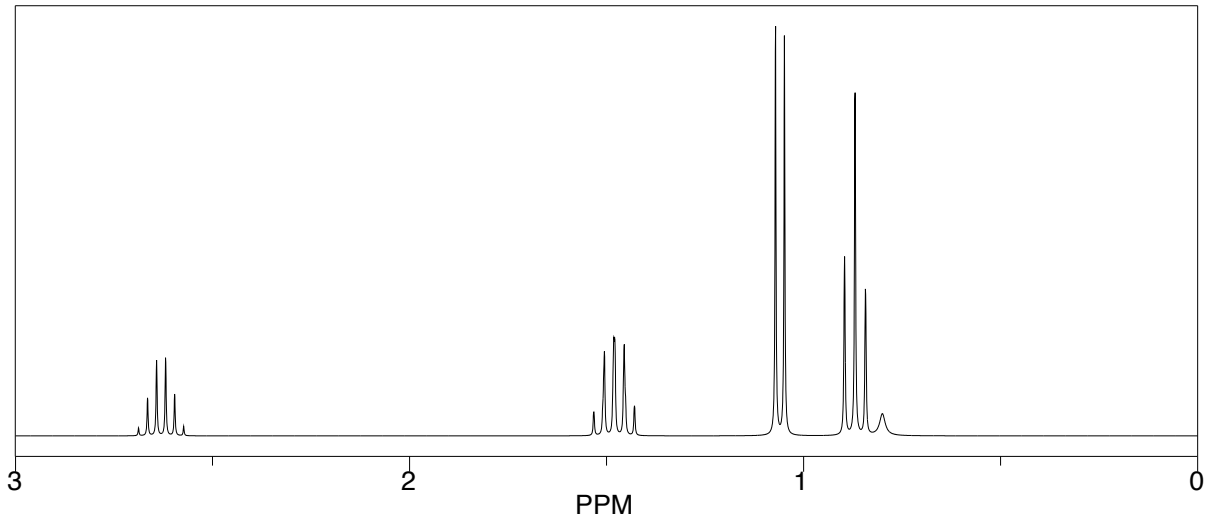
Let's reexamine the proton NMR spectrum of ethanol. We've previously assigned the peaks to the corresponding hydrogens in the structure. Now, let's reconcile the splitting. The protons labeled c have two neighbors, which are those labeled b. By the n + 1 rule, we know that these two neighbors split the signal for H_c into a triplet. The protons labeled b have three neighbors (H_c) on the adjacent carbon. Using the n + 1 rule, we therefore expect the signal for H_b to be split into a quartet. You might wonder why we did not count H_a as a neighbor of H_b. After all, H_a is the same distance from H_b as H_c is. The difference is that H_a can participate in hydrogen bonding. Hydrogen-bonding protons do not typically participate in splitting unless the sample is extremely dilute, which precludes hydrogen-bonding interactions. Under normal circumstances though, hydrogen-bonding protons do not couple to their neighbors. As a result, H_a does not further split H_b, and H_a itself is a singlet, albeit a broad one due to its hydrogen bonding.

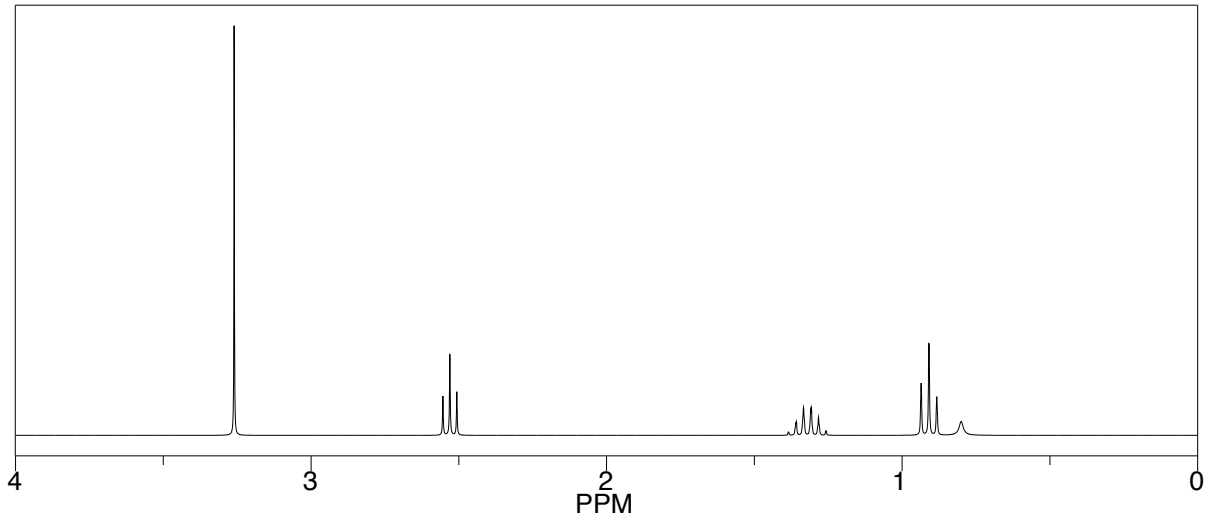


Problem 23. Which of the following spectra is consistent with this molecule?



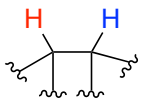






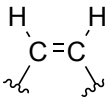
The magnitude of coupling constants

In order for nuclear spins to couple, the nuclei typically need to be in relatively close proximity. Most of the time, we expect nuclei to couple if they are separated by two or three bonds. The typical neighbor is a vicinal hydrogen, and vicinal hydrogens are separated by three bonds. The vicinal *J* value will usually be in the range of 6 – 8 Hz.

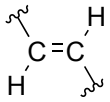


Vicinal (or neighboring) hydrogens

The coupling of *cis* and *trans* vicinal hydrogens of an alkene differs in magnitude and can be a useful tool in assigning the configuration of an alkene from the proton NMR spectrum.

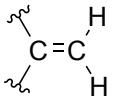


cis
J ranges from
8 - 12 Hz



trans
J ranges from
14 - 17 Hz

Geminal coupling refers to the splitting of chemically distinct protons separated by only two bonds. This can occur in more than one scenario. One example would be in an olefin, where the geminal coupling is relatively small. In order to observe this coupling, the two substituents on the alkene must differ in some way.

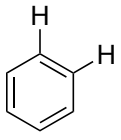


geminal
J ranges from
0.5 - 3 Hz

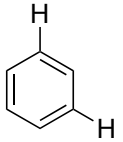
A second example would be two hydrogens stemming from the same sp^3 hybridized carbon. In order to split each other, these protons must be chemically inequivalent. Very shortly, we'll discuss how such a situation could arise.

geminal
J ranges from
12 - 15 Hz

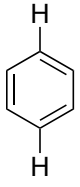
Aromatic rings also exhibit vicinal, as well as long-range, coupling. The magnitude of the coupling diminishes with increasing distance between the protons. Protons that are adjacent to one another on an aromatic ring are termed *ortho*. When there is one intervening carbon, the arrangement is *meta*. When the protons appear on opposite sides of the ring, they are said to be *para*. *Ortho* coupling is the largest, while *para* may even be too small to observe.



ortho
J ranges from
6 - 9 Hz

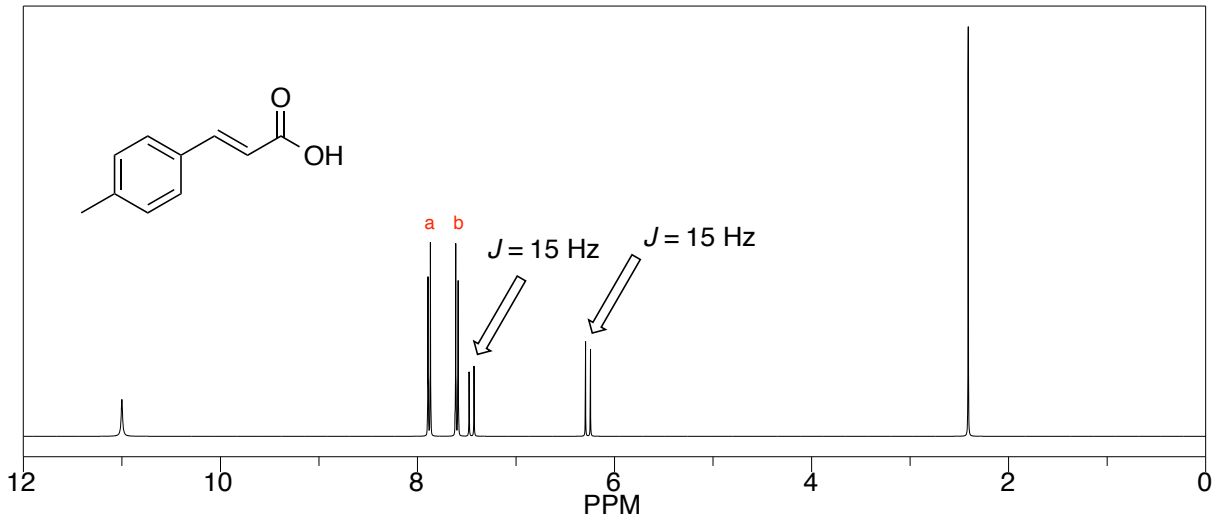


meta
J ranges from
1 - 3 Hz



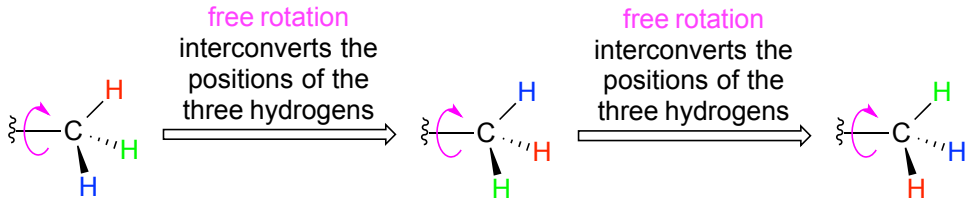
para
J ranges from
0 - 1 Hz

Problem 24. For the ^{1}H NMR spectrum of the following compound, what do the indicated *J* values reveal? Additionally, what would the expected *J* values be for signals a and b?



Chemical equivalence vs. magnetic equivalence

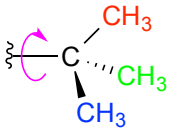
As we discussed earlier, chemical equivalence describes protons that exist in identical chemical environments. As a result, they contribute to a single signal. A methyl group is a convenient example of chemical equivalence. Typically, there is free rotation about the σ bond connecting the methyl group to the rest of the molecule, so each of the three hydrogens can occupy any point in space.



Magnetic equivalence is a more stringent comparison between protons. To be magnetically equivalent, the protons must not only exhibit the same chemical shift (i.e., be chemically equivalent) but they must also couple equally with other chemically equivalent protons. Another way of expressing "couple equally" is to say that the *J* values must be the same for coupling with other chemically equivalent protons.

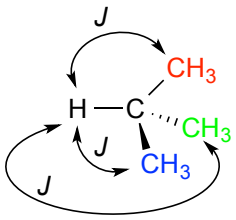
Let's take a look at some examples. A *tert*-butyl group contains three methyl groups that are likely to be both chemically and magnetically equivalent. Under normal circumstances, there will be free rotation about the σ bond linking the *tert*-butyl group to the rest of the molecule. The color-coding here parallels that which was used for the hydrogens in the methyl group above to illustrate that the methyls of the *tert*-butyl group will interconvert in the same way. These methyls are chemically equivalent. Furthermore, they must be

equidistant from any other set of hydrogens in the rest of the molecule, meaning that they will couple identically with them.



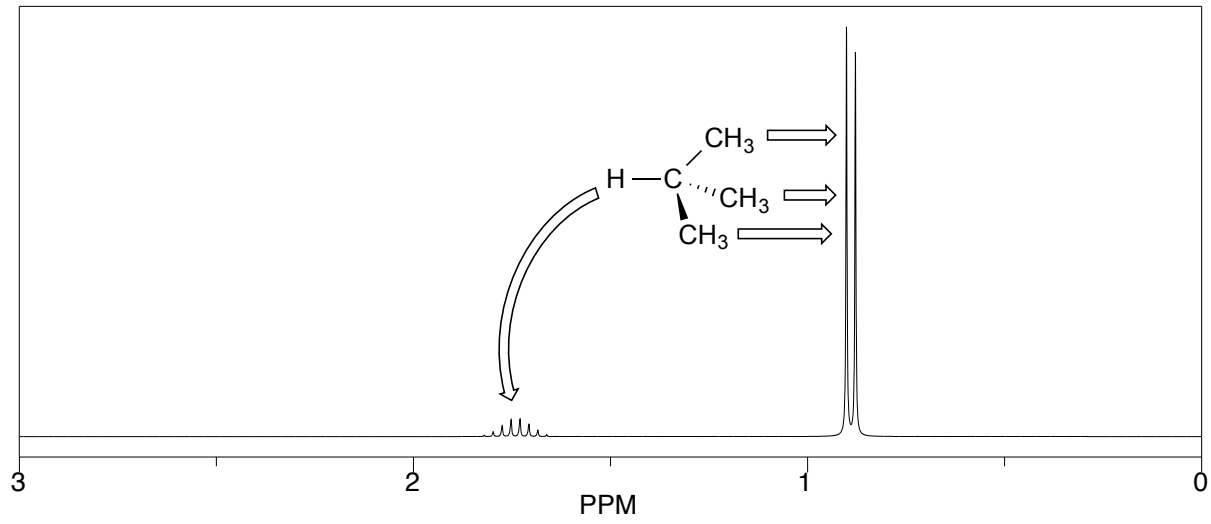
free rotation interconverts the positions of the three methyl groups

For instance, the simplest group we can insert to complete a molecule with the *tert*-butyl fragments is hydrogen. Doing so gives 2-methylpropane. The hydrogens of the methyl groups are all the exact same distance from the black methine hydrogen. There are three bonds separating the black methine hydrogen from any other hydrogen in the molecule. Therefore, we expect all of the *J* values to be identical and to have a magnitude consistent with vicinal coupling (6 – 8 Hz).

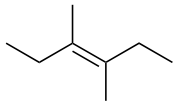


All *J* values are identical, so the methyl groups are magnetically equivalent.

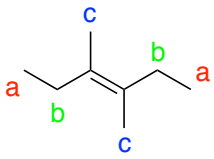
This is consistent with what we observe in the ^{1}H NMR spectrum. The signal for the three methyl groups is split into a doublet by the methine because it couples equally to all three methyls. The methine signal is a multiplet because it has so many neighbors (a total of nine).



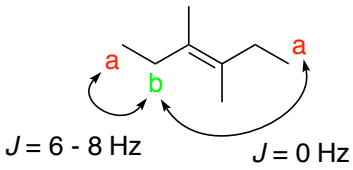
The following alkene provides an example of a molecule with magnetically *inequivalent* hydrogens.



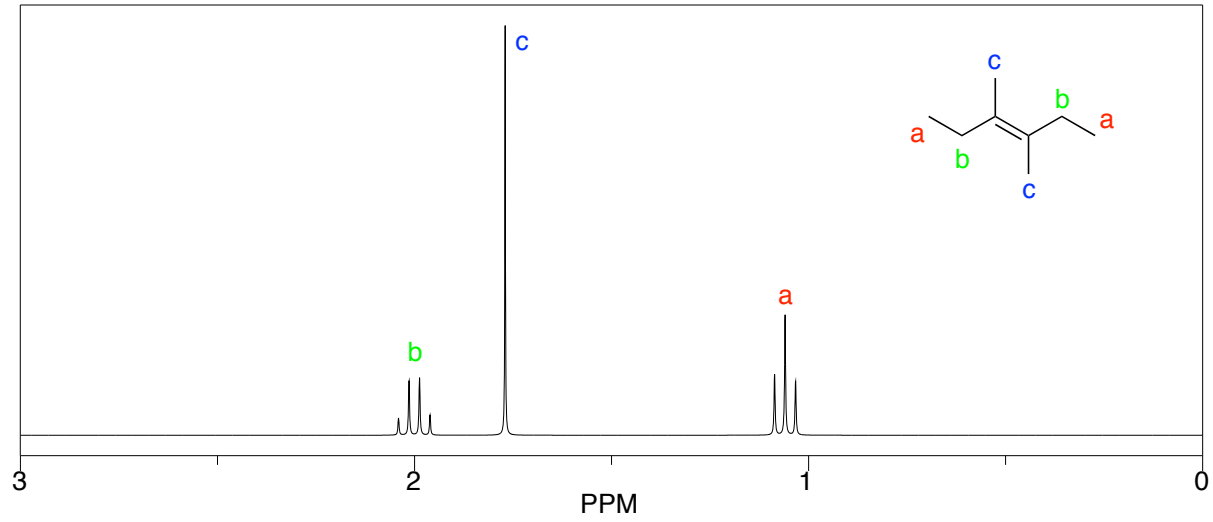
This alkene exhibits only three signals in the proton NMR due to its symmetry.



Let's consider one set of methylene (i.e., CH_2) protons, b. These protons will couple to the neighboring methyl group with a vicinal coupling constant of 6 – 8 Hz. However, although the two methyl groups a are chemically equivalent, b is too far from the methyl at the other end of the molecule to couple to it. As a result, these chemically equivalent hydrogens a couple differently to b and are therefore magnetically inequivalent.

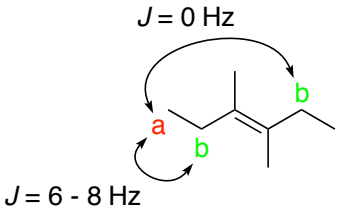


This is an instance where magnetic inequivalence simplifies the NMR spectrum. Since the second *J* value is zero, b appears only as a quartet due to its three vicinal neighbors. We observe no additional splitting of b due to the distal methyl protons a.

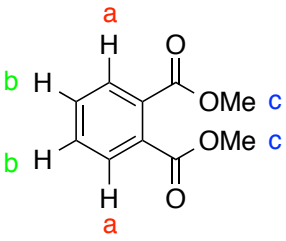


We can arrive at a related conclusion by considering a single set of methyl protons (a) and their interactions with the methylene protons (b). Protons a couple to the neighboring methylene b with a vicinal coupling constant of 6 – 8 Hz. However, this methyl group is too

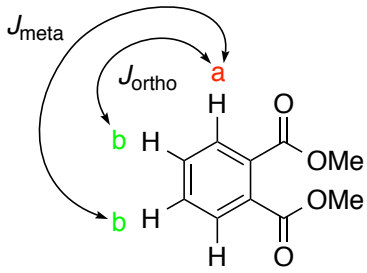
far from the other set of methylene protons b to couple to them. This shows that the chemically equivalent protons b are magnetically inequivalent.



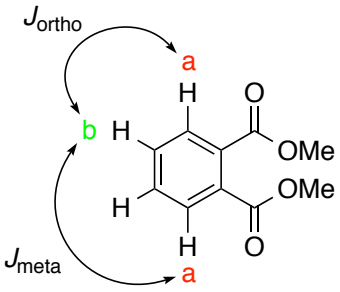
It is also possible for magnetic inequivalence to complicate an NMR spectrum. Dimethyl phthalate provides an illustrative example. Due to its symmetry, this molecule displays only three signals in the proton NMR spectrum.



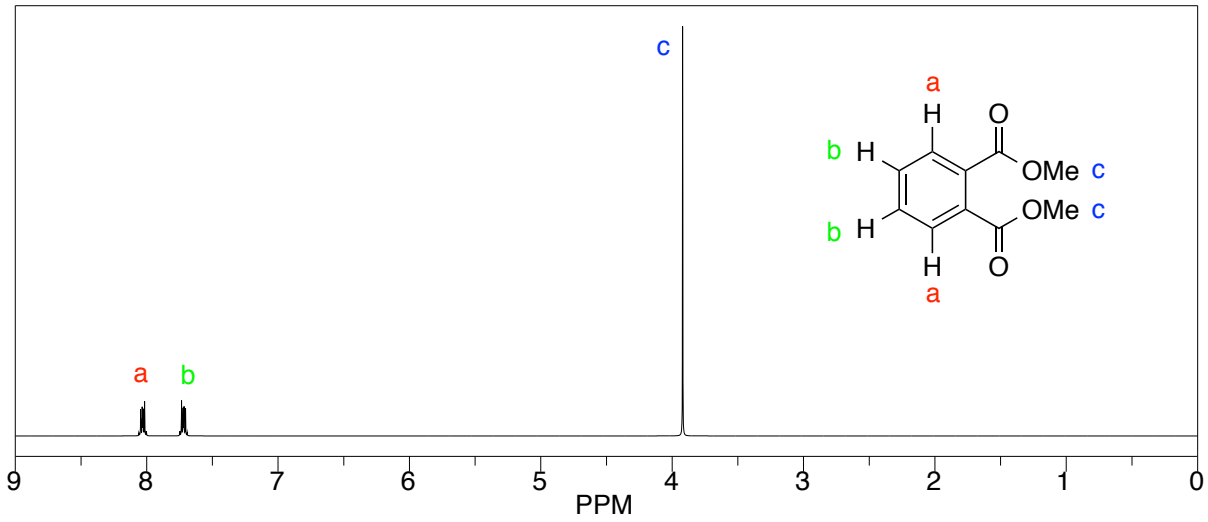
Let's consider the aromatic protons more carefully by isolating a single H_a proton. Although both H_b protons are chemically equivalent, they reside at different distances relative to H_a, so they couple to it with *J* values of different magnitudes. One coupling constant represents *ortho* splitting (6 – 9 Hz), while the other represents *meta* splitting (1 – 3 Hz).



Notice that we can reach a similar conclusion about the H_a protons by comparing their interaction with a single H_b proton. One H_a proton couples to H_b with an *ortho* coupling constant, but the other couples with a *meta J* value. This shows that the H_a protons are chemically equivalent yet magnetically inequivalent.

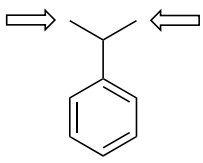


In this instance, the effect is to complicate the proton NMR spectrum. Since both H_a and H_b experience two splitting events with different *J* values, they both appear as doublets of doublets.

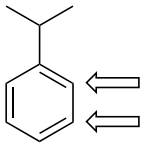


Problem 25. Classify the indicated protons in the following molecules as: chemically and magnetically equivalent; chemically equivalent but magnetically inequivalent; or chemically inequivalent.

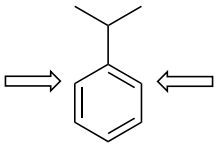
(a)



(b)



(c)

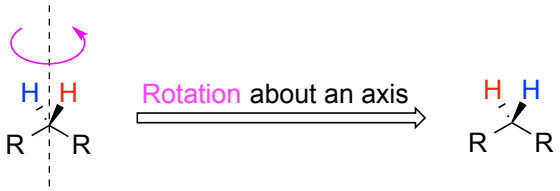


Methylene (CH_2) protons and magnetic inequivalence

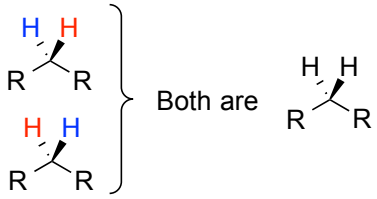
To this point, we've assumed that hydrogens stemming from the same sp^3 hybridized carbon are chemically equivalent. This is often, but not always, true. For a methyl group, the three hydrogens will be identical unless its rotation is somehow restricted, which would be quite rare. However, the two hydrogens of a methylene (CH_2) group are sometimes different from one another.

Methylene hydrogens can be placed into one of three categories, which will tell us about their spectroscopic behavior. These categories are: homotopic, enantiotopic, and diastereotopic. In order to place methylene hydrogens into one of these categories, we have to consider the symmetry of the molecule, and you can do this in one of two ways. The first method is a direct consideration of internal symmetry. The second method involves isotopic substitution of the methylene hydrogens, which indirectly tells us about symmetry. Let's examine each method for the three categories of methylene protons.

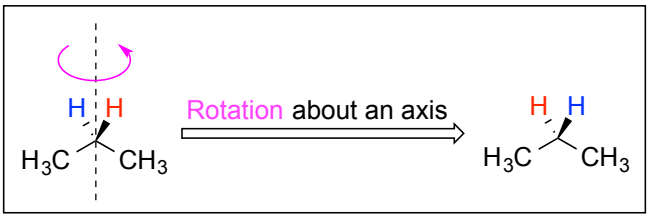
Homotopic methylene hydrogens are completely identical to one another in all respects and in all environments. They are totally indistinguishable, and this extends to spectroscopy. Homotopic methylene protons contribute to the same signal in NMR under all circumstances. Methylene protons are homotopic when there is a rotational symmetry axis within the molecule. By this, we mean that there is an axis about which you can rotate to interchange the two hydrogens without making any changes to the molecule.

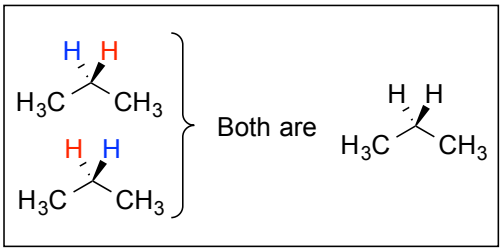


In this generic example, the 180° rotation has switched the location of the red and blue protons. When the R groups are identical, the structures before and after rotation are superimposable.

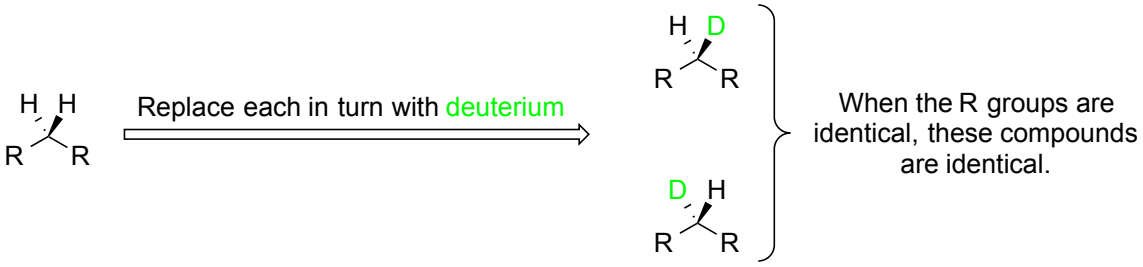


A specific example can be seen with the methylene protons of propane. Rotation about the internal axis reverses the locations of the highlighted protons, but the two structures are superimposable.

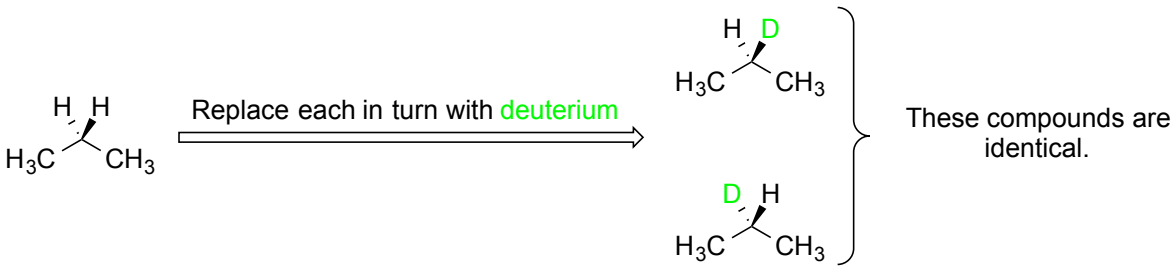




Some people have a difficult time visualizing the rotational axis of symmetry, so there is an alternative method to identify homotopic methylene protons. Draw the original structure twice, replacing each proton in turn with deuterium. Then, compare the two isotopically labeled structures. If they are identical (i.e., if they can be superimposed), then the methylene protons are homotopic.

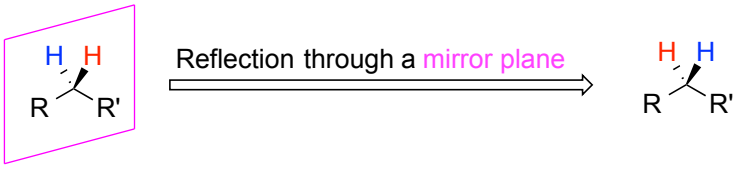


With our specific example, propane, we can clearly see that the sequential isotopic substitution results in identical compounds, meaning that propane's methylene hydrogens are homotopic.

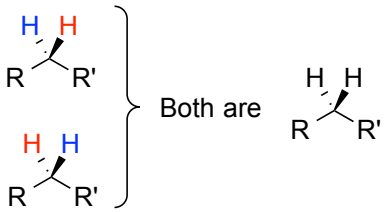


Methylene protons may be enantiotopic instead. Enantiotopic protons contribute to the same signal in NMR under normal circumstances. So, ordinarily they are spectroscopically indistinguishable. However, in a chiral environment, enantiotopic protons can be distinguished from one another.

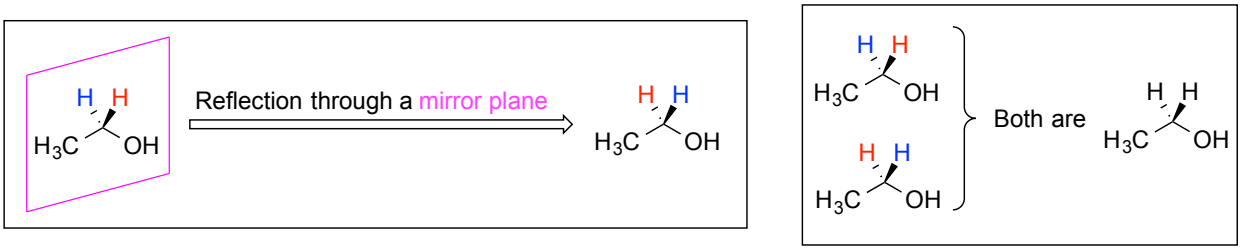
Enantiotopic protons are found when there is no rotational axis of symmetry in the molecule but there is an internal plane of symmetry. If reflection through this plane interchanges the methylene hydrogens and makes no alterations to the structure of the molecule, then those protons are enantiotopic.



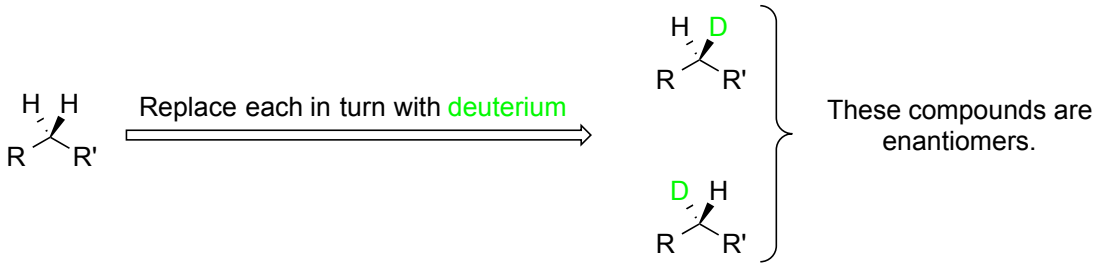
In this generic example, the plane of symmetry cuts right through the R-C-R' backbone and passes between the blue and red hydrogens. Reflection through that plane interconverts the position of the red and blue hydrogens but makes no change in the structure of the molecule. The methylene protons are therefore enantiotopic.



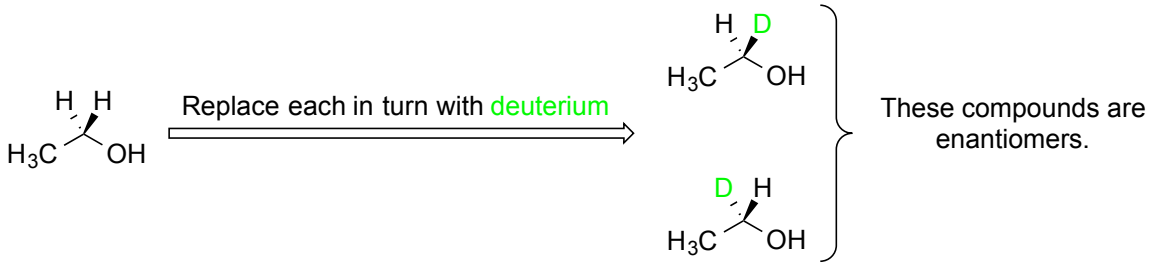
Ethanol provides a specific illustration of this principle. Reflection through the plane of symmetry cutting between the red and blue protons and passing directly through the H_3C-C-OH backbone interconverts the colored hydrogens without altering the structure of the molecule.



Again, some people find symmetry planes to be challenging to visualize. If that is the case for you, the isotopic-substitution method works equally well for the identification of enantiotopic hydrogens. The structure is drawn twice and each hydrogen in turn is replaced with deuterium. If the resulting compounds are enantiomers, then the methylene protons are enantiotopic.

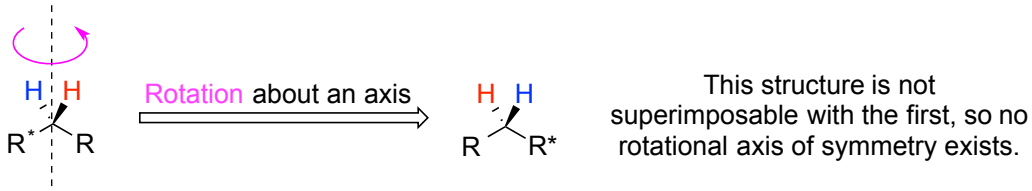


Our specific example, ethanol, illustrates this method nicely. Here, sequential isotopic substitution produces compounds that are enantiomers, meaning that the methylene protons are enantiotopic.

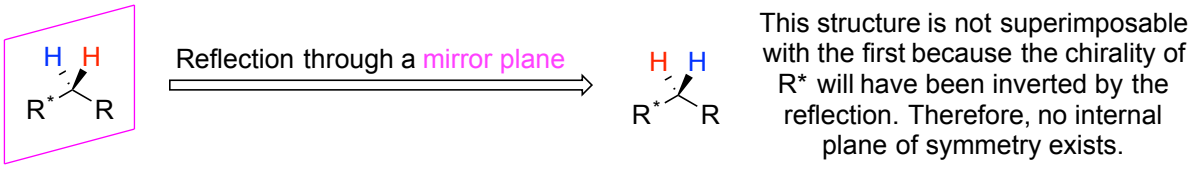


The final possibility is that methylene protons could be diastereotopic. Diastereotopic protons cause their own unique NMR signals despite the fact that they stem from the same carbon. This is a very important moment to take a step back and review the big picture. We have often assumed that hydrogens bonded to a single sp^3 hybridized carbon would give a single signal. We are now seeing that this is not necessarily the case. *In some molecules, hydrogens bonded to the same carbon can cause different signals.*

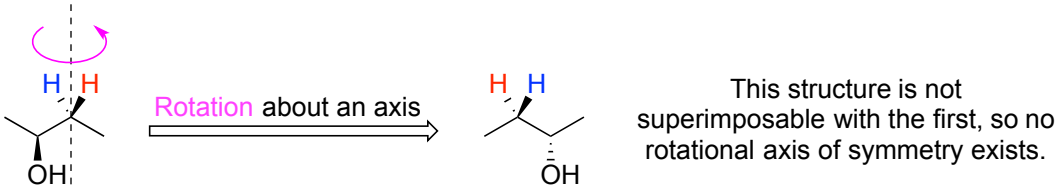
Diastereotopic protons can be identified in two ways as well. If there is *no* rotational axis of symmetry and *no* internal plane of symmetry, then the protons are diastereotopic. In generic structures we could see this by envisioning an R group containing chirality, which we'll call R*. Rotation about an axis through the methylene carbon yields a structure that *cannot* be directly superimposed with the first because R* and R do not line up.



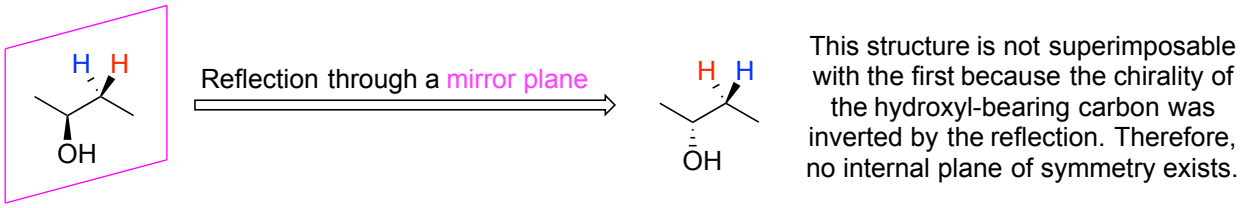
Additionally, this generic structure does not contain an internal symmetry plane. If reflection were attempted through a plane cutting along the R*-C-R backbone, the chirality in R* would be inverted from (*R*) to (*S*), or vice versa.



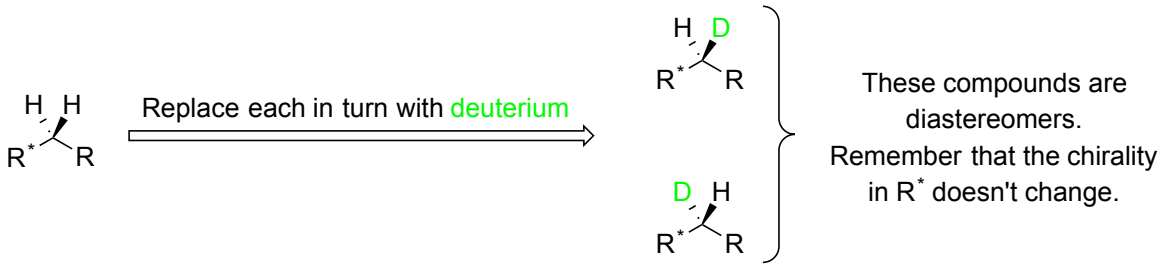
A specific instance of such a molecule is (*S*)-2-butanol. Rotation about an axis through the methylene carbon yields a structure that cannot be directly superimposed on the first because the methyl and alcohol-containing substituents do not line up.



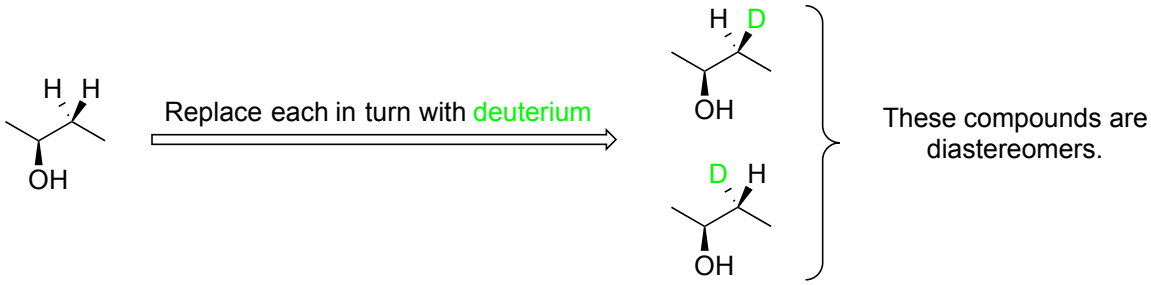
Similarly, we are unable to find an internal symmetry plane in (*S*)-2-butanol. Reflection through the plane dividing the red and blue hydrogens does interconvert them; however, the chirality of the alcohol has been inverted in the process. Therefore, the resulting structure is not superimposable on the original one.



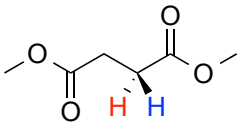
The isotopic substitution method provides an alternative way to identify diastereotopic hydrogens. Again, the structure is drawn twice and each methylene hydrogen is replaced in turn with deuterium. When the structure contains a pre-existing chiral center, the resulting compounds, which now bear a second chiral center, are diastereomers. This shows that the methylene protons are diastereotopic.



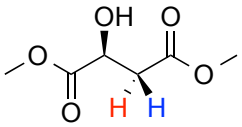
Continuing with our specific example, (*S*)-2-butanol, sequential isotopic substitution yields diastereomers, revealing that the methylene hydrogens are diastereotopic.



The ramifications of homotopic, enantiotopic, and diastereotopic hydrogens are observed in NMR spectra rather commonly. For example, if we compare dimethyl succinate to dimethyl (*S*)-malate, we'll see that their methylene hydrogens are of different types, and this will affect their spectra in a pronounced way.

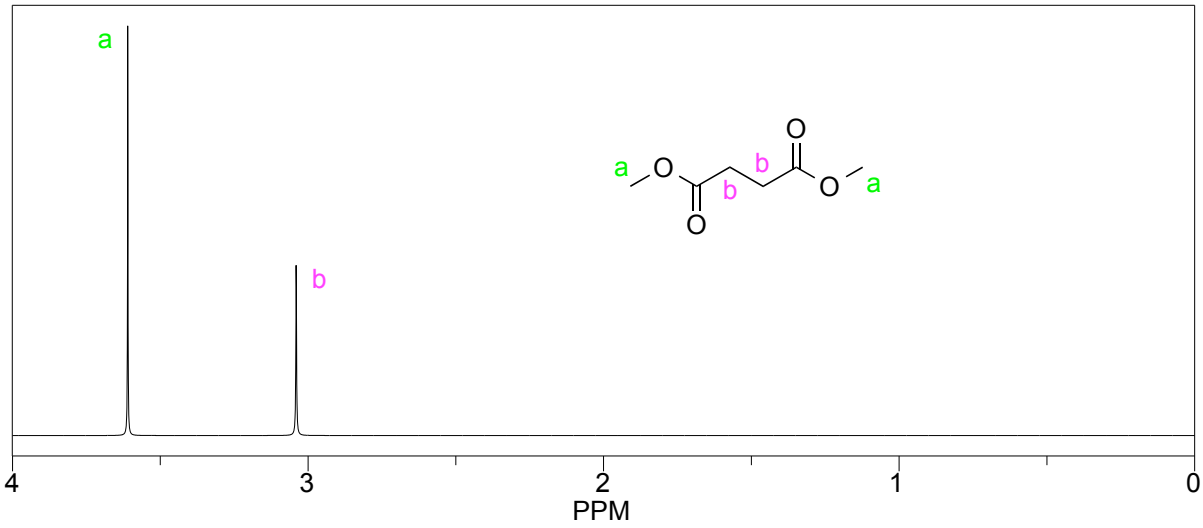


dimethyl succinate

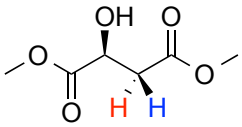


dimethyl (*S*)-malate

Dimethyl succinate has no rotational symmetry but possesses an internal plane of symmetry that can be used to interchange the red and blue hydrogens via reflection. This reveals that its methylene protons are enantiotopic. Alternatively, if we were to conduct sequential isotopic substitution, the compounds generated in that fashion would be enantiomers, leading us to the same conclusion. Consequently, we expect the blue and red methylene protons of this molecule to contribute to a single signal. We can see this in the following ^{1}H NMR prediction. In fact, we see that this compound only exhibits a total of two signals due to the fact that the two methyl groups are equivalent and the two methylene groups are equivalent as well.

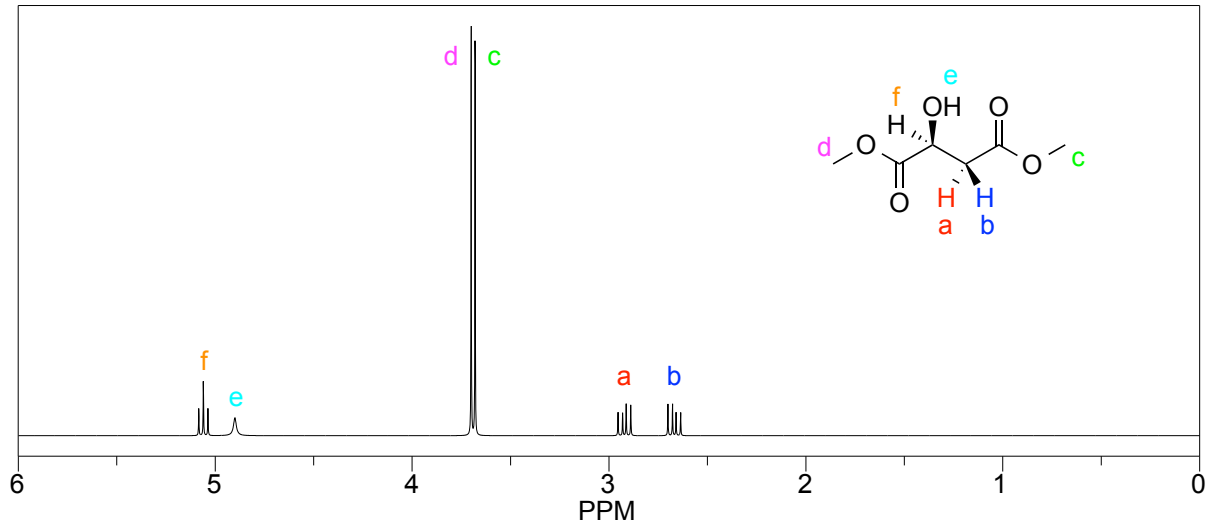


However, the methylene protons of dimethyl (*S*)-malate are another matter. Dimethyl (*S*)-malate does not exhibit rotational symmetry or an internal plane of symmetry. Consequently, its methylene protons are diastereotopic. We could also have arrived at this answer by citing the fact that sequential isotopic substitution of the methylene protons yields diastereomers. As a result, we expect the methylene protons to cause their own unique signals. This stands to reason from a common-sense perspective. In the conformation shown below, the blue hydrogen is closer to the hydroxyl group than the red hydrogen, so they exist in different chemical environments. Granted, many conformations about the central carbon-carbon bond are possible, but in all of them, the red and blue protons will reside in different locations relative to the adjacent hydroxyl group. This serves to differentiate them spectroscopically.

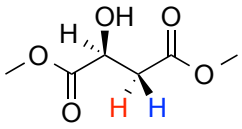


dimethyl (*S*)-malate

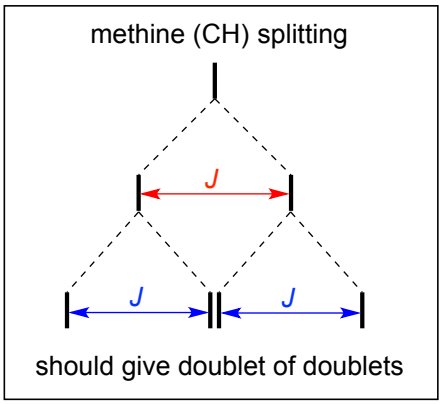
Furthermore, since the methylene protons are inequivalent, they split one another. The red proton (a) is split by its vicinal methine neighbor (f) and by its geminal blue neighbor (b) into a doublet of doublets. The blue proton exhibits a similar coupling. The following ^{1}H NMR prediction illustrates this. There are two doublets of doublets between 2.5 and 3.0 ppm.

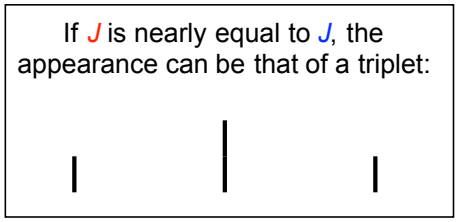


Another feature of this spectrum deserves comment. The methine signal (f) is an *apparent* triplet. Formally, its two neighbors (a and b) are different and should split the methine hydrogen with different *J* values, leading to a doublet of doublets. However, protons a and b are not that different from one another, so their *J* values are similar. As a result, accidental overlap of the central peaks in the splitting tree for f can result in something that looks very much like a triplet. This is sometimes referred to as an apparent triplet.



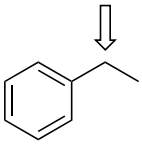
dimethyl (*S*)-malate



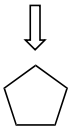


Problem 26. Classify the indicated methylene protons in each structure as homotopic, enantiotopic, or diastereotopic. Then, state whether they would be expected to cause one or two signals.

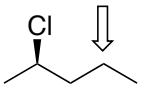
(a)



(b)



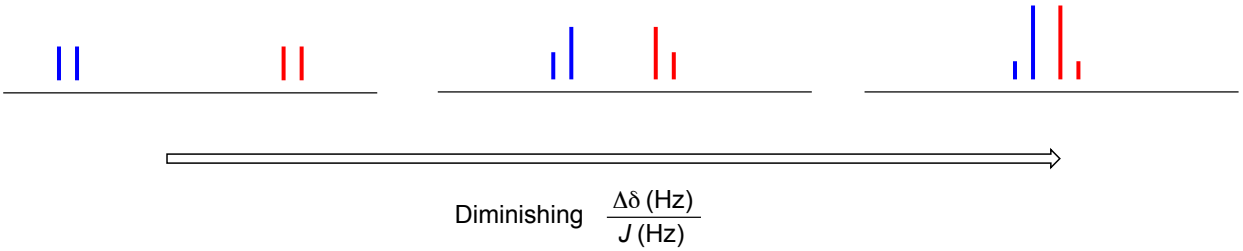
(c)



Second-order coupling

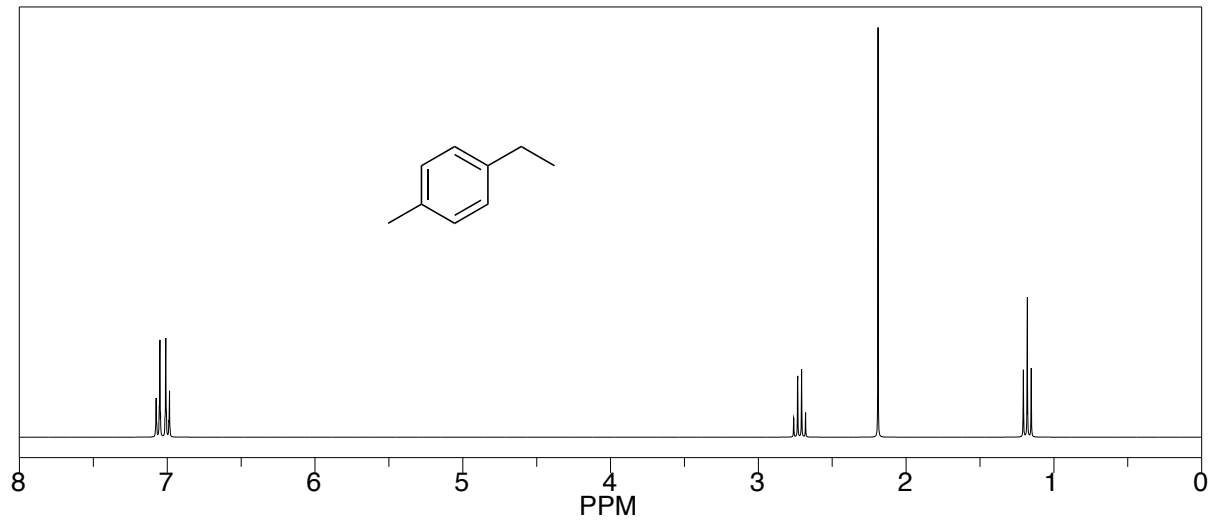
Second-order coupling is a phenomenon that is also termed strong coupling or roofing. As the difference in chemical shift between two coupled signals decreases, the inside peaks grow in intensity while the outer peaks diminish in intensity. An example using two doublets is presented graphically below. When the chemical shift difference is large relative to the coupling constant (i.e., $\frac{\Delta\delta\ (Hz)}{J\ (Hz)} \geq 10$), the doublets appear exactly as you would expect. Each doublet contains two peaks of equal height. As the chemical shift difference diminishes relative to the *J* value, the interior peaks grow larger while the exterior peaks

grow smaller. There are still two doublets, but they no longer appear as we would expect since there is a height difference between the two peaks of each doublet. Such a signal can be called an AB quartet to distinguish it from a true quartet, which would be due to the presence of three neighbors. Instead, an AB quartet results from two protons (A and B), each of which splits the other.



This phenomenon can be useful. In a spectrum with multiple doublets, roofing can help to illustrate which pairs result from adjacent hydrogens. However, this phenomenon can also be confusing since you may not know whether a signal is a true quartet or an AB quartet. This is one of the reasons that strong magnets are helpful in NMR spectroscopy. As the magnetic field strength increases, the number of Hz in a chemical shift unit increases. Since the coupling constant is an intrinsic property and does not change, the *J* value becomes a much smaller percentage of a ppm, which helps to clearly resolve individual signals.

Problem 27. Explain the appearance of the signal at 7 ppm in the following proton NMR spectrum.



Carbon-13 NMR

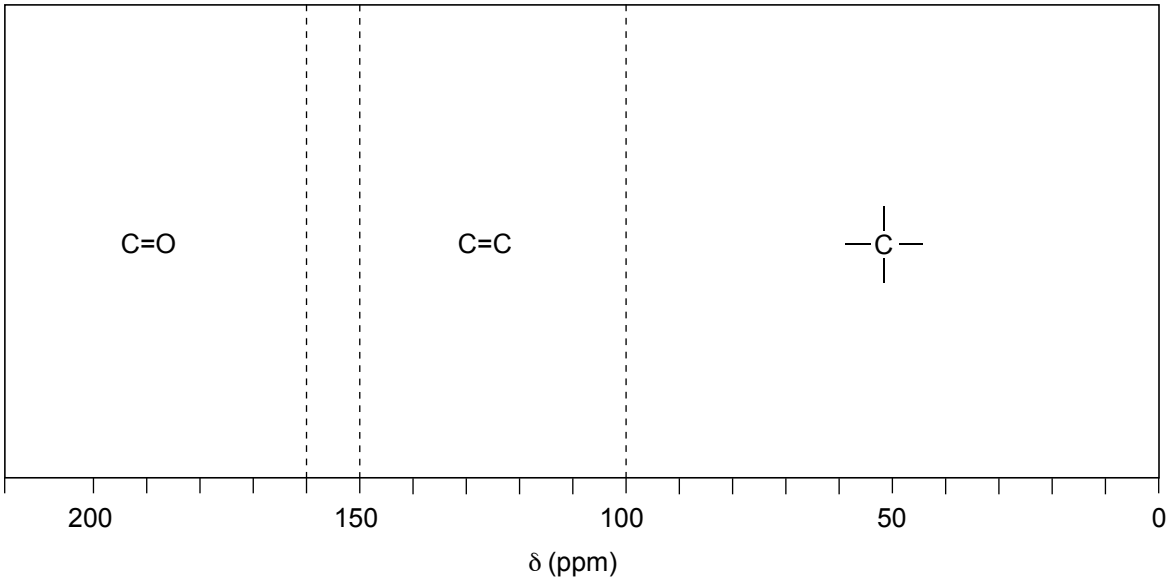
Carbon-13 is another NMR-active nucleus, but ^{13}C NMR faces some unique challenges. First, there is a relatively low abundance of the NMR-active isotope. This was not the case with ^{1}H NMR, in which the vast majority of hydrogen atoms are the NMR-active isotope. In

contrast, carbon-13 comprises only about 1.1% of any sample of carbon. This, in combination with other factors, typically lengthens ^{13}C NMR acquisition times.

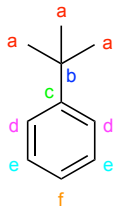
Another challenge is the coupling of ^{13}C nuclei to their protons. This can give carbon-13 signals with splitting patterns that, when they overlap one another, complicate the spectrum dramatically. For this reason, ^{13}C NMR spectra are often proton decoupled. This simply means that the protons are irradiated during the entire acquisition to keep them in the excited spin state. If the protons exist in only one spin state during this time, then coupling between carbons and their attached protons does not occur because splitting depends on two spin states being occupied.

Proton-decoupled ^{13}C spectra show all carbon signals as singlets, which greatly simplifies the analysis. In this process of decoupling, information about the number of attached protons was lost. For the sake of obtaining readily discernible signals, we have sacrificed the ability to determine how many protons exist in close proximity to each carbon. If that information is needed, there are other NMR experiments that can provide it.

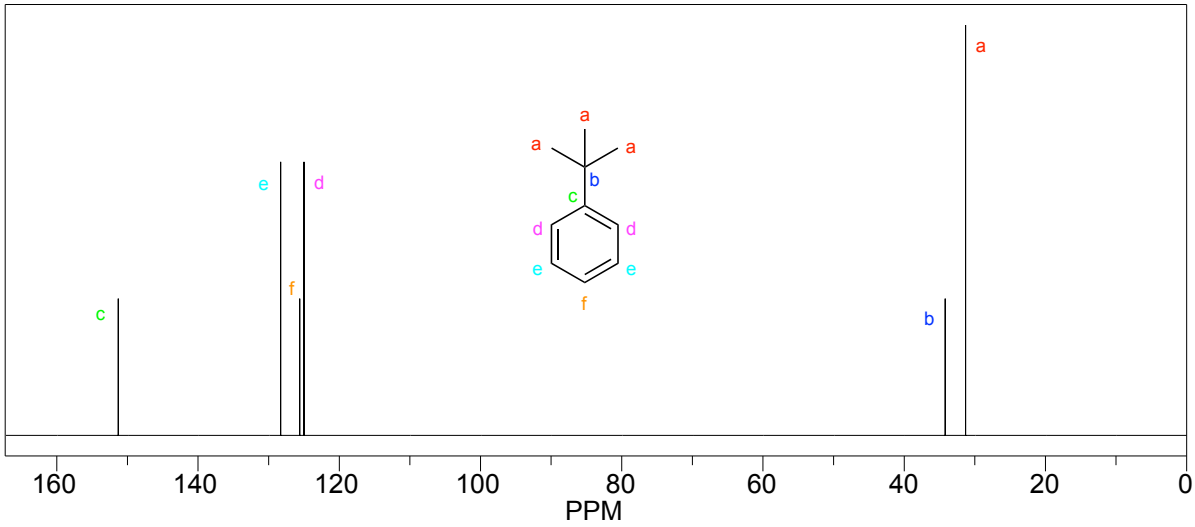
The chemical shift range for ^{13}C NMR is much larger than what we observed in ^{1}H NMR. ^{13}C spectra typically range from 0 to over 200 ppm. One convenient ramification of this is that carbon signals rarely overlap. If two carbons contribute to a single signal, it is typically because they are in chemically equivalent environments and are therefore indistinguishable. Accidental overlap of similar but distinct carbons is rare. Carbons involved in a double bond appear above 100 ppm. They will be in the range of 100 – 150 ppm if they are alkene or aromatic carbons and will appear over 160 ppm if they are carbonyl carbons. Most other types of carbons appear below 100 ppm. This typically means sp^3 hybridized carbons, although it is worth noting that alkyne carbons (sp hybridized) also appear in this range from about 65 – 90 ppm. This list is not completely inclusive, but provides enough categories for most situations.



When ^{13}C NMR spectra are proton decoupled, integration is rendered unreliable. Due to this phenomenon and the fact that accidental overlap of carbon signals is rare, most carbon signals are simply assumed to represent one carbon. When chemically equivalent carbons are present within a molecule, you may sometimes see carbon signals that are much taller than the others. This is a clue to the greater integration of those signals, but a specific integration value is still not typically calculated. We can see an example of this in the predicted spectrum for *tert*-butylbenzene. This molecule contains 10 carbons but only 6 different types of carbons.

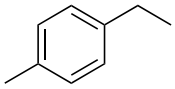


Just above 30 ppm in the predicted spectrum, we see two signals for the quaternary carbon (b) of the *tert*-butyl group as well as the three methyl groups (a). One signal is clearly larger than the other, and this is a clue to the fact that the larger signal likely represents the three equivalent carbons of the *tert*-butyl group. Similarly in the aromatic region, two signals are clearly larger than the others, suggesting that they are due to the two sets of equivalent methine carbons (labeled d and e).



In general, the interpretation of carbon-13 NMR spectra is simpler than the interpretation of proton NMR spectra because there are fewer pieces of information. In ^{13}C NMR, our primary focus is the number of signals and their chemical shift. Splitting information has been erased through proton decoupling, and this has also made integration unreliable.

Problem 28. Predict the ^{13}C NMR of the following molecule that we first examined in Problem 27.



Section 5: Structure Solving Using NMR Spectroscopy

A chemist working in the laboratory will often perform a reaction and then acquire IR and NMR spectra of the product. This information is used to determine the product's structure. In problems that mimic this real-world application of spectroscopy, you will often be given a molecular formula as well. This is a piece of data that can easily be acquired in the laboratory through a technique known as elemental analysis. While these pieces of information can be used in any order, the following algorithm is one streamlined approach to utilizing the data. This process simply expands upon the algorithm introduced in Section 3 to include what we've learned since then.

(1) Calculate degrees of unsaturation.

(2) Spot-check the key portions of the functional group region of the IR spectrum:

(a) the carbonyl-stretching region at 1700 cm^{-1};

(b) the carbon-hydrogen stretching region (sp^3 C-H: below 3000 cm^{-1}; sp^2 C-H: above 3000 cm^{-1});

(c) the heteroatom-hydrogen stretching region at ~3400 cm^{-1}.

(d) Compare any other significant signals to the correlation table.

(3) Analyze the ^1H NMR data, remembering that:

(a) the number of signals reveals the number of types of protons;

(b) a signal's chemical shift tells about its chemical environment;

(c) a signal's integration tells the number of protons causing that signal;

(d) and a signal's splitting reveals the number of neighboring hydrogens.

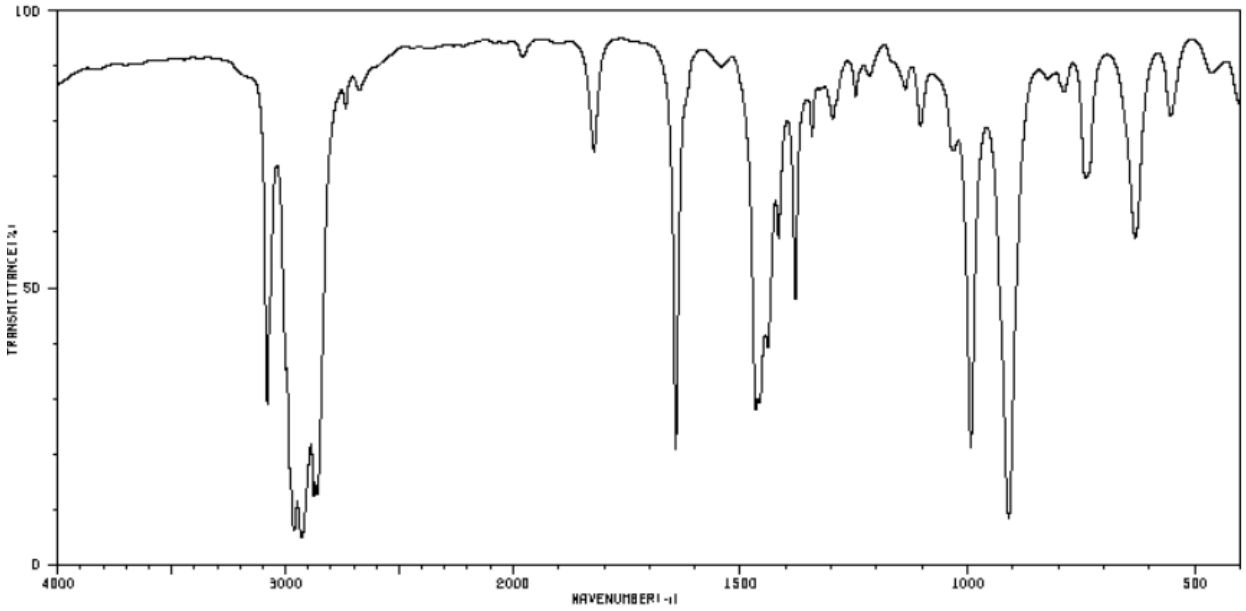
(4) Analyze the ^{13}C NMR data, focusing on:

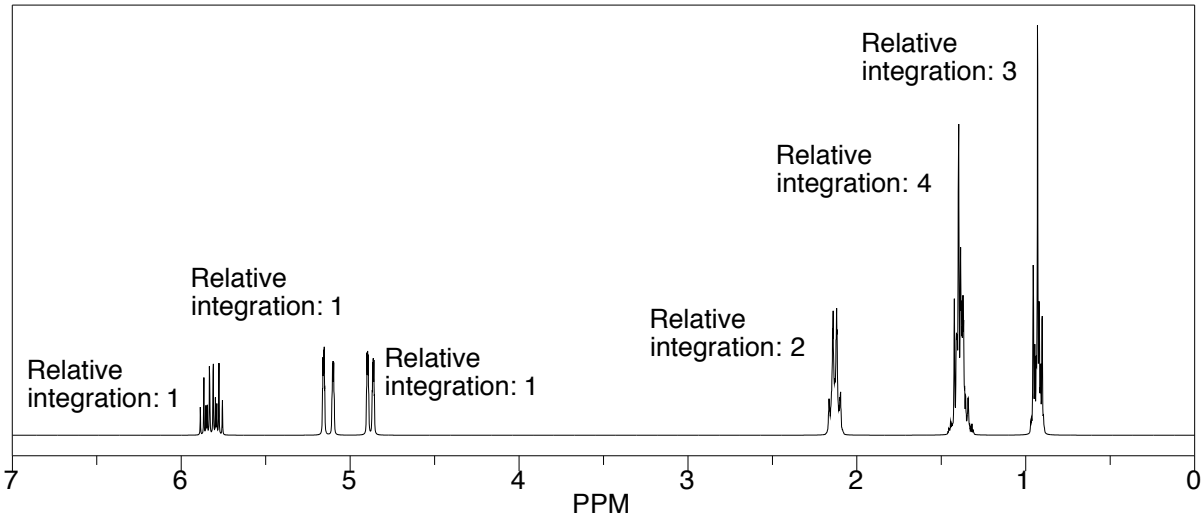
(a) the number of signals and

(b) their chemical shift.

(5) Propose a structure that is consistent with the available data.

Let's practice this algorithm using some problems. For our first problem, let's return to the first unknown considered in Section 3. It has the formula C_6H_{12} and the following infrared and proton NMR spectra.





We've just been presented with a great deal of information. One of the biggest challenges of this type of problem is managing the information so that you don't get overwhelmed by it. Our algorithm for structure solving is designed to help us do just that. When we saw this problem in Section 3, we began by calculating the degrees of unsaturation as shown below. This is step 1 of the algorithm.

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(6) + 2] - 12}{2} = 1$$

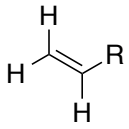
This reveals that the molecule contains one ring or one π bond.

Step 2 of the algorithm focuses on analysis of the IR spectrum. This spectrum reveals sp^2 C-H stretching just above 3000 cm^{-1} and sp^3 C-H stretching just below 3000 cm^{-1}. There is no heteroatom-to-hydrogen stretching, nor is there a carbonyl stretch. Nevertheless, we have gathered an important clue from the IR alone, which is that the degree of unsaturation must be a π bond. In order to have sp^2 C-H stretching just above 3000 cm^{-1}, an alkene is needed.

When we encountered this problem in Section 3, this was all the evidence that we had, and there were a variety of alkenes that were consistent with the data. However, we now have a proton NMR spectrum as well, and it will narrow the possible alkene structures to one.

It is typically easier to consider the signals in an NMR spectrum from left to right. The reason is that protons that are part of a functional group or are adjacent to functionality have higher chemical shift values. These unique types of protons provide some easily interpreted clues. However, the signals closer to zero tend to be further from functionality and are therefore less readily diagnostic.

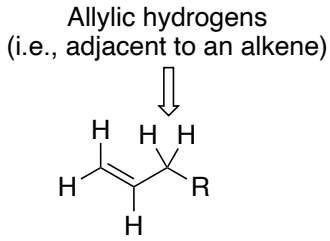
There are three signals in the range of 4.5 – 6.5 ppm. Vinyl protons tend to appear in this window. Each signal integrates for one hydrogen. Therefore, we know that the alkene must be monosubstituted:



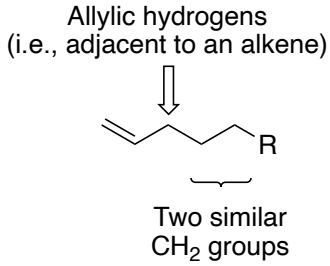
Each hydrogen of a monosubstituted alkene gives its own unique signal. The two terminal protons differ because one is *cis* to the R group while the other is *trans* to it (i.e., one is on the same side of the alkene as the R group while the other is on the opposite side).

Notice that you may not always need to analyze every facet of an NMR signal. In this instance, the vinyl protons have fairly complex splitting. One is a multiplet, and the other two are doublets of doublets where one *J* value is rather small. But, we didn't need to interpret these complex splitting patterns in order to determine that a monosubstituted alkene is present.

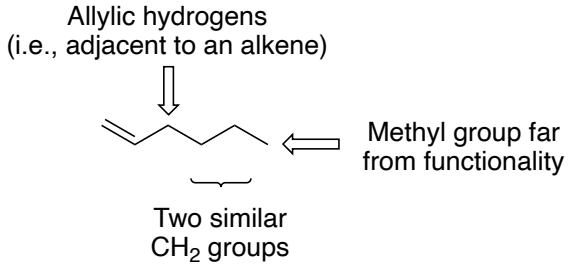
As we continue to move from left to right, the next signal encountered falls between 1.5 and 2.5 ppm, where we find protons adjacent to an alkene (i.e., allylic protons). This signal integrates for two hydrogens, showing that a CH_2 (or methylene) group is adjacent to the alkene.



The next signal appears just below 1.5 ppm and integrates for four hydrogens. The integration reveals that this signal must be the result of two similar types of protons whose signals are near enough that they overlap. We know this because there is no CH_4 group. CH_4, or methane, would be a discrete molecule and not a portion of another molecule. Two similar CH_2 groups could, however, yield a single signal integrating for four hydrogens, so we can add them to our expanding structure.

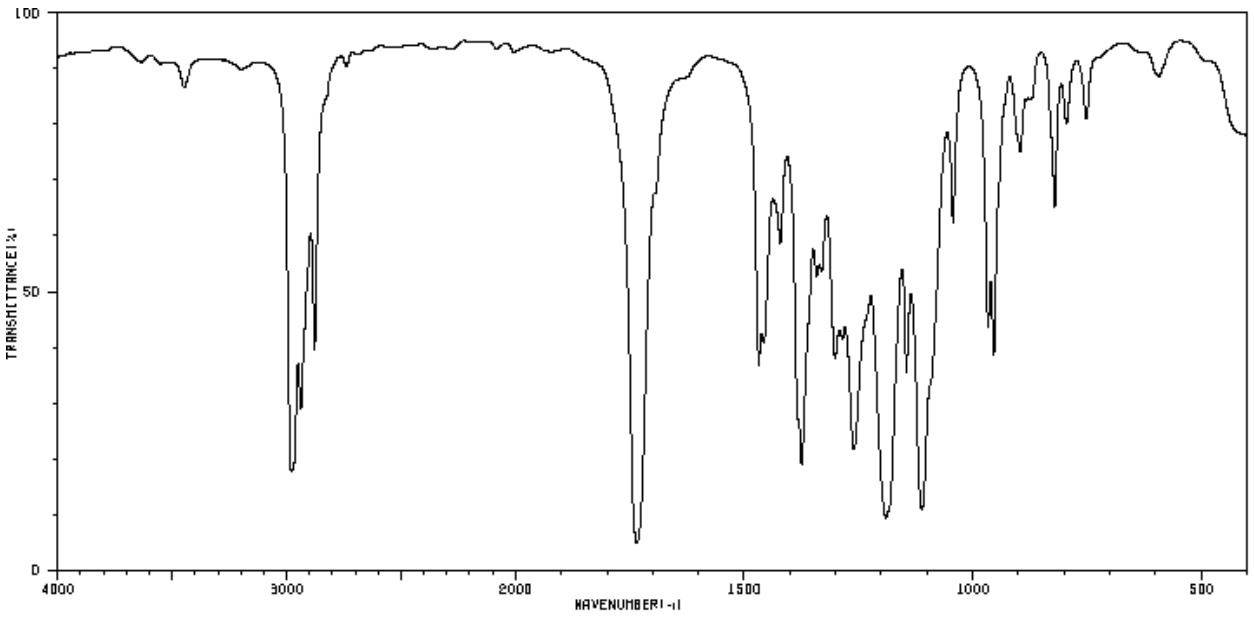


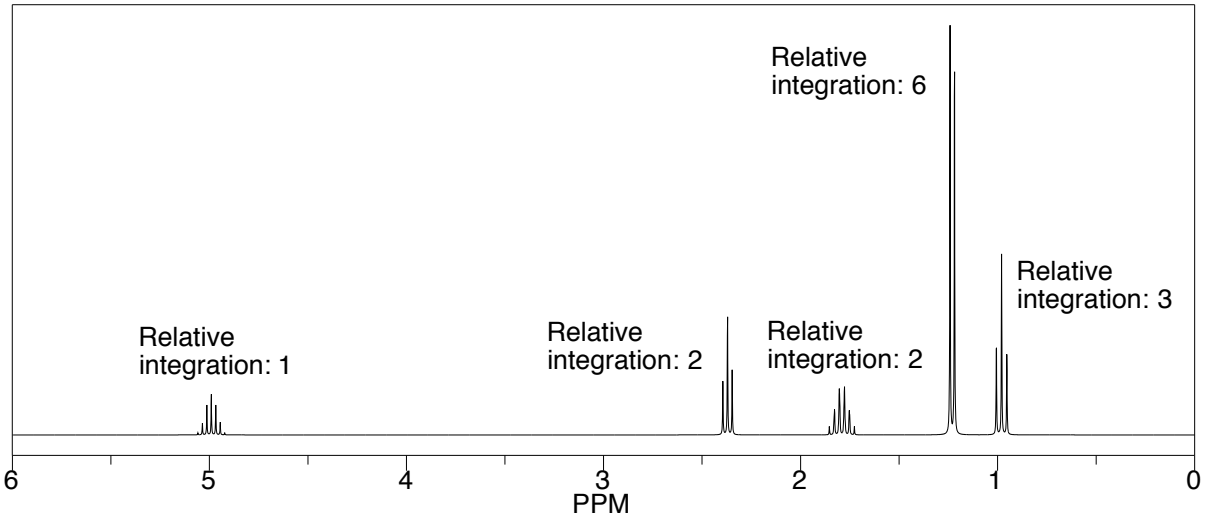
The last remaining signal in the NMR spectrum appears just below 1 ppm and integrates for three hydrogens. This must be a methyl group that is far from functionality, and it is the last fragment, which allows us to complete the structure of the unknown, which is a compound called 1-hexene.



Notice that much of the splitting throughout this example was complicated by the fact that most protons have multiple neighbors of different types. We cannot necessarily ignore splitting because it often gives valuable clues. But, this example illustrates that, even when the splitting is complex, it may still be possible to ascertain structural clues without getting mired down in the analysis of multiplets.

Let's consider another example. This unknown has the molecular formula $C_7H_{14}O_2$, as well as the IR and ^1H NMR spectra shown below.





The first step in our algorithm is to compute the degrees of unsaturation. Recall that oxygen does not impact the calculation.

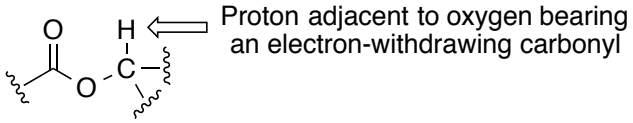
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(7)+2] - 14}{2} = 1$$

We now know that the compound contains either a ring or a π bond.

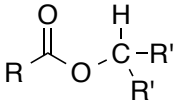
The fingerprint region of the IR spectrum shows sp^3 C-H stretching just below 3000 cm^{-1} and carbonyl stretching well above 1700 cm^{-1}. We now know that the degree of unsaturation is the π bond of a carbonyl.

The two oxygen atoms in the formula could be part of two separate functional groups. However, there are two pieces of evidence that suggest they are actually part of the same functional group. The first is that esters absorb around 1740 cm^{-1}, and the carbonyl resonance in the IR does fall well above 1700 cm^{-1}. The second piece of evidence concerns the NMR. The signal with the highest chemical shift appears at 5 ppm. This falls in the range for vinyl protons; however, this structure cannot have vinyl protons because it contains only one π bond, which is part of the carbonyl. However, an ester could contain a type of proton that would fall in this range:

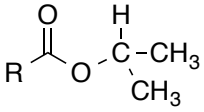


Protons on carbon bonded to oxygen fall in the range of 2.5 – 4.5 ppm. They also appear on the higher end of this range due to the powerful electron withdrawal by oxygen, which is a very electronegative element. In an ester, the oxygen atom is also bonded to an electron-withdrawing carbonyl, which makes that oxygen even more deshielding. Deshielding is cumulative, so multiple deshielding (i.e., electron-withdrawing) factors can result in a higher chemical shift value than you might initially have anticipated.

Furthermore, the signal at 5 ppm shows through its integration that there is exactly one hydrogen of this type.

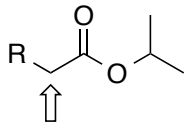


Note that there are seven carbons in the molecule, but only five signals in the proton NMR. The carbonyl carbon bears no protons, so it does not appear in the spectrum. But, there is still one signal fewer than we would have anticipated. Observing fewer signals than expected in the NMR spectrum is an indication of symmetry in the molecule. Notice that there is one signal with an integration of six, meaning that there are two equivalent methyl groups in this structure. Furthermore, this signal is a doublet, so these methyl groups have a single neighbor. These pieces of evidence suggest that an isopropyl group is present.



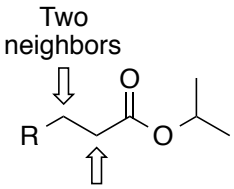
Here, we have linked one signal to another. The sole proton of the CH group will split its neighbor into a doublet. There is only one doublet in the spectrum, so we were able to identify that the two identical methyl groups are adjacent to the CH unit.

Of the remaining signals, the most deshielded is closest to the functionality in the molecule. The integration of this signal at ~2.4 ppm is two hydrogens. This enables us to place a CH_2 adjacent to the carbonyl.



Methylene (CH_2) next to carbonyl is deshielded

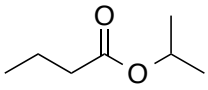
This signal also happens to be a clear triplet, showing that it has two neighbors, so we can add those to the molecule.



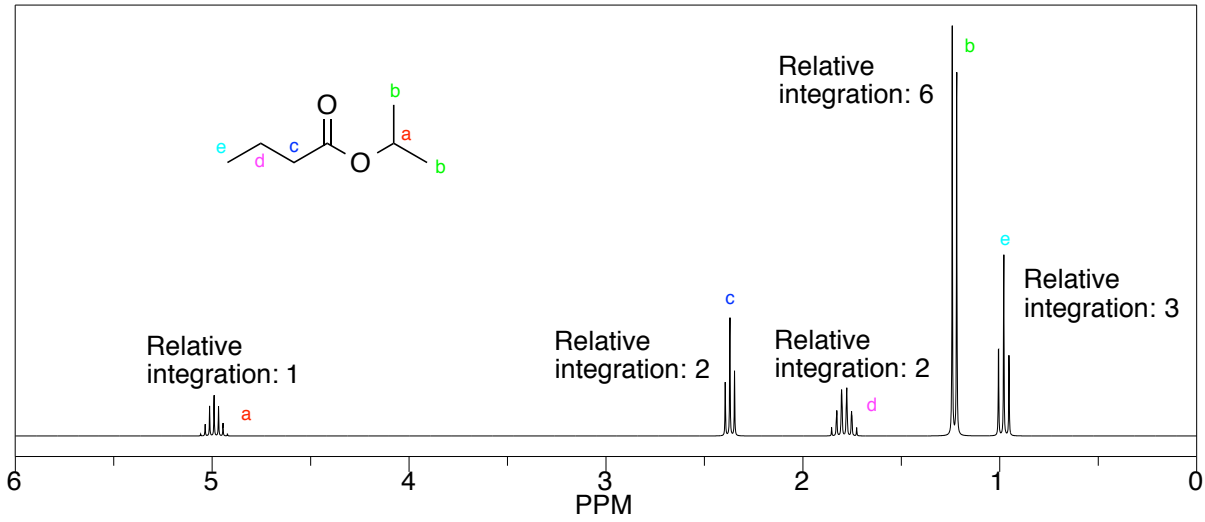
Methylene (CH_2) next to carbonyl is deshielded

There also happens to be another signal in the spectrum integrating for two hydrogens (at ~1.8 ppm), which is the signal for the two neighbors we have just added.

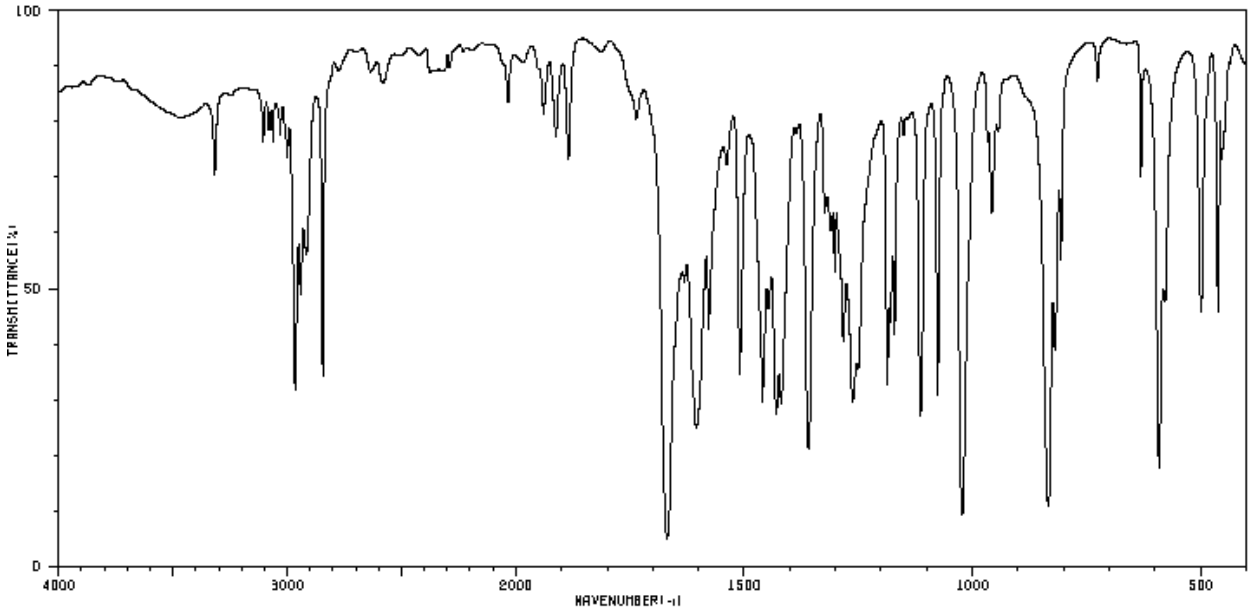
The sole remaining signal integrates for three hydrogens. It must be a methyl group that completes the structure.

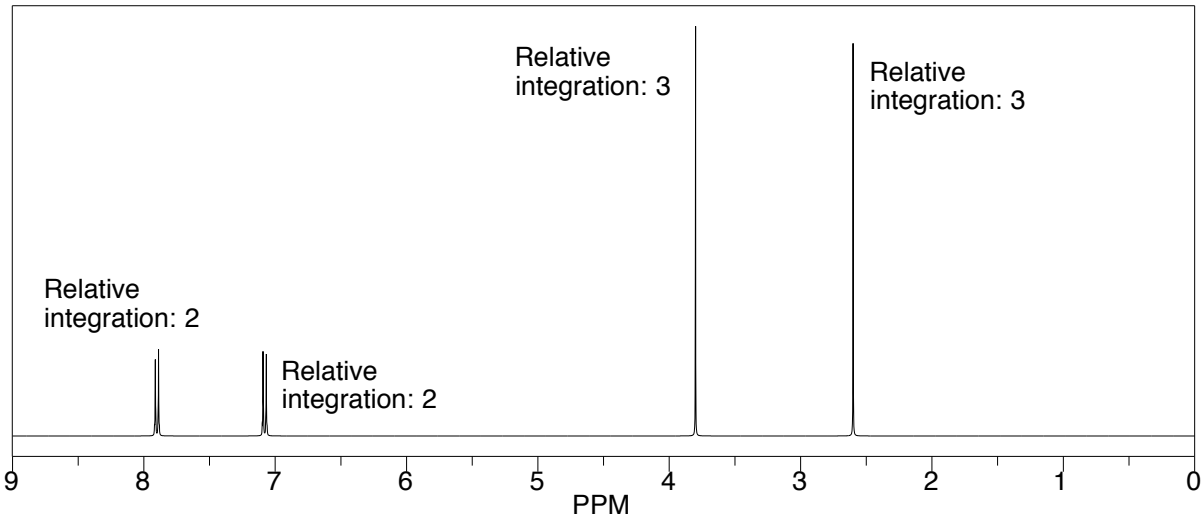


Reviewing the structure highlights the fact that everything we've proposed is in agreement with the evidence. The methine (i.e., CH) of the isopropyl group (a) is a multiplet, and it does indeed have many neighbors (b). The methylene (i.e., CH_2) adjacent to the carbonyl (c) is a triplet, and it has exactly two neighbors (d). The protons labeled d have many neighbors (c and e) and are therefore a multiplet. The methyl group (e) is a triplet because it has exactly two neighbors (d).



Let's try one more example together. This unknown has the molecular formula $C_9H_{10}O_2$, as well as the following IR and proton NMR spectra.





Our algorithm begins with the computation of degrees of unsaturation. The presence of oxygen in the formula does not impact this calculation.

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

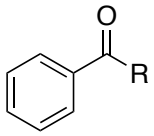
$$DOU = \frac{[2(9)+2] - 10}{2} = 5$$

Recall that, when many degrees of unsaturation are present, it is often useful to consider benzene rings, which account for four degrees of unsaturation. It is therefore likely that this molecule contains a benzene ring, as well as one additional ring or π bond.

The IR spectrum reveals that the fifth degree of unsaturation is the π bond of a carbonyl because a carbonyl stretch is visible below 1700 cm^{-1}. We now have two fragments: a benzene ring and a carbonyl.

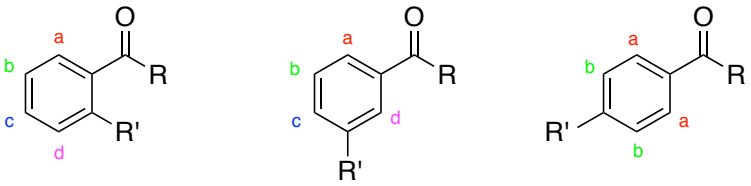
In the previous example, there were two oxygen atoms in the molecular formula, and these were part of a single functional group. There are two common functional groups containing two oxygen atoms: esters and carboxylic acids. In this problem, there is no evidence for an ester. An ester absorbs around 1740 cm^{-1}. If it were conjugated, it would absorb about 30 cm^{-1} lower at ~1710 cm^{-1}. However, the carbonyl in this IR spectrum actually absorbs below 1700 cm^{-1}. The other functional group containing two oxygen atoms is the carboxylic acid, but carboxylic acid protons have a very distinctive NMR signal around 12 ppm, which is not present in this unknown's ^1H NMR.

Therefore, we are compelled to consider the two oxygen atoms as part of two distinct functionalities. Given that the carbonyl absorbs below 1700 cm^{-1} in the IR spectrum, it appears to be conjugated and should therefore be bonded directly to the benzene ring. Recall that ketones and aldehydes absorb around 1715 – 1720 cm^{-1} but conjugation lowers the frequency by approximately 30 cm^{-1}. This observation enables us to condense our two fragments into one.



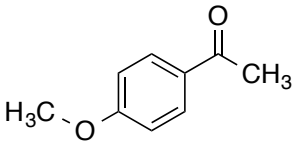
We've assembled a fairly sizeable fragment from the degrees of unsaturation and IR information alone. This serves as an important reminder to take your time with the data. It is often the case that much can be learned from a few clues that are carefully considered.

At this point, it is reasonable to turn our attention to the NMR. The most deshielded signals fall between 7 and 8 ppm. These are the protons of the aromatic ring. There are two key points to recognize about these aromatic signals: (1) the integration values and (2) the splitting. The two signals together account for a total of four protons, which reveals that the aromatic ring is disubstituted. In other words, two of the six protons of benzene have been replaced by substituents. The splitting pattern is also an important clue because it reveals the arrangement of the substituents on the ring. Of the three possible patterns for a disubstituted ring shown below, only the last one has the symmetry necessary to yield only two signals in the proton NMR.

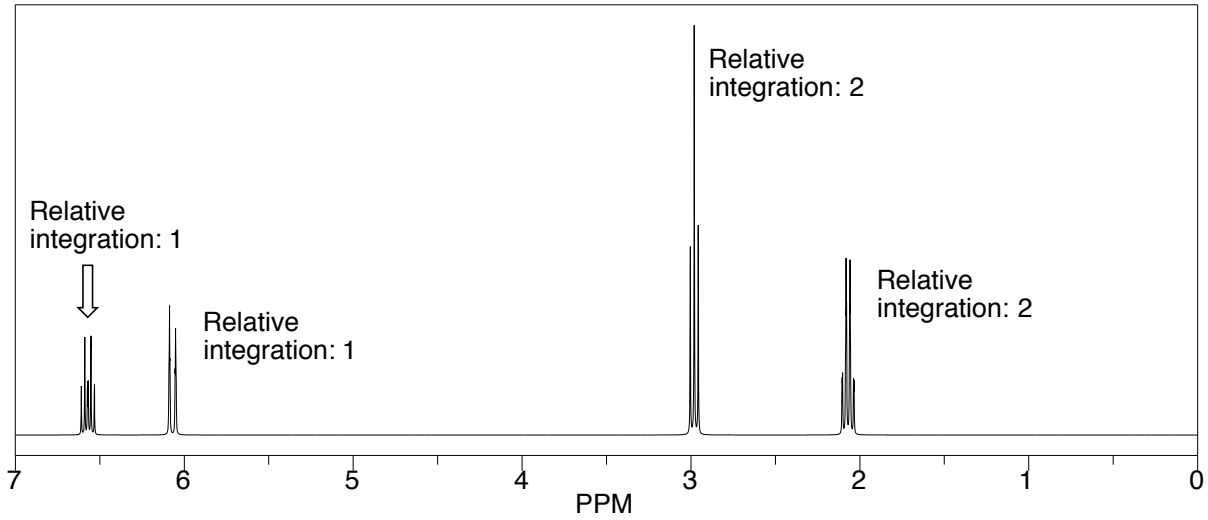


Now that we have the framework for the molecule in place, we need only address the two remaining NMR signals. These are both singlets and integrate for three hydrogens each. The signals therefore represent methyl groups with no neighbors. One falls in the range of 2.5 – 4.5 ppm and is therefore adjacent to an oxygen atom. The other appears almost exactly at 2.5 ppm, which is the boundary between two chemical shift regions. This signal could be consistent with protons adjacent to a carbonyl.

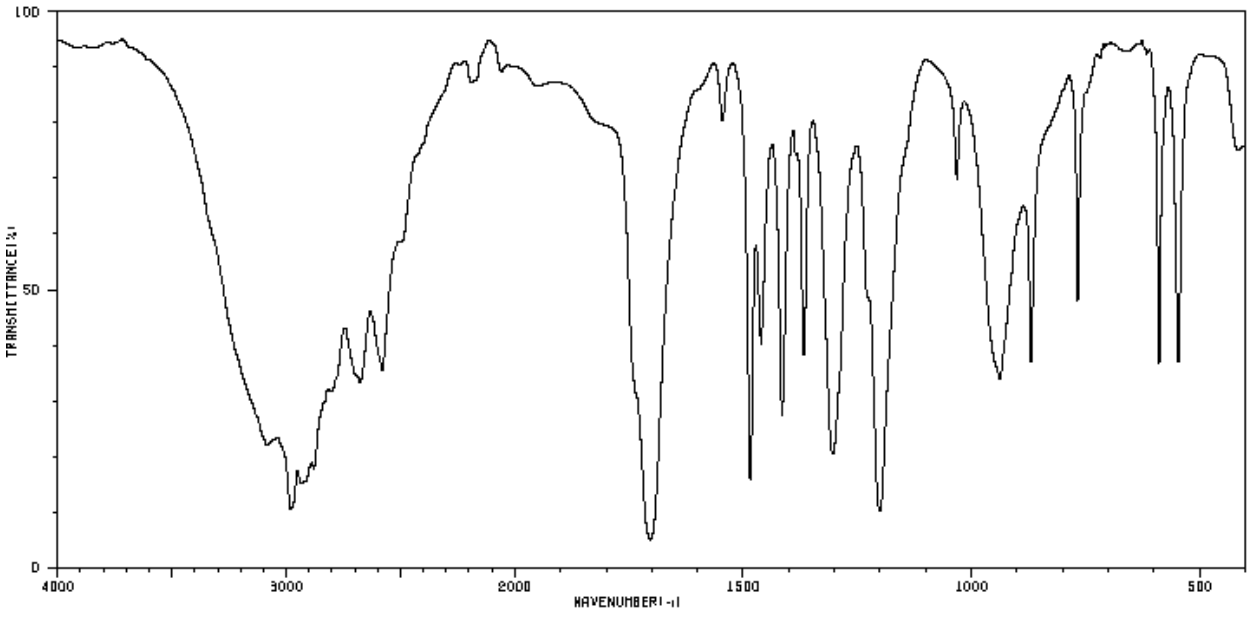
With these fragments in hand, we can complete the structure.



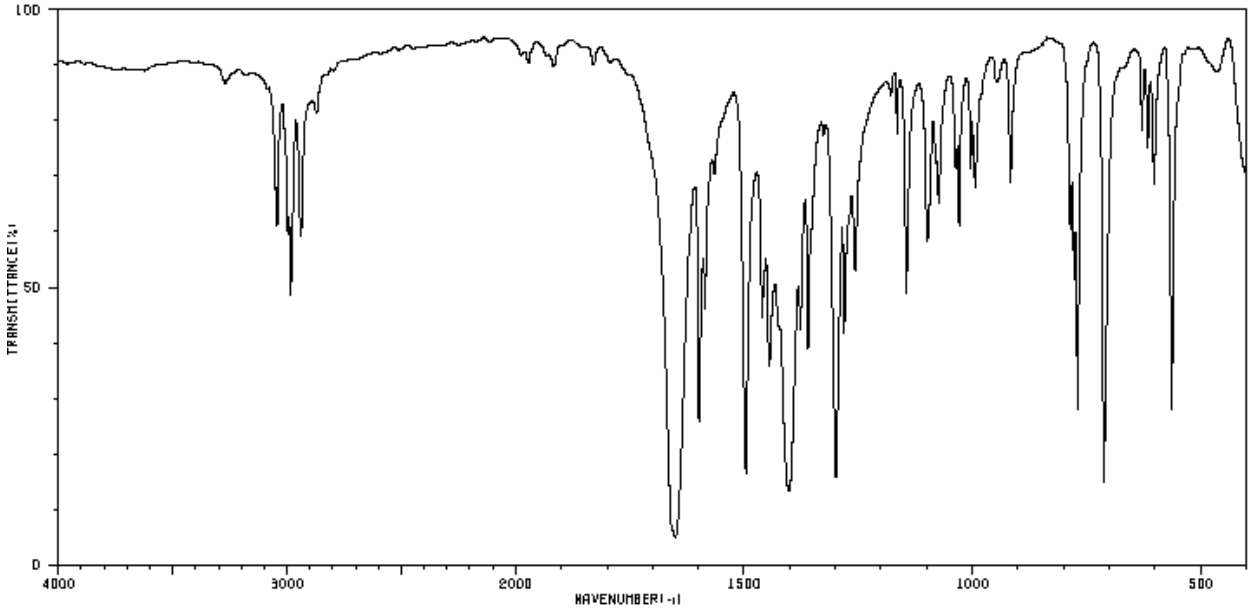
Problem 29. A compound with the molecular formula C_5H_6O has the following proton NMR spectrum. It also displays signals in the IR at 3080, 2920, 1710, and 1650 cm^{-1}. What is the structure of this compound?

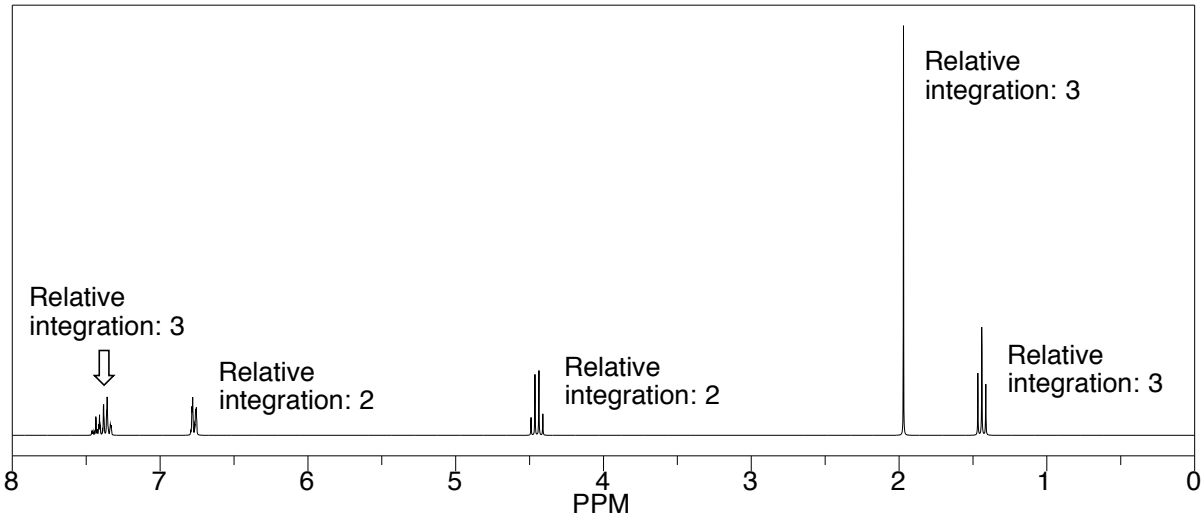


Problem 30. A compound with the molecular formula $C_5H_{10}O_2$ has the following IR spectrum. This molecule has only two signals in its proton NMR. What is its structure?



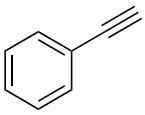
Problem 31. A compound with the molecular formula $C_{10}H_{13}NO$ has the following IR and ^1H NMR spectra. What is its structure?

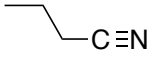


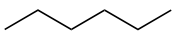


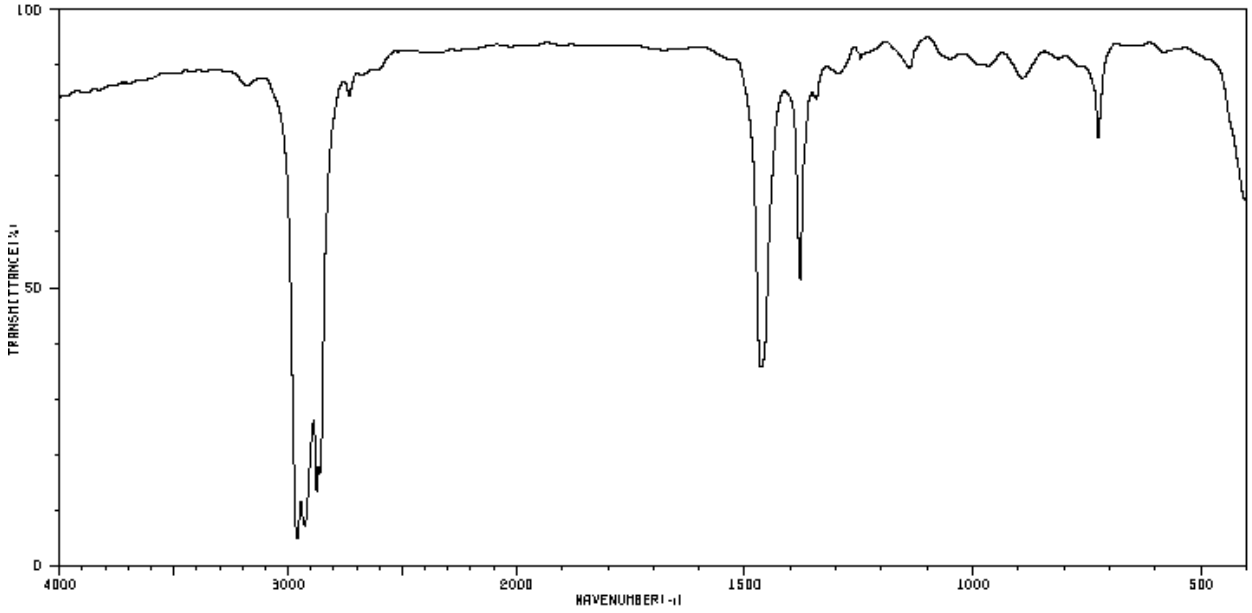
End-of-the-Chapter problems

Problem 32. Match the following three compounds with their IR spectra.





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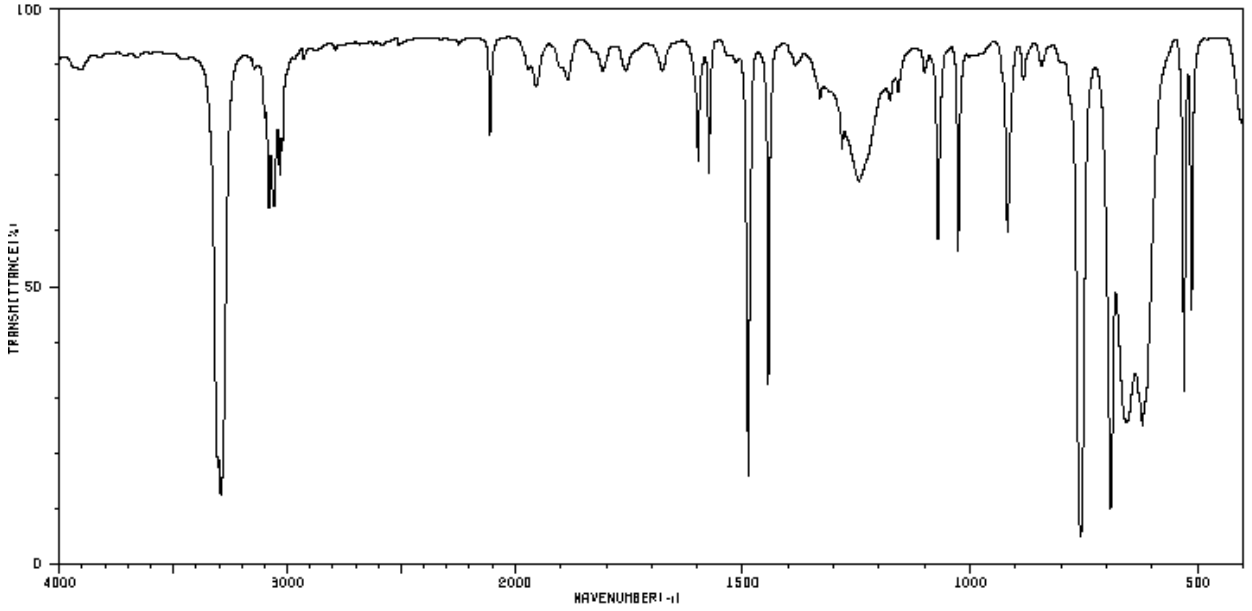
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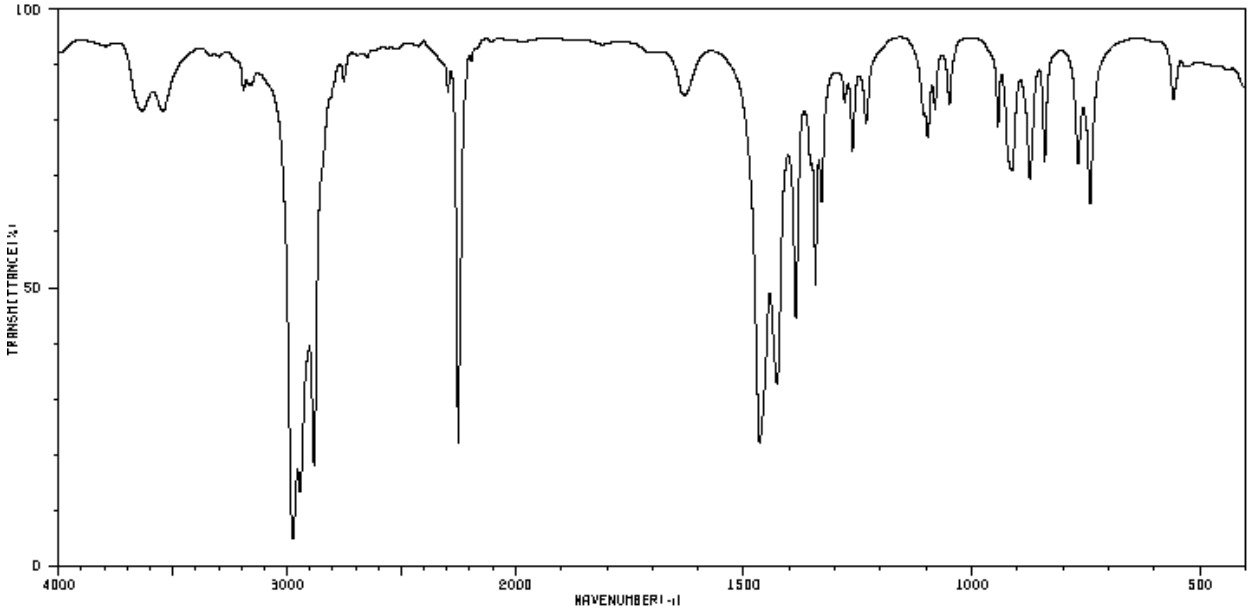
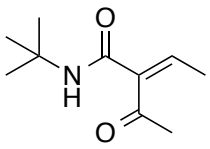
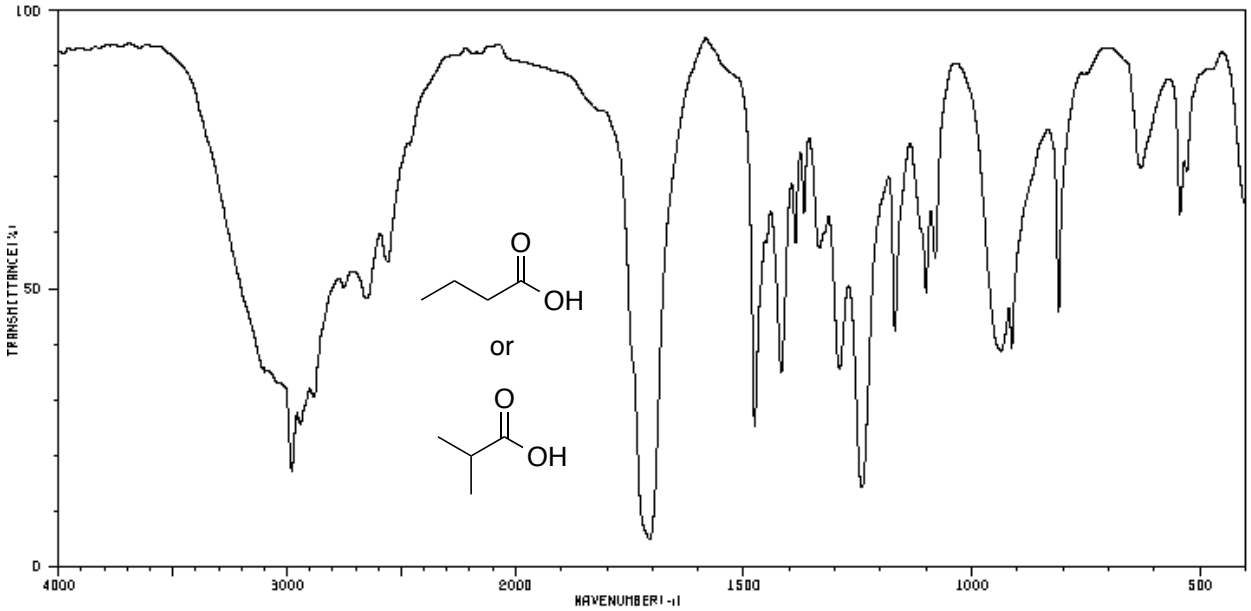
WAVENUMBER[-1]



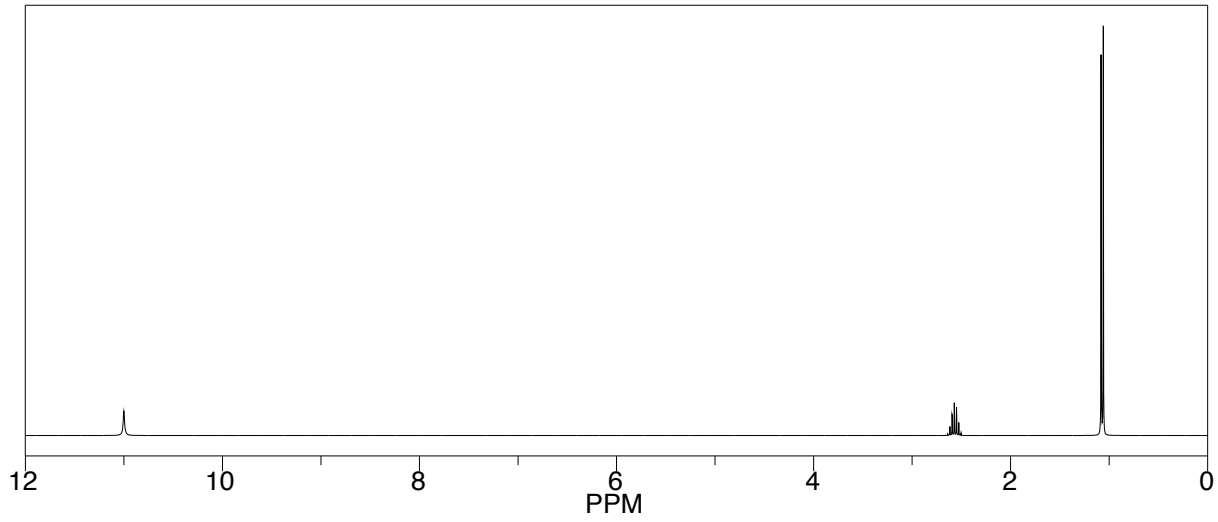
Problem 33. Draw the expected functional group region of the IR spectrum for the following compound.



Problem 34. In Problem 13, you used the molecular formula $C_4H_8O_2$ and the following IR spectrum to identify the unknown as one of two carboxylic acids.

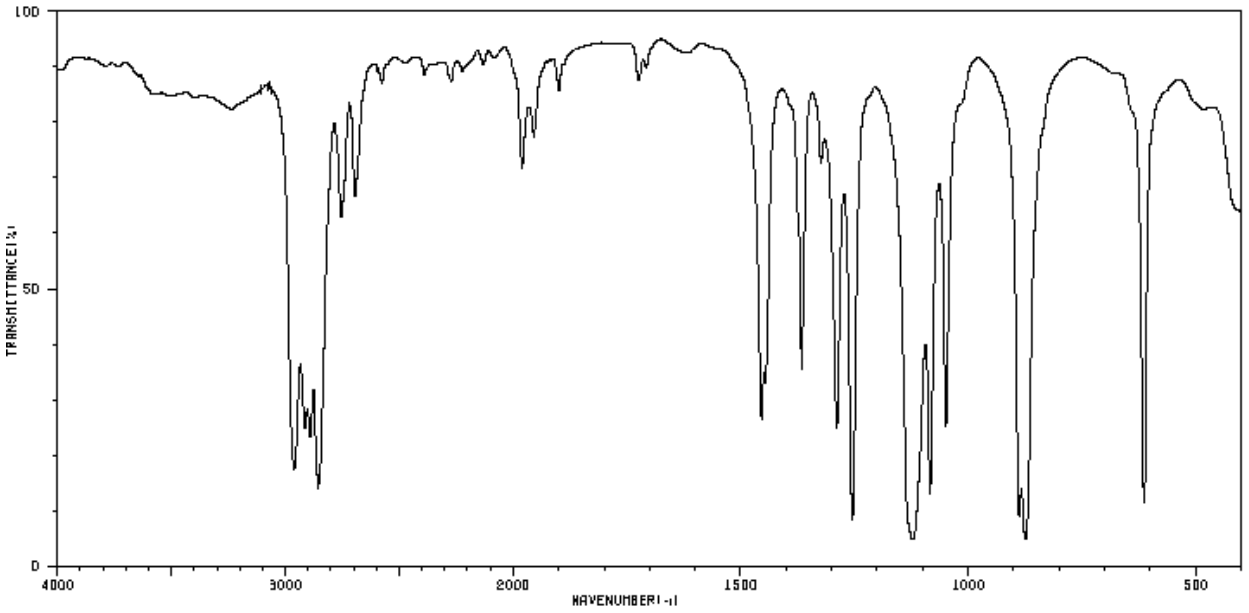


Now, using the ^{1}H NMR spectrum below, which of the structures is correct? Label the protons in the correct structure with letters, and assign those letters to the corresponding signals in the NMR spectrum.

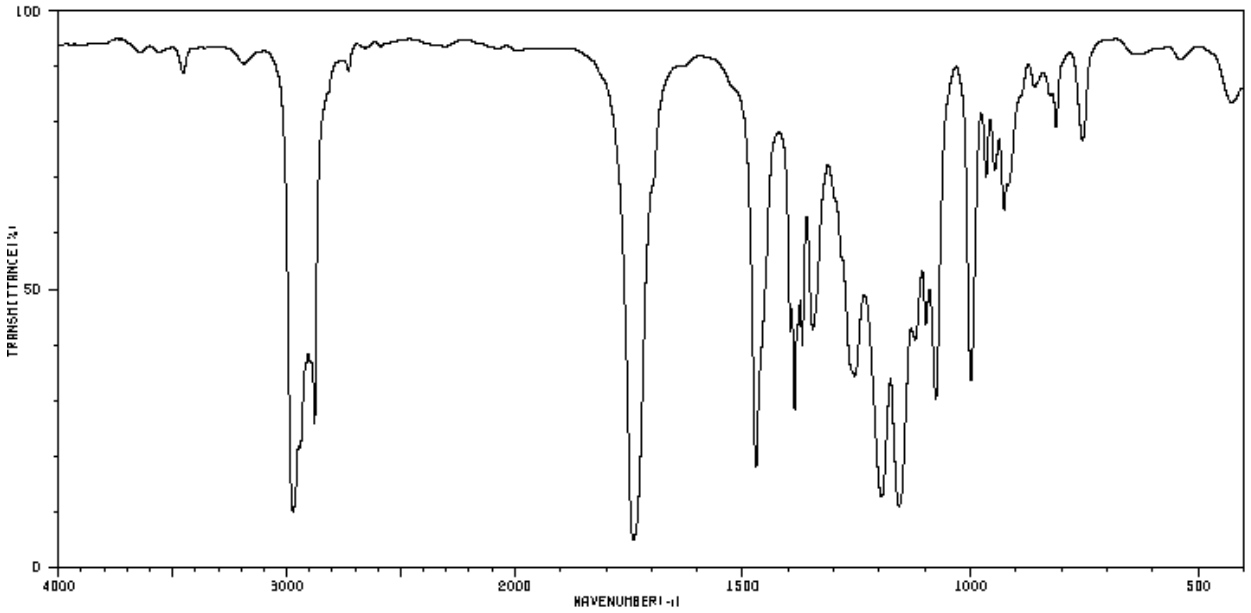


Problem 35. Cyclohexanol is a simple molecule with a surprisingly messy proton NMR spectrum. How many types of protons exist in cyclohexanol? Hint: Consider the methylene protons carefully.

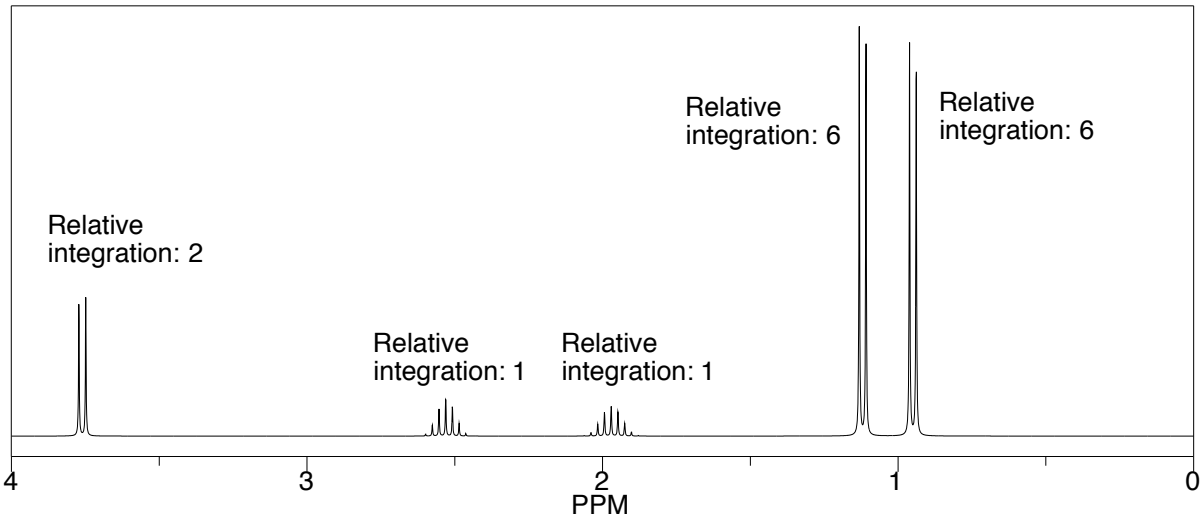
Problem 36. Which isomer of $C_4H_8O_2$ has the following IR spectrum, as well as a ^{1}H NMR spectrum with only one signal: a singlet appearing at ~3.7 ppm?



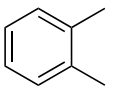
Problem 37. A molecule with the formula $C_8H_{16}O_2$ has the following IR spectrum. Provide three structures that are consistent with this information.



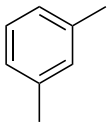
Problem 38. Given the following ^{1}H NMR spectrum, identify the exact structure of the unknown presented in Problem 37.



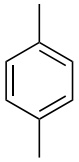
Problem 39. The three molecules shown below are known as *ortho*, *meta*, and *para*-xylene. Explain how they could be differentiated based on their proton NMR spectra.



ortho-xylene



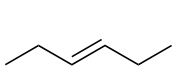
meta-xylene



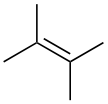
para-xylene

Problem 40. It turns out that, in order for a bond's stretching to resonate in the IR, there must be a net change in dipole moment. Dipole moment is merely the product of the charge at the ends of the dipole and the distance between these charges. A consequence of this criterion is that completely non-polar bonds do not yield IR signals.

Knowing this, which of the three IR spectra shown below belongs to *cis*-3-hexene? Hint: focus on the C=C stretch.

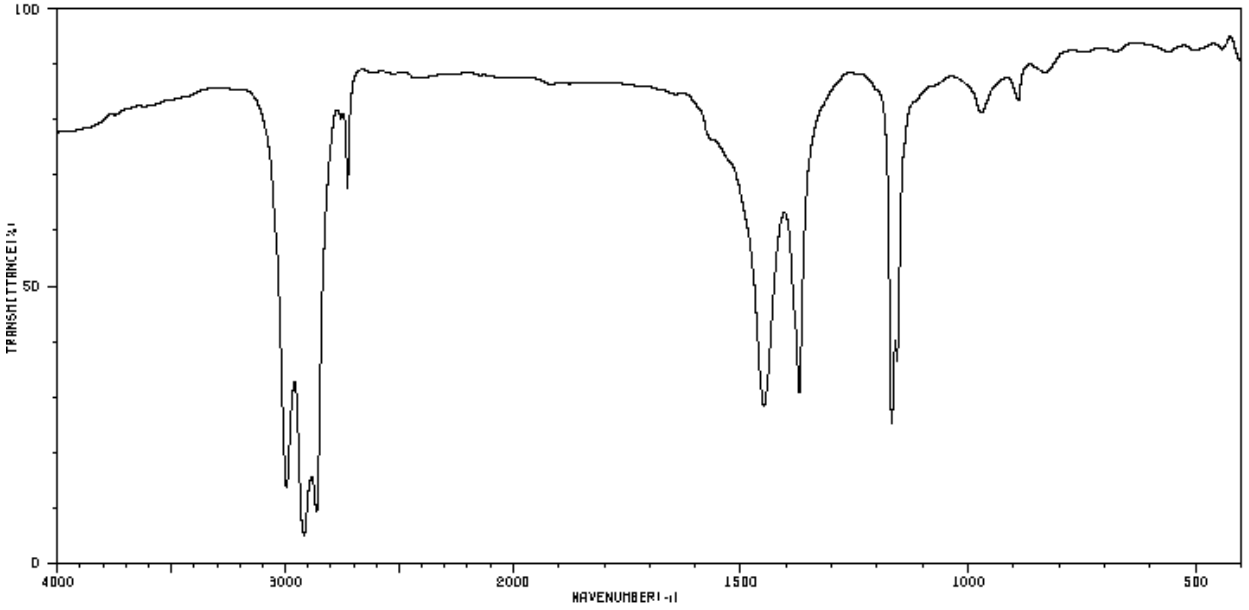


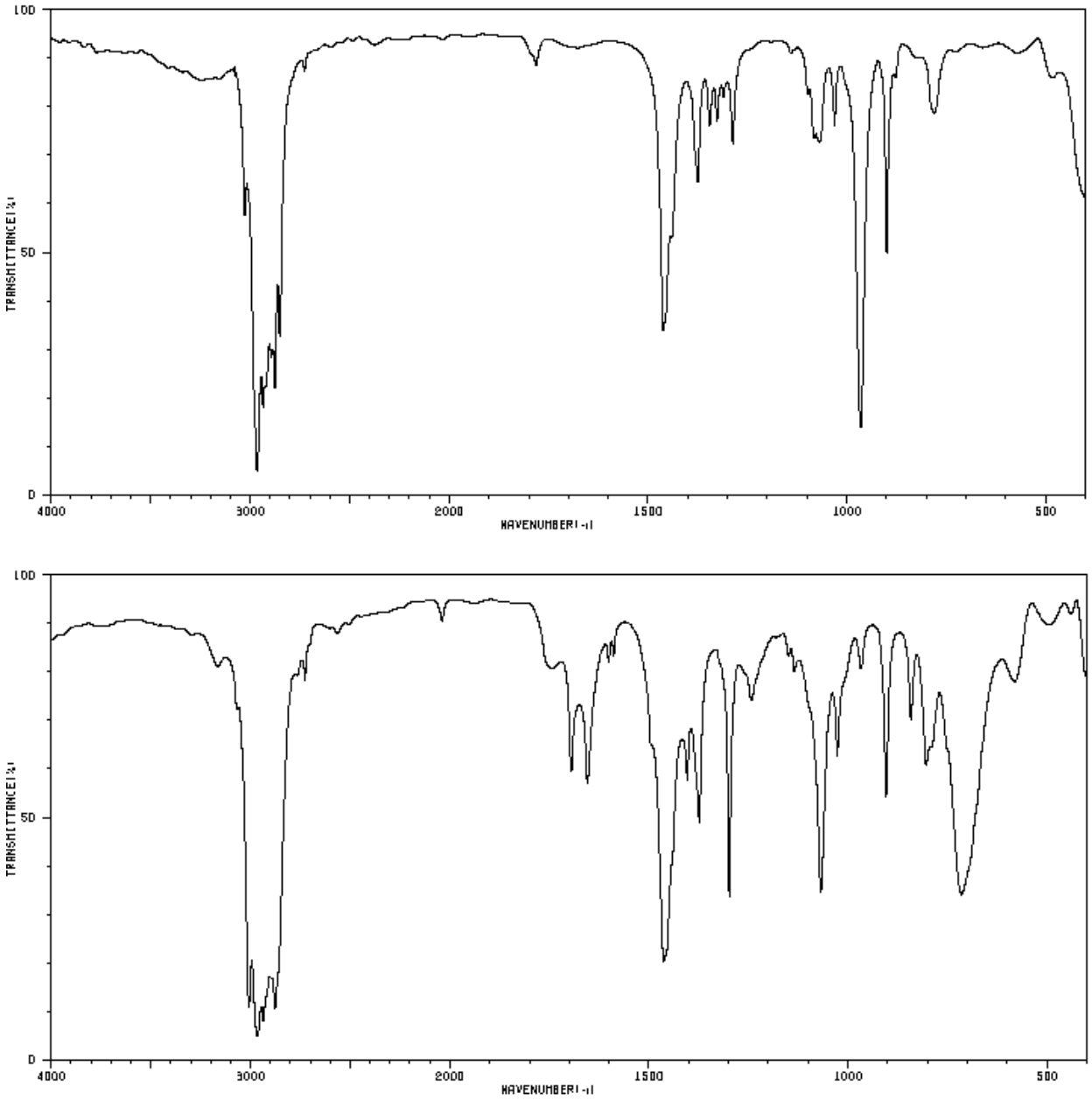
trans-3-hexene



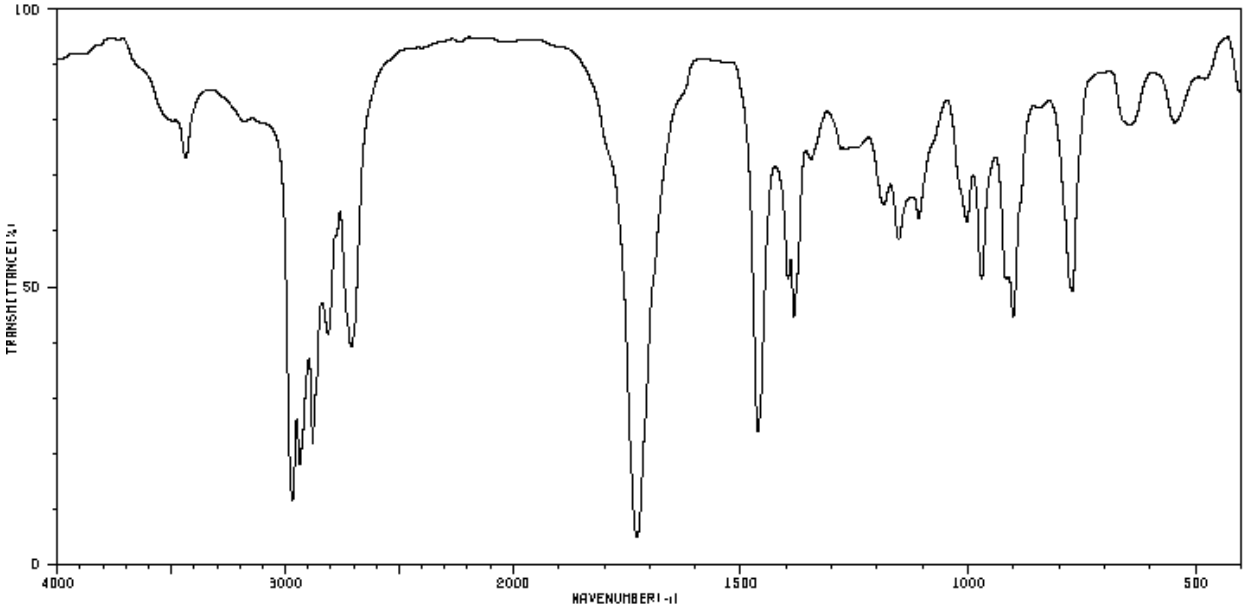
2,3-dimethyl-2-butene

cis-3-hexene





Problem 41. An unknown molecule has the following IR, ^{1}H NMR, and ^{13}C NMR spectra. Identify this substance.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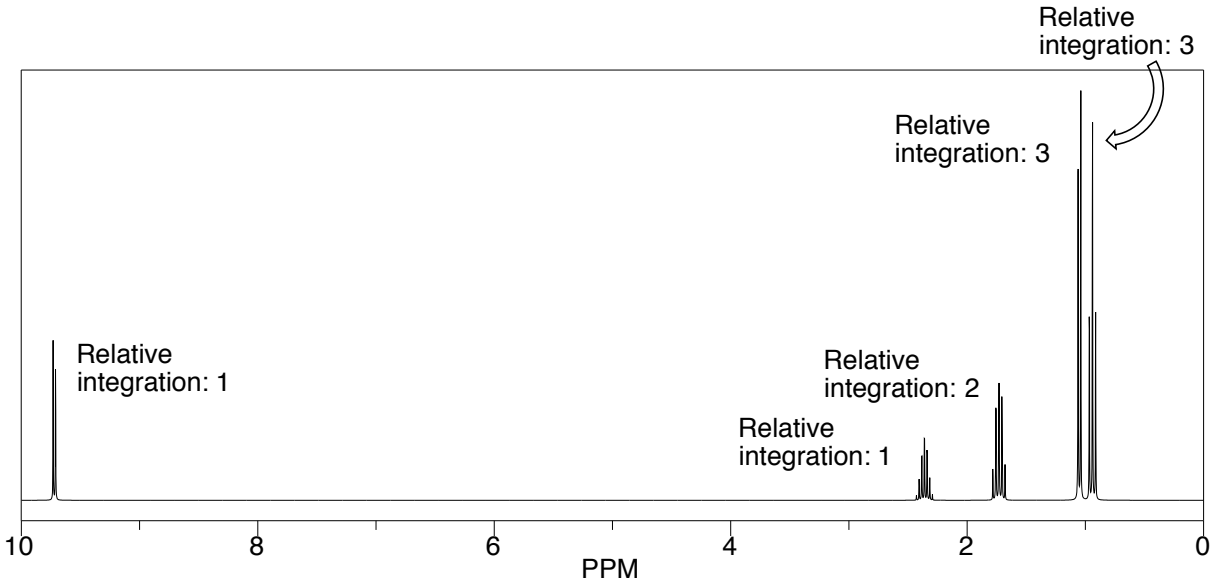
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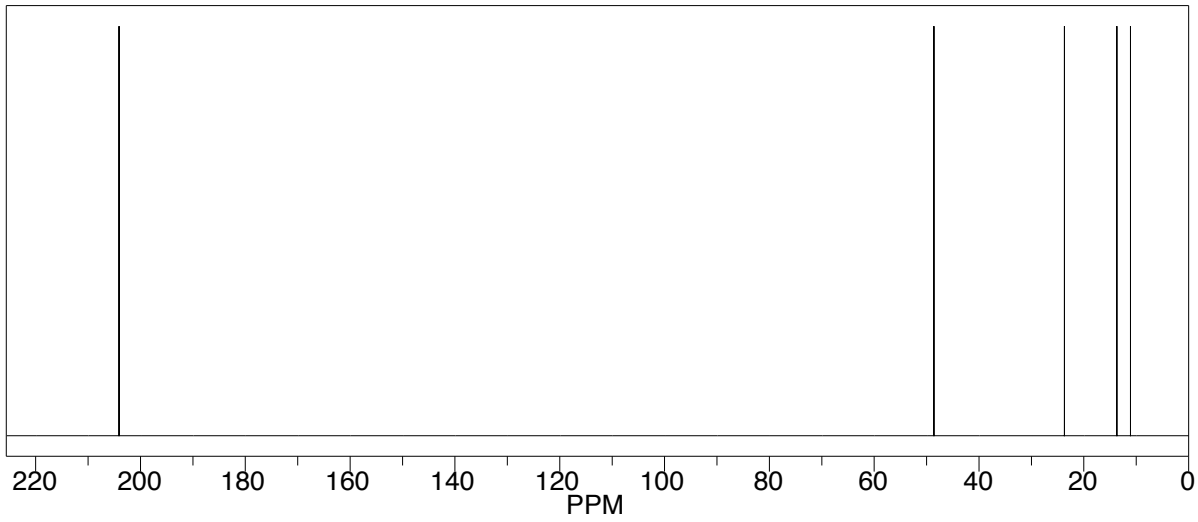
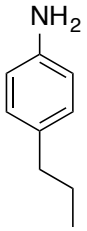
PPM

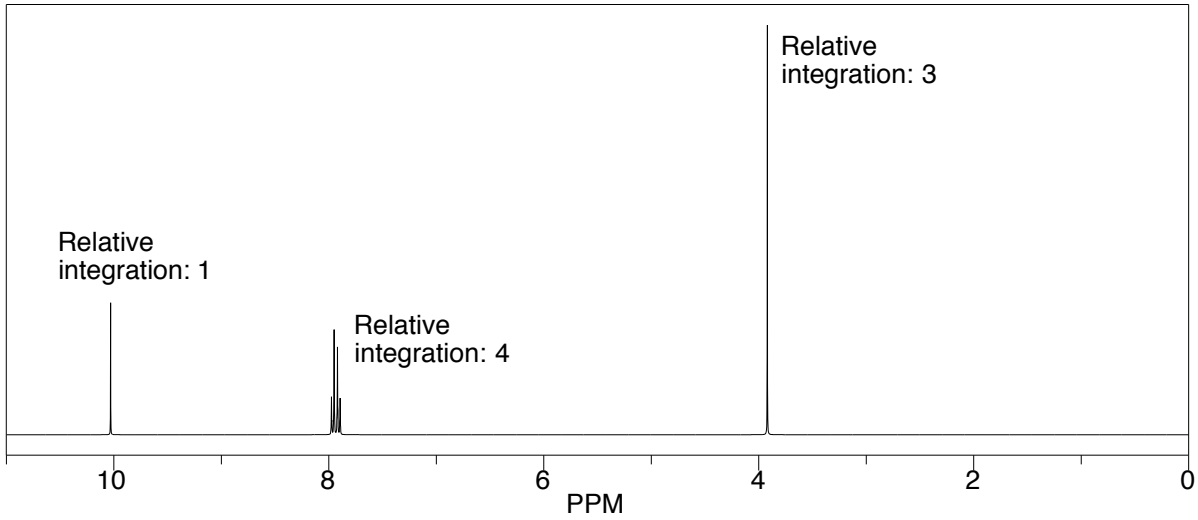


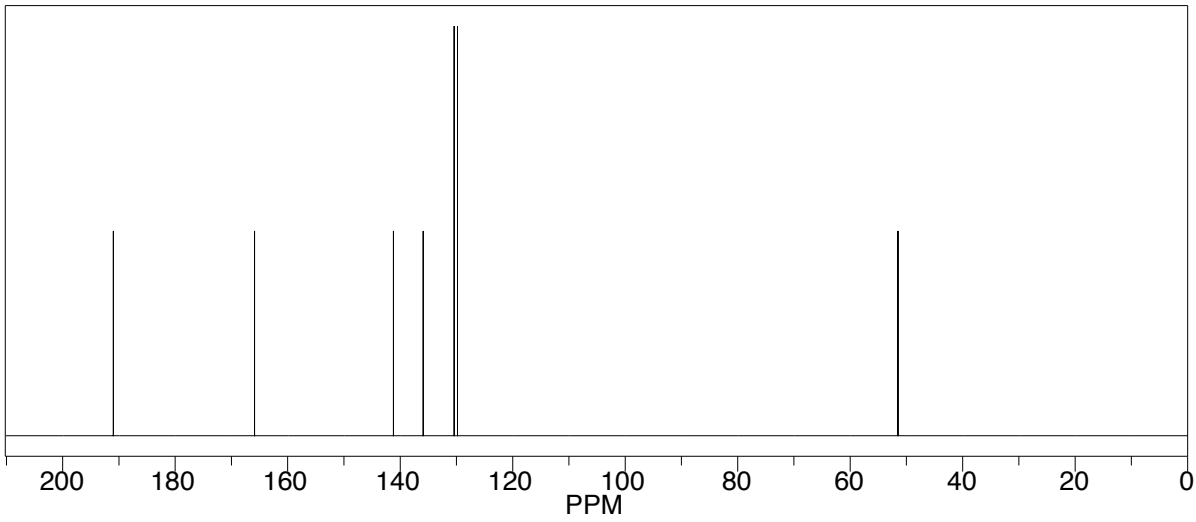
Problem 42. Draw the expected ^{1}H NMR spectrum of the following molecule.



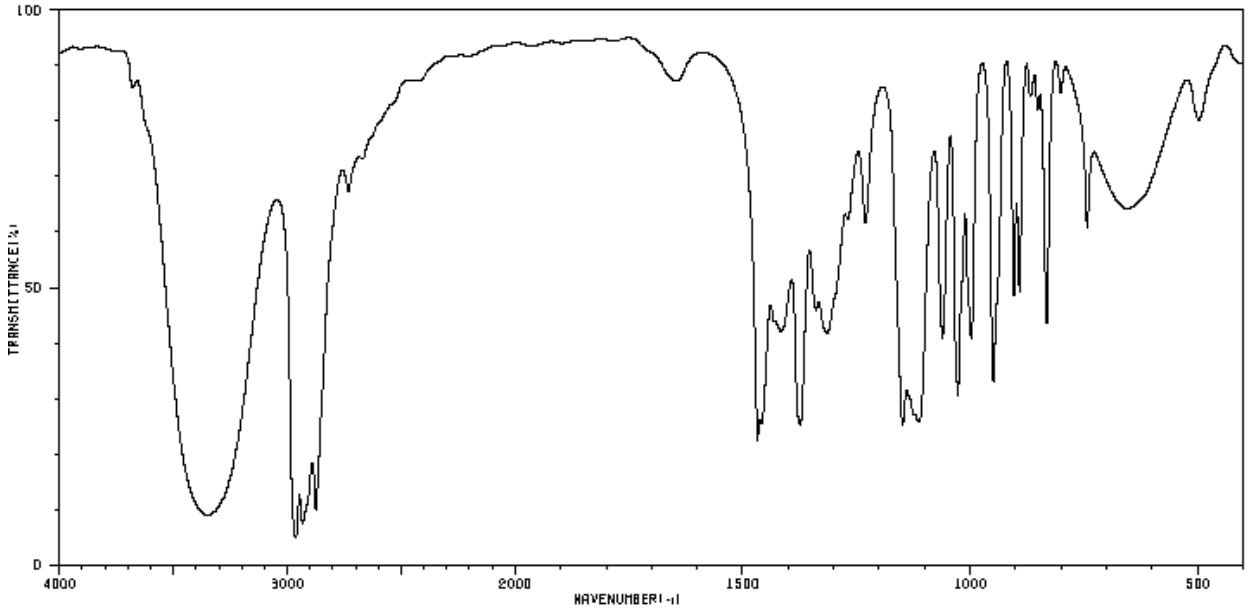
Problem 43. Draw the expected ^{13}C NMR spectrum for the compound shown in Problem 42.

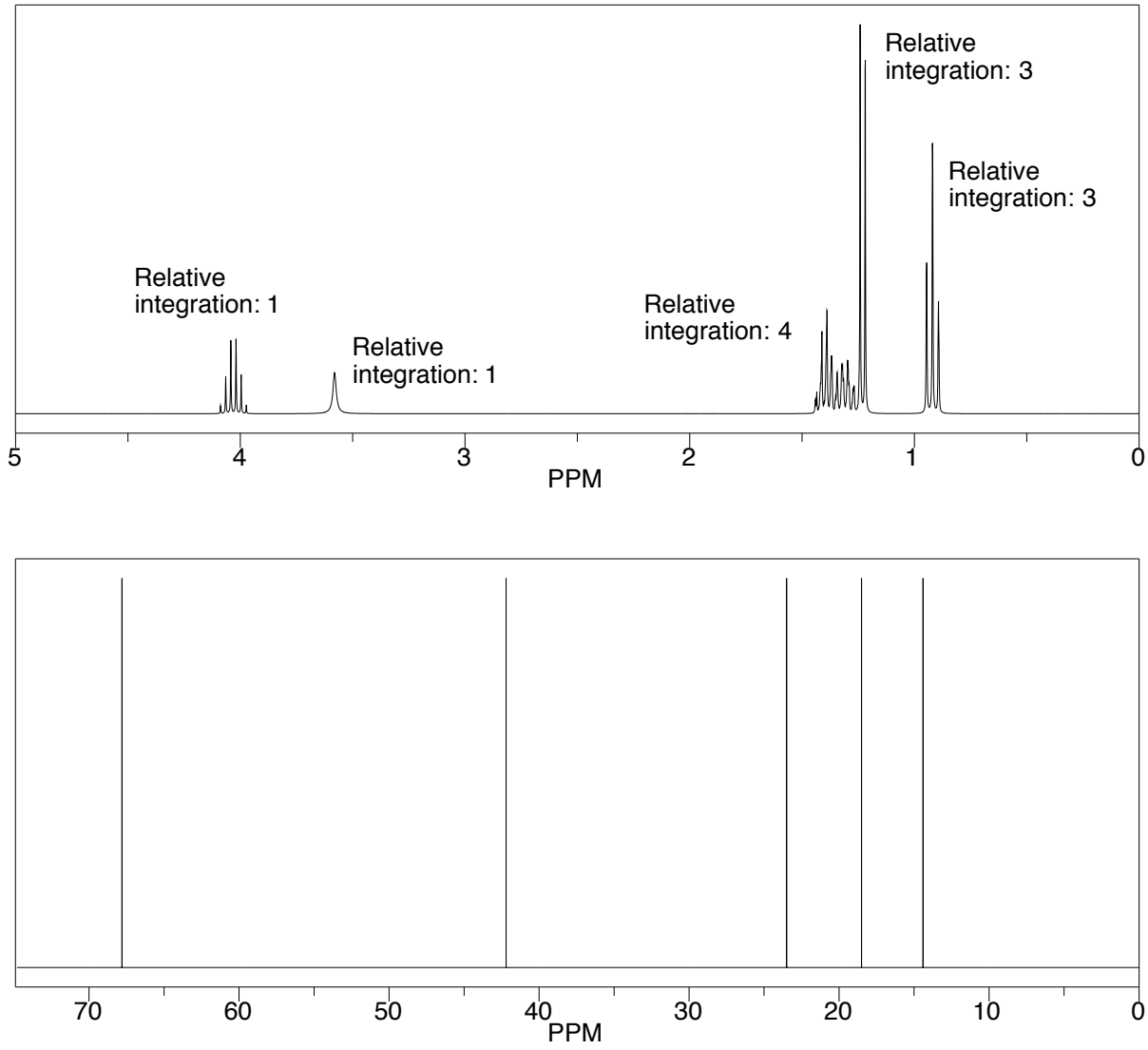
Problem 44. A compound with the molecular formula $C_9H_8O_3$ gives the following proton and carbon-13 NMR spectra. What is its structure?



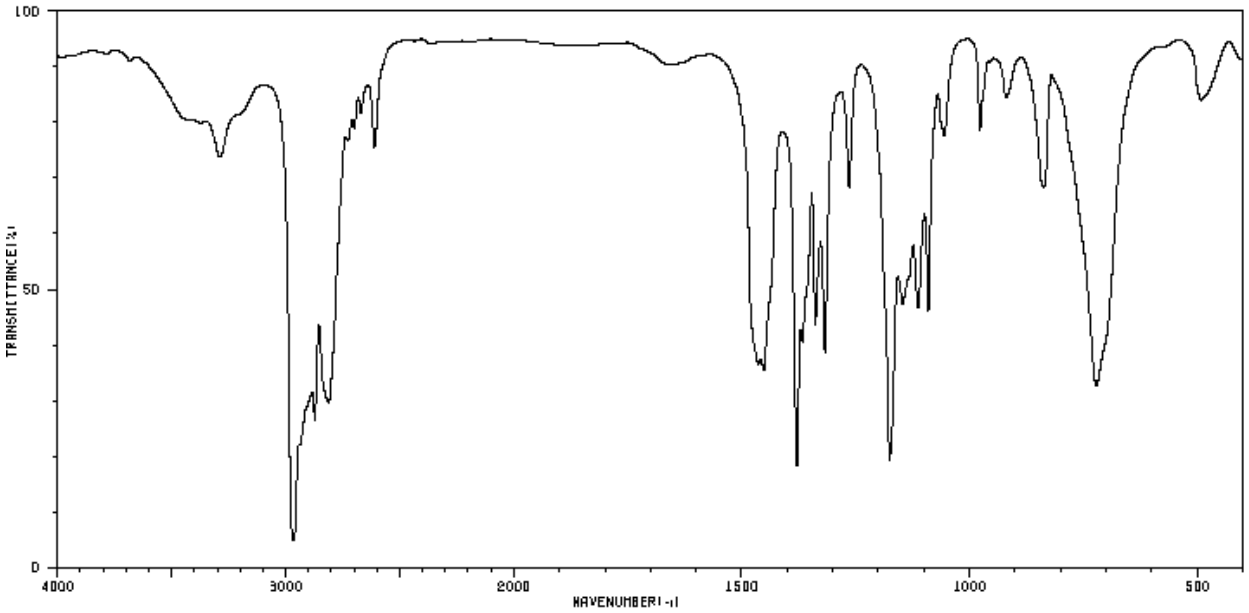


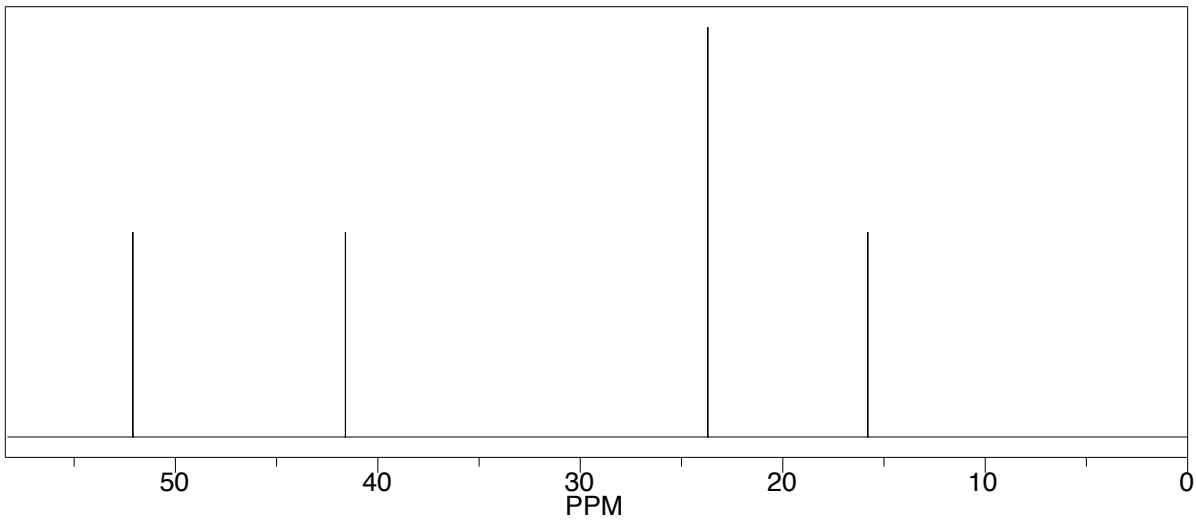
Problem 45. An unknown substance with a molecular weight of 88 g/mole has the following IR, ^{1}H NMR, and ^{13}C NMR spectra. What is its structure?



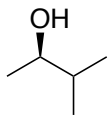


Problem 46. An amine with a molecular weight of 87 g/mole gives the following IR and ^{13}C NMR spectra. Additionally, its proton NMR spectrum contains five signals: a singlet, a doublet, a triplet, a quartet, and a multiplet. What is this compound's structure?

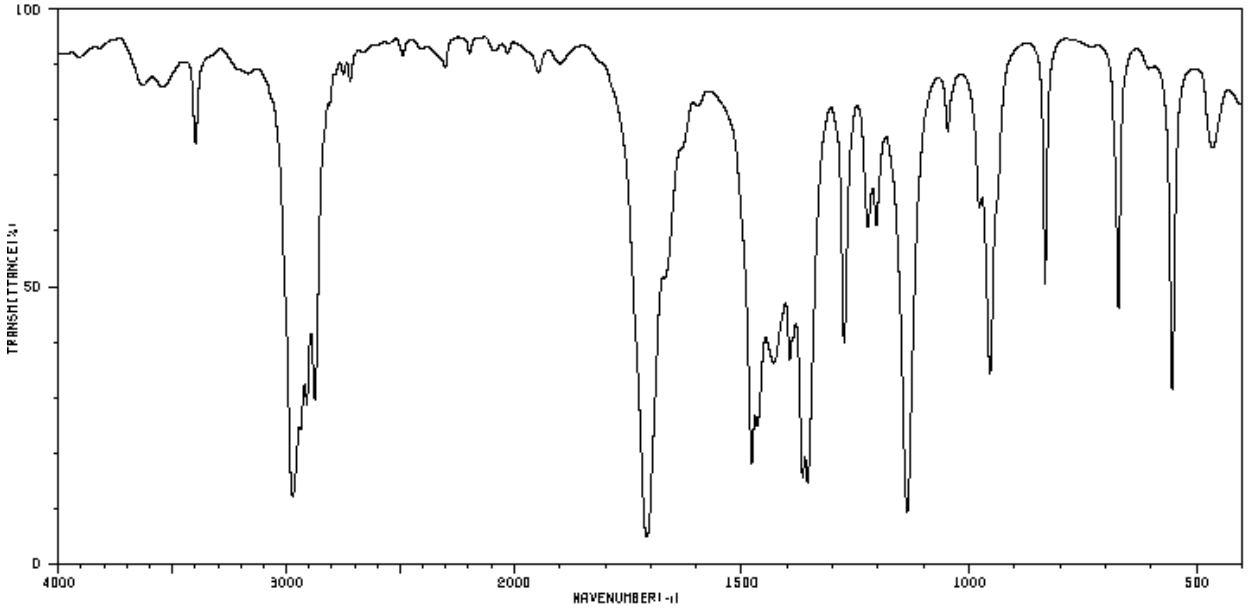




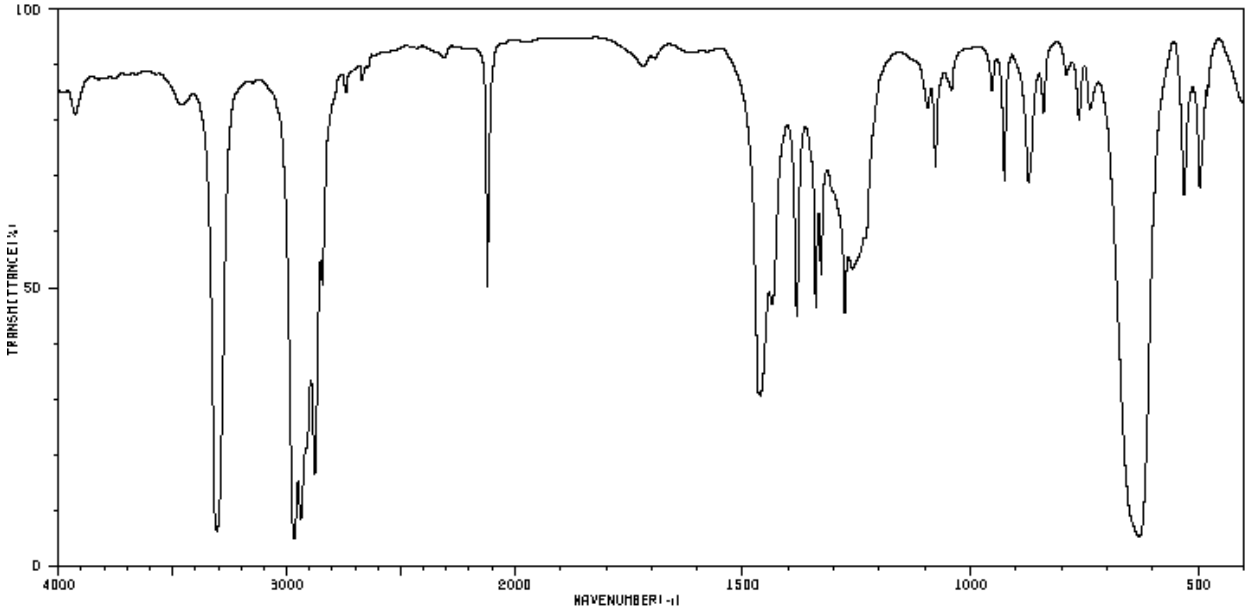
Problem 47. Why does the carbon-13 spectrum of the following molecule contain five signals rather than just four?

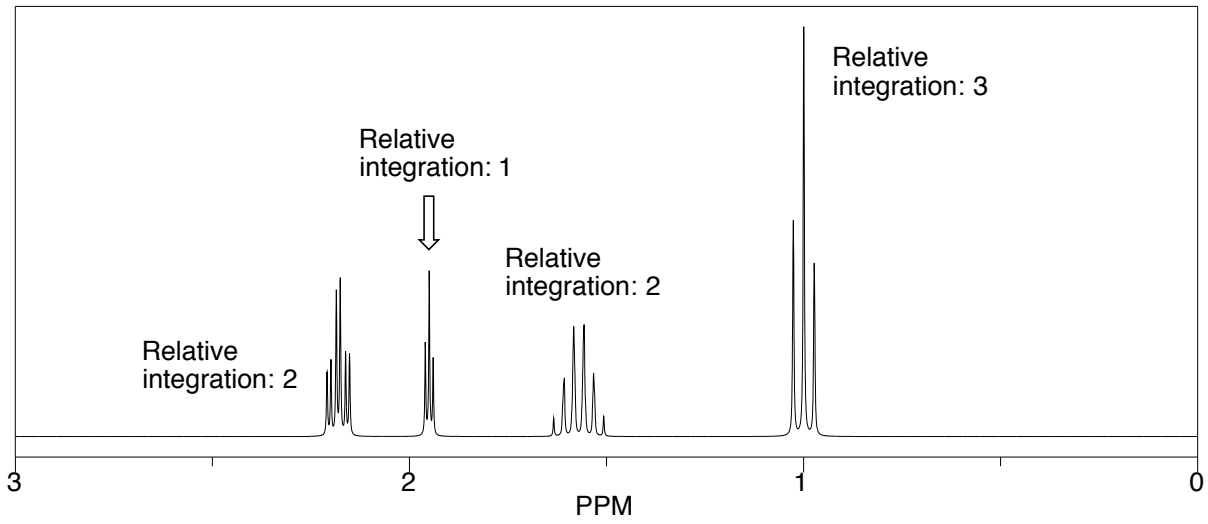


Problem 48. A compound with the molecular formula $C_6H_{12}O$ has the following IR spectrum. It also has a proton NMR spectrum with two signals and a carbon-13 NMR spectrum with four signals. What is its structure?

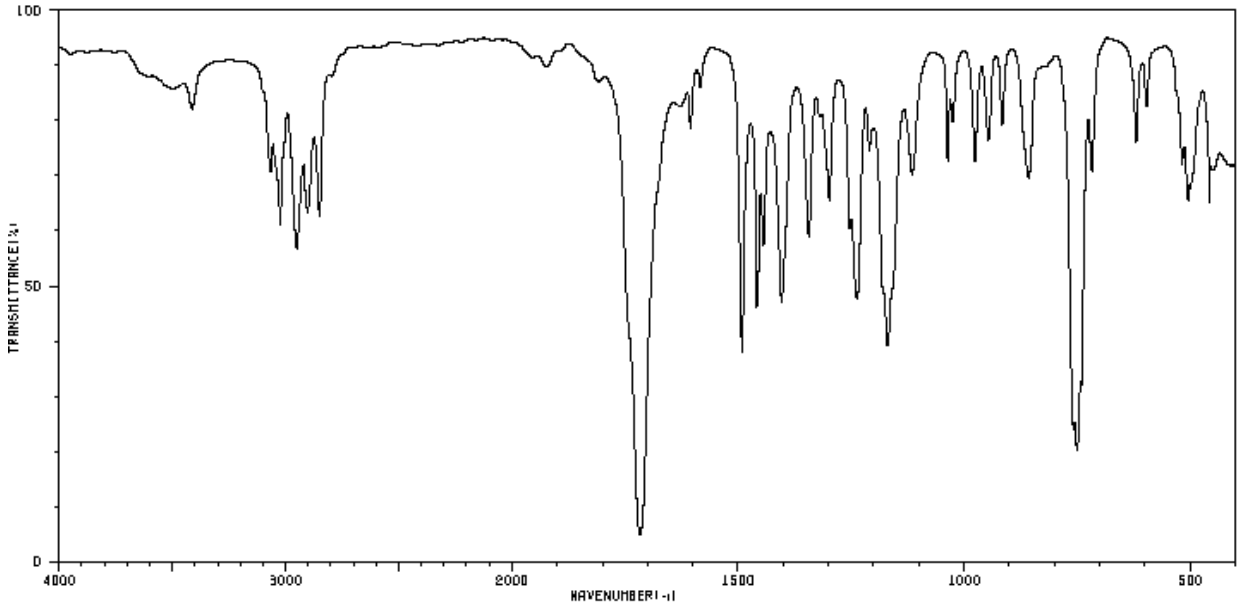


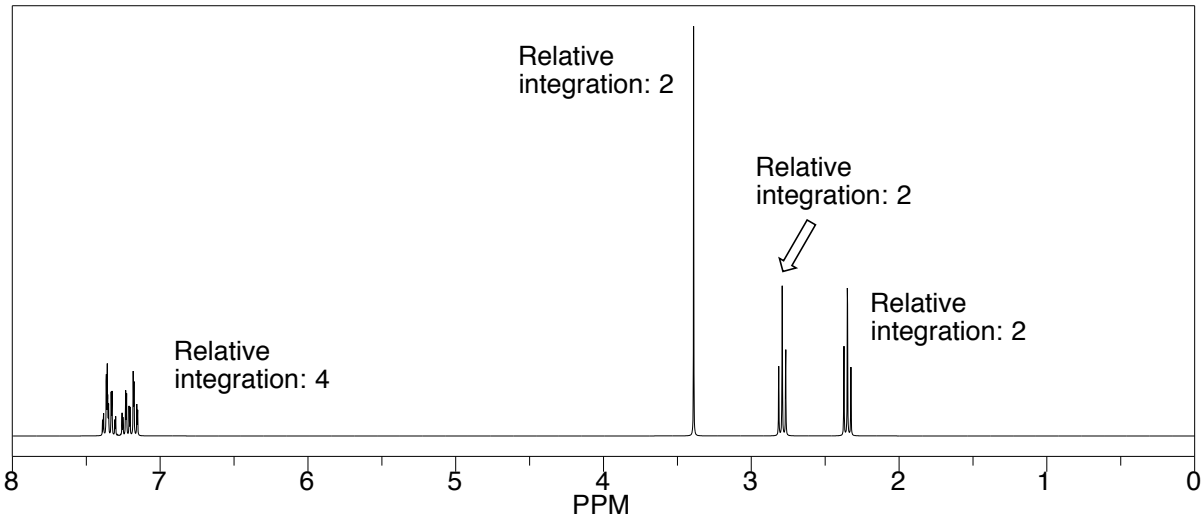
Problem 49. A molecule with the formula C_5H_8 has the following IR and proton NMR spectra. What is its structure?

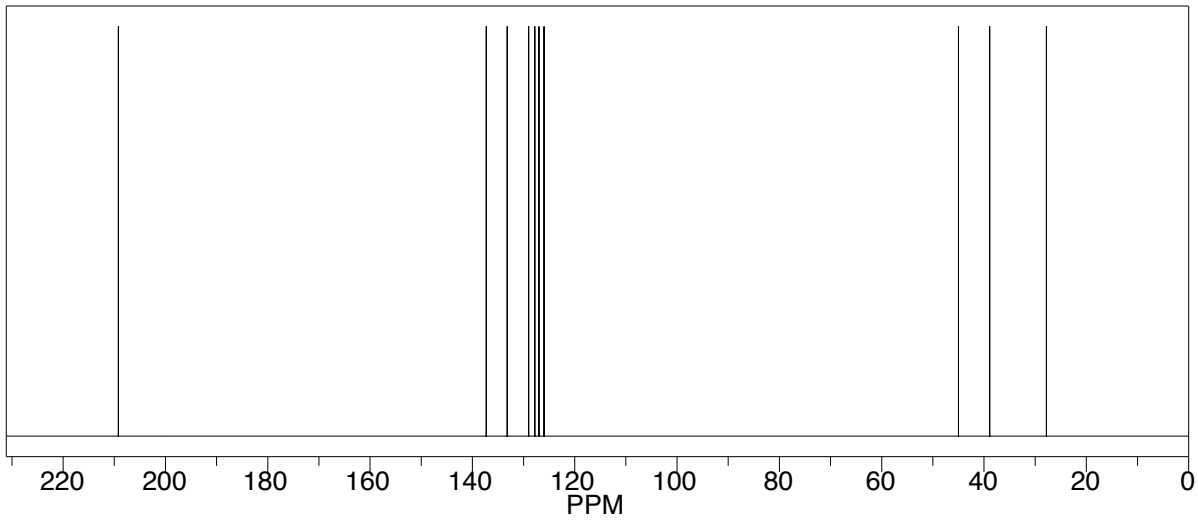




Problem 50. An unknown substance with a molecular weight of 146 g/mole produces the following spectra. What is its identity?




Relative integration: 2
Relative integration: 2
Relative integration: 2
Relative integration: 4
8
7
6
5
4
3
2
1
0
PPM


220
200
180
160
140
120
100
80
60
40
20
0
PPM

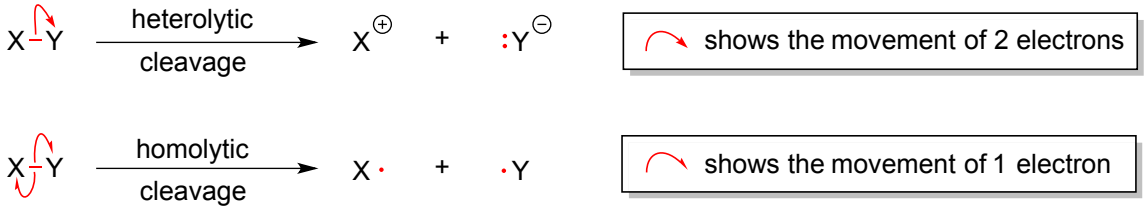
Chapter 6: Radical Reactions

Section 1: Radicals – formation, stability, and behavior
Section 2: Radical substitution reactions
Section 3: Reactivity and selectivity
Section 4: Radical substitution reactions at allylic or benzylic centers
Section 5: Radical addition to π bonds
Section 6: Radicals and polymerization
Section 7: Oxidation of fats and oils, vitamin E, and preservatives
Section 8: CFCs and ozone-layer depletion
Section 9: Moses Gomberg and the discovery of free radicals

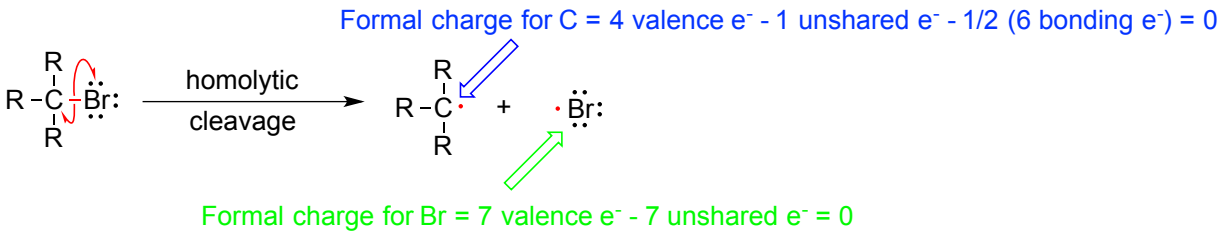
Section 1: Radicals – formation, stability, and behavior

Formation of radicals

Radicals (also known as free radicals) are formed when bonds undergo homolytic cleavage. The acid-base reactions in Chapter 2 involved heterolytic (or uneven) bond cleavage, in which both electrons of a given bond flow to one atom as the bond breaks. Such processes are represented using curved arrows, which signify the flow of two electrons. In homolytic (or even) bond cleavage, each atom acquires one of the bonding electrons as the bond breaks. Single-headed (or "fishhook") arrows are used to show the flow of a single electron.

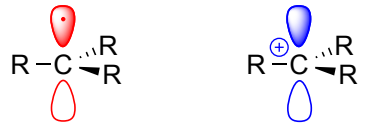


The energy required to break a bond homolytically is termed the bond dissociation energy, and this even bond cleavage results in species with unpaired electrons, which are known as radicals or free radicals. Often, radicals do not possess formal charges; nevertheless, they are electron-deficient because they lack a complete octet. This makes them reactive intermediates.



The electron deficiency can also be illustrated by considering the similarity in bonding patterns between a free radical and a carbocation. Both are sp^2 hybridized centers and

therefore have trigonal planar geometry. While the carbocation has a completely empty unhybridized p orbital, the free radical has a singly occupied p orbital. The carbocation has a sextet of electrons around it, and the free radical is surrounded by a septet of electrons.



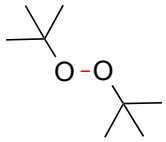
free radical carbocation

Incidentally, this trigonal planar geometry means that the stereochemical ramifications of reactions involving radicals or carbocations are identical. In short, there is no reason to expect a preference for reaction on one face of the molecule as opposed to the other, so if a radical reacts to form a stereocenter, both configurations are expected. The same is true for a carbocation.

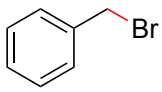
Problem 1. Show a mechanism for the homolytic cleavage of the indicated bonds in the following structures.

(a)

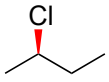
(b)



(c) For this part, show all resonance structures of the resulting radical.

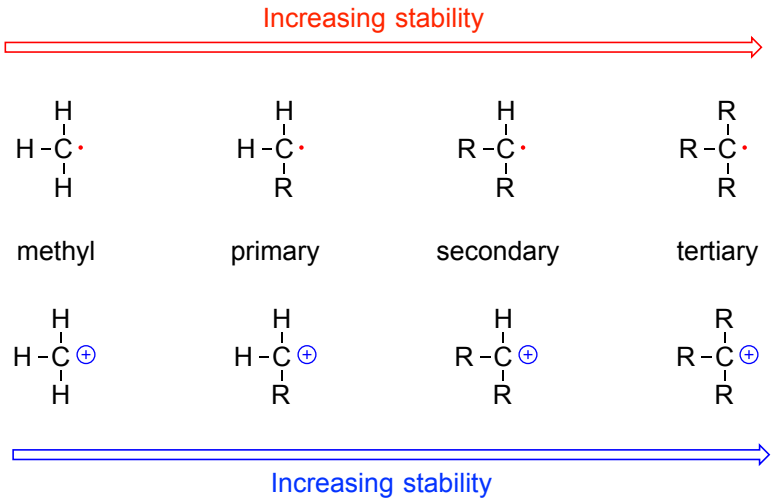


(d) For this part, comment on the stereochemistry of the radical formed.

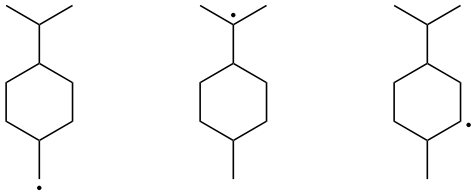


Stability of radicals

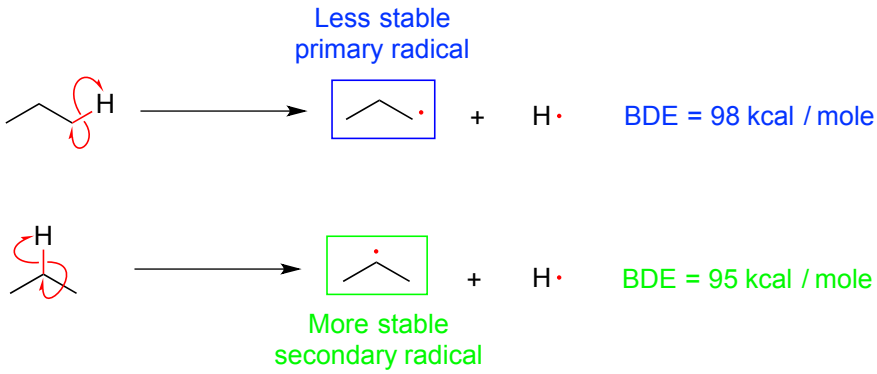
Radicals and carbocations, both of which are electron deficient, have parallel stability trends. The more highly substituted an electron-deficient species is, the more stable it is. Additionally, resonance can greatly stabilize these reactive intermediates.



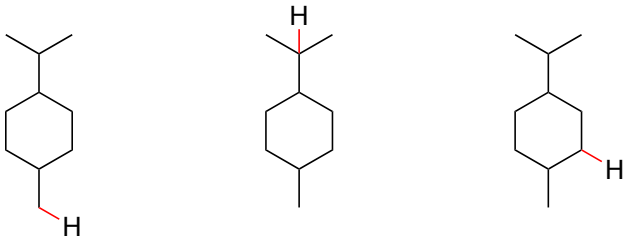
Problem 2. Which of the following isomeric radicals is the most stable?



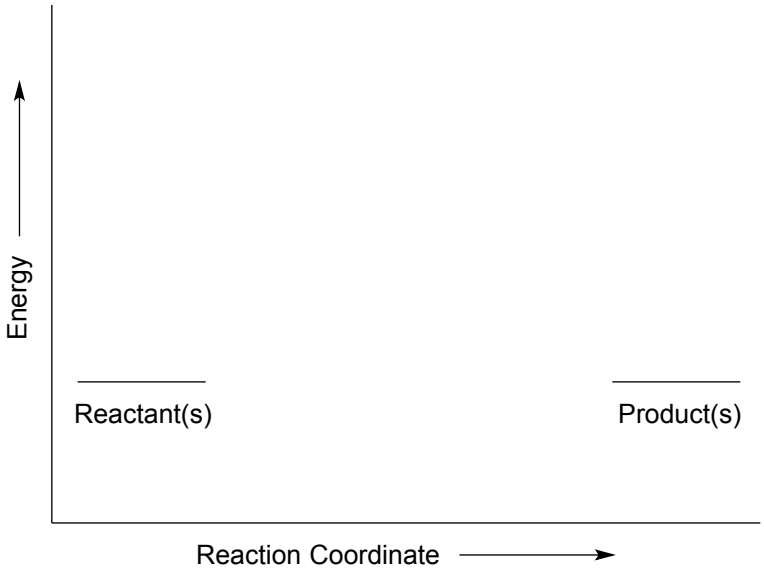
These differences in stability are reflected in bond dissociation energies (BDE). Recall that the BDE is the amount of energy needed to homolytically cleave a bond. It takes less energy to cleave a bond if the resultant radicals are more stable. To illustrate this point, let's consider propane. There are two types of C-H bonds in propane: primary and secondary. The secondary carbon-to-hydrogen bond has a lower BDE. It is easier to break this bond since its cleavage produces the more stable secondary radical.



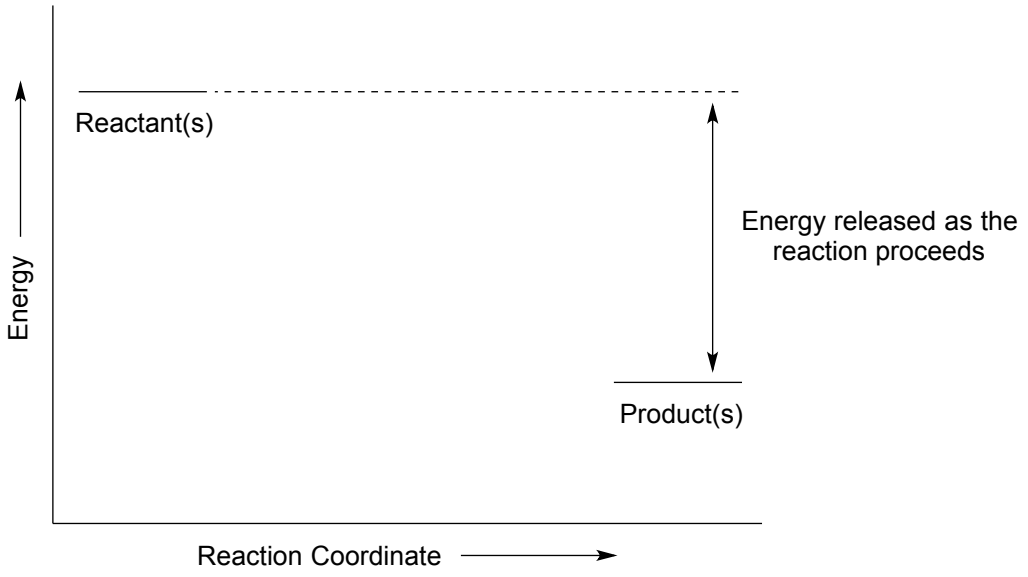
Problem 3. Which of the indicated carbon-hydrogen bonds has the largest bond dissociation energy?



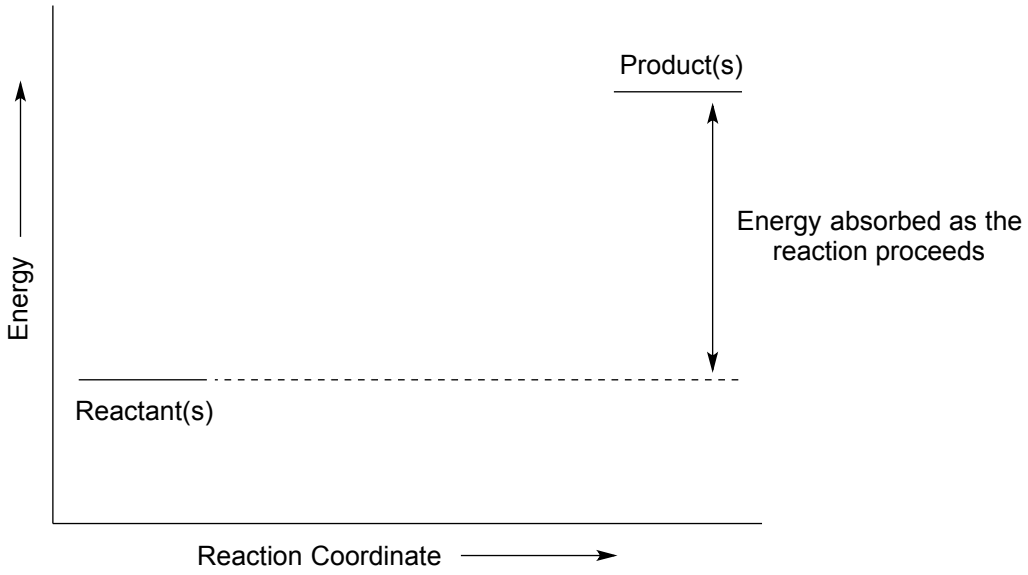
The same information can be communicated graphically as shown in the reaction energy profile below. An energy profile for a reaction is much like the energy profiles that we encountered during our study of conformational analysis in Chapter 3. In conformational analysis, the energy was shown as a function of dihedral angle because we were considering changes in the shape of a molecule. In the energy profile of a reaction, the energy is plotted as a function of reaction coordinate, which simply means the progress of the reaction. The reaction coordinate follows the progression of the reactants (on the left side of the x-axis) to the products (on the right side of the x-axis).



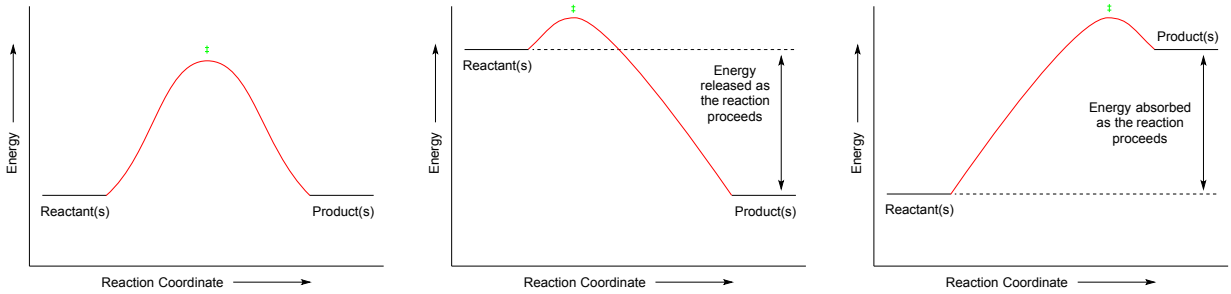
In the diagram above, the reactants and products are shown as having the same energy. That is not usually case. Typically, the reactants and products will differ in energy. When the reactants are higher in energy than the products, energy is given off during the reaction.



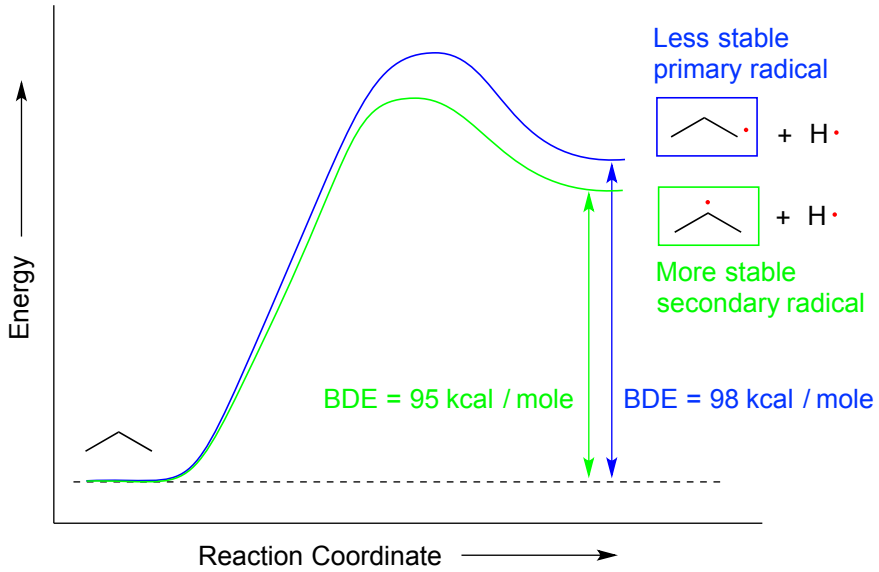
On the other hand, when the products are higher in energy than the reactants, the reaction requires an input of energy.



Each reaction (and in fact each step of a reaction) proceeds through a mechanism that describes how bonds are made and broken during the transformation. The transition state is the highest energy point on the path from reactants to products. At the transition state, any bonds being formed are partially formed and any bonds being broken are partially broken. The transition state is often represented by the double dagger symbol (‡).

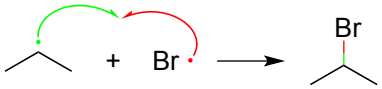


For the two homolytic cleavage events we were comparing, both reactions begin with the same reactant, propane. Breaking bonds always requires an input of energy. However, it requires more energy to form the less stable primary radical than it does to form the radical at the more highly substituted secondary center.



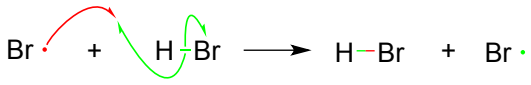
Problem 4. Match the three reactions below (a, b, and c) with the energy diagram that best describes them (i, ii, or iii).

(a)

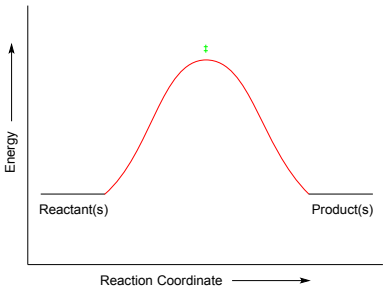


(b)

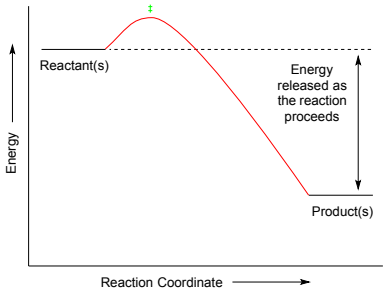
(c)



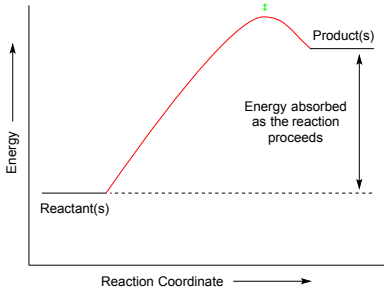
(i)



(ii)



(iii)



The components of radical reactions

There are differences in the way that heterolytic and homolytic mechanisms are drawn. In heterolytic mechanisms, the progression from reactant to intermediate(s) to product is conveyed as a series of steps, one drawn immediately after the other.

Heterolytic mechanism:

Reactant ⟶ Intermediate ⟶ Intermediate ⟶ Product

On the other hand, the steps of homolytic mechanisms are divided and drawn separately. This allows the classification of each step as initiation, propagation, or termination.

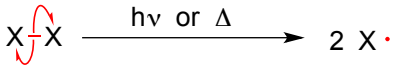
Homolytic mechanism:

Reactant ⟶ Intermediate

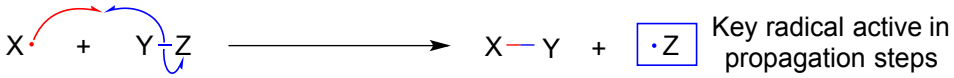
Intermediate ⟶ Intermediate

Intermediate ⟶ Product

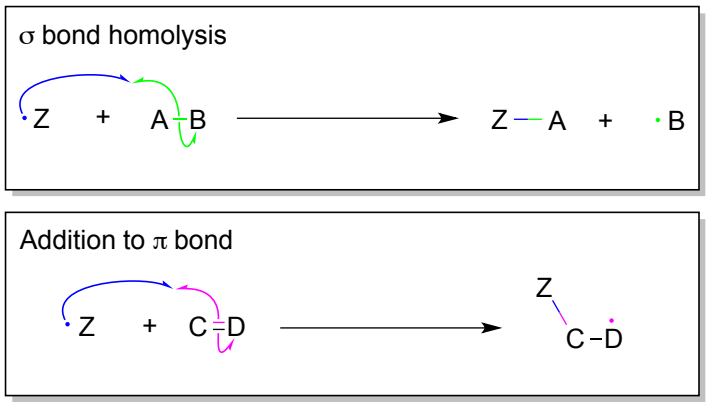
As the name implies, initiation steps start the radical process. They are often steps that begin without radicals but produce radicals. As we saw above, the spontaneous homolysis of a σ bond requires an input of energy from light (hν) or heat (Δ).



We will also see that sometimes a step that begins and ends with radicals will be termed initiation if it produces the key radical that is active in the subsequent propagation steps.



Propagation steps begin and end with radicals. In these steps, there are two primary options for the free radical. It can incite the homolysis of a σ bond, or it can add to a π bond. In either case, the radical process continues (or propagates) because a new radical results.

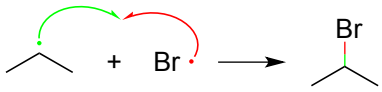


In termination steps, any two radicals combine, resulting in a compound with no unpaired electrons.

We'll see these core mechanistic steps (initiation, propagation, and termination) in the specific radical reactions discussed in subsequent sections.

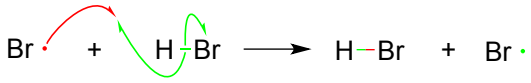
Problem 5. In Problem 4, we saw the following three processes. Now, categorize them as initiation, propagation, or termination steps.

(a)



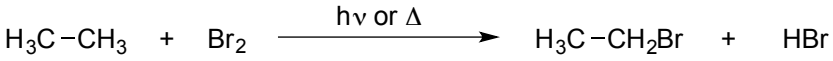
(b)

(c)

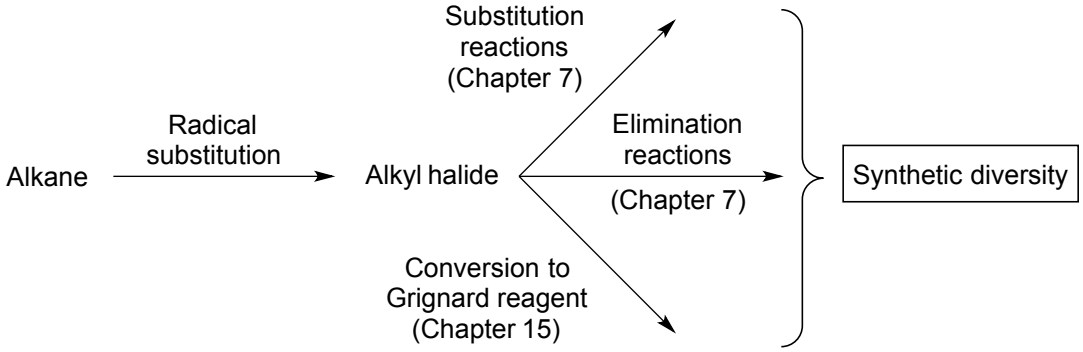


Section 2: Radical substitution reactions

Let's consider the reaction of ethane with bromine. Overall, the process yields bromoethane and HBr. The net result is that a hydrogen of the alkane has been substituted with a halogen.

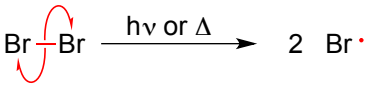


Radical substitution reactions are quite important because they enable the functionalization of alkanes, which are otherwise relatively unreactive. Once functionalized as alkyl halides, there are many transformations that can be used to produce a wide variety of compounds. A few examples are shown below.



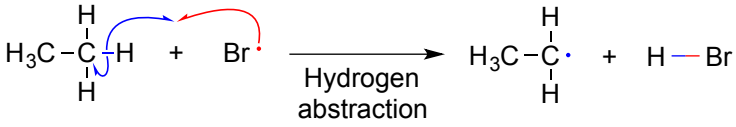
The reaction begins with the homolysis of bromine upon exposure to light or heat. It is critically important though to realize that *only a small number of bromine molecules undergo this homolysis*. Most remain unreacted and will be encountered again in the second propagation step.

Initiation:



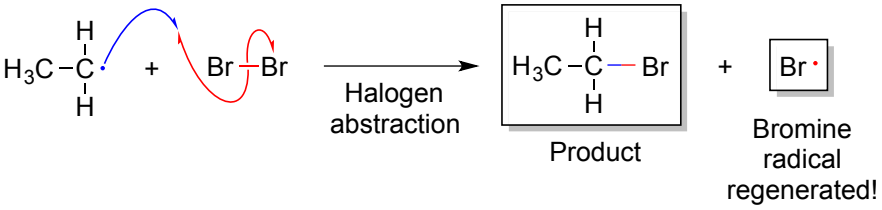
The propagation then begins as the electron-deficient bromine radical offers its electron and a hydrogen of ethane reciprocates with one electron, leading to the formation of HBr and an ethyl radical.

Propagation step 1:



In a second propagation step, the ethyl radical incites the homolysis of bromine forming ethyl bromide and a new bromine radical.

Propagation step 2:

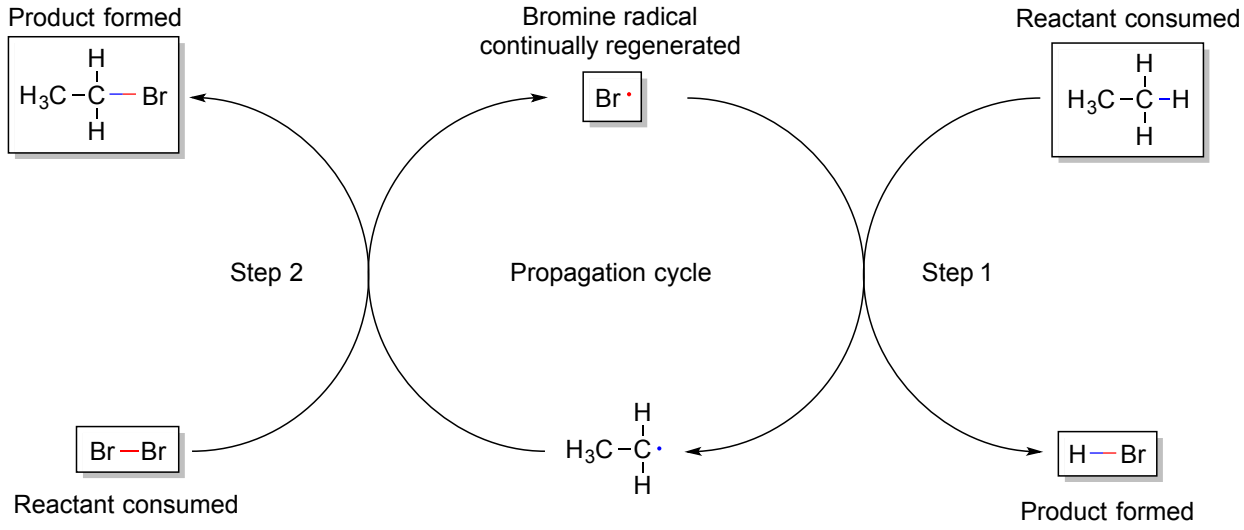


There are a few important comments regarding this step of the reaction. First, students are sometimes surprised to see Br_2 again in this step because they feel as though it was

consumed in the initiation step. However, as we noted earlier, only a few molecules of Br_2 homolyze during initiation. Most are unreacted until they are consumed during the second propagation step.

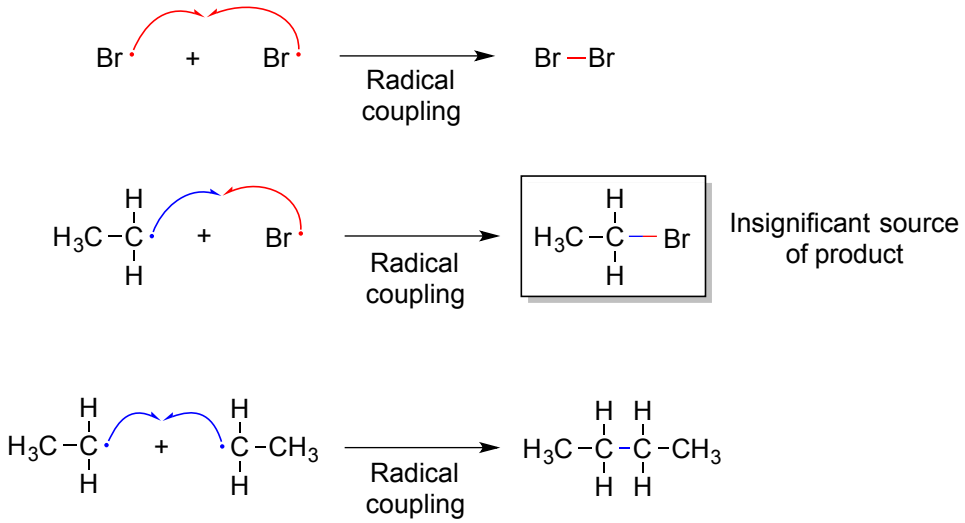
Additionally, product is formed in propagation step 2, and in fact this is where the vast majority of product is generated. You might feel as though the product should be formed at the end of the reaction (in the steps labeled termination), but in reality termination steps usually just explain the fate of the few residual radicals that remain after propagation concludes.

To further illustrate this point, notice that bromine radical is regenerated during the second propagation step. While bromine radical is used in the first propagation step, it is re-formed in the second propagation step. This phenomenon makes the process a chain reaction. Bromine radical enters the propagation sequence and ultimately produces product while replicating itself so that it can enter the cycle yet again. This cycle repeats time and again until all of the ethane and Br_2 are consumed. You could even illustrate this with a diagram that is more evocative of the cyclic nature of the propagation sequence.



The termination steps are almost an afterthought in this case. They aren't particularly important if your goal is merely to explain mechanistically how the products are formed. The termination steps arise from a very logical question. This propagation cycle cannot continue forever. Eventually, both reactants are consumed, so you might wonder: What happens to the remaining radicals at that point? These few radicals combine in the termination steps. Any pair of radicals can bond, so there are a number of termination possibilities.

Termination:

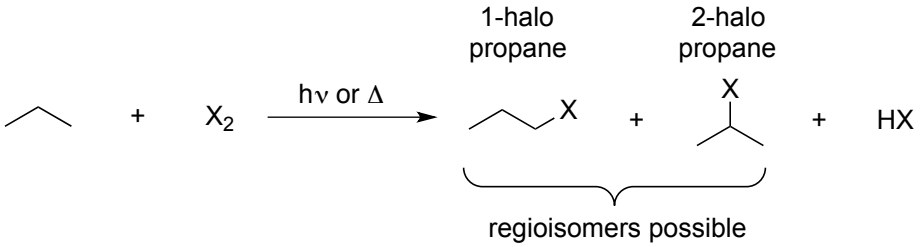


Radical substitution with Cl_2 or Br_2 can be used to prepare alkyl chlorides or alkyl bromides, respectively. The choices of halogen are typically limited to chlorine and bromine. Radical halogenation with fluorine is severely exothermic, making it a potentially dangerous reaction; whereas, the reaction with iodine is not favorable enough to be synthetically useful.

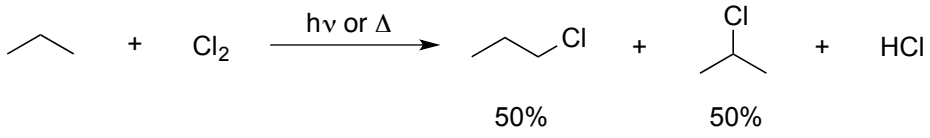
Problem 6. Draw a mechanism for the radical chlorination of cyclopentane.

Section 3: Reactivity and selectivity

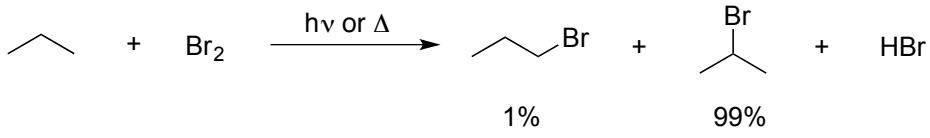
The free-radical halogenation of propane differs from that of ethane in that there is a regiochemical consideration. Regiochemistry arises when a reaction can produce constitutional isomers. In principle, it is possible to halogenate at the terminal or internal carbon to make either a 1-halopropane or a 2-halopropane. These compounds are constitutional isomers that result from a single reaction and can therefore also be termed regioisomers.



There is a pronounced difference in the selectivity of the chlorination and bromination reactions. Free-radical chlorination of propane yields roughly a 1:1 mixture of 1-chloropropane and 2-chloropropane.



On the other hand, the bromination reaction produces 2-bromopropane almost exclusively.



To account for this dramatic difference in selectivity, we need to consider the energy profile for each reaction. Let's examine chlorination first. Remember that Gibbs free energy changes (ΔG°) during a reaction depend upon changes in both enthalpy (ΔH°) and entropy (ΔS°).

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

However, with many organic reactions, the entropy term is negligible. This is true in this reaction where two reactant molecules (propane and chlorine) form two product molecules (alkyl chloride and hydrochloric acid). Consequently, the change in Gibbs free energy can be approximated as the change in enthalpy for the reaction.

$$\Delta G^\circ \approx \Delta H^\circ$$

The change in enthalpy is equal to the difference in bond dissociation energy between the bonds broken and formed.

$$\Delta H^\circ = \sum [H^\circ \; bonds \; broken] - \sum [H^\circ \; bonds \; formed]$$

Let's focus for the moment on the chlorination pathway that proceeds through the more stable secondary radical to yield 2-chloropropane. The relevant bond dissociation energy values are provided in the table below.

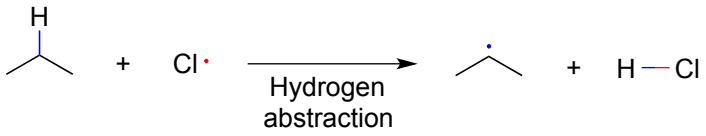
Bond	Bond Dissociation Energy (kcal/mole)
$(CH_3)_2CH$-H	95
Cl-Cl	58
$(CH_3)_2CH$-Cl	80
H-Cl	103

During the course of the reaction, the carbon-hydrogen and chlorine-chlorine bonds are broken, while the carbon-chlorine and hydrogen-chlorine bonds are formed. The calculation shows that the reaction is overall exothermic and releases 30 kcal/mole of energy.

$$\Delta H^{\circ} = [95 + 58] - [80 + 103] = -30\ kcal/mole$$

We can be quite specific about the change in energy at each stage of the reaction as well. The propagation steps constitute the bulk of the process (as we saw earlier), so we'll only consider those two steps. In the first propagation step, the carbon-hydrogen bond is broken and the H-Cl bond is formed.

Propagation step 1:

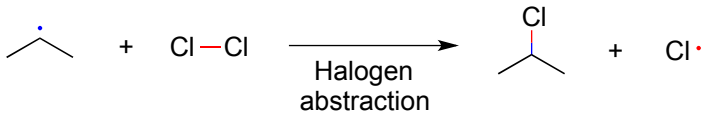


This step is exothermic and releases 8 kcal/mole.

$$\Delta H^{\circ} = [95] - [103] = -8\ kcal/mole$$

In the second propagation step, the Cl-Cl bond is broken and the carbon-to-chlorine bond is formed.

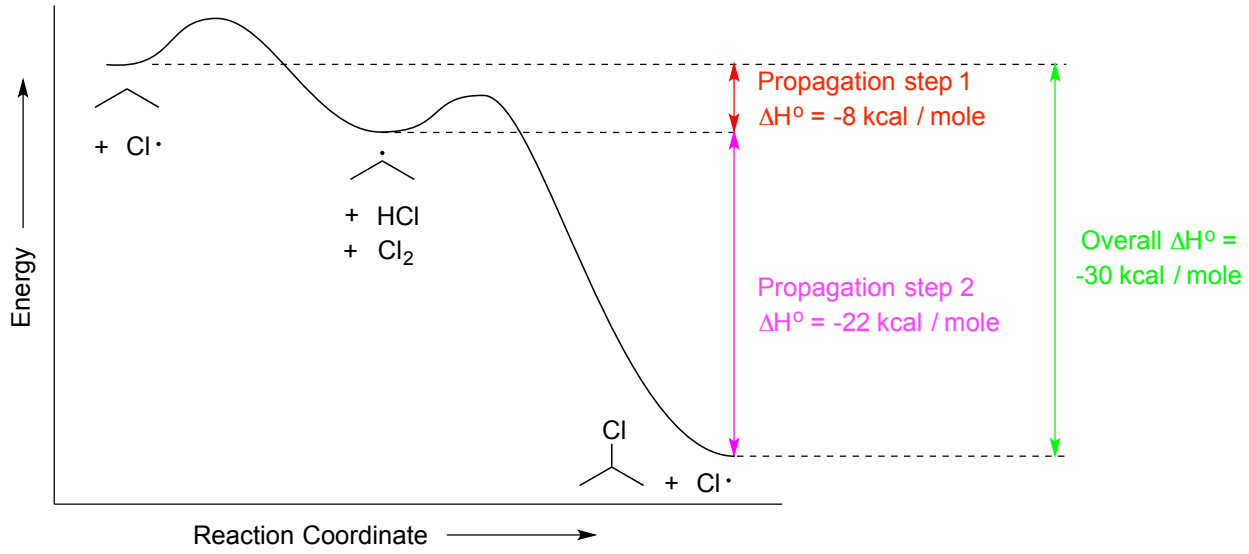
Propagation step 2:



This step is also exothermic, releasing 22 kcal/mole.

$$\Delta H^{\circ} = [58] - [80] = -22\ kcal/mole$$

Both steps are plotted on the following energy diagram.



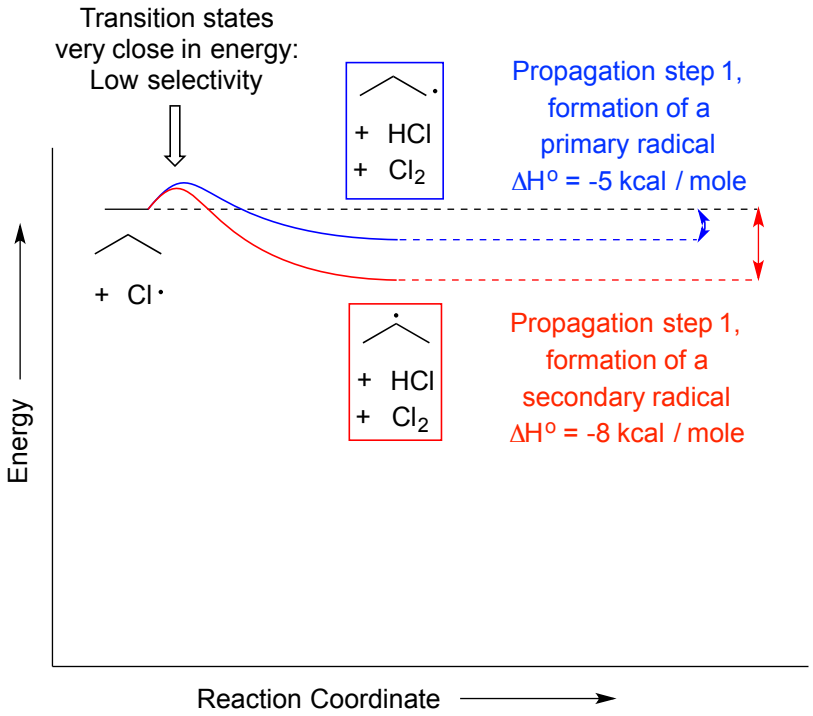
To address the selectivity (or lack thereof in this case), we need to consider the energetic difference between forming the primary and secondary radicals in the first propagation step. We already know that the formation of the secondary radical releases 8 kcal/mole. The following table lists the bond dissociation energies needed to determine the change in enthalpy for the formation of the primary free radical.

Bond	Bond Dissociation Energy (kcal/mole)
$CH_3CH_2CH_2$-H	98
H-Cl	103

The only value that differs is the bond dissociation energy of the carbon-to-hydrogen bond. This primary carbon-to-hydrogen bond is slightly stronger than the equivalent bond at the secondary center. Consequently, the first propagation step releases slightly less energy (5 kcal/mole) if the primary radical is formed.

$$\Delta H^{\circ} = [98] - [103] = -5\ kcal/mole$$

These two possibilities for the first propagation step are plotted together on the energy diagram below. To place the transition states for these two reactions, it is important to know the guiding principle provided by the Hammond postulate, which states that species that are close in geometry are close in energy and vice versa. The transition states of exothermic reactions will therefore more closely resemble the reactants in structure (i.e., they are close on the reaction coordinate). The reactants are higher in energy than the products in exothermic reactions. Since the transition state is the highest energy point in the mechanism of any given step, it will be closer in geometry to the higher energy species, which are the reactants in this case.



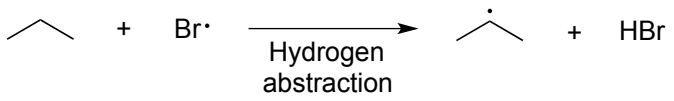
Given that is the case, the 3 kcal/mole difference in energy between the two free radical products has little relevance for the transition states. The transitions states for these exothermic reactions are quite close in energy because they resemble the common reactants from which both processes originate. Since the transition states are very close in energy, there's only a small preference for the formation of the secondary radical during chlorination, and this is offset by the fact that there are simply more primary hydrogens present in the molecule (six primary vs. two secondary). The statistical preference for removal of the more abundant primary hydrogens cancels the minor energetic preference for the transition state leading to the secondary radical. The net result is a roughly 50/50 mixture of the primary and secondary radicals, which leads to an equal mixture of 1-chloropropane and 2-chloropropane, respectively.

Let's examine free-radical bromination in an analogous fashion. The bond dissociation energies needed to calculate the changes in energy for the formation of 2-bromopropane are found in the following table.

Bond	Bond Dissociation Energy (kcal/mole)
$(CH_3)_2CH$-H	95
Br-Br	46
$(CH_3)_2CH$-Br	68
H-Br	88

In the initial propagation step, the secondary carbon-to-hydrogen bond is broken, and the HBr bond is made.

Propagation step 1:

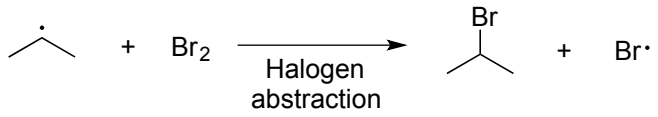


This results in an endothermic reaction, which requires an energetic input of 7 kcal/mole.

$$\Delta H^{\circ} = [95] - [88] = +7\ kcal/mole$$

The final propagation step involves cleavage of bromine and formation of the secondary carbon-to-bromine bond.

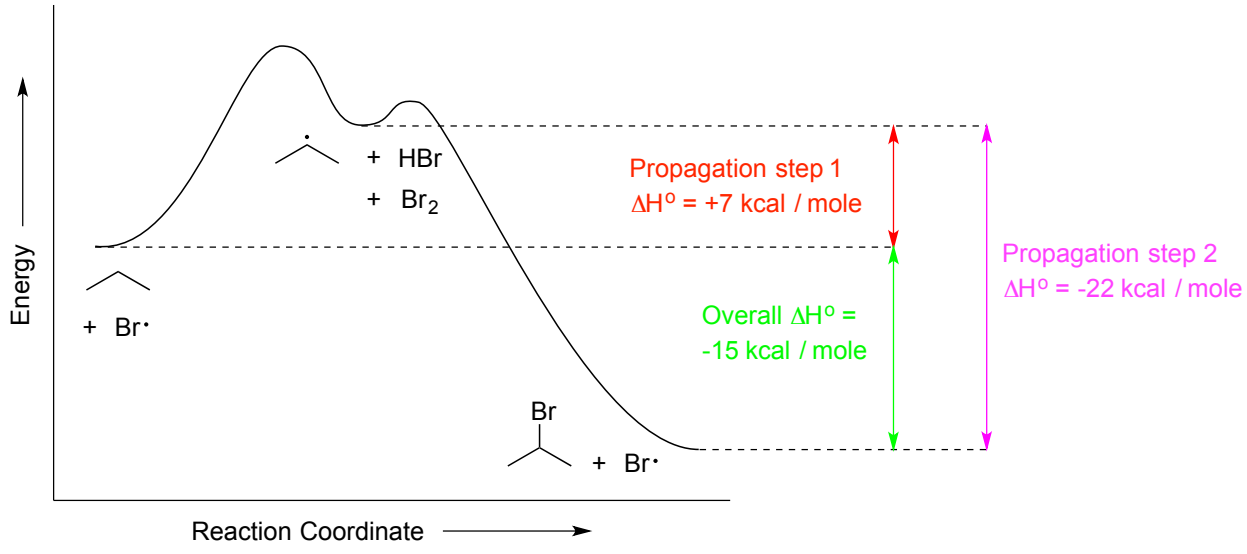
Propagation step 2:



This step is exothermic and releases 22 kcal/mole.

$$\Delta H^{\circ} = [46] - [68] = -22\ kcal/mole$$

The energy profile for this reaction looks very different from that of chlorination, in which both propagation steps were exothermic. Now, in bromination, the first step is *endothermic* instead. This, it turns out, makes all the difference.



Let's now consider solely the first propagation step and how it differs depending on whether a primary or secondary radical is formed. We already know that formation of the secondary radical requires an input of 7 kcal/mole. The bond dissociation energies needed

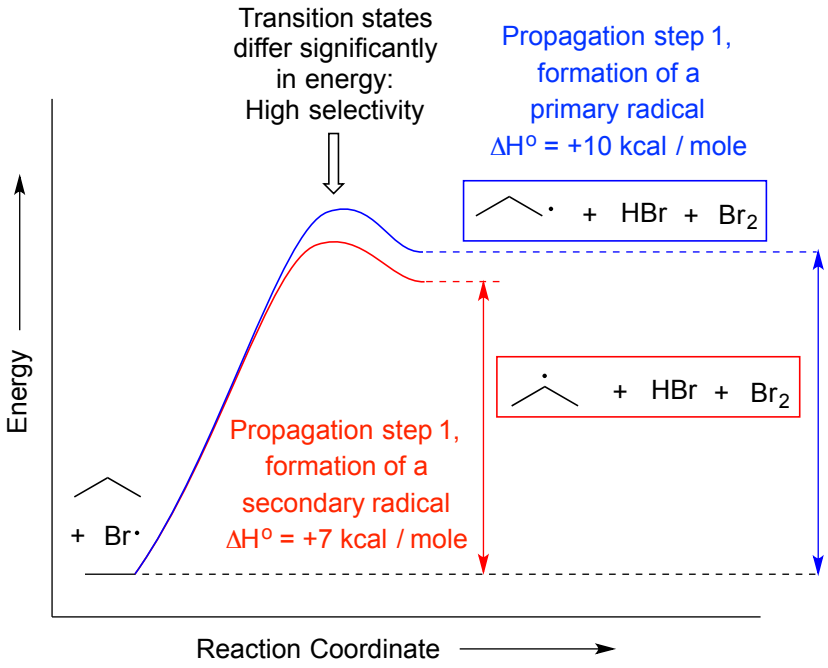
to calculate the change in enthalpy associated with formation of the primary radical are found in the table below. Again, all that differs is the carbon-to-hydrogen bond strength, since now we are considering cleavage at the primary center.

Bond	Bond Dissociation Energy (kcal/mole)
$CH_3CH_2CH_2$-H	98
H-Br	88

The primary carbon-to-hydrogen is broken, while the HBr bond is formed, resulting in an endothermic process requiring 10 kcal/mole.

$$\Delta H^{\circ} = [98] - [88] = +10\ kcal/mole$$

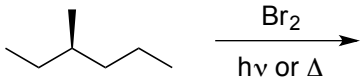
These two propagation step 1 alternatives are plotted together in the energy diagram below. As we place the transition states, it is still important to be guided by the Hammond postulate. Since these reactions are endothermic, the products are higher in energy than the reactants and therefore closer in energy to the transition state. As a consequence, we know that the transition states will also be closer in geometry to the products (i.e., closer on the reaction coordinate).



There's a 3 kcal/mole difference in energy between the two radicals, just as there was for the chlorination reaction. The difference is that, *in bromination, that energy gap is expressed much more prominently at the transition states*, which now are more similar to products than reactants. Consequently, there is a much greater selectivity for the lower energy pathway, resulting almost exclusively in the formation of the secondary radical and hence 2-bromopropane.

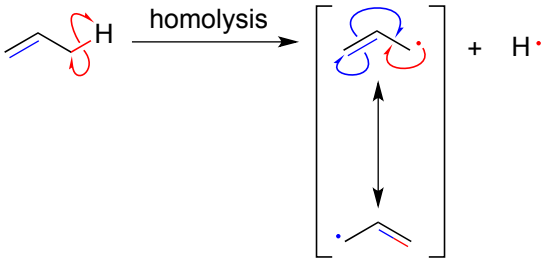
The phenomenon that we've discussed in depth here has sometimes been termed the reactivity-selectivity principle. This principle states that, often when a species is more reactive, the selectivity of its reaction is reduced. The principle is certainly not without exception,[1] but it does help us to attach a name to what has been observed with free-radical halogenation.

Problem 7. Draw a mechanism for the initiation and propagation steps of the following free radical bromination. Be sure to pay special attention to both regio- and stereochemistry.

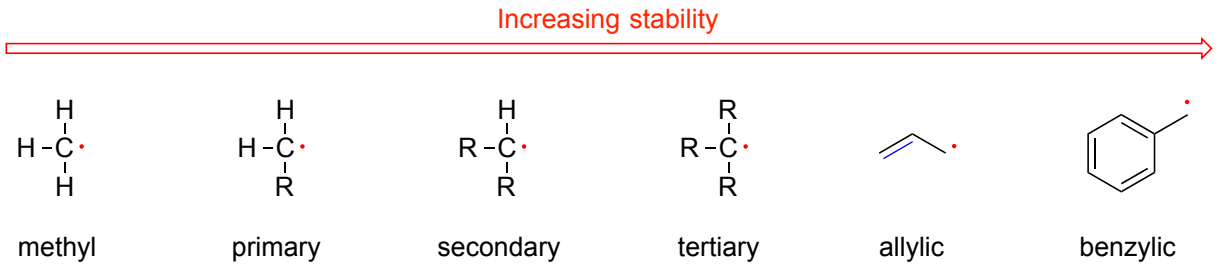


Section 4: Radical substitution reactions at allylic or benzylic centers

Thus far, we've discussed radical stability solely from the perspective of alkyl group substitution. The more highly substituted the radical, the more stable it is. Resonance is also a powerful stabilizing factor when it is present. For instance, in propene, homolysis of an sp^3 carbon-to-hydrogen bond would result in an allylic free radical that can be resonance delocalized to the other terminus of the allylic system. The term "allylic" refers to the position adjacent to an alkene.

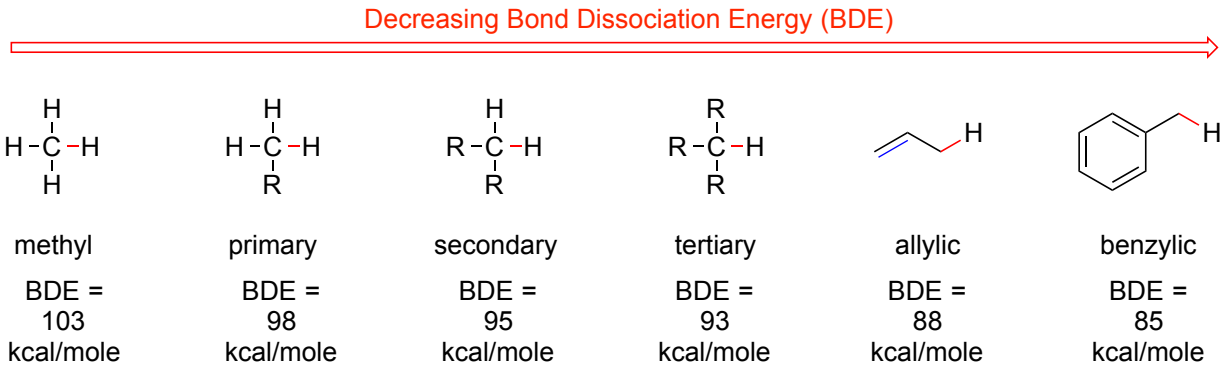


A benzylic radical (i.e., adjacent to a benzene ring) affords even greater resonance delocalization [see Problem 1(c)]. Both allylic and benzylic radicals are even more stable than tertiary radicals.

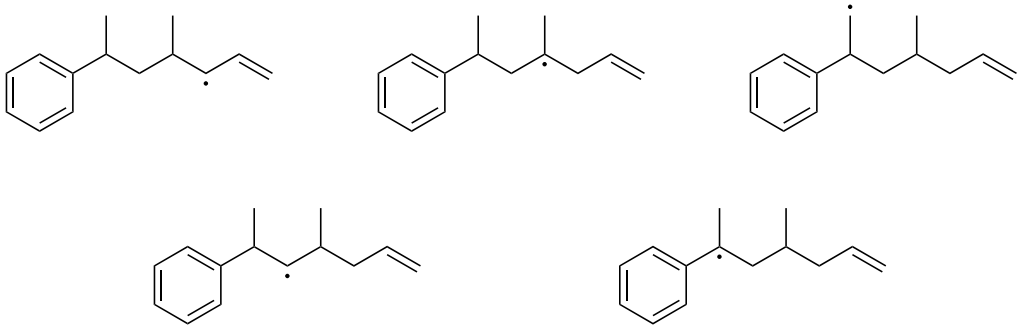


[1] For more discussion of this, see "The Reactivity-Selectivity Principle: An Imperishable Myth in Organic Chemistry," *Angewandte Chemie, International Edition*, **2006**, *45(12)*, 1844–1854.

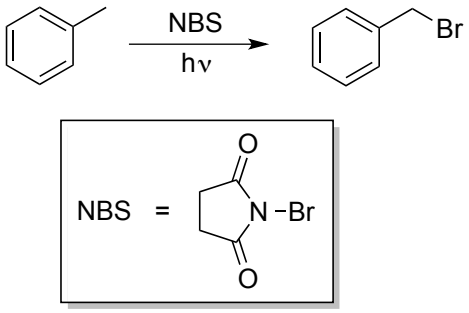
This fact is reflected in their bond dissociation energies. Increasing radical stability results in continually lower bond dissociation energies.



Problem 8. Rank the following isomeric radicals from most to least stable.

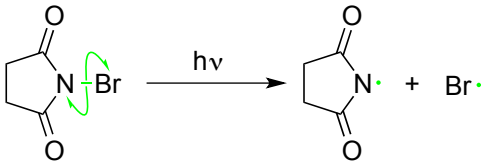


Ultimately, all of this means that, when an allylic or benzylic hydrogen is present, it should be particularly reactive in radical substitution. However, it turns out that alkenes can undergo reactions other than radical substitution in the presence of X_2 and HX. We'll learn about these ionic reactions in Chapter 10. Similarly, certain aromatic rings can undergo reaction with X_2. We'll learn about those processes in Chapter 14. Due to the potential for undesired side reactions of alkenes or aromatic compounds when using X_2, which produces HX as a byproduct, it is prudent to select alternative conditions for the radical substitution of these substrates. A reagent known as *N*-bromosuccinimide (NBS) supplies a constant low concentration of bromine and consumes HBr as it is formed, making it particularly convenient for such transformations.



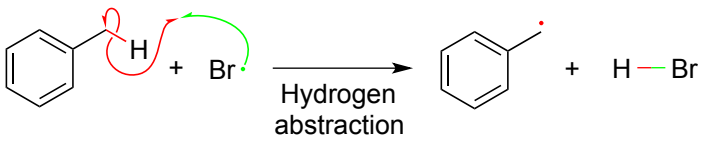
The sequence initiates with the homolysis of the weak nitrogen-to-bromine bond upon exposure to light or a radical initiator. It is important to remember that initiation occurs with only a small number of *N*-bromosuccinimide molecules. Most NBS molecules remain unreacted, and their fate is explained later in the mechanism.

Initiation:



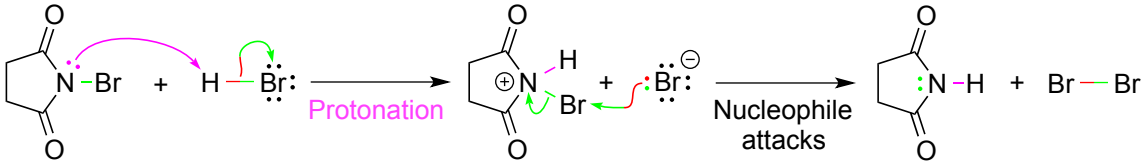
The bromine radical thus formed enters propagation step 1, where it abstracts a hydrogen from the benzylic carbon, leading to the formation of the most stable radical possible.

Propagation step 1:



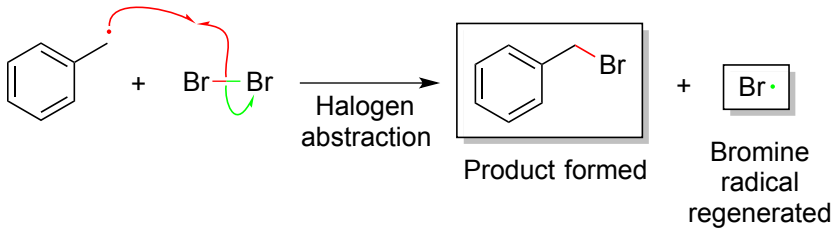
The HBr then reacts with NBS to form bromine. This occurs via two ionic steps. It is rather unusual to see ionic steps amidst what is otherwise a radical mechanism. The HBr, being a strong acid, protonates NBS that did not homolyze during initiation. The bromide that is released during this step then attacks the weak nitrogen-to-bromine bond, cleaving it to form succinimide and Br_2.

Ionic "interlude":

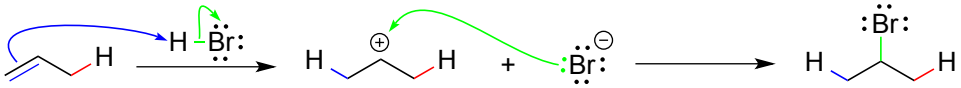


This process ensures two things: (1) HBr is consumed as it is formed and (2) a constant, low concentration of Br_2 is available throughout the reaction. Now that bromine has been generated, it interacts with the benzylic radical in propagation step 2, leading to product formation. Also in this step, the bromine radical needed for propagation step 1 is regenerated so that the cycle can repeat.

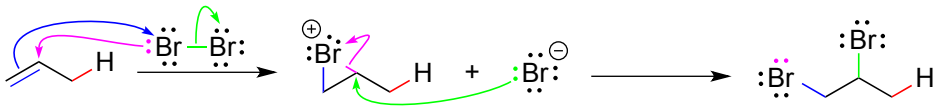
Propagation step 2:



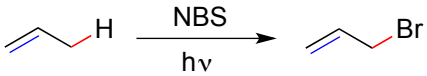
The use of NBS is more critical when the substrates are alkenes, which readily undergo ionic reactions with both HBr and Br_2. We'll cover these reactions more fully in Chapter 10, but what follows is a brief preview of these processes. If an allylic substrate were used and HBr were not consumed as it was formed, hydrohalogenation (addition of HX across the π bond of an alkene) would lead to an undesired side product.



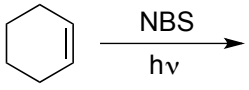
Similarly, if a large concentration of Br_2 were present, halogenation (addition of X_2 across the π bond of an alkene) would also lead to an undesired side product.



Due to the potential for these side reactions with the substances used for and present during traditional radical substitution, it is important to use NBS as the brominating agent for an allylic substrate.

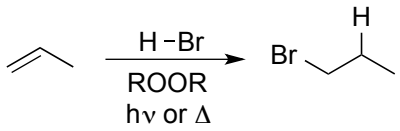


Problem 9. Draw a mechanism for the following free-radical bromination.



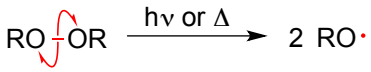
Section 5: Radical addition to π bonds

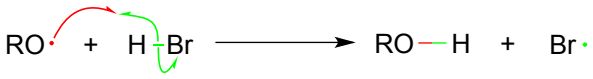
Early in this chapter, it was noted that radicals could cause the homolysis of σ bonds or they could add to π bonds. To this point, we've focused exclusively on the interaction of radicals with σ bonds in radical substitution reactions. Now, let's turn our attention to the addition reactions that radicals can undergo. In the presence of a peroxide (ROOR), HBr can be added across the π bond of an alkene.



Peroxide homolyzes in the presence of light or heat to begin the initiation sequence. The alkoxy radical thus formed then abstracts hydrogen from HBr to yield an alcohol and the critical bromine radical that will cycle through the propagation steps.

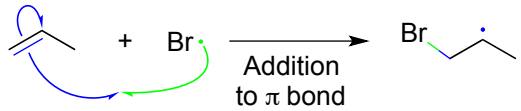
Initiation:





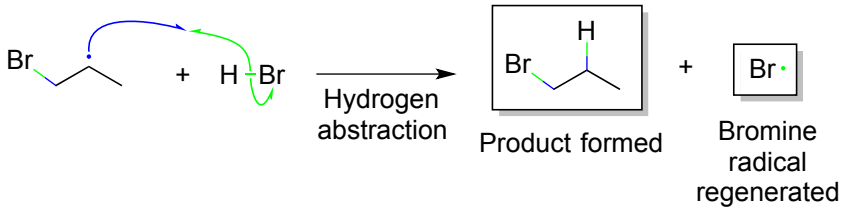
In the first propagation step, the bromine radical adds to the π bond so as to form the more stable secondary radical intermediate.

Propagation step 1:



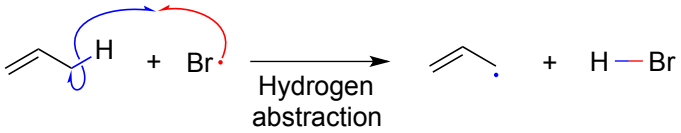
In the second propagation step, the carbon-centered radical incites the homolysis of a molecule of HBr, leading to the formation of product and the regeneration of the critical bromine radical. The carbon-centered radical abstracts a hydrogen atom (rather than bromine) because the resultant C-H bond is a stronger bond.

Propagation step 2:

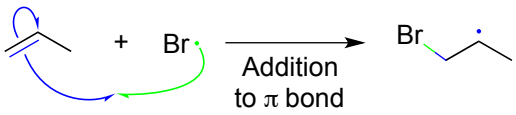


It is worth taking a step back at this moment to answer a question that might be on your mind. During the first propagation step of *radical substitution*, bromine radical abstracts an allylic or benzylic hydrogen atom. During the same step of *radical addition*, bromine radical adds to the π bond of an alkene instead. So, naturally you might wonder how you are supposed to know when bromine radical interacts with a σ bond or a π bond.

Propagation step 1 of radical substitution:

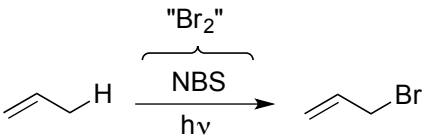


Propagation step 1 of radical addition:

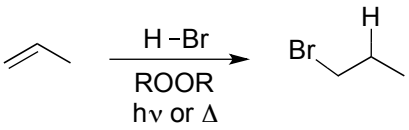


The answer comes from looking at the big picture. In radical substitution, the alkene is treated with NBS, which is effectively a source of a steady and low concentration of Br_2. On the other hand, in radical addition the alkene is treated with HBr. The difference in reagent ("Br_2" vs. HBr) explains the difference in reactivity.

Radical substitution:

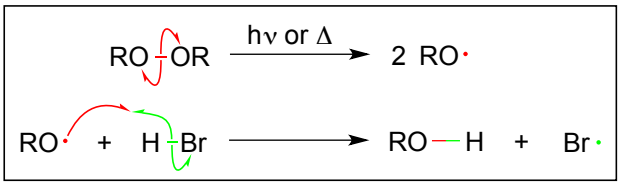


Radical addition:

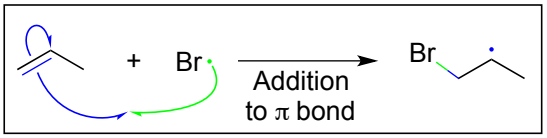


Let's consider what would happen if bromine radical abstracted the allylic hydrogen during *radical addition*. To help you put this "what if?" scenario in context, the actual, correct mechanism for radical addition is summarized below. Take special note of what happens during propagation step 1: Bromine radical adds to the π bond.

Initiation

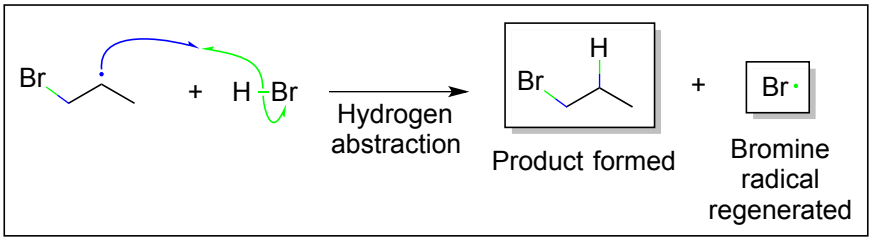


Propagation step 1



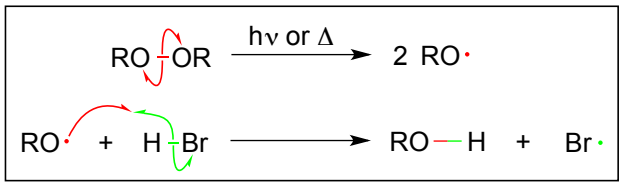
Radical addition as it actually occurs

Propagation step 2



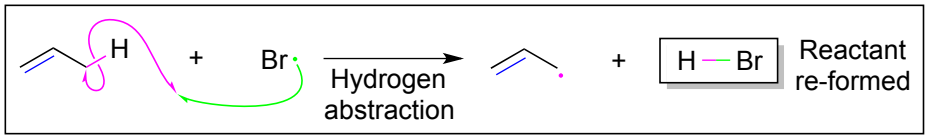
Now, let's consider our "what if?" scenario. What if bromine radical abstracted an allylic hydrogen instead during propagation step 1? The answer is shown below. This would result in the re-formation of HBr and the production of an allylic radical. In propagation step 2, the allylic radical would abstract a hydrogen from another molecule of HBr to re-form *the original* organic substrate, along with bromine radical.

Initiation

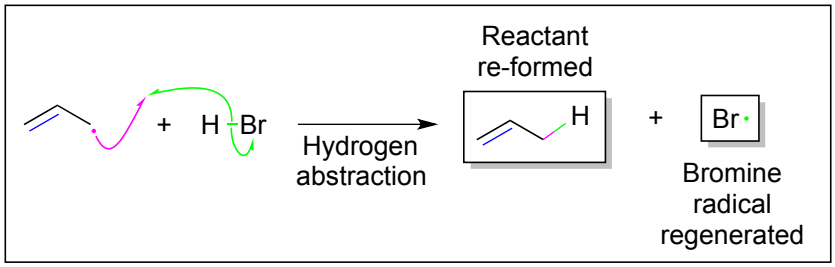


What if hydrogen abstraction happened in propagation step 1?

Propagation step 1



Propagation step 2



So, while bromine radical could abstract an allylic hydrogen in propagation step 1 of the radical addition reaction, we would be unable to detect that this process had occurred because *all that results is the re-formation of the original reactants*. The only reaction of bromine radical that leads to a new product is its addition to the π bond of the alkene.

We've seen that radical substitution reactions involving chlorine or bromine are thermodynamically favorable, although one is more selective than the other. You might also wonder whether the radical addition of HBr to the alkene π bond is favorable. The bond dissociation energy values needed to ascertain this are provided in the table below.

Bond	Bond Dissociation Energy (kcal/mole)
C-C	83
C=C	146
$(CH_3)_2CH$-H	95
$CH_3CH_2CH_2$-Br	68
H-Br	88

As before, we'll be considering the difference in enthalpy between the bonds broken and formed. However, you'll notice that only the π bond of the alkene is broken, and the table above does not contain a bond dissociation energy for just the π bond. This value is readily calculated though. It is merely the difference in bond dissociation energy of the C=C and C-C bonds (146 – 83 = 63 kcal/mole).

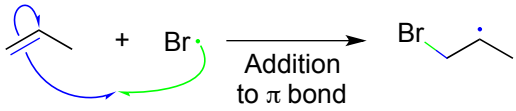
$$\Delta H^{\circ} = \sum [H^{\circ}\ bonds\ broken] - \sum [H^{\circ}\ bonds\ formed]$$

Therefore, we now have all of the values needed for the calculation. During the reaction, the alkene π bond is broken, as is the H-Br bond. On the other hand, the C-H and C-Br bonds are formed. Overall, the reaction is exothermic and releases 12 kcal/mole of energy.

$$\Delta H^{\circ} = [63 + 88] - [95 + 68] = -12\ kcal/mole$$

Furthermore, we can determine that both propagation steps of radical addition are exothermic. In propagation step 1, the π bond is broken and the carbon-to-bromine bond is formed.

Propagation step 1:

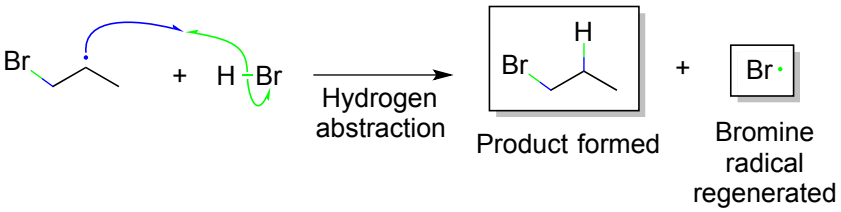


This results in a step that is exothermic by 5 kcal/mole.

$$\Delta H^{\circ} = [63] - [68] = -5\ kcal/mole$$

In propagation step 2, the H-Br bond is broken and the secondary carbon-to-hydrogen bond is formed.

Propagation step 2:



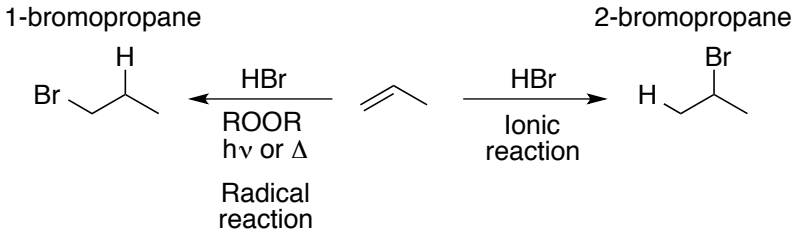
This results in a step that is exothermic by 7 kcal/mole.

$$\Delta H^{\circ} = [88] - [95] = -7\ kcal/mole$$

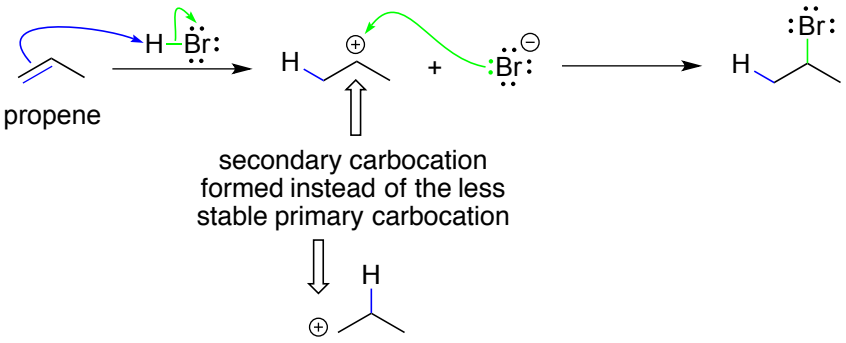
These calculations show that the radical addition of HBr across an alkene π bond is overall favorable and that each of the key propagation steps is favorable as well.

To conclude this section, let's foreshadow an aspect of regiochemistry that we'll revisit in Chapter 10 when we study the reactions of alkenes. The addition of HBr across an alkene can result in two regiochemical outcomes. As we saw above, the radical reaction in which HBr is added to the alkene in the presence of peroxide yields 1-bromopropane. On the

other hand, if we simply add HBr to the alkene without peroxide, an ionic reaction ensues, and this gives rise to the constitutional isomer 2-bromopropane.

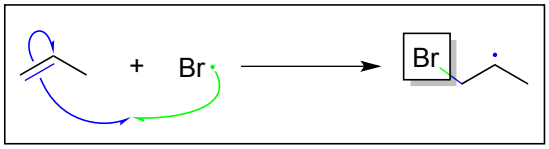


We'll revisit the ionic reaction in greater depth in Chapter 10, but for the moment, let's just consider the relatively simple example of propene reacting with HBr. In this ionic reaction, the π electrons of the alkene attack the electron-poor proton of HBr. As the proton acquires a new bond to carbon, its bond to bromine is cleaved. Noticed that the initial arrow originates from the π bond. This means that, in theory, the proton could be added to either carbon. The decision is made by proceeding through the lower energy carbocation intermediate. Just like radicals, carbocations that are more substituted are more stable. Therefore, the proton is added to the terminal carbon to make the more stable secondary carbocation intermediate. Bromide then adds to this carbocation to yield the product: 2-bromopropane.

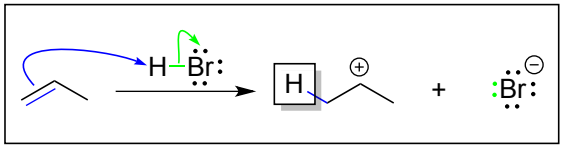


The regiochemistry of this ionic reaction is the reverse of what we saw previously for the radical process. To understand why there is a reversal of regiochemistry, we can compare the initial addition to the π bond in each reaction. In both instances, the reaction proceeds through the more stable secondary radical or carbocation. *What differs is the atom that was added to the alkene.* In the radical reaction, bromine was added, but in the ionic process it was a proton that was added. This is the source of the reversal of regiochemistry.

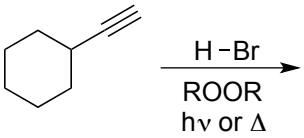
Propagation step 1 of the radical reaction:



First step of the ionic reaction:



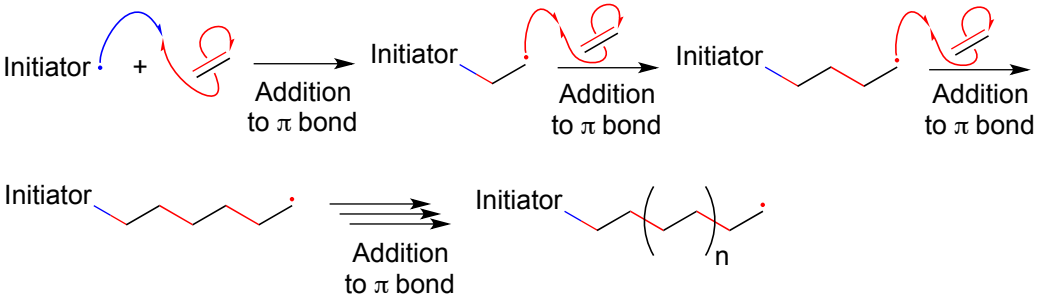
Problem 10. In a reaction analogous to the one covered in this section, HBr can be added across the π bond of an alkyne in a radical fashion. Show a mechanism for this process.



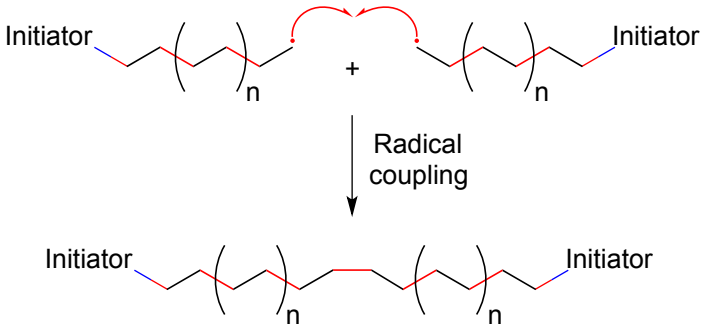
Section 6: Radicals and polymerization

Polymers are very large molecules—often called macromolecules—formed from small repeating subunits. These subunits are called monomers. In a polymerization reaction, monomers are covalently linked through successive iterations of a single reaction.

Radical reactions play a very important role in the synthesis of useful polymers. Let's consider a straightforward radical polymerization of a simple alkene known as ethylene. A radical initiator can add to the π bond of ethylene. This yields a new radical that adds to the π bond of another molecule of ethylene. The radical is propagated through the consecutive incorporation of additional ethylene monomers, and this process continues until the chain is very long.



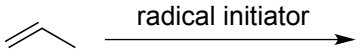
Eventually, the supply of ethylene monomers will be exhausted, at which point the polymerization must end. The sequence is terminated in one of two ways. One possible termination step is the union of two polymer chains.



A second termination possibility is known as disproportionation. One radical abstracts a hydrogen from the carbon adjacent to the other, resulting in an alkane and an alkene.

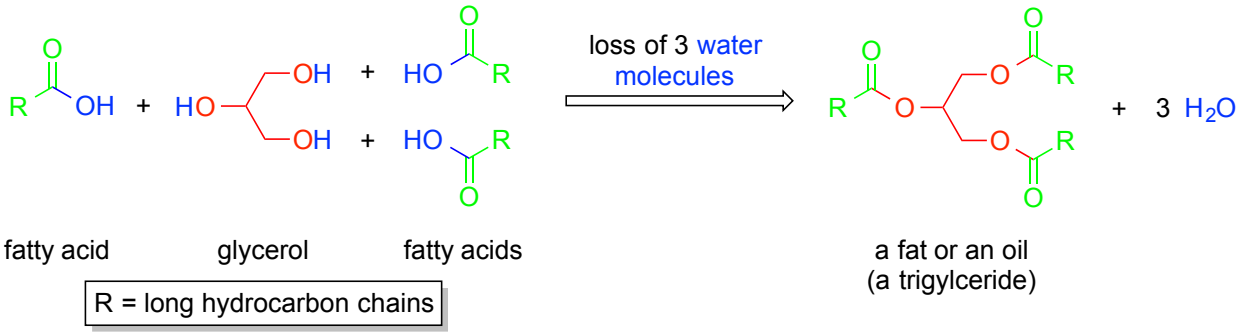
The polymer created through this reaction is known as polyethylene because it consists of many ("poly") ethylene (-CH_2CH_2-) units.

Problem 11. Provide a mechanism for the polymerization of propylene (shown below). Pay special attention to the stability of the radical intermediates.



Section 7: Oxidation of fats and oils, vitamin E, and preservatives

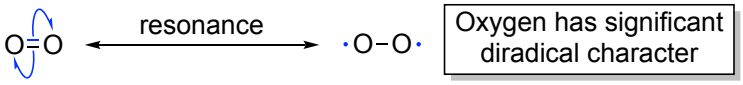
Fats and oils are biomolecules of a larger category known as lipids. Lipids are those naturally occurring, biologically relevant molecules whose water solubility is low. Fats and oils (a subset of this family) have quite similar structures. They are formed from the condensation of three fatty acids with glycerol, a three-carbon molecule bearing a hydroxyl group on each carbon. A carboxylic acid is termed a fatty acid if its R group is a long hydrocarbon chain.



Both fats and oils can also be termed triglycerides. What distinguishes fats from oils is the structure of the fatty acid R groups. Fats, being solids at room temperature, have saturated R groups that allow relatively close packing. On the other hand, oils possess R groups that disfavor this close packing, making them liquids at room temperature. The presence of unsaturation in the R group(s) will tend to disfavor packing because the naturally

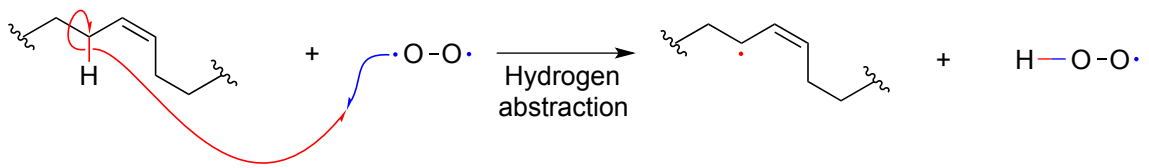
occurring alkenes in fatty acids have the *cis* configuration. This introduces a bend or kink into the hydrocarbon chain, which makes the close association of adjacent molecules awkward.

These unsaturated R groups contain allylic hydrogens, and as a consequence, they can undergo radical substitution with relative ease. Oxygen is the radical species with which they react. Although it is common to draw the Lewis structure of oxygen with a double bond, oxygen actually has significant diradical character that helps to explain much of its behavior.



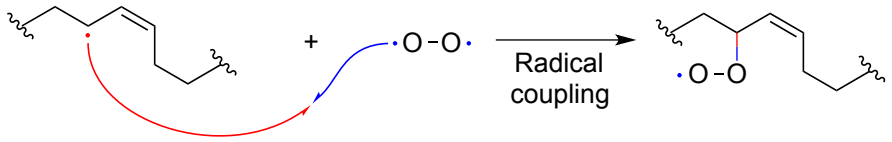
In the diagram below, most of the triglyceride's structure is omitted. Only a small portion of the unsaturated R group is shown. Oxygen can abstract hydrogen from an allylic center.

Initiation:



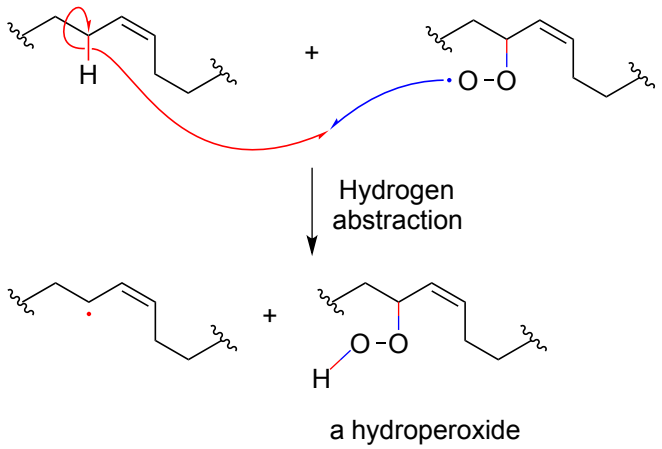
The coupling of the carbon-centered radical and another molecule of oxygen establishes a new carbon-to-oxygen bond.

Propagation step 1:



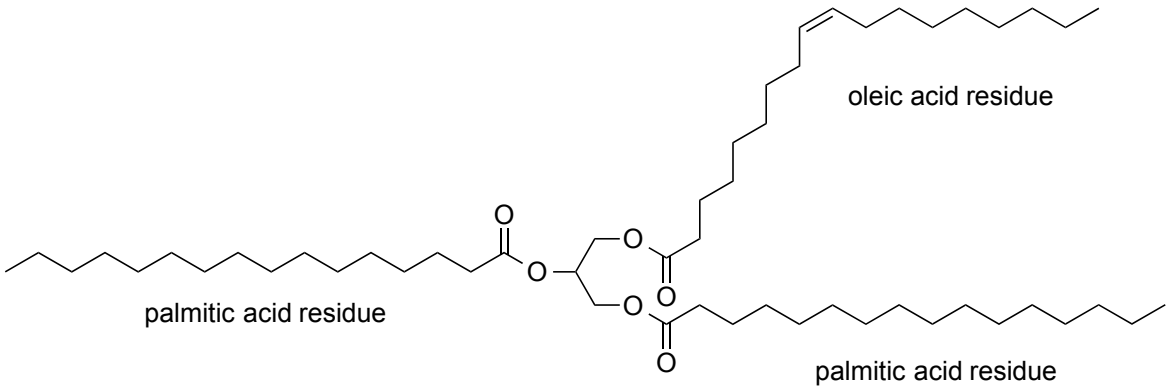
Finally, the abstraction of another allylic hydrogen by the peroxy radical yields a hydroperoxide, along with another radical capable of reentering the propagation cycle.

Propagation step 2:

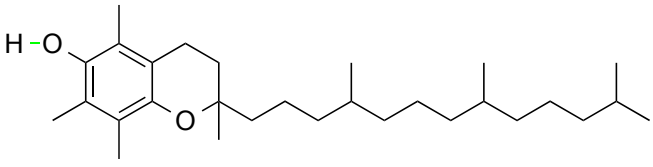


This process has been implicated in the oxidation, and therefore spoilage, of unsaturated triglycerides upon exposure to air. Saturated fats lack the π bonds that make radical substitution facile and as a result typically have longer shelf lives.

Problem 12. Olive oil contains a mixture of triglycerides. These triglycerides contain a variety of fatty acid residues, including oleic and palmitic acids. Such a triglyceride is shown below. Provide a mechanism for its oxidation.



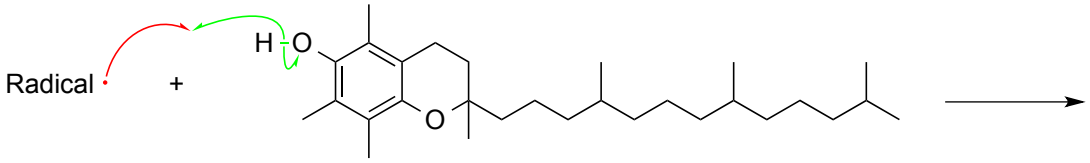
Preservatives provide one solution to the problem of oxidation of foodstuffs. Preservatives like BHT and BHA are antioxidants and share structural similarity and a common mode of action with the well-known antioxidant vitamin E.



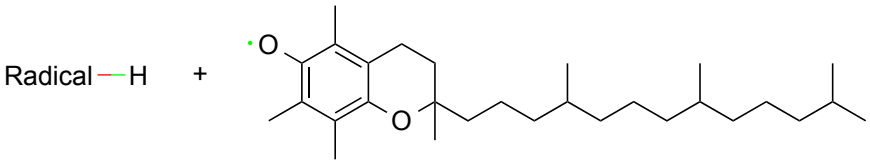
Vitamin E

Vitamin E contains a phenolic hydroxyl group. In the presence of a radical (perhaps the allylic radical seen above in the oxidation of unsaturated triglycerides), this group can serve as a hydrogen donor to quench the radical, returning it to its original form. The

phenoxy radical that results on vitamin E is much less reactive by virtue of its extensive resonance delocalization. Also, the flanking methyl groups reduce the likelihood of reaction at this site due to their bulk. In other words, they block the approach of other molecules—or sterically shield—the phenoxy radical.

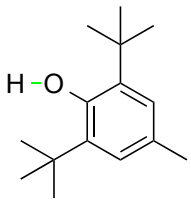


Vitamin E

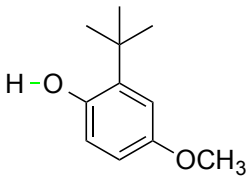


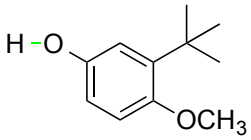
Problem 13. Provide a mechanism for quenching of the radical process described in Problem 12 by vitamin E. Focus on reaction of vitamin E with the allylic radical intermediate.

Preservatives like BHT and BHA mimic vitamin E. They too contain phenolic hydroxyl groups that can quench radicals. Furthermore, the resulting phenoxy radicals are similarly resonance stabilized by the aromatic rings and sterically shielded by nearby *tert*-butyl groups.



BHT (butylated hydroxytoluene)





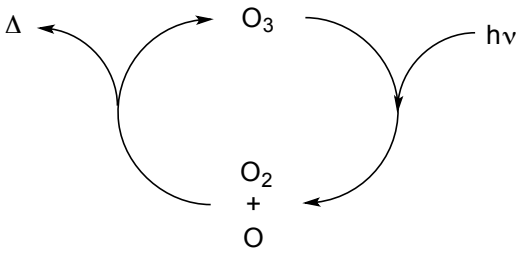
BHA (butylated hydroxyanisole)

Problem 14. Provide a mechanism that shows how BHT can play the same role as vitamin E in quenching the reactivity of the allylic radical formed from the triglyceride in Problem 12.

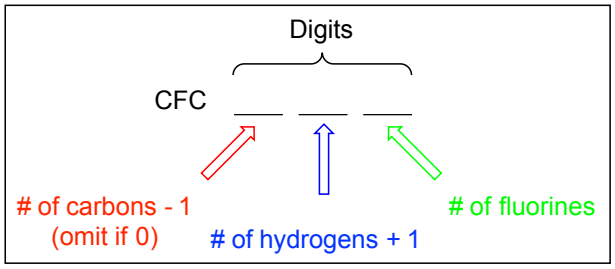
Section 8: CFCs and ozone-layer depletion

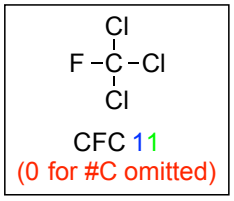
The ozone layer protects life on Earth's surface from high-energy cosmic radiation. There is a natural equilibrium between ozone (O_3) and its degradation products, atomic and molecular oxygen (O and O_2, respectively). The natural equilibrium between these processes can be pictured as a cycle. Ozone is degraded into molecular oxygen and atomic oxygen upon exposure to high-energy solar radiation ($h\nu$). When molecular and atomic

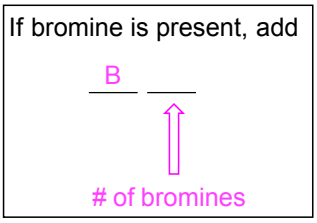
oxygen recombine to form ozone again, heat (Δ) is evolved. Consequently, this cycle essentially converts high-energy light into heat and warms our atmosphere.

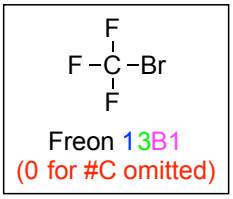


Unfortunately, this natural balance can be disrupted by ozone-depleting substances, such as chlorofluorocarbons (CFCs). In the 1920s, CFCs were developed as non-toxic and non-flammable refrigerants by Thomas Midgley, Jr. and Albert Henne of General Motors. These compounds are termed CFCs or Freons, followed by a number that is a code for their structure. This coding system helped to protect the proprietary discoveries. The code typically consists of two to three digits. The first digit is the number of carbons minus 1. If the value is zero, it is not written. The second digit is the number of hydrogens plus 1. The final digit is the number of fluorine atoms. The number of chlorine atoms is then inferred. In other words, the remainder of carbon's valences are filled with bonds to chlorine. When bromine is present in the molecule, the initial set of digits is followed by "B" and one more number to denote the bromine count in the molecule.









Problem 15. Provide structures for the following Freons.

(a) Freon 13

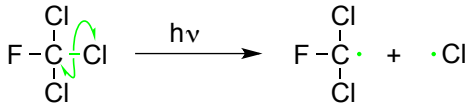
(b) Freon 31

(c) Freon 112 (note that two isomers are possible for this name)

Midgley announced the development of just such an improved refrigerant at the 1930 American Chemical Society meeting and illustrated its safety by inhaling the substance and then blowing out a candle as he exhaled the CFC over the flame.[2]

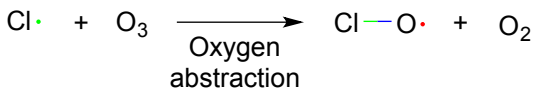
The stability of CFCs was both a blessing and a curse. They did serve as valuable refrigerants. However, once released into the environment, their stability enabled them to persist intact until they reached the upper atmosphere. There, exposure to high-energy light causes the homolysis of a carbon-to-chlorine bond, which generates a chlorine radical.

Initiation:



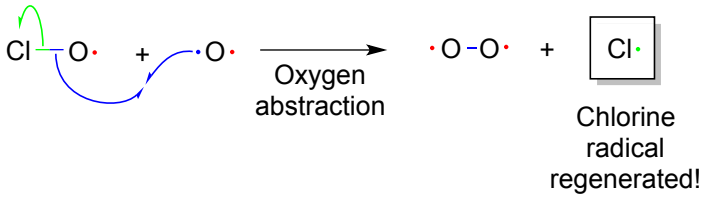
This chlorine radical can facilitate the degradation of ozone in a propagation step. The chlorine essentially abstracts an oxygen from ozone, thereby producing molecular oxygen. *Here is where we see the degradation of ozone into molecular oxygen and atomic oxygen, which happens to currently be bonded to chlorine.*

Propagation step 1:



In a second propagation step, the abstracted oxygen atom is donated to another atom of oxygen in the atmosphere to form a second molecule of O_2. The chlorine radical is also regenerated.

Propagation step 2:



The regeneration of chlorine radical means that this is another chain reaction. Chlorine can facilitate the degradation of many, many ozone molecules (about 100,000) before it is quenched. Therefore, the release of a relatively small amount of CFC can lead to a great deal of ozone-layer depletion. Since the discovery of this phenomenon in the 1970s, ozone-

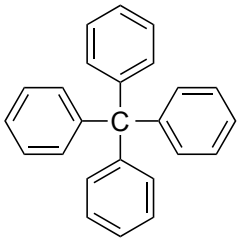
[2] See http://www.epa.gov/ozone/snap/refrigerants/safety.html (accessed February 11, 2013) for more on Refrigerant safety and history.

depleting substances have been continually phased out of usage, most notably because of the international agreement known as the Montreal Protocol.

Problem 16. Show how Freons 13, 31, and 112 (encountered in Problem 15) can each generate a radical that can degrade ozone.

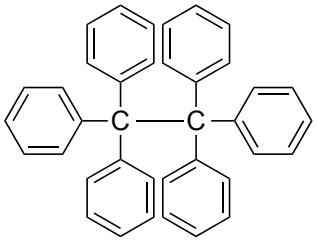
Section 9: Moses Gomberg and the discovery of free radicals

Moses Gomberg, who was a professor at the University of Michigan, is widely considered to be the father of free radical chemistry. A few years prior to 1900, he prepared tetraphenylmethane, which had proven to be quite the synthetic challenge.



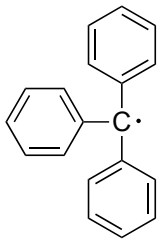
tetraphenylmethane

His next endeavor was the synthesis of the homologous hexaphenylethane.



hexaphenylethane

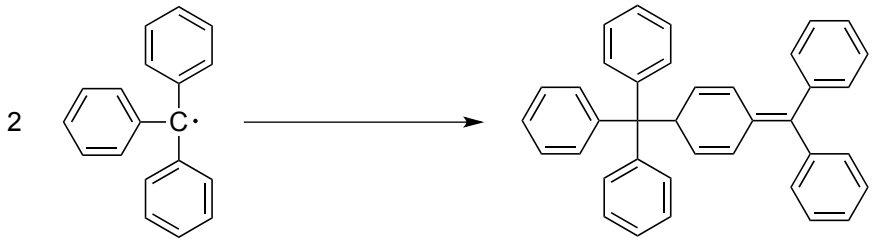
As he encountered unexpected experimental results, Gomberg hypothesized that he had observed a relatively stable free radical, the triphenylmethyl radical.



triphenylmethyl radical

This was quite the controversial idea at the time. Although Gomberg's conclusions about what he had isolated from the reaction were not entirely correct, his ideas about the existence of radicals were eventually proven to be true.[3]

Problem 17. What Gomberg actually isolated from his reaction was the dimer shown below. The term "dimer" refers to two like units ("monomers") that have been linked together. Provide a mechanism that shows how two triphenylmethyl radicals can combine to give this dimer.



triphenylmethyl radical dimer

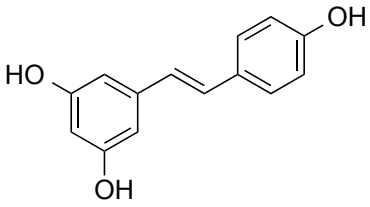
End-of-the-Chapter problems

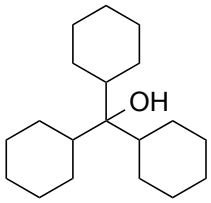
Problem 18. Free-radical fluorination is not commonly performed. Show a mechanism for the fluorination of ethane. Then, using the table of bond dissociation energies below, calculate the change in enthalpy for this reaction, and draw the reaction energy profile. Why is free-radical fluorination an uncommonly used reaction?

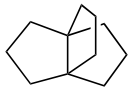
Bond	Bond Dissociation Energy (kcal/mole)
CH_3CH_2-H	98
F-F	36.8
CH_3CH_2-F	116
H-F	135

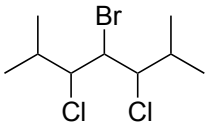
Problem 19. Based on what we learned about antioxidants in this chapter, which of the following compounds seems most likely to have antioxidant activity.

[3] For a more thorough discussion of Moses Gomberg's life and accomplishments, see "Moses Gomberg (1866 – 1947): A Biographical Memoir" by John C. Blair, Jr. (National Academy of Sciences: Washington, D.C., 1970) which can be accessed online via http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/gomberg-moses.pdf.

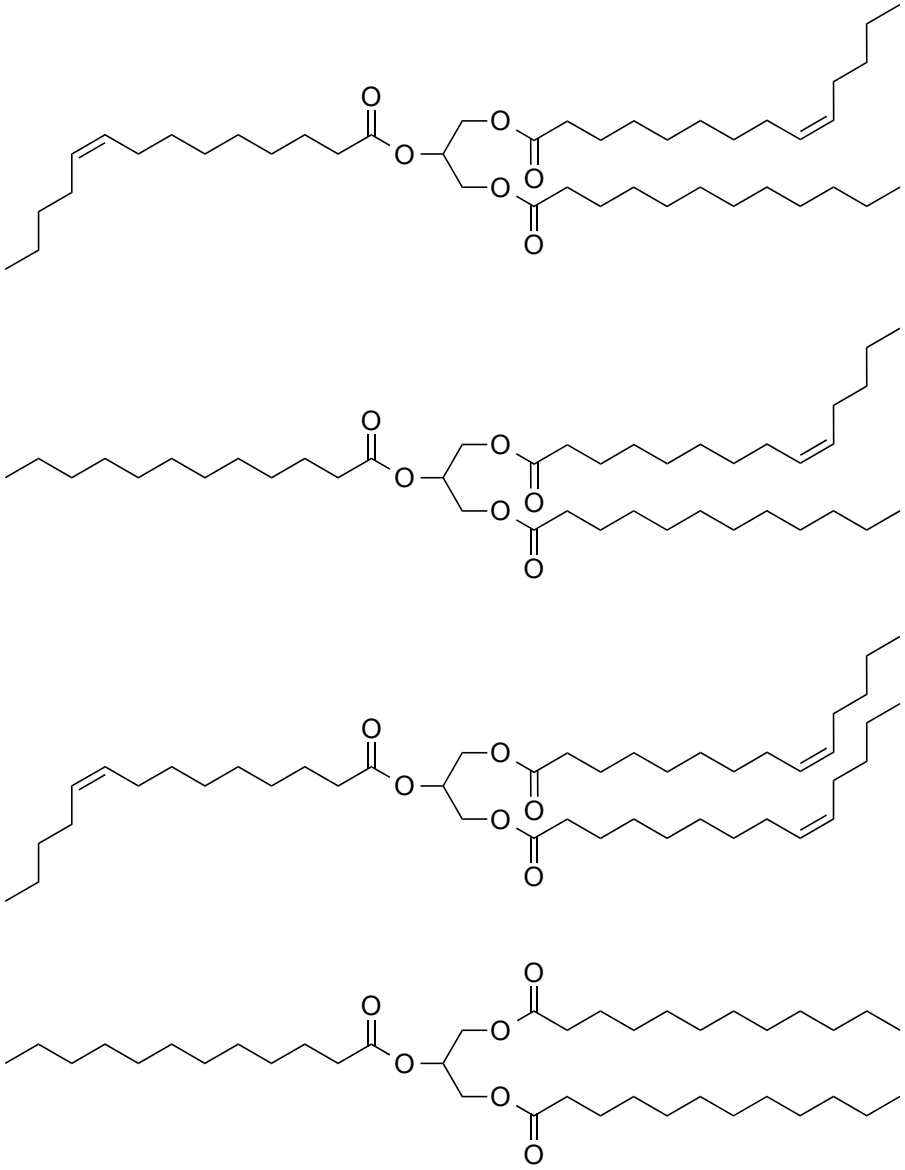




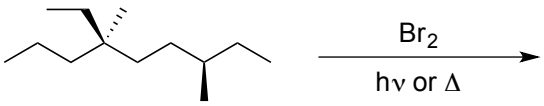




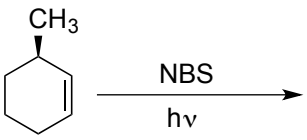
Problem 20. The following triglycerides contain the fatty acids lauric acid (saturated) and myristoleic acid (unsaturated). Rank these triglycerides in order of increasing propensity to undergo oxidation.



Problem 21. Provide the products of the following reaction, as well as a mechanism to explain their formation.



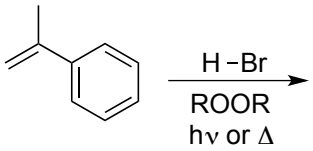
Problem 22. Provide a mechanism for the following allylic bromination. Also show all of the regioisomers and stereoisomers that are formed in the reaction.



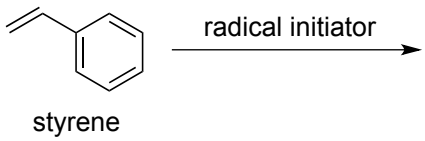
Problem 23. As we saw in Problem 18, free-radical fluorination is a highly exothermic process and is therefore not commonly employed. Free-radical iodination is also not commonly utilized. Using the table of bond dissociation energies below, calculate the change in enthalpy for the iodination of ethane, and draw the reaction energy profile. Why is free-radical iodination not especially useful?

Bond	Bond Dissociation Energy (kcal/mole)
CH_3CH_2-H	98
I-I	35.6
CH_3CH_2-I	57
H-I	71

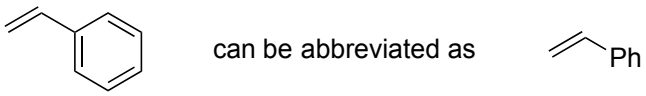
Problem 24. 2-Phenylpropene (shown below) can undergo the addition of HBr under radical conditions. Provide the product(s) of this transformation, along with a mechanism that explains the outcome.



Problem 25. Styrene can be polymerized under radical conditions to yield a macromolecule known as polystyrene. Show a mechanism for the formation of polystyrene.

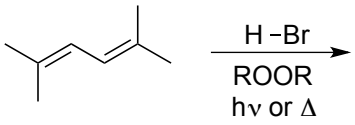


It will be helpful to know two things: (1) styrene can be abbreviated as shown below and



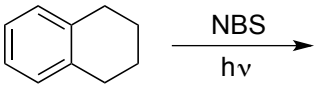
(2) the π bonds of the aromatic ring are far less reactive than the π bond of the alkene outside the ring.

Problem 26. Provide a mechanism for the following reaction in which a molecule containing two alkenes (known as a diene) reacts with 1 molar equivalent of HBr in the presence of a peroxide and light or heat.

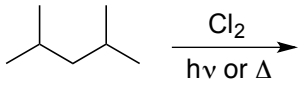


Problem 27. Predict the product(s) of the following reactions.

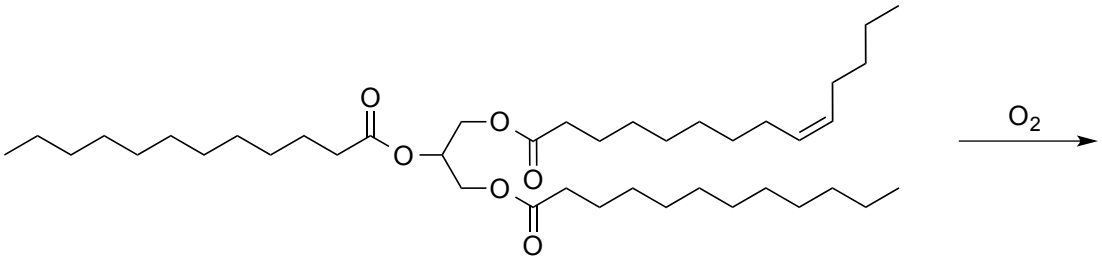
(a)



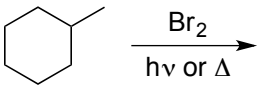
(b)



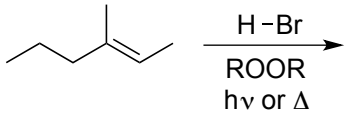
(c)



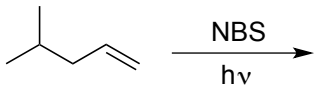
(d)



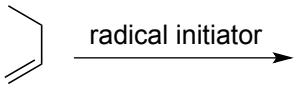
(e)



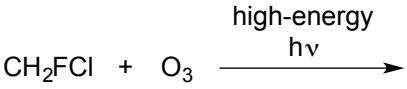
(f)



(g)

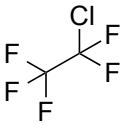


(h)

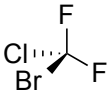


Problem 28. Provide names for the following CFCs and related compounds.

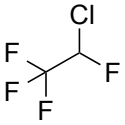
(a) This compound was used as a refrigerant but was banned as a result of the Montreal Protocol.



(b) This compound is used in fire extinguishers on aircraft.

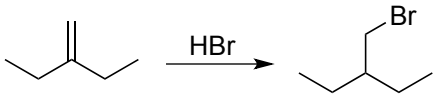


(c) This compound is used as a gaseous fire suppressant.



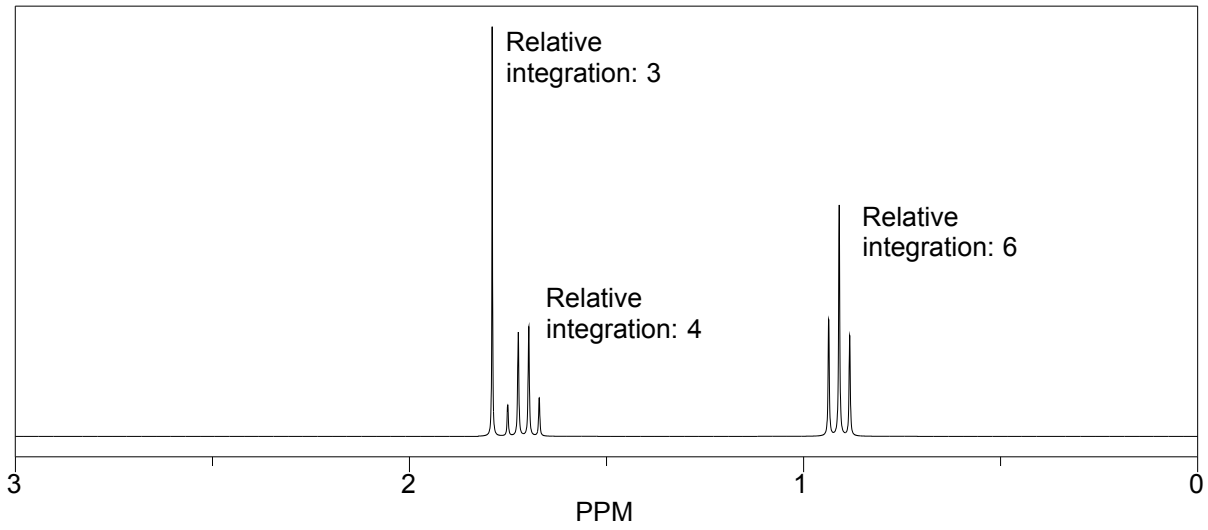
Problem 29. An alkane with the formula C_5H_{12} is treated with Cl_2 in the presence of light. Only a single chloroalkane is produced. What are the structures of the alkane and its chlorination product?

Problem 30. An investigator intended to conduct a radical addition of HBr across the π bond of the alkene shown below but forgot to add the peroxide. Consequently, the desired product was not obtained.



not obtained

A ^{1}H NMR of the product that was actually obtained from the reaction is shown below. Identify its structure.



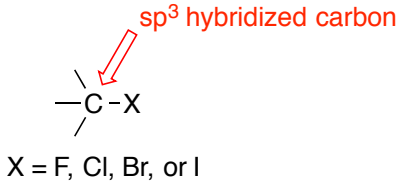
Chapter 7: Substitution and Elimination—Reactions of Alkyl Halides and Alcohols

Section 1: Alkyl halides
Section 2: Introduction to nucleophilic substitution reactions
Section 3: The S_N1 Reaction
Section 4: The S_N2 Reaction
Section 5: Alkenes
Section 6: Introduction to elimination reactions
Section 7: The E1 Reaction
Section 8: The E2 Reaction
Section 9: Deciding Between S_N1, S_N2, E1, and E2 Pathways
Section 10: Planning organic syntheses

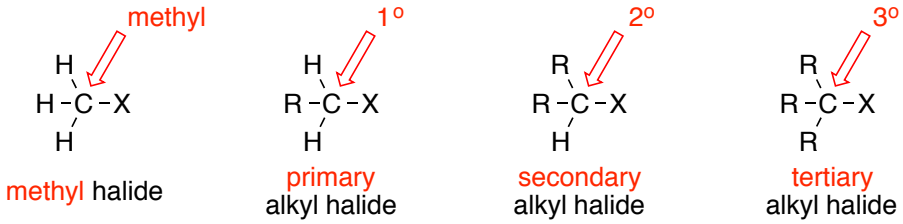
Section 1: Alkyl halides

Classification

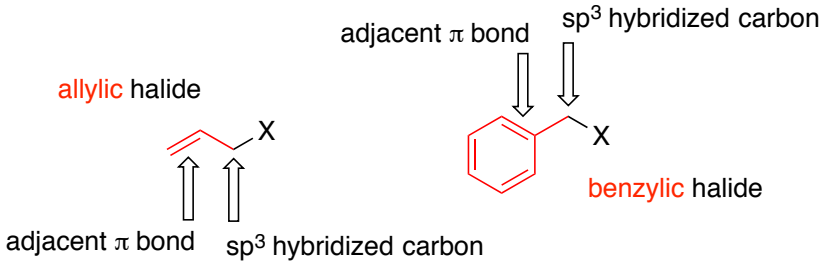
Alkyl halides contain a bond between an sp^3 hybridized carbon and a halogen.



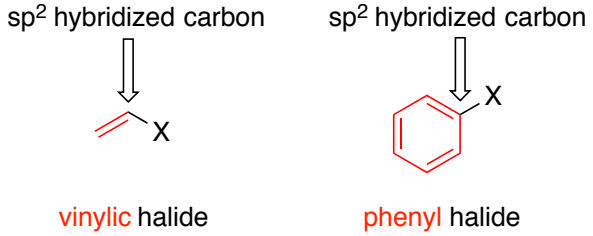
Alkyl halides can be subdivided into four categories (methyl, primary, secondary, and tertiary) based on the level of substitution of the carbon bearing the halogen.



Allylic and benzylic halides are a special subset of organohalides in which the halogen is bonded to an sp^3 hybridized carbon, but that carbon happens to be adjacent to a π bond. This affects their reactivity, as we'll see later in this chapter.

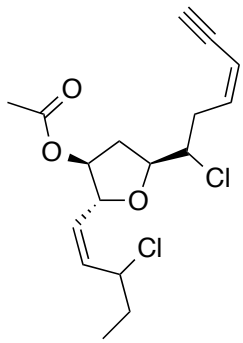


Vinylic and phenyl halides differ from all of the classifications above in that the halogen is bonded to an sp^2 hybridized carbon. As we'll see later in this chapter, this makes them unreactive in some of the types of reactions we'll be studying.



Problem 1. The following halogenated molecules were isolated from marine algae.[1] Some of them have promising antitumor or antimicrobial activity. Classify the halides in each molecule.

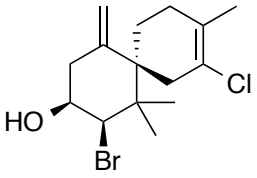
(a)



an acetogenin en-yne

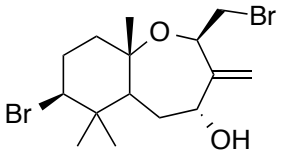
(b)

[1] Cabrita, M. T.; Vale, C.; Rauter, A. P. "Halogenated Compounds from Marine Algae," *Marine Drugs* **2010**, *8(8)*, 2301–2317.



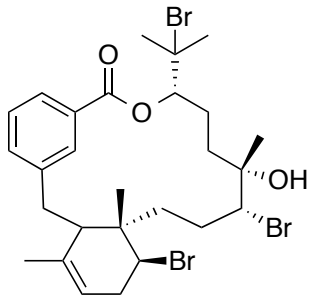
elatol

(c)



4-hydroxypalisadin C

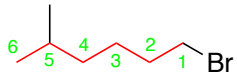
(d)



bromophycolide O

IUPAC nomenclature

Alkyl halides are named systematically as haloalkanes. In other words, *the halogen is treated just as any other substituent would be*. The substituent names for the halogens are: fluoro, chloro, bromo, and iodo. They appear, along with a locant, prior to the parent name. All of the rules of IUPAC nomenclature that we learned in previous chapters apply here as well.

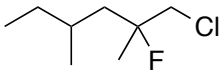


1-bromo-5-methylhexane

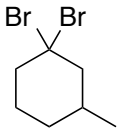
- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

Problem 2. Provide an IUPAC name for the following haloalkanes.

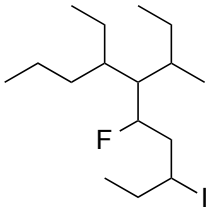
(a)



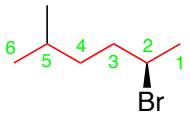
(b)



(c)



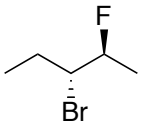
When stereochemistry arises, the Cahn-Ingold-Prelog rules allow us to assign the configuration.



(*R*)-2-bromo-5-methylhexane

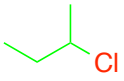
- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number = tie
- Number so as to give the second substituent the lowest possible number = tie
- Number so as to give the alphabetically first substituent the lowest possible number
- Add substituent names and numbers
- Add stereochemical designation

Problem 3. Provide a complete IUPAC name for the following compound.



Common nomenclature

Haloalkanes can also be given common names using the motif "alkyl halide." In other words, the name of the alkyl group is placed before the name of the halide to which it is attached. The halide names are: fluoride, chloride, bromide, and iodide.



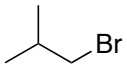
sec-butyl chloride

isopropyl fluoride

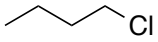
Problem 4. Provide common names for the following alkyl halides.

(a)

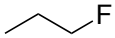
(b)



(c)



(d)

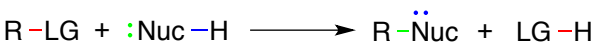


Section 2: Introduction to nucleophilic substitution reactions

The overall nucleophilic substitution reaction

In nucleophilic substitution, a nucleophile (Nuc) replaces a leaving group (LG) on an sp^3 hybridized carbon. The nucleophile may be negative.

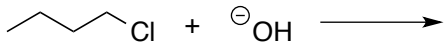
Or, the nucleophile may be neutral.



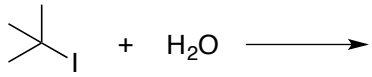
The schemes above only show the reactants and the products. They do not reveal anything about the mechanism of the reaction. It turns out that nucleophilic substitution can occur via two different mechanisms.

Problem 5. Given the generic reaction paradigms above, predict the products of the following reactions.

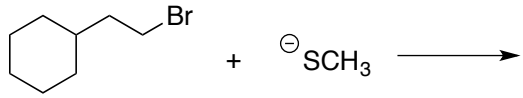
(a)



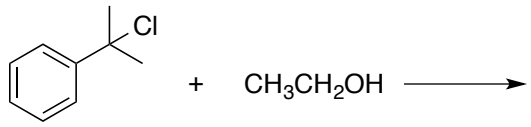
(b)



(c)

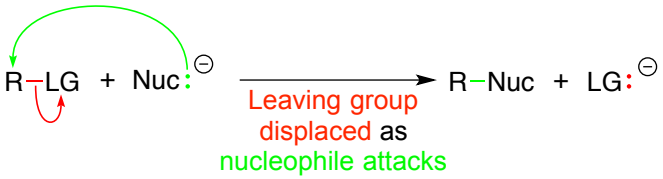


(d)

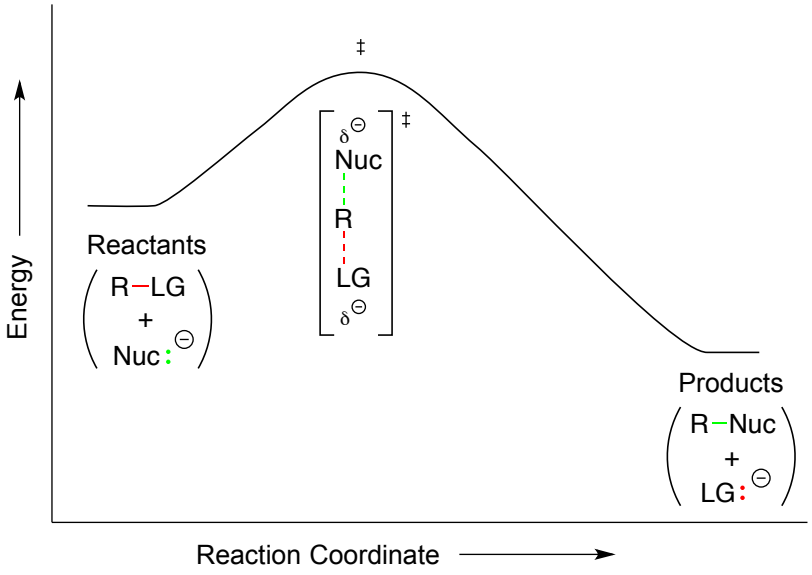


The two mechanisms for nucleophilic substitution

One mechanism for nucleophilic substitution is concerted. This means that all of the bond making and breaking happens simultaneously. In this case, the carbon-to-leaving group bond is broken as the carbon-to-nucleophile bond is formed.

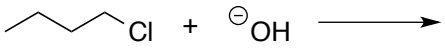


This sort of nucleophilic substitution is a single-step process. The transition state for this step would include a partially formed carbon-to-nucleophile bond and a partially broken carbon-to-leaving group bond.

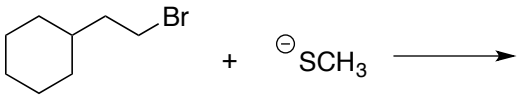


Problem 6. Draw mechanisms for the following concerted reactions that we saw in Problem 5.

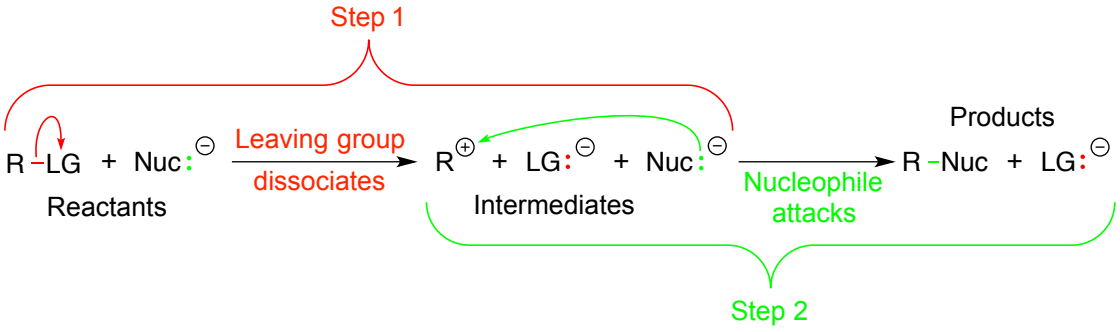
(a)



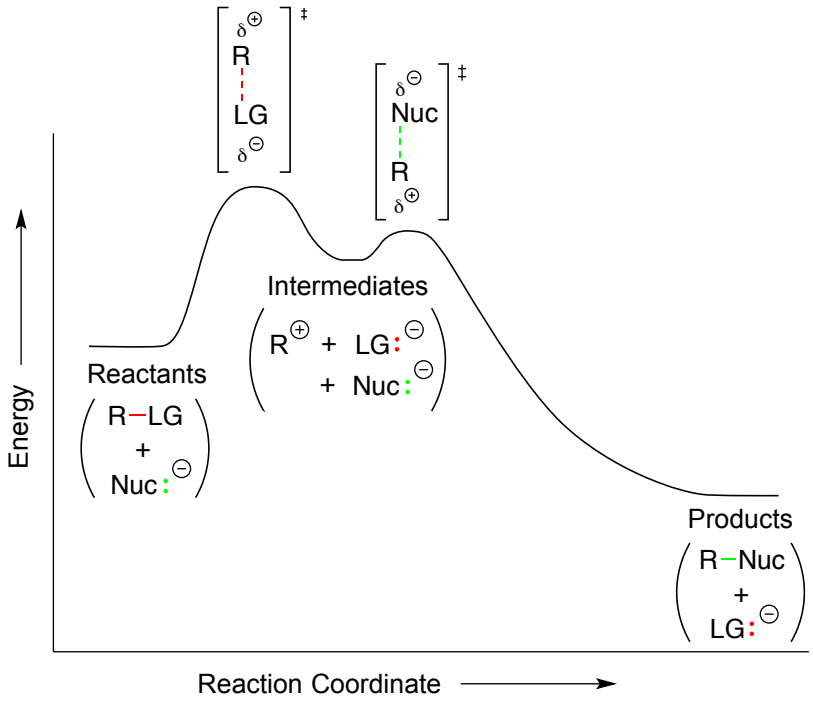
(b)



A second mechanistic possibility is that the bond making and breaking can happen in a stepwise fashion. We cannot simply add the nucleophile in the first step because this would lead to a carbon that exceeds the octet. However, in the first step of the reaction, the leaving group could be lost. This would result in the formation of a carbocation intermediate. Then, in step 2 of the reaction the nucleophile would add to the carbocation to generate the products.

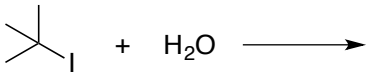


This two-step process has two transition states, one for each step. The transition state for step 1 has a partially dissociated carbon-to-leaving group bond. The transition state for the second step has a partially formed carbon-to-nucleophile bond.

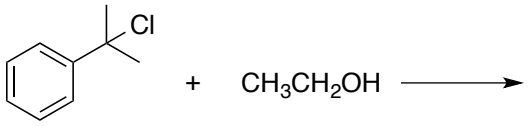


Problem 7. Draw mechanisms for the two stepwise reactions that we encountered in Problem 5. Note that, since the nucleophiles in these reactions are neutral, there will be one extra step at the end of the mechanism in which a proton is lost to neutralize the substitution product.

(a)



(b)

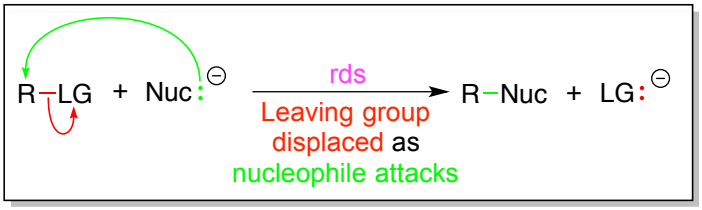


Which mechanism is at play: rate laws

We can acquire experimental evidence to suggest which mechanism is relevant for a specific nucleophilic substitution reaction. The rate of a reaction is dependent upon the

concentration of those species that are *mechanistically* involved in the rate-determining step. This dependence can be expressed in a rate law.

In a concerted nucleophilic substitution, there is only one step, so this must be the rate-determining step (rds). Notice that there are mechanistic arrows showing the involvement of both the substrate (R-LG) and the nucleophile ($Nuc:^-$) in this step. Therefore, the rate is equal to a rate constant (k) multiplied by the concentrations of both the substrate and the nucleophile. The rate constant encapsulates factors such as the percentage of collisions between reactant molecules that lead to productive reaction.



Rate = k [R-LG] [$Nuc:^-$]

When writing rate laws, each concentration term is raised to a power:

Rate = k $[R\text{-}LG]^x$ $[Nuc:^-]^y$

If the mechanism is known, then it can be used to determine x and y. They are the number of each molecule involved in the mechanism of the rate-determining step. In other words, one substrate molecule is attacked by one molecule of the nucleophile, so the rate law is:

Rate = k $[R\text{-}LG]^1$ $[Nuc:^-]^1$

or simply:

Rate = k [R-LG] [$Nuc:^-$]

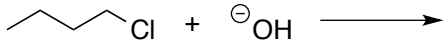
If the mechanism of a reaction is unknown, it can be experimentally determined. In this case, if we double the concentration of either reactant, the rate of the reaction will double. Furthermore, if we double the concentration of both reactants, the rate of the reaction will quadruple. The mathematical expression that captures these results is the rate law written above.

The concerted nucleophilic substitution can also be referred to as a second-order reaction. This name stems from the rate law. The order of a reaction is the sum of the exponents of the concentration terms in the rate law. In the diagram below, the implied exponents of 1 are shown for clarity.

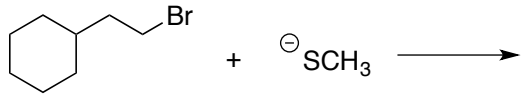
Rate = k $[R\text{-}LG]^1$ $[Nuc:^-]^1$
Sum of exponents of concentration terms = 1 + 1 = 2
Therefore, second-order reaction

Problem 8. We've now written mechanisms (in Problem 6) for the two concerted reactions that were introduced in Problem 5. Knowing that these are second-order reactions, explain the outcome of the following changes in concentration of the reactants.

(a) The concentration of the alkyl chloride is doubled and the concentration of hydroxide is tripled.

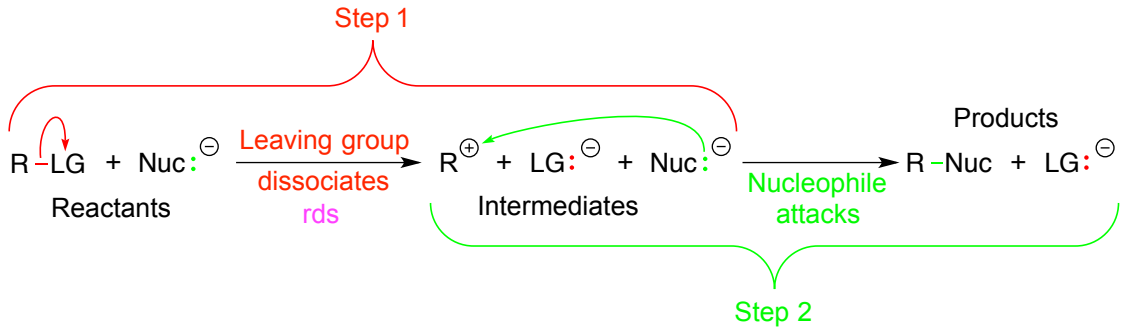


(b) The concentration of both the alkyl bromide and the thiolate is tripled.



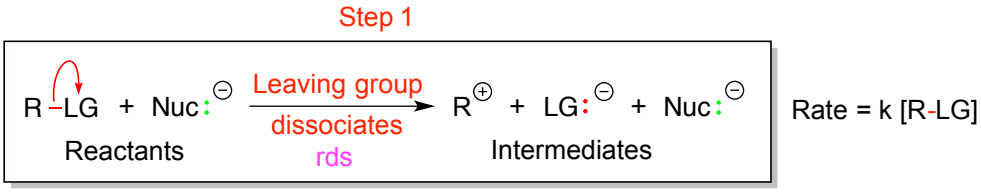
In stepwise nucleophilic substitution, it is not as obvious what the rate-determining step is. The rate-determining step is the slowest step of a chemical transformation. As such, *the overall rate of the reaction cannot be faster that the rate of this step*. It can be thought of as the bottleneck in a chemical reaction. It stands to reason that the slowest step will also be the most energetically demanding one. In other words, it is the hardest step to accomplish.

Let's look at the two steps of stepwise nucleophilic substitution through this lens. All atoms of the reactants begin with a complete octet, but during the first step of the reaction, a carbon atom loses the octet as it becomes a carbocation. This will definitely be energetically demanding; depriving a carbon atom of the octet will not be favorable. On the other hand, the second step of the reaction returns the octet to all atoms. This should be a facile process. This analysis has revealed that it is the dissociation of the leaving group that is the rate-determining step (rds) for this process.



When determining the rate law, we need only consider the rate-determining step, so we can now focus solely on step 1. In step 1, only the substrate (R-LG) is *mechanistically* involved. In other words, the mechanistic arrows include the substrate only, making the nucleophile merely a bystander in this step. Therefore, the rate of the reaction depends on the concentration of the substrate alone. This is counterintuitive for many students who

feel that the concentration of the nucleophile must matter since the nucleophile is part of the reaction's second step. The justification for the rate law we are writing is that the second step of the reaction, being much more favorable, is so fast relative to the first step that it is irrelevant in terms of the speed of the reaction. Getting through the first step is the slow part of the process. Once that has happened, everything else occurs very quickly. So, we focus only on the species *mechanistically* involved in the rate-determining step.

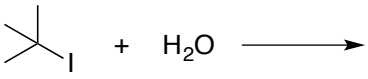


Based on this rate law, we can say that stepwise nucleophilic substitution is a first-order reaction. There is only one concentration term, and its exponent is 1 because only a single molecule of substrate is implicated. If this mechanism is indeed at play, we can go into the laboratory and double the concentration of the substrate, and we'll expect to see a doubling of the reaction rate. However, if we instead double the concentration of the nucleophile, we'll observe no alteration of the reaction rate.

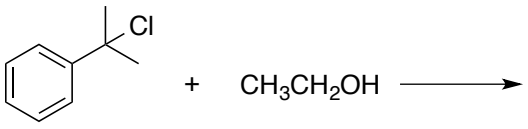
Rate = k [R-LG]^1
Sum of exponents of concentration terms = 1
Therefore, first-order reaction

Problem 9. In Problem 7, we drew mechanisms for the two first-order reactions that were introduced in Problem 5. Now that we better appreciate the kinetics of these reactions, describe the impact on rate made by each of the following changes.

(a) The concentration of the alkyl iodide is unaltered, but the concentration of water is doubled.



(b) The concentration of both species is tripled.



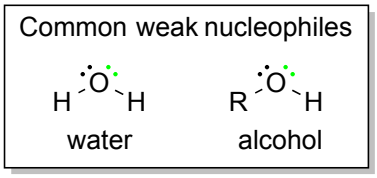
Now that we've seen how empirical evidence can tell us which mechanism is at play for a given reaction, let's turn our attention to factors that will allow us to predict the mechanism.

Factors that impact the reaction mechanism

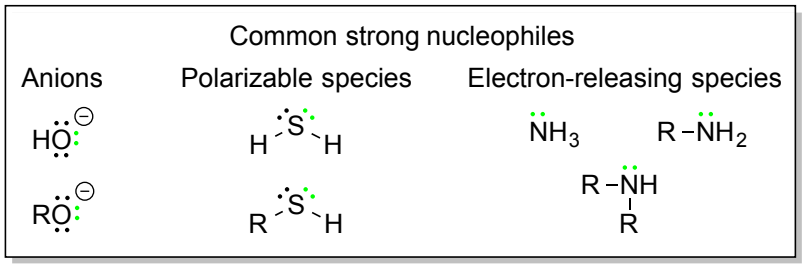
(1) The nucleophile

Notice that the substrate (R-LG) is always mechanistically involved in the rate-determining step. First- and second-order reactions are differentiated by whether or not the nucleophile is *mechanistically* involved in the rate-determining step. Therefore, the strength of the nucleophile helps us determine whether a first- or second-order mechanism occurs.

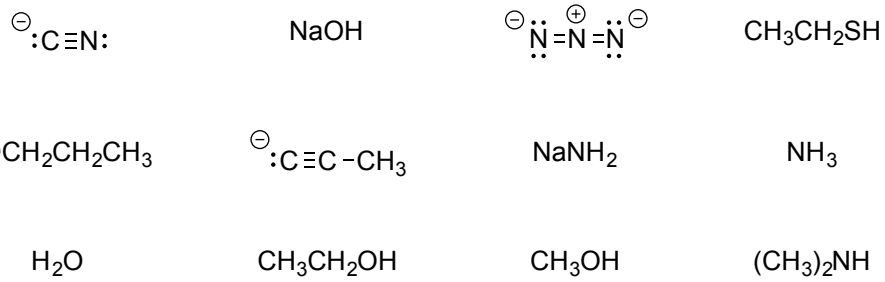
A weak nucleophile is unlikely to be involved in the rate-determining step, leading to a first-order reaction. Its relative stability makes it reluctant to engage in the transformation until a powerfully electrophilic carbocation draws it into the reaction. Weak nucleophiles tend to be neutral, although not all neutral compounds are weakly nucleophilic. The most common weak nucleophiles are water and alcohols.



On the other hand, strong nucleophiles are, by definition, highly reactive. These powerful nucleophiles are very likely to engage in the rate-determining step, leading to a second-order reaction. Strong nucleophiles include anions (other than F^-). Additionally, larger atoms have more polarizable electron clouds. This allows them to begin to form a bond to a substrate from a greater distance. As a result, these polarizable species, such as hydrogen sulfide (H_2S) or thiols (RSH), are also strong nucleophiles. Finally, electron-releasing neutral species include atoms that have lone pairs but do not have exceptionally high electronegativity, such as ammonia (NH_3) or amines (e.g., RNH_2, R_2NH). These compounds will share their lone pairs with electrophiles fairly readily, making them potent nucleophiles.



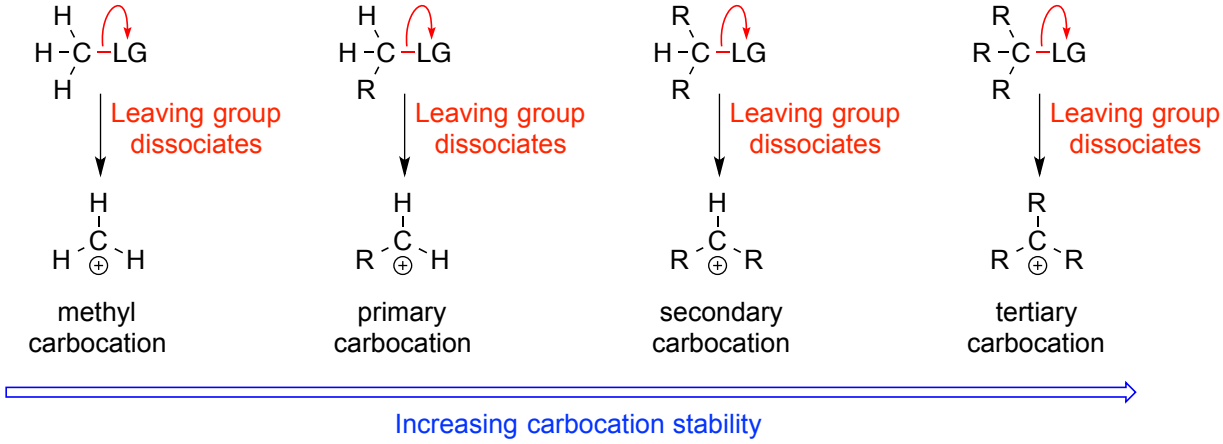
Problem 10. Classify the following nucleophiles as weak or strong.



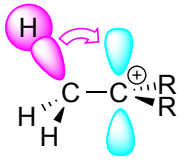
(2) The substrate

The substrate (R-LG) also wields tremendous influence over the mechanism. In a first-order reaction, dissociation of the leaving group leads to the formation of a carbocation intermediate. The substitution of the carbocation impacts its stability, and the more stable the carbocation intermediate, the more likely it is to form.

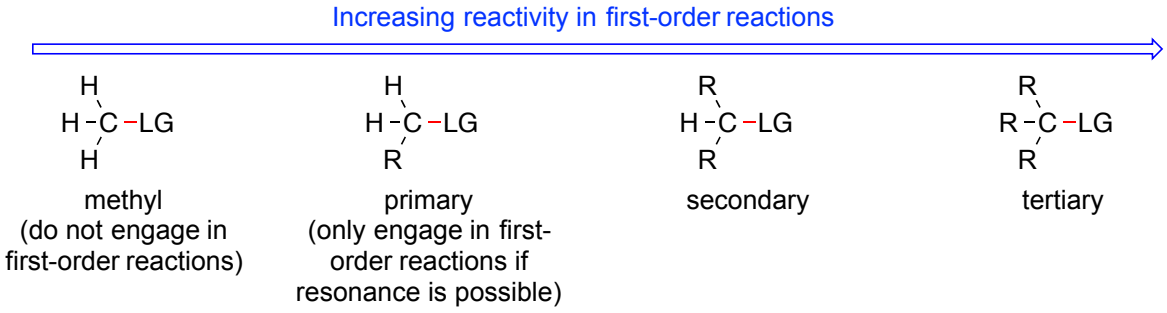
Alkyl groups are electron donating and therefore stabilize the electron-deficient carbocation. Consequently, the more alkyl groups a carbocation has the more stable it is. Tertiary carbocations are the most stable, while methyl carbocations are the least stable.



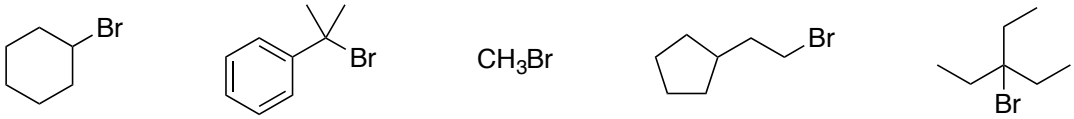
The fundamental reason that alkyl groups are electron donating is hyperconjugation. This term describes the partial overlap of a sigma bond with an adjacent p orbital. When a carbocation bears an alkyl group, such as methyl in the diagram below, there are conformations in which a σ bond lies in the same plane as the empty p orbital of the carbocation. In this conformation, the σ bond can donate some electron density to the carbocation, thereby alleviating its electron deficiency. The overlap is not as efficient as it is with a π bond, in which the adjacent orbitals are parallel, but it does stabilize the carbocation to some extent.



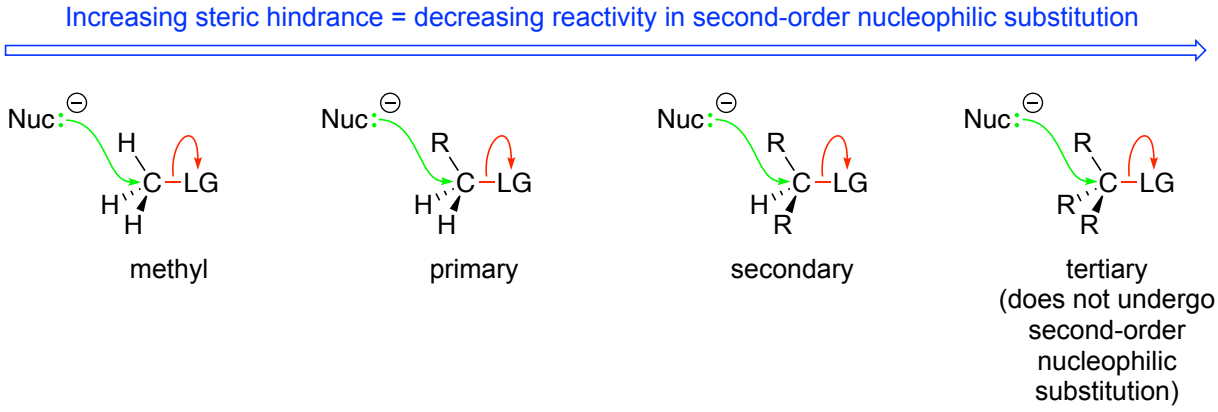
Knowing that tertiary carbocations are the most stable carbocations, we can say that tertiary alkyl halides are the substrates most likely to engage in a first-order reaction. As the substitution decreases so does the likelihood of participating in a first-order mechanism. In fact, primary and methyl halides do not go through first-order pathways unless there is a special source of stabilization, such as resonance.



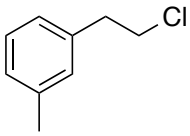
Problem 11. Rank the following substrates from most reactive to least reactive in a first-order substitution reaction.

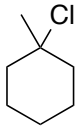


In a second-order reaction, the nucleophile attacks the electrophilic carbon of the substrate and actively displaces the leaving group. This process is sensitive to steric hindrance. In other words, the nucleophile must be able to physically approach the electrophilic center. The more alkyl groups there are surrounding that center, the more difficult this becomes. As a result, methyl and primary alkyl halides are ideal substrates for second-order nucleophilic substitution, as they have the least steric hindrance. Secondary alkyl halides, having a moderate amount of steric hindrance, can still undergo second-order substitution. However, tertiary alkyl halides have too much crowding around the electrophilic carbon of the substrate. This blocks the approach of the nucleophile, and we say that these tertiary substrates are too sterically hindered to undergo second-order nucleophilic substitution.

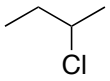


Problem 12. Rank the following substrates from least reactive to most reactive in second-order substitution reactions.



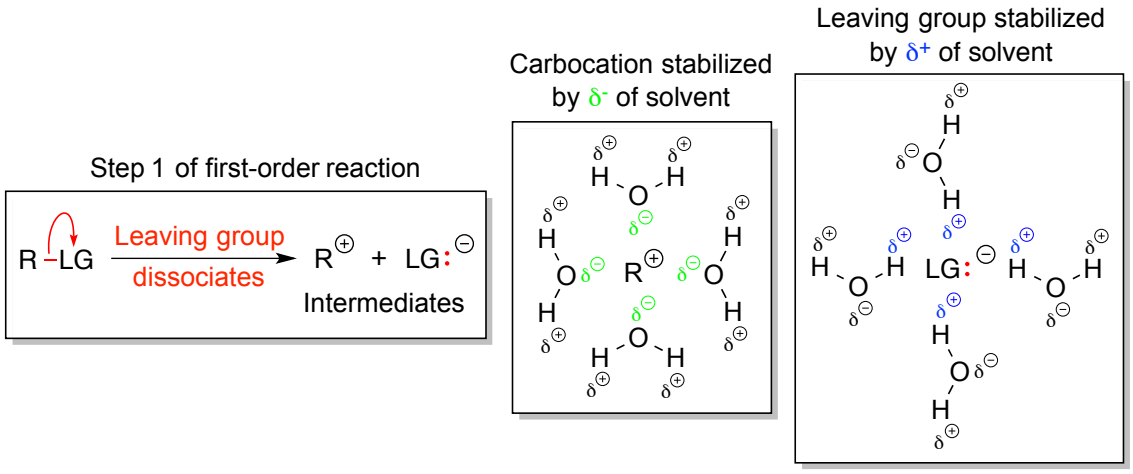


CH_3Cl

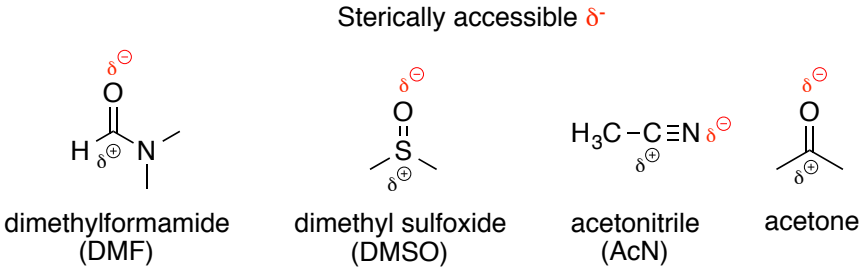


(3) The solvent

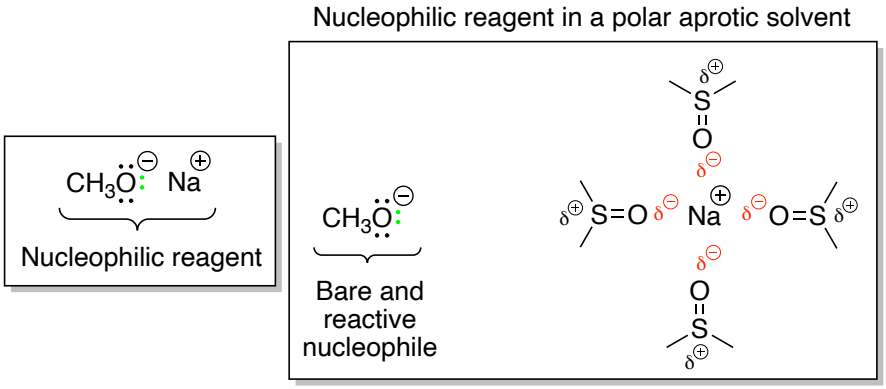
There are two principal kinds of solvents used in nucleophilic substitution reactions, and they favor different mechanisms. Polar protic solvents are one type. These are solvents containing a heteroatom-to-hydrogen bond: most commonly water or alcohols. Polar protic solvents have partial positive and partial negative charges that are sterically accessible. As a result, they are able to stabilize both the cations and anions formed when the substrate dissociates in step 1 of a first-order mechanism.



In contrast to polar protic solvents, there are polar *aprotic* solvents. These are solvents that contain polar bonds but lack a heteroatom-to-hydrogen bond. Some examples include dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (AcN), and acetone. These solvents contain a δ^- on the periphery of the molecule that is therefore sterically accessible; however, the δ^+ is on the interior of the molecule and is less accessible to other compounds.

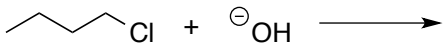


The consequence of these features is that polar aprotic solvents are able to stabilize cations (through association with the solvent's δ^-) but not anions. As a result, polar aprotic solvents strip away the cation from the reagent, leaving it bare and more reactive. This facilitates second-order reactions, which require a strong nucleophile.

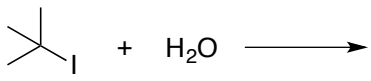


Problem 13. Select an appropriate solvent for each of the reactions below, which we first encountered in Problem 5.

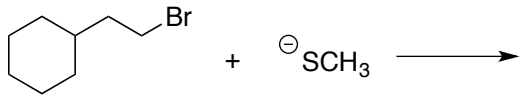
(a)



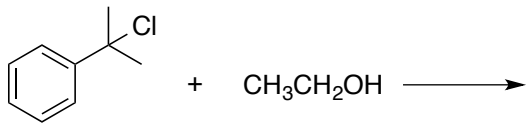
(b)



(c)

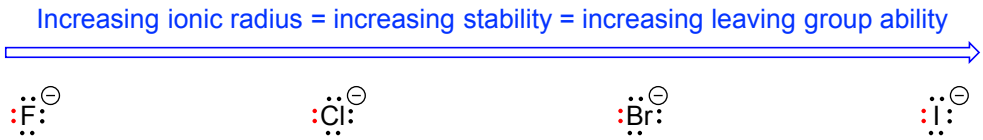


(d)



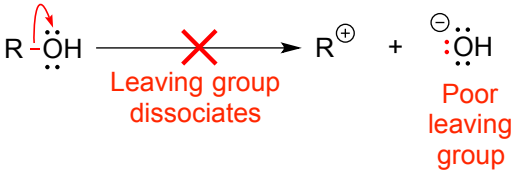
(4) The leaving group

Both first- and second-order processes require a good leaving group. The halides can serve as leaving groups, and as the halide grows larger, its leaving group ability improves because a larger ion is able to disperse—and therefore better stabilize—its charge. Consequently, fluoride is not a very good leaving group, but chloride, bromide, and iodide are good leaving groups, with iodide being the best.

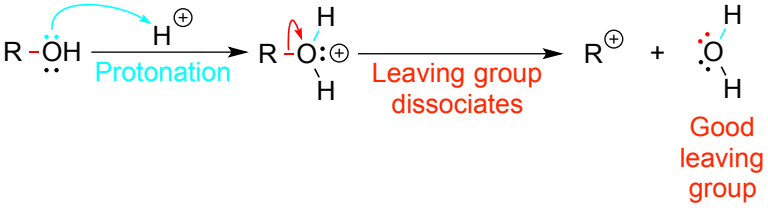


Problem 14. Rank the following substrates in order of increasing reactivity in substitution reactions.

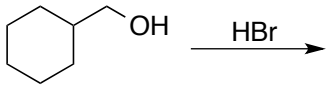
Alcohols can also be reactive in nucleophilic substitution, but they do not possess an inherently good leaving group. Hydroxide is too reactive to function as a good leaving group in either first- or second-order processes.



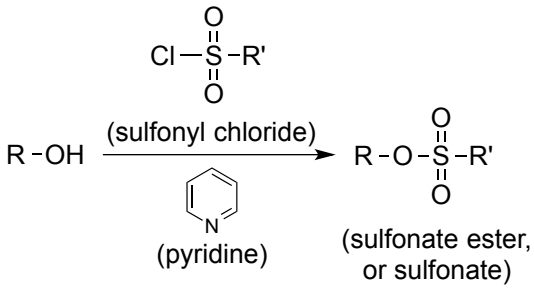
As a result, the hydroxyl group must be converted to a good leaving group before alcohols can engage in nucleophilic substitution. There are two common approaches to this. In the first, the hydroxyl group is merely protonated. This changes the leaving group from hydroxide to water. Water is more stable and is therefore a much better leaving group.



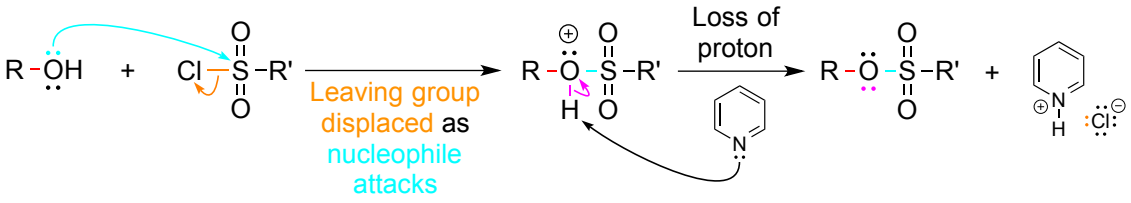
Problem 15. Propose a mechanism for the following substitution reaction.



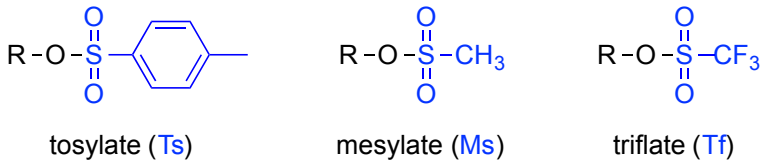
The other option for converting the hydroxyl group into a good leaving group is the formation of a sulfonate ester, which is often simply called a sulfonate. This requires treatment with a sulfonyl chloride and pyridine.



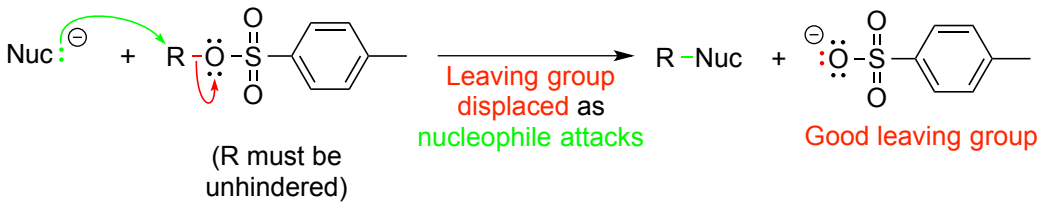
The reaction begins with the attack of the hydroxyl group on the electrophilic sulfur of the sulfonyl chloride. Chloride is displaced as a result. Then, pyridine serves as a base and removes the proton from the oxonium ion to yield the sulfonate.



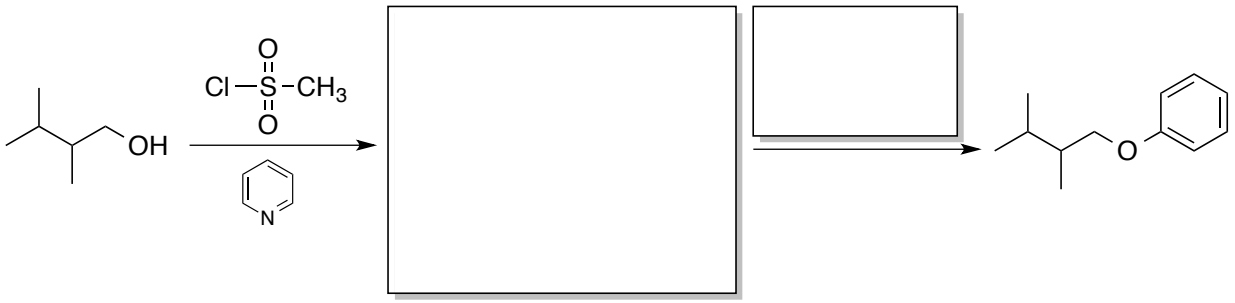
There are a variety of sulfonates that differ only in the identity of the R' group. Three common examples are the tosylate, mesylate, and triflate. Their abbreviations (Ts, Ms, and Tf, respectively) can be used in place of the structures of these groups.



Sulfonates serve as good leaving groups because the oxyanion is resonance stabilized. Its negative charge can be delocalized onto the other two oxygens of the sulfonate. The example below is shown as a second-order reaction, in which the R group of the substrate would have to be unhindered (i.e., not tertiary).

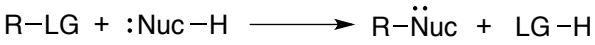


Problem 16. Fill in the missing intermediate and reagent in the following sequence.



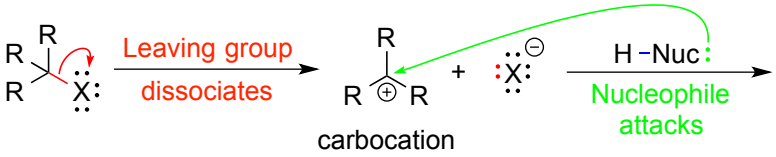
Section 3: The S_N1 Reaction

A first-order nucleophilic substitution reaction is known as an S_N1 reaction. S_N1 reactions employ a weak nucleophile. While there are weak anionic nucleophiles (e.g., fluoride), most are strong, so it is more common to see a first-order nucleophilic substitution with a neutral nucleophile.



Mechanistic considerations

A good leaving group, such as a halide (X^-), a sulfonate ($^-$OTs, $^-$OMs, or $^-$OTf), or water, dissociates from a secondary, tertiary, allylic, or benzylic center. The resulting carbocation is attacked by a weak nucleophile (typically water or an alcohol), and the oxonium ion then loses a proton to yield a neutral product.



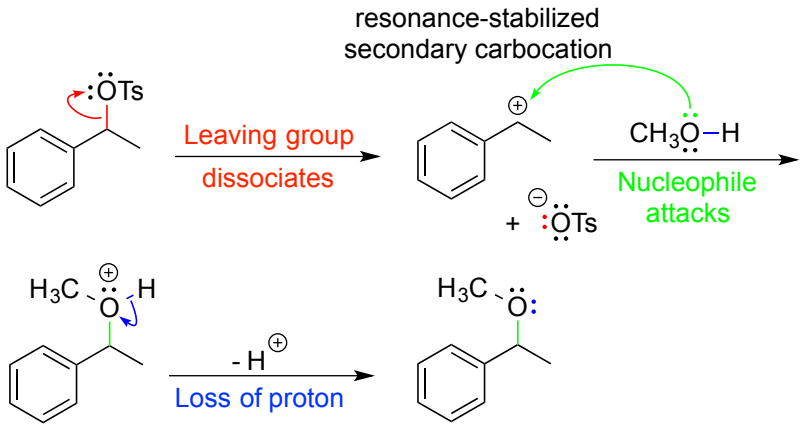
Loss of leaving group is the rate-determining step, so the reaction rate depends only on the concentration of the substrate (Rate = k [R-LG]), making it a first-order process.

Note that, while most weak nucleophiles are neutral, some are negatively charged, in which case the final mechanistic step (loss of proton) would not be necessary.

A specific example of the S_N1 reaction

In the following reaction, the tosylate first dissociates from the secondary, benzylic center. This affords a carbocation that is both secondary and resonance stabilized. It is

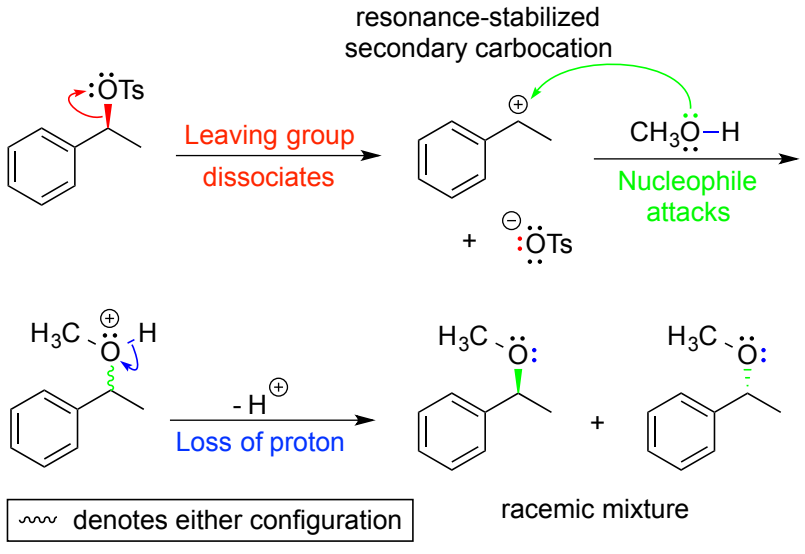
subsequently attacked by methanol, which then loses a proton to yield the ether as the final product of the reaction.



When the nucleophile is water or an alcohol, it is commonly used in a large excess. This allows it to serve not only as the reagent but also as a polar protic solvent, which facilitates this first-order reaction.

Stereochemical considerations

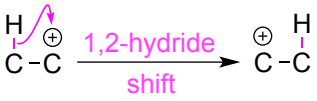
Although we did not initially consider stereochemistry in the preceding reaction, we can revisit the transformation using a single enantiomer of the substrate. When the tosylate dissociates, the stereochemistry is lost because the carbon atom rehybridizes from sp^3 (tetrahedral) to sp^2 (trigonal planar). The nucleophile can attack either side of the trigonal planar (i.e., flat) carbocation to yield both configurations. The product is therefore a racemic mixture of enantiomers.



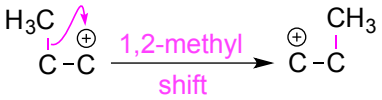
Carbocation rearrangement

Since S_N1 reactions involve carbocation intermediates, we need to be aware of a process known as carbocation rearrangement, which enables carbocations to migrate to *adjacent* centers under certain circumstances. There are three types of carbocation rearrangement:

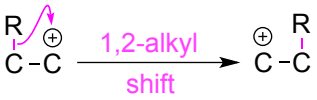
(1) A 1,2-hydride shift involves the migration of a proton with its σ bonding electrons to the adjacent atom.



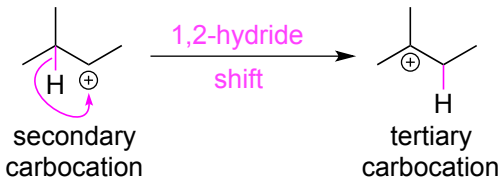
(2) A 1,2-methyl shift entails the migration of a methyl group with its σ bonding electrons to the neighboring center.



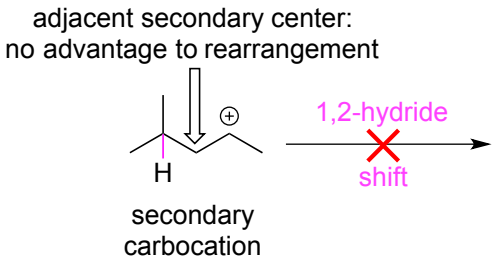
(3) A 1,2-alkyl shift is very similar to a 1,2-methyl shift. The only difference is that an alkyl group migrates with its σ bonding electrons.



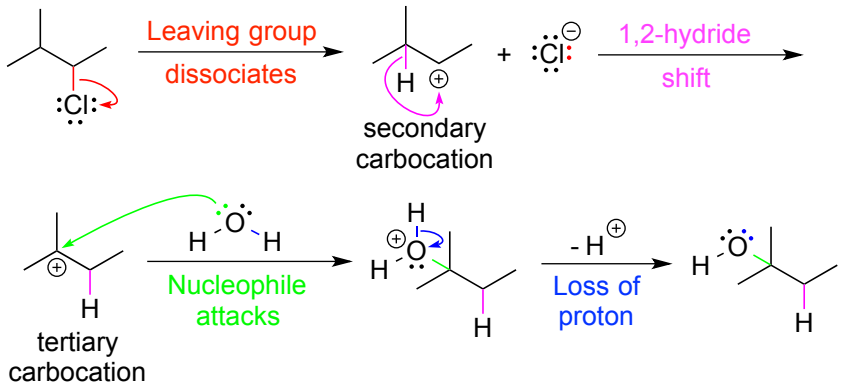
Carbocation rearrangement occurs if, and only if, there is an *immediate* increase in stability as a result of the migration. For instance, a rearrangement that allows a secondary carbocation to become a tertiary carbocation will occur because the molecule's stability is enhanced as a result of the shift.



A hydride, methyl, or alkyl group can only migrate to an *adjacent* atom. And, there must be an *immediate* payoff in terms of stability. For example, the following secondary carbocation cannot rearrange. There is a tertiary center in the molecule, but it is not adjacent to the carbocation. Furthermore, migration of the secondary carbocation to the adjacent secondary center would have no energetic benefit.



Since S_N1 reactions always involve carbocation intermediates, carbocation rearrangement will sometimes occur if the criteria described above are met. In the following example, the reaction is initiated by the dissociation of chloride. This affords a secondary carbocation, which happens to reside next to a tertiary center. A 1,2-hydride shift leads to the formation of a more stable tertiary carbocation to which the nucleophile then adds. Finally, the loss of a proton yields a product in which the hydroxyl group can be found at an unexpected location. Normally, the nucleophile replaces the leaving group where it stands. However, carbocation rearrangements can lead to alternative connectivity.

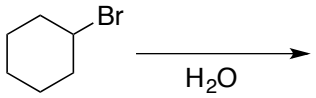


It is possible for the nucleophile to attack the secondary carbocation before it has a chance to rearrange. But, intramolecular processes (like the hydride shift) are typically fast in comparison to their intermolecular counterparts (such as nucleophilic attack), so the major product of the reaction results from the rearrangement.

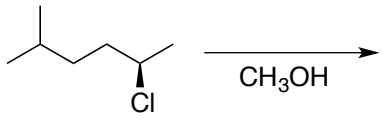
In summary, efficient S_N1 reaction requires a stable carbocation, so it does not occur with primary substrates, unless they are resonance stabilized (e.g., allylic or benzylic). A weak nucleophile is also a key feature of the reaction. Weak nucleophiles include water, alcohols, and fluoride. Stereochemistry is randomized at the reactive site, and carbocation rearrangement is possible.

Problem 17. Predict the products of the following S_N1 reactions.

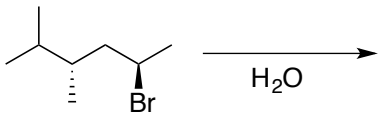
(a)



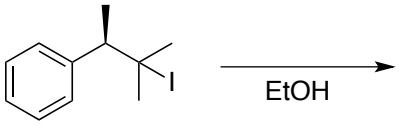
(b)



(c)

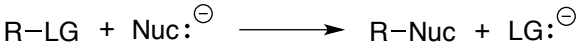


(d)

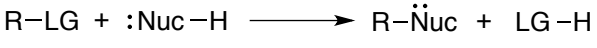


Section 4: The S_N2 Reaction

A second-order nucleophilic substitution reaction is known as an S_N2 reaction. S_N2 reactions employ a strong nucleophile. Strong nucleophiles are often negatively charged, in which case the S_N2 reaction follows the motif below.

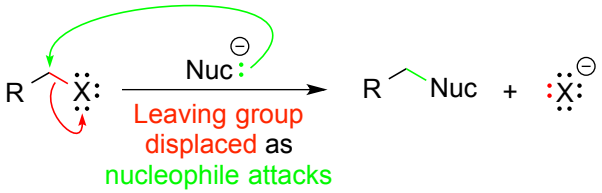


However, as we saw earlier in this chapter, some neutral species can also be strong nucleophiles. These include polarizable nucleophiles (e.g., H_2S, RSH) and electron-releasing nucleophiles (e.g., NH_3, RNH_2, R_2NH). In these cases, the reaction takes the following form.



Mechanistic considerations

In the S_N2 mechanism, a good leaving group, such as a halide (X^-) or a sulfonate ($^-$OTs, $^-$OMs, or $^-$OTf), is displaced from an unhindered carbon by the concurrent attack of a strong nucleophile.

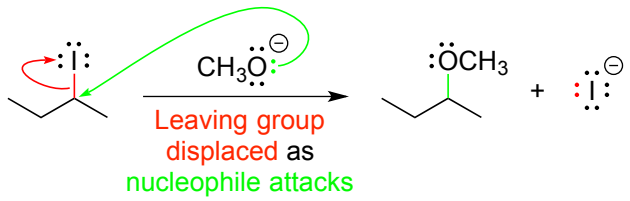


The rate-determining step involves both the substrate and the strong nucleophile, so the reaction rate depends on the concentration of both species (Rate = k [R-LG] [Nuc:$^-$]), making this a second-order process.

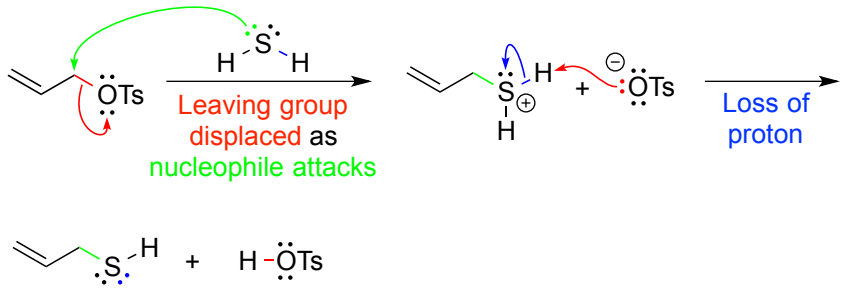
When a neutral strong nucleophile is used, one additional mechanistic step (loss of proton) is necessary.

Specific examples of the S_N2 reaction

S_N2 reaction does not occur on tertiary centers because they are too hindered to allow the nucleophile to approach the electrophilic carbon. However, secondary centers can undergo S_N2 reaction, as shown in the following example. The nucleophile (methoxide) attacks the electrophilic carbon of the substrate, concurrently displacing iodide.



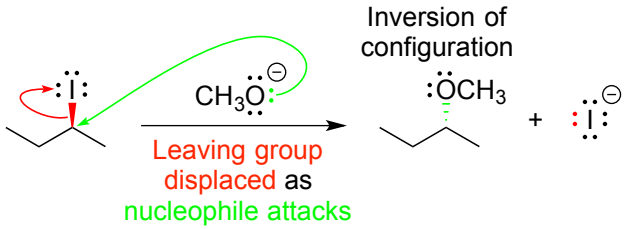
When the strong nucleophile happens to be neutral—as in the following instance—then an additional mechanistic step (loss of proton) is needed at the end of the reaction to show how the neutral product is formed.



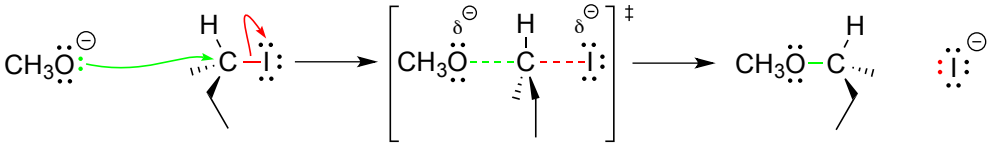
Stereochemical considerations

Since S_N2 reaction can occur at secondary centers, the reactive site may be a stereocenter. Let's revisit our first example above, using a single enantiomer of the substrate. Attack of the nucleophile occurs directly opposite (180° from) the leaving group, which results in inversion of configuration. Only a single enantiomer of the product is formed. This type of

reaction can be called stereospecific. In a stereospecific process, a particular stereochemistry of the substrate leads to a particular stereochemistry of the product.



This inversion of configuration is easier to understand when we consider the physical process of actively displacing the leaving group. As the nucleophile approaches directly opposite the leaving group, it works its way inside the "umbrella" of substituents surrounding the electrophilic carbon. As the new carbon-to-nucleophile bond begins to form and the carbon-to-iodine bond begins to break, the substituents on the electrophilic carbon flatten out in an sp^2-like transition state (‡). As the reaction completes and the carbon-to-nucleophile bond is fully established, the "umbrella" of substituents around the electrophilic center has inverted, much like an actual umbrella can on a windy day. This process may also be referred to as a Walden inversion.

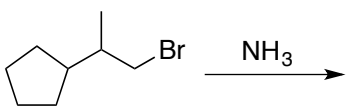


In conclusion, S_N2 reaction is a concerted process in which the nucleophile attacks at the same time as the leaving group is lost. This necessitates both an unhindered electrophilic carbon (methyl, primary, or secondary) and a strong nucleophile. Strong nucleophiles include most anions (other than F^-) as well as polarizable species—such as hydrogen sulfide (H_2S) or thiols (RSH)—and electron-releasing neutral species—such as ammonia (NH_3) or amines (e.g., RNH_2, R_2NH).

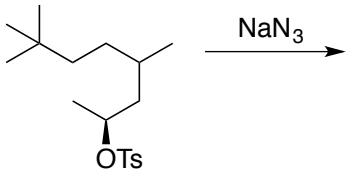
The concerted nature of the reaction results in stereospecificity. In other words, the configuration of the reactive center is specifically inverted; whereas, in S_N1 reaction the configuration of the reactive center is racemized. Another consequence of the concerted mechanism is the absence of a carbocation intermediate. Therefore, while S_N1 reaction may involve carbocation rearrangement, S_N2 reaction cannot.

Problem 18. Predict the products of the following S_N2 reactions.

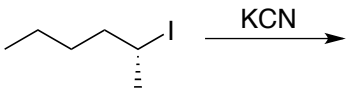
(a)



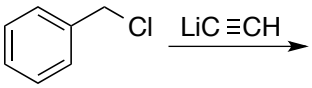
(b)



(c)



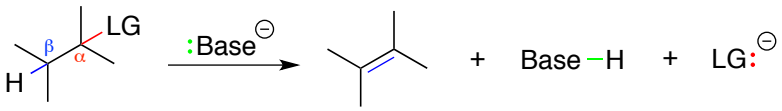
(d)



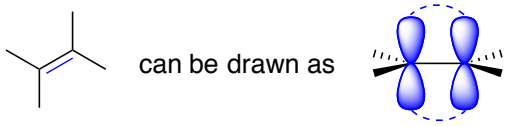
Section 5: Alkenes

Restricted rotation

Thus far, we've learned about substitution reactions in which a leaving group on carbon is replaced by a nucleophile. An entirely different reaction paradigm is elimination. In elimination reactions, the reagent acts as a base. It removes a proton from the β-carbon (i.e., the position adjacent to the functionality), and a leaving group is lost from the α-carbon (i.e., the functionalized carbon). The net result is the formation of an alkene. Alkenes are also referred to as olefins.

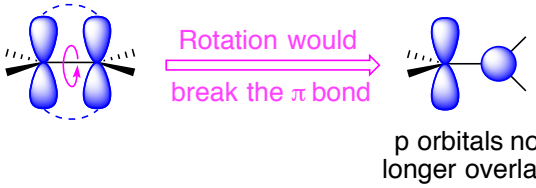


Chapter 10 is all about alkenes, their properties, and their reactions. For the moment, we need to understand just a bit about the bonding in alkenes to appreciate the nuances of elimination reactions. The π bond of an alkene is formed by the overlap of adjacent p orbitals that are parallel to one another.

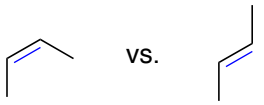


Since a π bond is a component of a double bond, there is restricted rotation about double bonds. In other words, you cannot rotate one carbon relative to the other because doing so

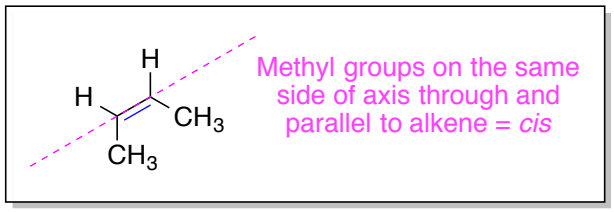
would break the π bond since the p orbitals would no longer be parallel. We saw in Chapter 3 that alkanes can experience free rotation about their σ bonds. Those conformational changes occur readily because they incur no change in the chemical structure. However, if an alkene is rotated about its double bond, the π bond would actually be broken, making this a chemical reaction rather than a conformational change.

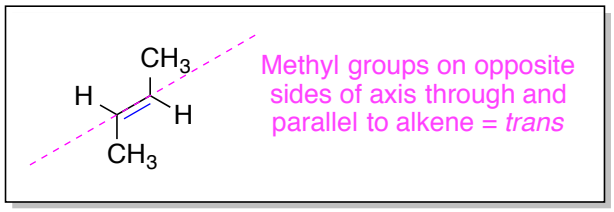


The consequence of this restricted rotation is a form of stereoisomerism known as geometric isomerism. To highlight this phenomenon, let's consider the following molecules. These are isomers that differ not in the connectivity of the atoms but in the geometry about the double bond.



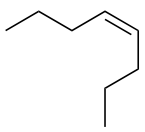
In the first molecule, the methyl groups are on the same side of the alkene; whereas, they reside on opposite sides of the alkene in the second structure. When the alkyl groups are on the same side of the alkene, it is called a *cis* alkene. When the alkyl groups are on opposite sides of the double bond, it is a *trans* alkene. Since there is no free rotation about the double bond, the *cis* and *trans* isomers cannot interconvert. They are therefore distinct substances with different properties and reactivity. This will be important in the sections to come.





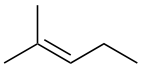
Problem 19. Assign the *cis* or *trans* configuration to each of the following alkenes. If a double bond does not have geometric isomerism, simply state that.

(a)

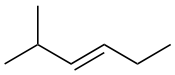


(b)

(c)

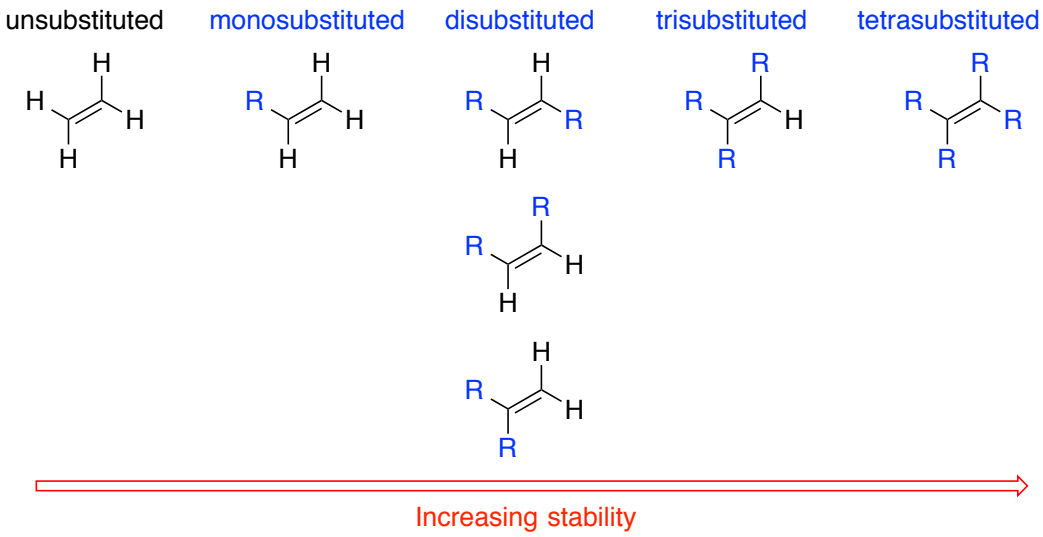


(d)

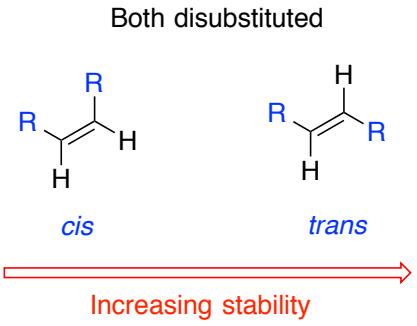


Stability

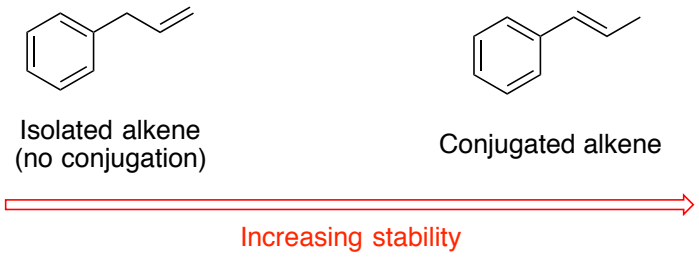
There are three main factors that impact the stability of an alkene: (1) the number of substituents on the olefinic (i.e., alkene) carbons, (2) its geometry, and (3) conjugation. In general, the more highly substituted an alkene is, the greater its stability.



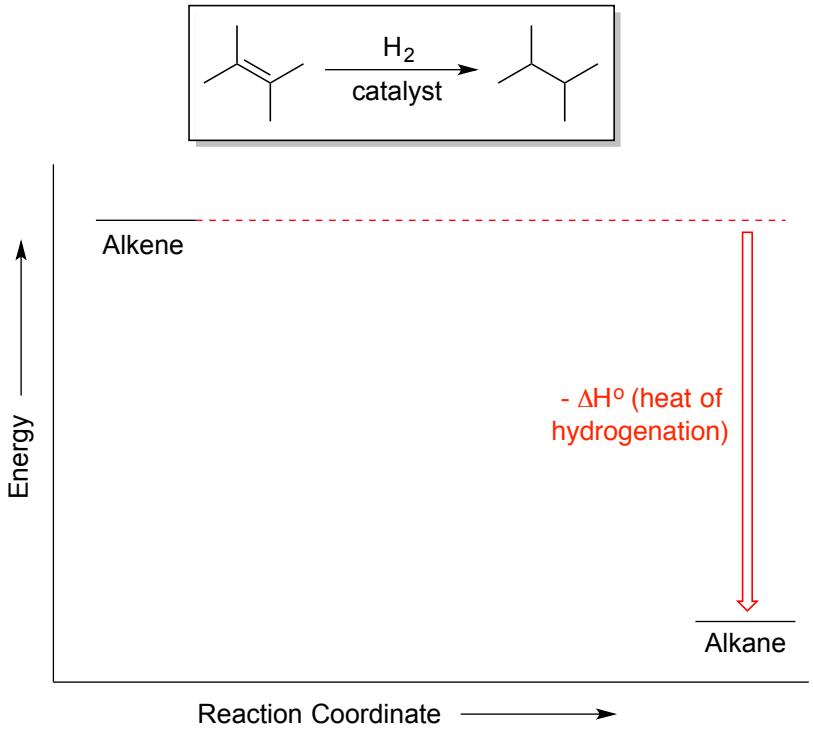
For alkenes of similar substitution, stability is enhanced by minimizing steric hindrance. For instance, a *trans,* disubstituted alkene is more stable than a *cis*, disubstituted alkene because the large R groups are kept further apart in the *trans* compound.



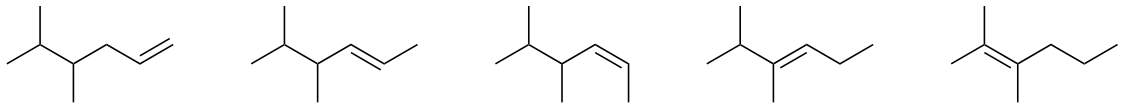
Finally, a conjugated alkene is more stable than an isolated alkene. Conjugation allows for resonance delocalization of the alkene's π electrons, and when these electrons are allowed to circulate around a greater number of nuclei, the resulting attractions lower the energy of the molecule.



Problem 20. An experimental method to ascertain alkene stability relies upon hydrogenation. When an alkene is hydrogenated, hydrogen gas (H_2) is added across the two alkene carbons in the presence of a catalyst. We'll learn more about this reaction in Chapter 10. For the moment, it is enough to know that this reaction liberates energy, which is known as the heat of hydrogenation.



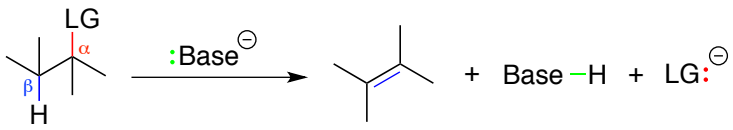
Given what you know about the stability of alkenes, rank the following isomeric olefins in order of decreasing heat of hydrogenation (i.e., decreasing absolute value of ΔH°).



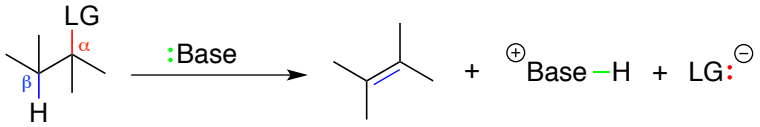
Section 6: Introduction to elimination reactions

The overall elimination reaction

In elimination, a base removes a proton from a carbon adjacent to the carbon bearing the leaving group. This can also be called a β-elimination because the carbon bearing the leaving group is called the α-carbon, while its neighbors are β-carbons. The base may be negative.



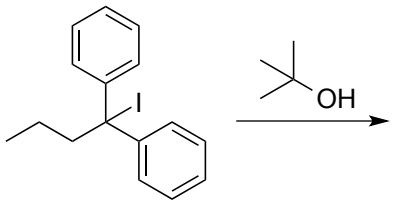
Or, the base may be neutral.



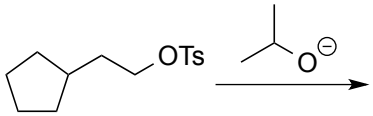
These schemes only show the reactants and the products. They do not reveal anything about the mechanism of the reaction. It turns out that elimination can occur via two different mechanisms.

Problem 21. Given the generic elimination reactions above, predict the products of the following reactions.

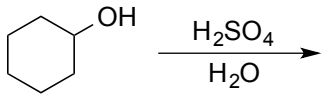
(a)



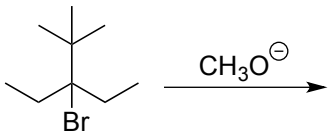
(b)



(c)



(d)

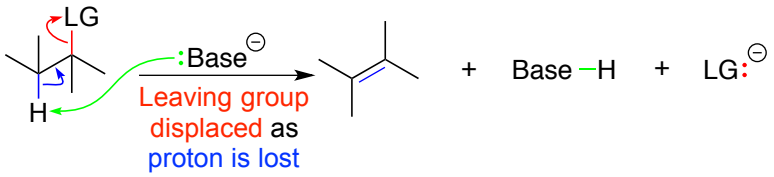


Additionally, it is worth noting that heat facilitates elimination reactions, so you may sometimes see heat (Δ) written below the reaction arrow.

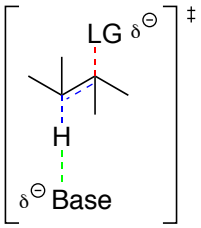
Problem 22. Propose a thermodynamic argument why heat would favor elimination.

The two mechanisms for elimination

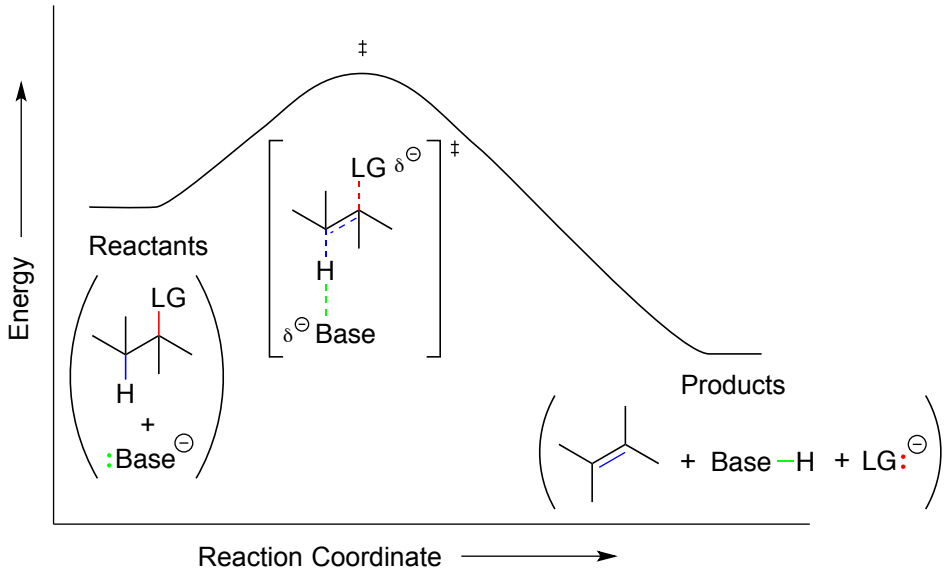
There are two possible mechanisms for elimination, much as there are for substitution. One mechanistic possibility is a concerted reaction. Recall that, in a concerted reaction, all of the bond making and breaking happens simultaneously. Therefore, the base removes a proton from the β position, and as it does so the C-H σ bonding electrons collapse in between the α and β-carbons to form the incipient π bond. This flow of electrons displaces the leaving group.



This one-step process has a single transition state in which all of the bonds being formed are partially formed and all of the bonds being broken are partially broken.

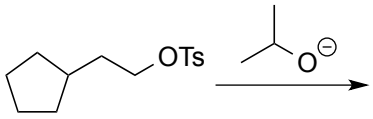


Since there is only a single mechanistic step in this reaction, it must be the rate-determining step. Both the substrate and the base are *mechanistically* involved in this step, meaning that the rate of the reaction depends on the concentration of both species: Rate = k [substrate] [base]. Adding the implied exponents of one on each concentration term, we see that this is a second-order elimination. It is therefore called the E2 reaction.

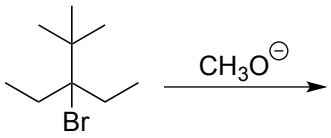


Problem 23. Draw mechanisms for the following concerted eliminations that we saw in Problem 21.

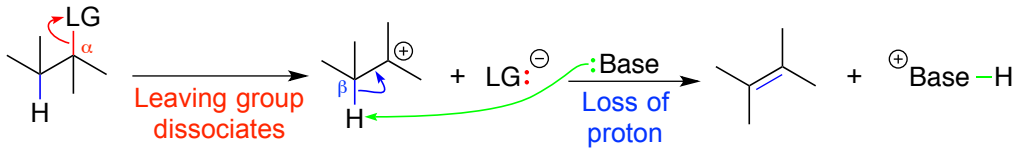
(a)



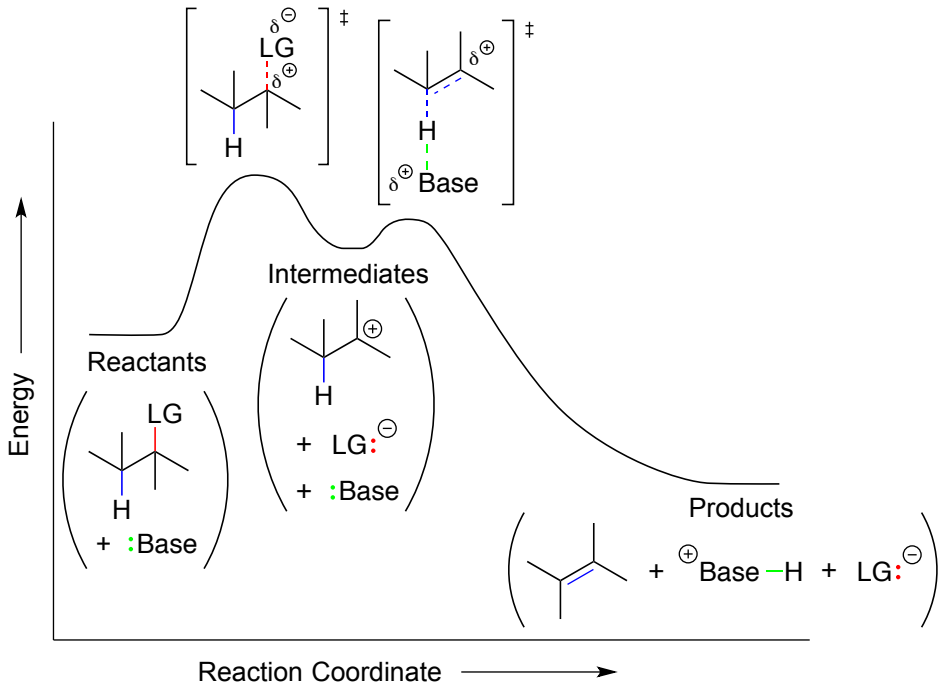
(b)



The alternative mechanism involves initial dissociation of the leaving group to form a carbocation intermediate. The base then removes a proton from the β position, enabling the formation of the carbon-carbon π bond.

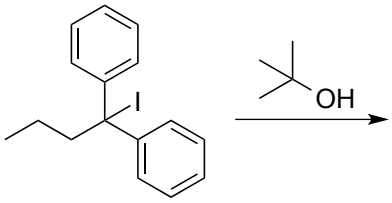


This is a two-step process, so there are two transition states. Additionally, it is the first step that is the rate-determining step, since it is the one in which carbon is deprived of the octet. Only the substrate is *mechanistically* involved in the rate-determining step, so the rate depends solely on the concentration of the substrate: Rate = k [substrate]. This is therefore a first-order elimination, which is commonly referred to as the E1 reaction.

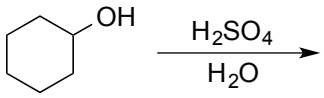


Problem 24. In Problem 21, we encountered the following two stepwise elimination reactions. Draw a complete mechanism for both.

(a)



(b)



Factors that impact the reaction mechanism

(1) The base

As with substitution reactions, the substrate is always mechanistically involved in the rate-determining step. It is whether or not the base is also *mechanistically* involved that differentiates first and second-order eliminations. As a result, the strength of the base helps us determine which mechanism occurs.

In general, nucleophilicity parallels basicity. This means that strong nucleophiles tend to also be strong bases. For instance, both hydroxide and the amide ion are strong nucleophiles as well as strong bases.

Strong nucleophiles and strong bases

Hydroxide Amide

We know this from our earlier discussion of pK_a values in Chapter 2. Water (the conjugate acid of hydroxide) has a pK_a of 15.7, and ammonia (the conjugate acid of the amide ion) has a pK_a of 32.5. These values illustrate that hydroxide and the amide ion are moderately to highly basic, respectively. We also know that anions are usually good nucleophiles, so in these cases, nucleophilicity certainly does parallel basicity.

The phrase "nucleophilicity parallels basicity" does come with some caveats though. For instance, large anions are strong nucleophiles due to the polarizability of their electron cloud. However, their size also enables them to disperse charge over a large area, which makes them less basic than their smaller counterparts. For instance, while both hydroxide and bisulfide are strong nucleophiles, bisulfide is far less basic because sulfur is a larger ion. This is reflected in a comparison of the pK_a values: 7 for H_2S vs. 15.7 for H_2O.

Strong nucleophiles

Hydroxide is also a strong base

Bisulfide is a weak base

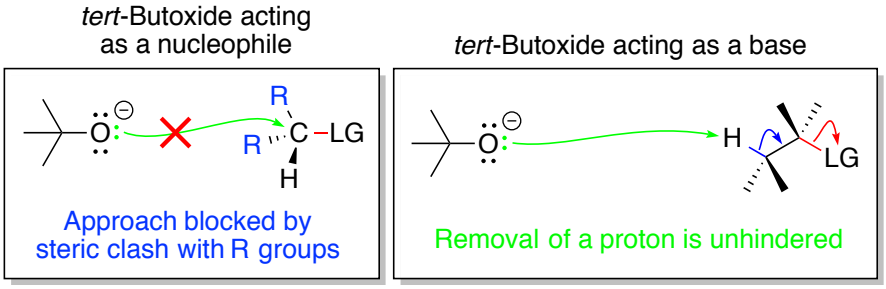
A second caveat is that steric hindrance diminishes the nucleophilicity of a reagent, while leaving its basicity unaffected. While ethoxide is both a strong base and a strong nucleophile, *tert*-butoxide is a strong base but a weak nucleophile.

Strong bases

Ethoxide is also a strong nucleophile

tert-Butoxide is a weak nucleophile

Due to its bulk, it is difficult for *tert*-butoxide to approach an electrophilic carbon. There is a steric clash between the *tert*-butyl group and the alkyl groups emanating from the electrophilic carbon. However, *tert*-butoxide's bulk does not diminish its ability to act as a base. After all, protons are often on the very outskirts of a molecule. Therefore, those that are acidic are easily plucked off by a base, regardless of its size.



Problem 25. In each of the following pairs, indicate which reagent is the stronger base.

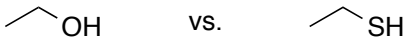
(a)

NaOH vs. $NaNH_2$

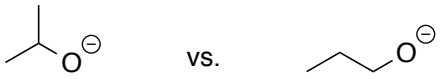
(b)

$^{\ominus}NH_2$ vs. $^{\ominus}PH_2$

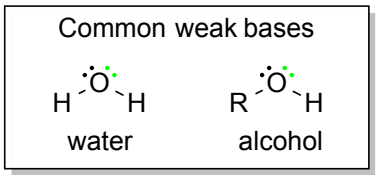
(c)



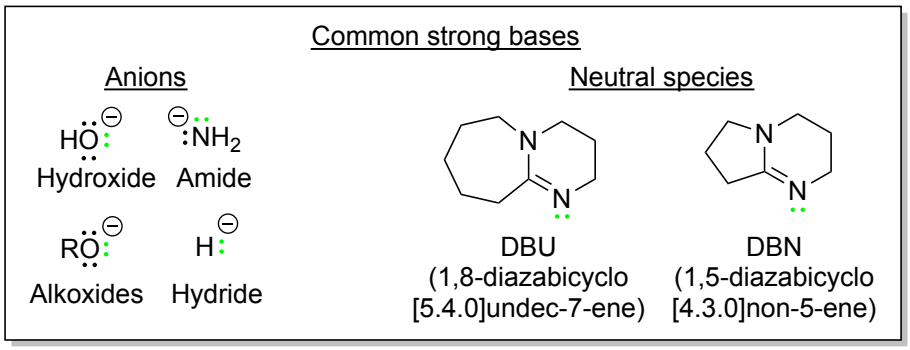
(d)



A weak base is unlikely to be involved in the rate-determining step, leading to a first-order reaction. It is too stable to engage in the reaction until a highly reactive carbocation forces it to do so. The most common weak bases are water and alcohols.



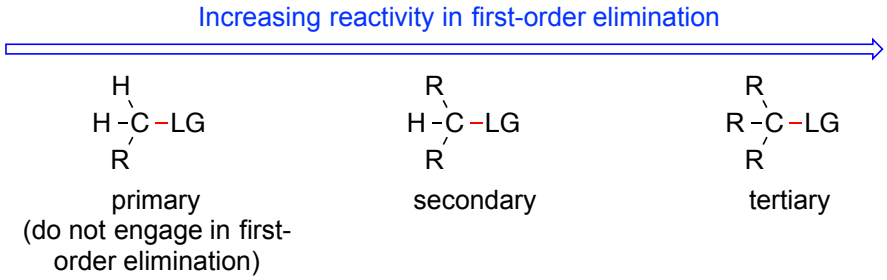
Conversely, strong bases readily remove a proton, leading to a second-order mechanism. Commonly used strong bases include the anions: hydroxide, alkoxides, amide, and hydride. Additionally, the neutral compounds DBU and DBN are also strong bases.



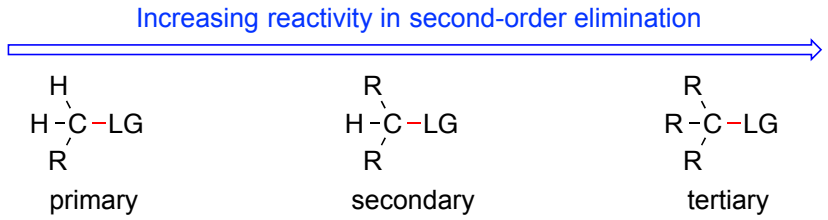
Problem 26. Why are DBU and DBN strong bases despite being neutral? Hint: Consider any stabilization that may be present in their conjugate acids.

(2) The substrate

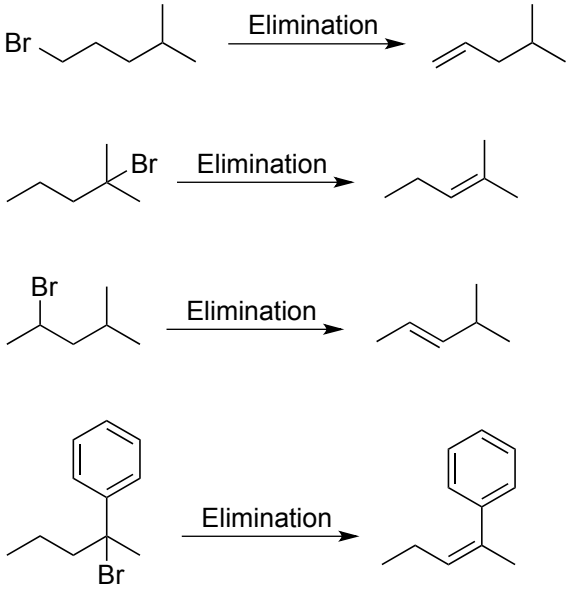
Since first-order eliminations involve a carbocation intermediate, the substitution of the substrate has the same impact that it did for S_N1 reactions. A more highly substituted substrate leads to a more stable carbocation. So, tertiary substrates react the most quickly. Secondary substrates are also suitable for first-order elimination. However, primary substrates will not engage in E1 reaction because the carbocation intermediate would be too high in energy.



Second-order elimination reactions do <u>not</u> follow the same reactivity trend with respect to the substrate as S_N2 reactions. In an S_N2 reaction, the nucleophile must approach the electrophilic carbon, so steric hindrance is an important factor. However, in E2 reactions sterics do not play the same role because the base is merely removing a proton rather than approaching a carbon atom. For E2, the reactivity stems solely from the stability of the product formed. A more highly substituted substrate will lead to a more highly substituted (and therefore more stable) alkene. Consequently, the reactivity increases with the substitution of the substrate.



Problem 27. Rank the following substrates in order of decreasing reactivity in the elimination reactions shown.



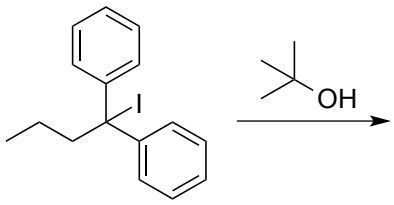
(3) The solvent

The solvent has the same impact on reactivity as it did with substitution. Both first-order reactions—be they substitution or elimination—commonly entail the formation of cations and anions due to the initial dissociation of the substrate during the rate-determining step. Therefore, the polar protic solvents (usually water or an alcohol) that are able to stabilize both types of ions facilitate these first-order reactions.

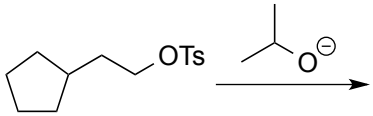
On the other hand, both the second-order processes necessitate a highly reactive reagent—be it a nucleophile or a base. Therefore, the polar aprotic solvents (e.g., DMF, DMSO, AcN, acetone) that strip away the reagent's counterion, thereby leaving it more reactive, accelerate second-order reactions.

Problem 28. Select an appropriate solvent for each of the elimination reactions below, which we first encountered in Problem 21.

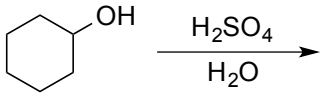
(a)



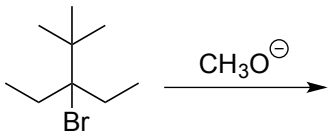
(b)



(c)



(d)



(4) The leaving group

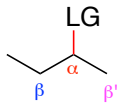
As with substitution, a good leaving group is needed for both first- and second-order elimination. The good leaving groups will fall into the same categories that we've seen previously: halides and sulfonates. Water is also a good leaving group. However, this oxonium ion is incompatible with strong base, so water is only a good leaving group in a special subset of elimination reactions known as dehydration, in which an alcohol is treated with a concentrated aqueous solution of sulfuric acid.

Problem 29. Why is an oxonium ion generated from an alcohol incompatible with strong base?

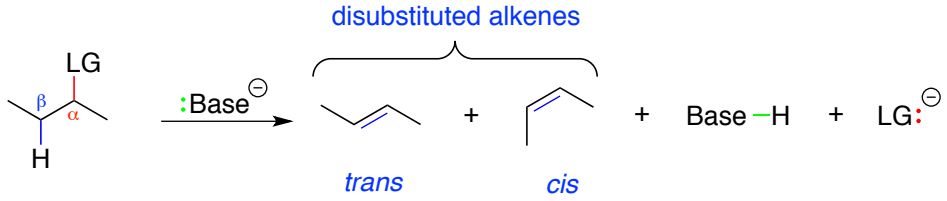
Zaitsev vs. Hofmann elimination

When an elimination occurs, there may be protons on more than one β-carbon. If this is the case, then more than one elimination product could be possible. The more highly substituted alkene product is usually more stable and is known as the Zaitsev product. The less highly substituted alkene, on the other hand, is termed the Hofmann product. Under certain circumstances, it may predominate.

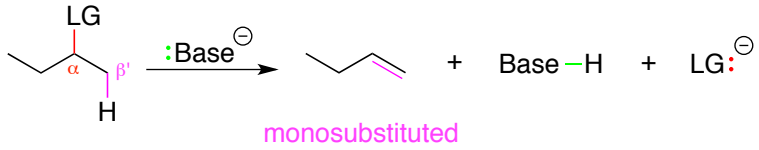
In the following molecule, α is the functionalized carbon (i.e., the carbon bearing the leaving group). Any immediately adjacent carbon can be called a β-carbon. In this case, there are two β positions: β and β'.



If a proton is removed from β, a disubstituted alkene will be formed. It may have either the *cis* or *trans* geometry as well.



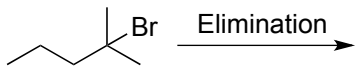
On the other hand, if a proton is removed from β', a monosubstituted alkene will be formed.



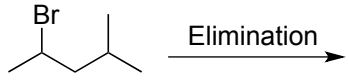
Since the disubstituted products are the more highly substituted alkenes, they are the Zaitsev products in this case. The monosubstituted alkene is the Hofmann product. Based on intrinsic stability alone, we would expect the *trans*, disubstituted product to be the major product, followed by the *cis*, disubstituted and monosubstituted alkenes respectively. However, as we'll see in the sections to come, there are sometimes factors other than intrinsic stability that impact the product distribution.

Problem 30. In each of the following reactions, two elimination products are possible. Draw both alkene products, and identify them as the Zaitsev or Hofmann product.

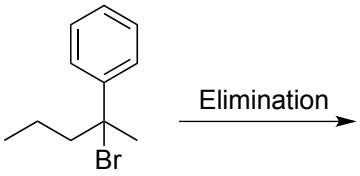
(a)



(b)

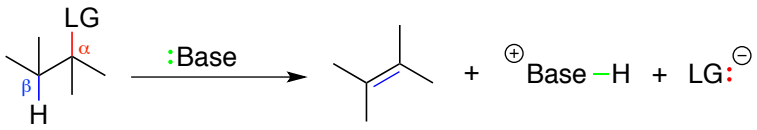


(c)



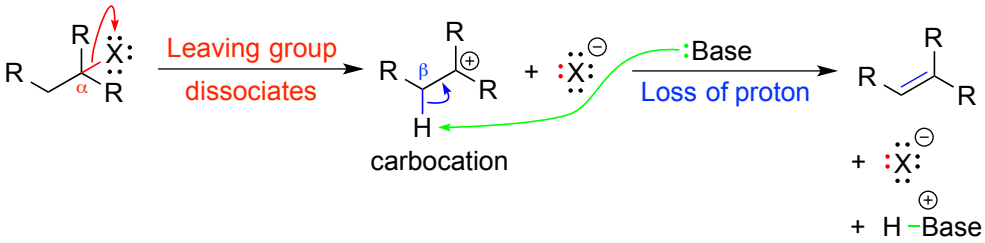
Section 7: The E1 Reaction

First-order eliminations (or E1 reactions) usually take the following form.



Mechanistic considerations

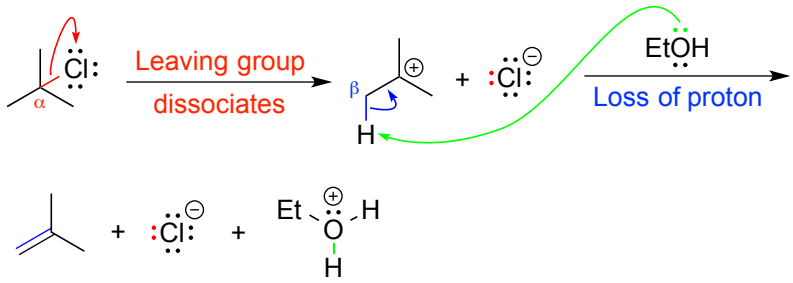
A good leaving group, such as a halide (X^-), a sulfonate ($^-$OTs, $^-$OMs, or $^-$OTf), or water, dissociates from a secondary or tertiary center. The resulting carbocation intermediate loses a proton from the adjacent (β) position to a weak base, such as water or an alcohol. The product is an alkene.



In this first-order elimination, loss of the leaving group is the rate-determining step. Only the substrate is *mechanistically* involved in this step, so the rate depends solely on the concentration of the substrate (Rate = k [substrate]).

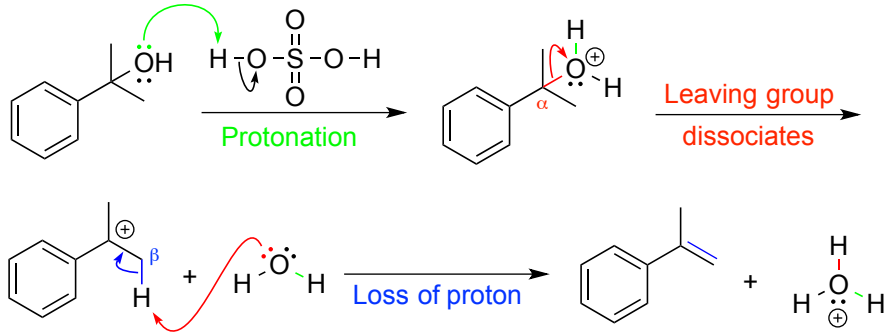
Specific examples of the E1 reaction

In the following reaction, chloride initially dissociates from the tertiary center to form a tertiary carbocation intermediate. With its reactivity thus enhanced, even ethanol is a strong enough base to remove a β-proton, leading to the formation of the product's π bond.



We've seen previously that, when water or an alcohol is a reagent, it is typical to use it in great excess. This allows it to function as a polar protic solvent for the reaction as well.

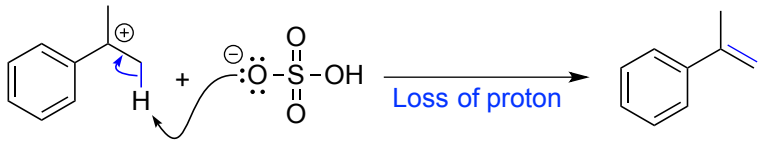
As with S_N1 reactions, water can also serve as a good leaving group. This occurs when a reactant alcohol is treated with strong aqueous acid. Protonation of the hydroxyl group leads to the formation of an oxonium ion that subsequently dissociates from the substrate. A proton is then lost to water as the alkene's π bond is created.



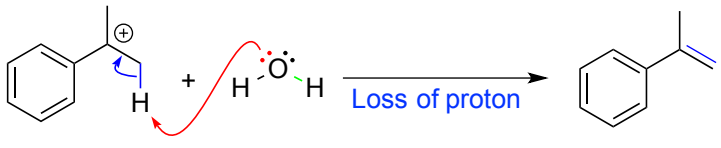
This is a special subset of elimination reactions, known as dehydration. It is worth noting that you may see the reagent for dehydration written in one of three formats, all of which have the same meaning. You may see H_2SO_4 in H_2O. Since sulfuric acid dissociates in water to yield the hydronium ion, you may also simply see H_3O^+. Alternatively, if we focus only on the acidic proton, you may see H^+ in H_2O. All three ways of writing the reagent lead to the same reaction.

Problem 31. In the final step of the preceding reaction, the proton may be lost to bisulfate (a) or to water (b). Furthermore, sometimes this step only shows the loss of the proton and not the base that removes it (c). Why are all three ways of drawing the last step of the mechanism ultimately identical?

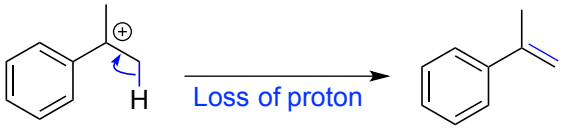
(a)



(b)

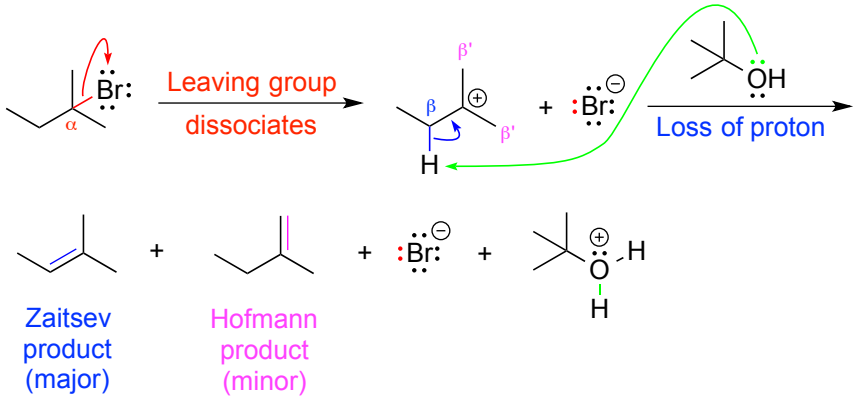


(c)



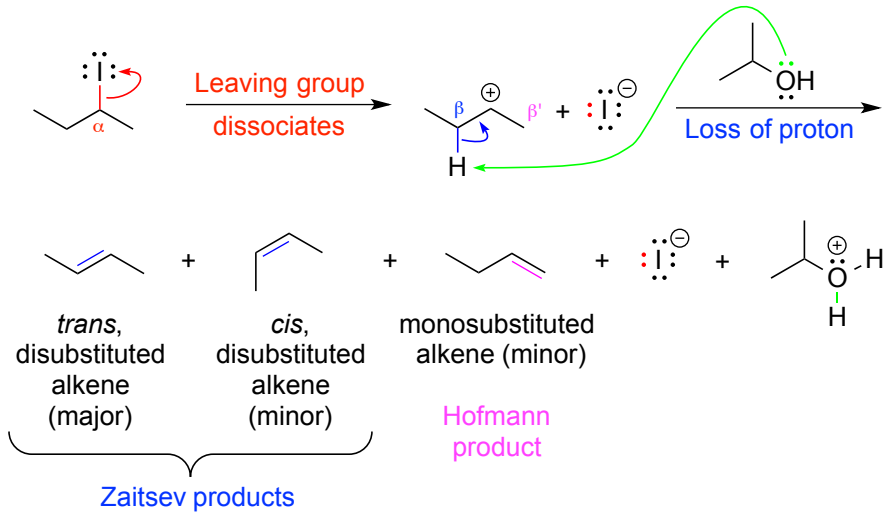
Regiochemical considerations

When multiple unique β positions are present (β and β' below), the major product is the more highly substituted alkene. The Zaitsev alkene predominates in E1 due to its greater stability. It may be arrived at quickly by using Zaitsev's rule, which is merely a mnemonic device. Zaitsev's rule says that the predominant product will be the one formed by removal of a proton from the more highly substituted β position. The Hofmann product, formed through the removal of a proton from β', is a minor product of the reaction.



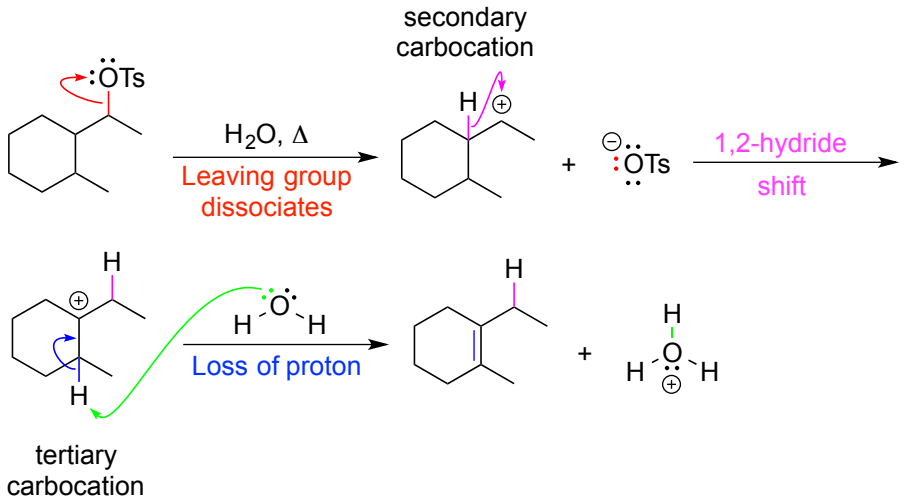
Stereochemical considerations

When elimination can yield *cis* or *trans* alkene products, the *trans* product predominates in E1 because it minimizes steric hindrance and is therefore more stable.



Carbocation rearrangement

Since the intermediate in E1 is a carbocation, rearrangement is possible. In the following example, dissociation of tosylate begins the reaction. The initial secondary carbocation undergoes a 1,2-hydride shift to form a more stable tertiary carbocation, which then loses a proton from a β position to form the most highly substituted alkene product possible. In this case, the predominant product is a tetrasubstituted alkene.

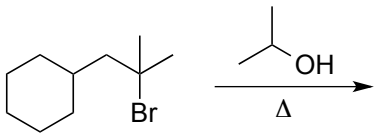


To recap, efficient E1 reaction requires a stable carbocation, so it does not occur with primary substrates. A weak base is also a key feature of the reaction. Weak bases include water and alcohols.

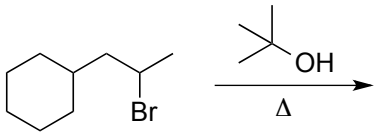
The predominant product of E1 possesses the more highly substituted alkene. When geometric isomers are possible, the *trans* arrangement of the larger substituents will be favored because it minimizes steric hindrance. Carbocation rearrangement is also possible.

Problem 32. Show all of the possible E1 products of the following reactions, and then specify which is the major product.

(a)



(b)



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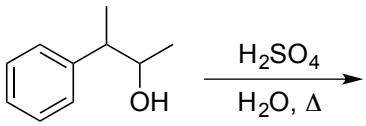
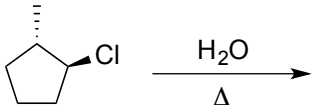
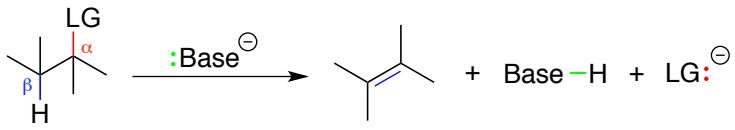


(d)



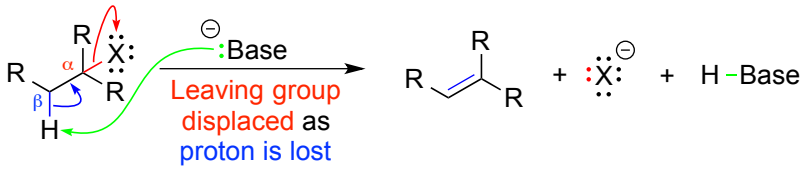
Section 8: The E2 Reaction

Second-order eliminations (or E2 reactions) typically proceed according to the following motif.



Mechanistic considerations

A good leaving group, such as a halide (X^-) or a sulfonate (^-OTs, ^-OMs, or ^-OTf), is displaced as a proton is lost from the adjacent (β) position to a strong base. The product is an alkene.

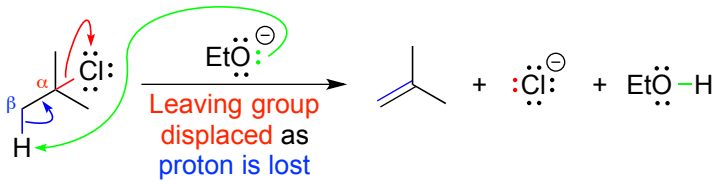


The rate-determining step of the E2 reaction involves both the substrate and the strong base, so the rate depends on the concentration of both species (Rate = k [substrate] [base]), making it a second-order process.

Recall that strong bases are often anions, such as hydroxide ($^-$OH), alkoxides ($^-$OR), hydride (H^-), or amides ($^-NH_2$ or $^-NR_2$). However, a strong base need not necessarily have a negative charge. DBU and DBN are two examples of neutral strong bases.

A specific example of the E2 reaction

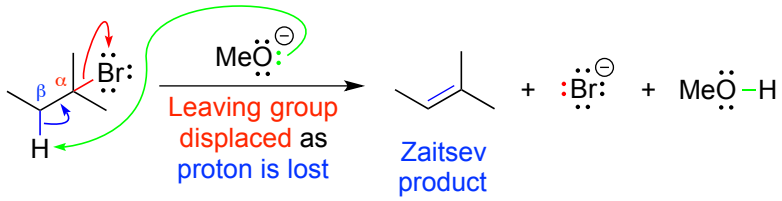
In the following example, ethoxide removes a proton from any one of the three equivalent β-carbons. The electrons from the breaking C-H σ bond fall between α and β to generate the alkene π bond. As a result, chloride is displaced.



Regiochemical considerations

The regiochemical outcome of an E2 reaction depends on the size of the base used. Small, nimble bases are able to remove a proton from the more highly substituted β position (β below) to yield the more highly substituted, and therefore more stable, Zaitsev product.

Methoxide is just such a small, nimble base. It removes a proton from the secondary β-carbon, rather than from either of the primary β-carbons. This leads to the formation of a trisubstituted alkene as bromide is expelled.

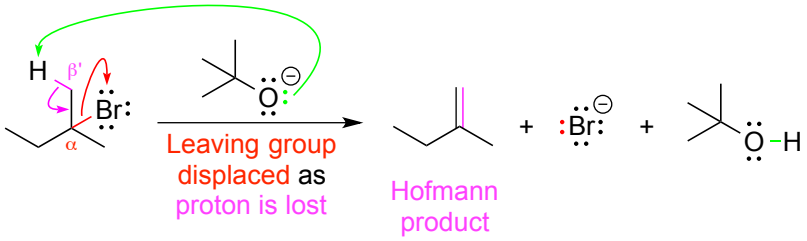


However, big, bulky bases remove a proton from the less highly substituted β' position so as to minimize steric hindrance in the transition state. This results in the less highly substituted, and therefore less stable, Hofmann product.

Lower-energy transition state when base approaches primary β'

Higher-energy transition state when base approaches secondary β

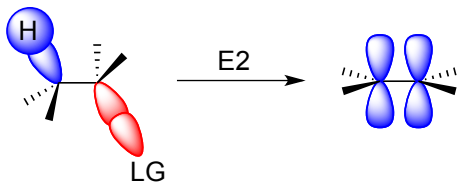
In the example below, *tert*-butoxide removes a proton from the primary β' position, rather than from the secondary β-carbon. This results in the formation of a disubstituted alkene as bromide is ejected. Compare the product of this reaction that of the previous one. Since the product in this case contains the less substituted alkene, it is termed the Hofmann product.



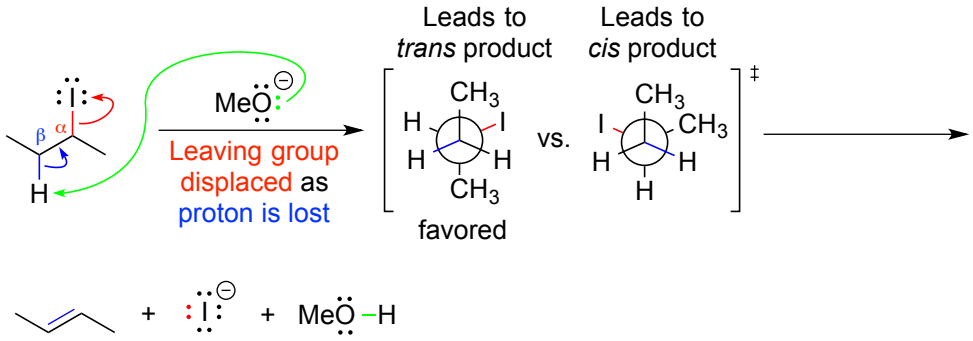
Stereochemical considerations

The E2 reaction proceeds through an anti-periplanar transition state. In other words, the β-proton and leaving group are aligned 180° relative to one another. This stems from the principle of least nuclear motion, which is sometimes referred to simply as the principle of least motion. The idea is that the lowest-energy transition state for a concerted process will require the least reorganization of the nuclei (i.e., the least movement).

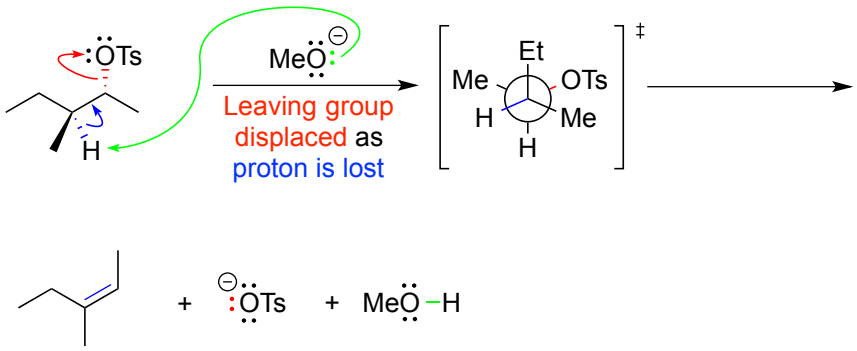
In the case of an E2 reaction, the least motion will be required if the orbitals of the breaking bonds are anti-periplanar. Since these orbitals will become the p orbitals of the π bond upon rehybridization, it is best if they are already in the same plane (i.e., periplanar), as p orbitals must be in a π bond. The anti arrangement minimizes the electronic repulsion between the incoming base and departing leaving group.



When two β-protons are available, the favored transition state minimizes the steric clash of the alkyl groups, resulting in a *trans* product.



However, when only one β-proton is available, the stereochemistry of the substrate dictates the configuration of the product alkene because the transition state must have the breaking C-H and C-LG bonds anti-periplanar to one another. In the example below, the reactant stereochemistry is such that the product has the ethyl group *cis* to its neighboring methyl. Although this is the less thermodynamically favorable outcome, it is an unavoidable consequence of the anti-periplanar transition state.



In summary, E2 is a concerted process in which the loss of leaving group and removal of a β-proton occur concurrently. A strong base is required for this second-order reaction.

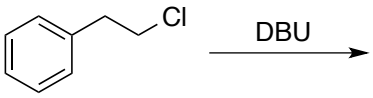
The regiochemical outcome depends on the steric bulk of the strong base. Bulky bases predominantly yield the Hofmann product, while unhindered bases provide the Zaitsev product as the major product.

The concerted nature of the reaction results in stereospecificity. The leaving group and the β-proton must be aligned anti-periplanar to one another during an E2 elimination. When two β-protons are available, the product will have the larger substituents in the more stable *trans* arrangement. When only one β-proton is present, the anti-periplanar elimination dictates which geometric isomer of the product will be formed.

Another consequence of the concerted mechanism is the absence of a carbocation intermediate. Therefore, while E1 reaction may involve carbocation rearrangement, E2 reaction cannot.

Problem 33. Provide the major products of the following E2 reactions.

(a)



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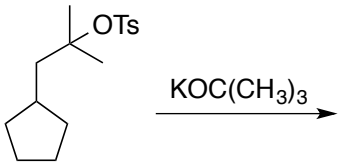
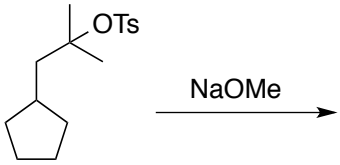
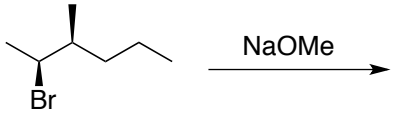


(c)



(d)



Section 9: Deciding Between S_N1, S_N2, E1, and E2 Pathways

The nature of the substrate, the reagent, and the solvent all affect which reaction pathway will predominate. It is important to note that product mixtures are often possible. The focus though is typically on predicting the major organic product, and a lesser emphasis is on the prediction of accompanying minor products.

Cutting the possibilities in half: the reagent

While there are many ways to go about this decision-making process, one helpful approach is to immediately divide the four possible reaction pathways in half by assessing the strength of the reagent.

First-order processes require weak nucleophiles/bases, and second-order processes require strong nucleophiles/bases. Water and alcohols are the most commonly encountered weak nucleophiles/bases. Most anions (other than F^-) will act as strong reagents. Some neutral species can also be strong reagents. Neutral strong nucleophiles are

polarizable (e.g., H_2S, RSH) or electron-releasing (e.g., NH_3, RNH_2, R_2NH) at the reactive atom. Neutral strong bases have powerfully resonance-stabilized conjugate acids (e.g., DBU, DBN).

If the reagent is weak, the predominant reaction will likely be S_N1 or E1. If the reagent is strong, the major pathway is likely to be S_N2 or E2.

Examining the substrate

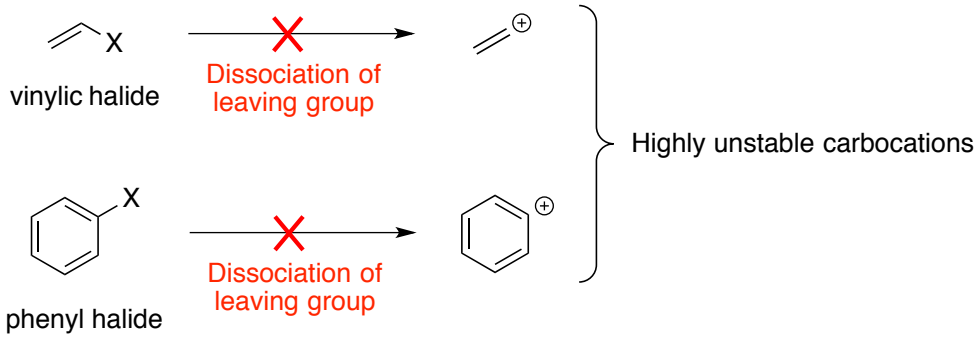
Certain substrates will essentially forbid particular reactions. Therefore, it is important to classify the substrate as methyl, primary, secondary, tertiary, allylic, vinylic, benzylic, or phenyl and consider the impact of this substitution pattern on reactivity.

First-order processes require a reasonably stable carbocation. As a result, primary substrates will not undergo S_N1 or E1 unless they are allylic or benzylic (and therefore yield resonance-stabilized carbocations). On the other hand, S_N2 reaction is sensitive to steric hindrance, so tertiary substrates do not undergo S_N2.

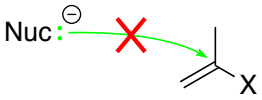
Secondary substrates will be suitable for first or second-order reactions. When deciding between S_N1 and E1 pathways for secondary substrates, two factors will guide us. The first is that heat favors elimination. The second is that larger reagents will be more likely to act as bases than nucleophiles.

When deciding between S_N2 and E2 pathways for secondary substrates, it is important to assess the reagent. Given that increasing hindrance decelerates substitution and that a secondary center is moderately hindered, a reagent that is both a strong base and nucleophile will tend to act as a base leading to E2. However, strong nucleophiles that are weak bases will result in S_N2 reaction instead.

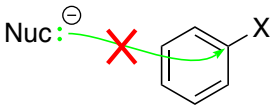
Vinylic and phenyl halides do not undergo substitution reactions. Both types of substrates would yield highly unstable carbocations, so S_N1 is precluded.



The approach of a nucleophile directly opposite the leaving group is also not feasible for these substrates, making S_N2 impossible.



vinylic halide



phenyl halide

We'll learn more about the elimination of vinyl halides in Chapter 11, and we'll see the elimination of phenyl halides in Chapter 14.

The role of solvent

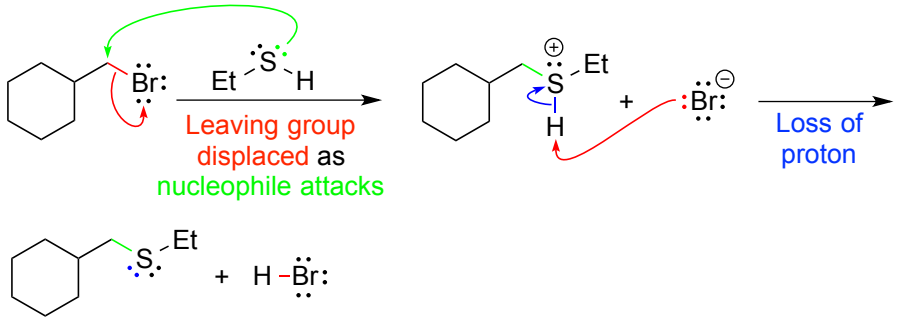
The solvent (if stipulated) can help to reveal the predominant pathway. Polar protic solvents are those with a heteroatom-to-hydrogen bond (e.g., water, alcohols). The dipole of the heteroatom-to-hydrogen bond stabilizes both cations and anions, which is useful in first-order reactions (S_N1 and E1) where cations and anions are often formed upon dissociation of the leaving group. If water or an alcohol is the reagent, it is likely used in excess and also serves as the solvent for the reaction.

Polar aprotic solvents contain a heteroatom but have no heteroatom-to-hydrogen bond. These include solvents such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (AcN), and acetone (CH_3COCH_3). Polar aprotic solvents have an accessible δ^- but no sterically accessible δ^+. Therefore, they only effectively stabilize cations using their accessible δ^-. This has the effect of stripping the cations away from anionic reagents, leaving them "bare" and consequently more reactive than they otherwise would have been. For example, the Na^+ would be stripped away from NaOMe, leaving "bare" and reactive $^-$OMe. As a result, polar aprotic solvents favor second-order reactions (S_N2 and E2), which require potent reagents.

<u>Examples:</u>

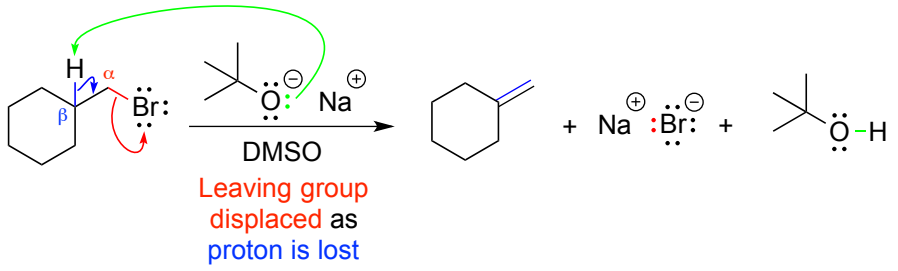
(a) In the following reaction, the reagent contains a polarizable sulfur atom, making it a strong nucleophile. Polarizable atoms serve as good nucleophiles because they can make partial bonds from a greater distance; however, they tend not to be particularly basic. Having identified a strongly nucleophilic reagent, S_N2 seems probable.

The primary substrate is relatively unhindered (although there is some nearby branching), so it is suitable for S_N2. Attack of the nucleophile displaces the leaving group. Since the nucleophile acquires a positive charge upon formation of the new C–S bond, a proton is then lost to provide the neutral product.



(b) In the example below, the reagent (*tert*-butoxide) is anionic and therefore strong. Additionally, the polar aprotic solvent (DMSO) will strip away the sodium counterion to make *tert*-butoxide even more reactive. These factors suggest a second-order reaction (S_N2 or E2).

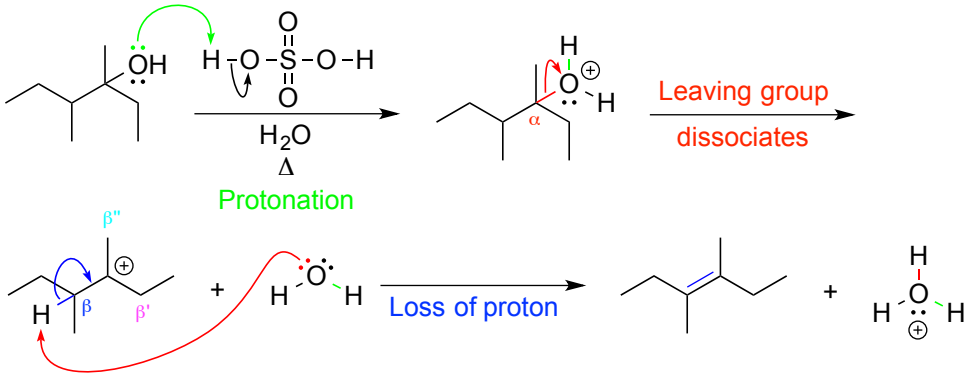
The primary substrate will allow either S_N2 or E2 reaction, so both are possible in principle. Given the steric bulk of *tert*-butoxide, the more sterically demanding S_N2 process will have a fairly high-energy transition state, rendering it less favorable. Consequently, the major pathway is expected to be E2 reaction. Here, there is only one β position, so regiochemistry is not an issue.



(c) In the following example, the reagents are an acid (H_2SO_4) and a weak nucleophile/base (H_2O). Therefore, first-order reaction (S_N1 or E1) seems probable. Notice that the hydroxyl group is not a good leaving group (because ^-OH is high in energy), so it must be protonated in order to make it a suitable leaving group. The substrate is tertiary, so a stable carbocation results from the subsequent dissociation of the leaving group.

While substitution is possible, it would merely regenerate the original reactant. Furthermore, heat (Δ) was indicated, and heating typically favors elimination. Recall that, in elimination, entropy increases. At higher temperatures, the entropy term (in $\Delta G = \Delta H - T\Delta S$) becomes more significant, making elimination the more favorable process. Therefore, the major pathway is E1.

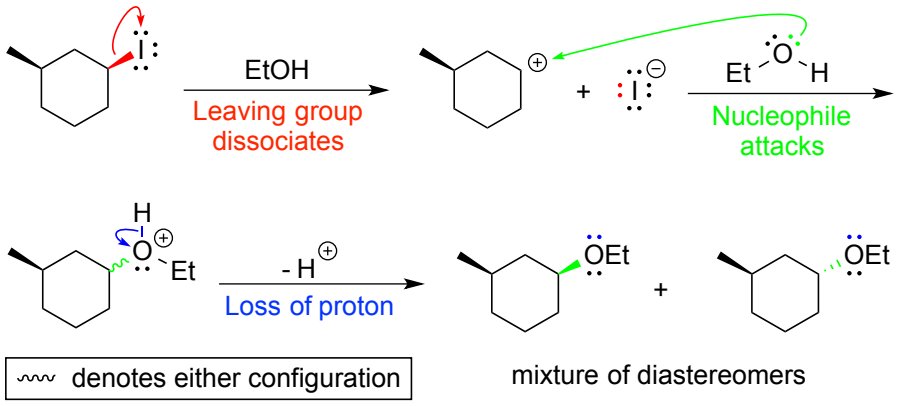
Loss of a proton can occur at one of three β positions; however, the most highly substituted (and therefore major) product results from removal of a proton from β. The favored geometric isomer places the larger ethyl groups *trans* to one another. Minor products could include the tetrasubstituted alkene with *cis* ethyl groups, as well as less highly substituted alkenes resulting from removal of a proton from either β′ or β″.



(d) In the example below, the reagent (ethanol) is a weak nucleophile/base, so first-order reaction (S_N1 or E1) is likely. The substrate is secondary, which does allow for the requisite carbocation formation. Therefore, the leaving group dissociates.

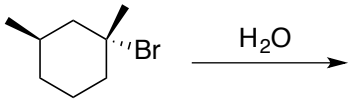
No heat is shown for this reaction, and ethanol is an unhindered reagent. These two factors suggest that substitution (S_N1) will predominate in this case. The weak nucleophile attacks the carbocation intermediate, and a proton is lost to form neutral ether products.

Notice two important subtleties in this reaction: (1) no carbocation rearrangement occurs (even though a tertiary center is present) because the carbocation can only move to an adjacent center and (2) the stereochemistry of the methyl group is unaltered by the reaction because that center does not participate in the S_N1 process.



Problem 34. Determine the major product of the following reactions.

(a)



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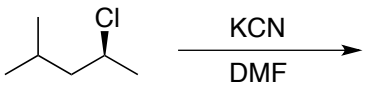

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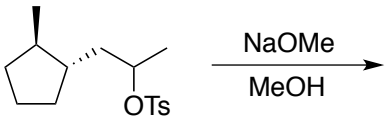
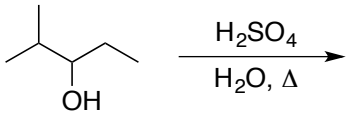


(d)



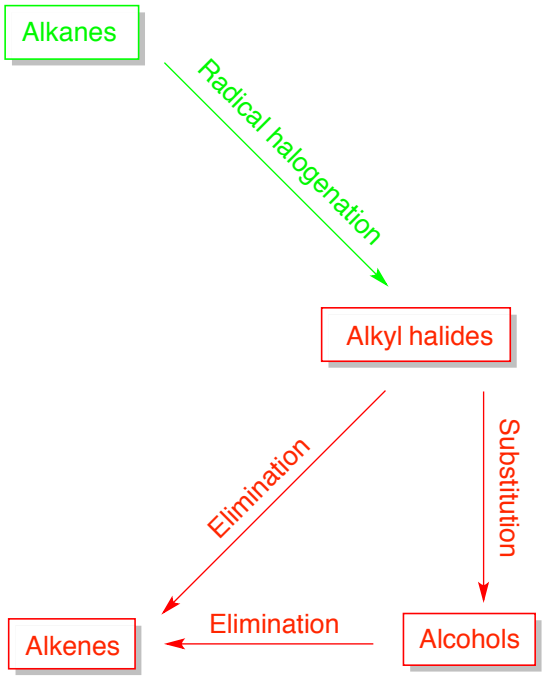
Section 10: Planning organic syntheses

To this point, most of the questions that involved reactions provided you with the substrate and the reagent(s) and asked you to predict the product. This develops a useful skill for organic chemists working in the laboratory: You want to be able to cogently predict the products when you combine substances in the lab.

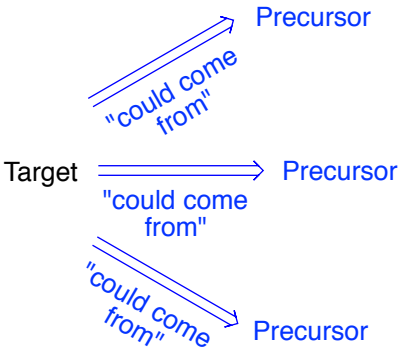
A different skill that is every bit as useful (if not more so) is the ability to plan out a sequence of reactions that would enable you to prepare a desired compound. Organic, medicinal, and materials chemists do this on a regular basis. They identify a substance of interest—be it a potential pharmaceutical or a new material that might have useful properties. Then, they embark upon its preparation in the laboratory. This is, however, a very different mode of thought than simply predicting the products of a single reaction. To plan a synthesis requires not only an understanding of reaction mechanism (so that you can coherently predict products) but also the ability to orchestrate several reactions into a viable synthesis of a more complex substance. This skill takes some time to develop. We'll begin to do so in this chapter, and we'll continue this process in nearly every chapter that follows.

One useful tool to illustrate possible syntheses is a sort of map of the functional groups and the reactions that enable their interconversions. Previously, we've seen that alkanes can be converted to alkyl halides through radical halogenation. Reactions introduced in this chapter are in red in the following diagram. For instance, we've learned that alkyl halides can be subject to substitution reactions, which can generate a wide variety of functional groups including alcohols. Both alkyl halides and alcohols can be converted to alkenes via elimination. We'll continue to expand upon this synthetic roadmap in the chapters to come because it will help you to envision routes from one type of functional group to another. For example, it is easy to see from this map that an alkene could be prepared from an alkane by sequential radical halogenation and elimination. Our synthetic options are fairly

limited at the moment, but they will continue to multiply in upcoming chapters as we learn about an increasing number of reactions.



Another very handy tool in planning syntheses is retrosynthetic analysis. Retrosynthetic analysis was developed by E. J. Corey, who won the Nobel Prize in Chemistry in 1990 as a result of this methodology that enabled thousands of chemists to plan syntheses of complex molecules in a methodical way. The basic idea of retrosynthetic analysis is that you begin with the structure of the desired product, which is often called the target molecule. You then think about reactions that could be used to prepare the target in a single step. This generates a set of possible precursors to the target structure. When drawing a retrosynthetic analysis, the target is connected to its potential precursors using a retrosynthetic arrow, which can be read as "could come from."

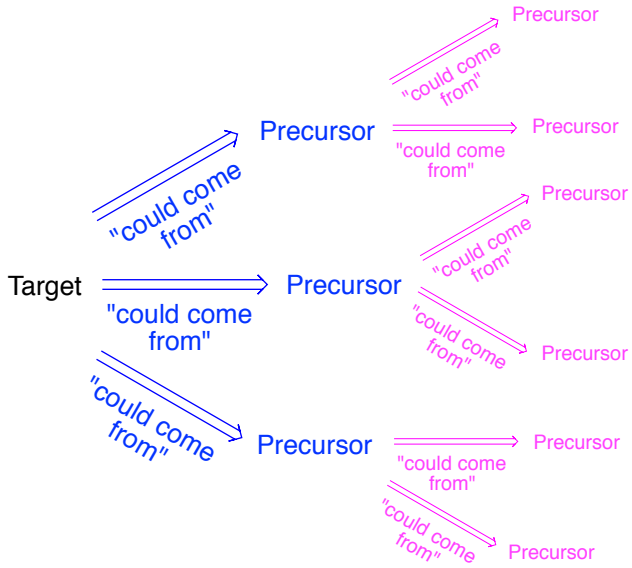


This is a bit like brainstorming when you are asked to write an essay. Any professor of composition will tell you not to simply put pen to paper and start writing the essay.

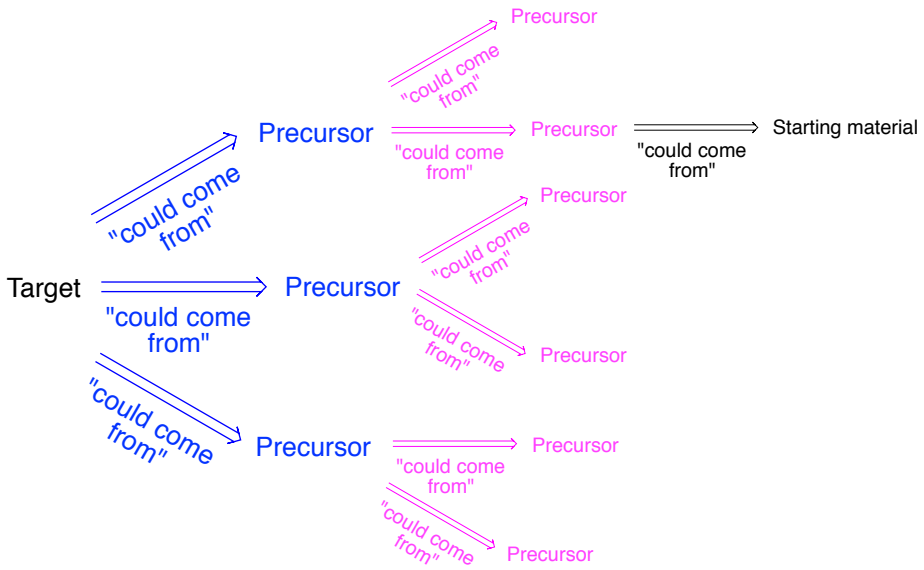
Instead, you are better served by brainstorming first. You develop an outline of the points that you wish to cover, and this prior organization of your thoughts helps you to craft a more polished and persuasive essay.

The same is true in synthesis. When asked to prepare a compound, we wouldn't want to begin haphazardly draw reactions that might lead to the substance of interest. Instead, we want to lay out all of our ideas in a systematic fashion, and retrosynthesis is a tool for doing so.

Now that we have a small collection of precursors to the target molecule, we think about what they could be made from in a single step. This second wave of retrosynthesis provides us with a set of compounds that are two steps removed from the target molecule.

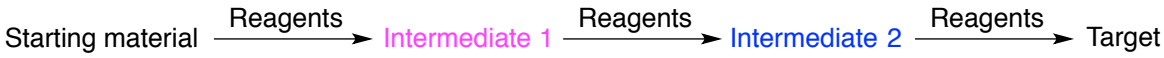


This process can continue through as many iterations as warranted by the size and complexity of the target. The goal is to ultimately find a retrosynthetic route back to the allowed starting material. This constitutes the pathway that is selected for the synthesis.



In the research laboratory, the allowed starting material would be a compound that you can purchase cheaply or a molecule whose synthesis is already known in the chemical literature. In textbook problems, you will simply be told what you are allowed to utilize in the synthesis.

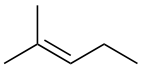
It is also important to note that the retrosynthesis is merely *planning* for the synthesis. Much as brainstorming is not the final essay in English classes, retrosynthesis is the final answer to a synthesis problem. Once you have identified a retrosynthetic route back to an allowed starting material, the actual synthesis must then be proposed. This begins with the starting material and utilizes *specific reagents* to convert it to the first intermediate, then the second, and finally the target product.



Notice that we didn't fill in the reagents until the very end of the process. This is one of the benefits of retrosynthesis. It allows you to tackle the problem one step at a time. First, you ask yourself what kinds of reactions can be used to achieve the desired transformations. Then, later in the process, you fill in the specific reagents needed for the desired transformations with the requisite selectivity.

Retrosynthetic analysis is not intuitive for many people. Although it may seem unnecessarily awkward and difficult to think backwards especially when the synthesis problems are short and fairly straightforward to solve, it is definitely worth the investment of effort to become comfortable with retrosynthesis. As the chapters progress and you learn more and more reactions that can be combined in many ways to generate a multitude of synthesis problems, you will be glad that you took the time to understand retrosynthesis now. Its application in subsequent chapters will save you a great deal of time, and it will likely earn you higher exam scores as well.

Problem 35. Draw a retrosynthesis for the following alkene. Try to include as many branches as possible in the retrosynthetic analysis. Then, based on your analysis, provide the shortest possible synthesis of this target molecule from an alkane.

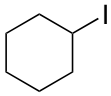


End-of-the-Chapter problems

36. The following names contain errors. Identify the mistakes, and provide the correct name for each compound.

(a) 3-bromo-2-methylbutane

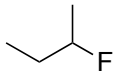
(b)



hexyl iodide

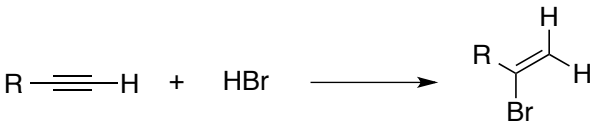
(c) 1-chloro-1-methylpentane

(d)

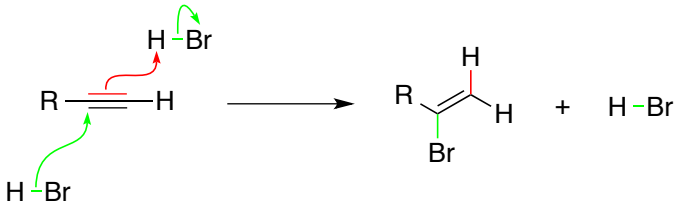


isobutyl fluoride

37. In this chapter, we've seen quite a number of first- and second-order reactions. These are exceedingly common, but they are not the only mechanistic possibilities. In Chapter 11 when we study alkynes, we'll learn about the following reaction, in which HBr is added across the π bond of an alkyne.



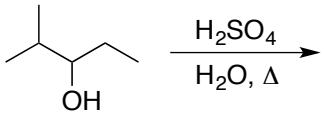
The mechanism for this reaction is as follows.



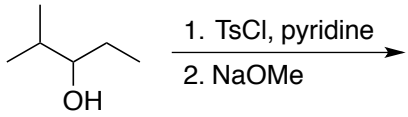
Based on the given mechanism, what is the rate law for this reaction? What is the order of this reaction?

38. We've learned about two ways to convert the hydroxyl group of an alcohol into a good leaving group. The first simply entails protonation. The second method is formation of a sulfonate. These two approaches will sometimes yield the same product, but in other scenarios, they will yield different products. Compare the results of the following three elimination reactions. Which method (protonation or conversion to the sulfonate) provides greater control? Why?

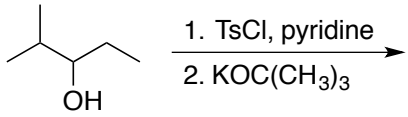
(a)



(b)

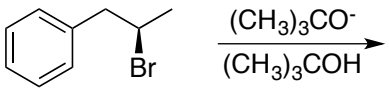


(c)

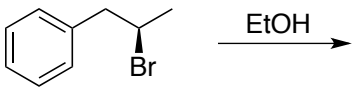


39. In the four reactions that follow, a single substrate engages in all of the reactions that we've studied in this chapter: S_N1, S_N2, E1, and E2. Indicate which of the four mechanisms applies to each reaction, and show their major products.

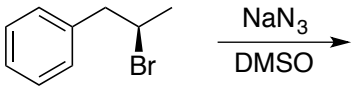
(a)



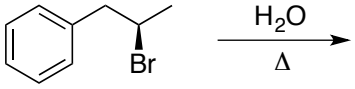
(b)



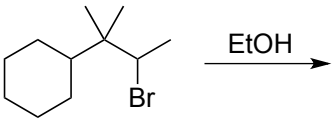
(c)



(d)

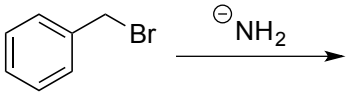


40. Provide a complete mechanism for the following reaction.

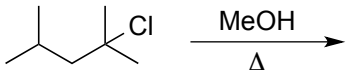


41. Draw an energy diagram for each of the following reactions. Include the reactants, products, transition states, and any intermediates.

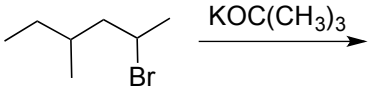
(a)



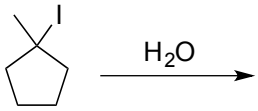
(b)



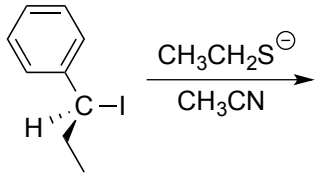
(c)



(d)

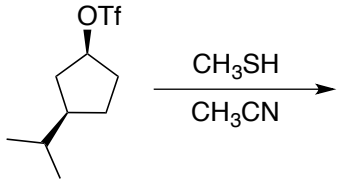


42. Provide a mechanism for the following transformation.

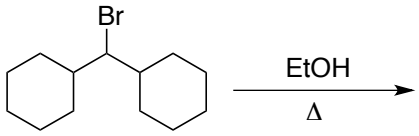


43. Predict the products of the following reactions.

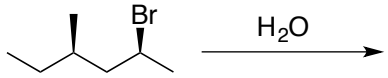
(a)



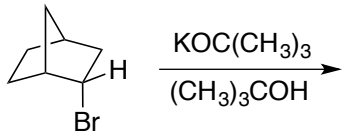
(b)



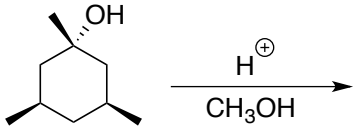
(c)



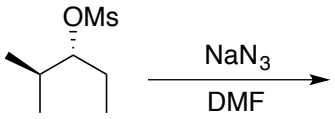
(d)



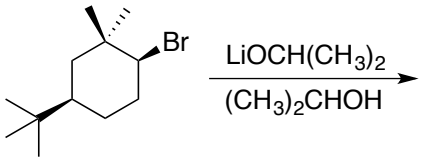
(e)



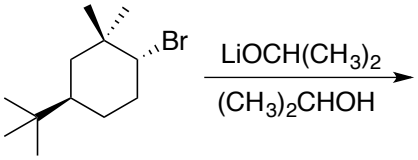
(f)



(g)

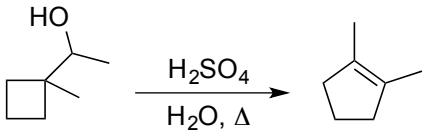


(h)

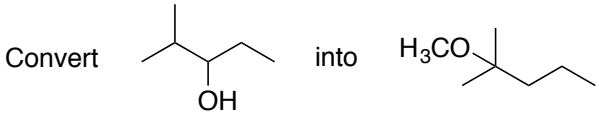


(i) The two reactions in parts (g) and (h) are quite similar, but they proceed at very different rates. Which one is faster and why?

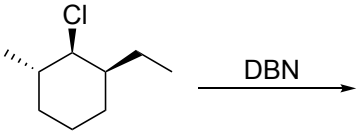
44. Provide a mechanism to explain the formation of the product in the following reaction.



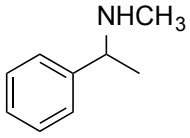
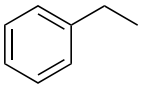
45. Provide a viable synthesis.



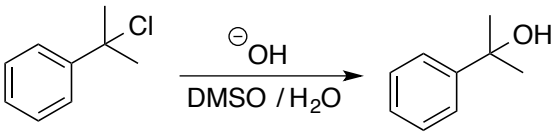
46. Provide the product of the following reaction, as well as a mechanism that explains its formation.



47. Provide a viable synthesis.

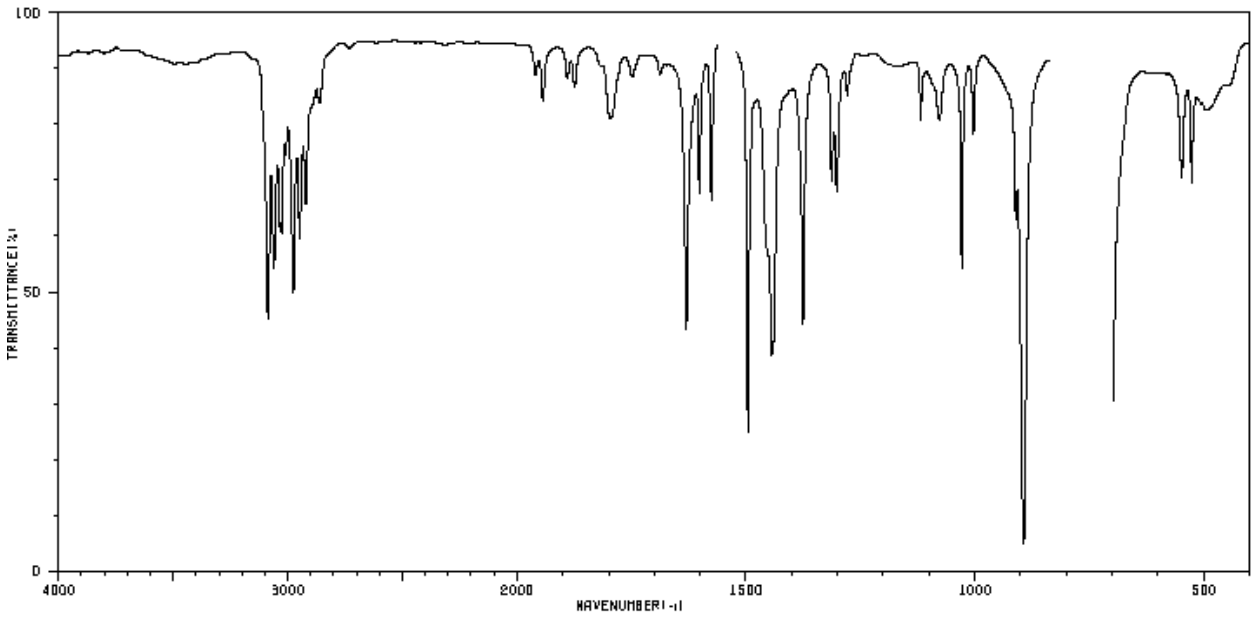
Prepare  from 

48. A chemist performs the following reaction in the hopes of obtaining the alcohol shown below (2-phenyl-2-propanol).

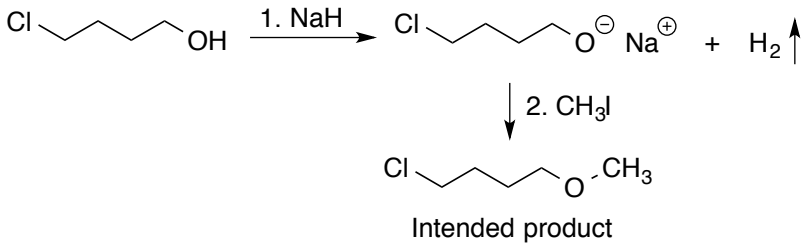


Intended product

The IR spectrum of the product follows. Was the intended product obtained? If so, what is the evidence for its formation? If not, what is the structure of the actual product?

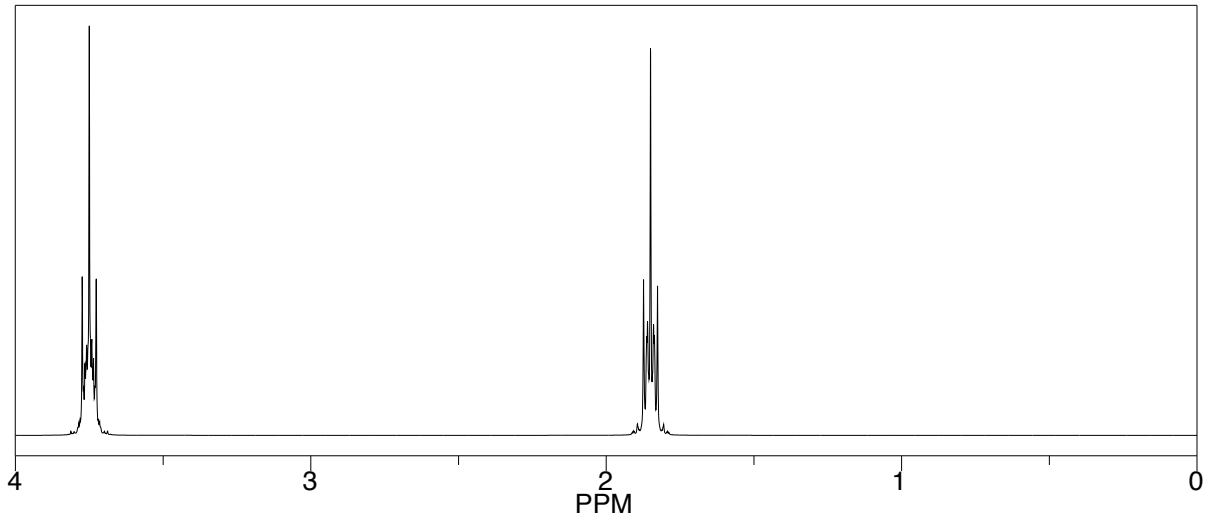


49. A chemist attempts to prepare a methyl ether by first deprotonating the alcohol shown below (4-chloro-1-butanol) using sodium hydride (NaH). The deprotonation yields an alkoxide and hydrogen gas, which bubbles out of the reaction mixture (↑). Methyl iodide was then added with the intention of completing the methylation of the oxygen and obtaining the methyl ether.



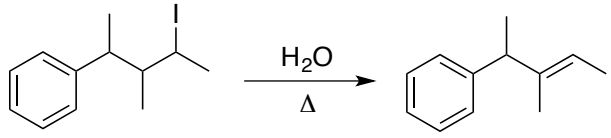
Intended product

However, the ^{1}H NMR spectrum shows only two signals. This is not consistent with the intended product, which is expected to contain five different types of protons.



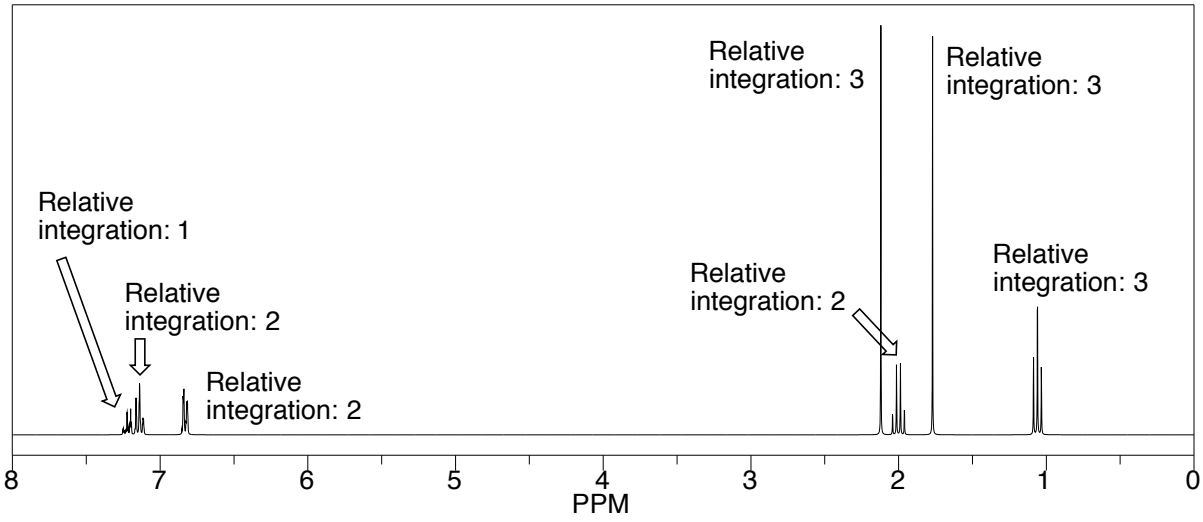
What actually transpired in this reaction?

50. The following alkyl iodide is heated in aqueous media in an attempt to produce the alkene shown below through loss of the leaving group and a proton from the more highly substituted β-carbon.



Intended product

However, the ^{1}H NMR of the product actually obtained from the reaction contains no vinyl protons between 4.5 and 6.5 ppm. How can this be explained? What actually occurred during this reaction?


Relative integration: 3
Relative integration: 3
Relative integration: 1
Relative integration: 2
Relative integration: 2
Relative integration: 2
Relative integration: 3
8
7
6
5
4
3
2
1
0
PPM

Chapter 8: Mass Spectrometry

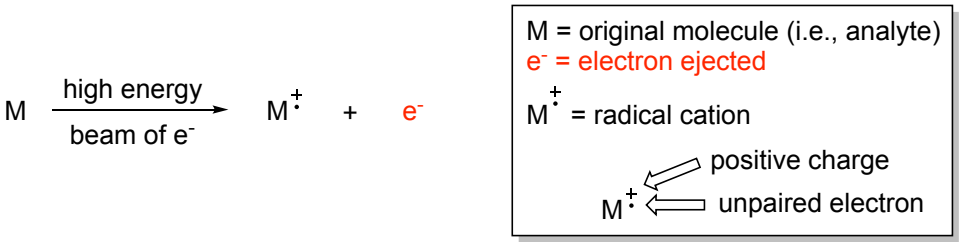
Section 1: Ionization and analysis
Section 2: Tandem techniques
Section 3: A simple mass spectrum
Section 4: The M+1 peak and the number of carbons in the molecule
Section 5: Using the molecular ion peak to determine molecular formula possibilities
Section 6: Chlorine, bromine, and their isotope patterns
Section 7: Alkane fragmentation
Section 8: Differentiation of isomers
Section 9: Functional groups and their effect on fragmentation: alkyl halides
Section 10: Functional groups and their effect on fragmentation: ethers
Section 11: Functional groups and their effect on fragmentation: alcohols
Section 12: Functional groups and their effect on fragmentation: ketones
Section 13: Using mass spectra data in problem solving

Section 1: Ionization and analysis

Mass spectrometry is a technique for the identification of the molecular mass of a compound of interest, known as an analyte. However, the technique gives far more information as well. The name "spectrometry" conveys both similarities to and differences from spectroscopic techniques, which use light to study matter. In spectrometry, light is not used as the means to acquire information about the analyte; however, the method generates a spectrum, analogous to those acquired through spectroscopic techniques such as NMR and IR.

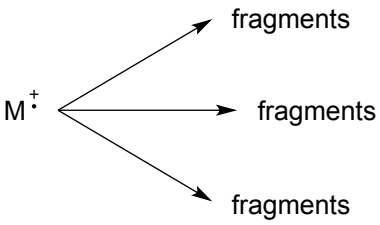
Mass spectrometry can be achieved in multiple ways, and a complete discussion of the instrumental methods is beyond the scope of this text. What follows is a brief overview of classical methods and modern variations.

A classical method uses electron impact (EI) to generate the ions that are critical to the technique. The sample is vaporized and then bombarded by a high-energy beam of electrons. Occasionally this bombardment will result in an electron being ejected from the analyte. What results is called a radical cation because it has both an unpaired electron and a positive charge. Assuming that, as is normal, all of the electrons were paired up in the original analyte, then the loss of one electron leaves the molecule with a single unpaired electron somewhere in its structure. As we learned in Chapter 6, a molecule with an unpaired electron is termed a radical. Additionally, if the original molecule was neutral, then the loss of one electron leaves it with a positive charge.

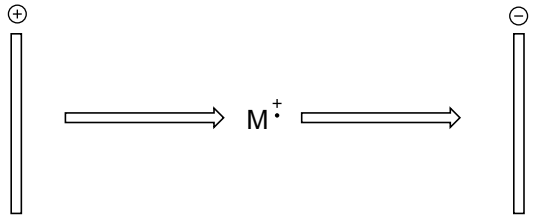


It is important to note that the mass of the radical cation is essentially the same as the mass of the original analyte (M) since the two species differ by only one electron, whose mass is negligible.

The radical cation is a high-energy species, and as a result it is fairly unstable. Consequently, this radical cation will frequently break down into smaller fragments, some of which will be detected through mass spectrometry as well. There will often be multiple degradation pathways possible, resulting in a wide variety of fragments. Later in the chapter, we'll see how the analysis of these fragments can help us to determine molecular structure.



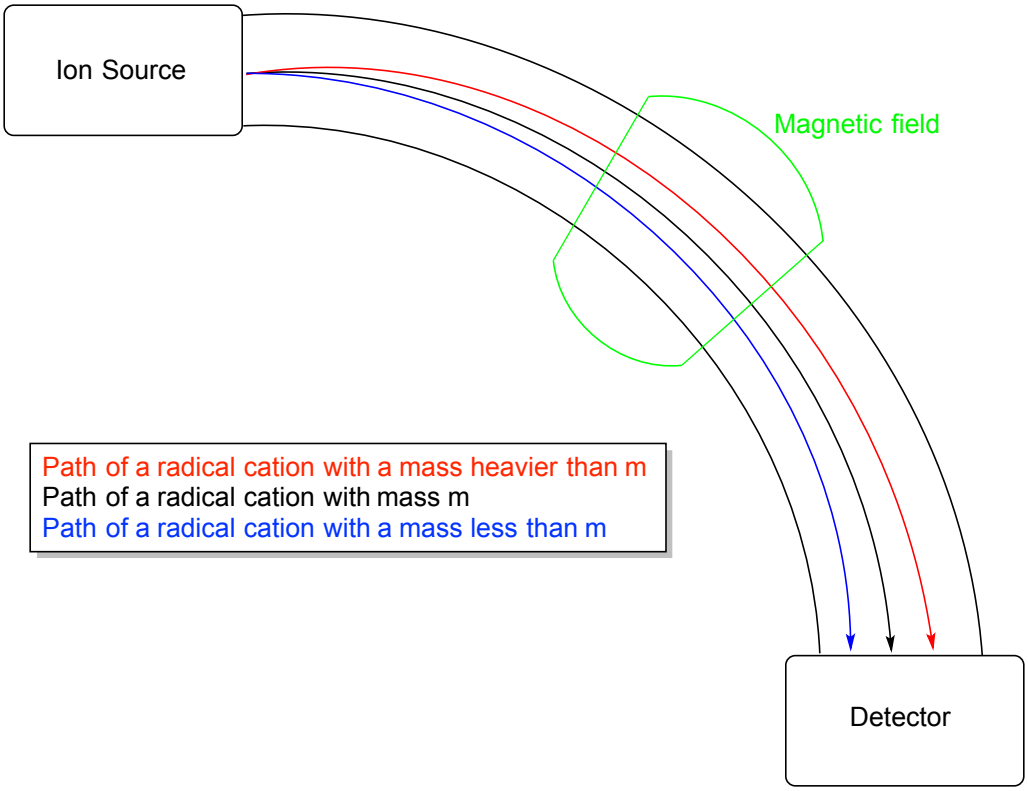
The charge of the radical cation serves as a means to manipulate it. The radical cation can be accelerated using an electric field. Attraction toward an oppositely charge plate will draw the radical cation through the mass spectrometer.



With large molecules, like proteins, the time that it takes the radical cation to traverse the distance from one plate to another can be correlated to the mass of the radical cation. This method of analysis is called time of flight (TOF).

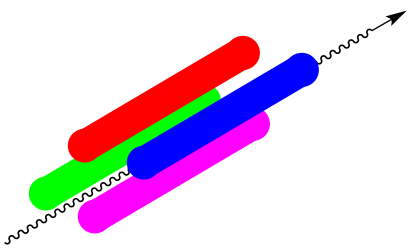
With smaller analytes, such as those molecules of interest to organic chemists, TOF analysis is not as practical. Instead, a magnetic field can be used to deflect the course of the radical cation as it travels through the instrument. The extent of the deflection depends upon the ratio of the radical cation's mass to its charge (m/z). For most small molecules, the charge will be +1, so the mass-to-charge ratio essentially equates directly to mass.

For a given magnetic field strength, a smaller radical cation will be deflected more than a larger radical cation. In this example, the location at which the various radical cations strike the detector reflects their masses.

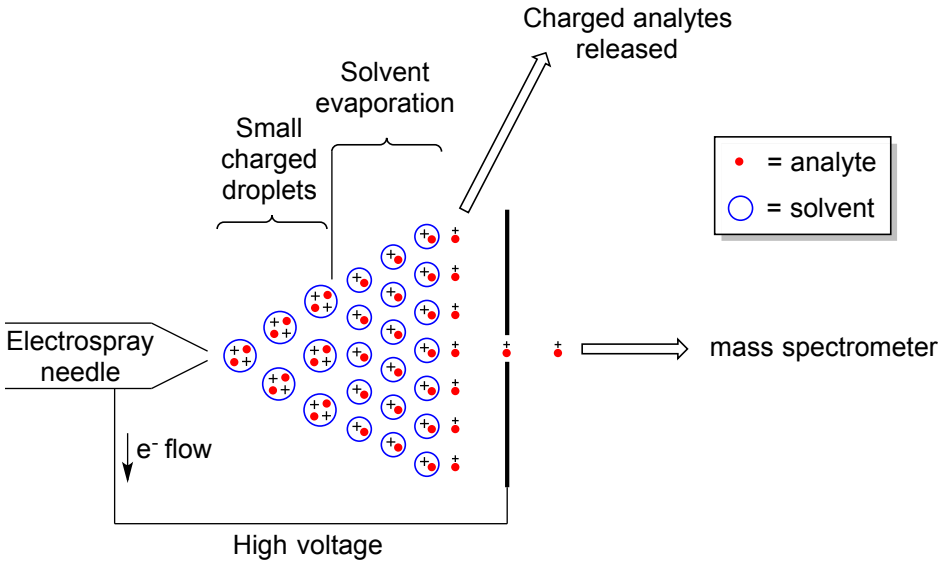


Alternatively, if the magnetic field is adjusted, then the instrument can scan for certain mass-to-charge ratios at a particular point of impact.

A more compact method of sorting ions is called a quadrupole mass analyzer. This device consists of two sets of parallel rods (blue and green are one set; red and purple are another set). The voltage applied across each set of parallel rods can be adjusted so that only an analyte with the proper mass can spiral between the rods and successfully make it to the other side. Other molecules having different masses develop trajectories that lead them to collide with the rods. In this fashion, it is possible to search for a single ion or scan for a range of ions.

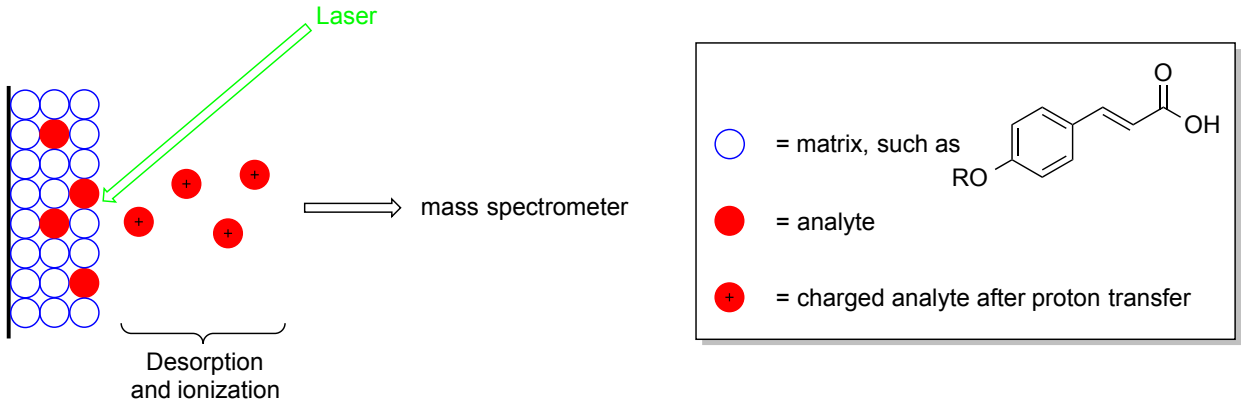


It is worth noting that other methods of ionization exist and play a critical role in the analysis of large molecules in particular. Until the 1980s, EI was the primary mode of ionization. However, very large molecules, like biomolecules, are extremely susceptible to fragmentation under these conditions. Electrospray ionization (ESI) was developed as a gentler method of ionization that enabled the successful analysis of much larger molecules. In ESI, electrospray is used to generate an aerosol of solvent containing the analyte. Small charged droplets are produced during ionization, and as the solvent molecules are shed, charged analytes are released. The development of ESI by Professor John B. Fenn of Virginia Commonwealth University led to his 2002 Nobel Prize in Chemistry.[1]



Another widely used gentle, or "soft," ionization technique is matrix-assisted laser desorption/ionization (MALDI). In this method, the analyte is dispersed in a matrix of molecules, such as cinnamic acid derivatives, that are typically acidic and absorb ultraviolet or infrared radiation effectively. The exposure to a laser causes the matrix to absorb energy leading to desorption and ionization through proton transfer. The charged analyte produced in this way allows for mass spectral analysis as well.

[1] For additional information on the 2002 Nobel Prize in Chemistry, see: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2002/



Section 2: Tandem techniques

Mass spectrometry is a very useful analytical tool, but the quality of the results is dependent upon the quality of the sample. A mass spectrum of a mixture of analytes will understandably be much more difficult to interpret than a mass spectrum of a single, pure substance. Consequently, mass spectrometry (MS) is sometimes used in tandem with a separation technique, such as gas chromatography (GC). In GC-MS, a mixture can be injected into the gas chromatograph and separated into its constituent components. As each analyte elutes from the column, it passes into a mass spectrometer for analysis. As a result, each peak in the GC has mass spectral data associated with it. This allows for the rapid analysis of mixtures.

Section 3: A simple mass spectrum

Let's consider a simple organic molecule, like methane (CH_4). Its bombardment by a high-energy beam of electrons in electron impact ionization produces a radical cation.

$$CH_4 \xrightarrow[\text{beam of } e^-]{\text{high energy}} \left[CH_4\right]^{+\bullet} + e^-$$

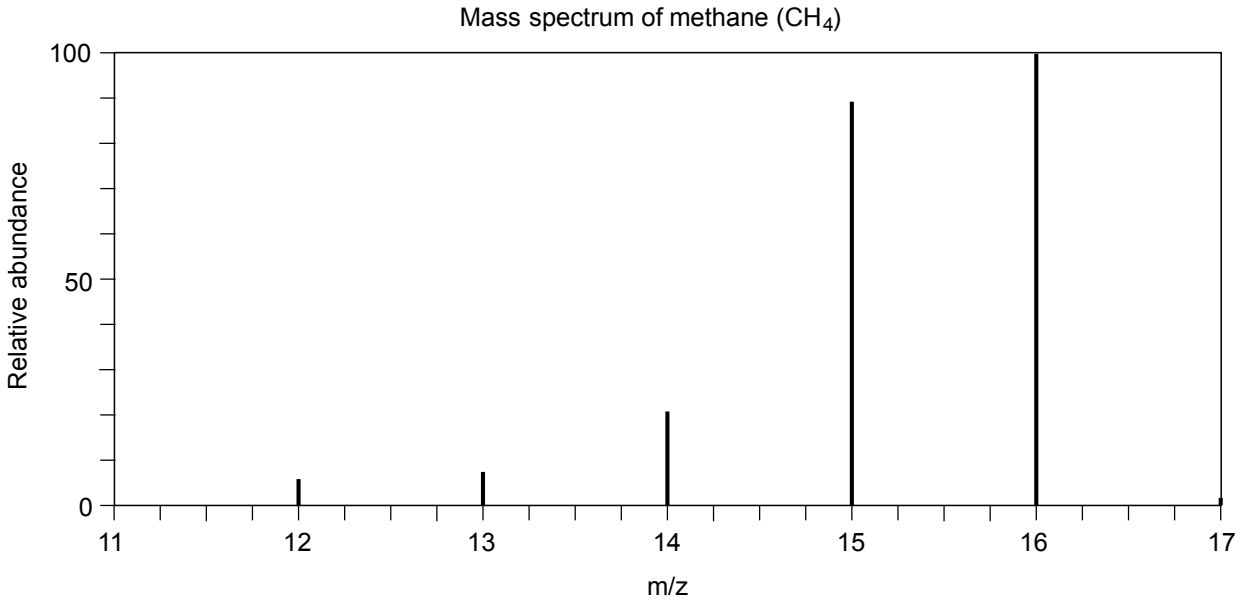
Since the radical cation has only lost a single electron, its mass is essentially the same as that of methane. That mass is 16 amu. When calculating mass for mass spectrometry, it is important to remember that individual molecules are detected in this technique. Therefore, the masses of the most commonly occurring isotopes are used to determine the most common molecular mass. This stands in contrast to using average molecular mass, which we commonly do when consider bulk samples, as in lab.

Molecular mass of methane	
C =	12.000 amu
H =	1.008 amu
H =	1.008 amu
H =	1.008 amu
+ H =	1.008 amu
	16.032 amu

Average molecular mass of methane	
C =	12.011 amu
H =	1.008 amu
H =	1.008 amu
H =	1.008 amu
+ H =	1.008 amu
	16.043 amu

Right now, the difference appears to be insignificant because to the nearest whole number (and even to the nearest tenth) both methods produce the same value. However, in subsequent examples as the molecules become larger, those small differences will add up to create greater disparities between the calculations.

On the mass spectrum of methane, we do indeed see a signal at m/z 16 corresponding to the radical cation. This signal is often called the molecular ion peak since it corresponds simply to the mass of the ionized molecule. This same signal also happens to be the most abundant one in this mass spectrum and is therefore called the base peak. The relative abundance of the base peak is arbitrarily set to 100%. It is coincidental in this instance that the molecular ion peak is also the base peak. The two are not necessarily the same. In other words, the heaviest ion is not necessarily the most abundant one, and we will see many cases where the molecular ion peak and base peak are different signals.



In the mass spectrum of methane, peaks at m/z 15, 14, 13, and 12 are also evident. These correspond to fragments of methane in which hydrogen atoms are successively lost.

Additionally, a very small peak is visible at m/z 17. At first glance, it would not seem possible to have a peak with a mass greater than that of the molecular ion. This is possible due to the fact that of 1.1% of carbon is ^{13}C, an isotope of ^{12}C with one additional neutron

and therefore one additional mass unit. The peak in the mass spectrum generated by $^{13}CH_4$ is sometimes called the M+1 peak, referring to the fact that it is one mass unit higher than the molecular ion peak (M).

Section 4: The M+1 peak and the number of carbons in the molecule

The relative abundance of the M+1 signal can be used to predict the number of carbons in the molecule, provided that carbon is the only element in the molecule with an isotope of significant abundance that is one mass unit heavier.

A simple formula relates the abundance of the M+1 signal for a molecule to its number of carbons (n). For each carbon, there is a 1.1% chance of finding a ^{13}C in that location. Therefore, multiplying the number of carbons by 0.011 will determine the chance of finding a ^{13}C somewhere in the molecule. If the relative abundance of the molecular ion peak is multiplied by this factor, the abundance of the M+1 peak is the result.

$$(Relative\ abundance\ of\ M+1) = n\ (0.011)\ (Relative\ abundance\ of\ M)$$

This equation can be rearranged if we have a mass spectrum and are interesting in using it to find the number of carbon atoms in the molecule.

$$n = \frac{(Relative\ abundance\ of\ M+1)}{(0.011)\ (Relative\ abundance\ of\ M)}$$

As noted above, for this equation to hold true, it is important that carbon be the only element with an isotope contributing significantly to the M+1 peak. For instance, if nitrogen is present in the molecule, the equation won't hold true due to the 0.4% abundance of ^{15}N, which is one mass unit heavier than the predominant isotope, ^{14}N.

Problem 1. Deuterium is an isotope of hydrogen that contains one neutron in the nucleus in addition to its proton. Why doesn't this affect the calculation described above?

Section 5: Using the molecular ion peak to determine molecular formula possibilities

A simple application of mass spectrometry is the prediction of reasonable molecular formulas for an unknown substance. Consider an unknown substance whose mass spectrum shows a molecular ion peak of m/z 180. The maximum number of carbons that such a substance could contain is 15.

$$\frac{180\ amu}{12\ amu\ per\ C} = 15\ C$$

However, the molecule probably doesn't contain 15 carbon atoms and 0 hydrogen atoms. Instead, a much more reasonable molecular formula could be produced by subtracting one carbon from the formula and replacing it with 12 hydrogen atoms to give $C_{14}H_{12}$. Such a

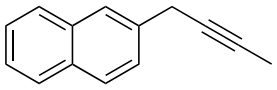
molecule would be highly unsaturated. Recall that degrees of unsaturation (DOU) are π bonds or rings. To calculate the degrees of unsaturation, the number of hydrogen atoms present in the formula is subtracted from the number of hydrogen atoms that a given number of carbons could hold (2n+2, where n = the number of carbons). This difference is then divided by two, since hydrogens are removed in pairs to form π bonds or rings.

$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ present}{2}$$

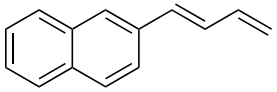
In this instance, for $C_{14}H_{12}$ there are nine degrees of unsaturation.

$$Degrees\ of\ Unsaturation = \frac{[2(14)+2] - 12}{2} = 9$$

While this is a highly unsaturated molecule, such structures are possible. Two of the many possibilities are shown below.



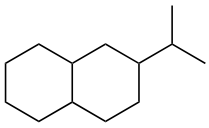
$C_{14}H_{12}$



$C_{14}H_{12}$

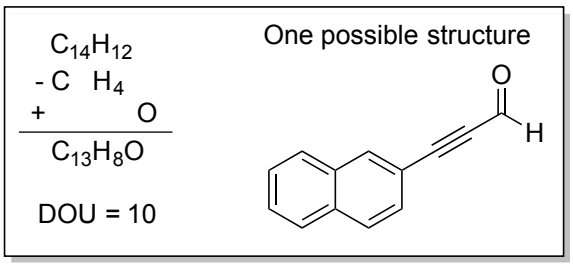
Of course, other structures with the same formula could also be drawn, and it isn't possible to determine which is the correct structure of the unknown substance without additional information, such as IR and NMR spectra.

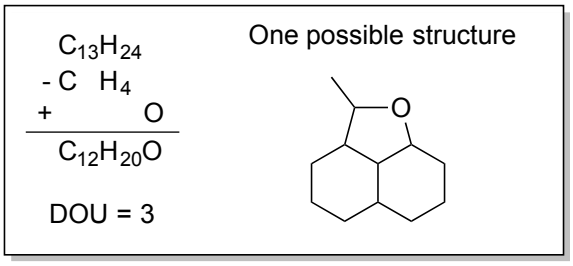
It is also important to note that $C_{14}H_{12}$ is not the only viable molecular formula for this unknown. Other reasonable formulas can be derived from the original one. Another carbon could be replaced with 12 more hydrogens, giving $C_{13}H_{24}$, and reducing the amount of unsaturation to just 2 degrees. One of many possible structures with that formula follows.



$C_{13}H_{24}$

Additionally, a CH_4 unit (mass 16 amu) can be removed from either formula and replaced with an oxygen atom (mass 16 amu). This produces even more viable molecular formulas for the unknown substance, as shown below. As you consider these examples, recall that the introduction of oxygen atoms into the formulas has no impact on the calculation of degrees of unsaturation (DOU).





Problem 2. Propose a formula for a saturated hydrocarbon with a molecular ion peak of *m/z* = 128. Then, use this formula to derive one containing oxygen that is also consistent with this molecular ion peak. Draw one possible structure for each formula.

The previous example of an unknown with a molecular ion peak at m/z 180 and its many viable formulas suggests that a better method is needed to reduce the number of possible formulas. This need is further highlighted by our current inability to distinguish between certain analytes. A classic example is the comparison of carbon monoxide (CO), nitrogen (N_2), and ethylene ($H_2C{=}CH_2$). When measured to the nearest whole number, each of these three substances has a mass of 28 amu. Low-resolution mass spectrometry (LRMS) provides mass spectral data to the nearest whole number. However, high-resolution mass spectrometry (HRMS) provides several more decimal places. The masses of the elements are measured relative to ^{12}C as the standard, which has been assigned a mass of exactly 12.0000 amu. The molecular weights below show that, while LRMS cannot distinguish these three analytes, HRMS can.

Mass of CO	Mass of N_2	Mass of $H_2C{=}CH_2$
		C = 12.0000 amu
		C = 12.0000 amu
		H = 1.00783 amu
		H = 1.00783 amu
C = 12.0000 amu	N = 14.0031 amu	H = 1.00783 amu
+ O = 15.9949 amu	+ N = 14.0031 amu	+ H = 1.00783 amu
27.9949 amu	28.0062 amu	28.0313 amu

It is also the case that molecular ion masses measured using HRMS are likely to correspond to only one (or at most a very few) possible formulas. For instance, a molecular ion at m/z 180.0939 would correspond to just one of the formulas we considered earlier as possible identities of our unknown substance.

Mass of $C_{14}H_{12}$

14 C = 14(12.0000 amu)
+ 12 H = 12(1.00783 amu)

180.0940 amu

Mass of $C_{13}H_{24}$

13 C = 13(12.0000 amu)
+ 24 H = 24(1.00783 amu)

180.1880 amu

Mass of $C_{13}H_8O$

13 C = 13(12.0000 amu)
8 H = 8(1.00783 amu)
+ O = 15.9949 amu

180.0575 amu

Mass of $C_{12}H_{20}O$

12 C = 12(12.0000 amu)
20 H = 20(1.00783 amu)
+ O = 15.9949 amu

180.1515 amu

These calculations reveal that the unknown substance must have the molecular formula $C_{14}H_{12}$.

Problem 3. An unknown analyte exhibits a molecular ion peak at m/z 72.0575. Identify the molecular formula that best matches these HRMS results. Propose a plausible structure corresponding to the correct molecular formula.

Section 6: Chlorine, bromine, and their isotope patterns

Earlier, when we examined the mass spectrum of methane, we saw that isotopes can lead to the presence of peaks heavier than the molecular ion peak. For instance, we saw that the 1.1% of methane molecules containing a ^{13}C would give rise to the M+1 peak. Carbon is not the only element with an isotope having sufficient abundance to lead to an observable signal of this type. Two of the halogens also lead to distinctive isotope patterns.

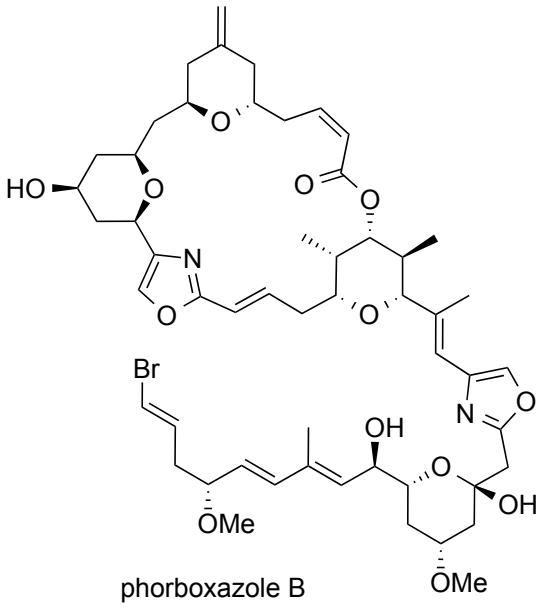
Chlorine has two predominant isotopes, ^{35}Cl and ^{37}Cl, that are present in nearly a 3:1 ratio. Consequently, a molecule containing chlorine will exhibit a molecular ion peak (M), as well as a peak two mass units higher (M+2). The M+2 peak is due to those molecules that contain ^{37}Cl and will be about one-third the height of the molecular ion peak.

Bromine also has two isotopes, ^{79}Br and ^{81}Br, whose masses differ by two, leading to an M and M+2 peak as well. However, for bromine these isotopes are present in nearly a 1:1 ratio, meaning that the M and M+2 peak heights will be almost identical.

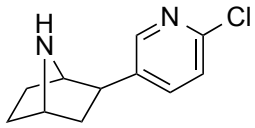
These distinctive isotope patterns are useful in identifying the presence of a halogen. Prominent M and M+2 peaks suggest that a halogen is contained in the analyte, and the relative abundance of the two signals reveals whether that halogen is chlorine or bromine.

Problem 4. Phorboxazole B was isolated from a sea sponge and kills cancer cells at very low concentrations. Epibatidine is a powerful poison found on the skin of certain kinds of poison dart frogs. Each of these natural products contains a halogen.

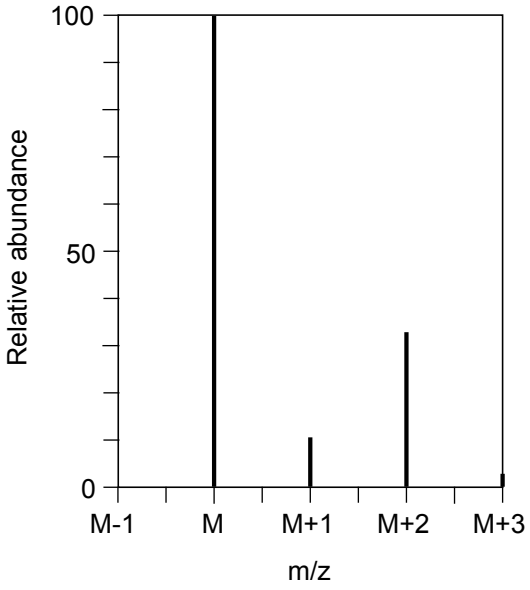
(a) Match each compound with its mass spectrum.

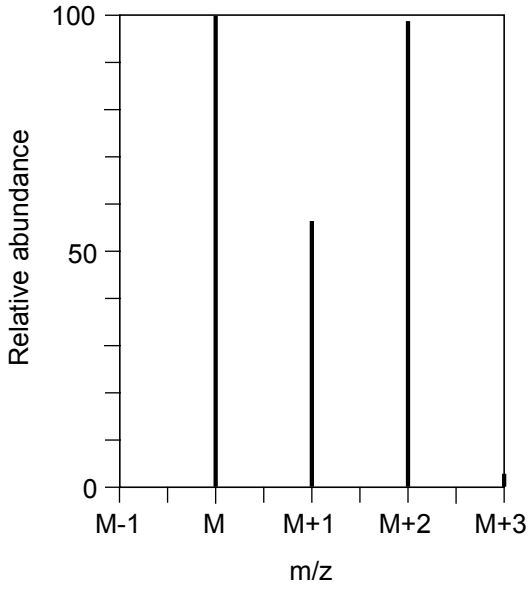


phorboxazole B



epibatidine





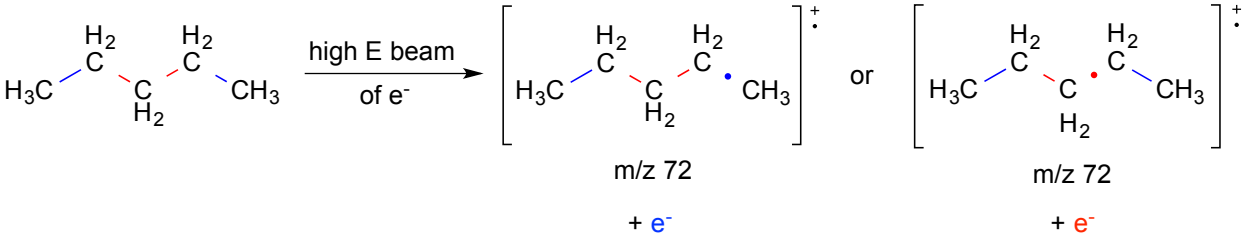
(b) Why does each compound exhibit an M+1 signal? Why is the M+1 signal so large in the second mass spectrum?

Section 7: Alkane fragmentation

With a very small molecule, like methane, the fragmentation options are quite limited as we saw previously. However, with slightly larger molecules containing a larger number of bonds, the options will be more varied, so it will help us to understand mass spectra if we make a systematic study of the fragmentation possibilities.

Let's consider the ionization of pentane. As pentane is bombarded by a high-energy beam of electrons, an electron will be ejected from a few molecules, leading to their ionization. Carbon-carbon bonds are typically weaker than carbon-hydrogen bonds. Bond dissociation energies (BDE) highlight this fact. The typical bond dissociation energy of a carbon-carbon bond is 83 – 85 kcal/mole, while the typical BDE for a carbon-hydrogen bond is 96 – 99 kcal/mole. The weaker carbon-carbon bond is more likely to experience the loss of an electron.

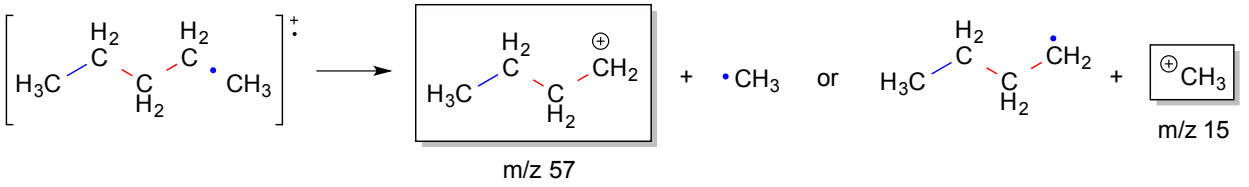
There are two types of carbon-carbon bonds in pentane, colored blue and red below, and an electron could be ejected from either to provide one of two possible radical cations. These are the molecular ions that generate the molecular ion peak (M) at m/z 72.



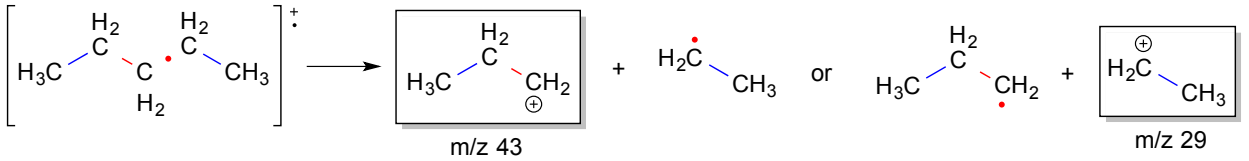
One bond in each of these radical cations has been dramatically weakened by the loss of an electron. Therefore, fragmentation is likely. The first radical cation, which lost a blue electron from a terminal C-C bond, can fragment in one of two ways:

(1) the methyl group can retain the unpaired electron, leaving a butyl carbocation or
(2) the butyl group can retain the unpaired electron, leaving a methyl carbocation

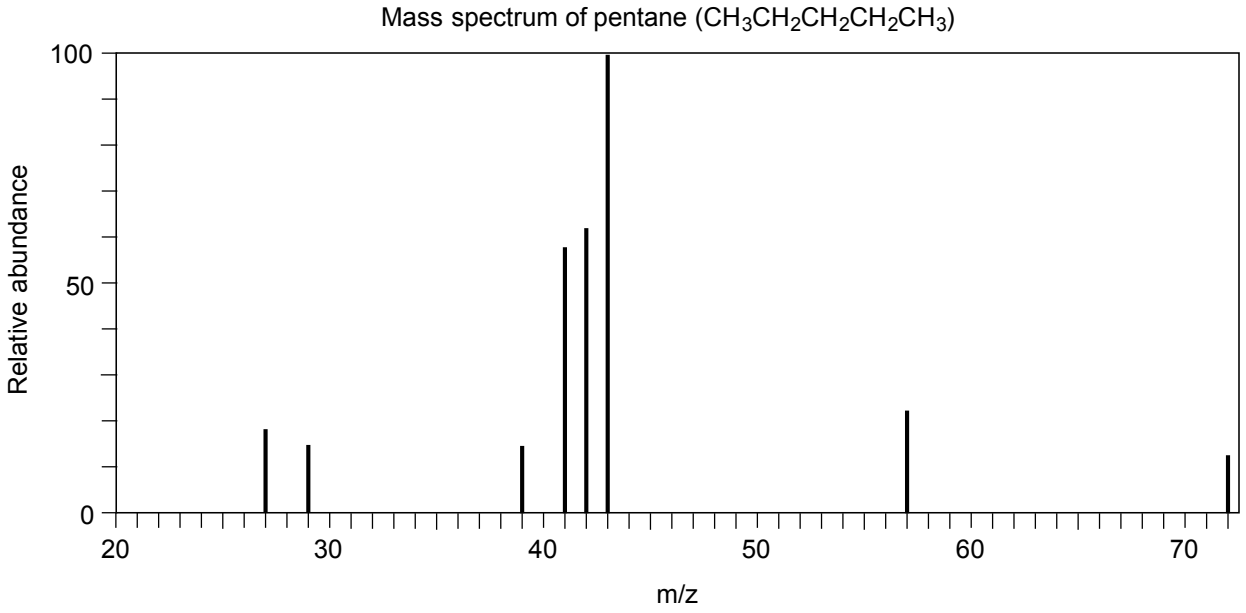
Remember that the *ions* will be detected in mass spectrometry, while the neutral radicals will not be directly observed.



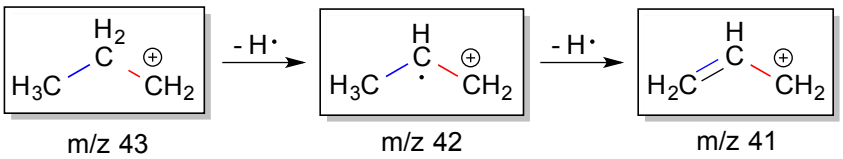
The second radical cation, the one that lost an electron from the interior C-C bond, can also undergo fragmentation in an analogous fashion to yield a propyl or ethyl carbocation.



All of these signals at m/z 72, 57, 43, 29, and 15 can be seen in the mass spectrum, although the signal at m/z 15 is miniscule and only fairly prominent signals are shown in the following diagram. The stability of the fragments determines their relative abundance. In general, more highly substituted carbocations and radicals will be more stable fragments.



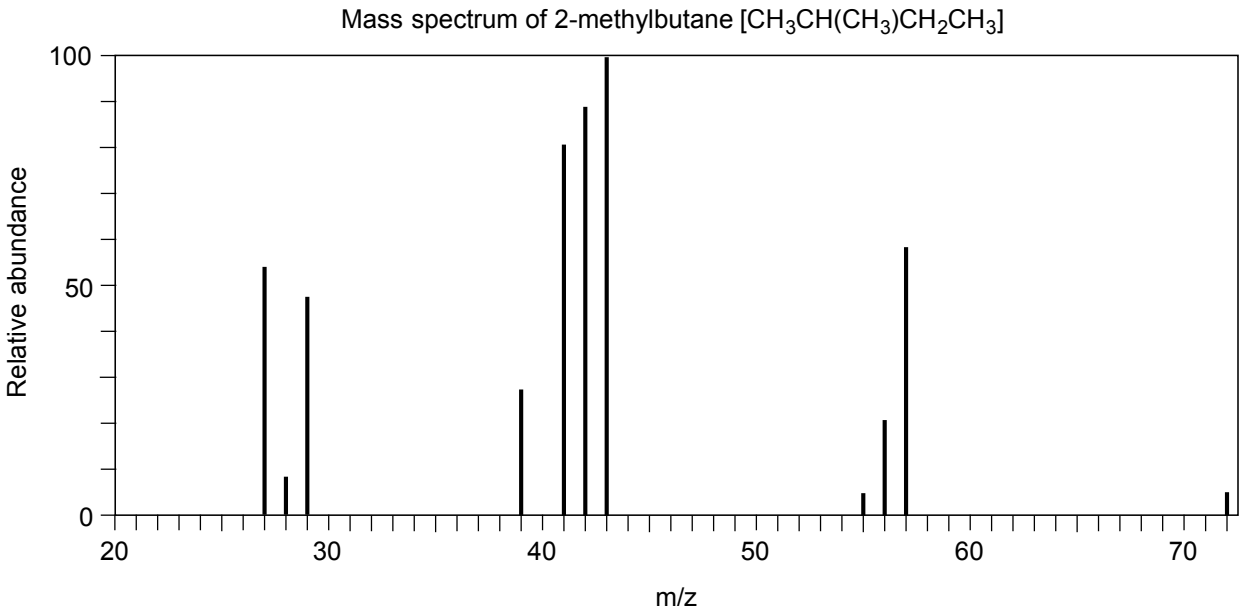
Additionally, we see that some signals on the mass spectrum have not yet been explained. For instance, there are prominent signals at m/z 42 and 41. These result from further fragmentation of the propyl cation. Successive fragmentations are sometimes possible if they enhance the stability of the molecule. A carbocation can be rendered more stable through resonance, and the loss of two hydrogens from the propyl cation would introduce a π bond, giving an allylic radical that enjoys resonance stabilization.



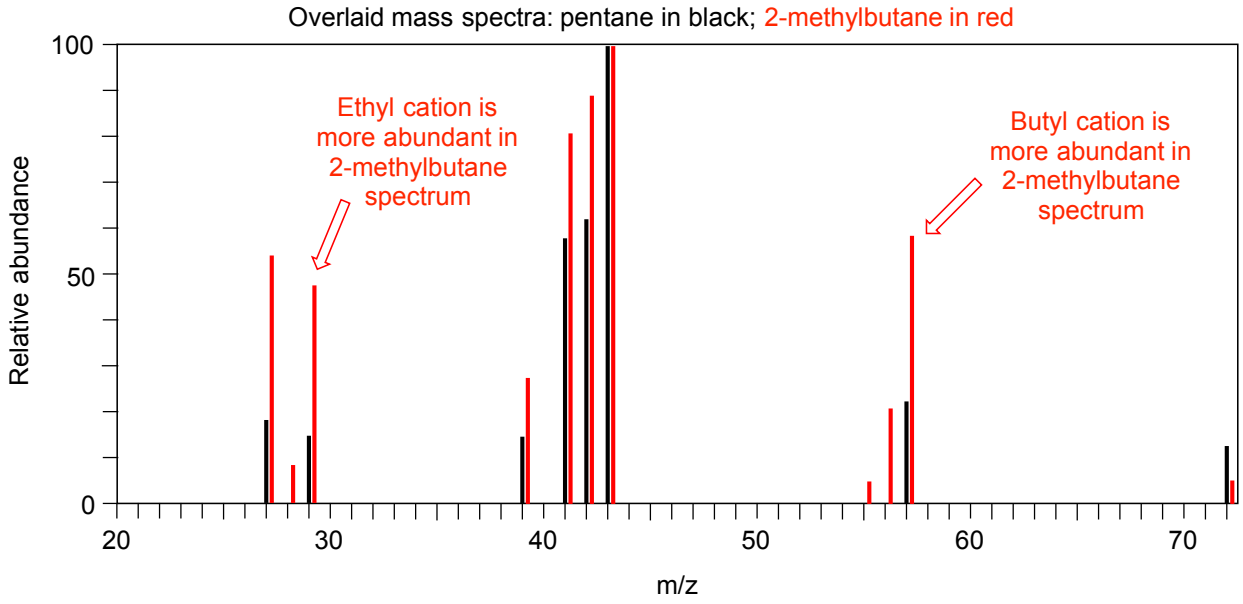
Problem 5. Show the formation of the fragments that you would expect to observe in the mass spectrum of hexane.

Section 8: Differentiation of isomers

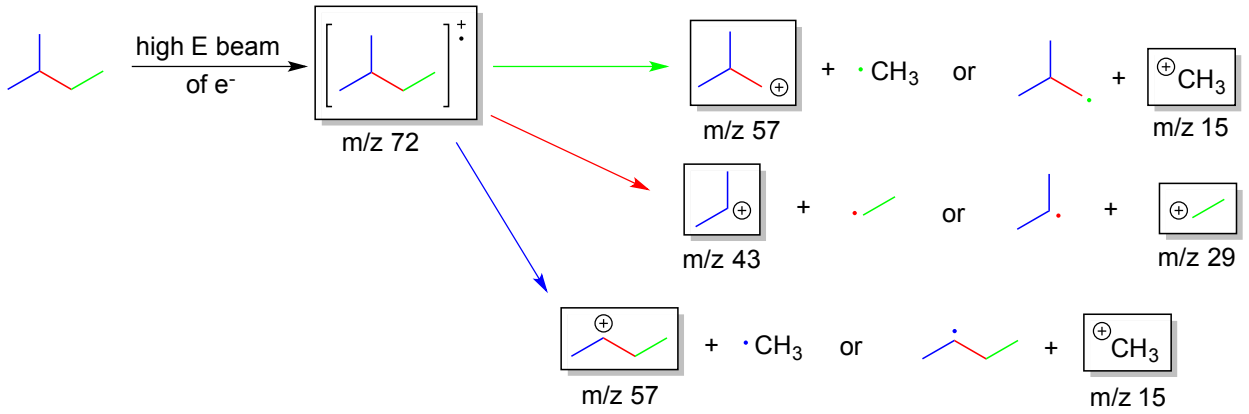
Sometimes isomers will experience fragmentation patterns that reflect their structural differences. 2-Methylbutane, an isomer of pentane, is an illustrative example. Its mass spectrum is shown below.



While the propyl cation remains the dominant fragment (i.e., the base peak), the abundances of both the butyl and ethyl cation fragments have grown in intensity relative to it. The mass spectra of pentane and 2-methylbutane are overlaid in the following diagram to highlight these differences. The abundance of the methyl cation signal at m/z 15 is also greater in the 2-methylbutane spectrum; however, that region of the mass spectrum is not included in the diagram.



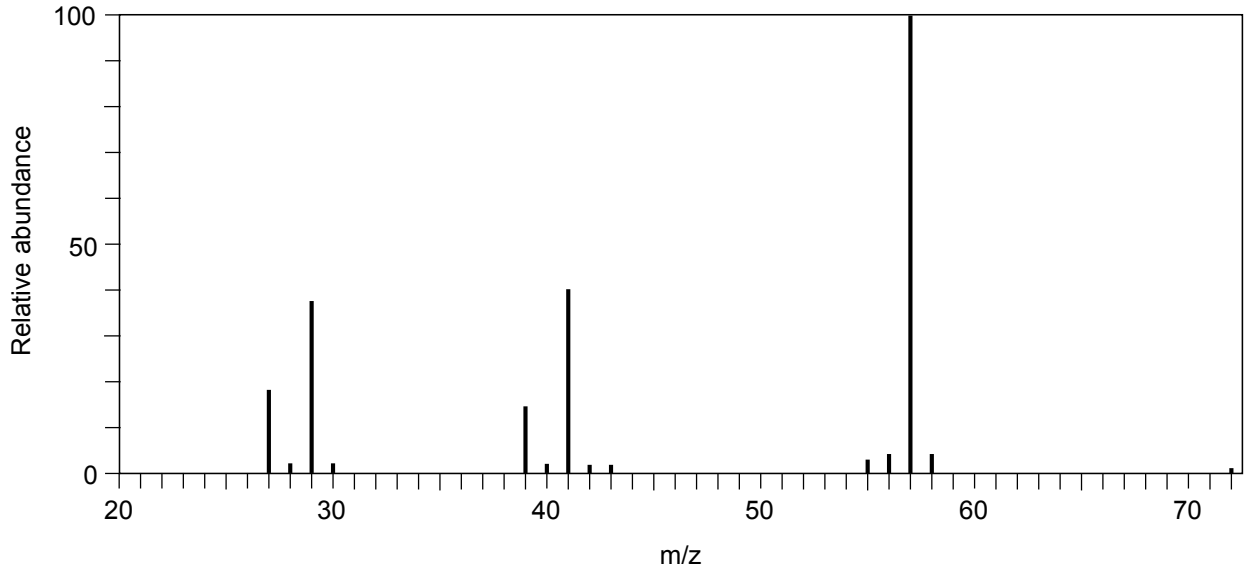
Examination of the structure and the relative stability of the possible fragments explains the differences in these spectra. 2-Methylbutane has three different types of carbon-carbon bonds, shown in blue, red, and green below. Any of these bonds could conceivably fragment during mass spectral analysis.

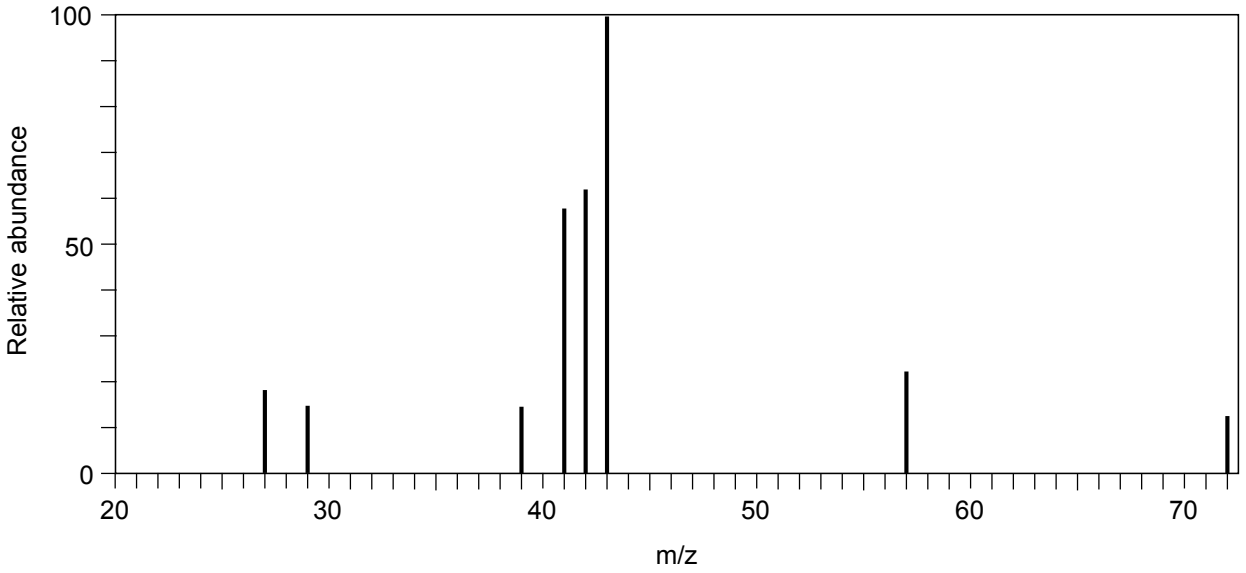


Notice that the fragmentation of a blue bond results in a secondary butyl carbocation (m/z 57). When a butyl carbocation was produced from pentane, it was primary. The more stable secondary butyl carbocation resulting from 2-methylbutane is therefore understandably greater in relative abundance.

Fragmentation of the central red bond leads to a primary ethyl carbocation (m/z 29) and a secondary radical. In contrast, when an ethyl carbocation was released from pentane, it was accompanied by a primary propyl radical. The more stable radical formed in the fragmentation of 2-methylbutane helps to explain the greater relative abundance of the m/z 29 signal.

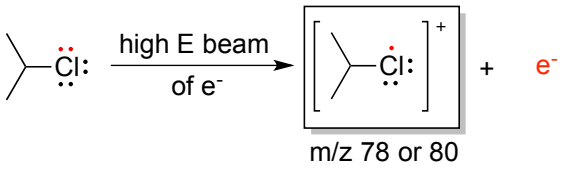
Problem 6. The mass spectra of pentane and neopentane [$C(CH_3)_4$] are shown below. Match each spectrum with the corresponding compound and explain the major differences between the spectra.



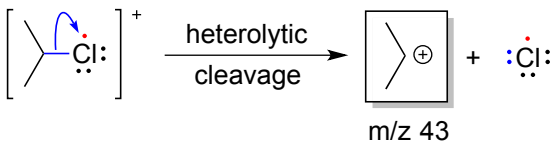


Section 9: Functional groups and their effect on fragmentation: alkyl halides

When we considered alkane fragmentation, the initial ionization resulted from the loss of an electron from a sigma bond. However, when heteroatom-containing functional groups are present in a molecule, there are non-bonding electrons present. These lone pair electrons are less tightly held than σ-bonding electrons, and as a consequence, they are more likely to be displaced during the ionization step. An alkyl halide provides an illustrative example.

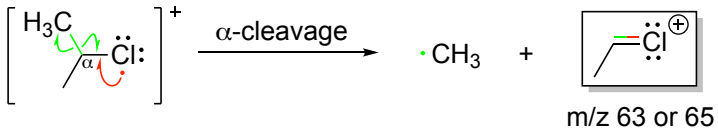


The molecular ion produced in this fashion can fragment in one of two ways. One option is known as heterolytic cleavage. In this case, the adjacent σ bond breaks with the electrons flowing onto the halogen as expected. The result is a neutral halogen radical and a carbocation.



Alternatively, α-cleavage may occur. In this scenario, the halogen's electron is used to form half of a π bond. The other electron needed to complete the π bond comes from the homolytic cleavage of one of the bonds stemming from the α-carbon. As this sigma bond fragments, a radical is released. Since each of these events involves the movement of a

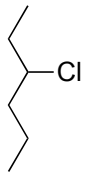
single electron, single-headed fishhook arrows are used to denote them. Also, note that the charged fragment still contains the halogen and therefore still exhibits an isotope pattern.



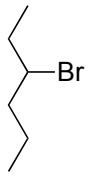
α-Cleavage is common for alkyl chlorides because the C-Cl bond has a bond dissociation energy (≈80 kcal/mole) close to that of C-C bonds (≈85 kcal/mole). For alkyl bromides, in which the carbon-to-halogen bond is weaker (≈65 – 68 kcal/mole), heterolytic cleavage occurs more frequently than α-cleavage, which would require the cleavage of the significantly stronger C-C bond.

Problem 7. Identify the fragments that you would expect to observe in the mass spectrum of each of the following alkyl halides.

(a)



(b)

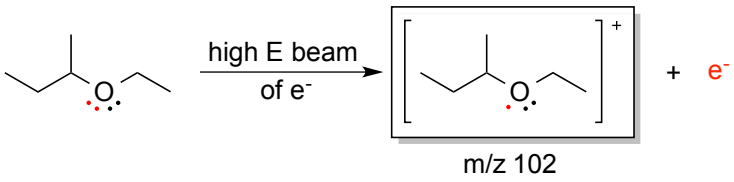


(c) Aside from the mass differences, how would you expect the spectra of the preceding compounds to differ?

Section 10: Functional groups and their effect on fragmentation: ethers

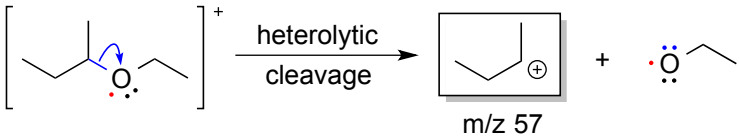
The behavior of ethers follows the same paradigms outlined above: heterolytic cleavage or α-cleavage. If we consider an unsymmetrical ether, it becomes clear that multiple fragmentations will be possible using only these two mechanistic paradigms.

In the ionization step, we would again expect an electron to be lost from the less tightly held non-bonding electrons to generate the molecular ion.

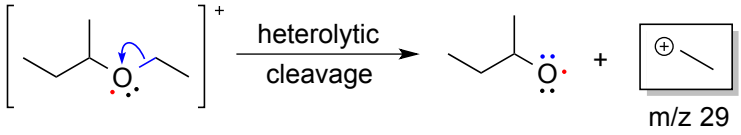


This radical cation could undergo two different heterolytic cleavage events.

(1)



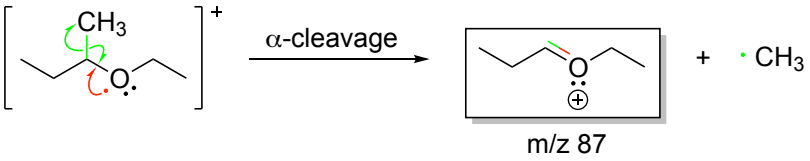
(2)



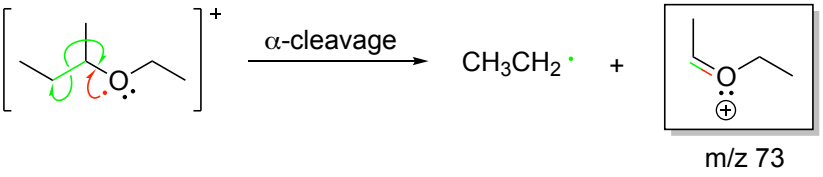
We might expect the fragment containing a secondary carbocation to be more prominent than the one containing a primary carbocation, but both fragments will likely be observed in the mass spectrum.

By the same token, there are multiple α-cleavage pathways. Two of these pathways (1 and 3, below) release a methyl group and therefore result in fragments that, though they are structurally distinct, have the same mass. The other pathway (2, below) releases an ethyl group and therefore results in a fragment with a different mass.

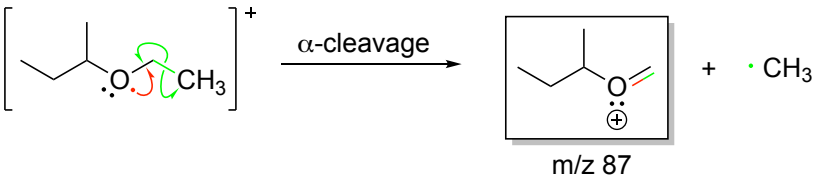
(1)



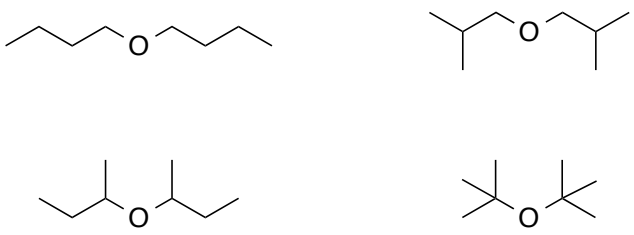
(2)



(3)



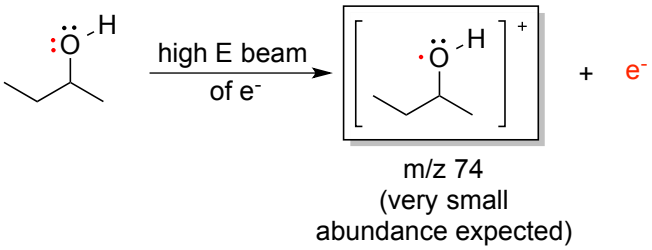
Problem 8. Which of the following ethers is most consistent with a mass spectrum showing signals at m/z 130, 115, and 57?



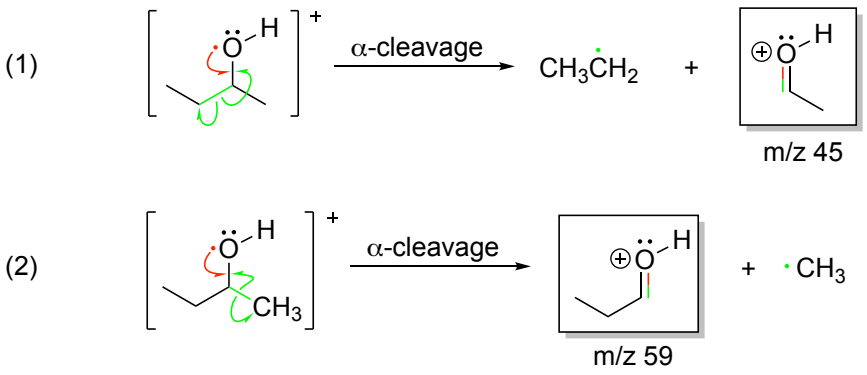
Section 11: Functional groups and their effect on fragmentation: alcohols

Alcohols present another instance of a heteroatom-containing functional group. They too lose an electron from a lone pair during ionization. However, alcohols are unique in that they rarely exhibit a prominent molecular ion peak in the mass spectrum. The electron-deficient oxygen is unstable enough that fragmentation is very likely. While α-cleavage is still possible, we'll see that dehydration is a more highly probable fragmentation.

Ionization of an alcohol yields a radical cation as expected.

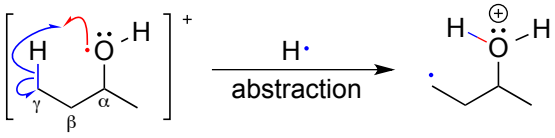


This radical cation rapidly fragments; however, heterolytic cleavage, which would result in a hydroxyl radical, is generally unfavorable because the electron-deficient oxygen has no electron-donating alkyl groups to stabilize it. Instead, α-cleavage may occur via one of two pathways.

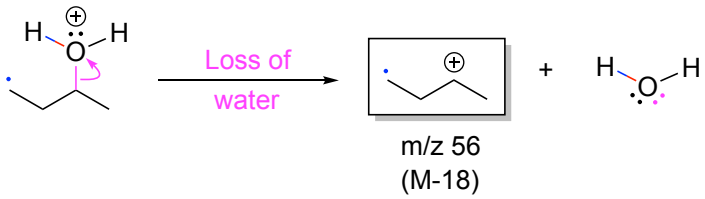


When the alcohol is sizable enough to have a hydrogen at a distance of five atoms from the oxygen, dehydration may also occur. This process begins with the abstraction of a hydrogen atom from the γ-carbon. Another way of phrasing this is to say that the hydrogen that is five atoms from the oxygen is abstracted. A note on terminology is in order here. We would not say that the γ-carbon is deprotonated. "Deprotonation" refers to the removal of a

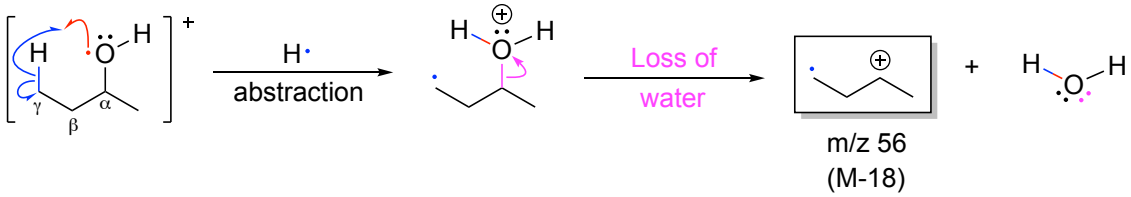
proton (i.e., H^+ is removed). In this case, a hydrogen atom (i.e., $H\cdot$) is removed, and so we say that "a hydrogen atom was abstracted."



This process has not yet resulted in any change in mass because the hydrogen atom was simply transferred from one location to another within the same molecule. The significance of this step is that the molecule now contains a good leaving group: water. The dissociation of water (or dehydration) occurs at this stage.

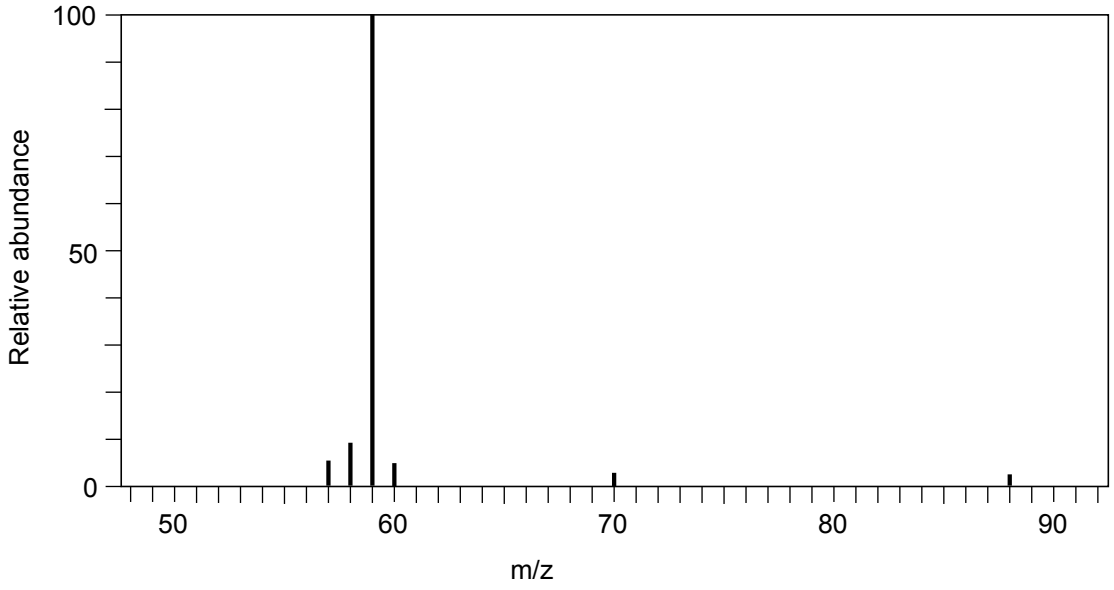


The new radical cation is a fragment of the original molecular ion with a mass that is 18 amu smaller because 18 amu is the mass of a water molecule. Consequently, this new radical cation gives rise to what is sometimes called the M-18 peak. The entire two-step process is shown together below. It is important to note that step 1 is homolytic (and therefore uses fishhook arrows), while step 2 is heterolytic (and therefore uses regular mechanistic arrows).



In the analysis of mass spectra of alcohols, it may not always be possible to see the molecular ion peak (M), but it will usually be possible to see the dehydration fragment (M-18).

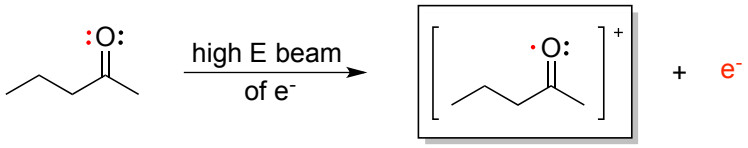
Problem 9. What is the structure of the alcohol that gives the following mass spectrum? Explain the origin of each of the peaks.



Section 12: Functional groups and their effect on fragmentation: ketones

Ketones have unique fragmentation behavior, but there is some analogy to the behavior of alcohols. For both functional groups α-cleavage is possible. Also, both functional groups can fragment in an alternative fashion that involves intramolecular hydrogen atom abstraction.

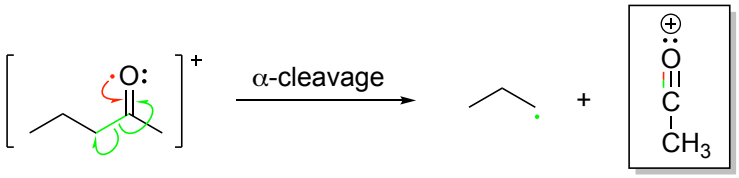
Ionization of ketones proceeds as expected, with the loss of an electron from a lone pair to produce the molecular ion.



m/z 86

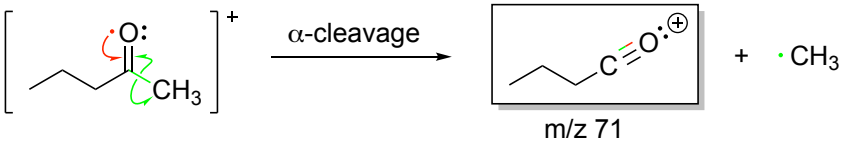
Fragmentation can occur via α-cleavage in one of two ways, given the asymmetry of the molecule.

(1)



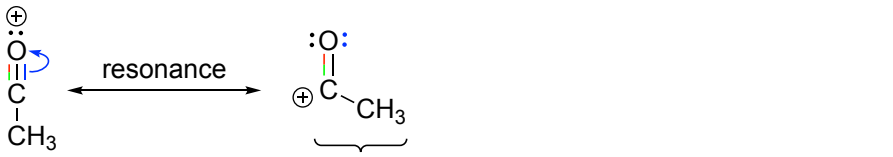
m/z 43

(2)

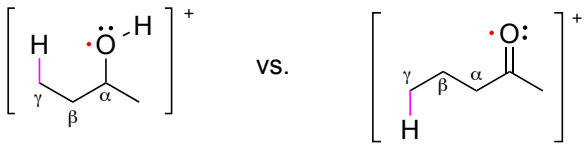


m/z 71

The C≡O⁺ species that are formed are known as acylium ions. These are resonance forms of carbonyl-containing groups bearing an alkyl substituent (i.e., acyl groups) that happen to also be positive (hence the "ium" suffix). These will play an important role in the Friedel-Crafts acylation, a reaction we'll cover in Chapter 14.

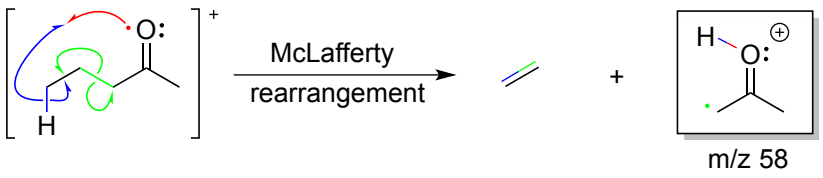


An alternative fragmentation motif for ketones is known as the McLafferty rearrangement, and it involves hydrogen abstraction from the γ-carbon. However, because of a difference in the use of Greek lettering for alcohols and ketones, the γ-carbon is at a different distance from the oxygen atom. With alcohols, the carbon bearing the functional group is the α-carbon; whereas, with carbonyl-containing compounds, it is the carbon adjacent to the one bearing oxygen that is labeled as the α-carbon. This means that for alcohols the γ-hydrogen is five atoms from the oxygen, but for ketones the γ-hydrogen is six atoms from the oxygen.

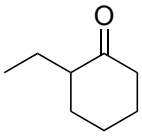


When alcohols dehydrate, the hydrogen five atoms from oxygen is abstracted because atoms that are separated by this distance are close in space to one another as the molecule rotates through different conformations. When ketones undergo McLafferty rearrangement, the hydrogen that is abstracted is slightly further away (six atoms) because of the larger bond angle of the sp^2 hybridized carbonyl carbon. This increase in bond angle from 109.5° to 120° separates the reactive oxygen from the closer hydrogen and renders its removal unlikely.

As the γ-hydrogen is abstracted, the remaining electron from the bond that is homolytically cleaved falls in between the γ and β-carbons. The β-carbon reciprocates through donation of an electron from the α,β-bond. This completes a π bond between what used to be the γ and β-carbons, and it also severs this olefin from the rest of the molecule.



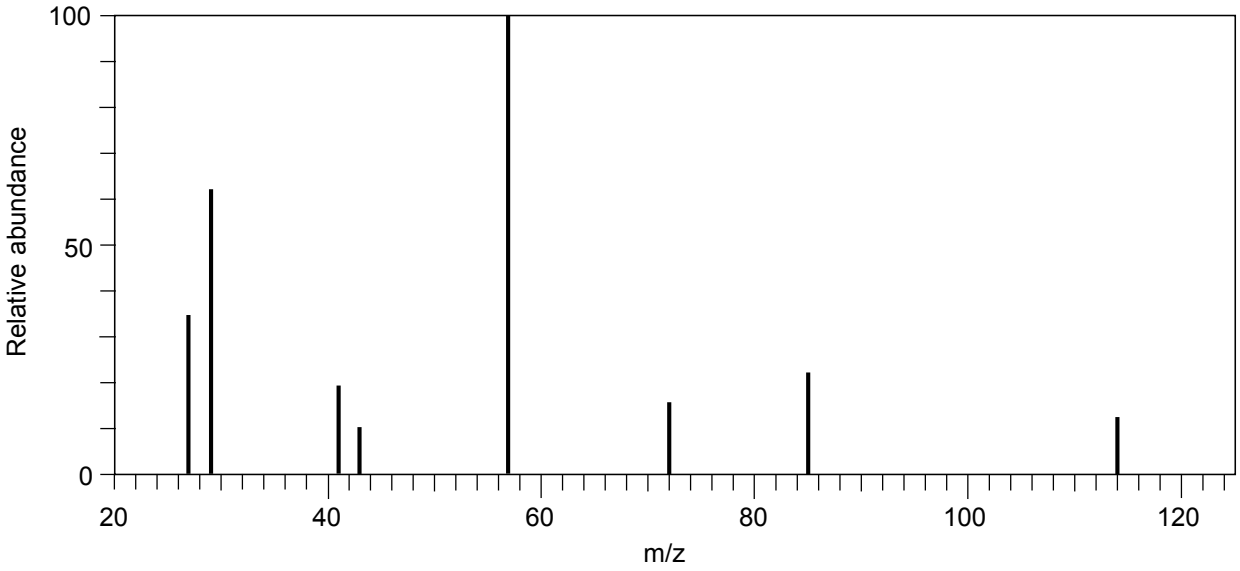
Problem 10. Which fragment is the expected base peak for the following ketone, known as 2-ethylcyclohexanone?



Section 13: Using mass spectra data in problem solving

Now that we understand how molecules behave during mass spectrometry, it might be useful to look at the information differently. In the research laboratory, you might not know the structure of your analyte (i.e., the compound being analyzed). Instead, you may acquire a mass spectrum of an unknown substance. Perhaps you have some clues as to its structure, but you may not know all of the details. You may be able to use mass spectrometry to clarify the analyte's structure. Here's an example.

Consider an analyte with the molecular formula $C_7H_{14}O$. It exhibits the following mass spectrum.



Let's try to propose a structure that is consistent with this information.

Our first task should be to calculate degrees of unsaturation.

$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ present}{2}$$

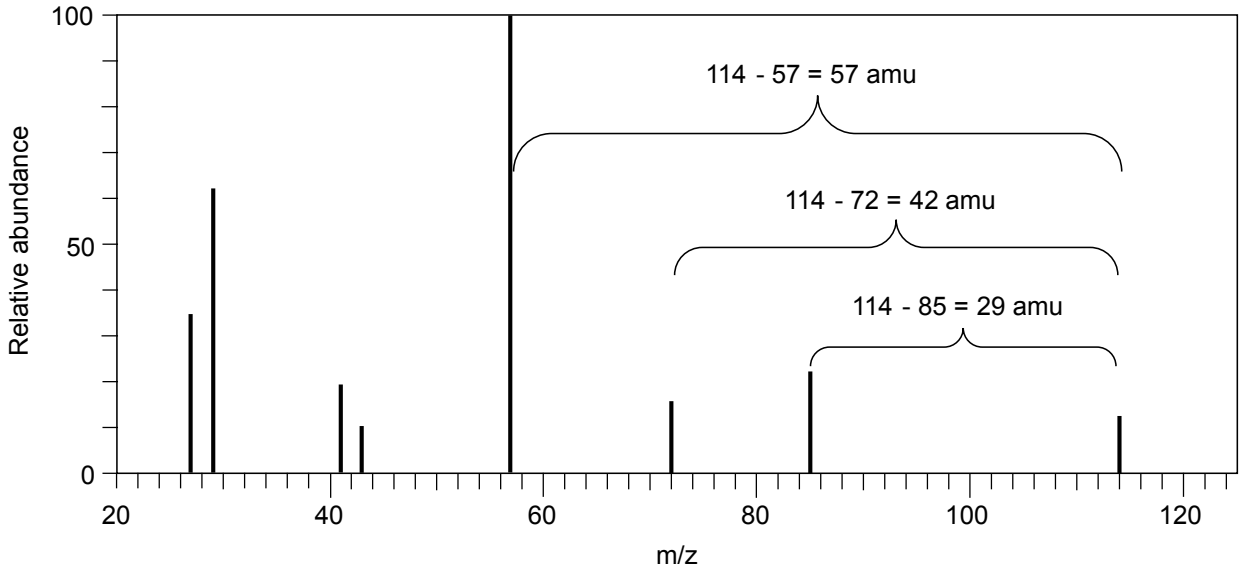
$$Degrees\ of\ Unsaturation = \frac{[2(7)+2] - 14}{2} = 1$$

The presence of an oxygen and a single degree of unsaturation suggests that a ketone is a possible functional group. Of course, it is also possible that we have an alcohol or an ether with a ring in the structure. Since these functional groups fragment quite differently, the mass spectrum should help us to identify which possibility is more probable.

Let's begin by considering a ketone. It can be challenging to devise structures for the fragments at m/z 114, 85, 72, 57, etc. Chemists usually prefer to look at the difference in mass between the molecular ion peak and the other prominent signals. These mass differences will typically be smaller values that correspond to the loss of commonly occurring fragments. Some examples are given below.

Mass Difference (amu)	**Group Lost**
15	methyl radical (CH_3·)
29	ethyl radical (CH_3CH_2·)
43	propyl radical ($CH_3CH_2CH_2$·) or the isomeric isopropyl radical [$(CH_3)_2CH$·]
57	butyl radical ($CH_3CH_2CH_2CH_2$·) or one of its isomers

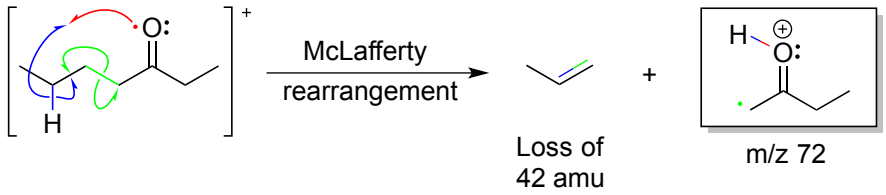
Looking back at our mass spectrum through this lens, we see two mass differences (29 and 57 amu) that correspond perfectly to the loss of ethyl and butyl radicals. The third mass difference does not match up perfectly with the loss of a propyl radical, and there must be an explanation for this.



We know that ketones can undergo α-cleavage, thereby releasing radical fragments. Furthermore, we know that an unsymmetrical ketone will release two different radical fragments from two unique α-cleavage pathways. We can use this knowledge to reconstruct a possible parent ketone from the fragments at hand. We know that butyl and

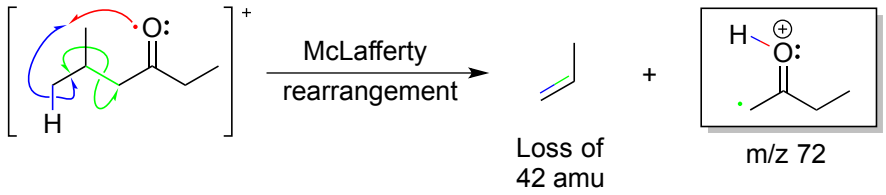
ethyl radicals were released. We also know that all ketones must contain a carbonyl. Let's simply combine these pieces to obtain a possible ketone structure: 3-heptanone.

We still need to explain the loss of 42 amu via a third fragmentation pathway. Ketones can also undergo McLafferty rearrangement. For 3-heptanone, McLafferty rearrangement would release propylene (a loss of 42 amu), producing the signal at m/z 72 for the resulting oxonium ion.



Consequently, this is a structure that is consistent with the data at hand. Another structure would also be consistent with the data. Remember that loss of 57 amu corresponds to the release of a butyl radical *or one of its isomers*. Therefore, we could have constructed other ketones using isobutyl, *sec*-butyl, or *tert*-butyl fragments. Only one of these would give fragments of the same mass in McLafferty rearrangement though, and that is the ketone constructed using an isobutyl fragment: 5-methyl-3-hexanone.

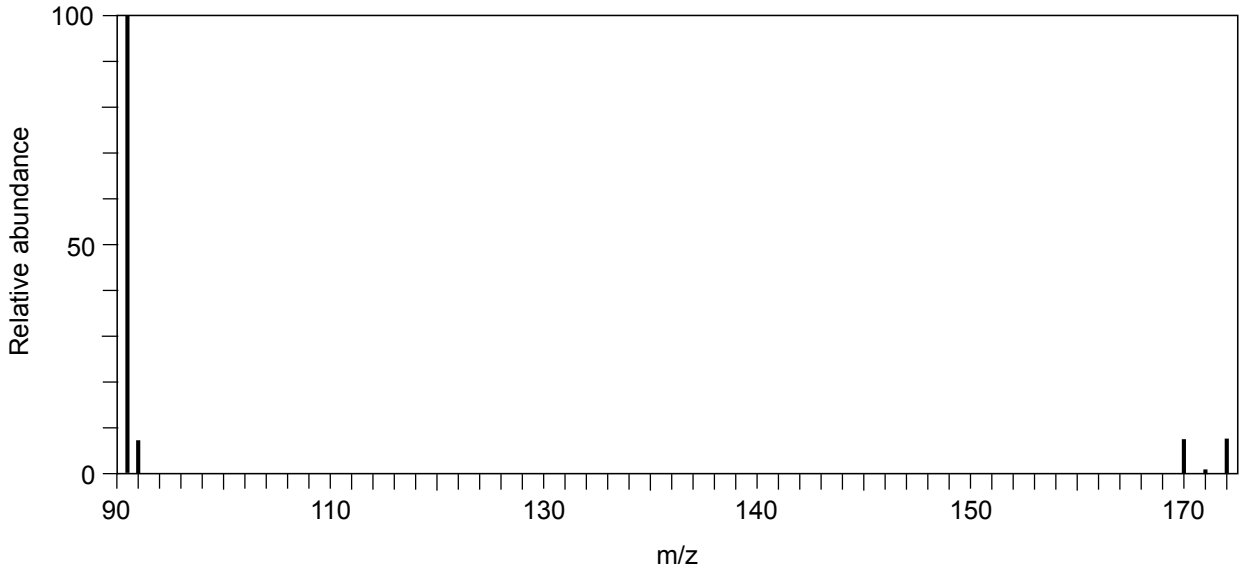
McLafferty rearrangement of 5-methyl-3-hexanone still releases propylene (for a loss of 42 amu) and yields an oxonium ion with m/z 72.



Deciding between 3-heptanone and 5-methyl-3-hexanone is more subtle. For instance, we might notice that 5-methyl-3-hexanone has more γ-hydrogens than 3-heptanone (6 vs. 2). Therefore, it would seem as though the peak resulting from McLafferty rearrangement

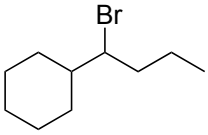
(m/z 72) would be large if the analyte were 5-methyl-3-hexanone and small if it were 3-heptanone. Since the signal at m/z 72 is fairly small, this suggests that the analyte is more likely 3-heptanone.

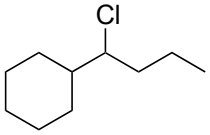
Problem 11. Identify the compound that exhibits the following mass spectrum.



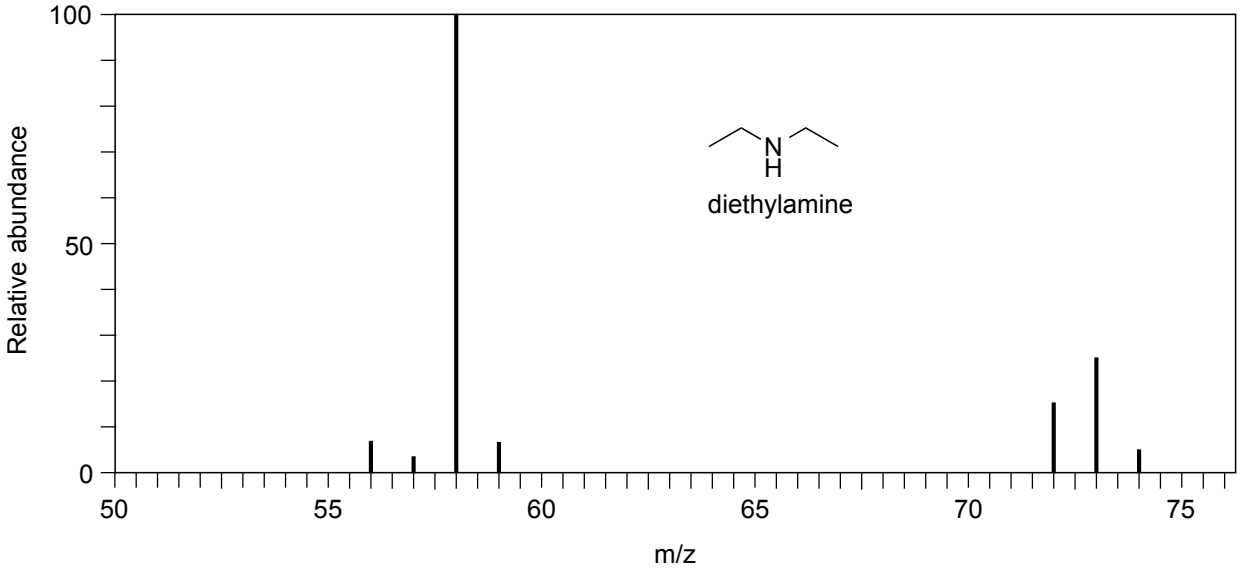
End-of-the-Chapter problems

Problem 12. For which of the following molecules would you expect to observe a larger M-43 signal?

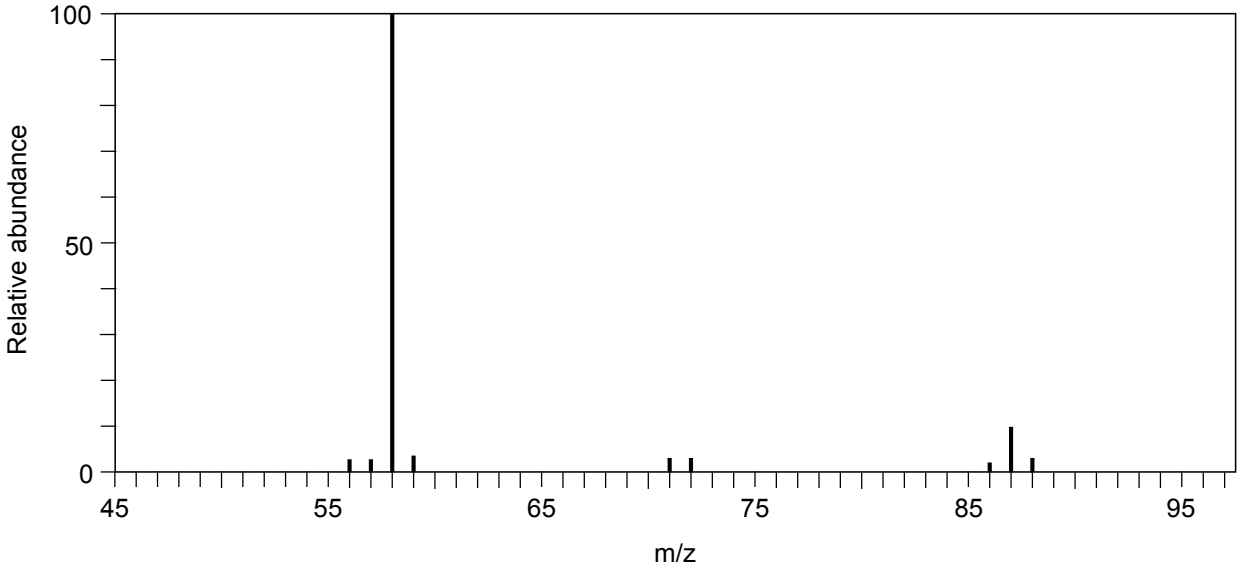




Problem 13. We did not discuss mass spectrometry of amines in this chapter. Nevertheless, we have seen trends in the fragmentation patterns of heteroatom-containing functional groups. Based on these trends, explain the formation of the base peak in the mass spectrum of diethylamine shown below.



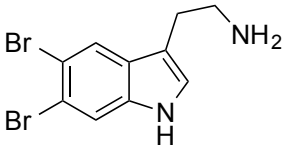
Problem 14. An interesting feature of amines is that they have odd molecular weights (provided that they contain an odd number of nitrogens). This is due to the odd valence of the nitrogen atom. Given this fact, identify the structure of the unknown substance that produces the following mass spectrum.



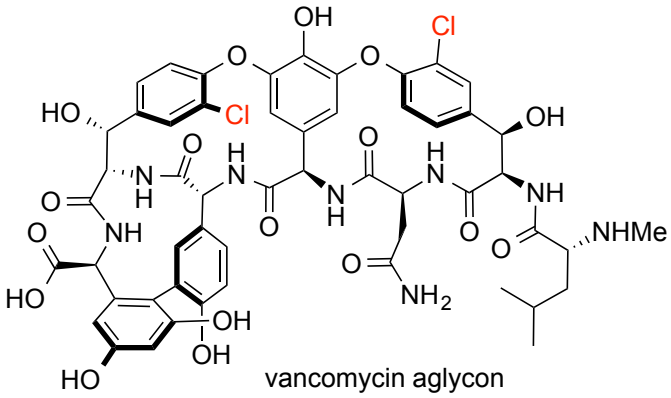
Problem 15. When molecules contain two halogens, interesting isotope patterns emerge.

(a) 5,6-Dibromotryptamine is an antibacterial compound isolated from a marine sponge.[2] What would the isotope pattern look like for the molecular ion?

[2] Longeon, A.; Copp, B. R.; Quévrain, E.; Roué, M.; Kientz, B.; Cresteil, T.; Petek, S.; Debitus, C.; Bourguet-Kondracki, M.-L. *Marine Drugs*, **2011**, *9*, 879-888.



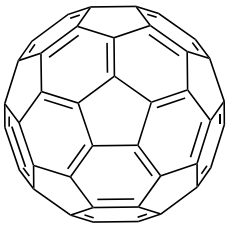
(b) Vancomycin, which has been referred to as the antibiotic of last resort, was isolated in 1953 from bacteria in a soil sample analyzed by a team of scientists at Eli Lilly led by Edmund Kornfeld. Vancomycin contains a carbohydrate segment in addition to the aglycon ("without sugar") portion shown below. Notice that the aglycon contains two chlorine atoms. What would the isotope pattern caused by these halogens look like?



vancomycin aglycon

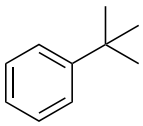
Problem 16. Show the mechanism for the possible fragmentations of 3-chloro-2,3-dimethylpentane during mass spectrometry.

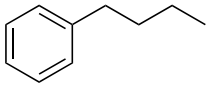
Problem 17. Buckminsterfullerene is a very unusual soccer ball-shaped molecule.

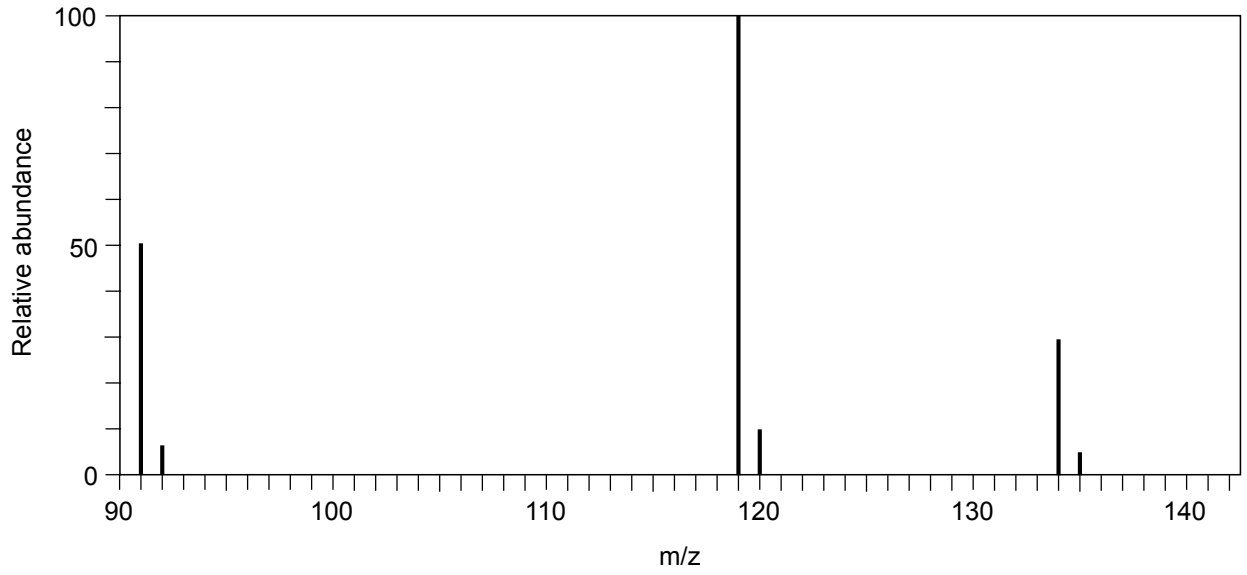


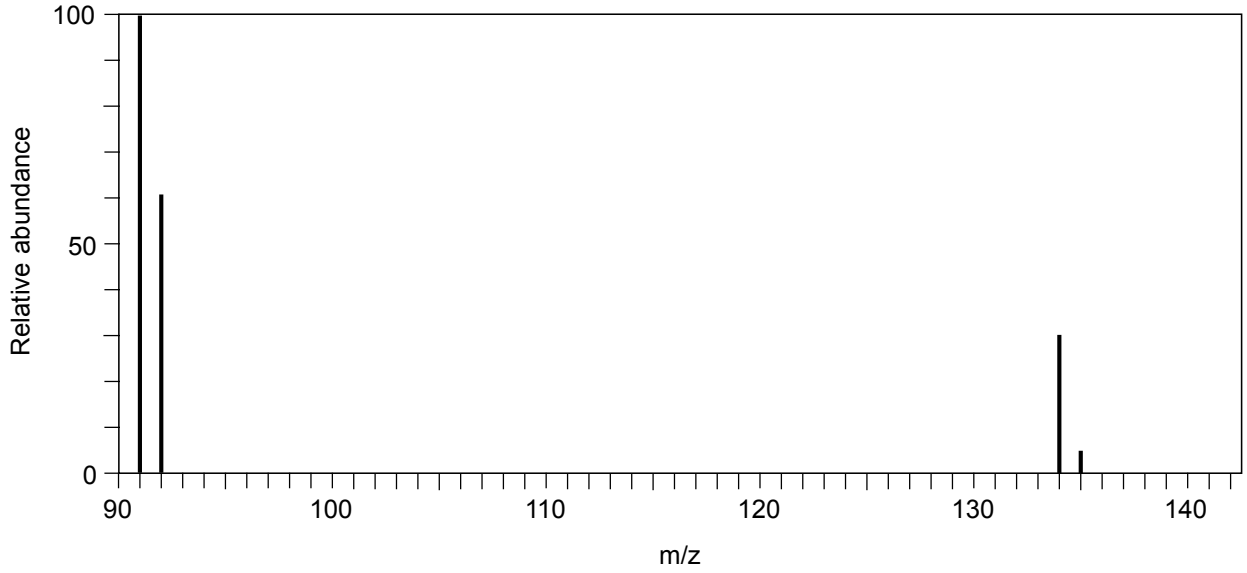
If the mass spectrum reveals M and M+1 peaks with relative abundances of 37% and 24.4%, respectively, how many carbons does buckminsterfullerene contain?

Problem 18. Match the following isomers with their mass spectra, and explain your rationale.

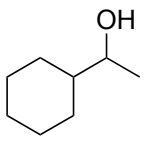




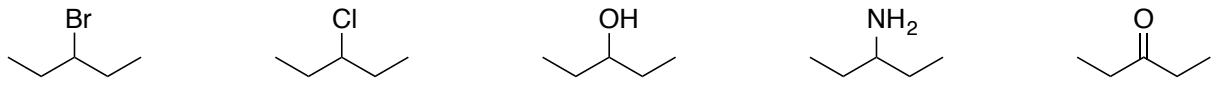




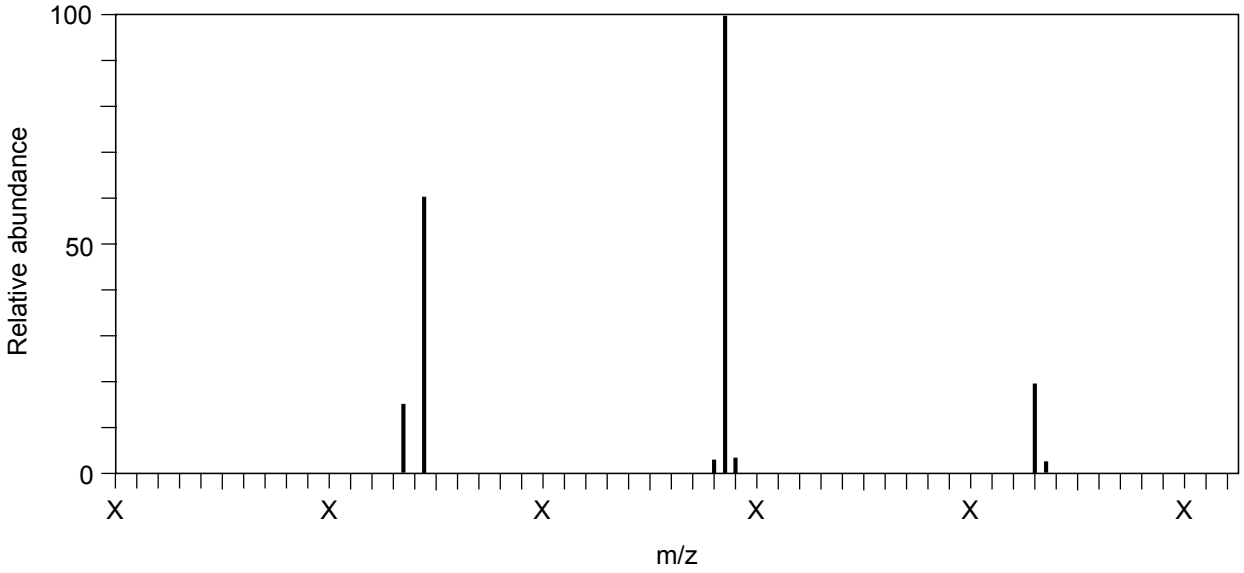
Problem 19. Draw a mechanism for the fragmentations of 1-cyclohexylethanol (shown below) that occur during mass spectrometry.

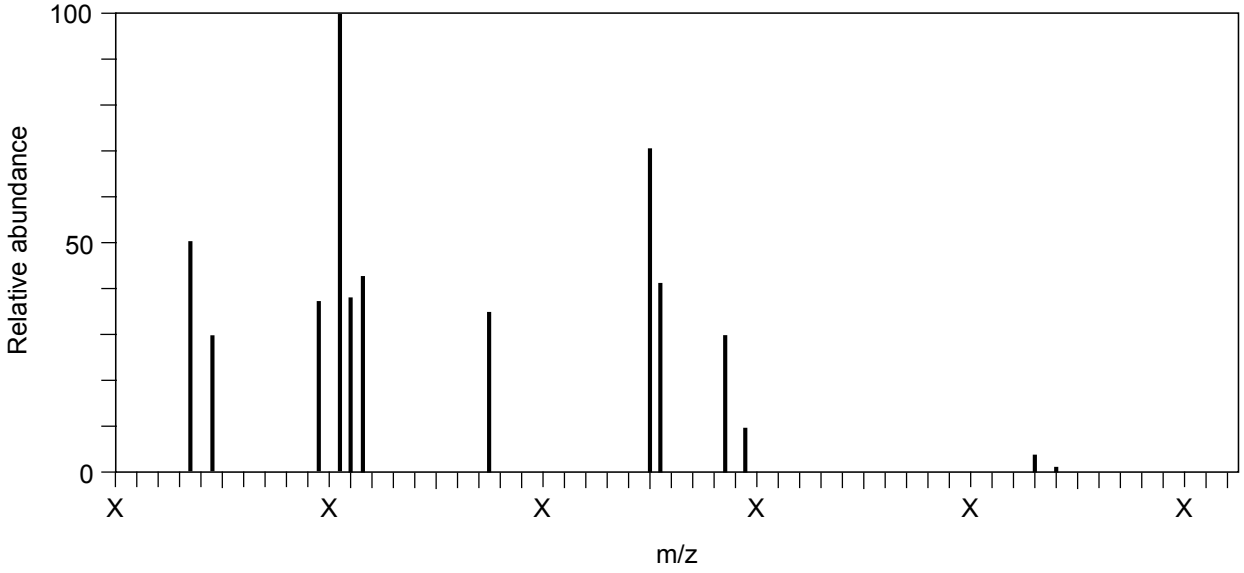


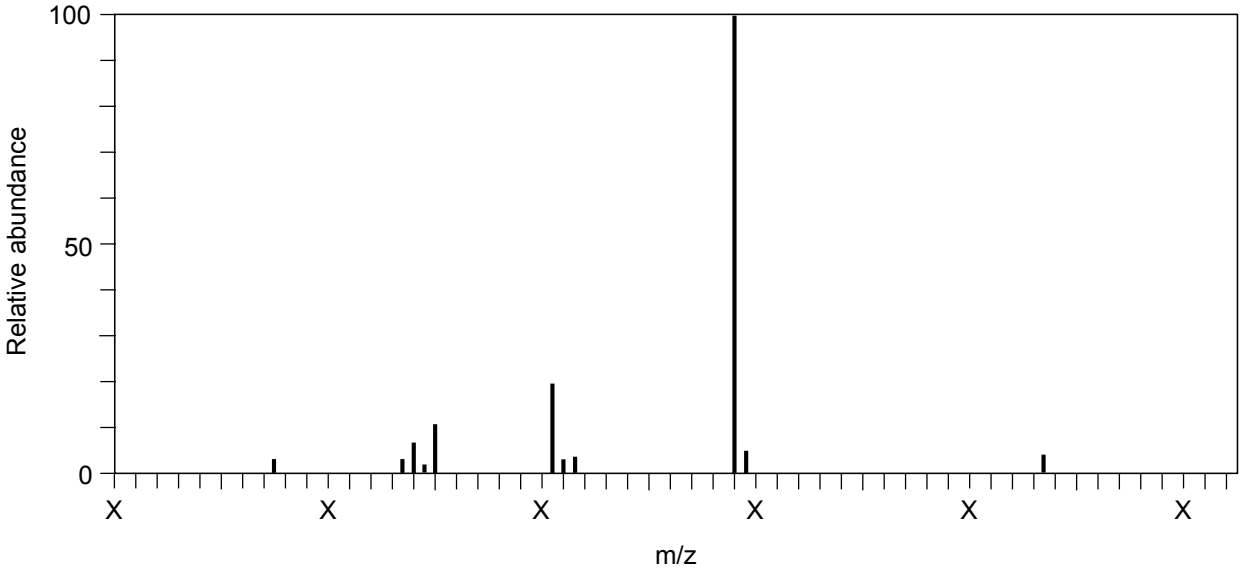
Problem 20. Match the following compounds with their mass spectra using the simplest clues possible.

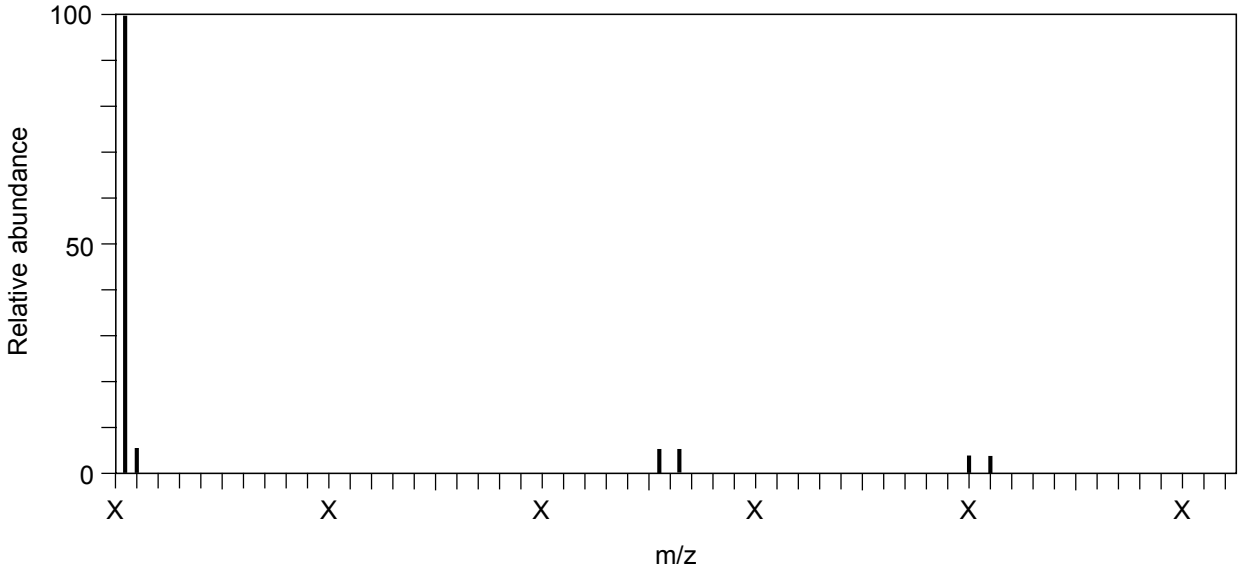


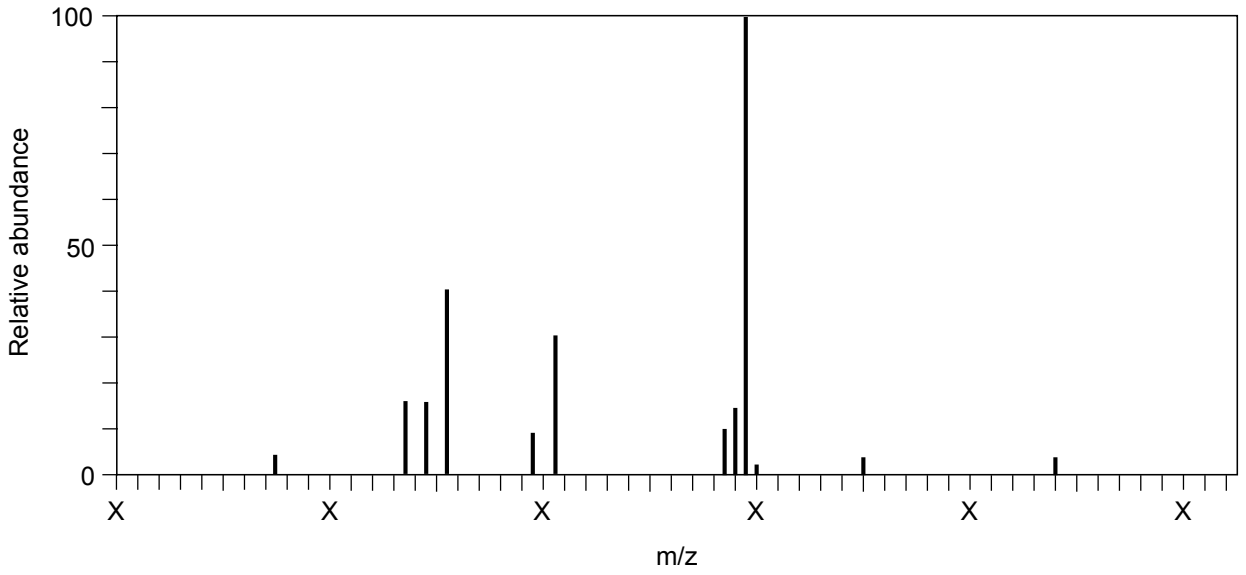
Note that you do *not* need to explain every peak in these mass spectra. Additionally, note that the Xs on the m/z scale represent intervals of 20 amu.



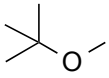



100
50
0
Relative abundance
X
X
X
X
X
X
m/z


100
50
0
Relative abundance
X
X
X
X
X
X
m/z

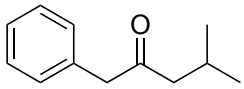


Problem 21. MTBE is an acronym for methyl *tert*-butyl ether (or more properly *tert*-butyl methyl ether). This compound has been used as an additive in gasoline to raise its octane rating. However, the detection of MTBE in water supplies is among the factors that have led to its diminishing use in the United States.

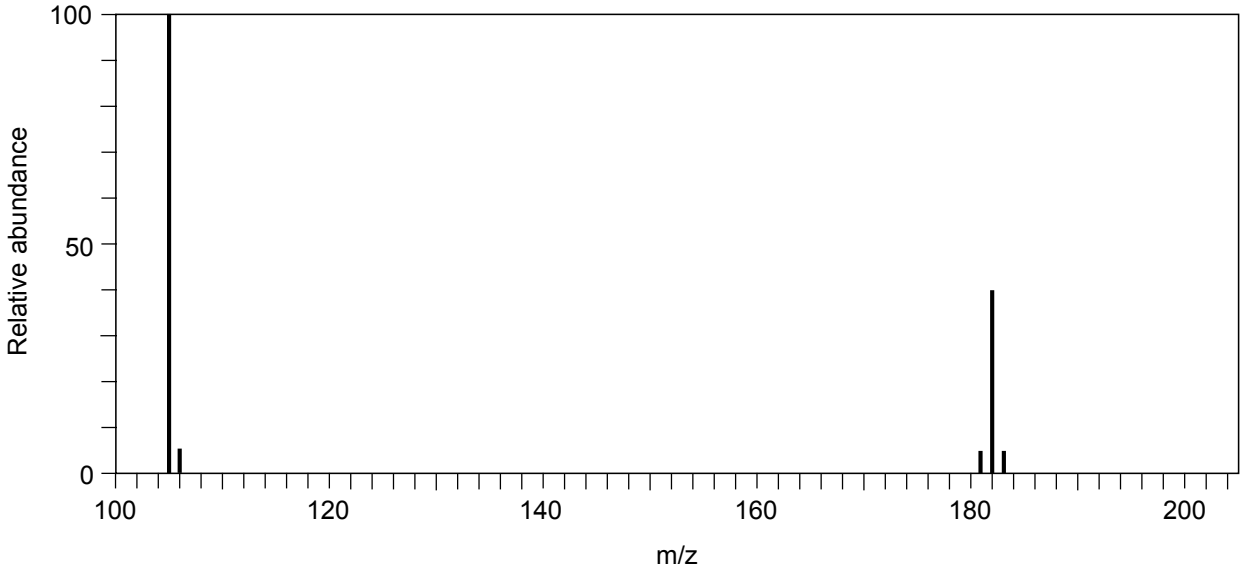


Provide a mechanism for the fragmentations of MTBE that occur upon analysis by mass spectrometry.

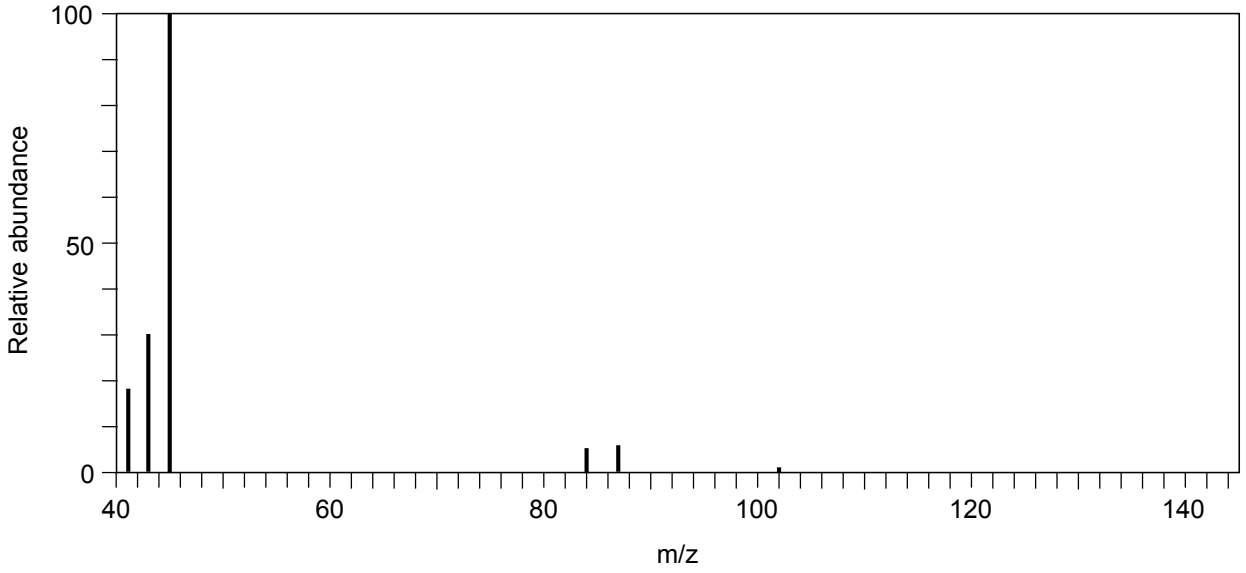
Problem 22. Provide mechanisms for the fragmentations of benzyl isobutyl ketone that occur when it is subjected to mass spectrometry.

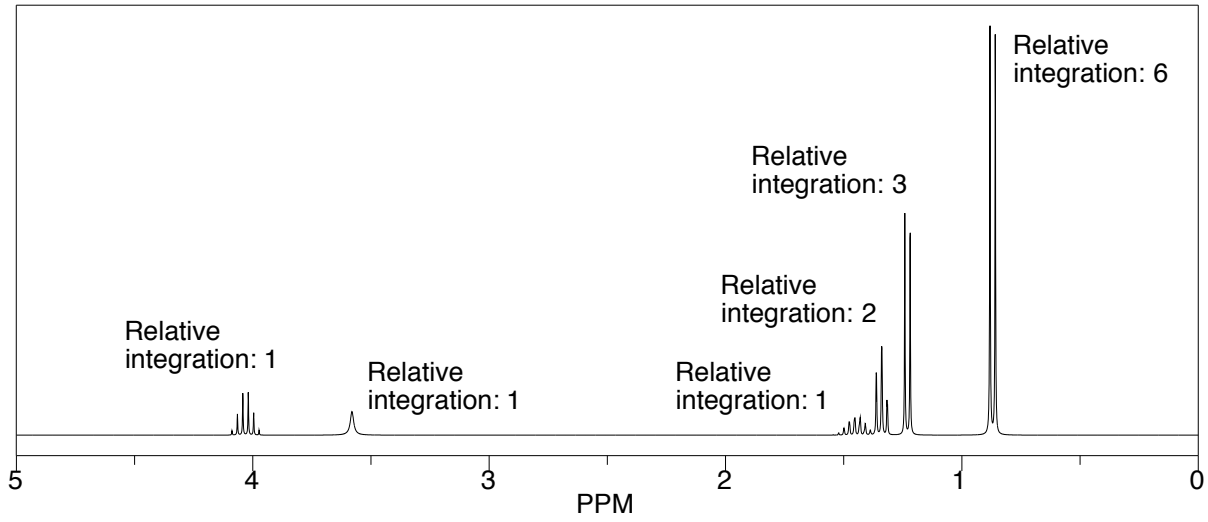


Problem 23. A compound with the molecular formula $C_{13}H_{10}O$ shows signals in the IR spectrum at approximately 3075, 1665, and 1600 cm^{-1}. It also exhibits the following mass spectrum. Provide the structure of this compound.

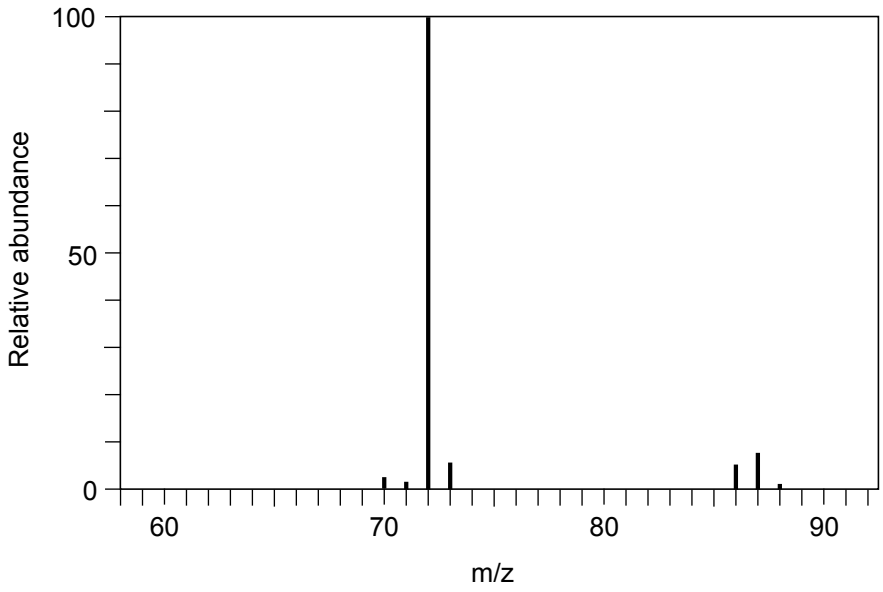


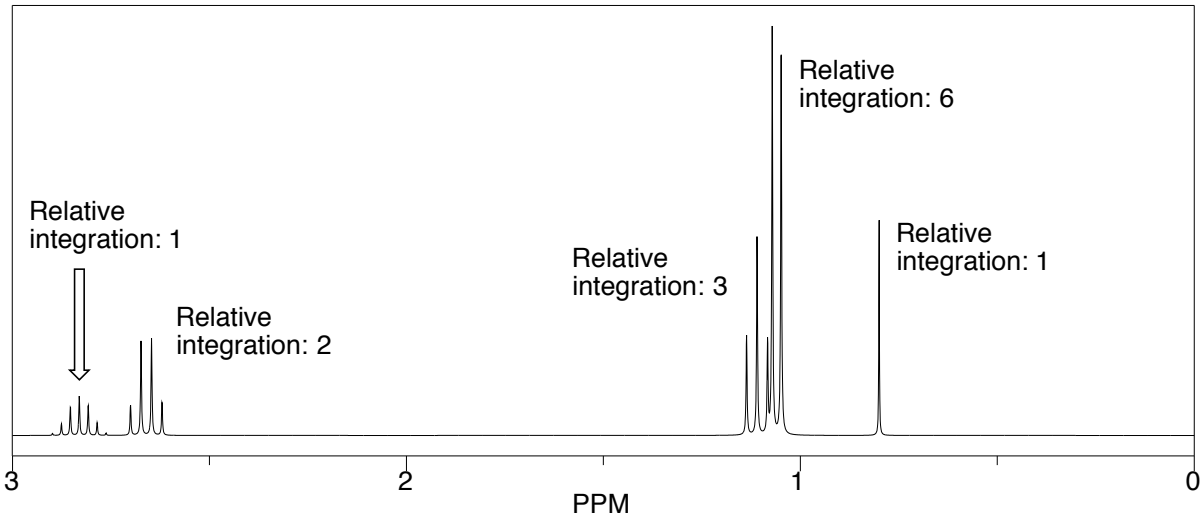
Problem 24. Identify the compound that produces the following mass spectrum and ^{1}H NMR spectrum.





Problem 25. An unknown compound has a single peak in the IR spectrum at around 3400 cm^{-1}. It also displays IR signals just below 3000 cm^{-1}. Additionally, it produces the following mass spectrum and proton NMR. What is the structure of this unknown compound?




Relative integration: 1
Relative integration: 2
Relative integration: 3
Relative integration: 6
Relative integration: 1
3
2
1
0
PPM

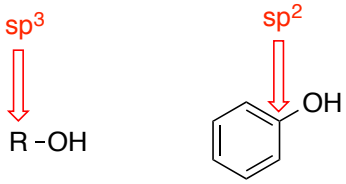
Chapter 9: Alcohols, Ethers, and Epoxides

Section 1: Nomenclature and properties of alcohols
Section 2: Reaction of alcohols with HX
Section 3: Reaction of alcohols with phosphorus tribromide
Section 4: Reaction of alcohols with thionyl chloride
Section 5: Dehydration of alcohols
Section 6: Oxidation of alcohols with chromic acid or PCC
Section 7: Williamson ether synthesis
Section 8: Nomenclature and properties of ethers
Section 9: Acidic cleavage of ethers
Section 10: Autoxidation of ethers
Section 11: Nomenclature and properties of epoxides
Section 12: Opening of epoxides under basic conditions
Section 13: Opening of epoxides under acidic conditions
Section 14: Synthesis

Section 1: Nomenclature and properties of alcohols

Classification

Alcohols contain a hydroxyl group (OH) bonded to an alkyl group. It is important to distinguish them from phenols, which have a hydroxyl group bonded to an aryl group.



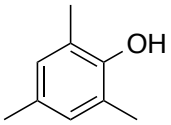
alcohol phenol

Alcohols are classified as unsubstituted, primary, secondary, or tertiary depending upon the number of R groups connected to the carbon bearing the hydroxyl group.

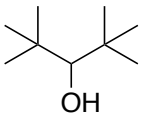
unsubstituted alcohol primary alcohol secondary alcohol tertiary alcohol

Problem 1. Classify each of the following as a primary, secondary, or tertiary alcohol or a phenol.

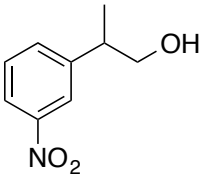
(a)



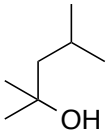
(b)



(c)



(d)



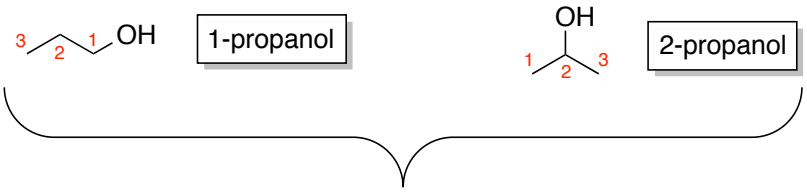
IUPAC nomenclature of alcohols

The systematic name of an alcohol is derived by first identifying the longest continuous carbon chain *that includes the functional group*. Then, the suffix "e" is replaced with "ol" to indicate the presence of an alcohol. The parent is numbered so as to give the lowest possible number to this functional group. In most cases, it will be necessary to specify where the hydroxyl group is located using a number. The only exceptions would be very small alcohols or cyclic alcohols, where there can be no ambiguity about the placement of the hydroxyl group.

- Two carbon parent = ethane
- Replace "e" of suffix with "ol"

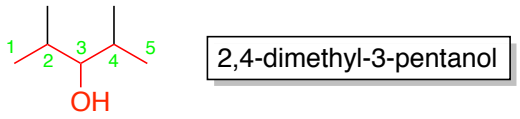
- Five carbon, cyclic parent = cyclopentane
- Replace "e" of suffix with "ol"

However, with most alcohols (even those as small as three carbons), a locant will be necessary.



- Three carbon parent = propane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number

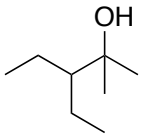
Substituents are added to the name in exactly the same fashion as for alkanes and alkyl halides.



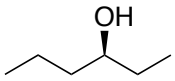
- Five carbon parent = pentane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number
- Add substituent names and numbers

Problem 2. Provide systematic names for the following selection of alcohols.

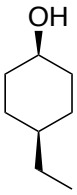
(a)



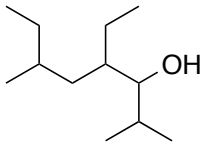
(b)



(c)

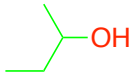


(d)



Common nomenclature of alcohols

Alcohols are given common names by placing the name of the alkyl group before the word "alcohol".

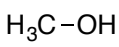


sec-butyl alcohol

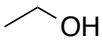
This method is only useful for small alcohols that have a simple alkyl group name. As the alkyl group becomes larger and more complex, a systematic name is typically preferable.

Problem 3. Provide common names for the follow alcohols.

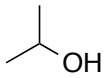
(a)



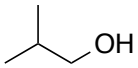
(b)



(c)

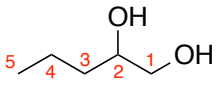


(d)



Nomenclature of diols

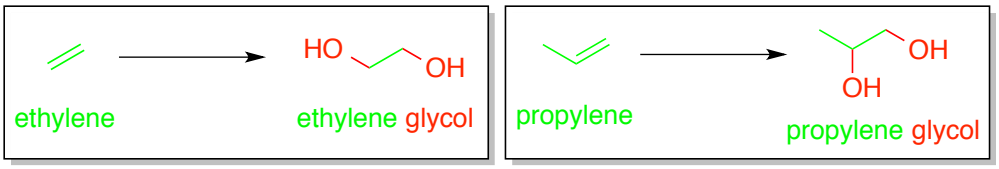
It is possible for a molecule to contain two (or more) hydroxyl groups. A compound containing two hydroxyl groups is known as a diol. A locant is given to each of the two hydroxyl groups in the systematic name.



1,2-pentanediol

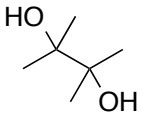
- Five carbon parent = pentane
- Add "diol" suffix to indicate two alcohols
- Number so as to give the alcohols the lowest possible numbers

When the two hydroxyl groups are vicinal (i.e., adjacent to one another), the molecule can be given the common name "glycol" preceded by the common name of the corresponding alkene.

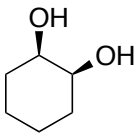


Problem 4. Name the following diols.

(a)

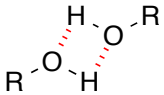


(b)



Hydrogen bonding

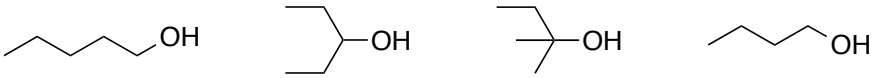
Since alcohols possess both a hydrogen bond donor and acceptor, this strong intermolecular interaction significantly influences their properties. For instance, their melting and boiling points will be higher than those of comparable compounds that have only dipole-dipole interactions or van der Waals forces.



The ability of alcohols to hydrogen bond extensively also enhances water solubility. The hydroxyl group is the hydrophilic portion of the molecule, while the alkyl group is the hydrophobic portion. As the size of the alkyl group increases, water solubility decreases as a result of the growing hydrophobicity. However, in small alcohols (those less than five-

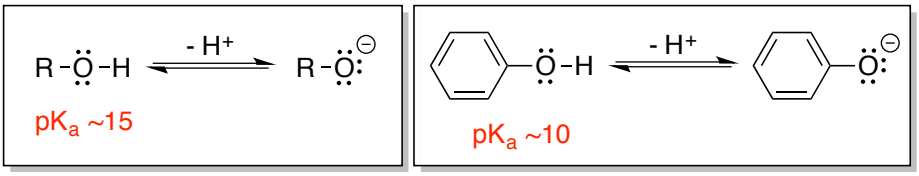
carbons in size), the hydrophilic hydroxyl group dominates. Many of these small alcohols are miscible with water, and all of them have at least fair water solubility.

Problem 5. Rank the following alcohols in order of decreasing water solubility.

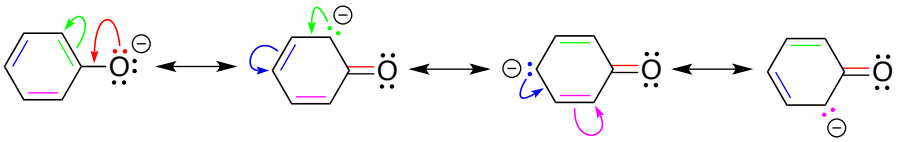


Acidity

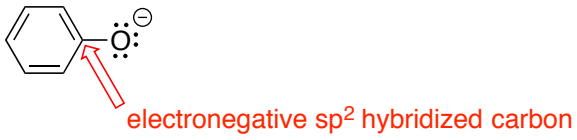
Alcohols have modest acidity on par with that of water. Their pK_a values are approximately 15. Phenols, on the other hand, are five orders of magnitude more acidic.



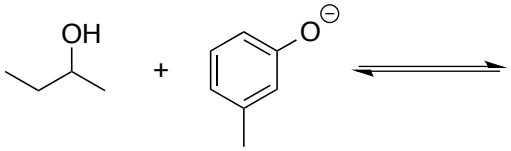
The enhanced acidity of phenols is often explained by their ability to resonance delocalize the anion of the conjugate base over three carbons of the aromatic ring. This spreading out of the negative charge stabilizes the conjugate base, which is known as a phenoxide or a phenolate, thereby enhancing the strength of the parent acid.



An alternative explanation of the greater acidity of phenols relies on the inductive effect. While sp^3 hybridized carbons are considered electron-donating groups, sp^2 hybridized carbons are more electronegative. The greater s character of an sp^2 hybrid orbital lowers its energy, making it a more attractive destination for electron density. As some electron density is drawn from the anion to the neighboring sp^2 carbon, the phenoxide is stabilized. Stabilization of the phenoxide increases the strength of the parent acid.

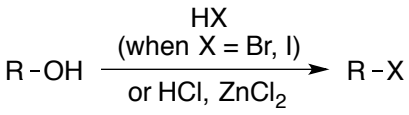


Problem 6. Predict the products of the following reaction. Then, state which side of the reaction is favored at equilibrium and by how much.



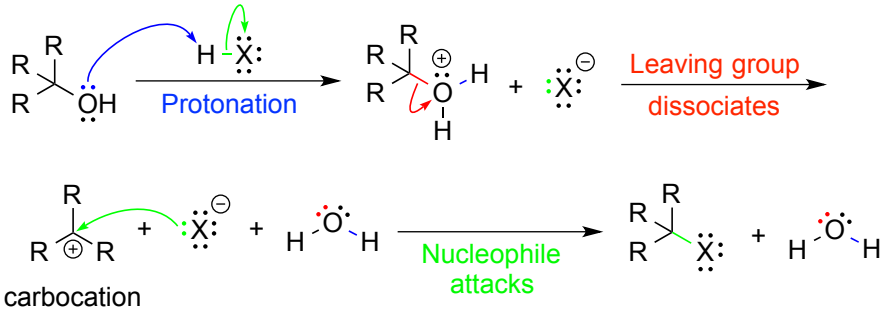
Section 2: Reaction of alcohols with HX

The reaction of alcohols with HX yields alkyl halides. The mechanism is either S_N1 or S_N2 depending on the substitution of the substrate. Tertiary and secondary substrates undergo S_N1 reaction, while primary substrates undergo S_N2 reaction.

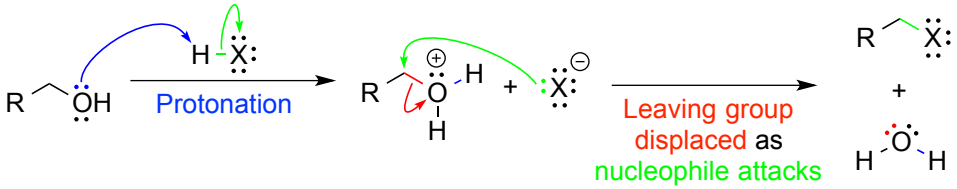


Mechanistic considerations

A tertiary (or secondary) alcohol will be protonated by the strong acid HX (HBr or HI). This converts the hydroxyl group from a poor leaving group into a good one. Water then dissociates, and the resulting carbocation is attacked by X^- to provide the alkyl halide product via an S_N1 mechanism.



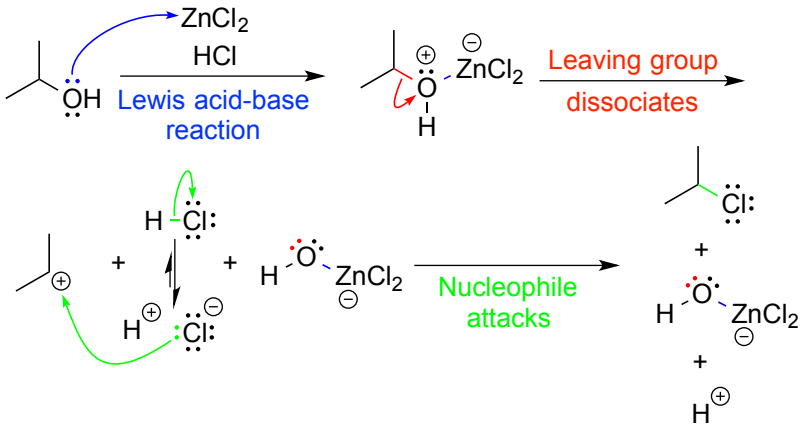
A primary alcohol is also initially protonated by the strong acid HX (HBr or HI). However, the oxonium ion (i.e., positively charged oxygen) does not dissociate because a primary carbocation would be especially unstable. Consequently, the halide attacks directly to displace water via an S_N2 mechanism, yielding the alkyl halide product.



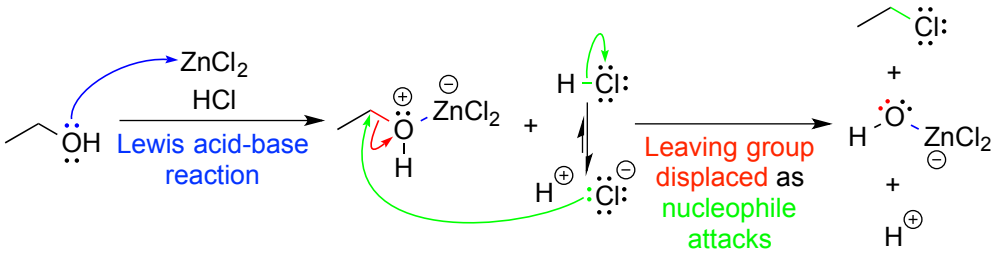
Specific examples of the reaction of alcohols with HX

Reactions of alcohols with HBr or HI proceed exactly as outlined above. However, when HCl is used, a Lewis acid is often also added to the reaction mixture. Specifically, HCl is combined with zinc chloride ($ZnCl_2$) to incite reaction, particularly with primary and secondary alcohols. The Lewis acid is needed to enhance the electrophilicity of the oxonium ion because chloride is a weaker nucleophile that bromide or iodide. The combination of HCl and $ZnCl_2$ is known as the Lucas reagent.

Below isopropyl alcohol is treated with the Lucas reagent. The reaction begins with the attack of the alcohol on zinc chloride. This Lewis acid-base reaction provides an oxonium ion from which the leaving group dissociates to yield a carbocation. The carbocation is attacked by chloride to generate the final secondary alkyl chloride product: isopropyl chloride.

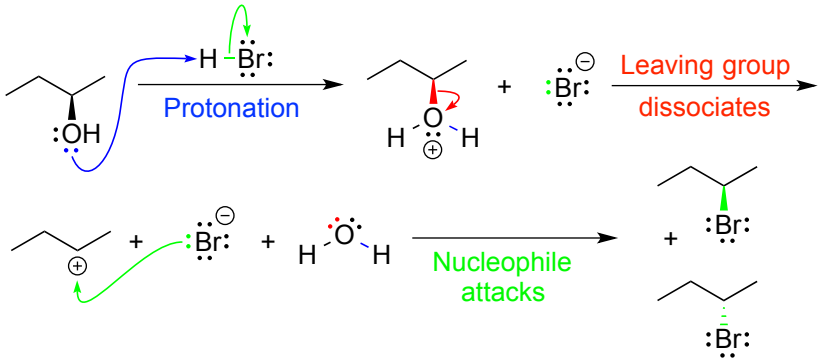


In the next example, ethanol is treated with the Lucas reagent. The initial Lewis acid-base reaction yields an oxonium ion that does not dissociate because the reactive center is primary and would become an especially unstable carbocation. Instead, direct attack of chloride simultaneously displaces the leaving group in S_N2 fashion to provide ethyl chloride as the product.

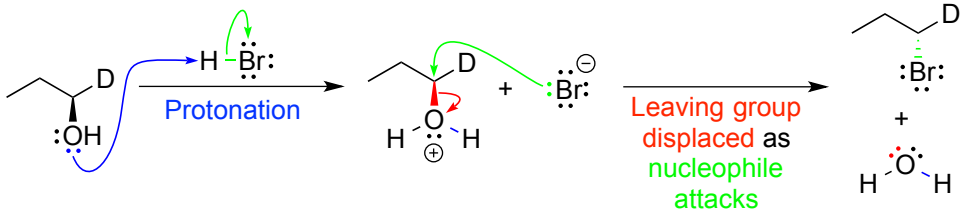


Stereochemical considerations

Since secondary and tertiary alcohols undergo S_N1 reaction with HX, stereochemistry at the reactive site will be randomized by this reaction because the carbocation intermediate is trigonal planar (i.e., flat) and is attacked from either side.

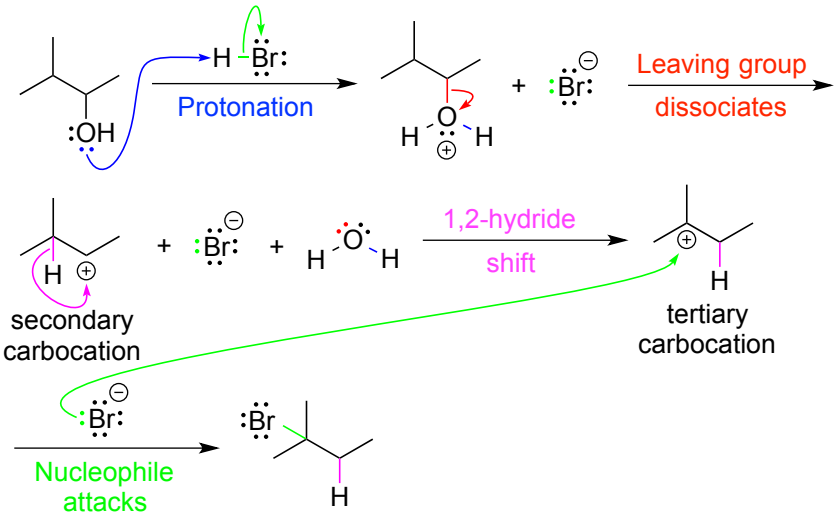


Primary substrates (RCH_2OH) undergo S_N2 reaction with HX, resulting in inversion. However, this only has a stereochemical ramification if one of the hydrogens at the reactive site is replaced with its isotope, deuterium.



Carbocation rearrangement

Since secondary and tertiary alcohols undergo S_N1 reaction with HX and produce a carbocation intermediate in the process, carbocation rearrangement is possible with these substrates. In the following reaction, the secondary alcohol is converted to the corresponding carbocation by treatment with HBr. However, there is an adjacent tertiary center, so a 1,2-hydride shift occurs to afford the more stable tertiary carbocation. Bromide adds to this new carbocation to generate the major product of the reaction.

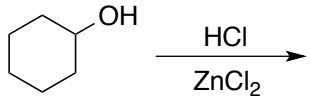


On the other hand, primary alcohols undergo S_N2 reaction with HX. This mechanism involves no carbocation intermediate, so rearrangement is not possible with primary substrates.

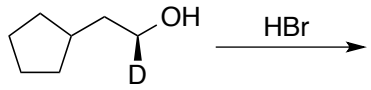
In summary, alcohols react with HBr or HI to yield alkyl bromides or alkyl iodides, respectively. Alcohols will also react with HCl in the presence of $ZnCl_2$ (the Lucas reagent) to yield alkyl chlorides. The mechanism is either S_N1 or S_N2 depending on the substitution of the substrate. Primary substrates undergo S_N2 reaction; whereas, secondary and tertiary substrates undergo S_N1 reaction.

Problem 7. Predict the products of the following reactions.

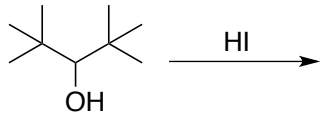
(a)



(b)

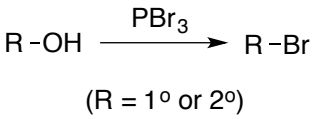


(c)

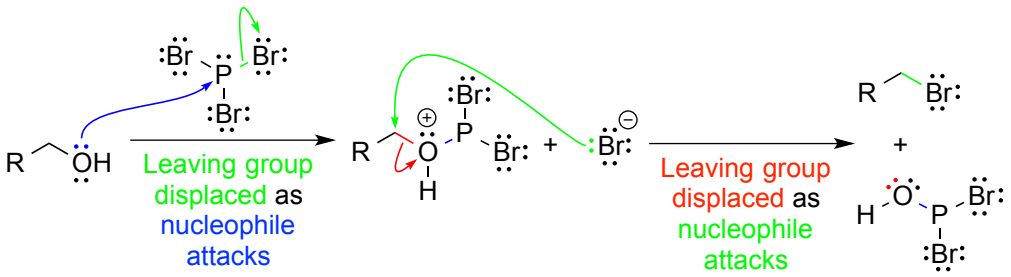


Section 3: Reaction of alcohols with phosphorus tribromide

The reaction of alcohols with phosphorus tribromide (PBr_3) yields alkyl bromides. Unlike reaction with HBr, carbocation rearrangement is *not* a concern with this process. The reaction works well with primary and secondary alcohols.



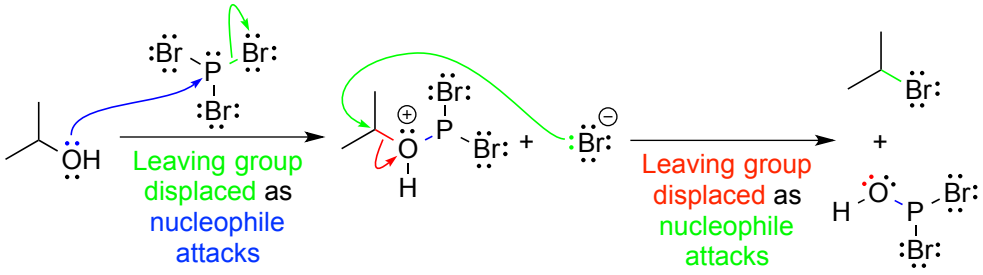
The reaction begins with the attack of the alcohol on the phosphorus of PBr_3, which is electrophilic due to the inductive electron withdrawal of its three bromine atoms. This attack displaces a bromide ion. The hydroxyl group has now been transformed from a poor leaving group into a good one that is displaced by the subsequent attack of bromide. The alkyl bromide product results.



Since the second step is an S_N2 reaction, this transformation works with primary and secondary alcohols, which are relatively unhindered.

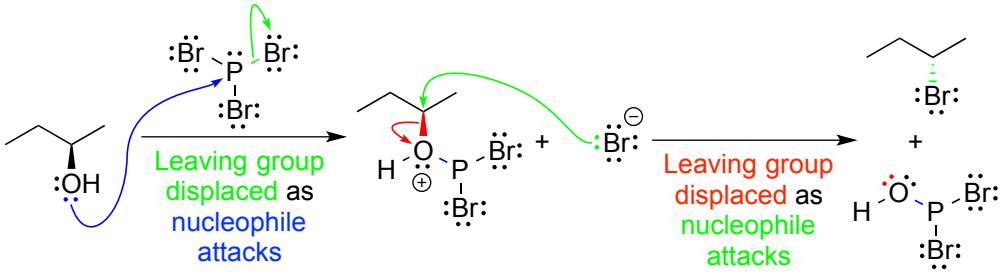
A specific example of the reaction of alcohols with phosphorus tribromide

In the example below, isopropyl alcohol attacks the electrophilic phosphorus of PBr_3, displacing bromide in the process. The displaced bromide ion then attacks the electrophilic carbon that now bears a good leaving group. This yields isopropyl bromide as the product.



Stereochemical considerations

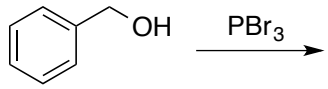
When the electrophilic carbon is a stereocenter, inversion is observed at that site owing to the S_N2 nature of the reaction's second step.



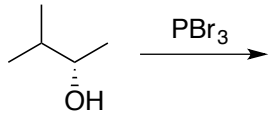
In conclusion, when primary or secondary alcohols are treated with phosphorus tribromide, they are converted to the corresponding alkyl bromides via S_N2 reaction. Inversion takes place at the reactive center. Since there are no carbocation intermediates, rearrangement is not a concern.

Problem 8. Predict the products of the following transformations. If no reaction occurs, explain why that is the case.

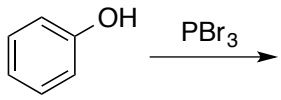
(a)



(b)

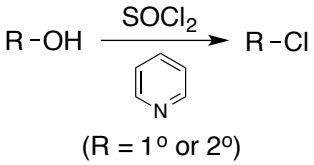


(c)

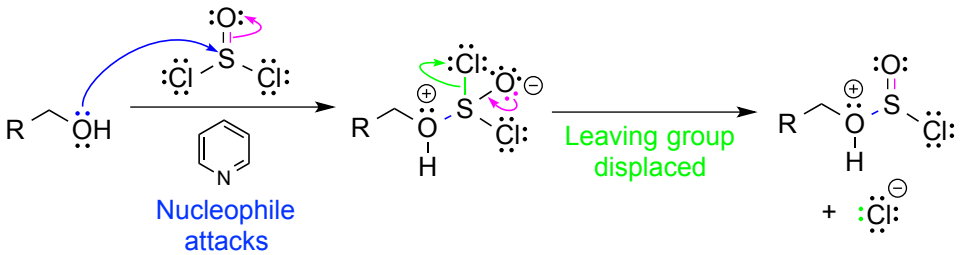


Section 4: Reaction of alcohols with thionyl chloride

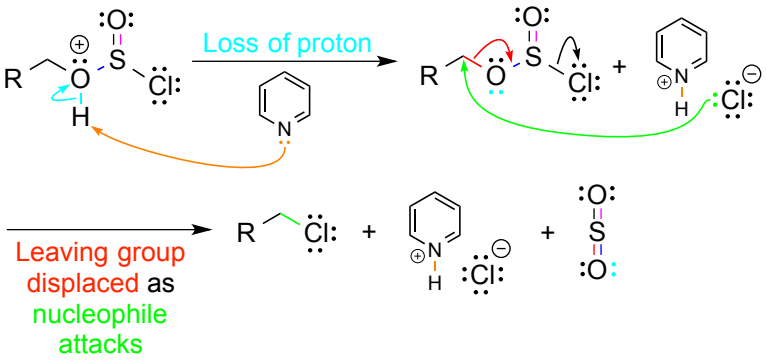
The reaction of alcohols with thionyl chloride ($SOCl_2$) in pyridine (C_5H_5N) yields alkyl chlorides. Unlike reaction with the Lucas reagent (HCl and $ZnCl_2$), carbocation rearrangement is *not* a concern with this process. The reaction works well with primary and secondary alcohols.



The reaction begins with the attack of the alcohol on the sulfur of $SOCl_2$, which is electrophilic due to the inductive electron withdrawal of the three electronegative elements surrounding it. This attack initially displaces the π-bonding electrons onto oxygen as a lone pair. This lone pair subsequently "collapses" to re-form the π bond, thereby displacing chloride.



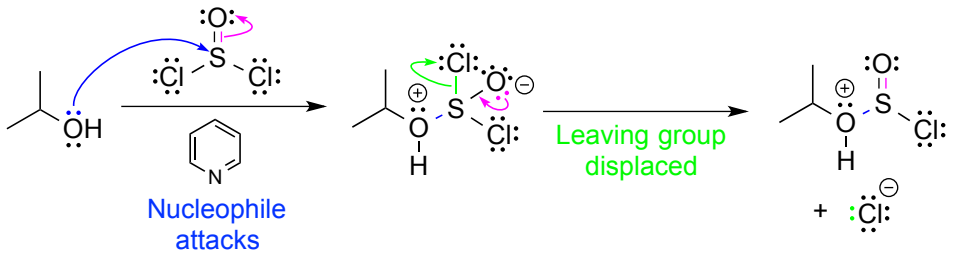
At this point, pyridine (a non-nucleophilic base) removes a proton from the oxonium ion. The net result of all these steps is that the hydroxyl group has been converted from a poor leaving group into a good one that is then displaced by the attack of chloride. This forms the alkyl chloride product, and the leaving group fragments (red and black arrows) into sulfur dioxide and chloride.



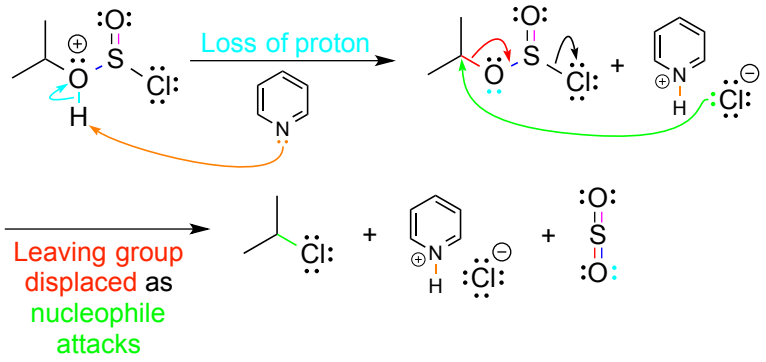
Since the final step is an S_N2 reaction, this transformation works with primary and secondary alcohols.

A specific example of the reaction of alcohols with thionyl chloride

In the example below, isopropyl alcohol attacks the electrophilic sulfur of $SOCl_2$, ultimately displacing chloride.

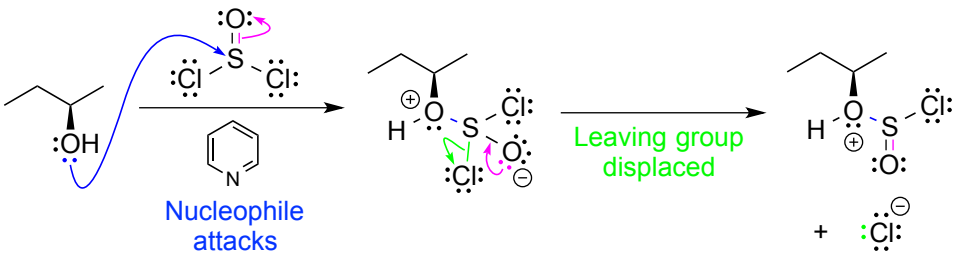


After loss of a proton, the displaced chloride ion attacks the electrophilic carbon that now bears a good leaving group. This yields isopropyl chloride as the product.

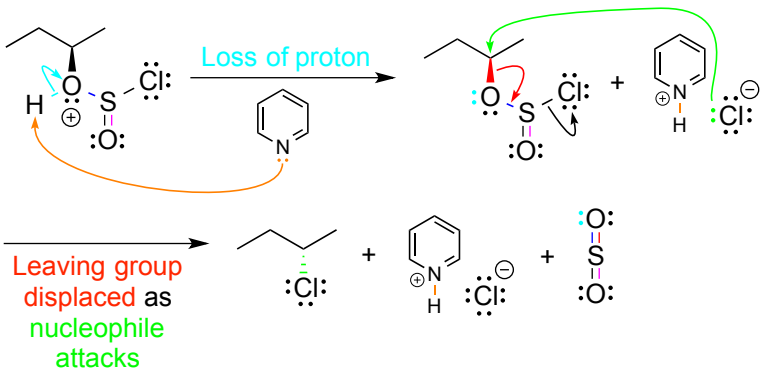


Stereochemical considerations

In the following example, the substrate is (*R*)-2-butanol.



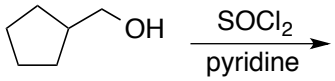
When the electrophilic carbon is a stereocenter as it is in this example, inversion is observed at that site owing to the S_N2 nature of the reaction's final step. In this case, the product is (*S*)-2-chlorobutane.



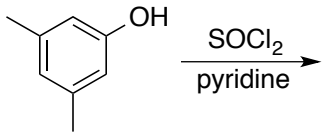
To recap, when primary or secondary alcohols are treated with thionyl chloride in the presence of pyridine, they are converted to the corresponding alkyl chlorides via S_N2 reaction. Inversion takes place at the reactive center. Since there are no carbocation intermediates, rearrangement is not a concern.

Problem 9. Predict the products of the following reactions. If no reaction occurs, explain why that is the case.

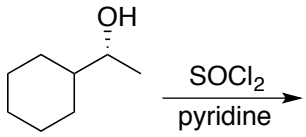
(a)



(b)

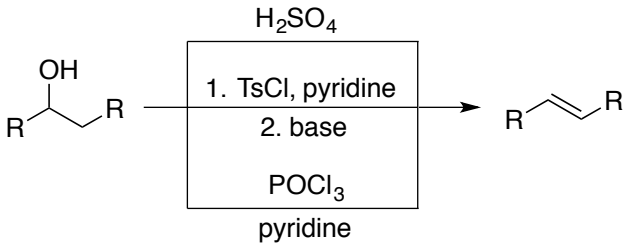


(c)



Section 5: Dehydration of alcohols

The dehydration of an alcohol is a specific example of elimination. The process can occur via an E1 or E2 mechanism, depending on the reaction conditions. The net result of the reaction is that water is removed from the substrate, leaving behind the newly installed π bond of an alkene.

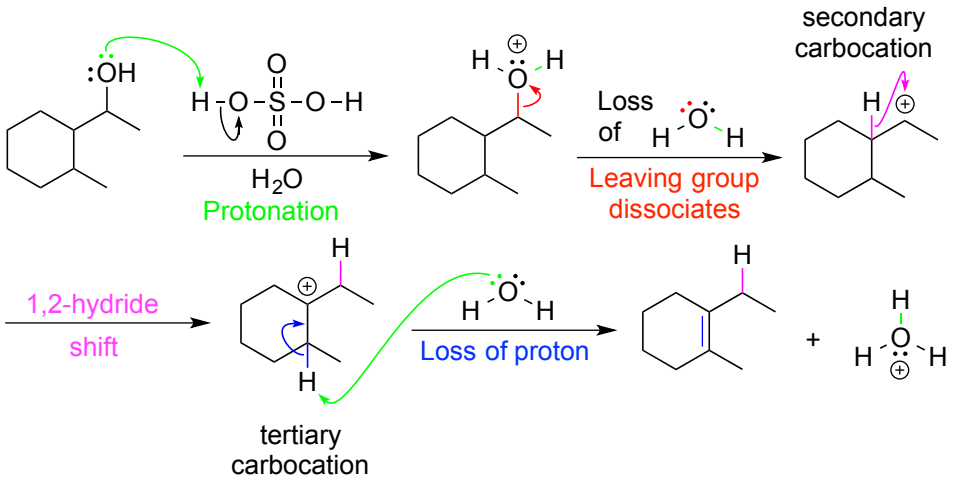


The mechanism of dehydration using sulfuric acid follows the E1 or E2 mechanism covered in Chapter 7. The predominant pathway depends upon the substitution of the alcohol. On the other hand, when the alcohol is converted to its tosylate and then treated with strong base, the E2 mechanism explains the reaction outcome.

A specific example of the dehydration of an alcohol

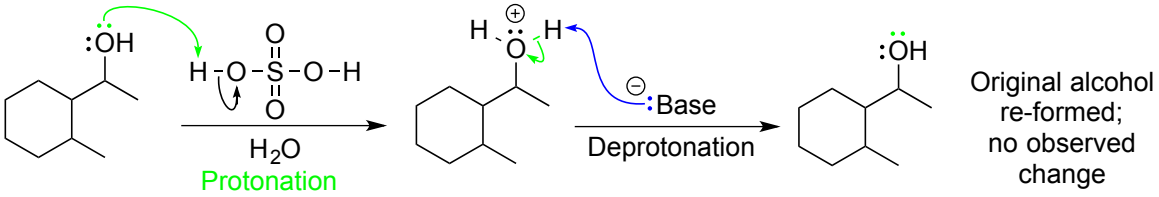
In Chapter 7, we saw that carbocation rearrangement is possible during the dehydration of an alcohol if it follows the E1 mechanism. Recall that the hydroxyl group is a poor leaving group because hydroxide ($^{-}$OH) is high in energy, so the hydroxyl group must first be converted to a better leaving group. One way to achieve this is through protonation. Water (a good leaving group) then dissociates, leaving behind a carbocation. In this case, the

secondary carbocation can be converted to a more stable tertiary carbocation via a 1,2-hydride shift. Finally, a proton is lost from the most substituted β position to form the Zaitsev product.

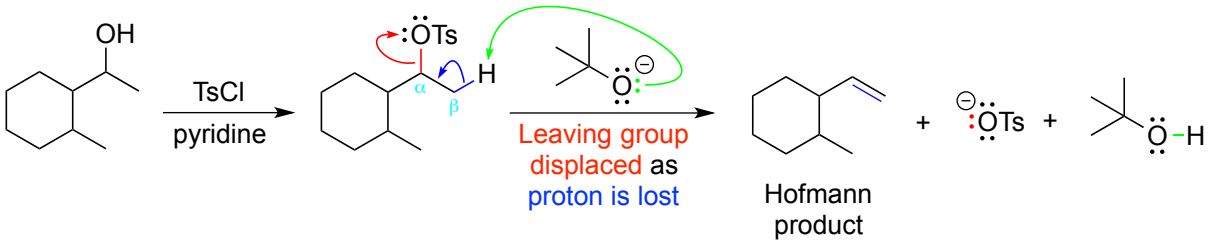


Regiochemical and stereochemical considerations

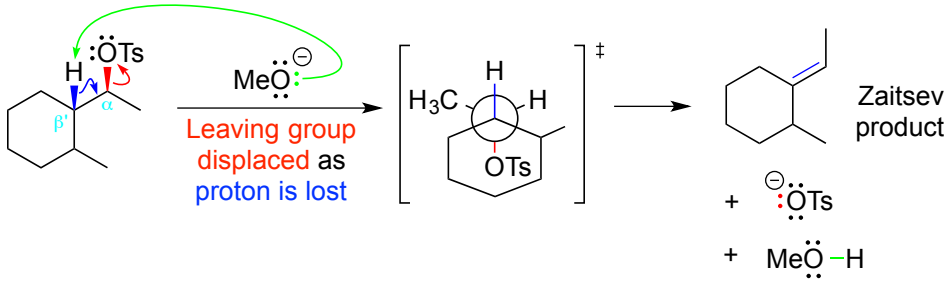
The preceding example does not allow for the formation of an alkene involving the carbon that originally possessed the hydroxyl group. In other words, the carbocation migration effectively moves the functionality to a new location. This can be avoided by employing an E2 mechanism. Again, the hydroxyl group must first be converted to a good leaving group; however, protonation is *not* a good choice in this instance. Remember that E2 reactions require strong base. The strong acid needed to protonate an alcohol will *not* be compatible with the strong base needed for E2 reaction. Additionally, strong base would simply deprotonate the oxonium ion, transforming it back into the original alcohol.



Instead, conversion of the alcohol to a sulfonate, such as tosylate (using TsCl and pyridine), provides the good leaving group needed for successful E2 reaction. This tosylate can then undergo E2 reaction with a large, bulky base to afford the Hofmann product via removal of a proton from β.



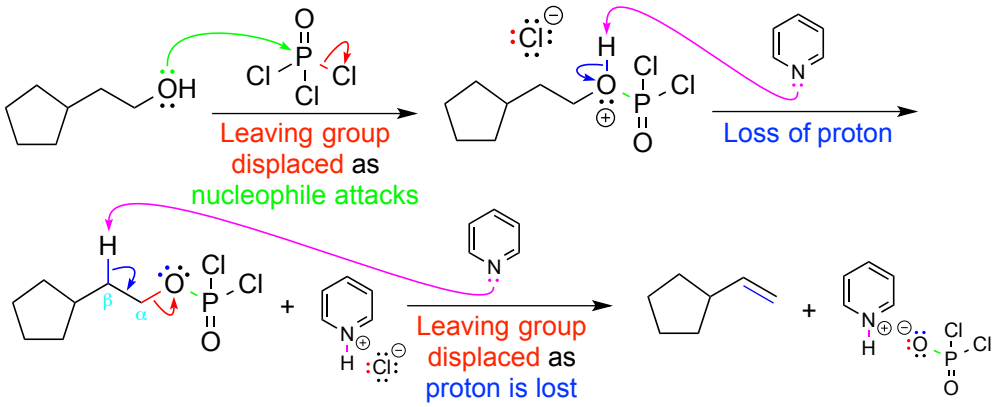
Alternatively, the same tosylate can be treated with a small, nimble base to yield the Zaitsev product via deprotonation at β'. Since β' has only one proton, the stereochemistry of the substrate will impact the configuration of the alkene product due to the requirement for anti-periplanar elimination in E2.



Alternative conditions for the dehydration of alcohols

Although the preceding methods are common, we saw that the use of sulfuric acid relinquishes some control over the regiochemical outcome of the reaction. Furthermore, the method utilizing the tosylate requires two synthetic procedures: (1) preparation of the tosylate followed by (2) the E2 reaction itself. It is possible to achieve E2 elimination of an alcohol in a single transformation using phosphorus oxychloride and pyridine. These conditions convert the hydroxyl group to a good leaving group that subsequently undergoes elimination in the same reaction vessel. This sort of process in which multiple reactions occur in one vessel is sometimes called a "one-pot" reaction.

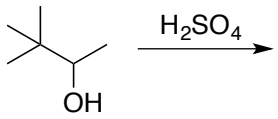
The mechanism begins when the hydroxyl group attacks the electrophilic phosphorus, thereby displacing a chloride leaving group. The resulting oxonium ion loses a proton to pyridine. A second molecule of pyridine then removes a β proton. As this proton is lost, the leaving group is simultaneously displaced from α, as expected for an E2 reaction.



To summarize, there are several available methods for dehydration. Strong acid can be used, or the hydroxyl group can be converted to the sulfonate and treated with strong base. The alcohol can also be dehydrated by phosphorous oxychloride and pyridine. All of these methods share a common feature: the hydroxyl group (a poor leaving group) is converted to a good leaving group prior to the elimination.

Problem 10. Predict the products of the following reactions.

(a)



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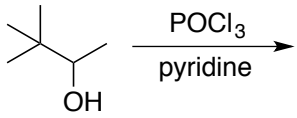

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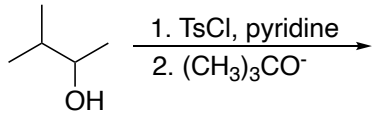
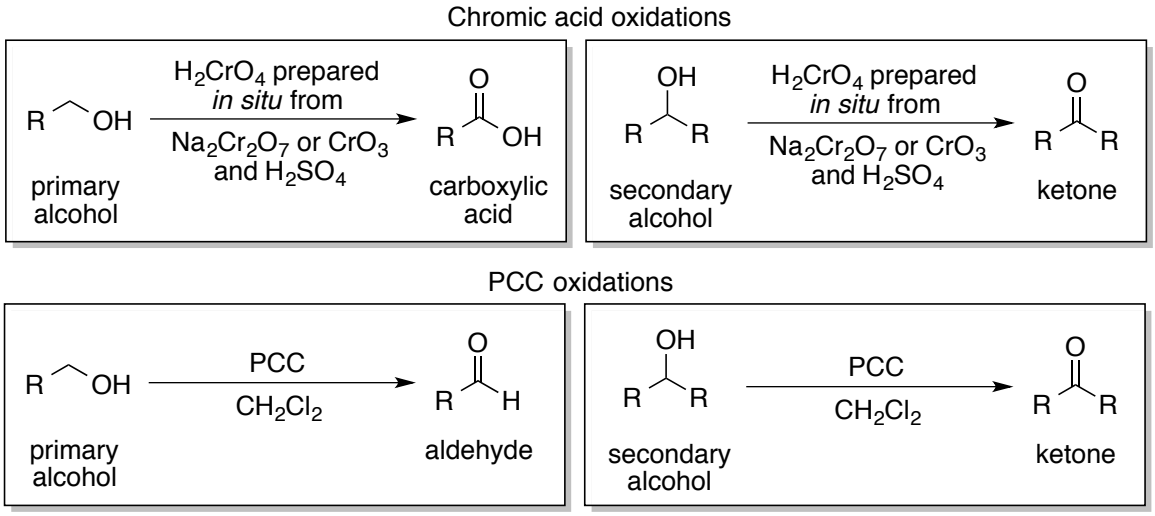


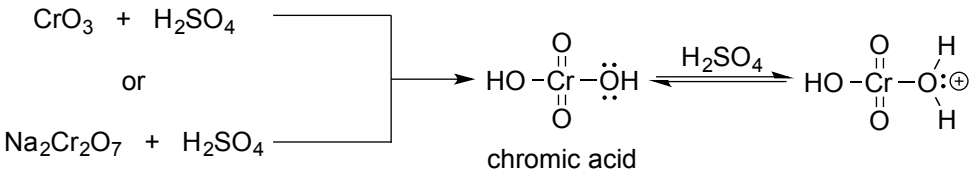
Section 6: Oxidation of alcohols with chromic acid or PCC

Primary and secondary alcohols can be oxidized with chromic acid (H_2CrO_4) to yield carboxylic acids and ketones, respectively. PCC is an alternative oxidant that converts primary alcohols to aldehydes.



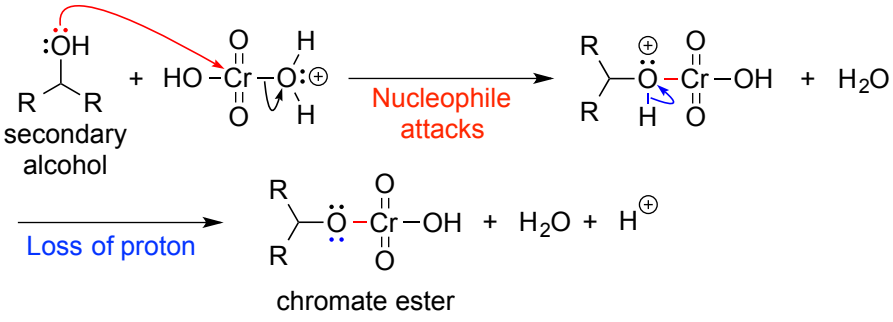
Mechanistic considerations

Chromic acid is prepared *in situ* from chromium trioxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) in sulfuric acid. Under these strongly acidic conditions, chromic acid can be protonated to activate one of its OH groups as a good leaving group.



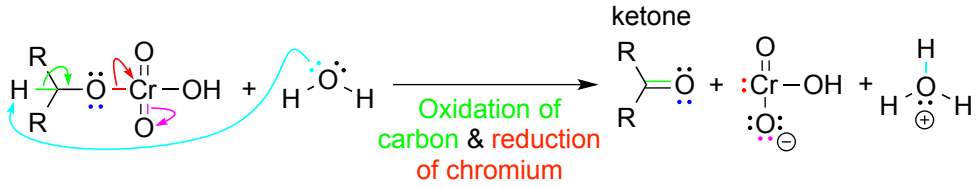
Reaction of chromic acid with a secondary alcohol

The attack of an alcohol displaces water from the protonated chromic acid molecule. After loss of a proton from the oxonium ion, a chromate ester is formed.



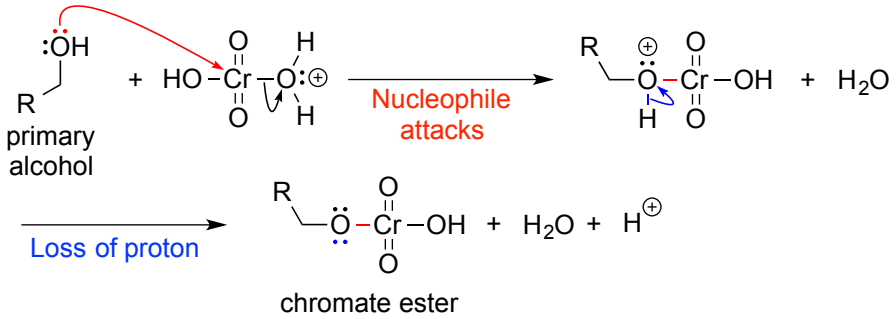
At this point in the mechanism, the oxidation occurs. As water removes a proton from the carbon of the chromate ester, the electrons in the breaking H–C bond become a carbon-oxygen π bond. The carbon is now at a higher oxidation state than it was previously (i.e., it has more bonds to oxygen). This displaces the electrons in the O–Cr bond onto chromium

as a lone pair, thereby reducing the chromium. To prevent the chromium from acquiring a formal negative charge, a pair of chromium-oxygen π-bonding electrons is displaced onto oxygen, allowing this more electronegative element to hold the formal negative charge. Since a secondary alcohol was used as the substrate, the product is a ketone.

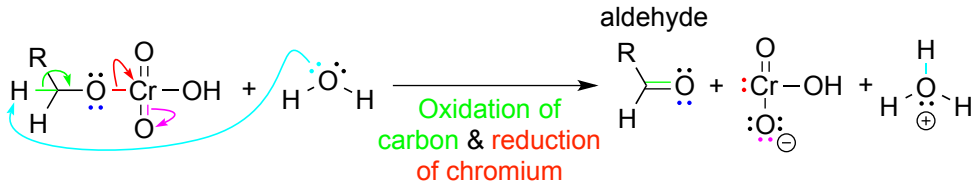


Reaction of chromic acid with a primary alcohol

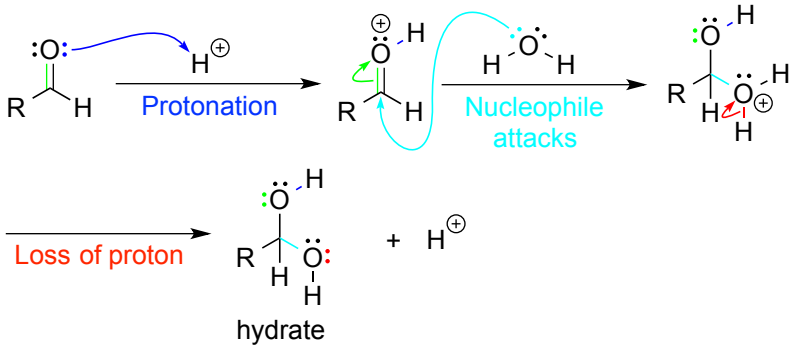
When the substrate is a primary alcohol, the beginning phase of the mechanism is identical, but the initial oxidation product can react further. As expected, the reaction begins with the formation of a chromate ester.



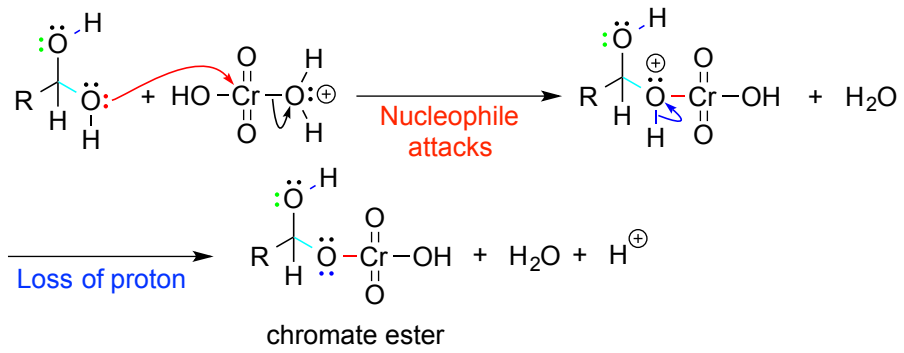
This chromate ester undergoes an analogous oxidation-reduction process to yield an aldehyde. However, the aldehyde cannot be isolated. It is merely an intermediate in the reaction of a primary alcohol with chromic acid.



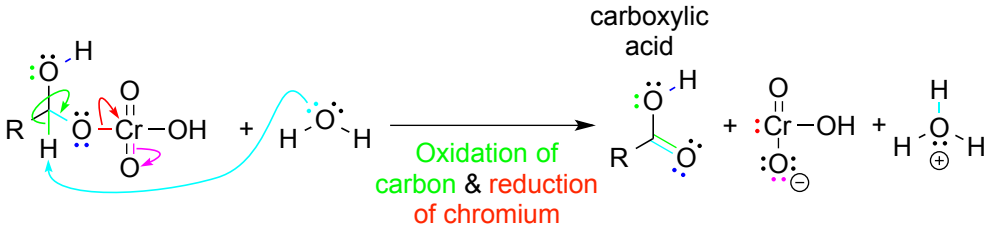
In aqueous acid, the aldehyde is converted to its corresponding hydrate through three mechanistic steps. The aldehyde is first protonated. Then water attacks the carbonyl carbon, pushing the π-bonding electrons onto the carbonyl oxygen to neutralize its charge. Finally, the remaining oxonium ion loses a proton to afford the hydrate. This molecule is called a hydrate because water has been added across the carbonyl of the aldehyde.



The hydrate has all of the components needed to undergo a second round of oxidation. It possesses a nucleophilic hydroxyl group that can attack chromic acid to yield a chromate ester.



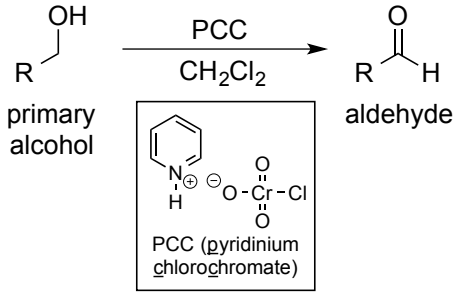
The hydrate also possesses one more proton on the reactive carbon. This proton is removed by water during the second oxidation of the substrate, which affords a carboxylic acid as the final reaction product.



Reaction of PCC with a primary alcohol

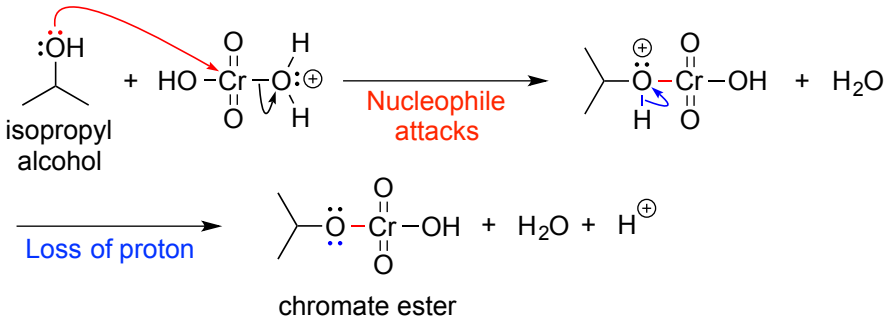
If the aldehyde (rather than the carboxylic acid) is the desired product, a different oxidizing agent can be used to produce it. Pyridinium chlorochromate (PCC) is an oxidizing agent that is very similar to chromic acid. As we saw in the mechanisms above, when chromic acid is used, water is formed during the reaction. The presence of water leads to hydrate formation and therefore the second round of oxidation that yields the carboxylic acid. PCC on the other hand does not produce water during the oxidation, and it is soluble in organic

solvents, such as dichloromethane (CH_2Cl_2). Without water, no hydrate is formed, and no further oxidation of the aldehyde can occur.

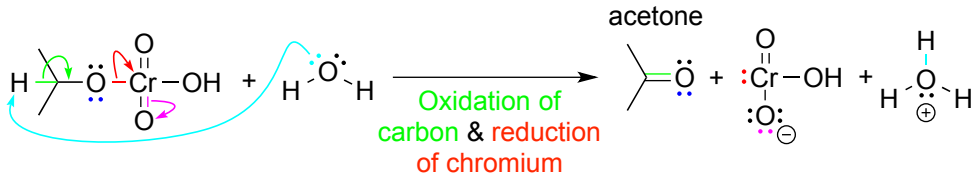


Specific examples of the oxidation of alcohols

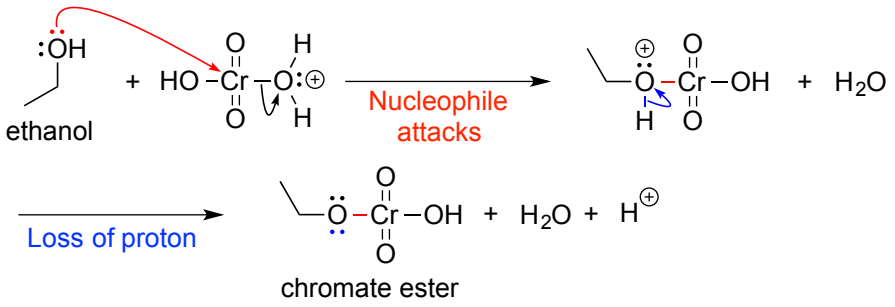
In the following example, isopropyl alcohol (a secondary alcohol) is the reactant. It initially forms a chromate ester when treated with chromic acid.



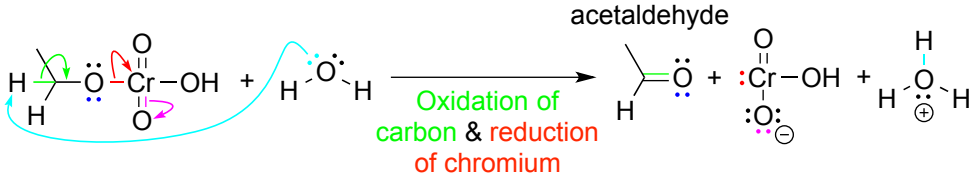
The subsequent removal of a proton from the secondary carbon of isopropyl alcohol incites the oxidation-reduction process that yields acetone as the particular ketone product of this reaction.



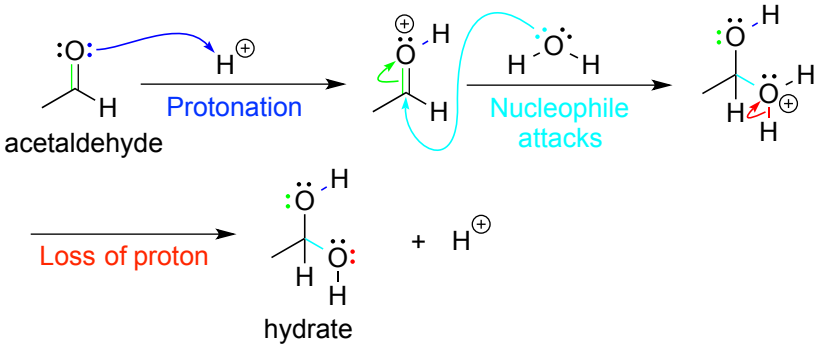
In the next example, ethanol (a primary alcohol) is the substrate. It too forms a chromate ester upon treatment with H_2CrO_4.



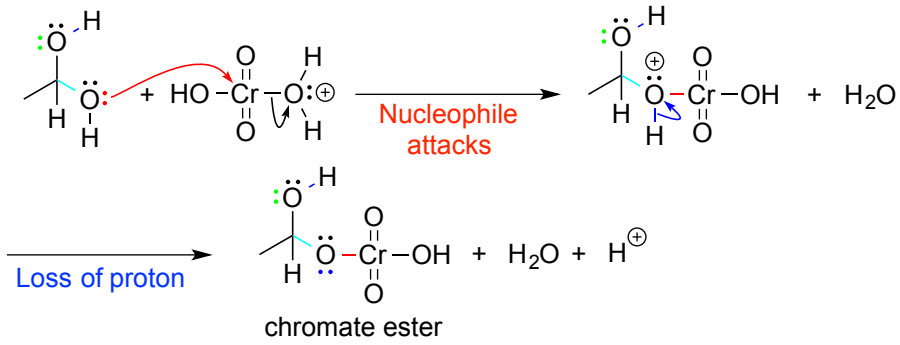
The first round of oxidation of this primary alcohol yields acetaldehyde.



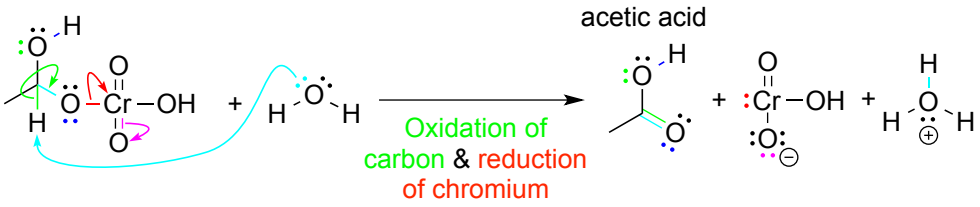
However, in the presence of water, acetaldehyde is converted to its hydrate.



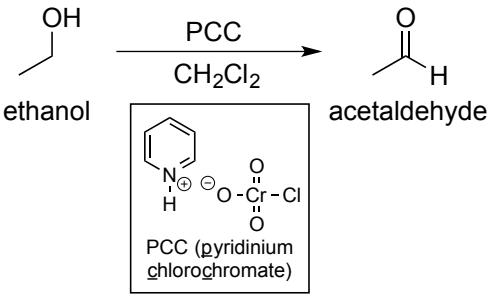
The hydrate then forms a new chromate ester.



This chromate ester fragments upon loss of a proton to yield acetic acid as the final product of the reaction between ethanol and chromic acid.



If acetaldehyde were the desired reaction product, ethanol would need to be treated with PCC instead of chromic acid. In this anhydrous (i.e., without water) environment, oxidation stops at the aldehyde.



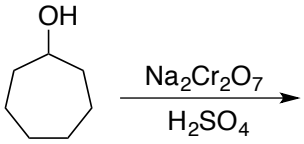
In conclusion, primary and secondary alcohols can be oxidized with chromic acid or PCC. When a primary alcohol is treated with PCC, it is oxidized once to the aldehyde. If a primary alcohol is treated with chromic acid, it undergoes two oxidations to yield a carboxylic acid.

Secondary alcohols have only one proton on the carbon bearing the hydroxyl group. Therefore, secondary alcohols can only undergo one round of oxidation to produce ketones, regardless of whether they are treated with chromic acid or PCC.

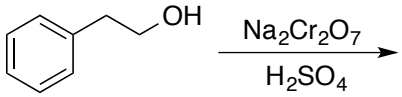
Tertiary alcohols possess no protons on the carbon bearing the hydroxyl group and are therefore unreactive under these conditions.

Problem 11. Predict the outcome of the following oxidation reactions. If there is no reaction, explain why that is the case.

(a)



(b)



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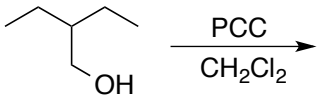
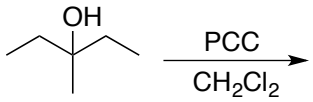
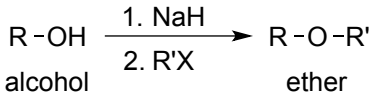


(d)

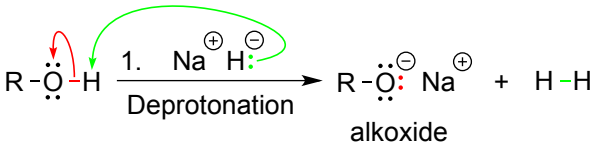


Section 7: Williamson Ether Synthesis

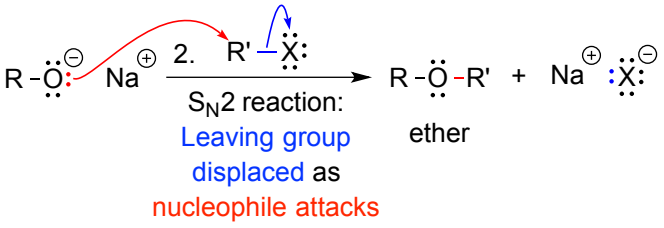
The Williamson ether synthesis converts an alcohol to an ether in a two-step sequence: (1) treatment with strong base followed by (2) S_N2 reaction with an *unhindered* alkyl halide.



The alcohol is initially deprotonated by a strong base, such as sodium hydride (NaH). The conjugate base of the alcohol, known as an alkoxide, is the product of this step. The alkoxide can also be formed by treatment of the alcohol with other strong bases or with sodium metal.



The second step is merely an S_N2 reaction in which the leaving group is displaced as the alkoxide attacks.

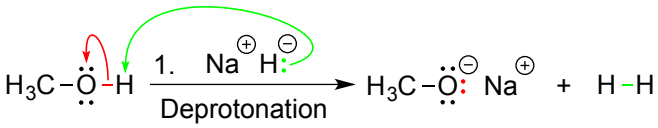


Since this latter step is an S_N2 reaction, it is critical that the carbon bearing the leaving group in R' be unhindered. Ideally, the alkyl halide should be methyl or primary. Recall that steric hindrance slows the rate of the S_N2 reaction, and tertiary alkyl halides cannot undergo S_N2.

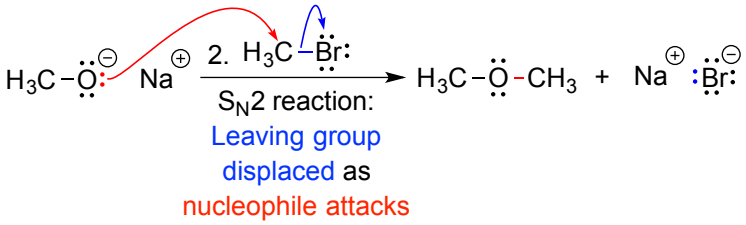
Also note that the leaving group need not necessarily be a halide. A sulfonate (⁻OTs, ⁻OMs, or ⁻OTf) would be suitable as well.

Specific examples of the Williamson ether synthesis

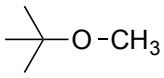
In the following example, a symmetrical ether (dimethyl ether) is produced using the Williamson ether synthesis. Methanol is first deprotonated by sodium hydride to yield sodium methoxide.



Methoxide then attacks methyl bromide, displacing bromide as the new O–C bond is formed.

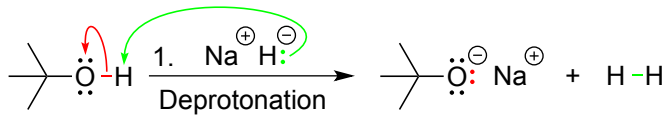


When unsymmetrical ethers are made using the Williamson ether synthesis, careful consideration must be given to the selection of the alcohol and alkyl halide. Consider the preparation of *tert*-butyl methyl ether.

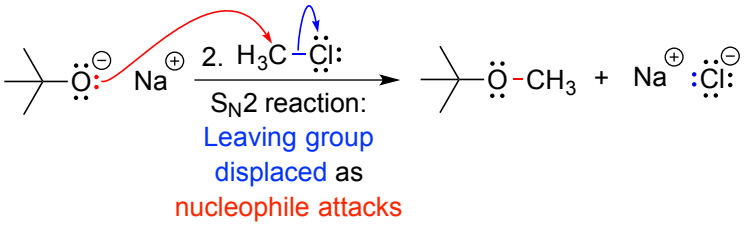


tert-butyl methyl ether
(aka methyl *tert*-butyl
ether, or MTBE)

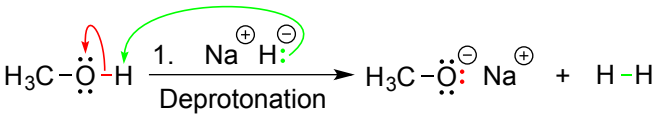
This ether can be made successfully if *tert*-butanol is deprotonated to give *tert*-butoxide.



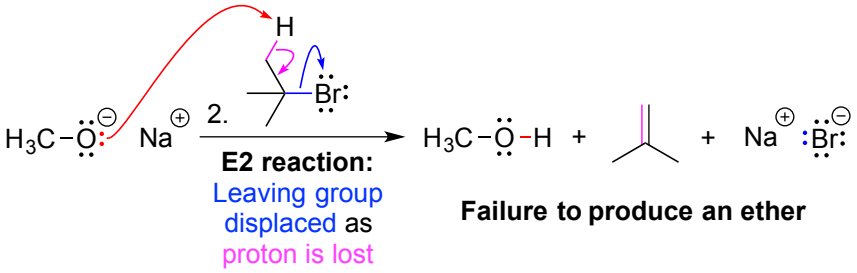
Tert-butoxide then attacks the unhindered electrophile methyl chloride. Chloride is displaced as the new O–C bond is created.



However, the synthesis of *tert*-butyl methyl ether will fail if methanol is used as the alcohol component. Methanol can, of course, be readily deprotonated by sodium hydride.

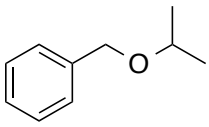


However, *tert*-butyl bromide is a tertiary alkyl halide and *cannot* undergo S_N2 reaction. Since methoxide is a strong nucleophile and base, it will act as a base if it cannot act as a nucleophile. This causes *tert*-butyl bromide to undergo E2 elimination. Since the reaction proceeds through the E2 (rather than S_N2) pathway, it fails to produce the desired ether as the reaction product.



To review, the Williamson ether synthesis is a particular application of the S_N2 reaction. An alcohol is deprotonated in order to convert it into a strong nucleophile. This strong nucleophile (the alkoxide) then reacts with an unhindered alkyl halide to yield an ether.

Problem 12. Provide a suitable synthesis of the following ether using the Williamson method.



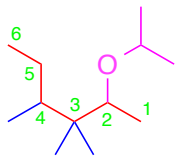
Section 8: Nomenclature and properties of ethers

IUPAC nomenclature of ethers

In systematic nomenclature, ethers are named as alkoxyalkanes. In other words, the parent is the longest continuous hydrocarbon chain. The OR substituent on that chain is known as an alkoxy group. The names of alkoxy groups are derived from those of alkyl groups by replacing the "yl" ending with "oxy" to denote the presence of oxygen. A few simple alkoxy groups are shown in the table below.

Alkyl groups		Alkoxy groups	
$-CH_3$	methyl	$-OCH_3$	methoxy
$-CH_2CH_3$	ethyl	$-OCH_2CH_3$	ethoxy
$-CH_2CH_2CH_3$	propyl	$-OCH_2CH_2CH_3$	propoxy
$-CH(CH_3)_2$	isopropyl	$-OCH(CH_3)_2$	isopropoxy
$-CH_2CH_2CH_2CH_3$	butyl	$-OCH_2CH_2CH_2CH_3$	butoxy
$-CH_2CH(CH_3)_2$	isobutyl	$-OCH_2CH(CH_3)_2$	isobutoxy
$-CH(CH_3)CH_2CH_3$	*sec*-butyl	$-OCH(CH_3)CH_2CH_3$	*sec*-butoxy
$-C(CH_3)_3$	*tert*-butyl	$-OC(CH_3)_3$	*tert*-butoxy

The alkoxy group is treated like any other substituent and *gets no special preference*, so our prior rules for deriving IUPAC names are simply applied here as well.

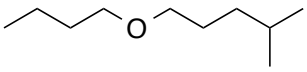


2-isopropoxy-3,3,4-trimethylhexane

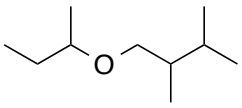
- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

Problem 13. Provide systematic names for the following ethers.

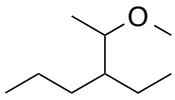
(a)



(b)

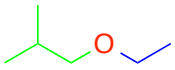


(c)



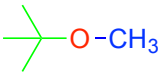
Common nomenclature of ethers

Ethers are given common names by placing the names of the two alkyl groups attached to oxygen before the word "ether".



ethyl isobutyl ether

Ideally, the alkyl group names should be alphabetized; however, that guideline is not always strictly followed. For instance, in the section on the Williamson ether synthesis, we saw that *tert*-butyl methyl ether is sometimes referred to as MTBE, which stands for methyl *tert*-butyl ether.



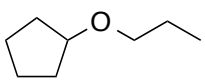
tert-butyl methyl ether
(aka methyl *tert*-butyl ether, or MTBE)

There are some other liberties taken with the common names of ethers that aren't formally correct but are encountered in practice. Diethyl ether is a very commonly used solvent in laboratory settings. It is also referred to as ethyl ether. This isn't formally correct; however, we can unambiguously determine the structure from this name. An ether must have two R groups on oxygen. If the only alkyl group name given is ethyl, then we know that both R groups must be ethyl. Given its prevalence in the lab, it is also sometimes referred to simply as ether.

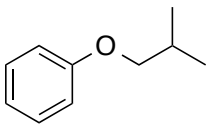
diethyl ether
(aka ethyl ether, or ether)

Problem 14. Provide common names for the following ethers.

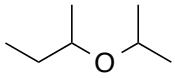
(a)



(b)

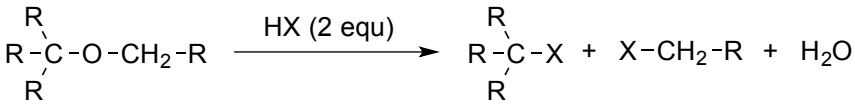


(c)

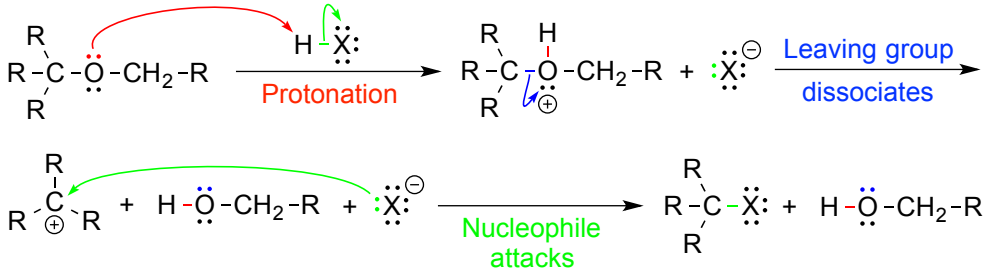


Section 9: Acidic cleavage of ethers

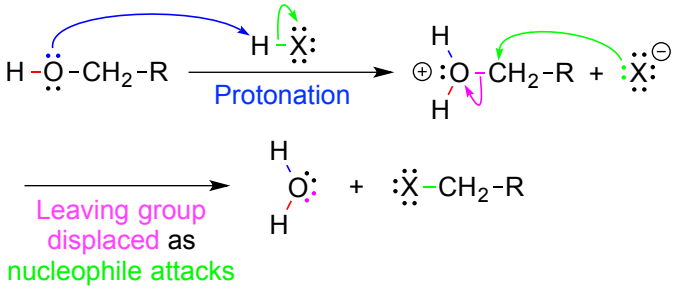
Although ethers have limited reactivity, they can be cleaved by treatment with strong acid (HBr or HI). The reaction typically involves the use of at least two equivalents (or simply excess) HX and yields alkyl halides and water in most scenarios.



The reaction begins with the protonation of the ether by HX. The resulting oxonium ion will undergo either S_N1 or S_N2 reaction, depending upon the substitution of the carbons bonded to oxygen. Secondary or tertiary carbons will proceed through an S_N1 mechanism, so the oxonium ion dissociates from the tertiary center, leaving behind a stable carbocation. This tertiary carbocation is then attacked by the halide to afford a tertiary alkyl halide.

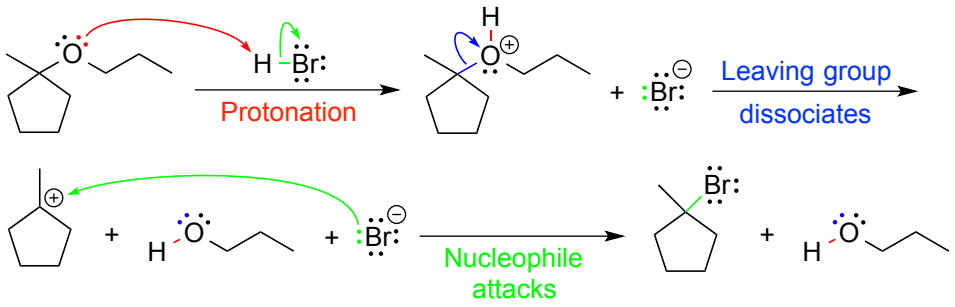


However, the reaction is not yet finished. The alcohol formed during dissociation can undergo further reaction with HX. It may be helpful to refer back to Section 2 ("Reaction of alcohols with HX"). The alcohol is protonated by a second molecule of HX. The primary carbon would yield an unstable carbocation, so this center engages in S_N2 reaction instead. The halide attacks the primary carbon, concurrently displacing water.

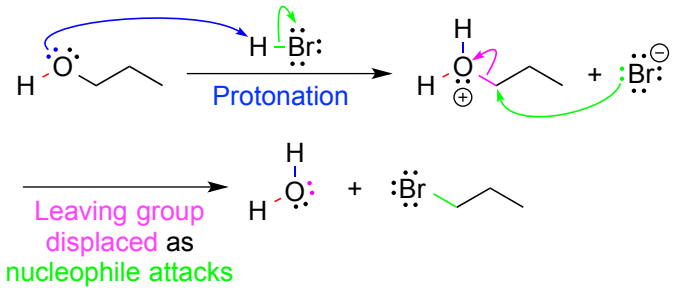


Specific examples of the acidic cleavage of ethers

In the following example, the ether is first protonated by HBr. The oxonium ion thus formed has electrophilic carbons that are tertiary and primary. The tertiary center would make a suitable carbocation, so the oxonium ion dissociates from it. The carbocation is then attacked by bromide to yield 1-bromo-1-methylcyclopentane.

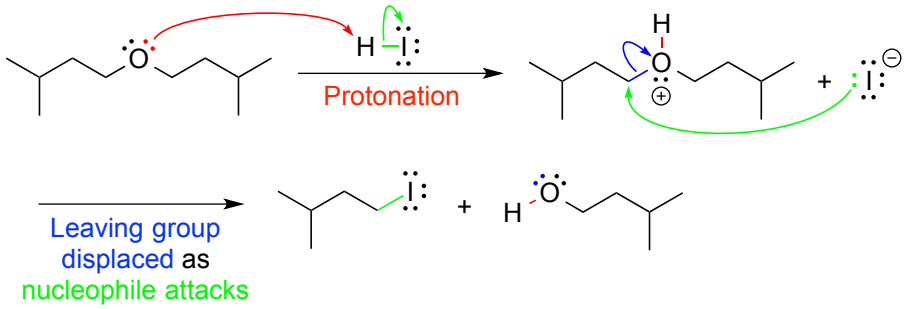


The reaction is not yet finished though. The propyl alcohol that was formed previously can be protonated by a second equivalent of HBr. Since the carbon bearing the leaving group is primary, it can only react through an S_N2 pathway. Consequently, bromide attacks the primary center and simultaneously displaces water to afford the second reaction product: propyl bromide.

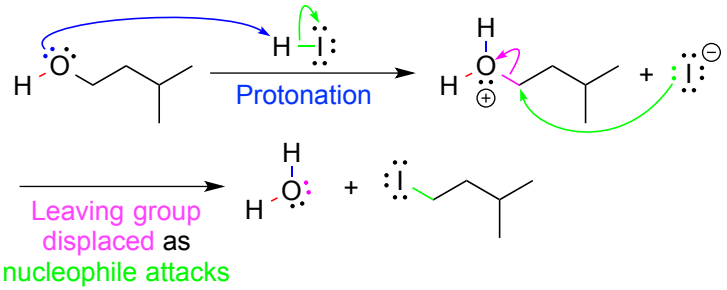


In the generic mechanism presented at the beginning of this section and in the preceding example, the reaction proceeded through one S_N1 and one S_N2 mechanism. However, it is certainly possible for ethers to react through other mechanistic combinations. In the example below, both of the carbons bonded to oxygen are primary. Therefore, cleavage of this ether can only occur through S_N2 mechanisms.

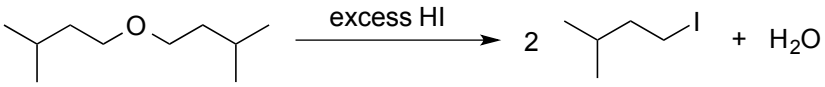
The initial protonation of the ether is followed by S_N2 attack of iodide on one of the primary centers to displace an alcohol.



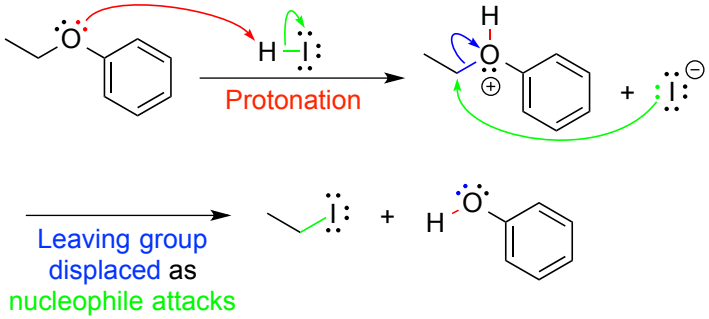
However, the reaction is not yet complete. The alcohol formed above can be protonated by a second equivalent of HI. Another S_N2 reaction occurs in which water is displaced as iodide approaches the electrophilic primary center.



The net result of the preceding example is the formation of two equivalents of 1-iodo-3-methylbutane.



It is also possible for certain ethers to be capable of only one round of substitution. For instance, in the example below, ethyl phenyl ether is first protonated by HI. One of the centers adjacent to oxygen is primary, but the other one is sp^2 hybridized. Carbons that are sp^2 hybridized do not participate in S_N1 or S_N2 reaction. Consequently, the ester is cleaved by S_N2 attack of iodide on the electrophilic primary carbon, which displaces phenol.

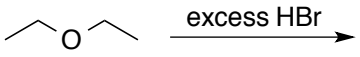


This reaction can proceed no further because phenol will not undergo S_N1 or S_N2 reaction, so in this case, the final products are not two alkyl halides. Instead, they are ethyl iodide and phenol.

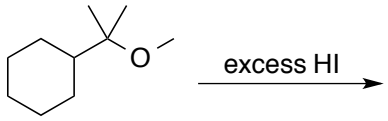
In conclusion, ethers can be cleaved by treatment with excess strong acid (HBr or HI). The reaction proceeds through an S_N1 and/or S_N2 pathway. The mechanism depends upon the substitution of the electrophilic carbon atoms. All of the rules of the S_N1 and S_N2 mechanisms apply (refer to Chapter 7). The final products are typically alkyl halides, unless one of the carbons is part of an aromatic ring, which would preclude reaction at that center.

Problem 15. Predict the products of the following reactions.

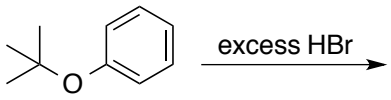
(a)



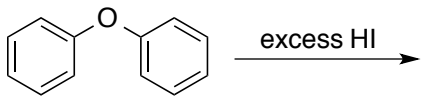
(b)



(c)

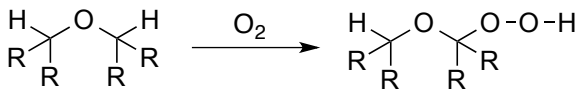


(d)



Section 10: Autoxidation

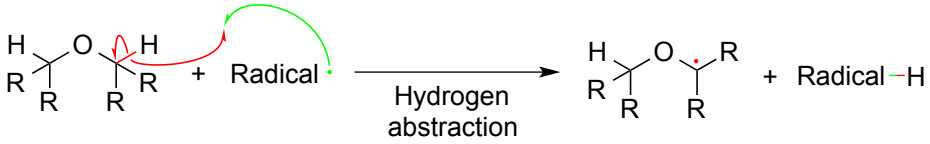
Ethers can undergo autoxidation in the presence of oxygen. A trace of radical can initiate propagation steps that result in the formation of hydroperoxides. These hydroperoxides are a safety concern, especially when concentrated, and can lead to an explosion. Therefore, the concentration and heating of ethers can be problematic laboratory procedures.



hydroperoxide

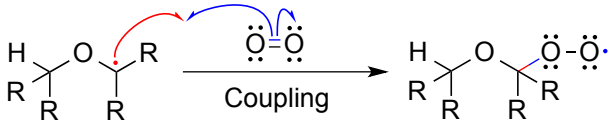
A trace of radical is needed to initiate the process. The source of the radical may not always be clear. Once formed however, the radical will abstract a hydrogen atom from the position adjacent to the ether oxygen (the α position).

Initiation:

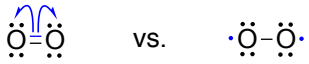


The carbon-centered radical thus produced will couple with oxygen in a propagation step.

Propagation step 1:

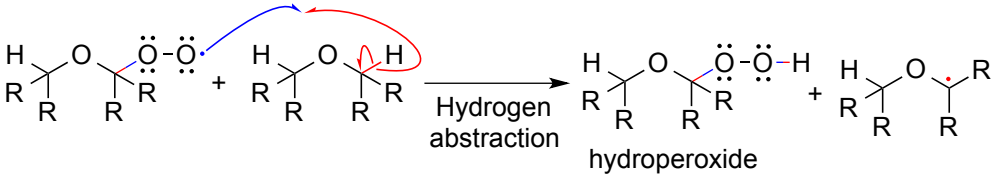


The above mechanism for propagation step 1 uses oxygen (O_2) shown as having a double bond between the oxygen atoms. Oxygen actually behaves much like a diradical. So, the mechanism may also be drawn using the diradical form in propagation step 1. In fact, in some cases it may even be oxygen (acting as a diradical) that abstracts the hydrogen atom during the initiation step.



The oxygen-centered radical formed in propagation step 1 then abstracts a hydrogen atom from the α position of an unreacted ether molecule. This affords a hydroperoxide product, as well as another carbon-centered radical that can cycle through an additional round of propagation steps. Since the active radical is regenerated in propagation step 2, this is a chain reaction.

Propagation step 2:

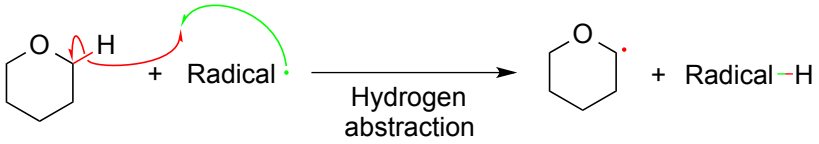


Termination steps are of little consequence and are therefore not shown. Termination steps explain the fate of the few remaining radicals left over once the reaction has neared completion. However, the vast majority of the hydroperoxide is formed during propagation step 2.

A specific example of autoxidation

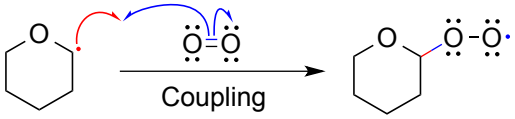
In the following example, a heterocycle known as tetrahydropyran undergoes autoxidation. The process begins when a trace of radical abstracts a hydrogen from the α position.

Initiation:



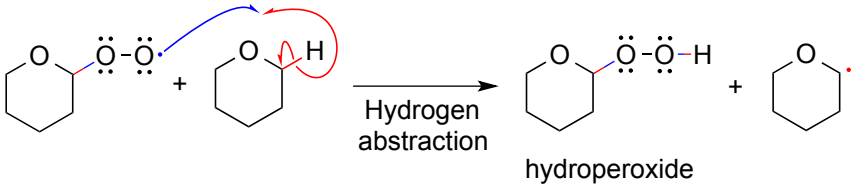
Then, the carbon-centered radical and oxygen couple in the first propagation step.

Propagation step 1:



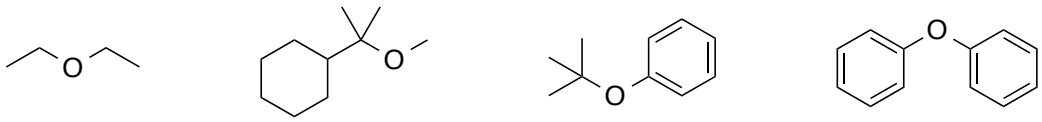
Finally, the oxygen-centered radical abstracts a hydrogen from an unreacted molecule of tetrahydropyran to yield the hydroperoxide product. The tetrahydropyranyl radical is regenerated and will engage in another round of propagation steps.

Propagation step 2:



To recap, the autoxidation of ethers is a radical chain process that takes place in the presence of oxygen. It yields hazardous hydroperoxides.

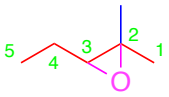
Problem 16. Which of the following ethers are susceptible to autoxidation?



Section 11: Nomenclature and properties of epoxides

IUPAC nomenclature of epoxides

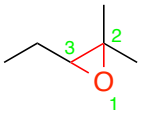
There are two options for systematically naming epoxides. The first method entails naming the alkane parent and adding the prefix "epoxy" to denote the presence of the epoxide. Two numbers are used to identify the two carbons bridged by the oxygen atom.



2,3-epoxy-2-methylpentane

- Five carbon parent = pentane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

In the second method, the smallest possible epoxide is treated as the parent and is termed "oxirane". The oxygen atom is position one, and the carbon atoms are numbered so as to give the lower number to the first substituent. If the first substituent receives the same number either way, the ring is numbered so as to give the second substituent the lower number.

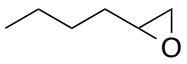


3-ethyl-2,2-dimethyloxirane

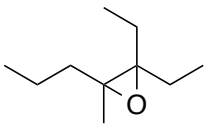
- Parent = oxirane
- Number so as to give the first substituent the lower number = tie
- Number so as to give the second substituent the lower number
- Add substituent names and numbers

Problem 17. Provide two names for each of the following epoxides.

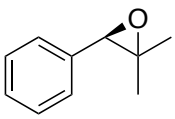
(a)



(b)

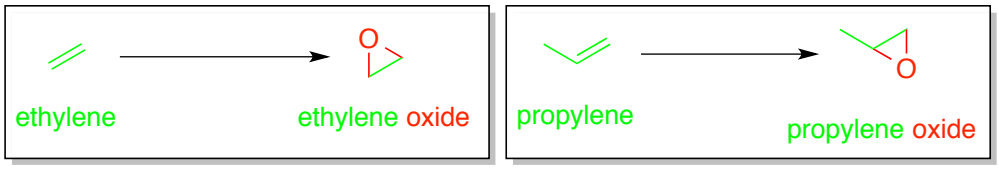


(c)



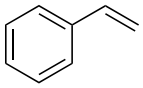
Common nomenclature of epoxides

In common parlance, epoxides are named using the common name of the *alkene* from which they are derived followed by the word "oxide".

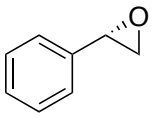


We'll learn more about the common names of alkenes in the next chapter.

Problem 18. The following alkene is known as styrene.

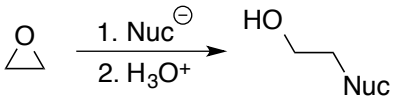


Using this knowledge, provide a common name for the following epoxide.

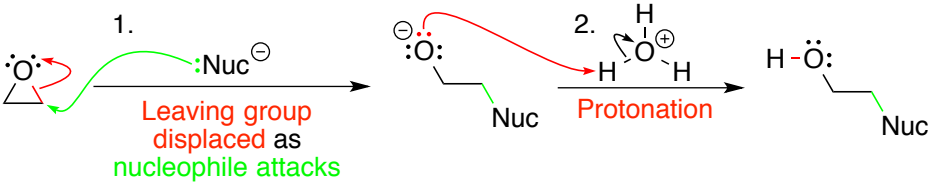


Section 12: Opening of epoxides under basic conditions

Epoxides can be opened under both acidic and basic conditions. In this section, we'll examine the cleavage of the epoxide under basic conditions. The net result of the two-step reaction is that a C-O bond is broken, and a nucleophile is added to the same carbon, while a proton is added to the oxygen.

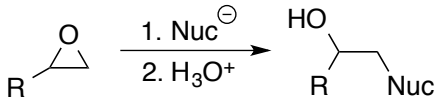


This process begins with an S_N2 reaction in step 1. The strong nucleophile attacks one of the two epoxide carbons from the direction opposite the C-O bond. As it does so, the C-O bond cleaves, releasing the strain of the three-membered ring and ejecting an alkoxide leaving group. Alkoxides are not typically good leaving groups; however, in this case, the poor leaving group ability of the alkoxide is offset by the reduction in strain energy that accompanies the opening of the ring. In step 2, the alkoxide is protonated when aqueous acid is added to the reaction mixture.

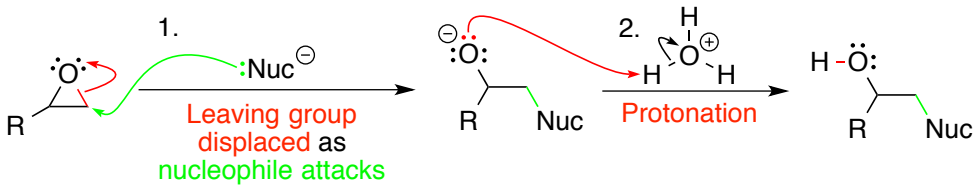


Regiochemical considerations

When the epoxide is unsymmetrical, the regiochemistry of the nucleophilic attack in step 1 becomes a concern.

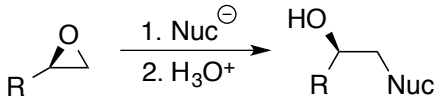


Thinking of the first step as an S_N2 reaction is helpful. We can be guided by the fact that S_N2 reactions are sensitive to steric hindrance. They occur more slowly at centers that are more hindered. Consequently, the nucleophile attacks the less sterically hindered carbon of the epoxide.

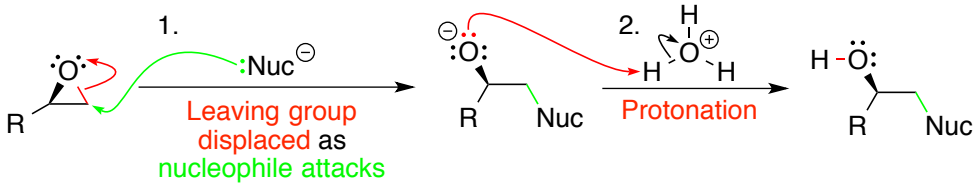


Stereochemical considerations

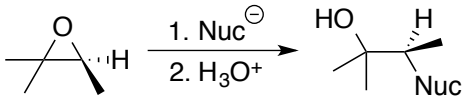
Only one carbon of the epoxide is mechanistically involved in the transformation. Therefore, only the stereochemistry of that center can be altered during the reaction. In the example below, there is a stereocenter in the molecule, but it is *not* the site of reaction and is therefore unchanged.



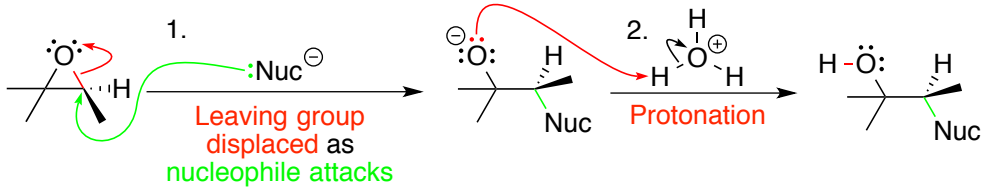
In step 1, S_N2 reaction takes place at the less hindered (primary) epoxide carbon. *Notice that there are no mechanistic arrows involving the stereocenter itself. Therefore, there can be no change in configuration at that center.* The protonation step also does not involve the stereocenter, which is carbon and not oxygen. Therefore, the configuration is constant throughout this transformation.



In the next example however, the reaction takes place at the stereocenter, leading to an inversion of configuration.

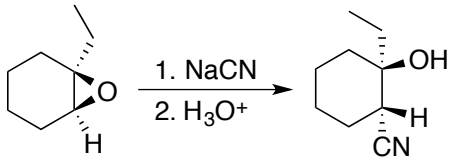


In step 1, the S_N2 reaction takes place at the less hindered (secondary) epoxide carbon. As in any other S_N2 reaction, the nucleophile attacks opposite the leaving group. Since the site of attack also happens to be a stereocenter, an inversion of configuration is observed. During the second step, there is no further change in stereochemistry because the protonation does not involve the stereocenter.

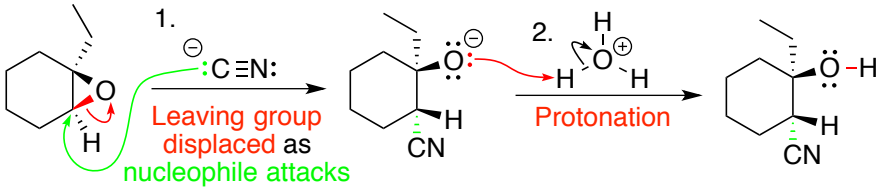


A specific example of the opening of an epoxide under basic conditions

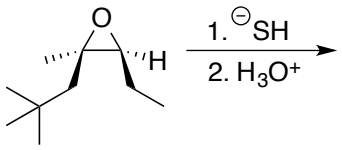
The following specific example has both regiochemical and stereochemical ramifications. The substituted epoxycyclohexane is treated with sodium cyanide followed by aqueous acid to yield a single stereoisomer of the hydroxynitrile product.



The sequence begins with S_N2 reaction between the epoxide and cyanide. The first consideration is regiochemical. The two epoxide carbons are secondary and tertiary, and the attack takes place at the less hindered (secondary) center. Furthermore, the attack occurs opposite the breaking C-O bond, which results in an inversion of configuration at that stereocenter. By the end of step 1, both the regiochemistry and the stereochemistry are set, and no further changes occur during step 2 when the alkoxide is protonated.

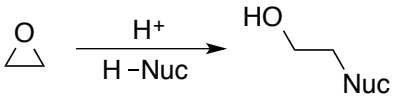


Problem 19. Provide a mechanism for the following epoxide opening that addresses both regiochemical and stereochemical concerns.

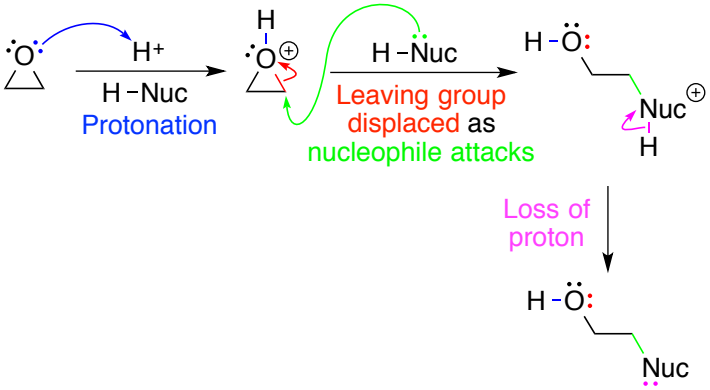


Section 13: Opening of epoxides under acidic conditions

In the previous section, we explored the opening of epoxides under basic conditions. Now, we'll turn our attention to the analogous opening under acidic conditions. Strong nucleophiles are typically also fairly basic and therefore incompatible with acid. So, in this reaction, a weaker nucleophile (H-Nuc) is used. The net result of the reaction is once again to cleave a C-O bond, adding a nucleophile to the same carbon and a proton to oxygen.

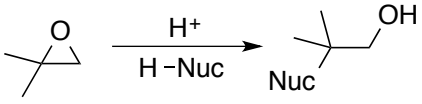


The reaction in acid begins with the protonation of the epoxide oxygen. This enhances the electrophilicity of the two adjacent epoxide carbons. The weak nucleophile is attracted to one of these carbons, and as it attacks, the C-O bond is broken expelling an alcohol as a leaving group. Finally, a proton is lost from the nucleophilic moiety to neutralize its charge.



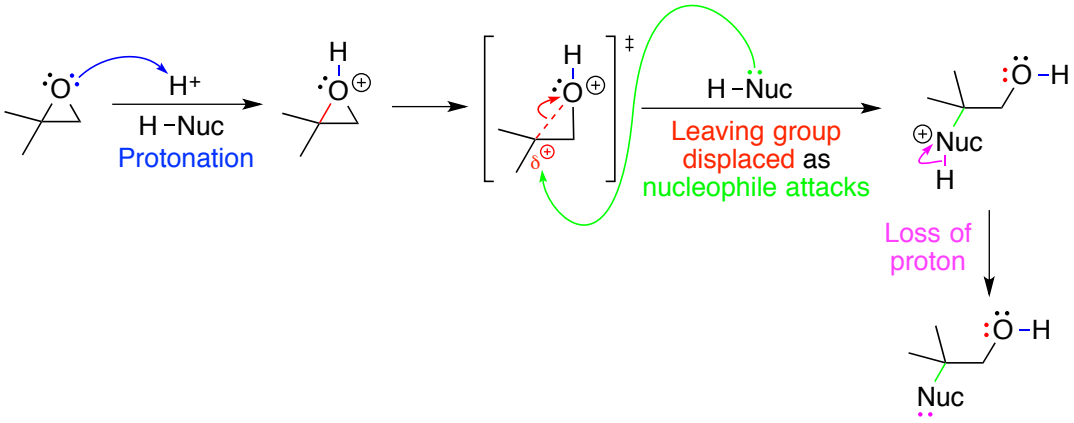
Regiochemical considerations

Acidic epoxide opening possesses attributes of both the S_N1 and S_N2 reactions. Notice that the regiochemistry of the following transformation is the opposite of what we would predict under basic conditions.



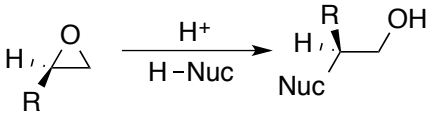
The rationale stems from the S_N1-like characteristics of this reaction. Upon protonation of the epoxide, the oxonium ion begins to pull away from the two carbons to which it is

attached. However, the bond to the more substituted carbon is weakened more because that center is better able to stabilize a partial positive charge (δ^+). It is this δ^+ that draws in the weak nucleophile, so attack occurs at the more hindered site, in direct contrast to what occurs during basic epoxide opening.

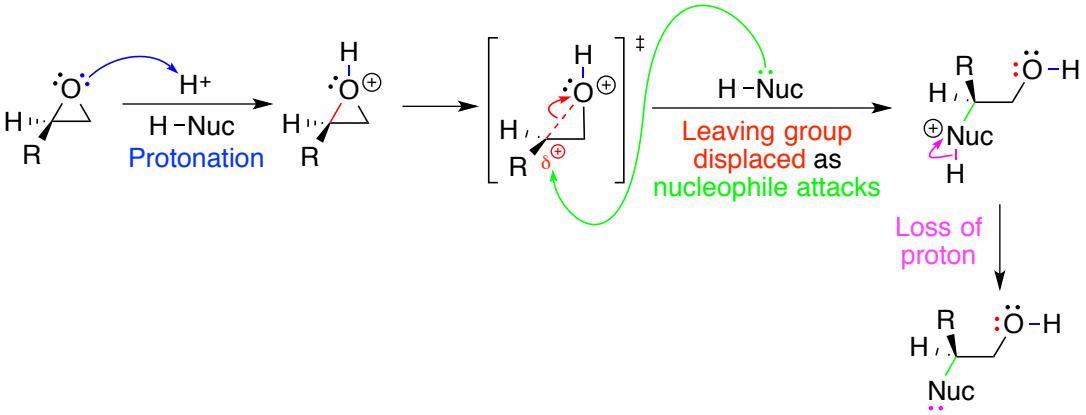


Stereochemical considerations

When there is stereochemistry at the site of reaction, an inversion of configuration is observed, just as we saw with basic epoxide openings.

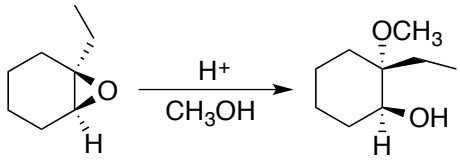


While the transition state for the epoxide opening has a partially dissociated C-O bond (giving the reaction some S_N1 character), the fact that the bond is only partially broken means that the nucleophile still attacks opposite the leaving group. This is the source of the Walden inversion.

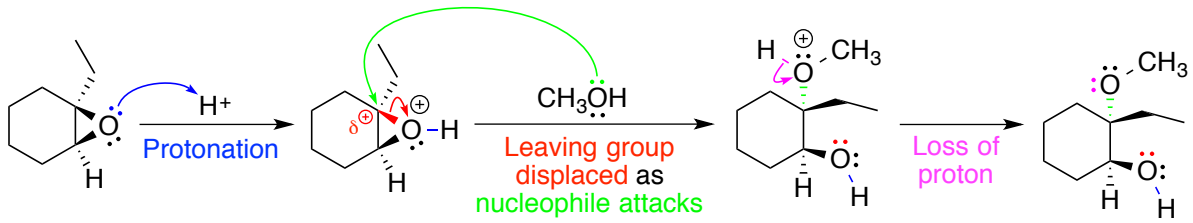


A specific example of the opening of an epoxide under acidic conditions

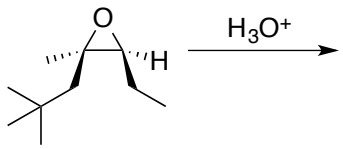
The following substituted epoxycyclohexane was subjected to basic opening in the previous section. Now, let's examine the regiochemistry and stereochemistry of an acidic opening.



The reaction begins with protonation of the epoxide oxygen. This enhances the electrophilicity of the epoxide carbons, and the more substituted one acquires the greater δ^+, which draws in the weak nucleophile. Methanol attacks this more hindered center, and there is an inversion of configuration at this center only as the alcohol is displaced. Notice that the stereochemistry of the other center is unaffected. Finally, the loss of a proton neutralizes the oxonium ion and completes the mechanism.

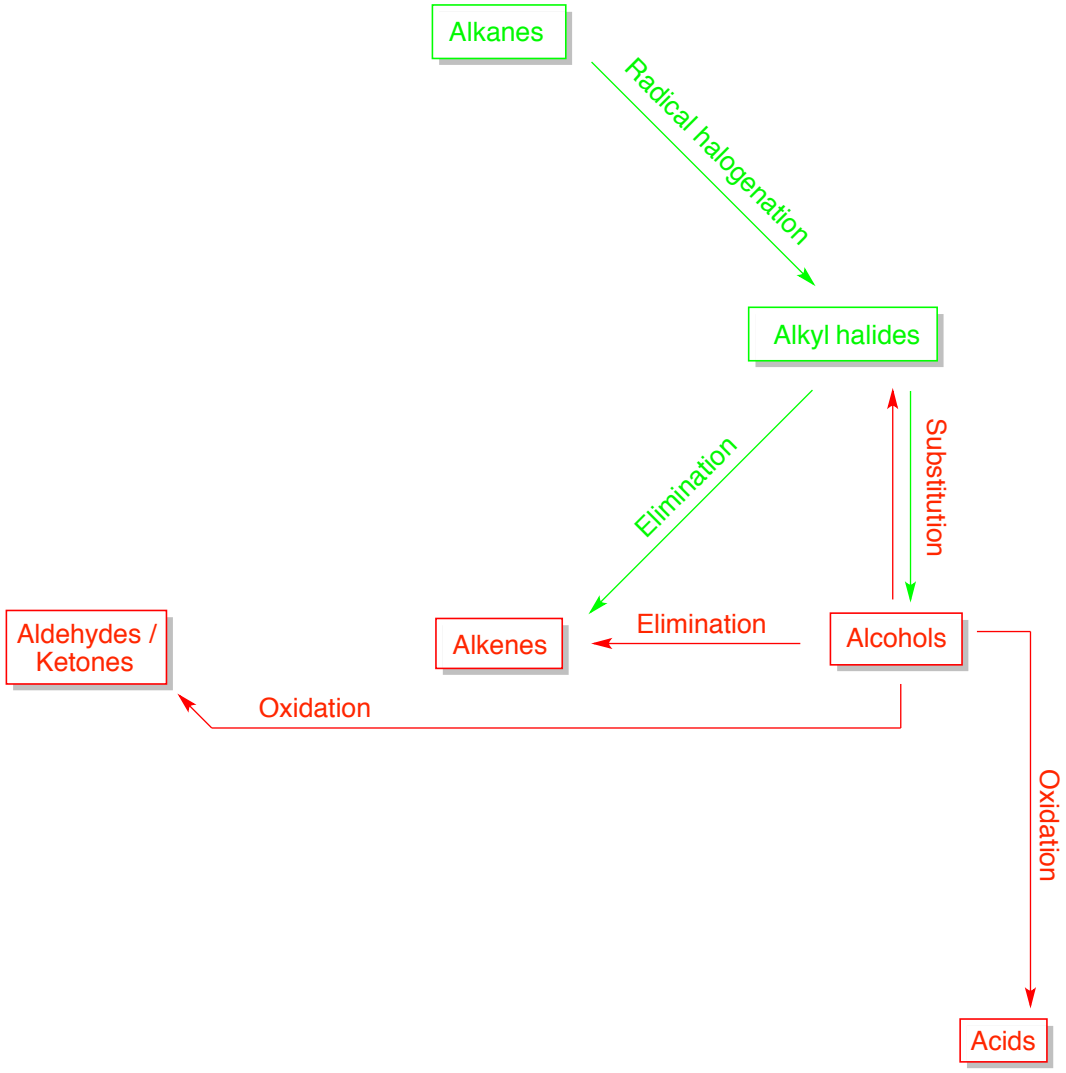


Problem 20. Provide a mechanism for the following epoxide opening that addresses both regiochemical and stereochemical concerns.

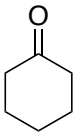


Section 14: Synthesis

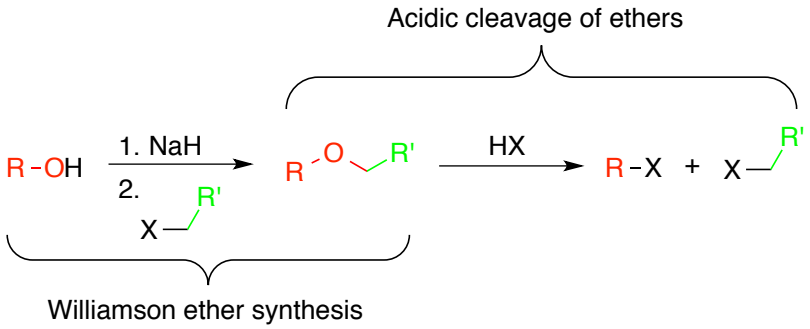
As we continue to flesh out our map of functional group interconversions, we have added some new transformations to those that we've encountered previously. In this chapter, we have seen ways in which alcohols can be converted to alkyl halides via substitution reactions that utilize HX, PBr_3, and $SOCl_2$. We've revisited dehydration and learned how it can be accomplished using not only sulfuric acid but also $POCl_3$. Additionally, we've learned that oxidation can convert alcohols to aldehydes, ketones, or carboxylic acids depending on the substitution of the alcohol and the reagent chosen for the oxidation (i.e., chromic acid or PCC).



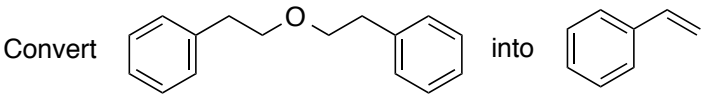
Problem 21. Provide a viable synthesis.

Prepare  from 

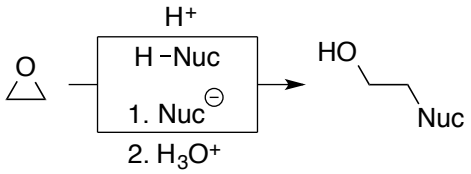
We've also encountered reactions that make and break ethers, as well as reactions that open epoxides. We'll keep these separate from our developing synthetic map because they will be used less frequently in the chapters to come. The Williamson ether synthesis unites an alcohol and an unhindered alkyl halide to form and ether. That ether can, in turn, be broken into two alkyl halides (most of the time) upon treatment with HX.



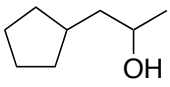
Problem 22. Provide a means to achieve the following conversion.



We'll learn how to prepare epoxides in the next chapter. For the moment, we know that epoxides can be opened in either acidic or basic media. The hydroxyl group and the nucleophile are separated by two intervening carbons in the products of such reactions.



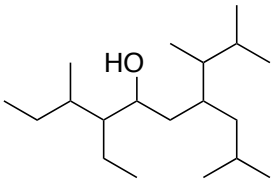
Problem 23. In Chapter 15, we'll learn all about making and using Grignard reagents. These are compounds having the form R-MgBr. Since the carbon-magnesium bond is polarized toward the more electronegative carbon atom, Grignard reagents essentially act as carbanions (i.e., negatively charged carbon). Given this information, propose a viable synthesis of the following molecule from propylene oxide and an appropriate Grignard reagent.



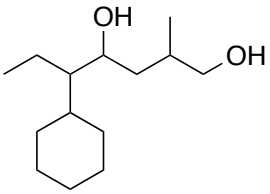
End-of-the-Chapter problems

Problem 24. Provide systematic names for the following compounds.

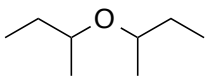
(a)



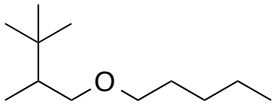
(b)



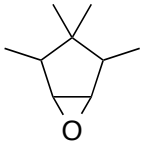
(c)



(d)

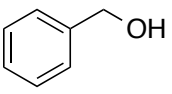


(e)

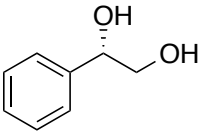


Problem 25. Provide common names for the following compounds.

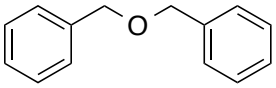
(a)



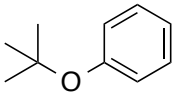
(b)



(c)



(d)

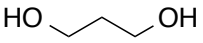


(e)

Problem 26. The following names contain errors. Identify the errors, and supply the correct name for each compound.

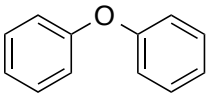
(a) 2,4-dimethyl-6-heptanol

(b)



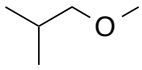
propylene glycol

(c)



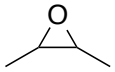
dibenzyl ether

(d)



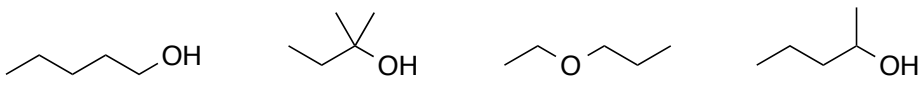
methyl *sec*-butyl ether

(e)

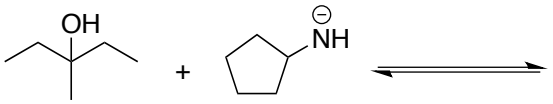


dimethyloxirane

Problem 27. Rank the following isomeric compounds in order of increasing boiling point.

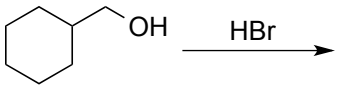


Problem 28. Predict the products of the following acid-base reaction. Then, state which side of the reaction is favored at equilibrium and by how much.

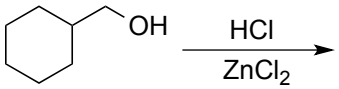


Problem 29. Provide mechanisms for both of the following reactions. Then, explain why $ZnCl_2$ is needed for the latter reaction.

(a)

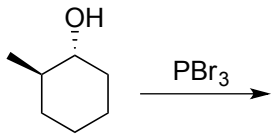


(b)



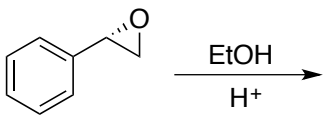
Problem 30. A tertiary alcohol having the formula $C_7H_{16}O$ is treated with $POCl_3$ and pyridine. This reaction yields a single trisubstituted alkene product. What is the structure of the alcohol and its dehydration product?

Problem 31. Provide a mechanism for the following reaction.

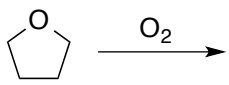


Problem 32. Predict the products of the following reactions.

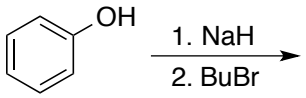
(a)



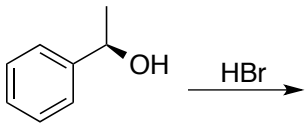
(b)



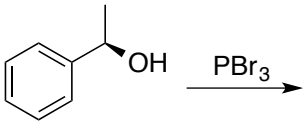
(c)



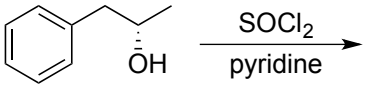
(d)



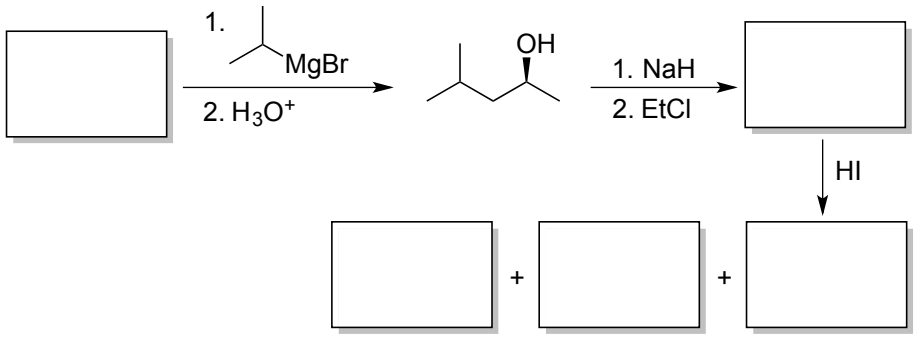
(e)



Problem 33. Draw a mechanism for the following reaction.



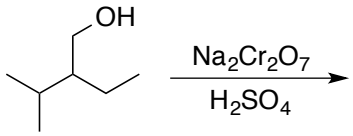
Problem 34. Fill in the missing reactant, intermediates, and products in the following scheme.



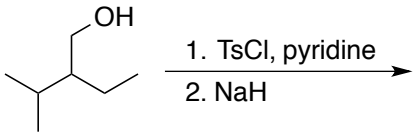
Problem 35. Propose a mechanism for the dehydration reaction in Problem 30.

Problem 36. The following reactions all employ the same reactant. Some of these transformations are similar but yield different results. Predict the product in each case.

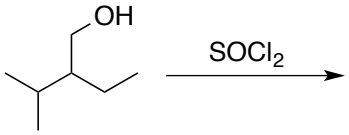
(a)



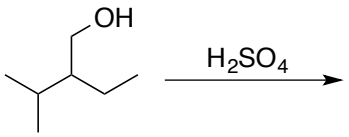
(b)



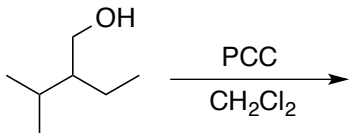
(c)



(d) Hint: For this problem, remember than a π bond can serve as a base.

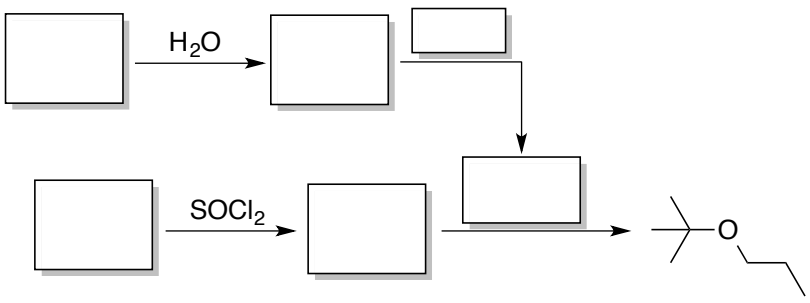


(e)



Problem 37. Propose a mechanism for the oxidation conducted in Problem 36(a).

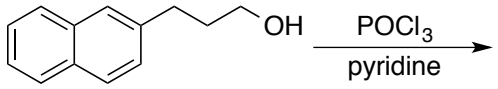
Problem 38. Fill in the missing reactants, reagents, and intermediates in the following scheme.



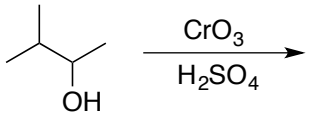
Problem 39. Draw a mechanism for the chromic acid oxidation of cyclohexanol.

Problem 40. Predict the products of the following reactions.

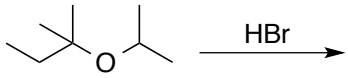
(a)



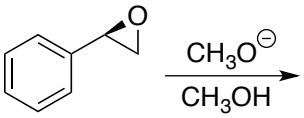
(b)



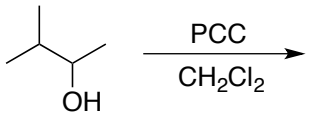
(c)



(d)



(e)



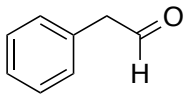
Problem 41. A Williamson ether synthesis was among the reactions utilized in Problem 38. Provide a mechanism for this part of the sequence.

Problem 42. Acetone is a common laboratory solvent. Devise a synthesis of acetone beginning with propane.

acetone

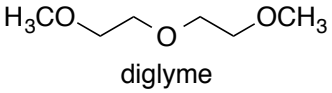
Problem 43. The last step of the sequence in Problem 34 was an acidic ether cleavage. Show the mechanism for this step.

Problem 44. Devise a viable synthesis.

Prepare  from 

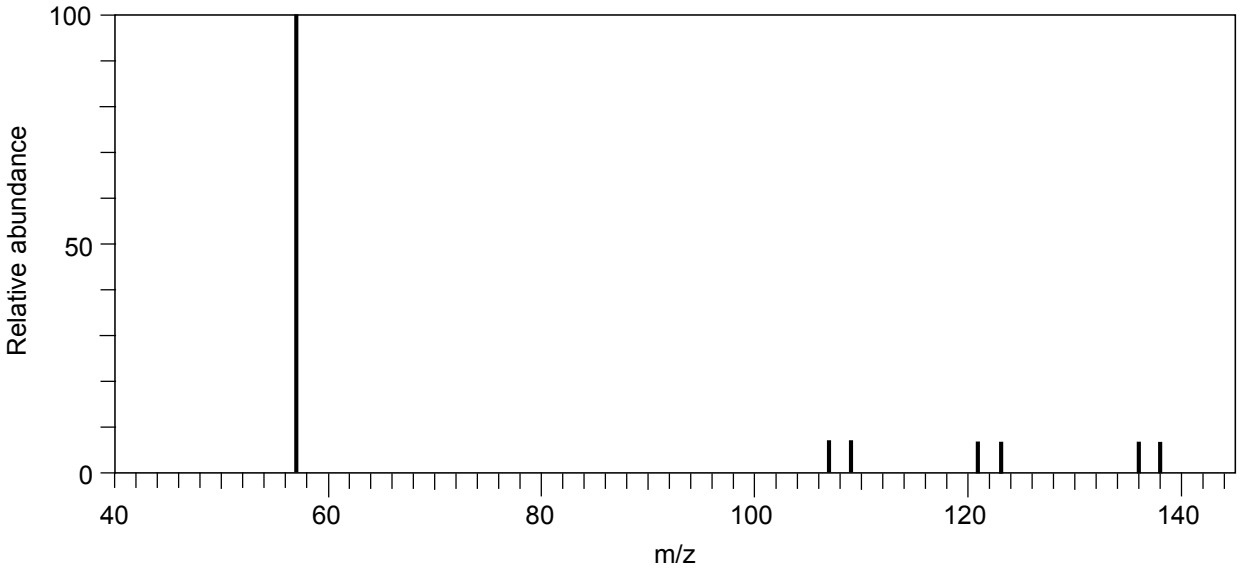
Problem 45. Draw a mechanism for the autoxidation of diethyl ether.

Problem 46. Diglyme is a high boiling solvent that is miscible with water. Synthesize diglyme using ethylene oxide and methanol as the only sources of carbon.

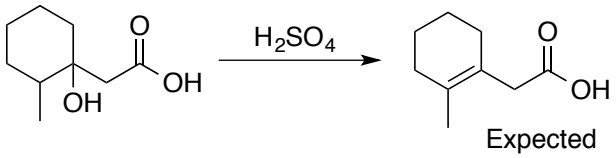


diglyme

Problem 47. An alcohol with the molecular formula $C_4H_{10}O$ is treated with HX. The resulting alkyl halide gives the following mass spectrum. Identify the structures of the alcohol and alkyl halide.



Problem 48. An investigator performed the following dehydration with the expectation of obtaining the tetrasubstituted alkene shown below, which is the Zaitsev product.

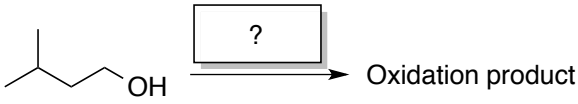


Expected

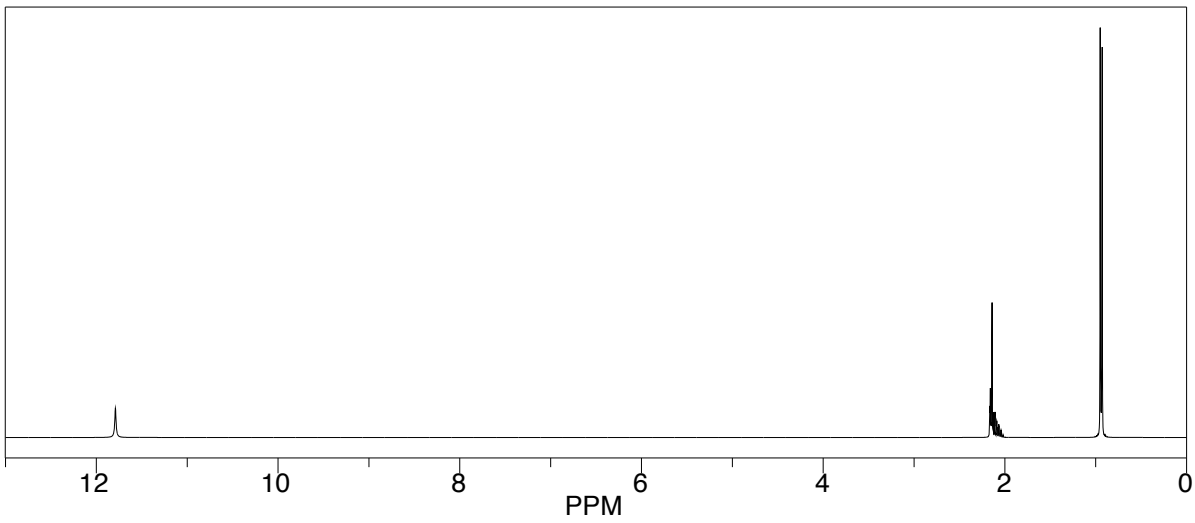
The IR data were not consistent with this structure though. C=C stretching appears around 1650 cm^{-1}, and the intensity of IR signals is related to the bond's dipole moment (i.e., the

magnitude of the charge difference and the distance between the nuclei). Consequently, the alkene's signal was expected to be a weak signal near 1650 cm^{-1} due to the low polarity of the expected carbon-carbon double bond. While the C=C signal did appear around 1650 cm^{-1} as expected, it was much more prominent than anticipated. Based on this clue, propose the actual outcome of the dehydration reaction.

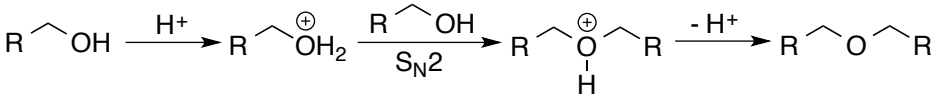
Problem 49. The substrate 3-methyl-1-butanol was treated with an oxidizing agent.



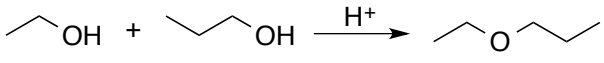
The ^1H NMR spectrum of the oxidation product is shown below. Based on this spectrum which oxidizing agent was used and what is the oxidation product?

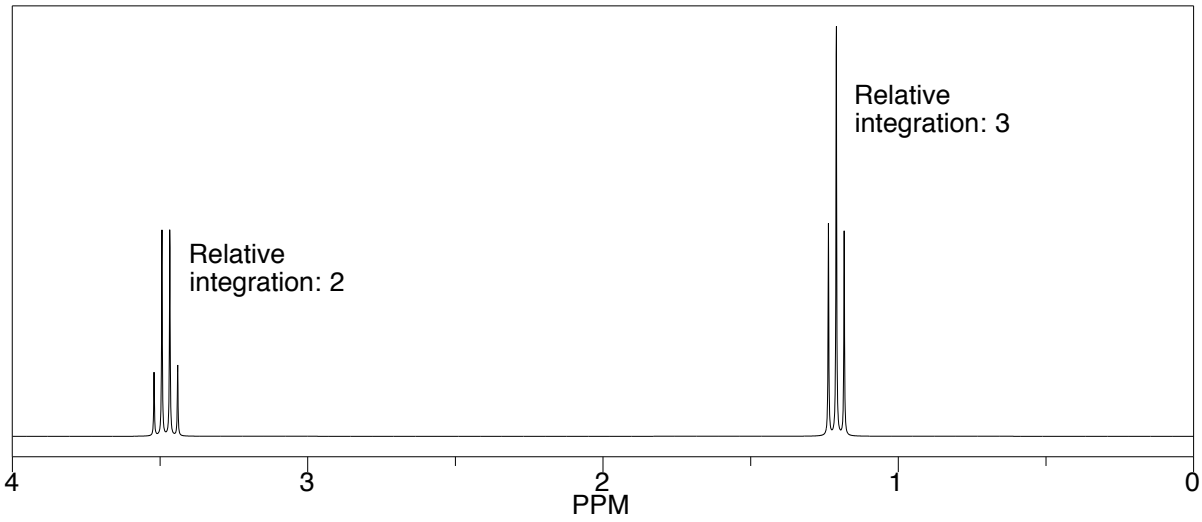


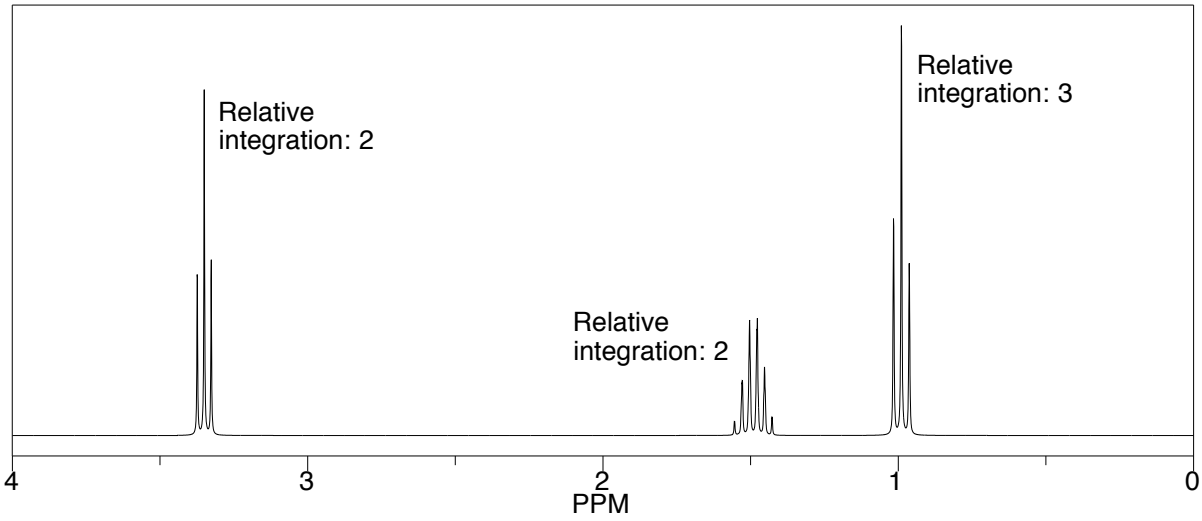
Problem 50. In this Chapter, you learned about the Williamson ether synthesis, but there are other methods to prepare ethers as well. A simple one entails the treatment of an alcohol with catalytic acid. This approach is typically only useful for the synthesis of symmetrical ethers, in which the carbons bearing oxygen are unhindered.

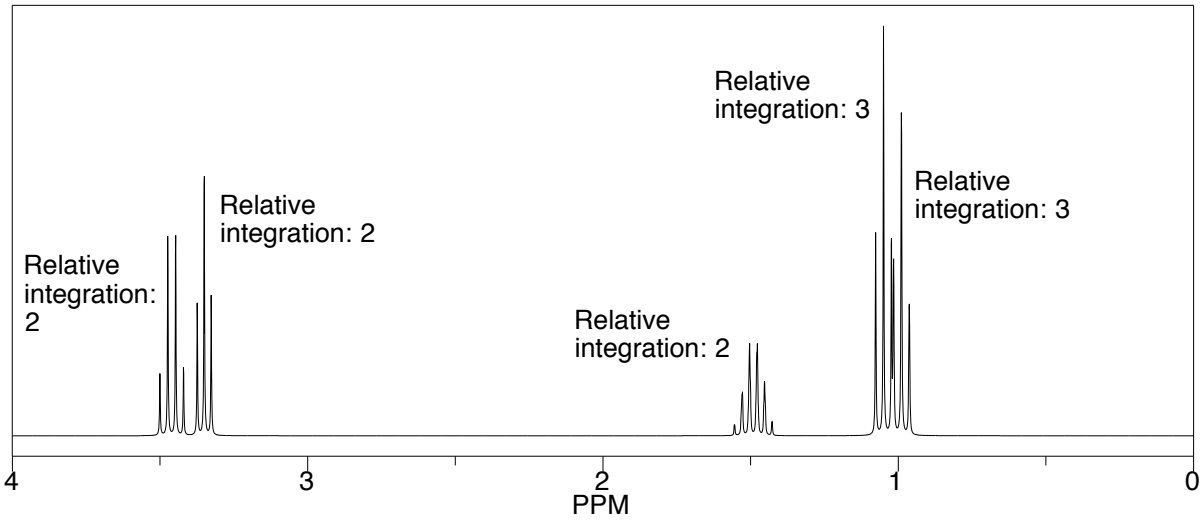


An investigator conducted the following reaction in the hopes of preparing ethyl propyl ether; however, three products were obtained. Their ^1H NMR spectra are shown below. Identify the products of the reaction.




Relative integration: 3
Relative integration: 2
4
3
2
1
0
PPM


Relative integration: 3
Relative integration: 2
Relative integration: 2
4
3
2
1
0
PPM


Relative integration: 3
Relative integration: 3
Relative integration: 2
Relative integration: 2
Relative integration: 2
4
3
2
1
0
PPM

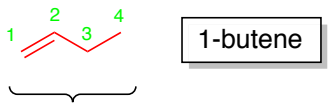
Chapter 10: Alkenes

Section 1: Nomenclature
Section 2: Introduction to reactions of alkenes
Section 3: Allylic bromination
Section 4: Ionic hydrohalogenation
Section 5: Radical hydrohalogenation
Section 6: Acid-catalyzed hydration
Section 7: Oxymercuration-demercuration
Section 8: Hydroboration-oxidation
Section 9: Hydrogenation
Section 10: Halogenation
Section 11: Halohydrin formation
Section 12: Epoxidation
Section 13: Anti-dihydroxylation
Section 14: Syn-dihydroxylation
Section 15: Cyclopropanation
Section 16: Ozonolysis
Section 17: Synthesis

Section 1: Nomenclature

IUPAC nomenclature

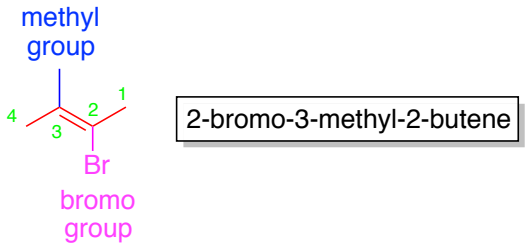
Alkenes contain a carbon-carbon double bond. Their IUPAC names are derived by first locating the parent, which is the longest continuous carbon chain that includes the double bond. The suffix "ene" denotes the presence of an alkene. The parent carbon chain is numbered so as to give the lowest possible numbers to the alkene, and if there would otherwise be ambiguity, a single number is used to indicate where the double bond begins. In the following example, there is a four-carbon parent with the double bond starting at position 1. This molecule can therefore be called 1-butene or but-1-ene. The locant can appear before the parent's name or before the suffix. Both are acceptable, but in this simple case, 1-butene is more commonly used.



- Four carbon parent = butane
- Replace "ane" suffix with "ene"
- Provide a number for the site where the double bond begins

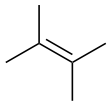
Substituents, when present, are added to the name according to the same IUPAC rules that we've learned previously. In the example below, the parent is 2-butene, and it possesses bromo and methyl substituents. The alkene would be assigned the number 2 regardless of the direction of numbering. Similarly, the substituents will get the numbers 2 and 3

whether we number the parent from left-to-right or from right-to-left. Therefore, our guideline of last resort is to assign the lower number to the substituent that appears first alphabetically.

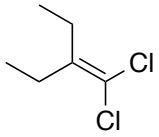


Problem 1. Provide IUPAC names for the following molecules.

(a)

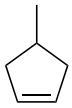


(b)

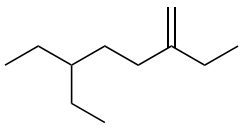


(c)

(d)

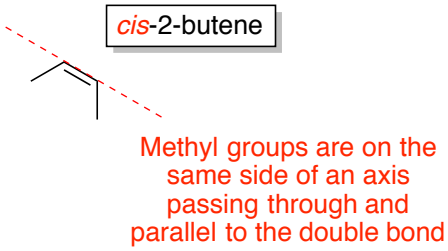


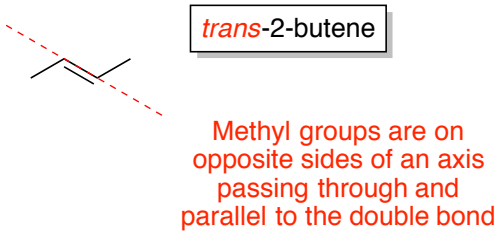
Problem 2. Provide a systematic name for the following alkene.



As we saw in the chapter on stereochemistry, alkenes can have *cis* and *trans* forms. For instance, the name 2-butene is not sufficient because two different compounds could

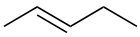
correspond to that name. *Cis*-2-butene and *trans*-2-butene must be differentiated from one another.



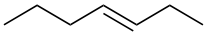


Problem 3. Name the following compounds.

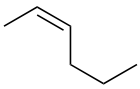
(a)



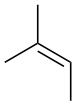
(b)



(c)

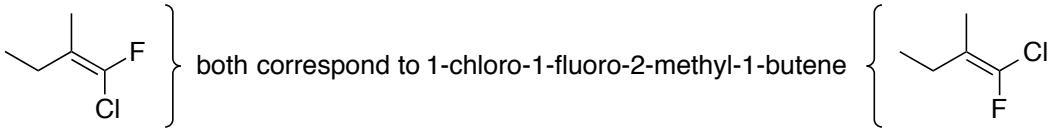


(d)

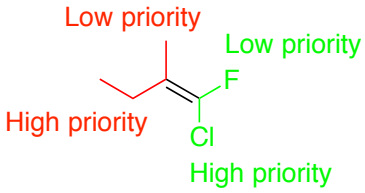


Problem 4. Explain why *trans*-cyclopentene does not exist.

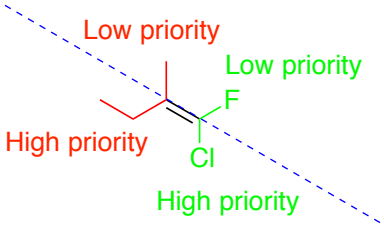
In the previous examples, when we said that an alkene was *cis* or *trans*, the groups to which we were referring were obvious. For instance, *cis*-2-butene has the methyl groups on the same side of the double bond. However, there are many alkenes that exhibit geometric isomerism for which the *cis*/*trans* nomenclature scheme is inadequate. Consider the two molecules below. Using only the rules that we've discussed thus far, they would both have the same name: 1-chloro-1-fluoro-2-methyl-1-butene. But we know that no two molecules can have the same systematic name. Therefore, we need to add a description of the geometry of these isomers. However, if we try to use a *cis* or *trans* descriptor with the following molecules, how would we know which of the groups are on the same side or opposite sides of the double bond? It would not be clear, so we need a better approach.



In cases like this, we use *E* and *Z* nomenclature. It is a simple system that allows us to clearly describe the geometry of an alkene. On each carbon of the alkene, the two groups are assigned high or low priority using the Cahn-Ingold-Prelog rules that we learned in the chapter on stereochemistry. On the right-hand alkene carbon, chlorine is the high priority group because it has a higher atomic number than fluorine. On the left-hand alkene carbon, the ethyl group has the higher priority because its carbon is bonded to another carbon, whereas the methyl group is bonded only to hydrogens.



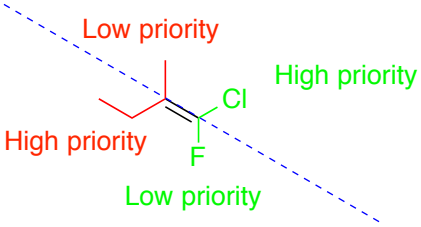
Then, an axis is drawn through and parallel to the double bond. If the high priority groups are on the same side of that axis (as they are in this case), the alkene is termed *Z*, which comes from the German "zusammen" for "together".



(*Z*)-1-chloro-1-fluoro-2-methyl-1-butene

High priority groups on the same side = *Z*

If the high priority groups are on opposite sides of the axis, the alkene is called *E*, from the German "entgegen" for "opposite".

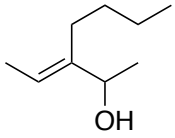


(*E*)-1-chloro-1-fluoro-2-methyl-1-butene

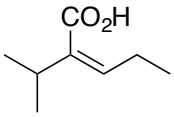
High priority groups on opposite sides = *E*

Problem 5. Designate the following alkenes as *E* or *Z*.

(a)

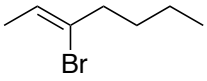


(b)

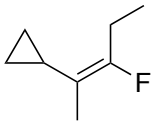


Problem 6. Name the following molecules.

(a)

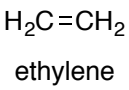


(b)

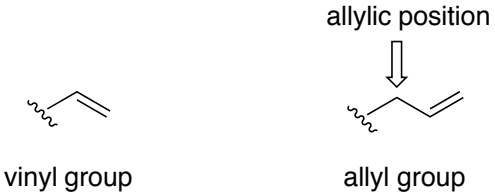


Common nomenclature

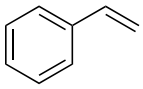
There are a few common names of alkenes and alkene-containing groups that are used frequently. For instance, the smallest possible alkene has the IUPAC name ethene, but is more commonly called ethylene.



The smallest possible alkene-containing substituent is known as a vinyl group, while its one-carbon homologue is known as an allyl group. Also, the position adjacent to an alkene is known as the allylic position.



A benzene ring bearing a vinyl group is called styrene.



styrene

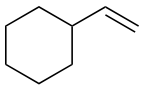
When the CH_2 group of a terminal alkene is discussed as a substituent, it is referred to as a methylene group.

methylene group

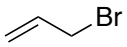
It is also worth noting that alkenes are sometimes called olefins.

Problem 7. Give common names for the following compounds.

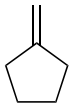
(a)



(b)

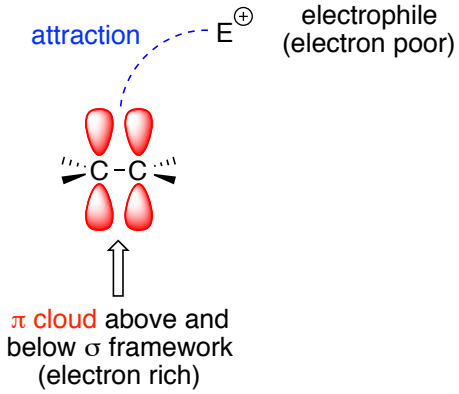


(c)

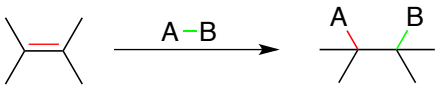


Section 2: Introduction to reactions of alkenes

Most of the remaining sections in this chapter describe the reactions of alkenes. We'll begin with a radical reaction of the allylic position. Then, we'll consider a series of reactions involving the alkene pi bond itself. Most of these reactions fall under the broad umbrella of electrophilic addition, meaning that addition will occur across the pi bond and that it is induced by an electrophile. Since the alkene is electron rich (and therefore nucleophilic) due to its pi bond, it stands to reason that an electrophile would be an appropriate reagent.



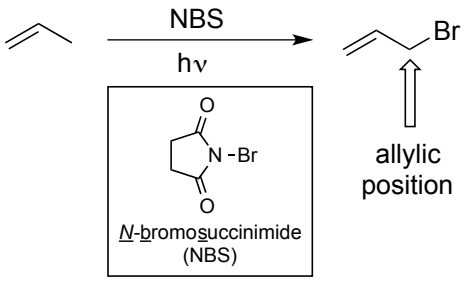
In electrophilic addition, it is common for the reaction to take this general form. A and B represent generic atoms or groups. The electrons in the pi bond and those in the A-B σ bond are responsible for forming the two new σ bonds: C-A and C-B.



A and B may be different, or in some cases, they may be the same. We'll even see some examples in which a single atom is added across the alkene pi bond. Regardless, this general paradigm for understanding the attraction between the reagents and the fate of the electrons in the key bonds will be useful throughout the chapter.

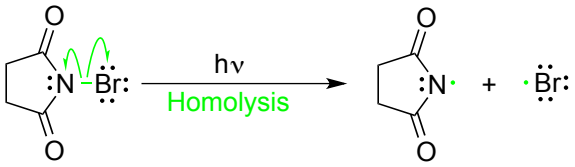
Section 3: Allylic bromination

Alkenes undergo bromination in the allylic position upon exposure to *N*-bromosuccinimide (NBS) and light (or a radical initiator). Allylic bromination is a radical process in which NBS acts as a source of a steady but small concentration of bromine (Br_2).



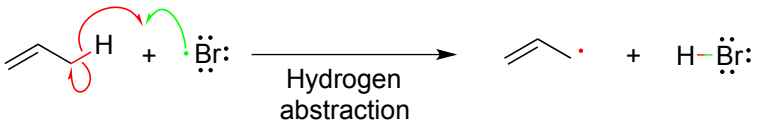
The reaction begins with the homolysis of a few molecules of NBS by light. The weak N–Br bond breaks evenly to produce succinimide and a bromine radical.

Initiation:

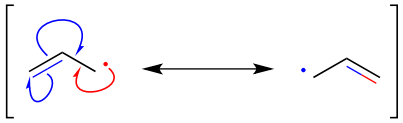


The bromine radical is the active radical involved in propagation step 1. It abstracts a hydrogen atom from the allylic position because this affords a resonance-stabilized radical.

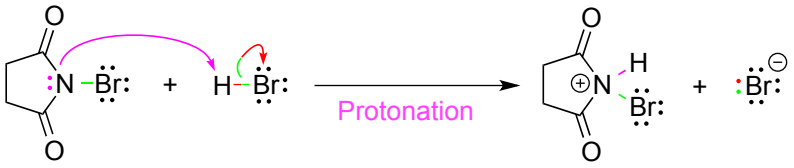
Propagation step 1:



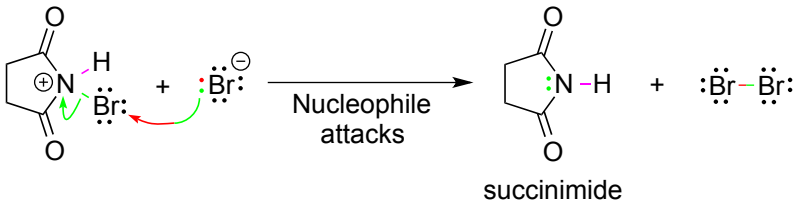
Resonance stabilization of the carbon-centered radical lowers its energy:



The HBr that was formed in propagation step 1 then protonates an unreacted molecule of NBS.

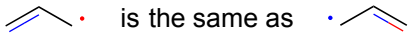


The bromide that was liberated during protonation then attacks the bromine on the conjugate acid of NBS. This cleaves the weak N–Br bond and neutralizes the charge on nitrogen as succinimide is formed.



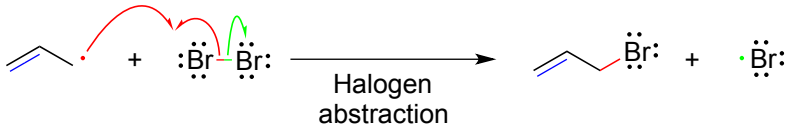
In the course of the two preceding steps, two important things have happened. First, the HBr formed in propagation step 1 has been consumed. This is significant because, as we will see in the next section ("Ionic Hydrohalogenation"), HBr can engage in a different reaction with alkenes. Secondly, a molecule of bromine (Br_2) has been produced. This Br_2 is needed for propagation step 2.

In this simple example, the resonance forms of the allylic radical are identical to one another due to the molecule's symmetry.



Consequently, either resonance form can be used in the next step, and the same connectivity will result in the product, regardless. In propagation step 2, the allylic radical abstracts a bromine atom from Br_2. This forms the allylic bromide product, and it also regenerates a bromine radical that can cycle back into propagation step 1, making this a chain reaction.

Propagation step 2:

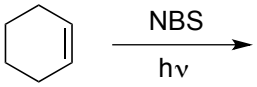


Termination steps are of little consequence and are therefore not shown. Termination steps explain the fate of the few remaining radicals left over once the reaction has neared completion. However, the vast majority of the product is formed during propagation step 2.

It is worth highlighting the fact that this reaction has two ionic steps (using regular arrows) that explain the formation of succinimide and Br_2 from NBS and HBr. However, the rest of the steps involve radicals and therefore use fishhook arrows.

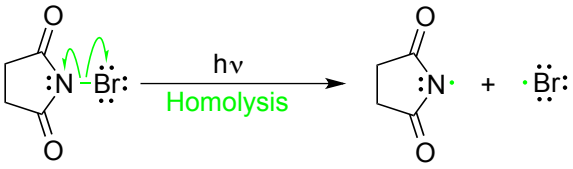
A specific example of allylic bromination

In the following example, cyclohexene is brominated in the allylic position by NBS and light.



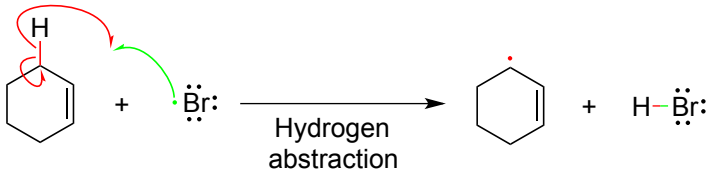
The homolysis of NBS initiates the process.

Initiation:



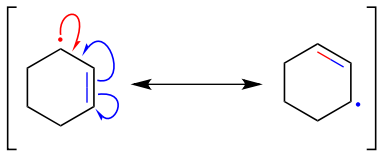
The bromine radical thus formed abstracts an allylic hydrogen from cyclohexene.

Propagation step 1:

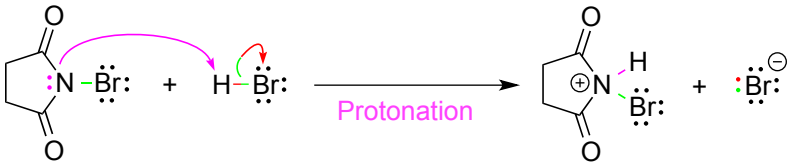


Only by abstracting one of the four equivalent allylic hydrogens in the molecule can a resonance-stabilized radical be formed.

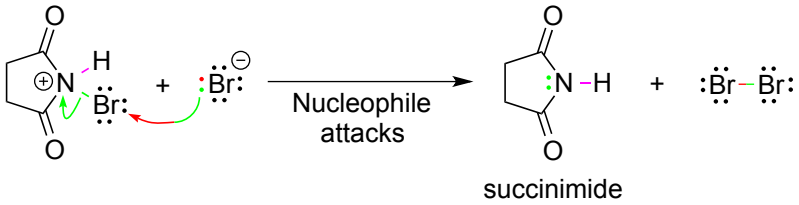
Resonance stabilization of the cyclohexenyl radical lowers its energy:



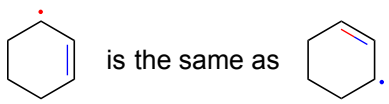
Then, two ionic steps (using regular mechanistic arrows) explain how NBS and HBr form succinimide and Br_2. First, NBS is protonated.



Then, the conjugate acid of NBS loses its bromine upon the attack of bromide.

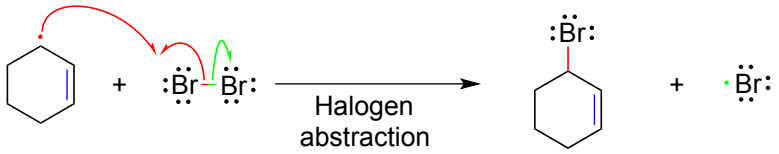


With Br_2 now available, the cyclohexenyl radical can abstract a bromine atom to complete the mechanism. Since both resonance forms of this radical are equivalent due to the symmetry of the molecule, either can abstract the bromine atom to give a single product.



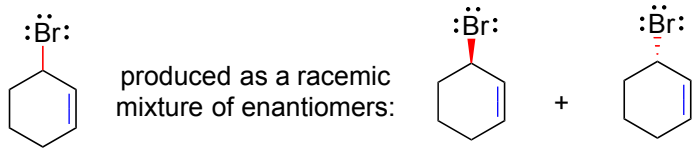
The allylic bromide product is accompanied by the bromine radical needed for a new round of propagation steps.

Propagation step 2:



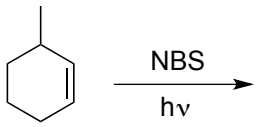
Stereochemical considerations

In the preceding reaction, a stereocenter was formed when the carbon-centered radical abstracted a bromine atom from Br_2. Since the radical is sp^2 hybridized and therefore trigonal planar (flat), the bromine atom can be added from either side. Consequently, a racemic mixture of enantiomers is produced.



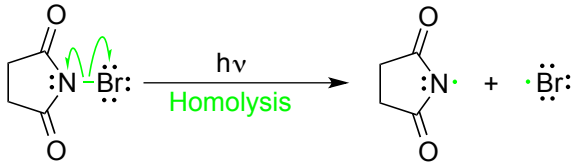
Regiochemical considerations

In the example that follows, 3-methylcyclohexene is treated with NBS and light.



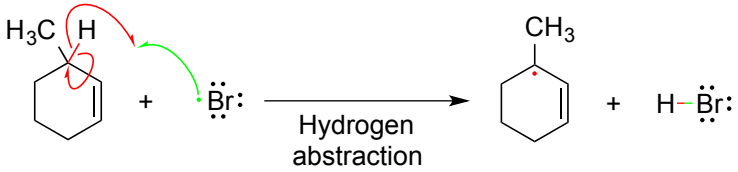
Homolysis of NBS initiates the reaction as expected.

Initiation:

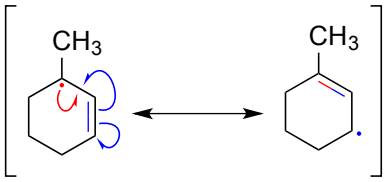


The bromine radical thus formed abstracts a hydrogen atom so as to make the most stable radical intermediate possible. In this case, abstraction of hydrogen from the tertiary allylic position leads to a radical that is both tertiary and resonance stabilized.

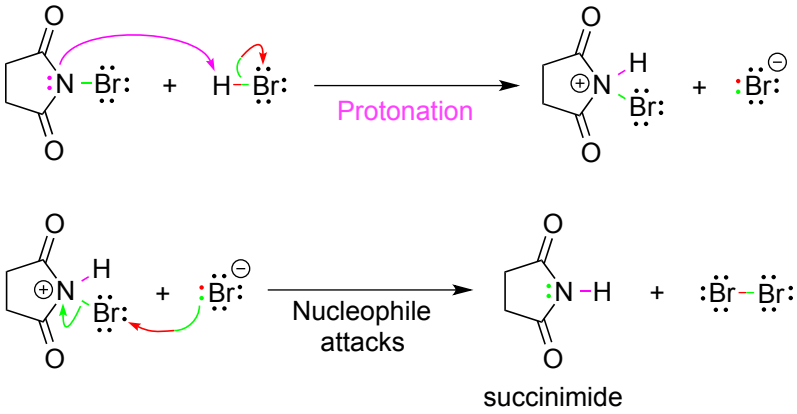
Propagation step 1:



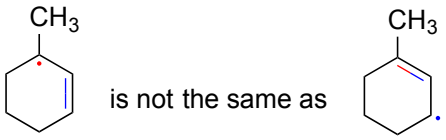
Resonance stabilization of the carbon-centered radical lowers its energy:



Two ionic steps then explain how NBS and HBr react to yield succinimide and Br_2.

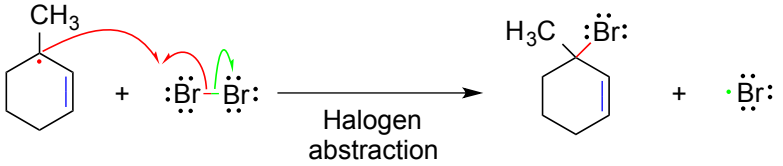


In propagation step 2, abstraction of a bromine atom will yield the final products. In this instance, the resonance forms of this carbon-centered radical are not identical as they were in the previous examples. Reaction can take place at either of the two locations bearing radical character.



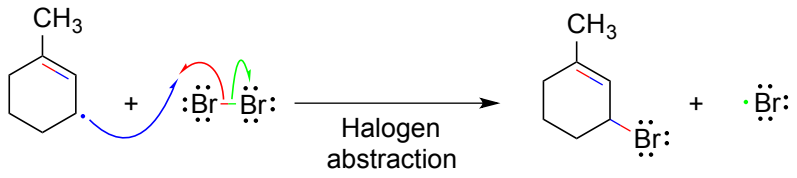
These two possibilities for propagation step 2 are shown below. If radical character at the tertiary allylic center abstracts a bromine atom, a tertiary allylic bromide is formed.

Propagation step 2:

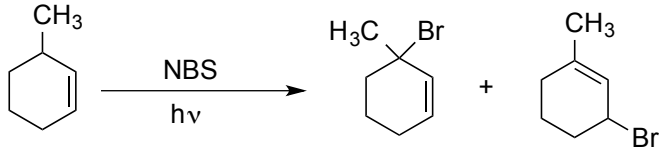


If radical character at the secondary allylic center abstracts a bromine, a secondary allylic bromide is produced.

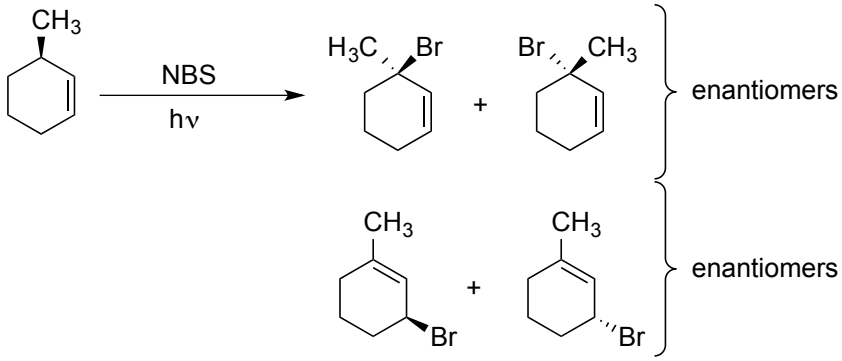
Propagation step 2:



Overall, this reaction has yielded two regioisomeric bromination products.

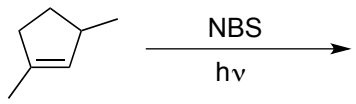


Additionally, a stereocenter is present in the reactant, as well as in each product. Reaction takes place at the stereogenic carbon in the reactant, and the stereochemical information at that center is lost when the trigonal planar (flat) radical is formed. Since the radical is flat, bromine can add to either side. Consequently, each regioisomer is formed as a mixture of enantiomers.



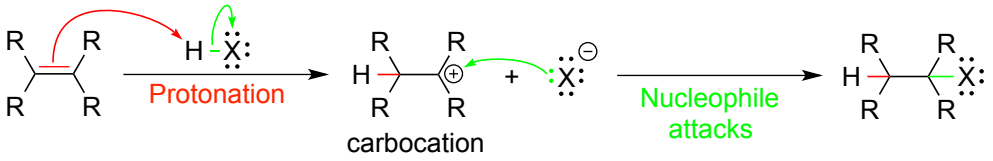
In summary, NBS and light (or a radical initiator) can be used to brominate an alkene in the allylic position. The transformation is a radical chain reaction that proceeds through the resonance-stabilized allylic radical. Any site in the molecule bearing radical character through resonance can be brominated in propagation step 2, leading to the possibility for regioisomeric products. If a stereocenter is formed during the reaction, both configurations will be produced at that center.

Problem 8. Provide the product(s) of the following allylic bromination.



Section 4: Ionic hydrohalogenation

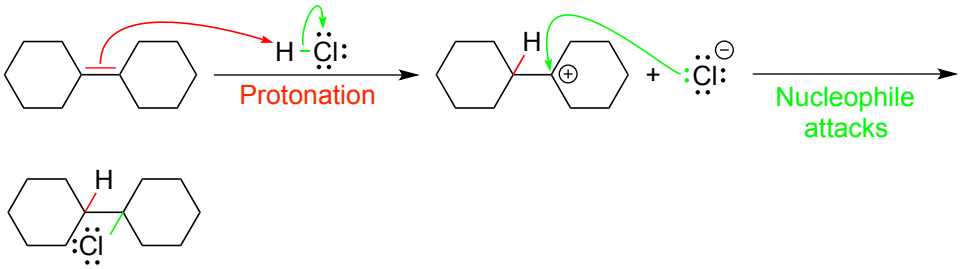
Ionic hydrohalogenation is the addition of HX (HCl, HBr, or HI) across a π bond. The mechanism begins with protonation of the π bond, which results in the formation of a carbocation intermediate. The halide (X^-) then attacks the carbocation to yield an alkyl halide.



Ionic hydrohalogenation has charged intermediates: the carbocation and halide are ions. Radical hydrohalogenation can achieve the addition of HBr across a π bond as well; however, as we will see in the next section, the regiochemistry of that reaction is different.

A specific example of ionic hydrohalogenation

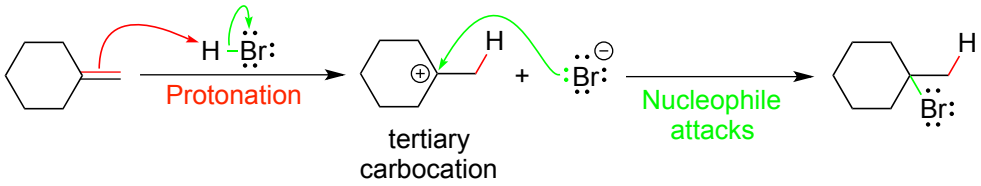
In the following example, the alkene is symmetrical, so it does not matter which alkene carbon acquires the new proton in the protonation step. Protonation at either alkene carbon will yield the same carbocation intermediate due to the molecule's symmetry.



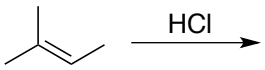
Regiochemical considerations

When the alkene substrate is unsymmetrical, protonation occurs so as to yield the more stable carbocation intermediate. The more stable carbocation is typically derived using Markovnikov's rule, which states that the alkene carbon possessing more hydrogens acquires the new proton. This is a useful guideline that serves us well in simple cases. However, note that conjugation can be a complicating factor because the more stable carbocation will typically be the one with resonance delocalization.

In the following example, protonation could yield a primary or tertiary carbocation, so the reaction proceeds through the more stable tertiary carbocation intermediate to ultimately yield a tertiary alkyl bromide upon attack of the nucleophile. Notice that Markovnikov's rule facilitates finding the more stable carbocation. If the proton is initially placed on the alkene carbon bearing more hydrogens, then the tertiary carbocation is formed.



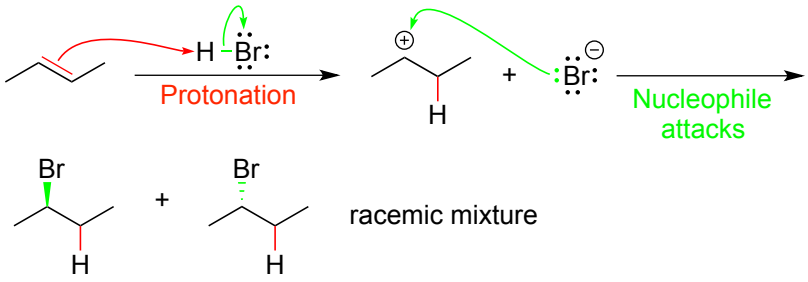
Problem 9. Predict the product of the following reaction, and provide a mechanism for its formation.



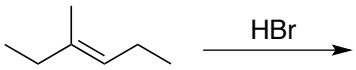
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction. In the preceding examples, no stereocenters were created.

In the example below, a single stereocenter is formed during the second step of the reaction when the nucleophile attacks the carbocation. Since the carbocation is trigonal planar (sp^2 hybridized) and therefore flat at the reactive site, it may be attacked from either side. The result is a mixture of both configurations at the center bearing bromine. These products, (*R*)- and (*S*)-2-bromobutane, are enantiomers.



Problem 10. Predict the product(s) of the following ionic hydrohalogenation.

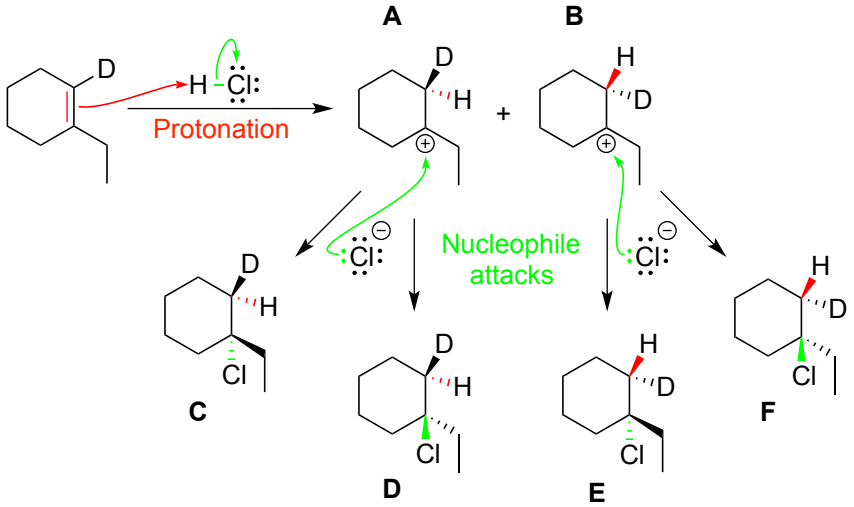


In the following example, the reactant bears a deuterium atom (D). Deuterium is an isotope of hydrogen. From the perspective of chemical reactivity, it is nearly the same as hydrogen. However, because deuterium is not identical to hydrogen, they count as different substituents.

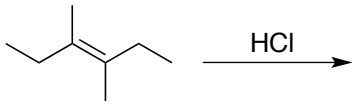
Since deuterium is analogous to hydrogen in terms of reactivity, the alkene is protonated to make the more stable tertiary carbocation. In this instance, the protonation generates a stereocenter. The alkene carbons are trigonal planar (sp^2 hybridized) and therefore flat, so

the hydrogen may be added to either side of the molecule, thereby creating both configurations (carbocations **A** and **B**).

The halide then adds to the carbocation, generating a second stereocenter. Again, the carbocation is trigonal planar (sp^2 hybridized) and therefore flat at the reactive site, so it may also be attacked from either side. Carbocation **A** is attacked from above and below to yield products **C** and **D**. Carbocation **B** is attacked from above and below to yield products **E** and **F**. In this case, all four stereoisomeric products are produced. Products **C** and **F** are a pair of enantiomers. Products **D** and **E** are another pair of enantiomers. Any other comparison of products is diastereomeric (e.g., **C** and **D**).

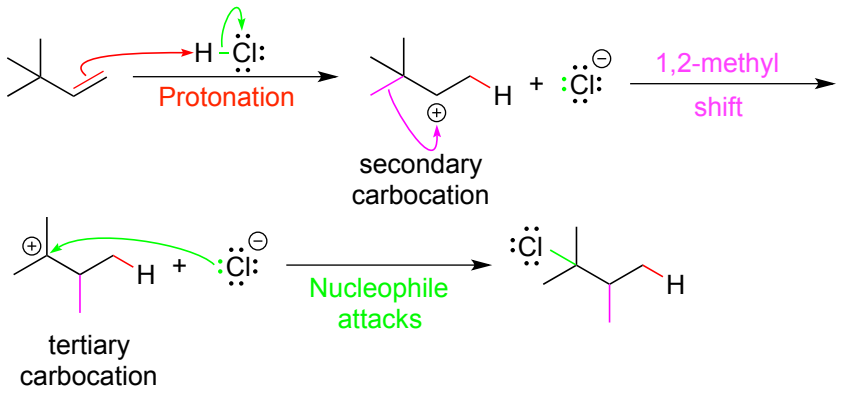


Problem 11. Predict the product(s) of the transformation shown below.

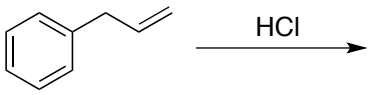


Carbocation rearrangement

Since ionic hydrohalogenation proceeds via a carbocation intermediate, carbocation rearrangement is possible. In the following scenario, protonation affords a secondary carbocation according to Markovnikov's rule. This secondary carbocation is adjacent to a quaternary center, so a 1,2-methyl shift produces an even more stable tertiary carbocation. This tertiary carbocation is then attacked by chloride to yield the product.



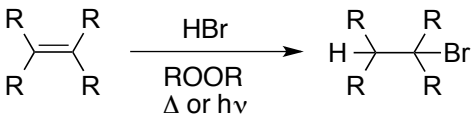
Problem 12. Provide a mechanism for the following reaction.



In conclusion, ionic hydrohalogenation adds HX across a π bond with Markovnikov regiochemistry. If stereocenters are created, both configurations will be possible at any new stereocenter because all reactive sites are trigonal planar (flat). Carbocation rearrangement is also possible.

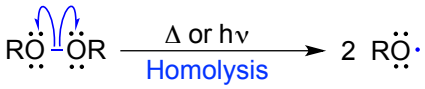
Section 5: Radical hydrohalogenation

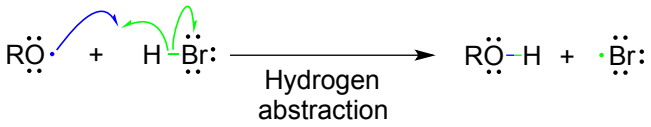
Radical hydrohalogenation is the addition of HBr across a π bond in the presence of peroxide (ROOR). Unlike ionic hydrohalogenation, the intermediates for this reaction are radicals, or species bearing an unpaired electron. The radical mechanism leads to anti-Markovnikov regiochemistry. In other words, the hydrogen is added to the alkene carbon having *fewer* hydrogens, which is the reverse of Markovnikov's rule.



The mechanism begins with the homolysis of a small amount of a radical initiator, such as a peroxide, upon exposure to heat (Δ) or light (hν). The subsequent abstraction of a hydrogen atom from HBr generates bromine radical.

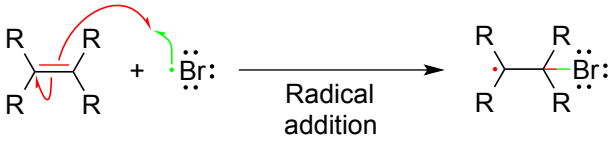
Initiation:





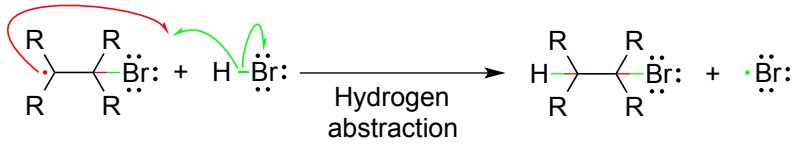
This bromine radical then adds to the alkene π bond in propagation step 1, forming a carbon-centered radical.

Propagation step 1:



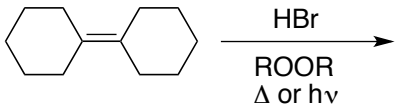
In propagation step 2, the carbon-centered radical abstracts a hydrogen atom from another molecule of HBr. This yields the alkyl bromide product and also regenerates the bromine radical, which can then cycle through another set of propagation steps. For this reason, the process is a chain reaction.

Propagation step 2:



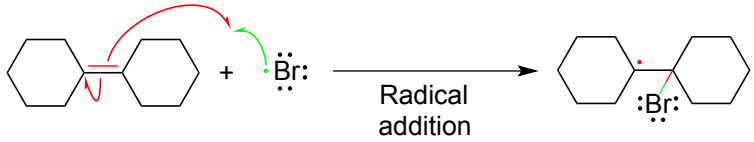
Termination steps explain the fate of the few radicals remaining after the consumption of the reactants. Any two radicals can combine in a termination step. It is important to note though that the vast majority of product is generated in propagation step 2, and as a result, the termination steps are fairly inconsequential (and are therefore not shown here).

A specific example of radical hydrohalogenation

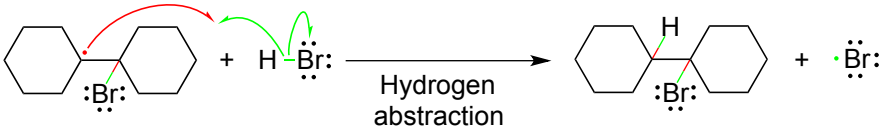


In this example, the alkene is symmetrical, so it does not matter which alkene carbon the bromine adds to during the radical addition step. Addition at either alkene carbon will yield the same radical intermediate due to the molecule's symmetry.

Propagation step 1:



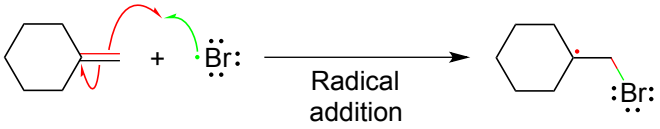
Propagation step 2:



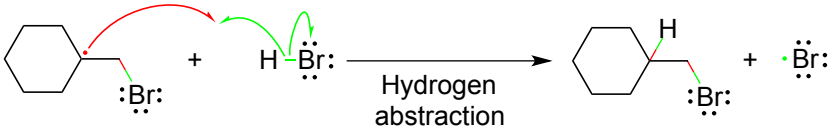
Regiochemical considerations

When the alkene substrate is unsymmetrical, addition of bromine occurs so as to yield the more stable radical intermediate. In the following example, the addition could yield a primary or tertiary radical, so the reaction proceeds through the more stable tertiary radical intermediate to ultimately yield a primary alkyl bromide product.

Propagation step 1:



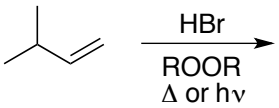
Propagation step 2:



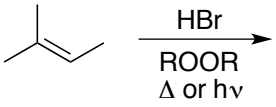
Note that the overall process exhibits anti-Markovnikov regioselectivity (i.e., the alkene carbon with more hydrogens did *not* acquire the new hydrogen atom). Nevertheless, this reaction proceeds through the more stable radical intermediate, much as ionic hydrohalogenation proceeds through the more stable carbocation intermediate. The reversal of regioselectivity stems from the fact that in ionic hydrohalogenation the proton adds first; whereas, in radical hydrohalogenation the bromine adds first. The first atom is added in each case so as to yield the more stable intermediate.

Problem 13. Provide the products of the following radical hydrohalogenations.

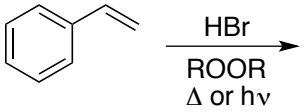
(a)



(b)



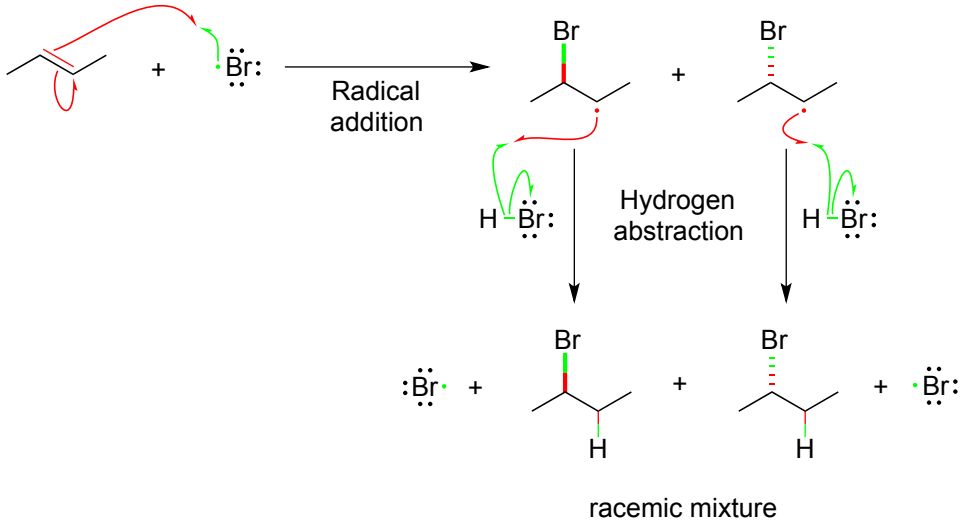
(c)



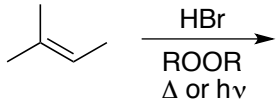
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

In the example below, a single stereocenter is formed during propagation step 1 when bromine radical adds to the π bond. Since the alkene carbons are trigonal planar (sp^2 hybridized) and therefore flat, they may be attacked from either side. The result is a mixture of both configurations at the center bearing bromine. These products, (*R*)- and (*S*)-2-bromobutane, are enantiomers.

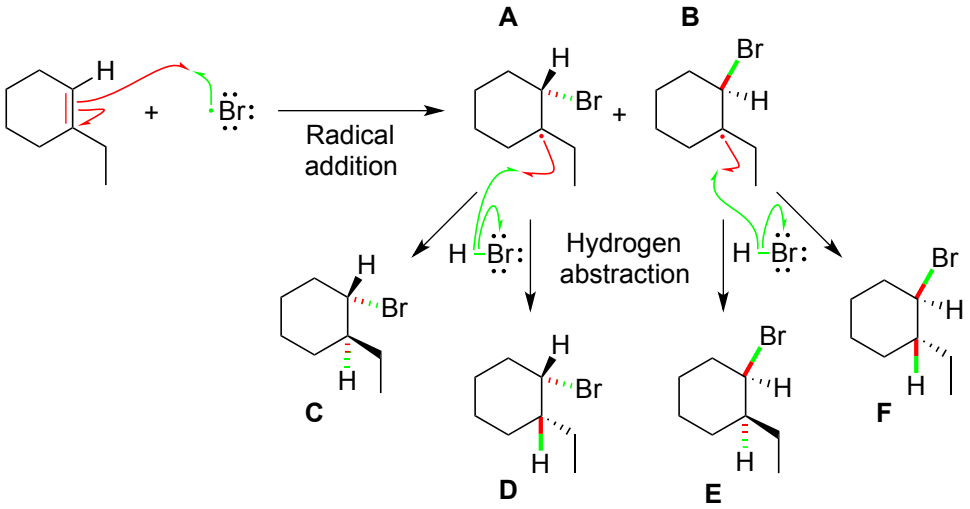


Problem 14. In Problem 13(b), we considered the following reaction from a two-dimensional perspective. Now, show the stereochemical outcome of this transformation.

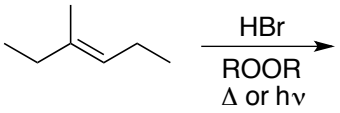


In the next example, two stereocenters are formed during the reaction. The alkene undergoes radical addition of bromine to make the more stable tertiary radical. This step generates a stereocenter. Since the alkene carbons are trigonal planar (sp^2 hybridized) and therefore flat, the bromine atom may be added to either side of the molecule, thereby creating both configurations (radicals **A** and **B**).

The carbon-centered radical then abstracts a hydrogen atom from HBr, generating a second stereocenter. Again, the radical is trigonal planar (sp^2 hybridized) and therefore flat at the reactive site, so it may undergo addition of the hydrogen atom from either side. Radical **A** adds a hydrogen atom from above and below to yield products **C** and **D**. Radical **B** adds a hydrogen atom from above and below to yield products **E** and **F**. In this case, all four stereoisomeric products are produced. Products **C** and **F** are a pair of enantiomers. Products **D** and **E** are another pair of enantiomers. Any other comparison of products is diastereomeric (e.g., **C** and **D**).



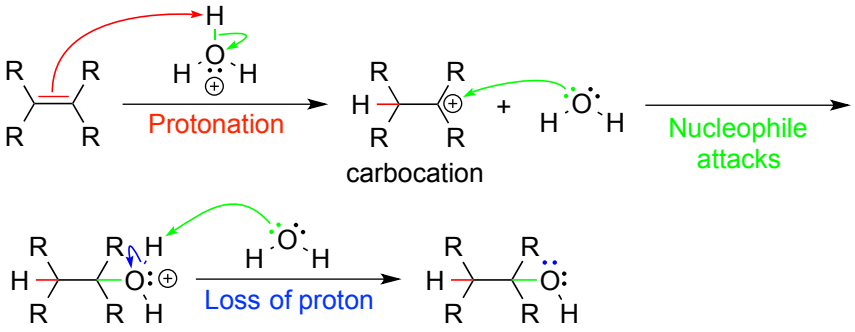
Problem 15. Provide the product(s) of the following reaction.



To recap, radical hydrohalogenation adds HBr across a π bond in the presence of peroxide with anti-Markovnikov regiochemistry. If stereocenters are created, both configurations will be possible at any new stereocenter because all reactive sites are trigonal planar (flat). Radicals do not rearrange as carbocations do, so rearrangement is not a concern in this reaction.

Section 6: Acid-catalyzed hydration

Acid-catalyzed hydration achieves the addition of water across a π bond. The mechanism begins with protonation of the π bond, which results in the formation of a carbocation intermediate. Water then attacks the carbocation to yield an oxonium ion (i.e., positively charged oxygen). Loss of a proton affords an alcohol as the final product.

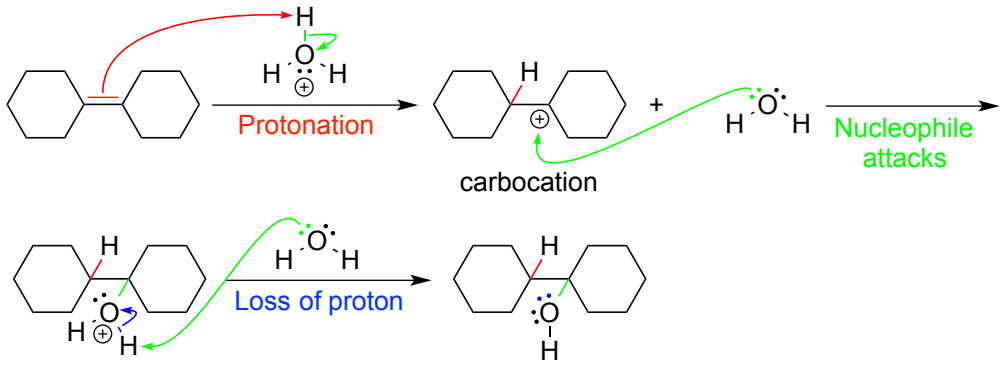


The acid catalyst may be represented as H^+ / H_2O, H_3O^+, or H_2SO_4 / H_2O. All of these representations amount to the same thing: aqueous acid. It is merely the level of specificity that varies.

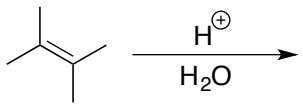
Notice that the reaction is catalytic in acid because, while a hydronium ion is consumed during protonation, it is re-formed during the loss of proton.

A specific example of acid-catalyzed hydration

In the following example, the alkene is symmetrical, so it does not matter which alkene carbon acquires the new proton in the protonation step. Protonation at either alkene carbon will yield the same carbocation intermediate due to the molecule's symmetry.



Problem 16. Show the product of the following hydration as well as a mechanism to explain its formation.

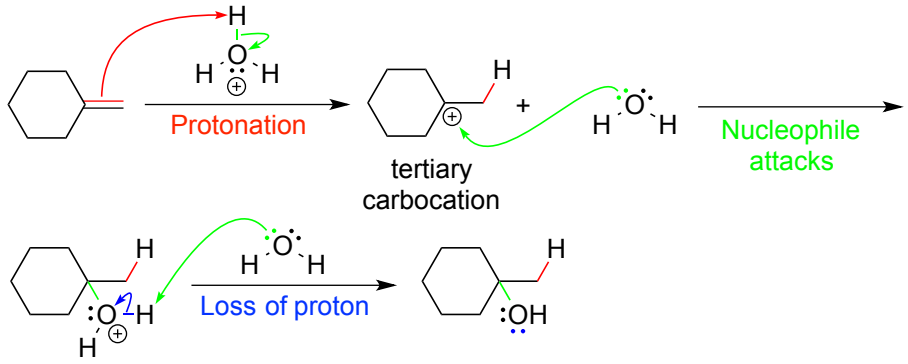


Regiochemical considerations

When the alkene substrate is unsymmetrical, protonation occurs so as to yield the more stable carbocation intermediate. The more stable carbocation is typically derived using Markovnikov's rule (i.e., the alkene carbon possessing more hydrogens acquires the new

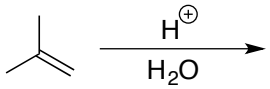
proton). However, as noted earlier, conjugation can be a complicating factor because the more stable carbocation will typically be the one with resonance delocalization if it is available.

In the following example, protonation could yield a primary or tertiary carbocation, so the reaction proceeds through the more stable tertiary carbocation intermediate to ultimately yield a tertiary alcohol.

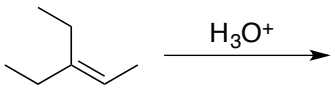


Problem 17. Provide the product for each of the following reactions.

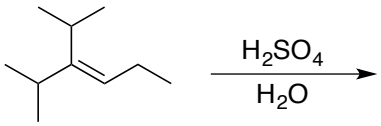
(a)



(b)



(c)

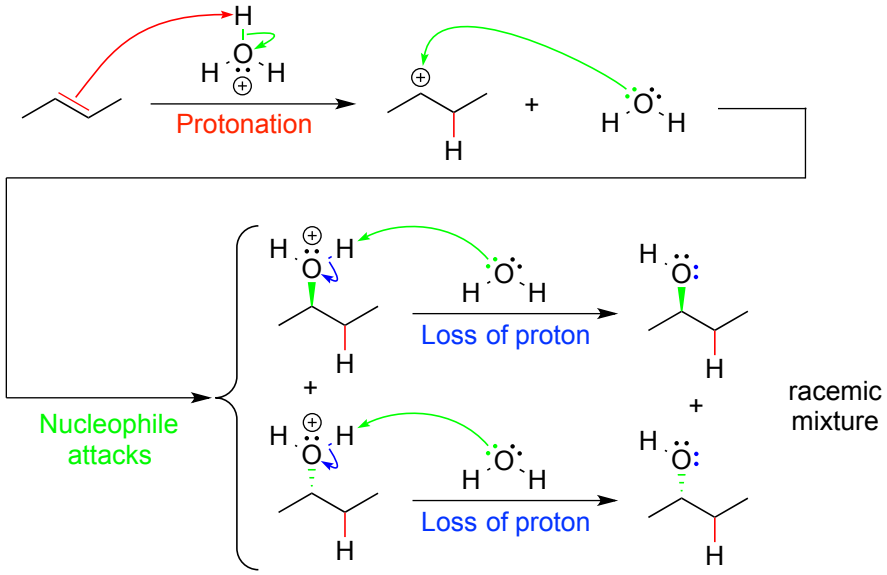


Stereochemical considerations

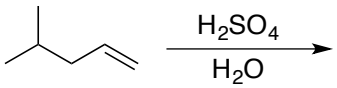
Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction. In the preceding reactions, no stereocenters were formed.

In the example below, a single stereocenter is formed during the second step of the reaction when the nucleophile attacks the carbocation. Since the carbocation is trigonal

planar (sp^2 hybridized) and therefore flat at the reactive site, it may be attacked from either side. The result is a mixture of both configurations at the center bearing the oxonium ion. Each of the enantiomeric oxonium ions then proceeds to lose a proton, yielding enantiomeric alcohol products: (*R*)- and (*S*)-2-butanol.

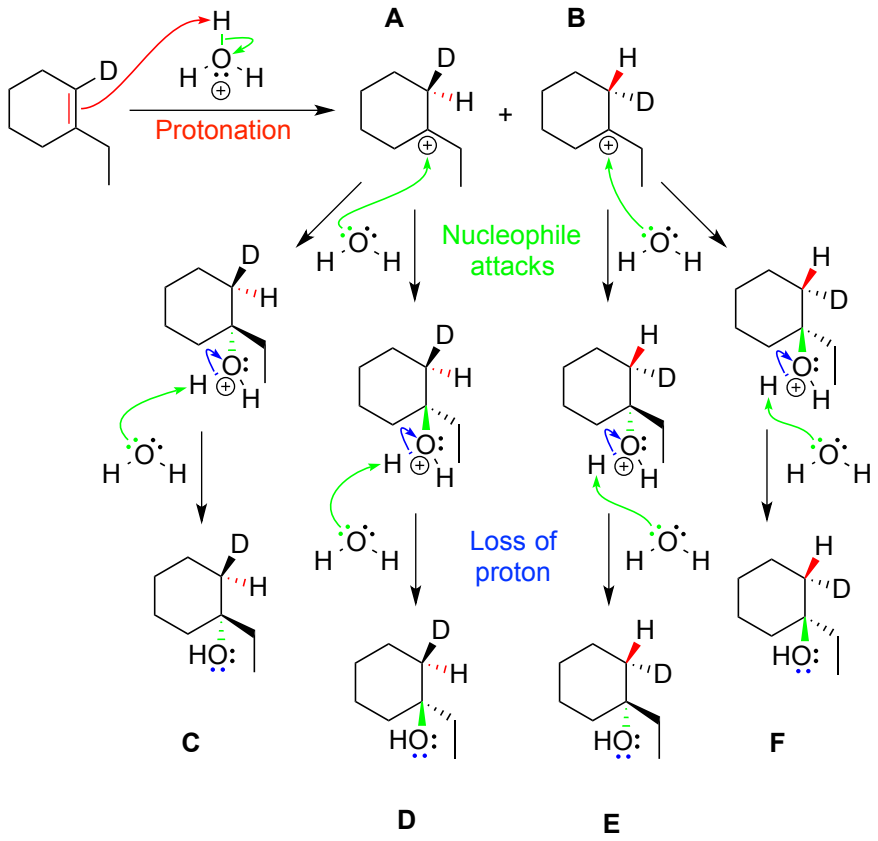


Problem 18. Show the products of the hydration below.

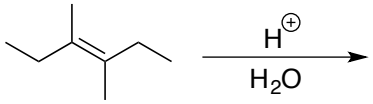


In the following example, the reactant bears a deuterium atom (D). Since deuterium is analogous to hydrogen in terms of reactivity, the alkene is protonated to make the more stable tertiary carbocation. In this instance, the protonation generates a stereocenter. The alkene carbons are trigonal planar (sp^2 hybridized) and therefore flat, so the hydrogen may be added to either side of the molecule, thereby creating both configurations (carbocations **A** and **B**).

Water then adds to the carbocation, generating a second stereocenter. Again, the carbocation is trigonal planar (sp^2 hybridized) and therefore flat at the reactive site, so it may also be attacked from either side. Carbocation **A** is attacked from above and below to yield two oxonium ions. Carbocation **B** is attacked from above and below to yield two additional oxonium ions. Each oxonium ion then loses a proton to form products **C** – **F**. In this case, all four stereoisomeric products are produced. Products **C** and **F** are a pair of enantiomers. Products **D** and **E** are another pair of enantiomers. Any other comparison of products is diastereomeric (e.g., **C** and **D**).

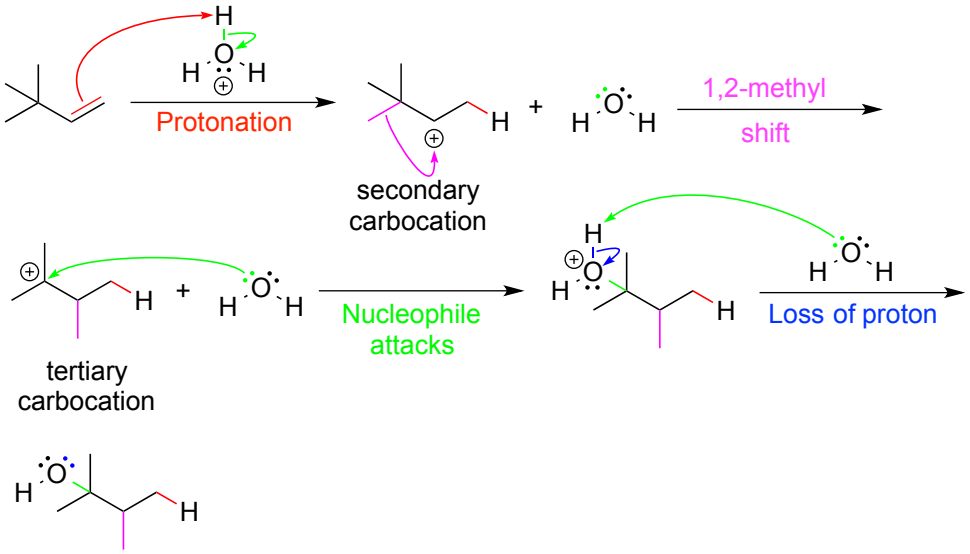


Problem 19. Show the product(s) of the reaction below.

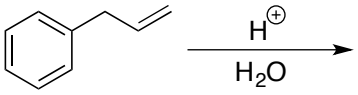


Carbocation rearrangement

Since acid-catalyzed hydration proceeds via a carbocation intermediate, carbocation rearrangement is possible. In the following scenario, protonation affords a secondary carbocation according to Markovnikov's rule. This secondary carbocation is adjacent to a quaternary center, so a 1,2-methyl shift produces an even more stable tertiary carbocation. This tertiary carbocation is then attacked by water to yield an oxonium ion that subsequently loses a proton to form a tertiary alcohol as the final product.



Problem 20. Provide the product(s) of the following hydration.

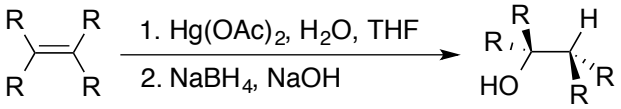


In summary, acid-catalyzed hydration adds water across a π bond with Markovnikov regiochemistry. If stereocenters are created, both configurations will be possible at any new stereocenter because all reactive sites are trigonal planar (flat). Carbocation rearrangement is also possible.

It is also worth noting that this reaction can be performed with an alcohol (ROH) in place of water as a reagent. The transformation is nearly identical except for the fact that an alkoxy group (OR) will be added instead of an OH group as a result of the nucleophilic attack and loss of proton steps. Consequently, the product of this variation is an ether instead of an alcohol.

Section 7: Oxymercuration-demercuration

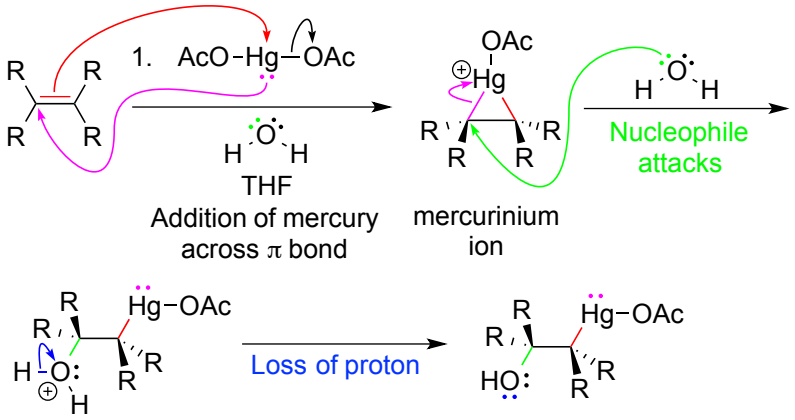
Oxymercuration-demercuration achieves the addition of water across a π bond in two steps. The first step is oxymercuration. This step uses mercuric acetate [$Hg(OAc)_2$] and water as reagents. THF (tetrahydrofuran) is a common solvent. The second step is demercuration, which employs sodium borohydride ($NaBH_4$) in basic conditions. As we'll see in this section, the regiochemistry of this reaction always follows Markovnikov's rule, and the reaction is *not* susceptible to rearrangement.



Oxymercuration begins when mercury adds across the π bond. Three mechanistic arrows describe this addition. The π bond attacks the electrophilic mercury, displacing an acetate ($^-$OAc) ligand. The mercury simultaneously attacks the carbon of the alkene that is losing a bond. The resulting intermediate is known as a mercurinium ion (positively charged mercury). This bridging mercurinium ion avoids the formation of a high-energy carbocation intermediate.

Water then attacks one of the carbons of the mercurinium ion, opening the three-membered ring. Finally, a proton is lost from the oxonium ion to yield a product that has incorporated both oxygen and mercury (hence an oxymercuration product).

Oxymercuration (step 1):

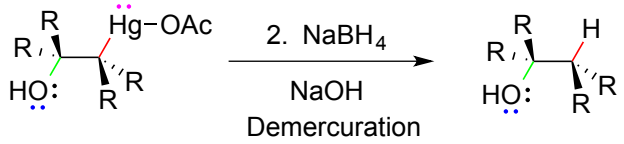


Note that some textbooks show dissociation of an acetate ($^-$OAc) ligand first (the black arrow), followed by addition of $^+$Hg(OAc) across the π bond via the red and purple arrows. This will result in the same mercurinium ion.

Also note that the attack of water occurs opposite the mercurinium ion. This means that the oxymercuration step is an anti addition.

The second step of the process is demercuration. Treatment with sodium borohydride ($NaBH_4$) in basic medium removes the mercury and replaces it with a hydrogen. Mechanistic arrows are often not drawn for this step, which may involve single-electron transfer.

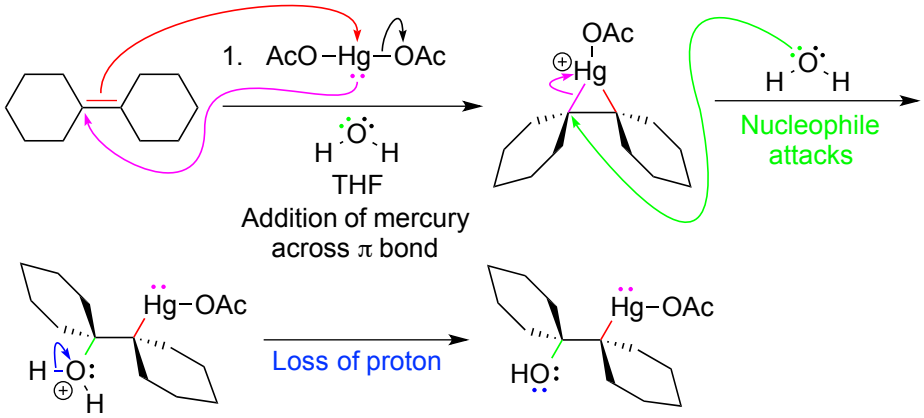
Demercuration (step 2):



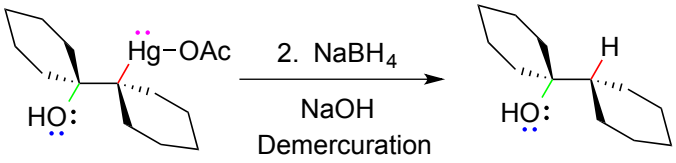
A specific example of oxymercuration-demercuration

In the following example, the alkene and mercurinium ion are symmetrical, so it does not matter which carbon of the mercurinium ion is attacked by water. Attack of water at either carbon will yield the same oxymercuration product due to the molecule's symmetry.

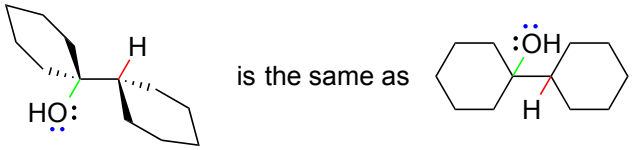
Oxymercuration (step 1):



Demercuration (step 2):



Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.

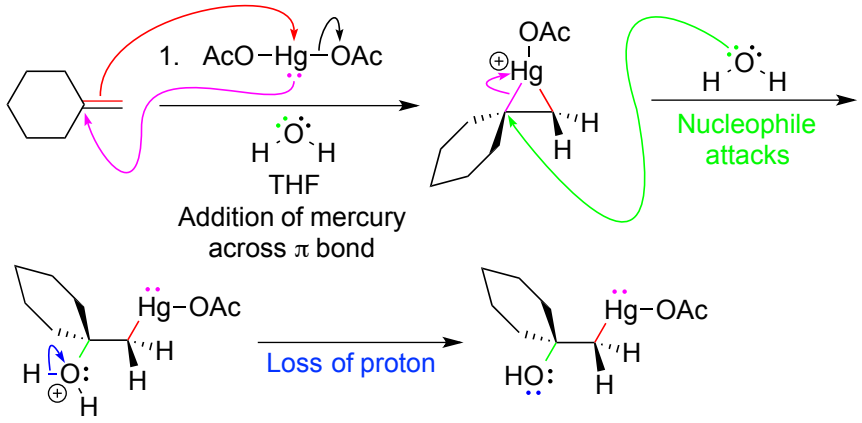


Regiochemical considerations

When the alkene substrate is unsymmetrical, an unsymmetrical mercurinium ion will result. The attack of water occurs at the center with the greater partial positive charge (δ^+). The more highly substituted carbon of the mercurinium ion has the greater δ^+. This is because a more highly substituted δ^+ is more stable, much like a more highly substituted carbocation is more stable.

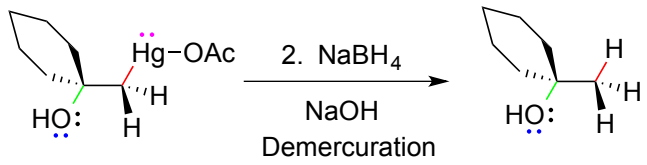
If Markovnikov's rule is phrased more broadly as "the alkene carbon possessing more hydrogens acquires the electrophile," then we can see that oxymercuration follows Markovnikov's rule. The electrophilic mercury is ultimately added to the carbon bearing more hydrogens.

Oxymercuration (step 1):

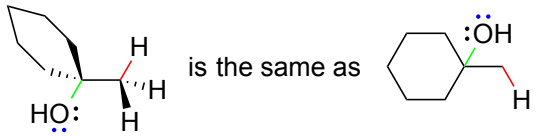


After demercuration, it is even more clear that oxymercuration-demercuration proceeds with Markovnikov regioselectivity. The alkene carbon possessing more hydrogens does, in fact, acquire the new hydrogen.

Demercuration (step 2):

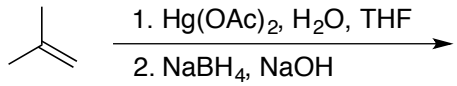


Again, in this reaction no stereocenters have been formed.

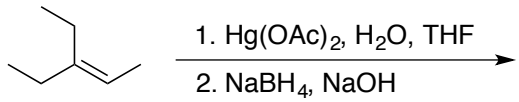


Problem 21. Provide the product for each of the following reactions.

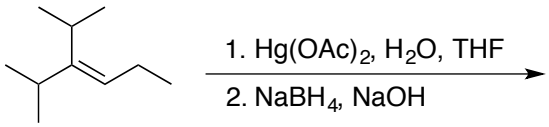
(a)



(b)



(c)

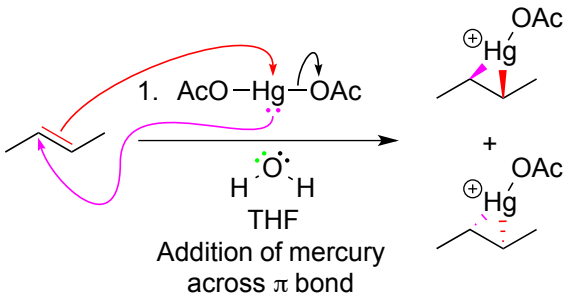


Stereochemical considerations

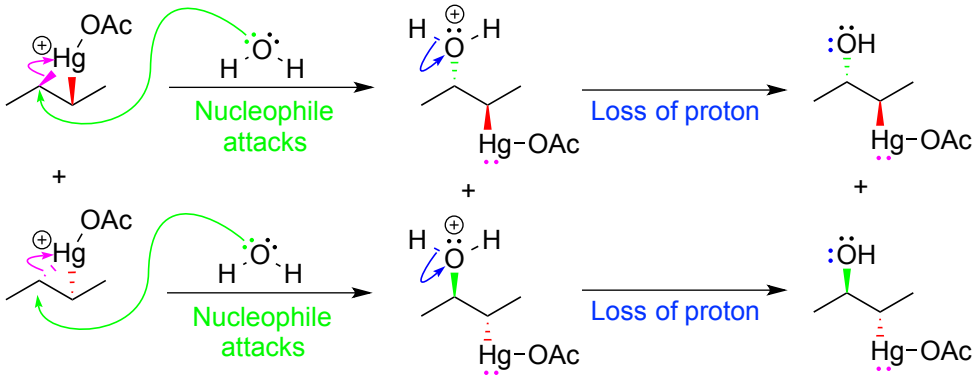
Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction. In the preceding examples, no stereocenters were formed.

However, in the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so mercury can add to either face of the alkene to give enantiomeric mercurinium ions.

Oxymercuration (step 1):

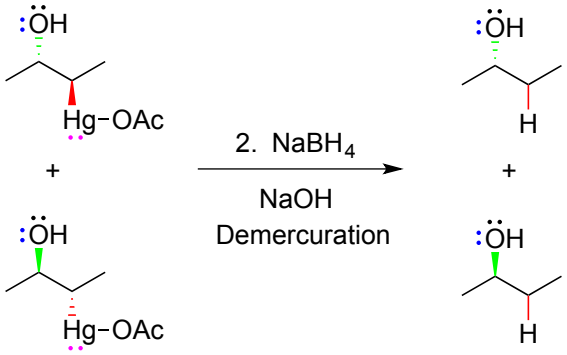


When water opens the mercurinium ions in an anti fashion (i.e., via attack opposite the leaving group), two enantiomeric oxymercuration products result.



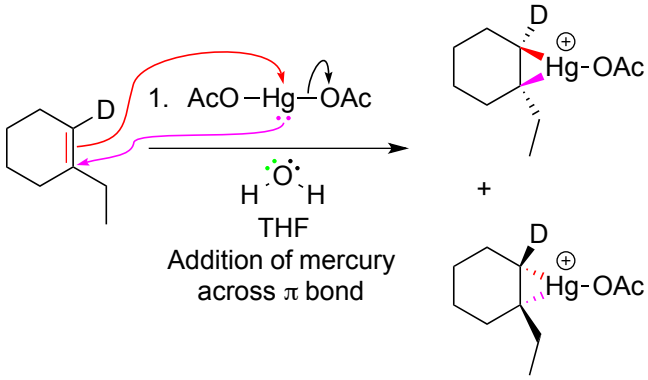
In the demercuration step for this substrate, one stereocenter is destroyed, and the products are enantiomeric alcohols: (*S*)- and (*R*)-2-butanol.

Demercuration (step 2):

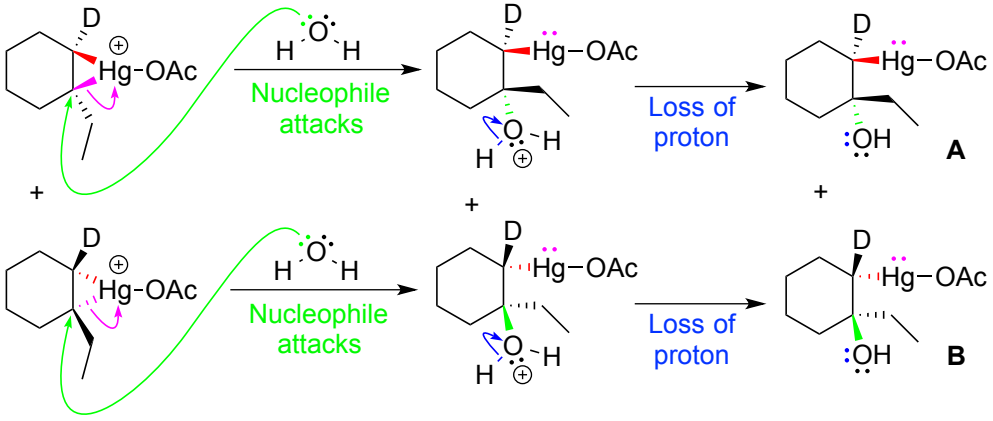


In the following example, two stereogenic centers will be formed during the course of the transformation. As in the previous reaction, the flat alkene may undergo addition of mercury from either face to give enantiomeric mercurinium ions.

Oxymercuration (step 1):

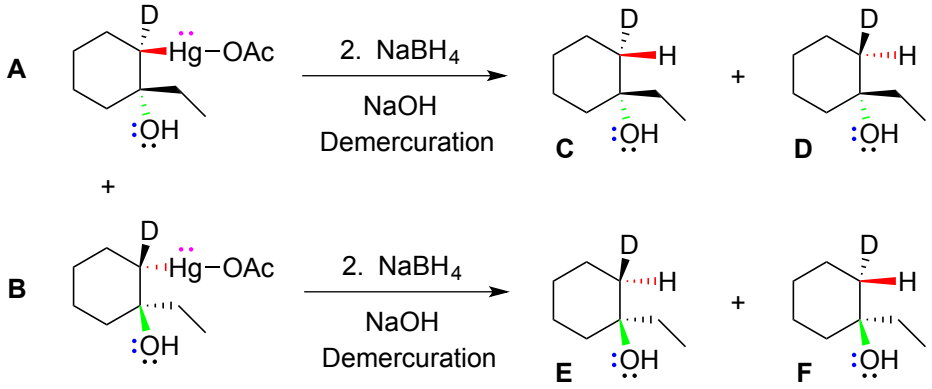


Since deuterium is analogous to hydrogen in terms of reactivity, each mercurinium ion is attacked by water at its tertiary center, which bears the greater δ^+. This attack occurs opposite the mercury leaving group and sets the stereochemistry of the carbon bearing the alcohol in the enantiomeric oxymercuration products **A** and **B**.



In the demercuration step, the stereochemistry of the new C–H bond is randomized. As a result, oxymercuration product **A** yields two alcohols, **C** and **D**. Similarly, oxymercuration product **B** yields two alcohols, **E** and **F**. All four stereoisomeric alcohols are produced. Products **D** and **F** are a pair of enantiomers. Products **C** and **E** are another pair of enantiomers. Any other comparison of products is diastereomeric (e.g., **C** and **D**).

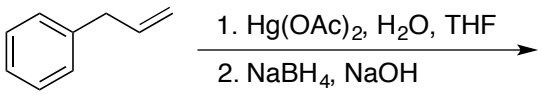
Demercuration (step 2):



Carbocation rearrangement

Take another look at the mechanisms for oxymercuration-demercuration shown above. You'll notice that at no point in the mechanism is a carbocation formed. Since no carbocation intermediate is produced, no carbocation rearrangement is possible in this reaction. *This is what really differentiates oxymercuration-demercuration from acid-catalyzed hydration.* While acid-catalyzed hydration can include carbocation rearrangement, oxymercuration-demercuration cannot.

Problem 22. Predict the product of the following reaction.

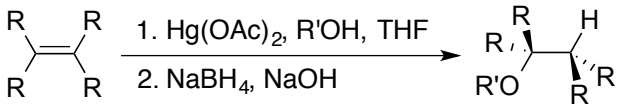


To recap, oxymercuration-demercuration adds water across a π bond with Markovnikov regiochemistry. The oxymercuration step occurs with anti stereochemistry; however, the stereochemistry of the new C–H bond is randomized during demercuration. Consequently, if stereocenters are created, both configurations will be possible at any new stereocenter.

Since oxymercuration-demercuration does not involve a carbocation intermediate, no carbocation rearrangement is possible. This provides a distinct advantage over acid-catalyzed hydration, which also proceeds with Markovnikov regioselectivity in simple cases but is vulnerable to carbocation rearrangement.

It is also worth noting that this reaction can be performed with an alcohol (ROH) in place of water as a reagent. The transformation is nearly identical except for the fact that an alkoxy

group (OR) will be added instead of an OH group during the first step. Consequently, this variation is called alkoxymercuration-demercuration, and its product is an ether instead of an alcohol.

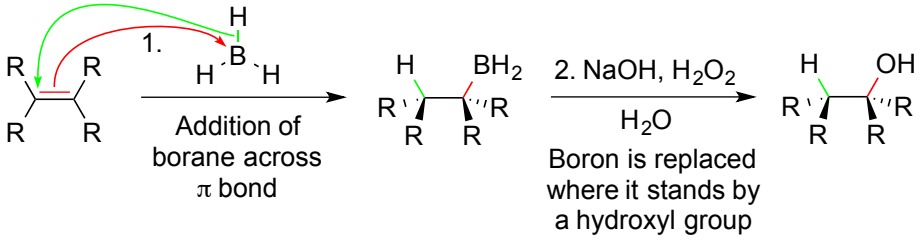


Section 8: Hydroboration-oxidation

Hydroboration-oxidation is another method for the hydration of an alkene. It is distinguished from other methods (acid-catalyzed hydration and oxymercuration-demercuration) by the fact that it affords anti-Markovnikov regioselectivity.

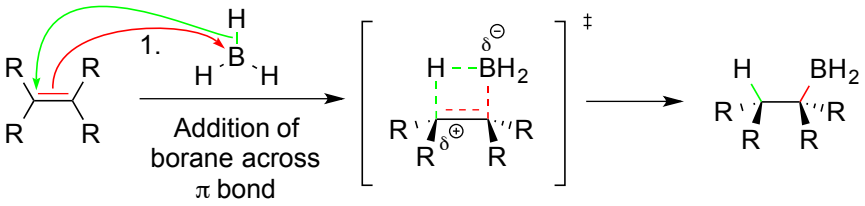
The reaction involves two steps. In the first step, an H–B bond of borane adds across the alkene π bond. This step is called hydroboration because hydrogen and boron are added to the alkene carbons.

The second step of the reaction is oxidation using hydroxide and hydrogen peroxide. This step converts the BH_2 group to a hydroxyl group.



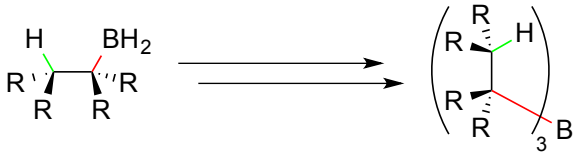
The mechanism is presented below in its entirely and becomes rather involved in the second step. It will help to keep this basic framework in mind as you read further.

During hydroboration, an H–B bond of borane adds across the alkene π bond in a concerted fashion, meaning that the new C–B and C–H bonds are formed simultaneously. Consequently, the addition is syn (same side). The nucleophilic alkene attacks the electron-poor boron. As the boron develops a δ^- charge, its hydride is donated to the alkene carbon that is concurrently developing a δ^+ charge.



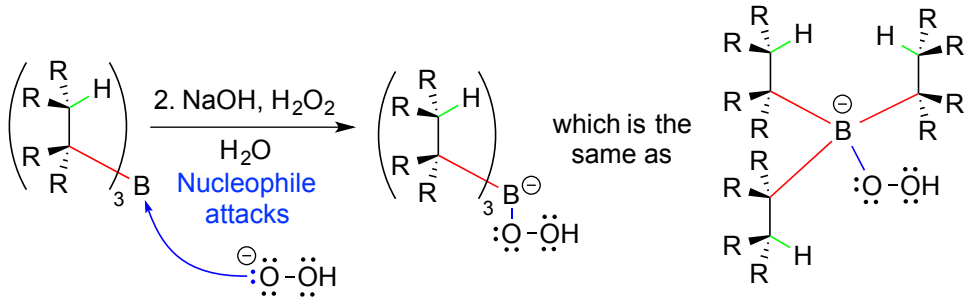
It is worth noting that you may encounter borane written simply as BH_3, or you may see diborane (B_2H_6) or a borane-THF complex (BH_3•THF) used as alternative sources of BH_3.

The initial hydroboration product still contains two more boron-hydrogen bonds. Each of these remaining boron-hydrogen bonds adds across the π bond of another molecule of alkene. Ultimately, the final hydroboration product contains boron tethered to three substrate molecules. This fact is often ignored when drawing the reaction in a concise way, as shown initially in this section.

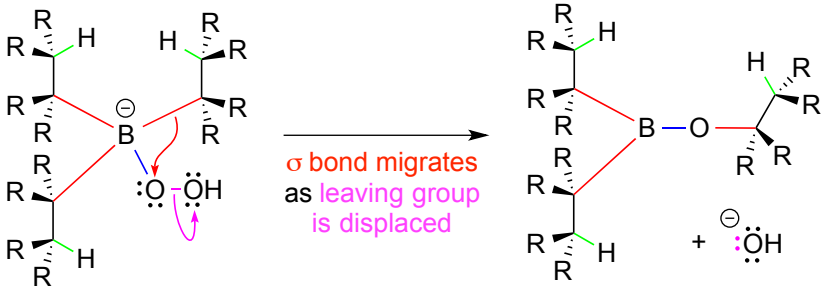


The second step, oxidation, is much more mechanistically involved than the first step, so it is often not drawn out in detail. The full mechanism for oxidation is shown below. Keep in mind that ultimately boron will simply be replaced where it stands (i.e., in the exact same position) by a hydroxyl group.

Oxidation begins with the attack of the conjugate base of peroxide (formed from hydrogen peroxide in basic medium) on boron. The boron becomes anionic as a result.

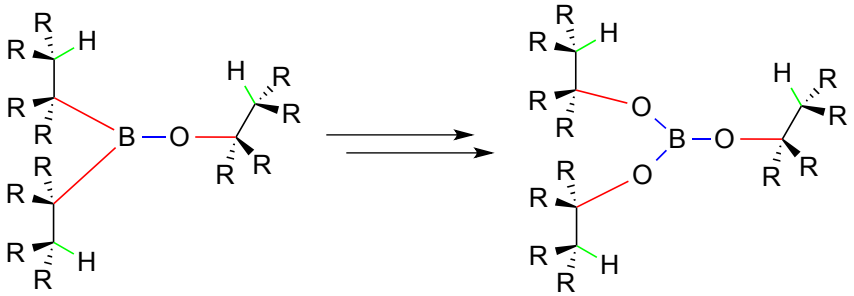


At this point, the weak O–O bond is cleaved as a B–C σ bond migrates. This returns the boron to a neutral state, breaks the weak oxygen-oxygen bond, and displaces hydroxide as a leaving group.

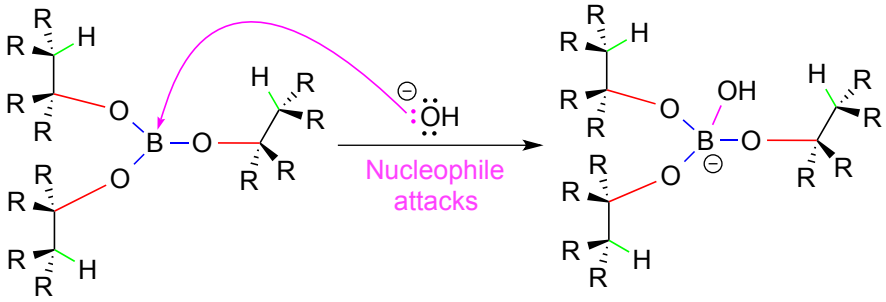


Notice that the net result of the two preceding steps is the insertion of an oxygen atom between boron and an alkyl group. Two more iterations of this sequence (nucleophile

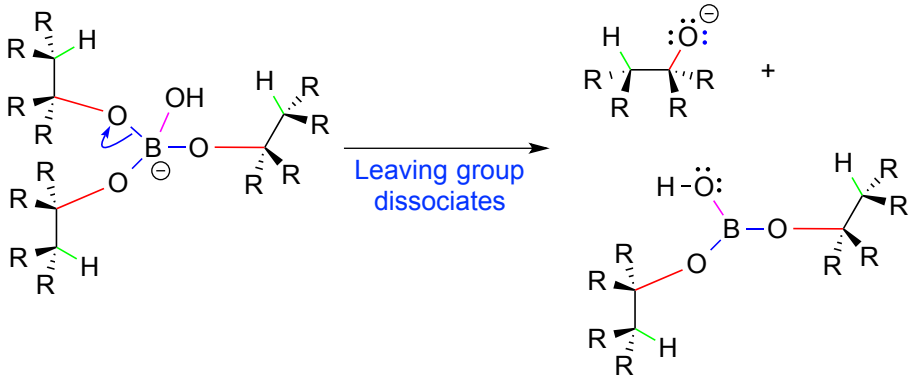
attacks then σ bond migrates as leaving group is displaced) result in the insert of oxygen atoms between boron and all three of its alkyl groups.



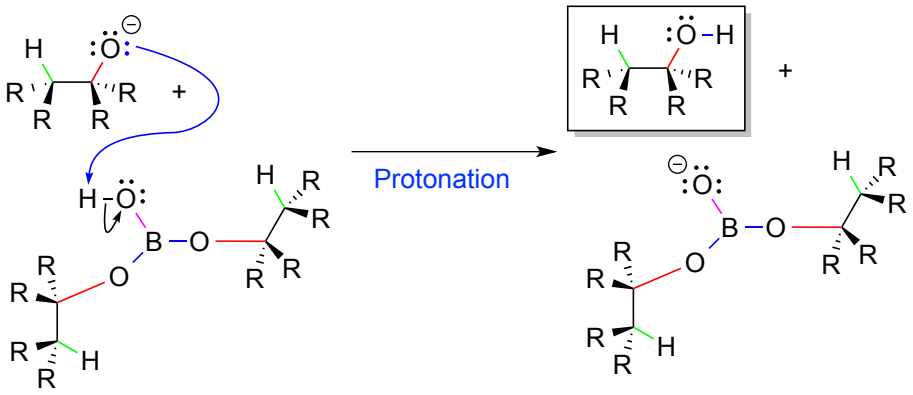
Now, in two more steps, an alkoxide ligand on boron is swapped for hydroxide. This begins with the attack of hydroxide on the electrophilic boron.



An alkoxide ligand now dissociates from the anionic boron.

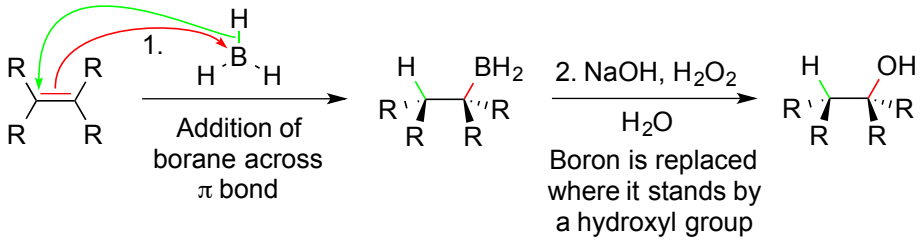


Finally, the alkoxide is protonated by the O–H bond, and this generates the alcohol product.



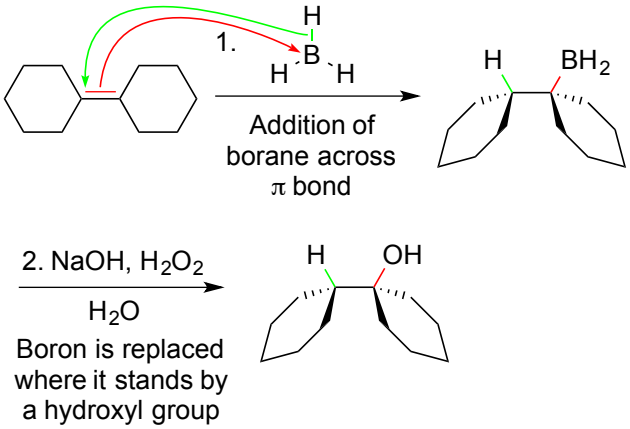
The attack of hydroxide, dissociation of an alkoxide ligand, and protonation occur two more times to produce a total of three molecules of alcohol product as well as borate (BO_3^{3-}) as an inorganic byproduct.

Although the oxidation step is much more mechanistically involved than the hydroboration step, it is in some ways less significant that the hydroboration step. As we will see shortly, the hydroboration step sets both the regiochemistry and stereochemistry of the reaction. Therefore, it is common for the mechanism to be drawn only for the hydroboration step as shown below.

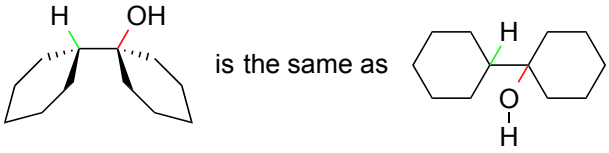


A specific example of hydroboration-oxidation

In the following example, the alkene is symmetrical so the regiochemistry of the addition across the π bond is immaterial. After oxidation, the same alcohol product is produced either way.

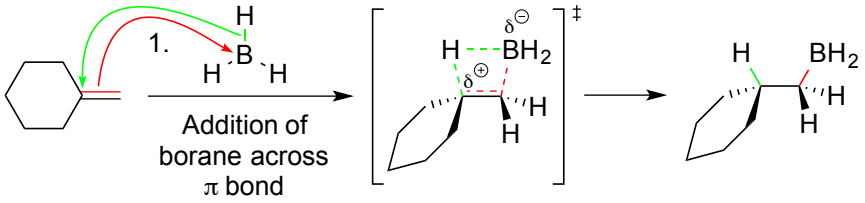


Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.

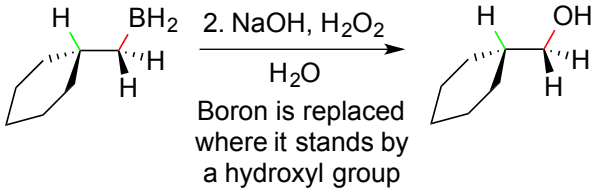


Regiochemical considerations

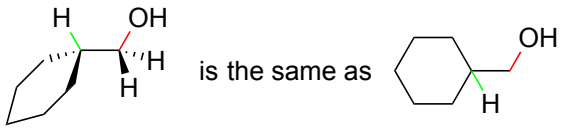
When the alkene reactant is unsymmetrical, the regiochemistry of hydroboration becomes significant. The regiochemical outcome is anti-Markovnikov and is explained by the transition state. As the alkene attacks borane and the C–B bond begins to form, boron acquires a δ^-, and one of the two alkene carbons must develop a δ^+. The δ^+ is placed where it is more stable: on the more highly substituted alkene carbon, which in this case is tertiary.



After oxidation, it is plain to see that anti-Markovnikov regiochemistry results since the alkene carbon with more hydrogens did *not* acquire the new hydrogen during the reaction.

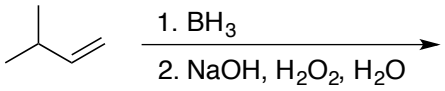


Again, in this reaction no stereocenters have been formed.

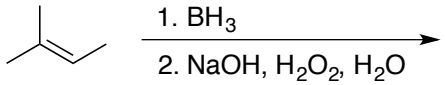


Problem 23. Provide products for the following hydroboration-oxidation reactions.

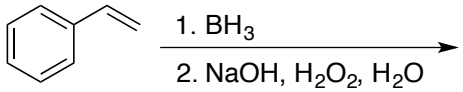
(a)



(b)



(c)

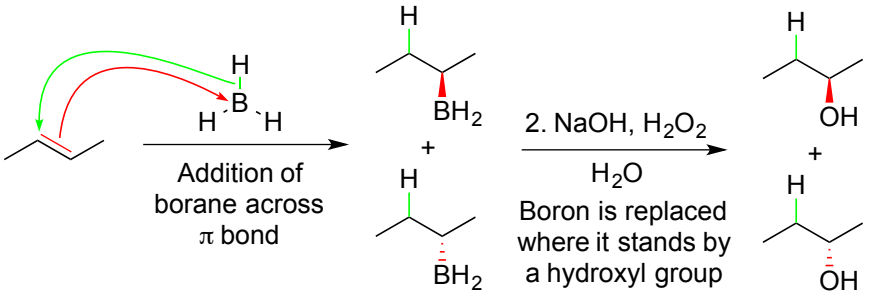


Stereochemical considerations

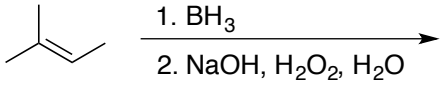
Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so the hydroboration can occur from either side. Hydroboration is a syn addition, so boron and hydrogen add to the same side of the alkene. However, the center bearing the new hydrogen is not a stereocenter. During oxidation, the boron is replaced exactly where it stands by a hydroxyl group. If you refer back to the complete mechanism for oxidation shown earlier, you'll see that there is no change in the stereochemistry of the carbon bearing boron as it exchanges its bond to boron for a bond to oxygen.

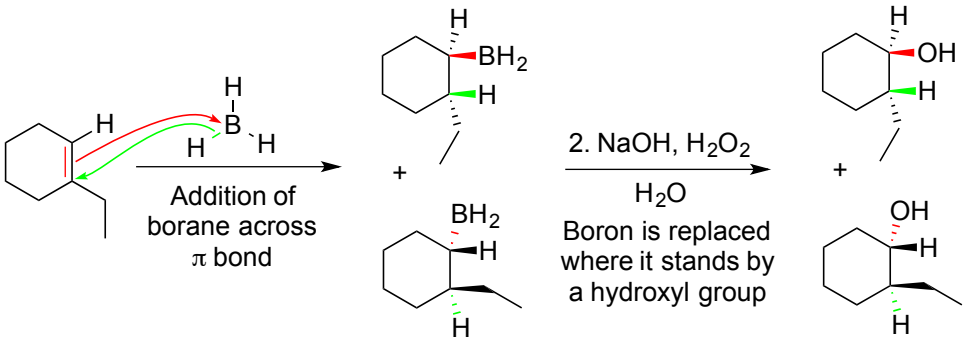
The products are enantiomeric alcohols: (*R*)- and (*S*)-2-butanol.



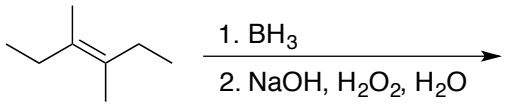
Problem 24. Let's revisit Problem 23b. We previously considered the following reaction from a two-dimensional perspective. Now show the stereochemical outcome of this transformation.



In the next example, two stereocenters are formed during hydroboration as the B–H bond adds across the alkene with anti-Markovnikov regiochemistry. Since hydroboration is a syn addition and boron and hydrogen add to the same side of the alkene, *only two of four possible stereoisomers are formed*. The hydroboration products are the syn enantiomers. During oxidation, boron is replaced where it stands by a hydroxyl group to yield the two enantiomeric syn alcohols.



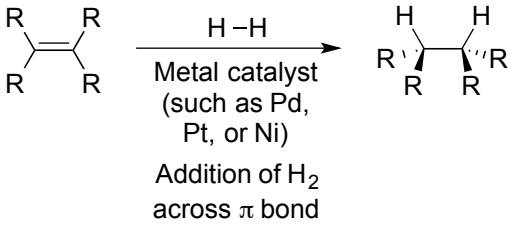
Problem 25. Provide the product(s) of the following hydroboration-oxidation.



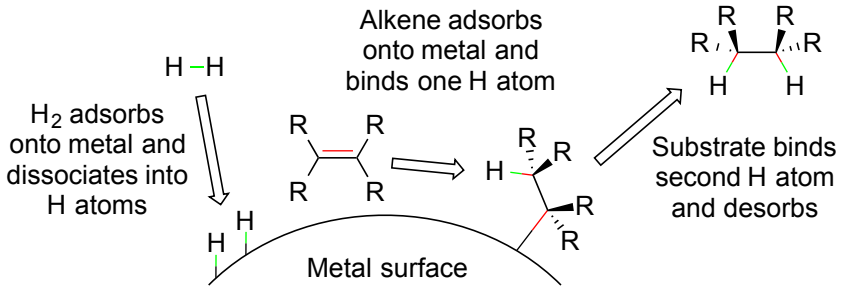
In summary, hydroboration-oxidation adds water across a π bond with anti-Markovnikov regiochemistry. The hydroboration step occurs with syn stereochemistry, and no change in stereochemistry occurs during the oxidation step. Since hydroboration-oxidation does not involve a carbocation intermediate, no carbocation rearrangement is possible.

Section 9: Hydrogenation

Hydrogenation is the addition of hydrogen (H_2) across a π bond. The reaction is typically conducted in the presence of a metal catalyst, such as Pd, Pt, or Ni. Sometimes the catalyst is adsorbed onto carbon, which is written as Pd/C ("palladium on carbon").



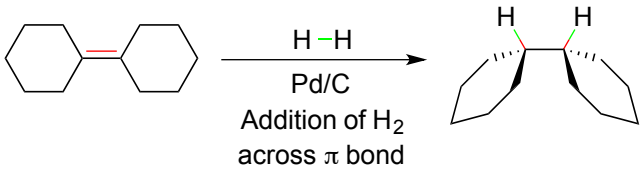
This is a reaction for which an arrow-pushing mechanism is not typically drawn. The mechanism is sometimes illustrated schematically and consists of three main steps: (1) hydrogen adsorbs onto the metal catalyst and dissociates (or homolyzes) into hydrogen atoms; (2) the alkene substrate adsorbs onto the metal catalyst as well and adds a single hydrogen atom; (3) addition of a second hydrogen atom to the substrate generates the alkane product.



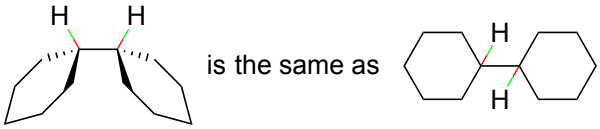
Both hydrogen atoms add to the same side of the alkene substrate, making this a syn addition.

A specific example of hydrogenation

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is *not* an issue in hydrogenation because the same group (H) is added to each alkene carbon.



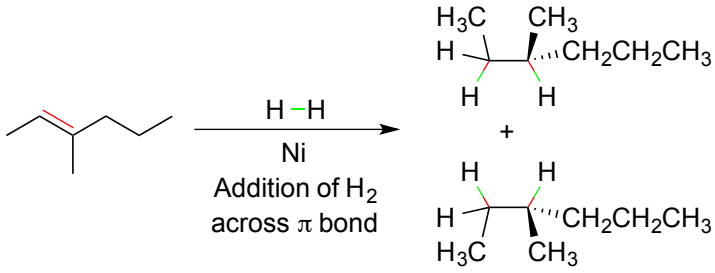
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



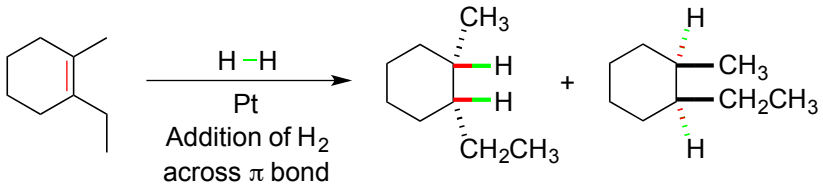
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction. No stereocenters were formed in the examples above.

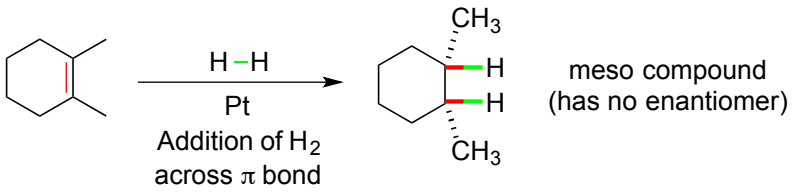
In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so the hydrogenation can occur from either side. Although hydrogenation is a syn addition and the hydrogens add to the same side of the alkene, only one of the two new tetrahedral (sp^3) centers in the product is a stereocenter. This is emphasized by drawing only that center with wedges and dashes. The products are enantiomers: (*S*)- and (*R*)-3-methylhexane.



In the next example, two stereocenters are formed. Since hydrogenation is a syn addition and the hydrogens add to the same side of the alkene, *only two of the four possible stereoisomers are formed*. The alkane products are the syn enantiomers.



While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where two of the same atom are added across a π bond. The following example is extremely similar to the previous example; however, syn addition of hydrogen to this alkene yields a meso alkane product. Since meso compounds are overall achiral, this is the sole product of the reaction (i.e., it has no enantiomer).



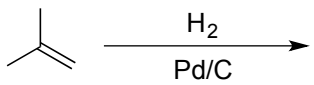
In conclusion, hydrogenation adds H_2 across a π bond in the presence of a metal catalyst. The stereochemistry of the addition is syn. There is no carbocation intermediate, so no rearrangement is possible.

Note that there are additional catalysts that can be employed in hydrogenation reactions. For instance, Wilkinson's catalyst is $RhCl(PPh_3)_3$. It could be used in the hydrogenation reactions shown above. Additionally, the PPh_3 (triphenylphosphine) ligands on rhodium can be replaced with chiral, non-racemic ligands to give a chiral catalyst for use in asymmetric hydrogenation.

Asymmetric hydrogenation would produce only one of the syn enantiomers as a reaction product. It is typically not feasible to predict which syn enantiomer would predominate. At the moment, it is sufficient to know that enantioselectivity is possible. Asymmetric hydrogenation can also be performed with other metals, such as ruthenium, bearing chiral, non-racemic ligands.

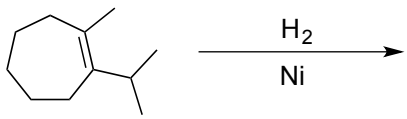
Problem 26. Predict the products of the following reactions.

(a)

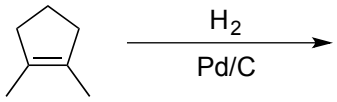


(b)

(c)



(d)

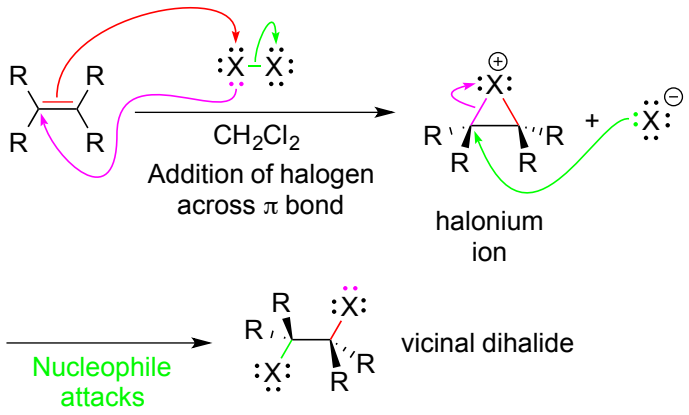


Section 10: Halogenation

Halogenation is the addition of chlorine (Cl_2) or bromine (Br_2) across a π bond.

The reaction begins with the addition of a single halogen atom across the two carbons of the alkene π bond. Three mechanistic arrows describe this addition. The π bond attacks one of the halogen atoms, thereby displacing the other as a halide. The halogen being added to the substrate simultaneously attacks the carbon of the alkene that is losing a bond. The resulting intermediate is known as a halonium ion (positively charged halogen).

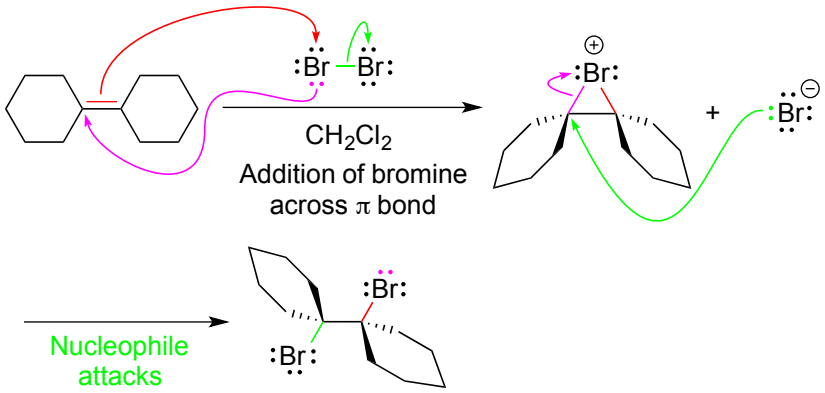
The halide then attacks one of the carbons of the halonium ion, opening the three-membered ring. The halide must attack opposite the halonium ion, making this an anti addition. The product is a vicinal (i.e., neighboring) dihalide.



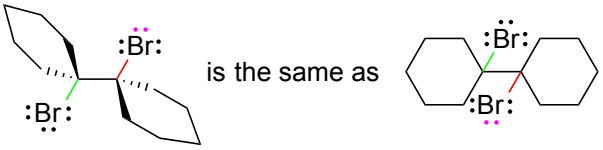
The reaction takes place in an inert solvent, such as dichloromethane (CH_2Cl_2).

A specific example of halogenation

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is not an issue in halogenation because the same halide is added to each alkene carbon.



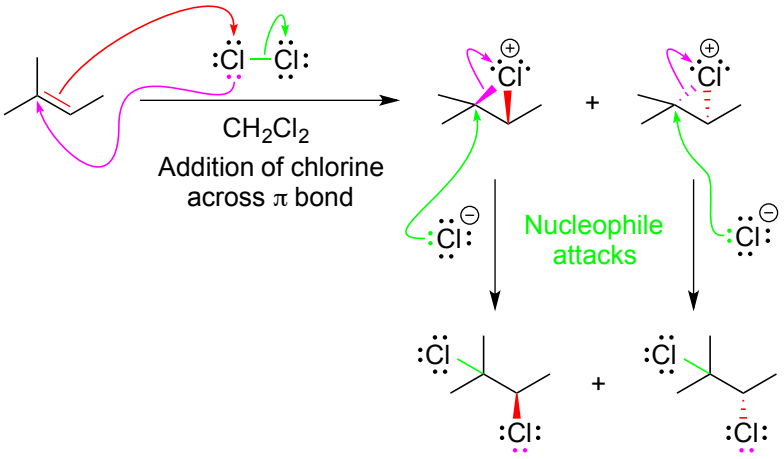
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



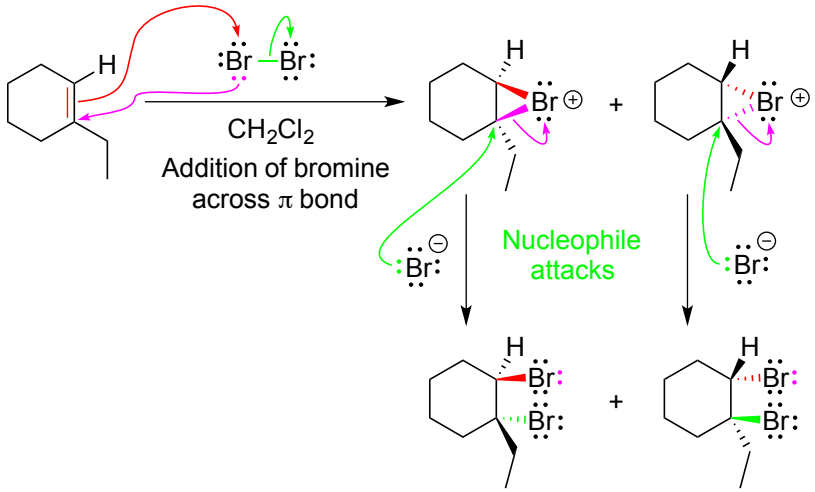
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

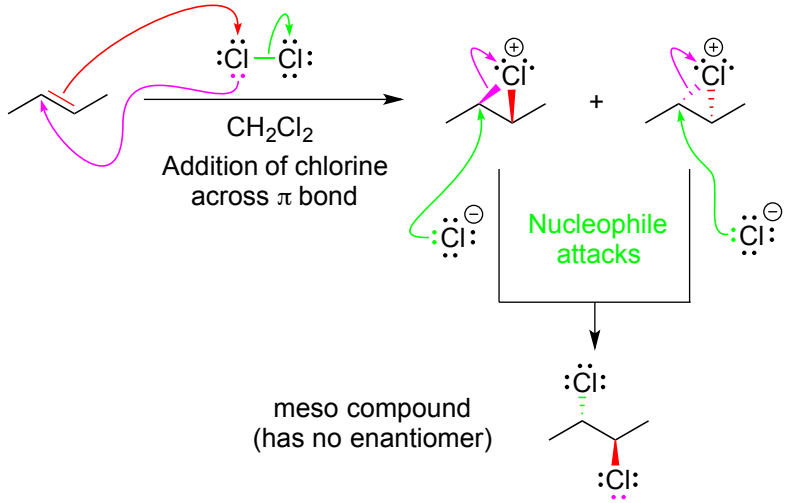
In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so chloronium ion formation can occur from either side. Although the chloride ion attacks opposite the chloronium ion (anti addition), only one of the carbons bearing chlorine in the product is a stereocenter. This is emphasized by drawing only that center with wedges and dashes. The products are enantiomers: (*R*)- and (*S*)-2,3-dichloro-2-methylbutane.



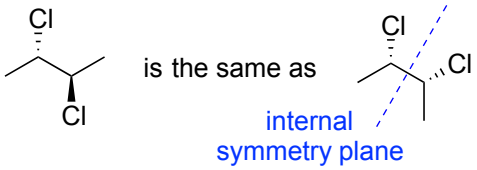
In the next example, two stereocenters are formed. Since halogenation is an anti addition and the bromines add to opposite sides of the alkene, *only two of the four possible stereoisomers are formed*. The vicinal dibromide products are the anti enantiomers.



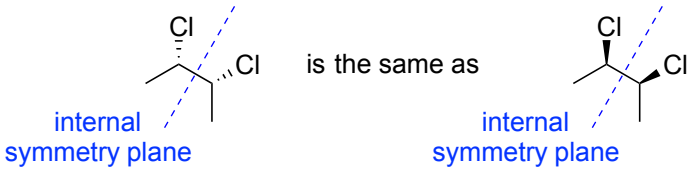
While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where two of the same atom are added across a π bond. In the following example, enantiomeric chloronium ions are formed as intermediates in the reaction, but they converge on a single meso product. Since meso compounds are overall achiral, this is the sole product of the reaction (i.e., it has no enantiomer).



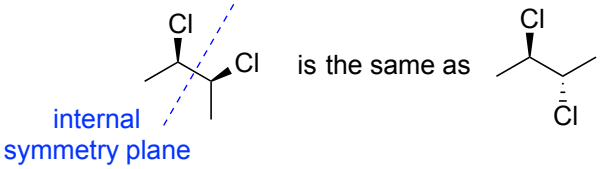
The internal symmetry is not obvious in this instance unless you rotate about the central C-C bond. Doing so places the molecule in a conformation where the internal symmetry is readily apparent. Note that the color-coding of electrons has been omitted below for clarity.



Since this molecule possesses internal symmetry, it is identical to its mirror image.



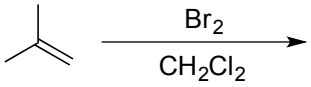
Rotating this identical mirror image around the central C-C bond produces a different conformation of the same molecule. But at first glance, you might have thought this to be a second reaction product. We can now see that, since all of these structures are identical, there is only one reaction product in this case.



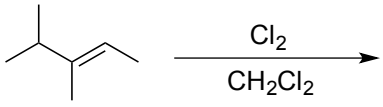
In conclusion, halogenation adds X_2 across the π bond of an alkene. The stereochemistry of the addition is anti. There is no carbocation intermediate, so no rearrangement is possible.

Problem 27. Provide products for these halogenation reactions.

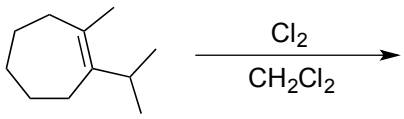
(a)



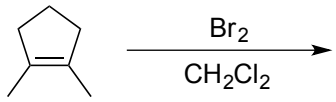
(b)



(c)



(d)

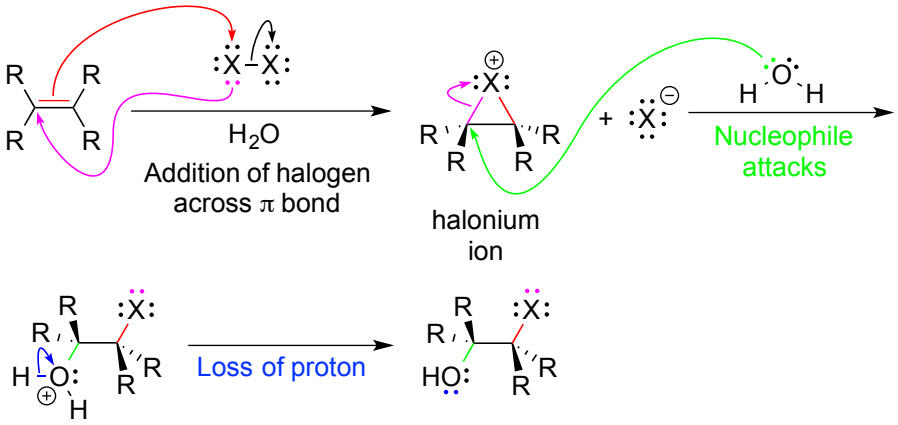


Section 11: Halohydrin formation

Halohydrin formation is the addition of a halogen (Cl or Br) and a hydroxyl group (OH) across a π bond. Mechanistically, the reaction is quite similar to halogenation. The difference stems from use of a nucleophilic solvent (H_2O), which acts as the nucleophile in the second step of the mechanism.

The reaction begins with the addition of a single halogen atom across the two carbons of the alkene π bond. Three mechanistic arrows describe this addition, exactly the same as in halogenation. The π bond attacks one of the halogen atoms, thereby displacing the other as a halide. The halogen being added to the substrate simultaneously attacks the carbon of the alkene that is losing a bond. The resultant intermediate is known as a halonium ion (positively charged halogen).

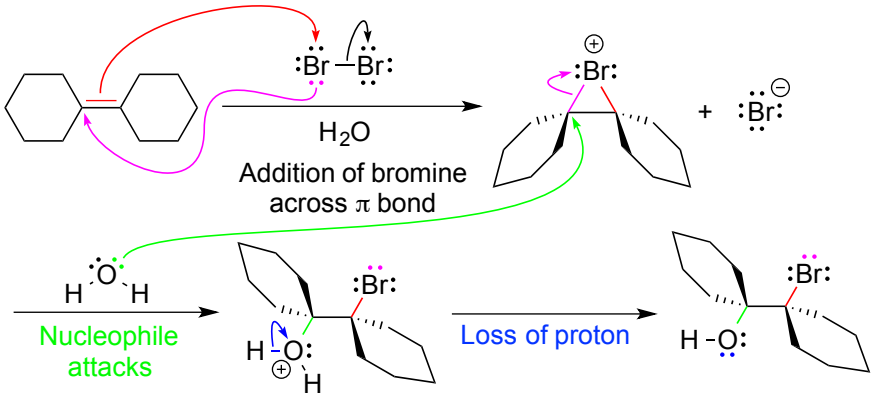
When water is used as a solvent, there are two nucleophiles that could attack the halonium ion: the displaced halide or water. Since water is the solvent, it is present in a much greater abundance than the halide and is therefore much more likely to encounter and attack the halonium ion. When water attacks one of the carbons of the halonium ion, the three-membered ring is opened. The product incorporates a halogen and a hydroxyl group, so it is called a halohydrin.



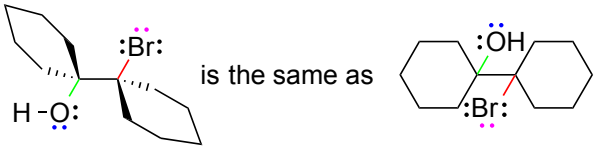
Water must attack opposite the halonium ion, making this an anti addition.

A specific example of halohydrin formation

In the following example, the alkene and bromonium ion are symmetrical, so it does not matter which carbon of the bromonium ion is attacked by water. Attack of water at either carbon will yield the same halohydrin product due to the molecule's symmetry.



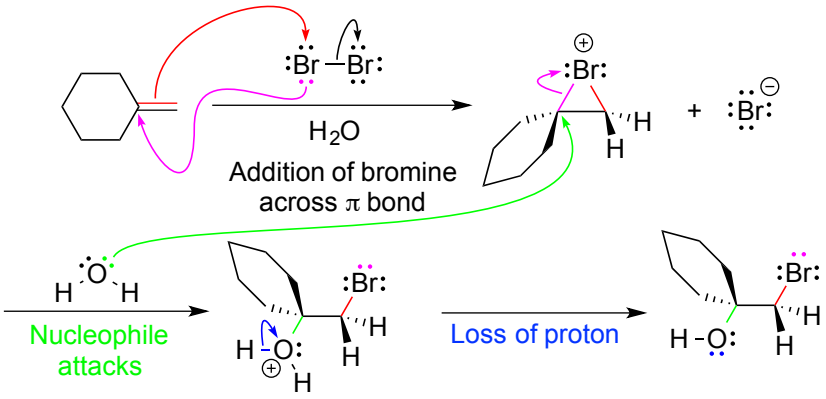
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



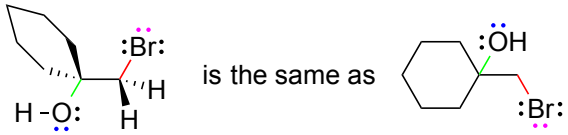
Regiochemical considerations

When the alkene substrate is unsymmetrical, an unsymmetrical halonium ion will result. The attack of water occurs at the center with the greater partial positive charge (δ^+). The more highly substituted carbon of the halonium ion has the greater δ^+. This is because a more highly substituted δ^+ is more stable, much like a more highly substituted carbocation is more stable.

If Markovnikov's rule is phrased more broadly as "the alkene carbon possessing more hydrogens acquires the electrophile," then we can see that halohydrin formation follows Markovnikov's rule since bromine was the electrophile in this reaction.



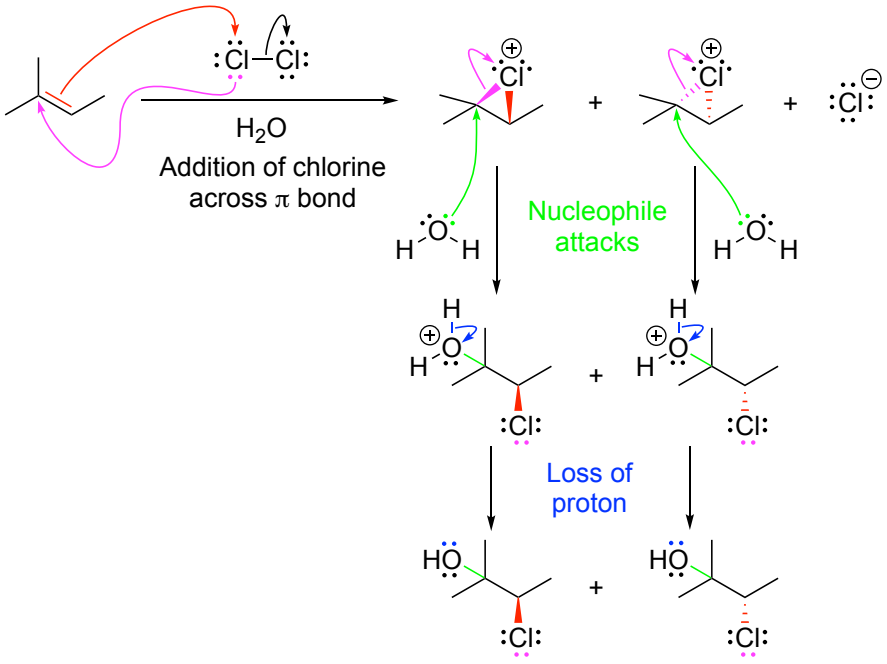
Again, in this reaction no stereocenters have been formed.



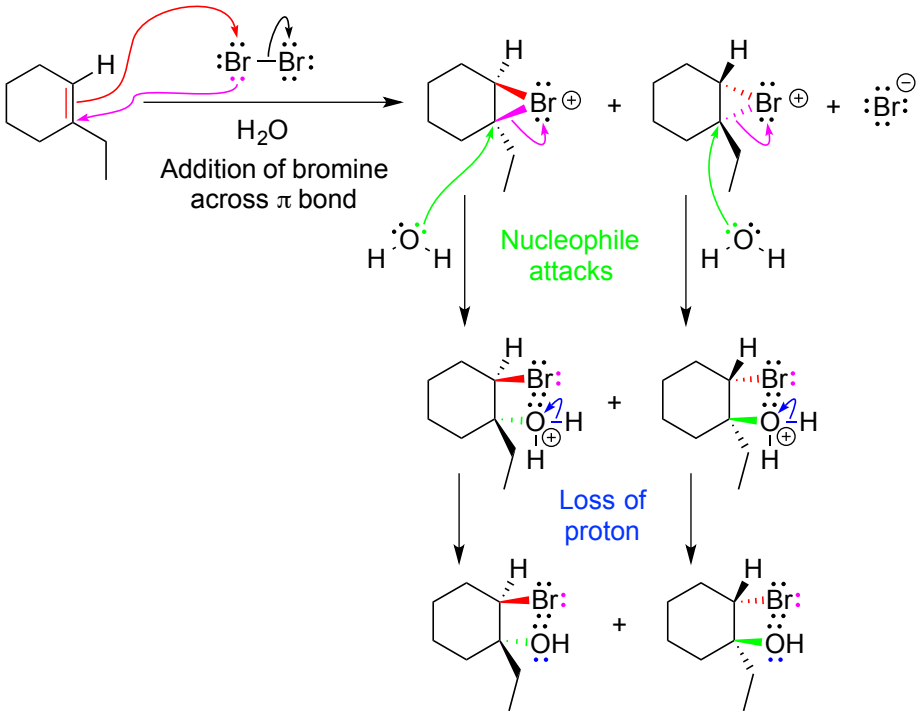
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so chlorine can add to either face of the alkene to give enantiomeric chloronium ions. When water opens the chloronium ion and a proton is lost, two enantiomeric halohydrin products result.

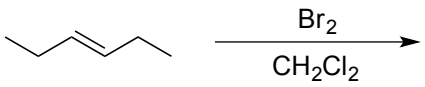


In the next example, two stereocenters are formed. Since halohydrin formation is an anti addition and the new groups (Br and OH) add to opposite sides of the alkene, *only two of the four possible stereoisomers are formed*. The halohydrin products are the anti enantiomers.

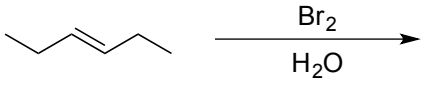


Problem 28. Consider the two reactions in parts (a) and (b) below. One of these reactions yields a single product, while the other yields two products. Why do such similar transformations have very different outcomes?

(a)

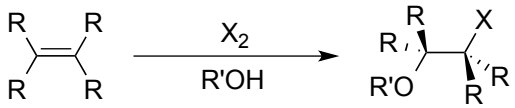


(b)



In summary, halohydrin formation adds X and OH across the π bond of an alkene. The hydroxyl group is placed at the more highly substituted alkene carbon, and the stereochemistry of the addition is anti. There is no carbocation intermediate, so no rearrangement is possible.

A variation of this reaction uses an alcohol (ROH) as the solvent rather than water. The alcohol plays the same role as water in the mechanism, so the product exhibits the addition of X and OR across the π bond with the same regiochemical and stereochemical outcomes (see Problem 39).

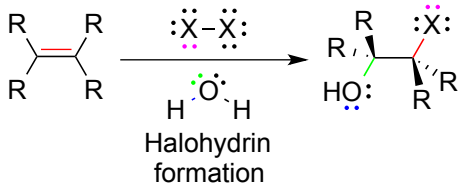


Section 12: Epoxidation

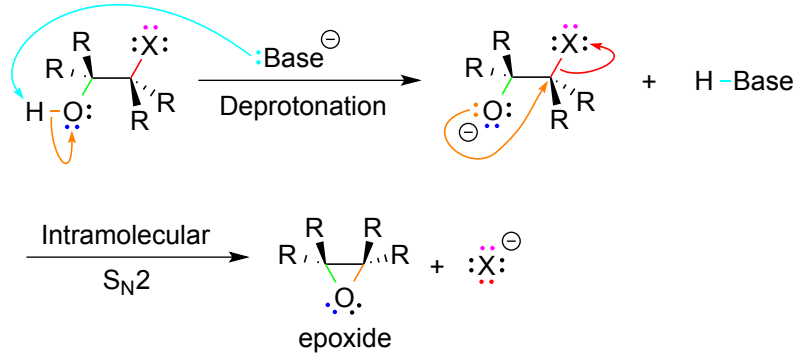
An epoxide is a three-membered ring containing one oxygen atom. An epoxide-forming reaction can be called epoxidation.

an epoxide

There are two common approaches to epoxidation. One uses a halohydrin as the reactant. Recall from the previous section that a halohydrin can be prepared from an alkene.

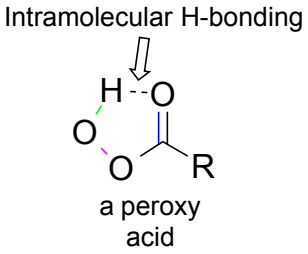


Deprotonation of the halohydrin yields an alkoxide (the conjugate base of an alcohol). In this case, the alkoxide happens to be adjacent to a carbon bearing a leaving group (X^-). Intramolecular S_N2 attack of the alkoxide on the adjacent carbon closes the three-membered ring of the epoxide and displaces the halide leaving group.

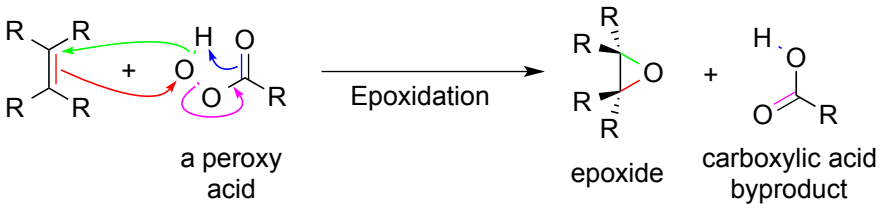


A second approach to epoxide formation uses an alkene as the reactant and a peroxyacid as the reagent. A peroxyacid is a carboxylic acid containing one additional oxygen atom

(RCO_3H). The peroxyacid exhibits intramolecular hydrogen bonding between the carbonyl oxygen and the acidic proton. This weakens the O–H bond.

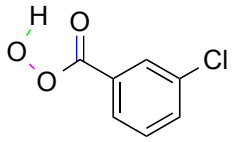


The donation of an oxygen atom from the peroxyacid to the alkene is a concerted process that can be described with four mechanistic arrows. As the carbonyl oxygen completely removes the proton to which it is hydrogen bonding, the electrons in the O–H bond are freed to attack one of the two alkene carbons. The alkene π electrons then attack oxygen, thereby cleaving the weak O–O bond. Those electrons flow toward the carbonyl carbon to replace the π bond that it is losing. The epoxide is the product, and the carboxylic acid is considered to be a byproduct.



Since the donation of oxygen to the alkene is concerted, this is a syn addition.

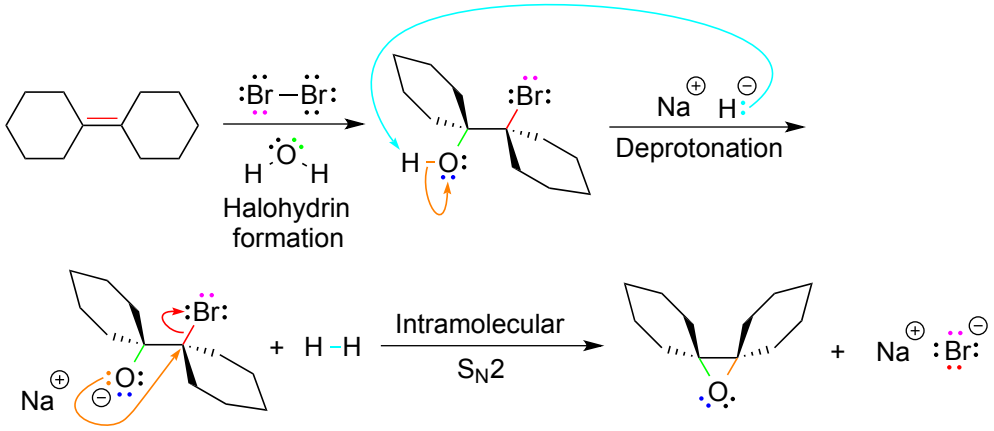
A commonly used peroxyacid is *meta*-chloroperoxybenzoic acid (mCPBA).



meta-chloroperoxybenzoic acid (mCPBA)

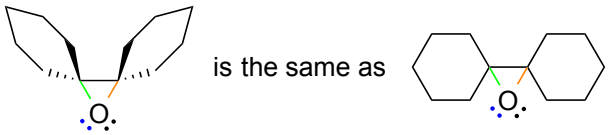
A specific example of epoxidation

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is not an issue in epoxidation because the same group is added to each alkene carbon.



Sodium hydride (NaH) was used as the base in this example, but other bases can be used as well.

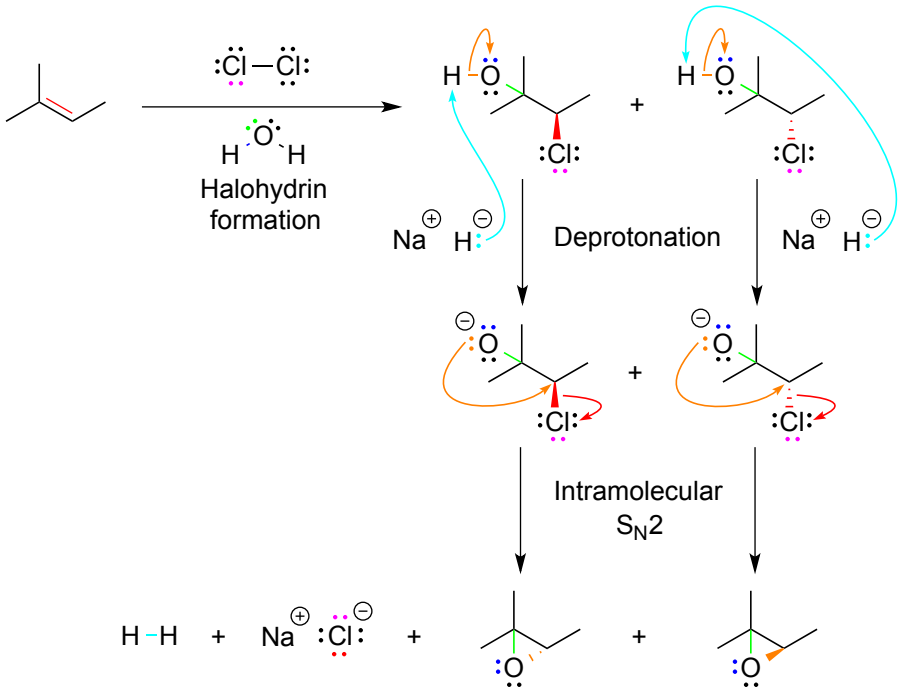
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



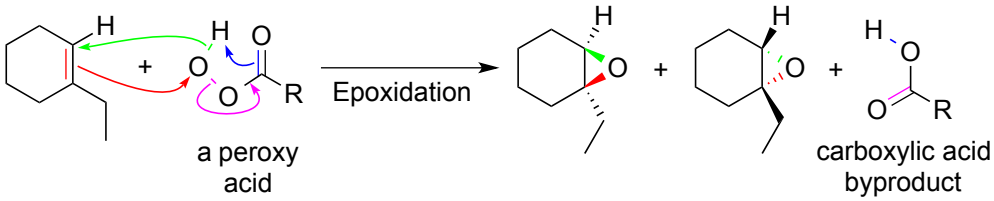
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so two enantiomeric halohydrin products are produced upon treatment with Cl_2 and H_2O. When the halohydrins are deprotonated, the resulting alkoxides must attack their neighboring carbons from the side opposite the chloride leaving group. Only one of the epoxide carbons is a stereocenter. This is emphasized by drawing only that center with wedges and dashes.

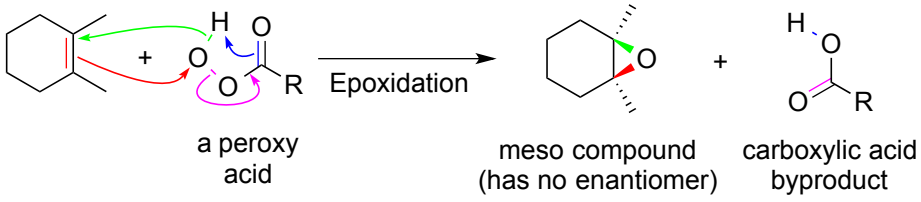


In the next example, two stereocenters are created. Since epoxidation is a syn addition, *only two of the four possible stereoisomers are formed*. The epoxide products are the syn enantiomers.



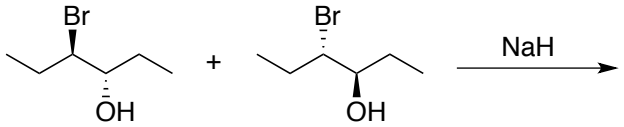
It is worth noting that, had the alkene been converted to the epoxide via the halohydrin instead, the stereochemical outcome would have been the same.

While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where the same group is added to each carbon of a π bond. The following example is extremely similar to the previous one; however, epoxidation of this alkene yields a meso product. Since meso compounds are overall achiral, this is the sole epoxide product of the reaction (i.e., it has no enantiomer).



Problem 29.

(a) When the halohydrins made in Problem 28(b) are treated with sodium hydride, a pair of epoxide enantiomers is formed. Show the structures of these compounds and provide a mechanism for their formation.

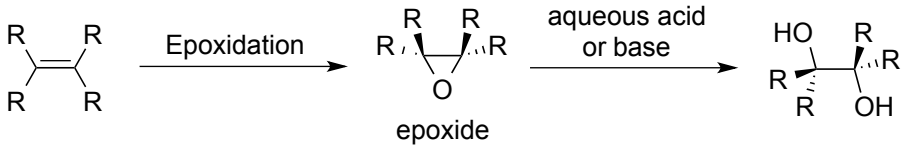


(b) Provide an alternate method for the preparation of the epoxides generated in part (a).

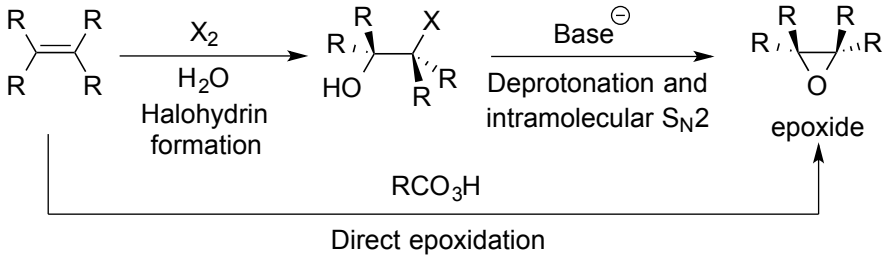
In conclusion, epoxidation can be performed by converting an alkene to a halohydrin, followed by treatment of the halohydrin with base. Alternatively, the alkene may be treated directly with a peroxyacid to yield an epoxide. The stereochemical outcome is the same for both approaches: a net syn addition of the epoxide oxygen across the π bond. There is no carbocation intermediate in either instance, so no rearrangement is possible.

Section 13: Anti-dihydroxylation

Anti-dihydroxylation of an alkene adds two hydroxyl (OH) groups across the π bond in an anti fashion.



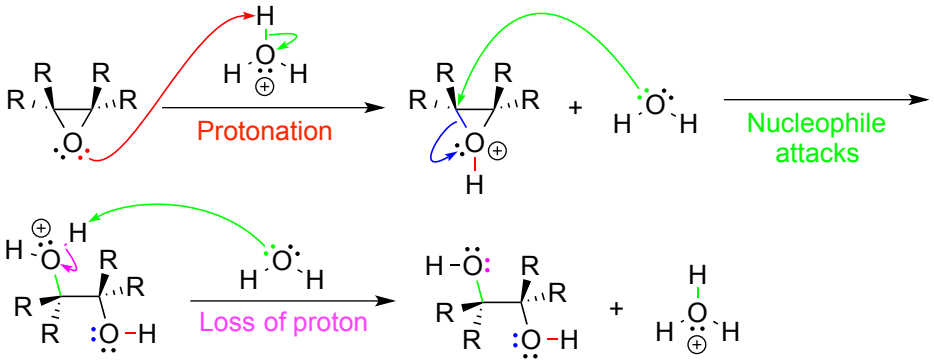
This transformation proceeds via the epoxide. Recall the two ways to prepare an epoxide shown in the previous section: (1) halohydrin formation followed by treatment with base or (2) direct epoxidation with a peroxy acid (RCO_3H).



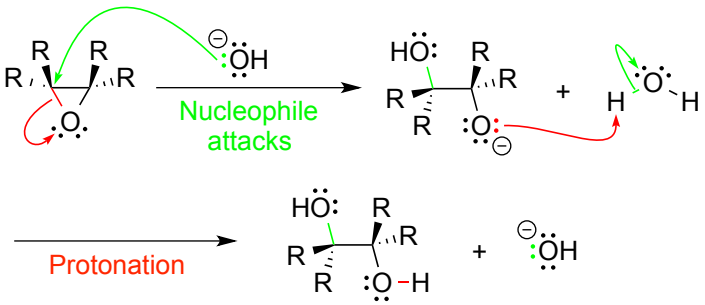
The epoxide is then opened in aqueous acid or aqueous base to complete the anti-dihydroxylation.

Acidic epoxide opening begins with protonation of the epoxide oxygen. Water then attacks one of the two epoxide carbons, thereby opening the three-membered ring. Since the attack

of water occurs opposite the breaking C–O bond, the oxygens are anti to one another. The resultant oxonium ion then loses a proton to provide the vicinal (i.e., neighboring) diol.

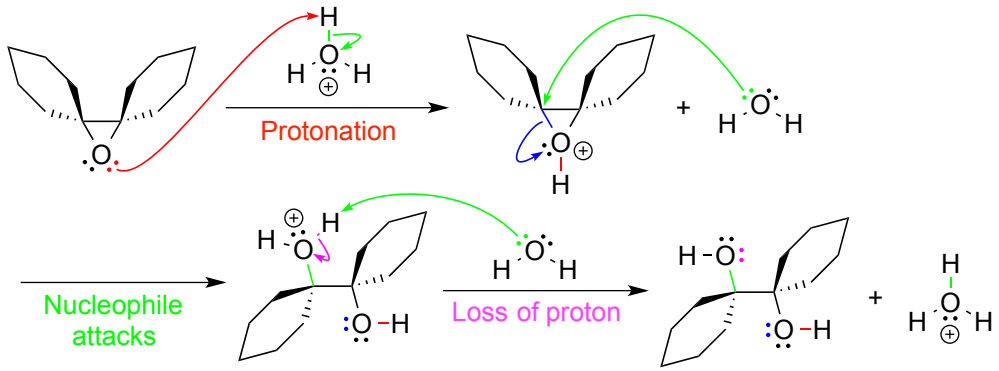


In basic epoxide opening, hydroxide directly attacks one of the two epoxide carbons to open the three-membered ring. Since the attack occurs opposite the breaking C–O bond, the oxygens are again anti to one another. The alkoxide intermediate is then protonated by water to yield the vicinal diol.

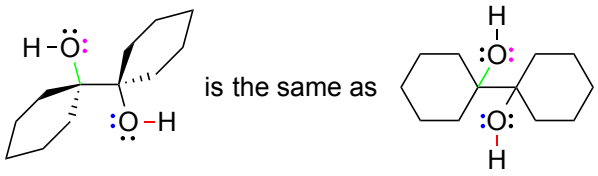


Specific examples of anti-dihydroxylation

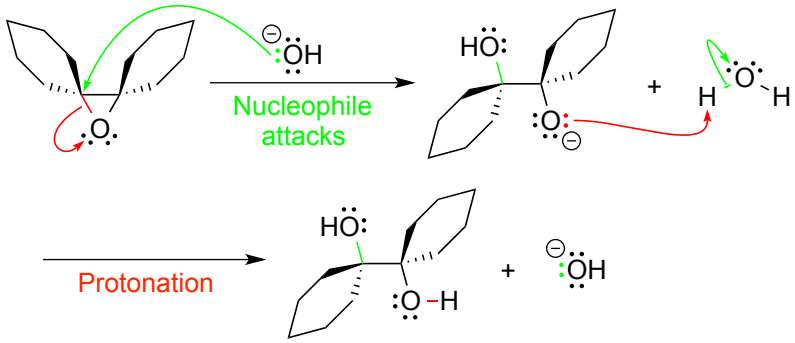
In the following example, the reactant is symmetrical, so it does not matter which epoxide carbon is attacked by water. Attack of water at either carbon will yield the same vicinal diol product due to the molecule's symmetry.



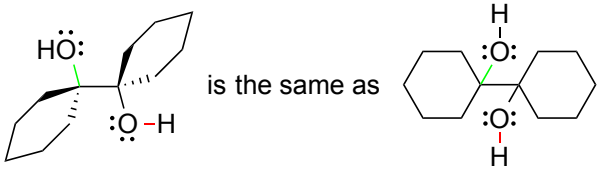
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



Subjecting the same symmetrical epoxide to basic epoxide opening also yields the same vicinal diol product regardless of which carbon is attacked by hydroxide.

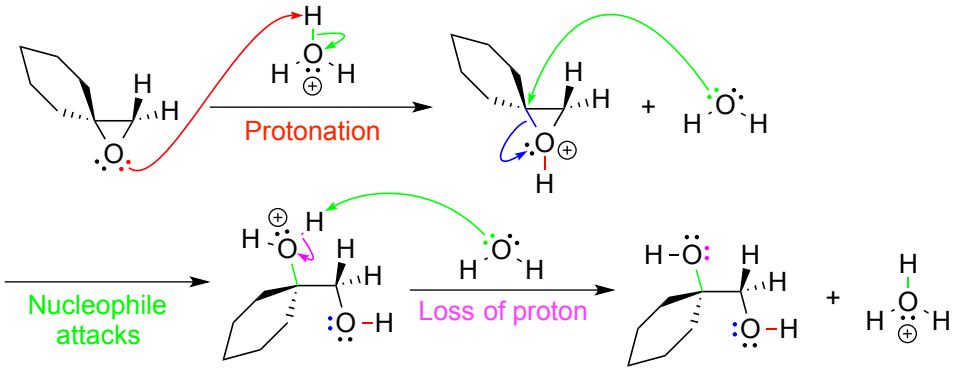


Again, in this reaction no stereocenters have been formed.

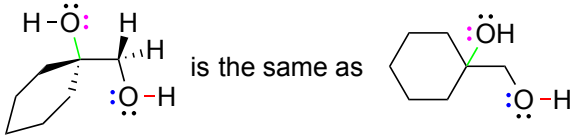


Regiochemical considerations

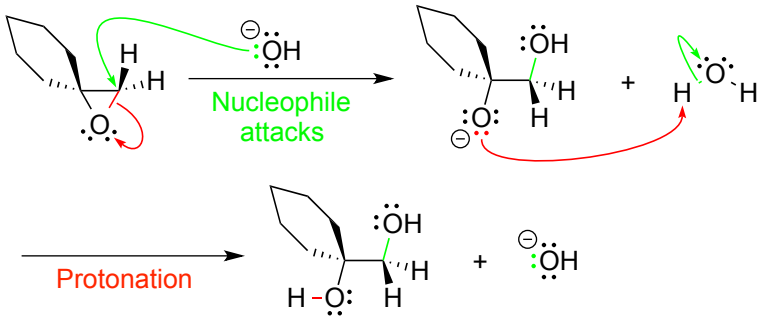
When an unsymmetrical epoxide substrate is treated with aqueous acid, the attack of water occurs at the center with the greater partial positive charge (δ^+), which draws in the weak nucleophile (H_2O). The more highly substituted carbon of the protonated epoxide ion has the greater δ^+. This is because a more highly substituted δ^+ is more stable, much like a more highly substituted carbocation is more stable.



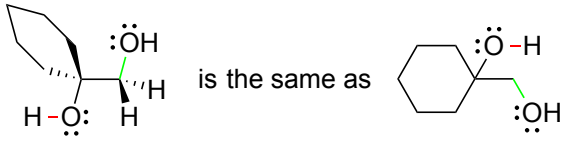
While this initially appears not to matter because the same group is added to each carbon anyway, we'll soon see that the regiochemistry of attack can have ramifications in reactions where stereochemistry is a consideration. In this particular instance though, no stereocenters are formed.



When an unsymmetrical epoxide is treated with aqueous base, the regiochemistry of attack differs. In this case, the nucleophile is strong, and as it approaches the substrate, steric hindrance is the primary concern. Hydroxide can more easily approach the less hindered site and therefore attacks a different carbon than that attacked by water in the preceding example.



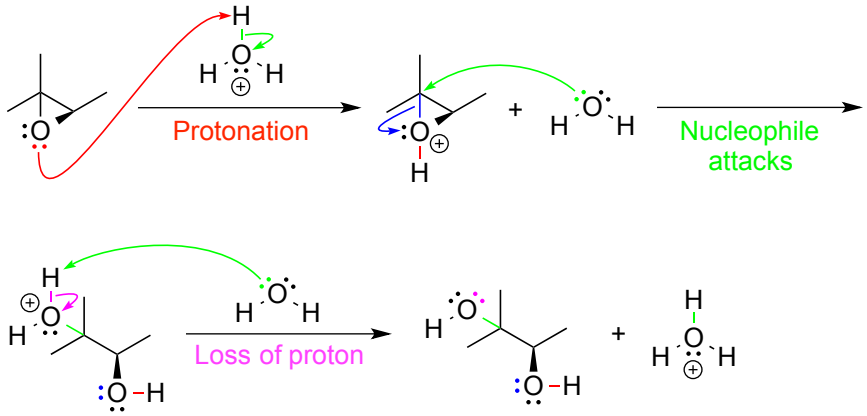
Again, no stereocenters were formed in this particular reaction.



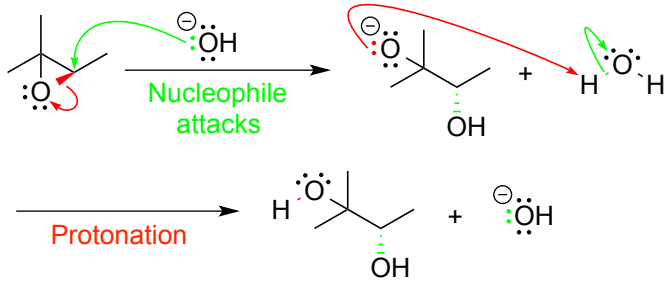
Stereochemical considerations

Since the epoxide undergoing the transformation involves two carbon atoms, there may be 0, 1, or 2 stereocenters in the product.

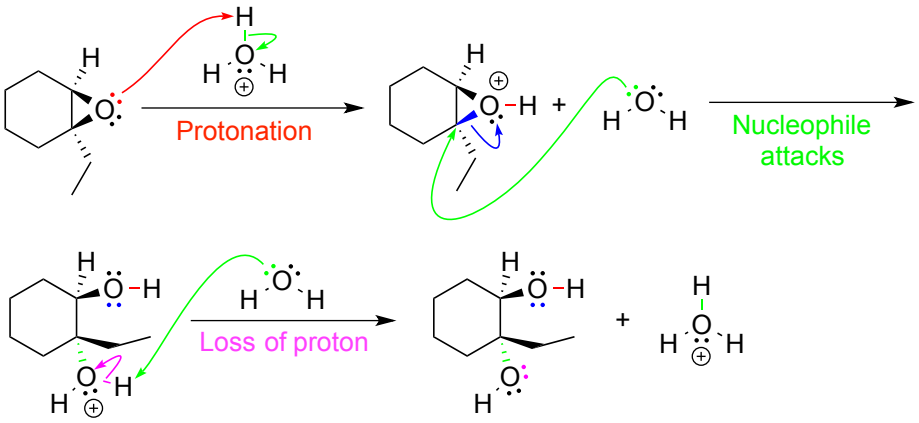
In the example below, the product contains a single stereocenter. In this acidic epoxide opening, water is drawn to the more highly substituted carbon of the protonated epoxide. Consequently, the nucleophilic attack occurs at a site that is not a stereocenter. The configuration of the sole stereocenter is therefore preserved during this reaction.



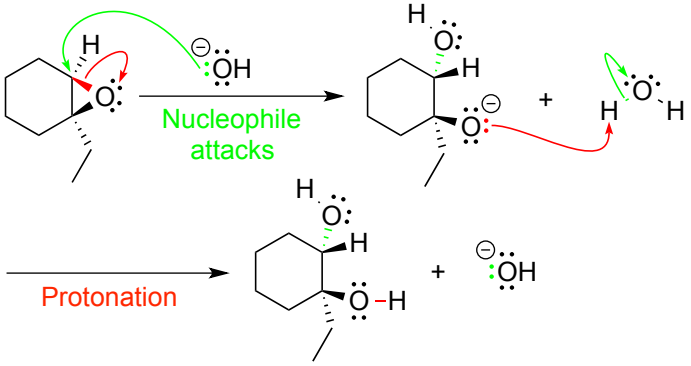
If the same epoxide is subjected to basic conditions, the stereochemical outcome differs. Hydroxide attacks the less hindered epoxide carbon, which happens to be the stereocenter. Since hydroxide attacks opposite the breaking C–O bond, the configuration of this center is inverted, and the product is the enantiomer of the product formed in the previous example.



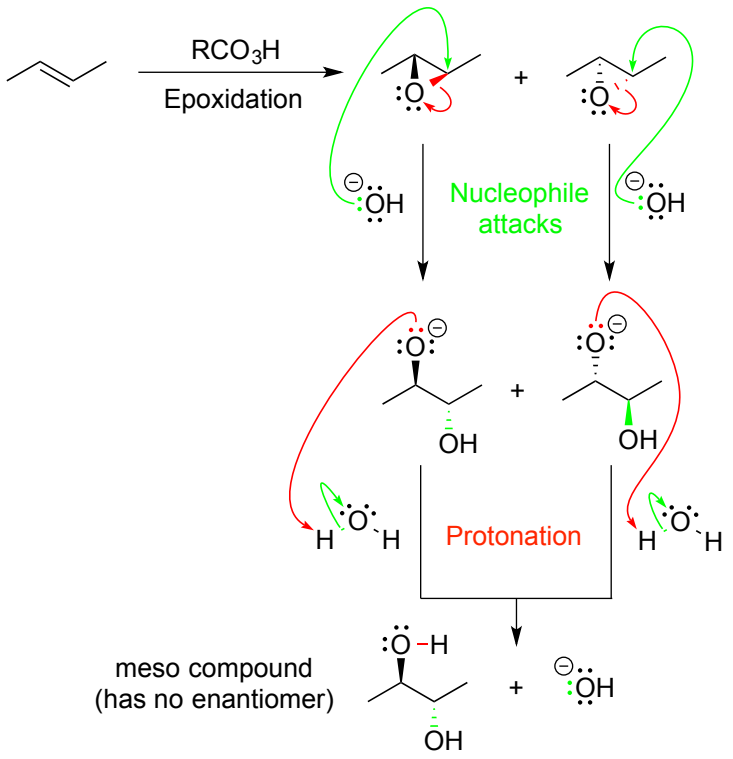
In the next example, the reactant and product both contain two stereocenters. In acidic epoxide opening, water is drawn to the more highly substituted carbon of the protonated epoxide. It attacks opposite the breaking C–O bond, inverting the configuration of that center only to yield the anti vicinal diol.



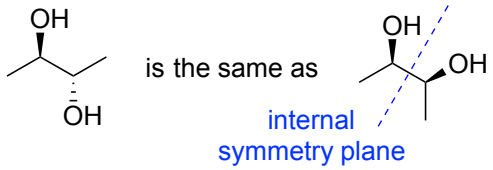
If the same substrate is subjected to basic opening, hydroxide attacks the less hindered epoxide carbon opposite the breaking C–O bond, thereby inverting the configuration of that center only. This also yields an anti vicinal diol; however, it is the enantiomer of the one formed in acidic conditions.



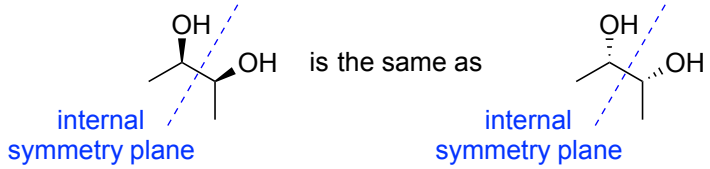
While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where the same group is added to each carbon of a π bond. In the following example, a *trans*-alkene is treated with a peroxyacid to yield enantiomeric epoxides. However, as these epoxides are opened in aqueous base (or aqueous acid), they converge on a single meso product. Since meso compounds are overall achiral, this is the sole product of the reaction (i.e., it has no enantiomer).



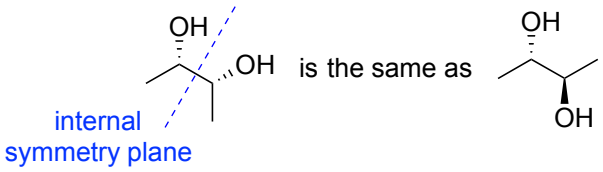
The internal symmetry is not obvious in this instance unless you rotate about the central C-C bond. Doing so places the molecule in a conformation where the internal symmetry is readily apparent. Note that the color-coding of electrons has been omitted below for clarity.



Since this molecule possesses internal symmetry, it is identical to its mirror image.

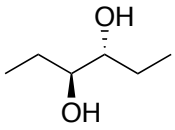


Rotating this identical mirror image around the central C-C bond produces a different conformation of the same molecule. But at first glance, you might have thought this to be a second reaction product. We can now see that, since all of these structures are identical, there is, in fact, only one reaction product in this case.

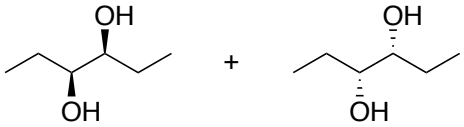


Problem 30. Devise a method for the synthesis of the following diols beginning with an alkene and using anti-dihydroxylation in each case.

(a)



(b)



In summary, the anti-dihydroxylation of an alkene is accomplished through conversion to the epoxide followed by opening of the epoxide in aqueous acid or base. The regiochemistry of the nucleophilic attack depends on the conditions used, but the hydroxyl groups in the vicinal diol product are always anti to one another. There are no carbocation intermediates, so no rearrangement is observed.

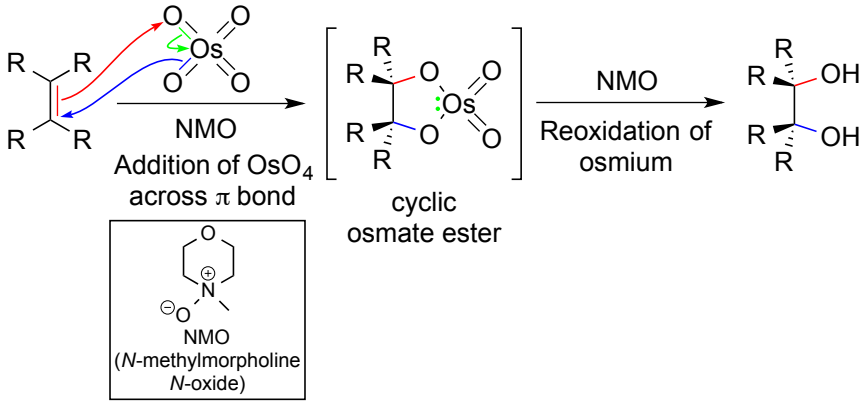
Section 14: Syn-dihydroxylation

Syn-dihydroxylation of an alkene adds two hydroxyl (OH) groups across the π bond in a syn fashion. There are two commonly employed oxidants for this transformation: osmium tetraoxide (OsO_4) and potassium permanganate ($KMnO_4$).

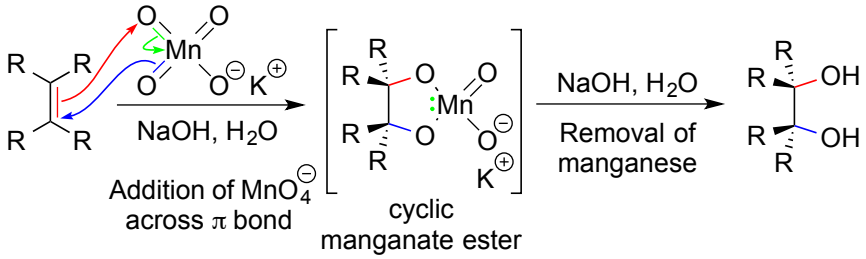
When using osmium tetraoxide as the oxidant, addition across the π bond is the first step. Three mechanistic arrows describe this step: (1) the π bond attacks one of the oxygen atoms of OsO_4; (2) an osmium-oxygen π bond is pushed onto osmium as a lone pair; and (3) a second osmium-oxygen π bond attacks the carbon of the alkene that is losing a bond. A cyclic osmate ester is the intermediate that results from these three mechanistic arrows. Since the addition is concerted, it proceeds with syn geometry.

The cyclic osmate ester can then be cleaved to yield a vicinal diol product in several ways. One common approach is to use a stoichiometric co-oxidant, such as *N*-methylmorpholine *N*-oxide (NMO). This allows for the use of small, catalytic amounts of osmium tetraoxide, which is toxic and expensive. The NMO reoxidizes the osmium, allowing it to act on another alkene. Peroxides can be used as alternative co-oxidants. It is also possible to use

stoichiometric OsO_4 and then treat the cyclic osmate ester with sodium sulfite (Na_2SO_3), sodium bisulfite ($NaHSO_3$), or hydrogen sulfide (H_2S) in a second step.

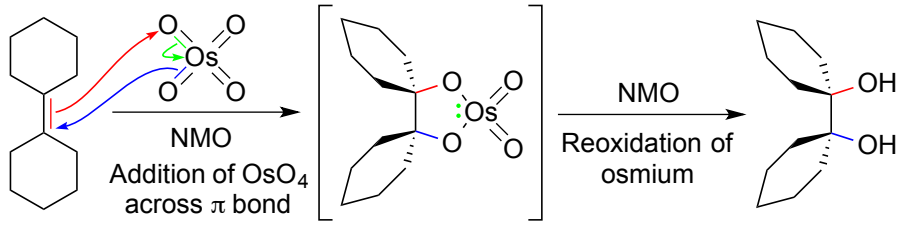


A second commonly employed oxidant is potassium permanganate, which adds across the alkene π bond much like osmium tetraoxide does. The cyclic manganate ester that results is cleaved in aqueous base. This reaction is typically conducted at low temperatures, so you will sometimes see the designation "cold" above or below the reaction arrow. At higher temperatures the central carbon-carbon bond may be cleaved.

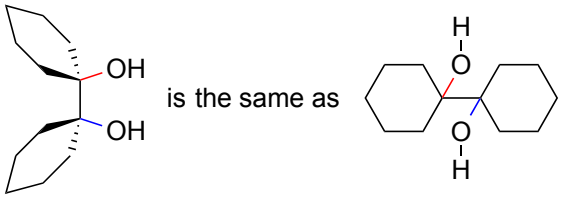


A specific example of syn-dihydroxylation

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is not an issue in syn-dihydroxylation because the same group is added to each alkene carbon.



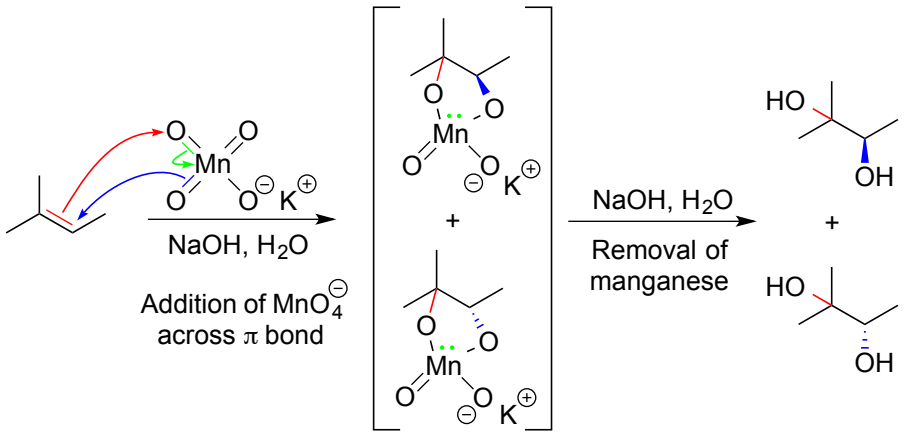
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



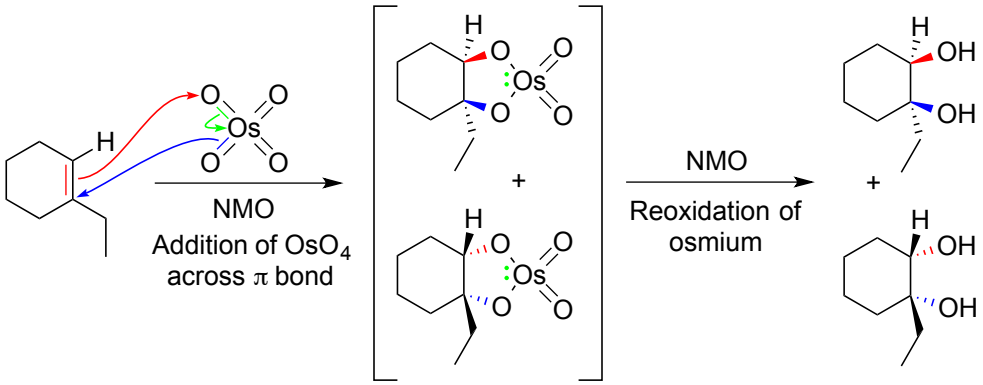
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

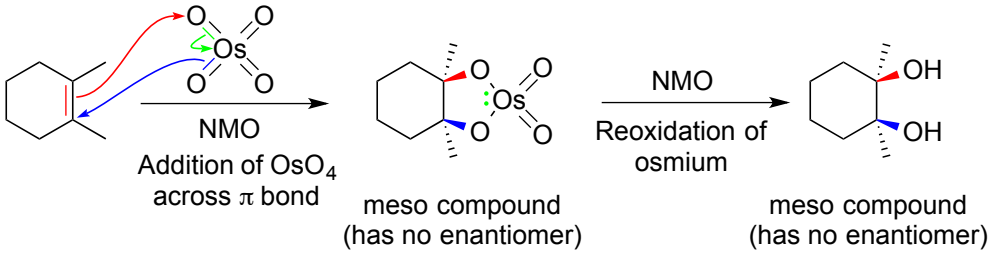
In the example below, a single stereocenter is formed. The alkene is flat (both alkene carbons are trigonal planar), so addition of permanganate can occur from either side to give two enantiomeric intermediates. Only one of the cyclic manganate ester carbons is a stereocenter. This is emphasized by drawing only that center with wedges and dashes. Upon cleavage of the manganese from the intermediate, enantiomeric vicinal diol products are formed.



In the next example, two stereocenters are created. Since this is a syn addition, *only two of the four possible stereoisomers are formed*. The vicinal diol products are the syn enantiomers.



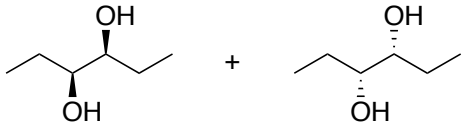
While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where the same group is added to each carbon of a π bond. The following example is extremely similar to the previous one; however, syn dihydroxylation of this alkene yields a meso product. Since meso compounds are overall achiral, this is the sole vicinal diol product of the reaction (i.e., it has no enantiomer).



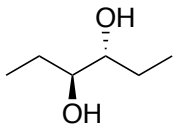
In conclusion, the syn-dihydroxylation of an alkene is accomplished by treatment with OsO_4 or $KMnO_4$. The cyclic intermediates formed in each case are cleaved in different ways, but the hydroxyl groups in the vicinal diol product are always syn to one another. There are no carbocation intermediates, so no rearrangement is observed.

Problem 31. Devise a method for the synthesis of the following diols beginning with an alkene and using syn-dihydroxylation in each case.

(a)

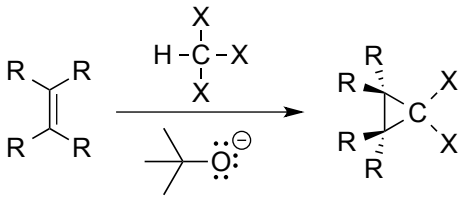


(b)

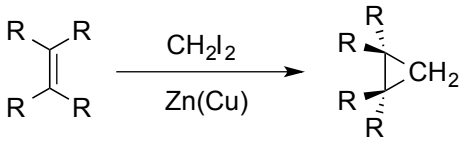


Section 15: Cyclopropanation

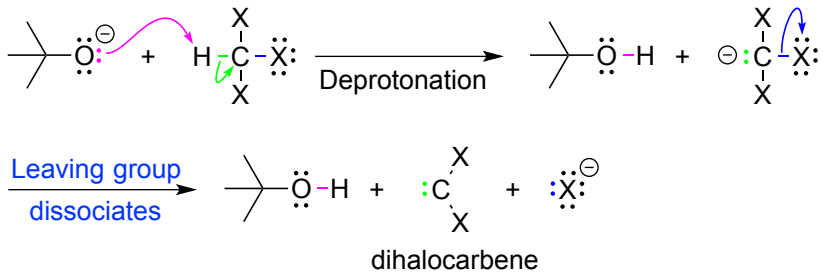
When a cyclopropane ring is formed from an alkene, the process can be called cyclopropanation. One common way to achieve this transformation employs a haloform (CHX_3), commonly chloroform ($CHCl_3$) or bromoform ($CHBr_3$), along with a fairly strong base, such as *tert*-butoxide. The product of this approach is a dihalocyclopropane.



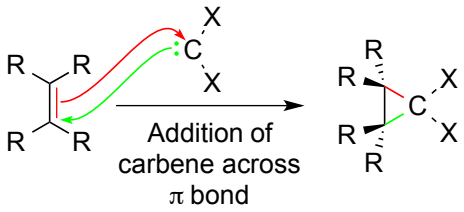
An alternate strategy for the formation of cyclopropane rings is called the Simmons-Smith reaction, in which an alkene is treated with diiodomethane and a zinc-copper couple.



In the first method, the base removes a proton from the haloform. The resulting carbanion is stabilized to some extent by the inductive electron withdrawal of the electronegative halogens. The subsequent dissociation of a halide yields a dihalocarbene. This process can be termed α elimination because a proton is lost from the same carbon from which the leaving group dissociates (in contrast to β elimination—E1 or E2 reaction—in which the proton is removed from a carbon adjacent to that which loses the leaving group).

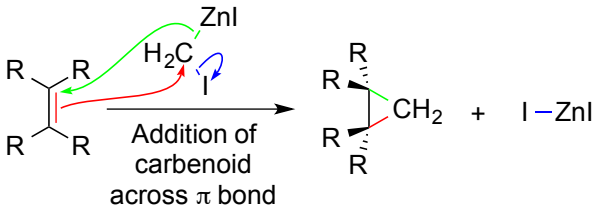


The carbene is electron deficient because it has only six electrons around it, as opposed to the desired octet. This incites the attack of the π bond. As a new C–C bond begins to form, the carbene carbon develops a δ^-, enabling it to attack the alkene carbon that is losing a bond. Since both new carbon-carbon bonds of the dihalocyclopropane are formed simultaneously, the addition is syn.



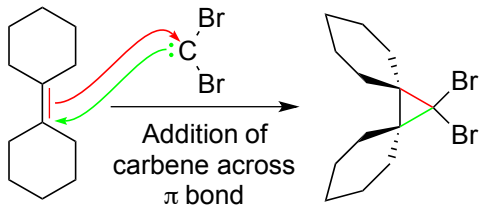
In the Simmons-Smith reaction, zinc donated from the zinc-copper couple inserts into a carbon-iodine bond of diiodomethane. This Simmons-Smith reagent (ICH_2ZnI) is called a carbenoid because it behaves like a carbene but does not formally contain the divalent

carbon with a lone pair that is the hallmark of a true carbene. The π bond attacks the carbenoid carbon and displaces iodide. Simultaneously, the electrons from the C–Zn bond attack the carbon of the alkene that is losing a bond. The products are a cyclopropane and zinc iodide (ZnI_2).

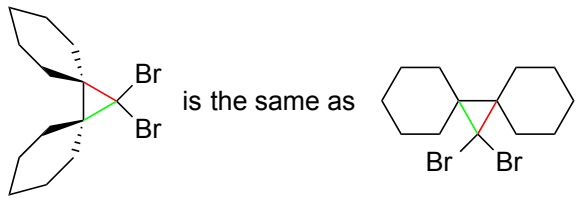


A specific example of cyclopropanation

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is not an issue in cyclopropanation because the same group is added to each alkene carbon.



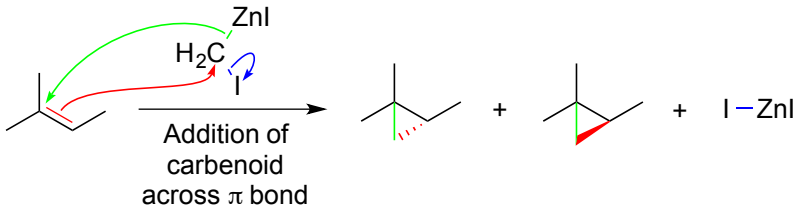
Note that no stereocenters are formed in this particular reaction, so wedges and dashes need not be used in drawing the product.



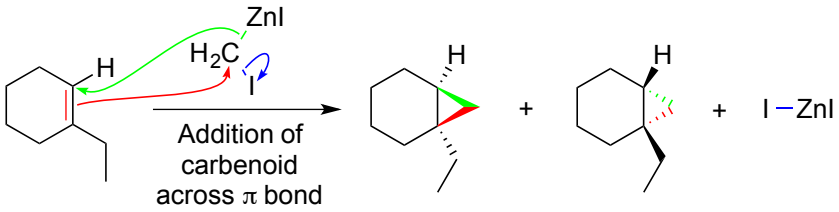
Stereochemical considerations

Since two carbons of the reactant are involved in this transformation, it is possible that 0, 1, or 2 stereocenters can be formed during the reaction.

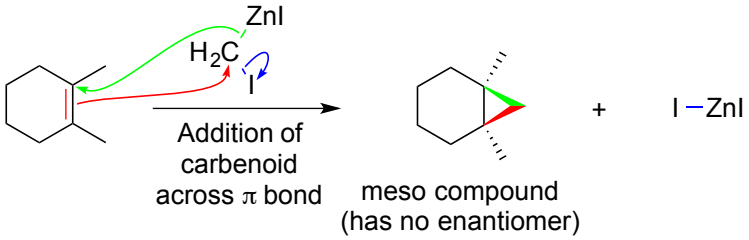
In the example below, a single stereocenter is created. The alkene is flat (both alkene carbons are trigonal planar), so addition of the carbenoid can occur from either side to give two enantiomeric cyclopropanes. Only one of the cyclopropane carbons is a stereocenter. This is emphasized by drawing only that center with wedges and dashes.



In the next example, two stereocenters are produced. Since this is a syn addition, *only two of the four possible stereoisomers are formed*. The cyclopropane products are the syn enantiomers.



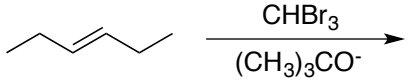
While it is always important to be on the lookout for internal symmetry, it is especially important in reactions where the same group is added to each carbon of an alkene π bond. The following example is extremely similar to the previous one; however, cyclopropanation of this alkene yields a meso product. Since meso compounds are overall achiral, this is the sole cyclopropane product of the reaction (i.e., it has no enantiomer).



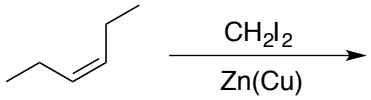
To summarize, the cyclopropanation of an alkene is accomplished by treatment with a haloform and base or through use of the Simmons-Smith reagent (ICH_2ZnI). The addition of the carbene or carbenoid, respectively, is syn. There are no carbocation intermediates, so no rearrangement is observed.

Problem 32. Predict the product(s) of the following cyclopropanation reactions.

(a)

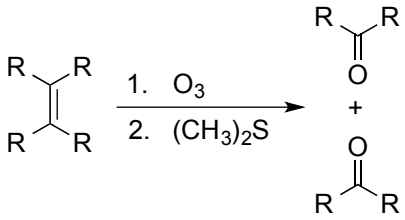


(b)



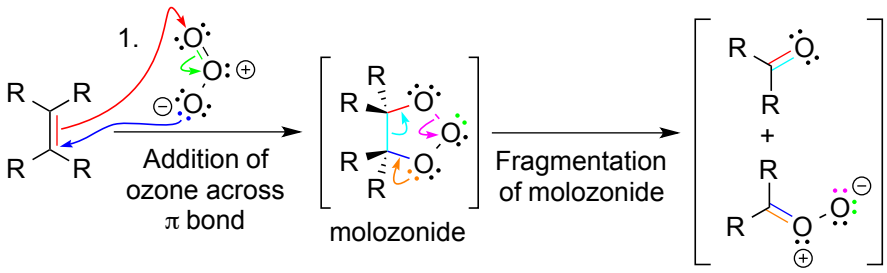
Section 16: Ozonolysis

Ozonolysis involves the use of ozone (O_3) to cleave both carbon-carbon bonds (π and σ) of an alkene. The reaction has two steps: treatment with ozone followed by a reductive workup. The products are carbonyl-containing compounds (ketones or aldehydes).

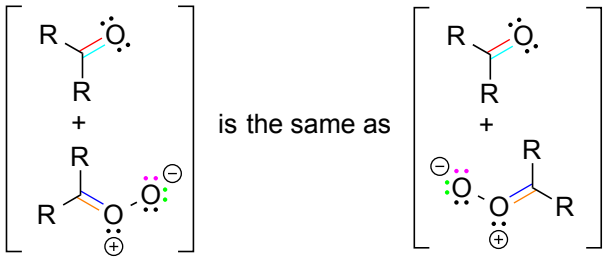


In the first step of ozonolysis, ozone initially adds across alkene π bond. This addition is described using three mechanistic arrows: (1) the alkene π bond attacks a terminal oxygen of ozone; (2) the oxygen-oxygen π bond is pushed onto the central oxygen of ozone, thereby neutralizing its charge; and (3) the anionic oxygen of ozone attacks the carbon of the alkene that is losing a bond. This results in the formation of an intermediate known as a molozonide.

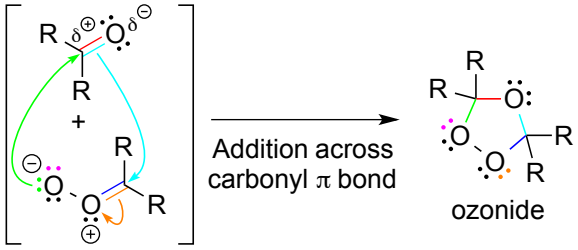
The molozonide contains not just one, but two weak oxygen-oxygen bonds, so it quickly fragments. The carbon-carbon σ bond of what was once the alkene breaks and forms a carbon-oxygen π bond. This displaces the central oxygen of the molozonide as an anion. The last oxygen of the molozonide donates a lone pair of electrons to form a π bond with the carbon that is losing a bond, thereby maintaining its octet.



The fragment bearing two formal charges is unstable, so these two molecules recombine rapidly. To see this recombination clearly, it is helpful to first flip one of the fragments.

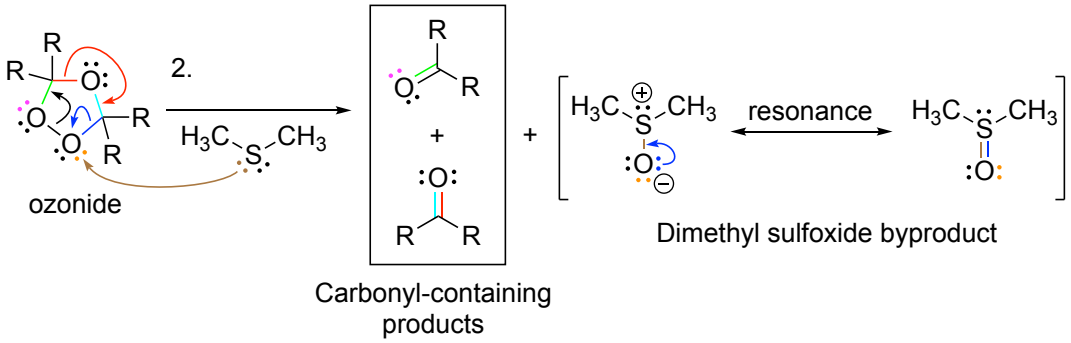


Now, the fragments are aligned so that the negative oxygen is near the δ+ carbonyl carbon of the ketone. Attack of this oxygen anion yields a new C–O bond. The ketone π bond then attacks the other carbonyl carbon, producing a second new C–O bond. Finally, the last remaining carbon-oxygen π bond is displaced onto the oxonium ion and eliminates its charge. This affords the product of step 1, known as an ozonide.



The ozonide can then be subjected to a reductive workup to yield carbonyl-containing (ketone or aldehyde) products. Dimethyl sulfide [$(CH_3)_2S$] is commonly used for this step, although other reagents such as zinc can be used instead.

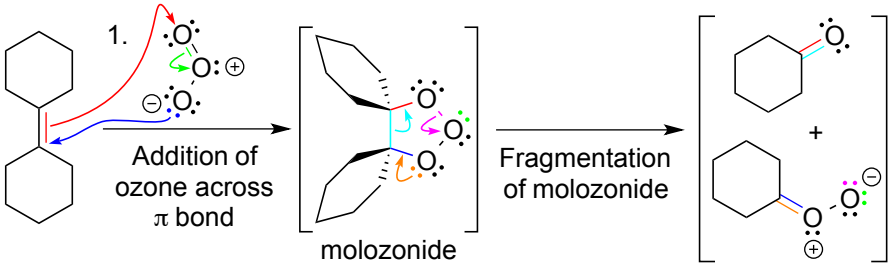
Mechanistic arrows are often not drawn for this step. However, to understand the process, you could envision the flow of electrons as follows. Dimethyl sulfide attacks one of the two oxygens participating in the weak O–O bond. That bond breaks forming a carbon-oxygen π bond (black arrow). The formation of that new π bond causes the cleavage of a C–O σ bond. The electrons from that σ bond become the other carbon-oxygen π bond. Finally, the oxygen that was originally attacked by dimethyl sulfide is cleaved from the rest of the molecule entirely as one more C–O σ bond breaks. The products include two carbonyl-containing molecules and dimethyl sulfide as a byproduct.



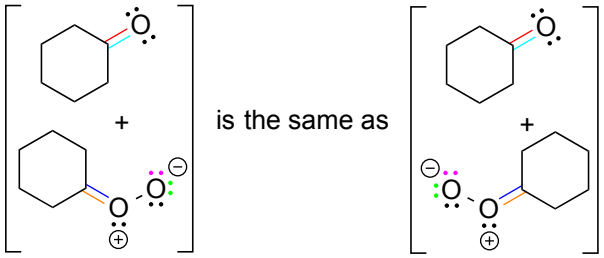
A specific example of ozonolysis

In the following example, a symmetrical alkene reactant is used. However, even when the alkene is unsymmetrical, regiochemistry is not an issue in ozonolysis since both alkene carbons are transformed into carbonyl carbons.

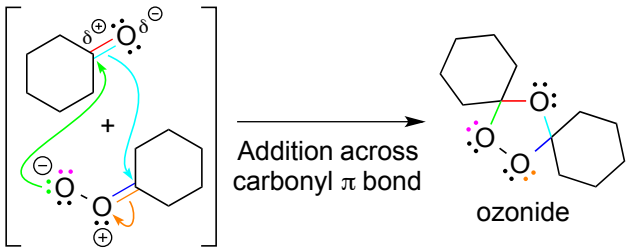
The initial addition of ozone across the alkene yields a molozonide that quickly fragments.



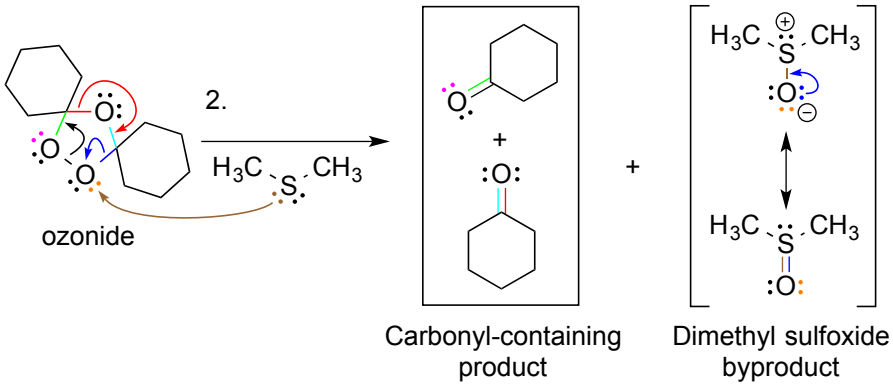
Again, it is helpful to flip one fragment so as to align the two molecules with complementary electronics.



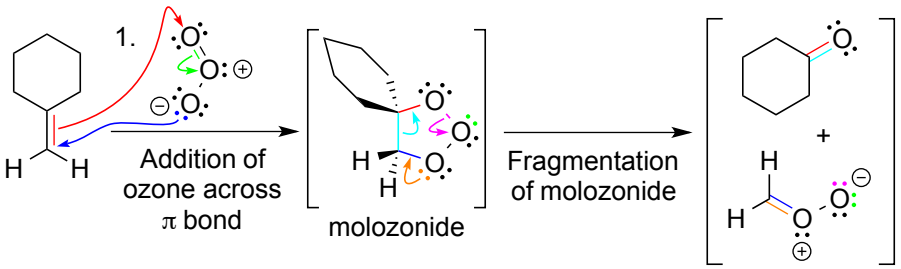
The recombination of these fragments provides the ozonide.



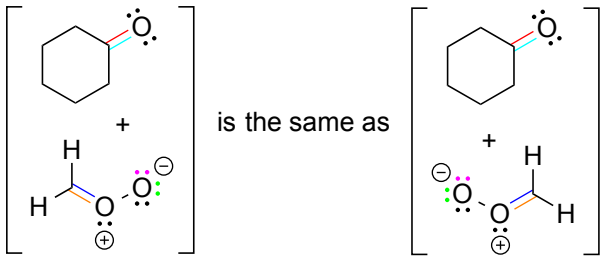
In step 2, the ozonide is cleaved by treatment with dimethyl sulfide. When the alkene is symmetrical, two molecules of the exact same carbonyl-containing product are formed. In this case, the reaction products are two molecules of cyclohexanone and the dimethyl sulfoxide byproduct.



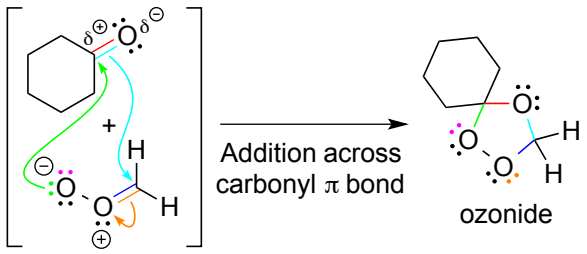
When the substrate in an ozonolysis reaction is an unsymmetrical alkene, the products will be two different carbonyl-containing molecules. In the following example, the unsymmetrical alkene affords an unsymmetrical molozonide, which fragments as expected.



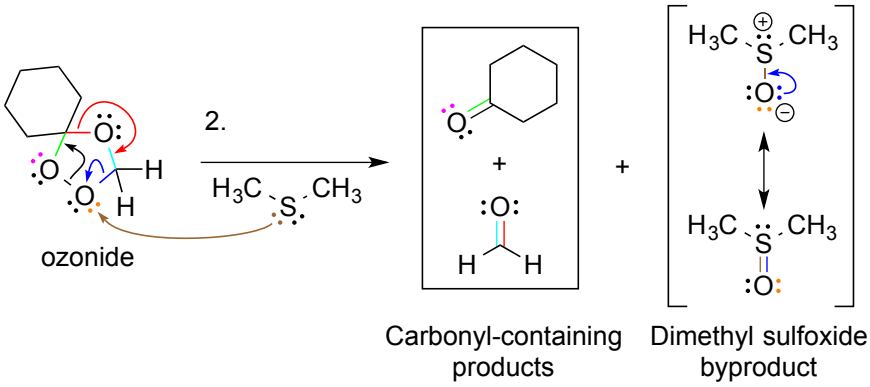
Again, we flip one fragment to better see the imminent recombination.



As the fragments recombine, an unsymmetrical ozonide is produced.



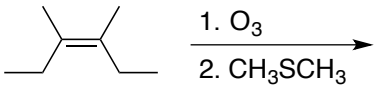
During the reductive workup, the unsymmetrical ozonide is degraded into two unique carbonyl-containing products: cyclohexanone and formaldehyde.



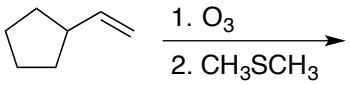
To conclude, ozonolysis cleaves both carbon-carbon bonds of an alkene (π and σ) and yields carbonyl-containing products (ketones and/or aldehydes) upon reductive workup with dimethyl sulfide or zinc. Regiochemistry is not an issue since both alkene carbons are converted into carbonyl carbons. Stereochemistry is also not a concern since the sp^2-hybridized alkene carbons become sp^2-hybridized carbonyl carbons. These trigonal planar centers cannot be stereocenters. There are no carbocation intermediates, so carbocation rearrangement is not relevant.

Problem 33. Predict the product(s) of the following ozonolysis reactions.

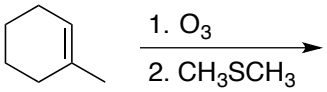
(a)



(b)



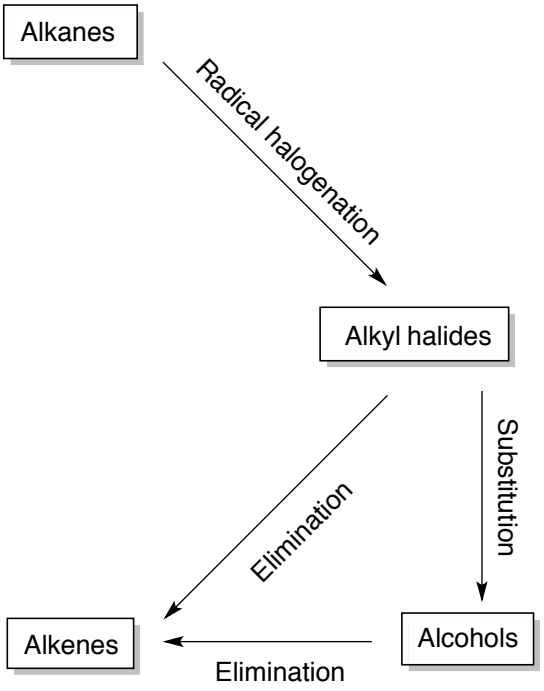
(c)



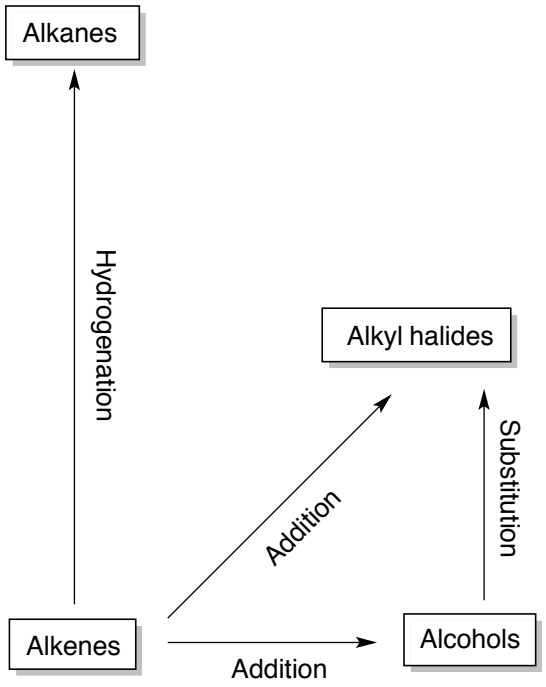
Section 17: Synthesis

Synthesis problems are challenging because they require, in some senses, the highest level of understand of all that you have learned. You must understand mechanism in order to rationally predict reaction products, and you must have a strong command of the reactions in order to orchestrate them into the synthesis of a desired molecule. We've previously discussed retrosynthetic analysis as a tool for approaching synthesis in a stepwise fashion.

However, as you learn more and more reactions, it is also useful to map out some of the ways in which the various functional groups can be interconverted. For example, we've learned that the simplest molecules, alkanes, can be functionalized through radical halogenation, which yields alkyl halides. Alkyl halides can undergo substitution reactions to generate a wide variety of compounds, including alcohols. Alternatively, alkyl halides can undergo elimination to prepare alkenes. Elimination can also convert alcohols to alkenes, although the specific reaction is sometimes termed dehydration.



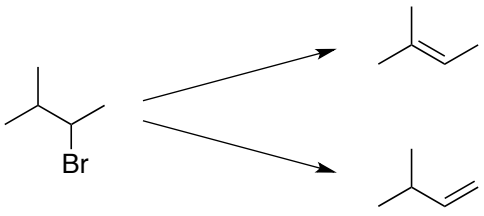
Some of these conversions can be performed in the opposite sense. For instance, alkenes can undergo addition reactions to prepare alkyl halides or alcohols. We learned about such reactions in this chapter. Both ionic and radical hydrohalogenation convert alkenes into alkyl halides. Alcohols are prepared from alkenes via acid-catalyzed hydration, oxymercuration-demercuration, or hydroboration-oxidation. Alkenes can also be reduced via hydrogenation to prepare alkanes.



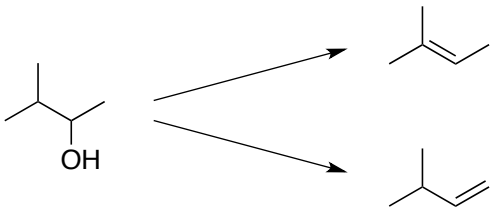
Having these options in mind will help you to navigate synthesis problems successfully.

Problem 34. Select the reagents needed to convert each of the following substrates into the alkenes indicated.

(a)

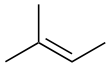
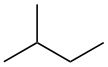


(b)

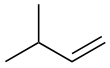
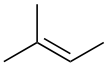


Problem 35. Complete the following syntheses.

(a)

Prepare  from 

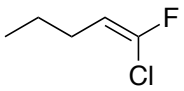
(b)

Prepare  from 

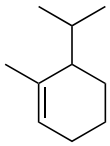
End-of-the-Chapter problems

Problem 36. Name the following alkenes.

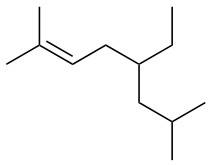
(a)



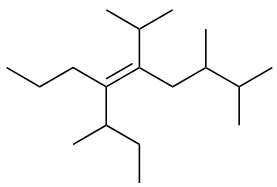
(b)



(c)

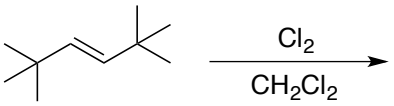


(d)

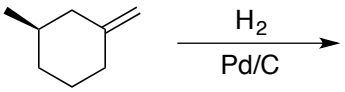


Problem 37. Predict the products of the following reactions.

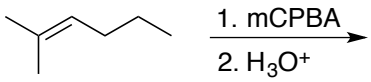
(a)


Cl_2
CH_2Cl_2

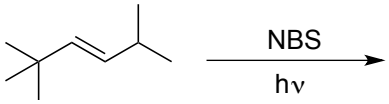
(b)


H_2
Pd/C

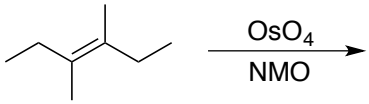
(c)


1. mCPBA
2. H_3O^+

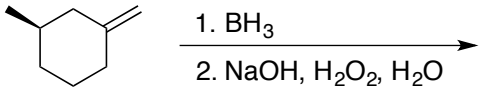
(d)


NBS
hν

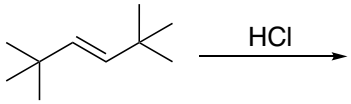
(e)


OsO_4
NMO

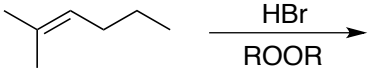
(f)


1. BH_3
2. NaOH, H_2O_2, H_2O

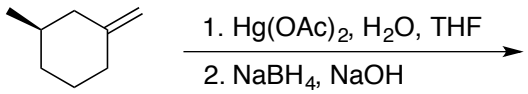
(g)


HCl

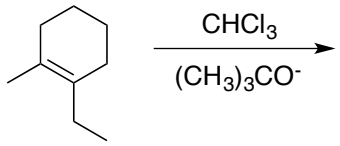
(h)


HBr
ROOR

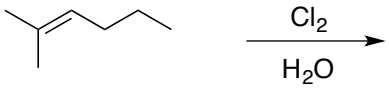
(i)



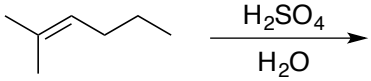
(j)



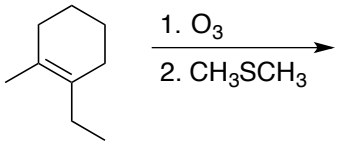
(k)



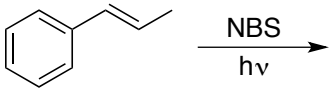
(l)



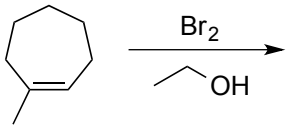
(m)



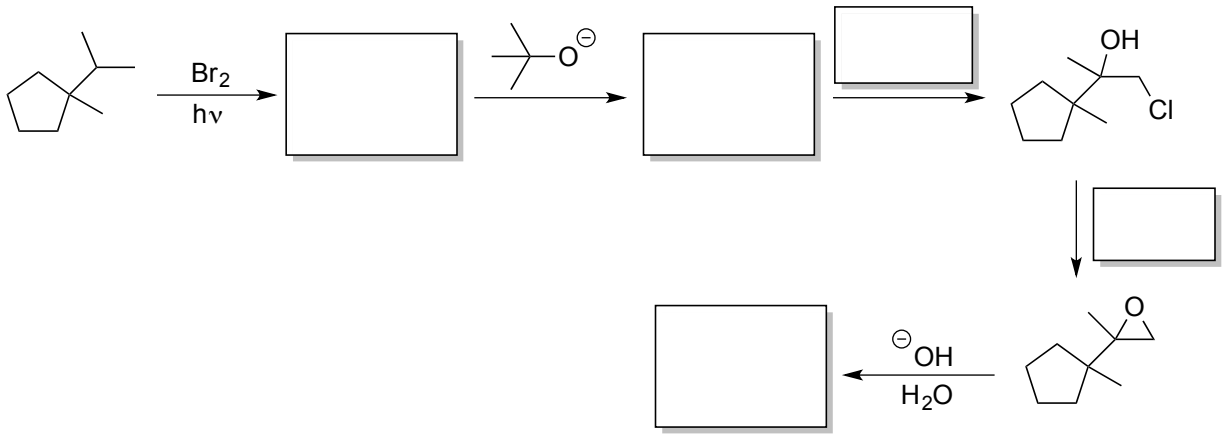
Problem 38. Predict the products of the following transformation, and provide a mechanism to explain their formation.



Problem 39. As noted in the section on halohydrin formation, an alcohol can be used in place of water to give an analogous reaction. Provide the products of the following reaction, as well as a mechanism to explain their formation.

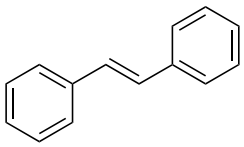


Problem 40. Fill in the missing intermediates and reagents in the following scheme.

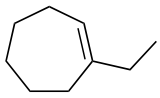


Problem 41. Which of the following substrates would produce different products upon acid-catalyzed hydration, oxymercuration-demercuration, or hydroboration-oxidation? When different products are formed by one or more of these reactions, show their structures.

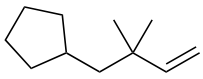
(a)



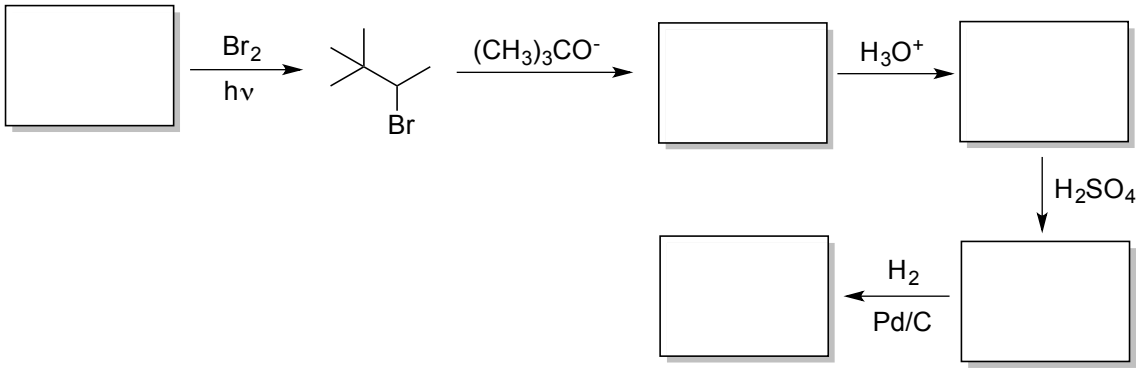
(b)



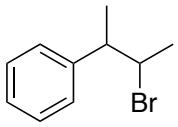
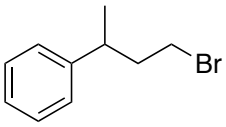
(c)



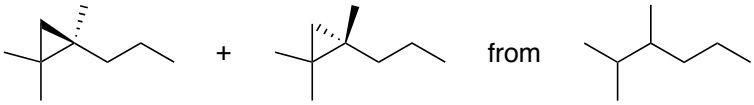
Problem 42. The following sequence begins and ends with an alkane, but not the same alkane. Explain why the substrate and final product differ.



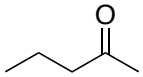
Problem 43. Provide the reagents and synthetic intermediates needed for the following conversion.

Convert  to 

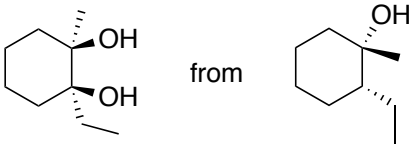
Problem 44. Provide reagents and synthetic intermediates to accomplish the following.

Prepare 

Problem 45. Provide a synthesis of the following ketone from 2-methylpentane.

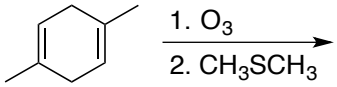


Problem 46. Provide a method to accomplish the following synthesis.

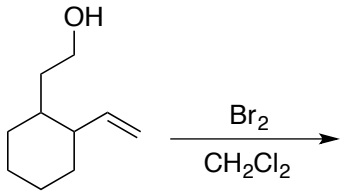
Prepare 

(and its enantiomer)

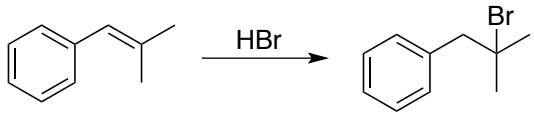
Problem 47. The following ozonolysis affords a single product containing two signals just above 1700 cm^{-1} in the IR spectrum. What is the structure of the product?



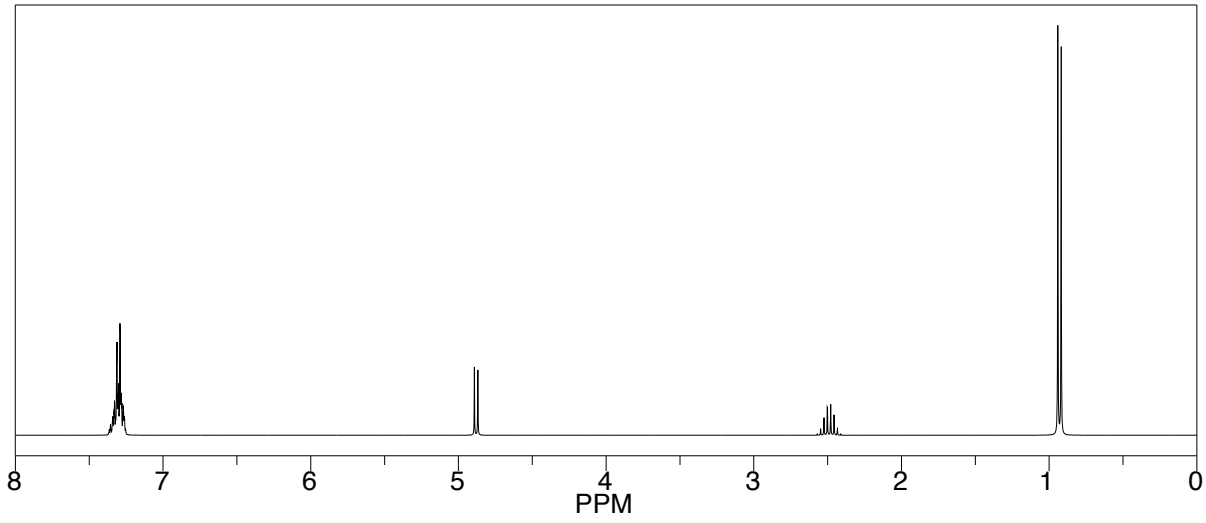
Problem 48. The following bromination reaction was expected to provide a vicinal dibromide. The mass spectrum of a compound containing two bromine atoms would exhibit M, M+2, and M+4 peaks due to molecules containing two ^{79}Br, one ^{79}Br and one ^{81}Br, or two ^{81}Br, respectively. However, the mass spectrum of the reaction product only shows M and M+2 peaks. Explain this outcome.



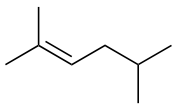
Problem 49. An investigator performed the following ionic hydrohalogenation, expecting to prepare the product shown.



A proton NMR spectrum was obtained for the product, but it did not contain the expected singlet for 6 hydrogens, singlet for 2 hydrogens, and multiplet for 5Hs. Instead, it contained the peaks shown below. What happened in this reaction and why?



Problem 50. The following alkene exhibits six signals in its ^{1}H NMR spectrum, but its hydrogenation product (obtained upon treatment with H_2 and Pd/C) shows only three. How can this be?



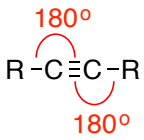
Chapter 11: Alkynes

Section 1: Nomenclature
Section 2: Preparation of alkynes
Section 3: Introduction to reactions of alkynes
Section 4: Ionic and radical hydrohalogenation
Section 5: Hydration
Section 6: Reduction
Section 7: Halogenation
Section 8: Ozonolysis
Section 9: Alkylation
Section 10: Synthesis

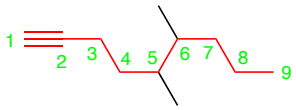
Section 1: Nomenclature

IUPAC nomenclature

Alkynes contain a carbon-carbon triple bond. The rules for systematically naming alkynes are much like those for alkenes, only simpler because there is no need for stereochemical designations. Alkynes are linear due to the two sp hybridized carbons, which have 180° bond angles. This fact negates *cis*/*trans* and *E*/*Z* isomerism.



The parent is the longest continuous carbon chain containing both alkyne carbons. The "ane" suffix of the corresponding alkane is removed and replaced with "yne" to signify the presence of an alkyne. Then the parent is numbered so as to give the alkyne carbons the lowest possible numbers, and a single number (or locant) is used to indicate where the triple bond begins. Substituents are named according to the guidelines that we've already established.

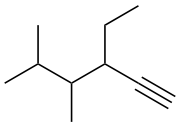


5,6-dimethyl-1-nonyne

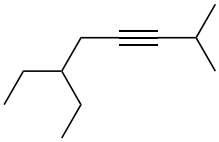
- Nine carbon parent = nonane
- Replace "ane" suffix with "yne"
- Provide a number for the site where the triple bond begins
- Add substituent names and numbers

Problem 1. Name the following alkynes.

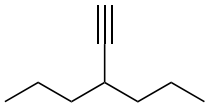
(a)



(b)



(c)



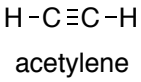
Problem 2. Draw the structures of the following alkynes.

(a) 8-bromo-7-ethyl-4-isopropyl-2-methyl-5-decyne

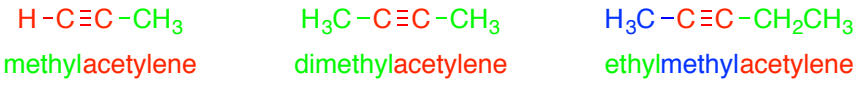
(b) 4-chloro-5-ethyl-3-fluoro-6,7-dimethyl-1-octyne

Common nomenclature

The simplest alkyne is ethyne, which is usually referred to by its common name: acetylene.

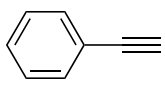


Simple alkynes can be named as acetylene derivatives. The common name is constructed from the designations for the alkyl groups followed by the word “acetylene”.

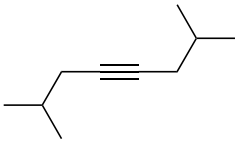


Problem 3. Provide a common name for each of the following alkynes.

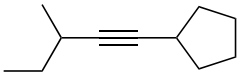
(a)



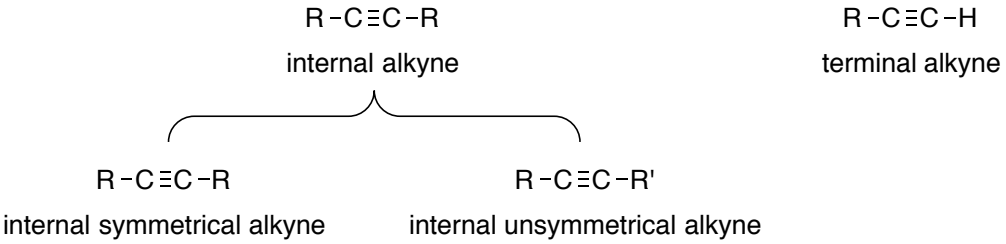
(b)



(c)



It is also worth noting that alkynes fall into two broad categories: internal and terminal. Internal alkynes have two R groups on the triple bond; whereas, terminal alkynes have only one R group on the triple bond. The internal alkynes can be further subdivided into those that are symmetrical and those that are unsymmetrical. These categorizations will be useful as we turn our attention to reactions.

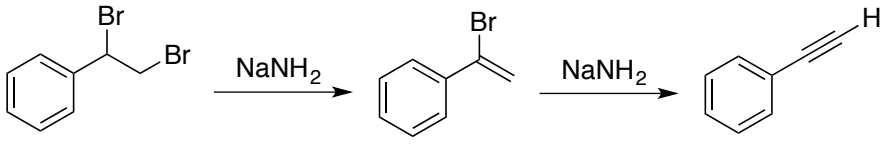


Finally, the smallest alkyne-containing group may be referred to as the ethynyl group.

ethynyl group

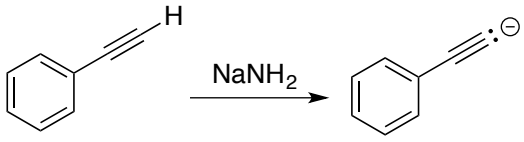
Section 2: Preparation of alkynes

Much as alkenes are prepared through elimination, alkynes can be prepared through double elimination. A single elimination forms a pi bond, so two successive eliminations can form the two pi bonds of an alkyne. The dihalide substrate can be vicinal or geminal, meaning that the two halogens can reside on adjacent carbons or the same carbon, respectively. The mechanism for elimination is just like you would expect for any other E2 reaction.



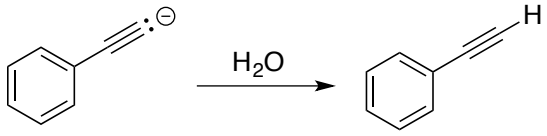
a vicinal dibromide

This method is most commonly used to prepare terminal alkynes because terminal alkynes have a reasonably acidic proton (pK_a ~25), which can be removed by the base to drive the reaction to completion. The conjugate base of an alkyne is known as an alkynide ion.

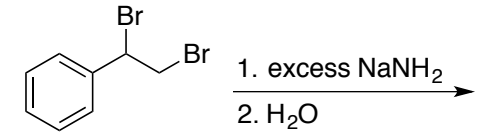


an alkynide ion

The alkynide ion is then quenched by water in the second step of the reaction.

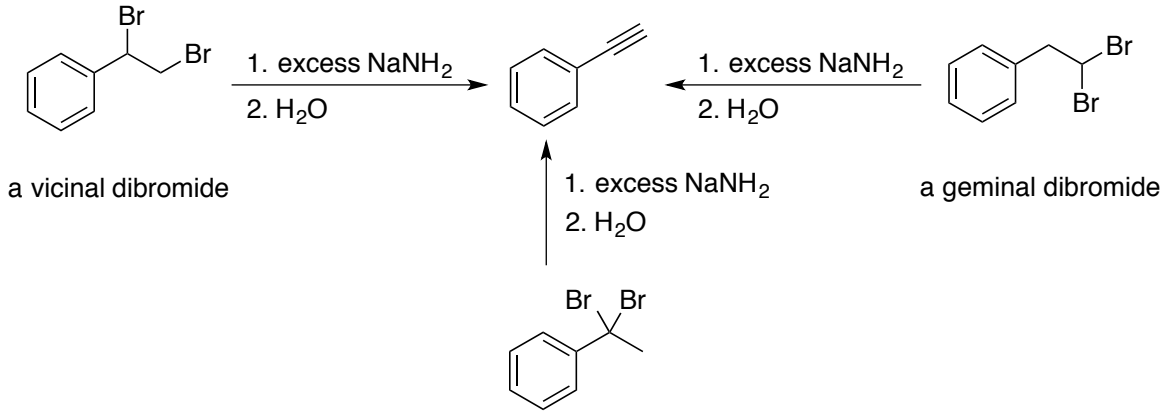


Problem 4. Draw a complete mechanism for the double elimination reaction that was just discussed. The reaction conditions are summarized below. Refer to the discussion above for the structures of the intermediates.



a vicinal dibromide

Sometimes more than one dihalide can be used to make the same alkyne. As shown below, a vicinal dibromide and two geminal dibromides can all converge on the same alkyne product when they are treated with excess sodamide followed by water.



a vicinal dibromide

a geminal dibromide

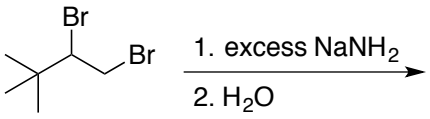
a geminal dibromide

When the method is used to make internal alkynes, isomerization is often possible. The initially formed alkyne can be isomerized to a terminal one through a series of deprotonation and reprotonation events. Deprotonation of the terminal alkyne ultimately drives the equilibrium. Problem 29 will give us some experience with this phenomenon.

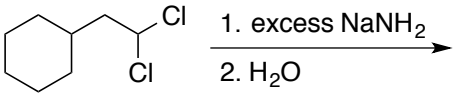
While sodamide is frequently used as the base for double elimination reactions, it is not the only suitable base. For instance, *tert*-butoxide can sometimes be used instead [Problem 5(c)].

Problem 5. Predict the product of the following reactions.

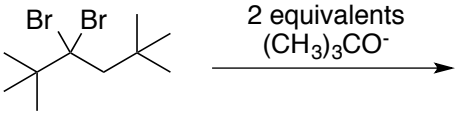
(a)



(b)

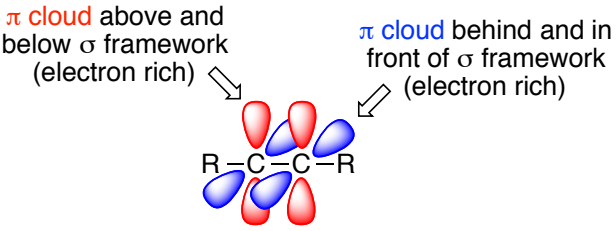


(c)



Section 3: Introduction to reactions of alkynes

Alkynes undergo electrophilic addition reactions, much like alkenes. They do so because the σ bond of the alkyne is surrounded by the π clouds of two π bonds. Since this functional group is electron rich, it is attracted to electrophilic reagents.



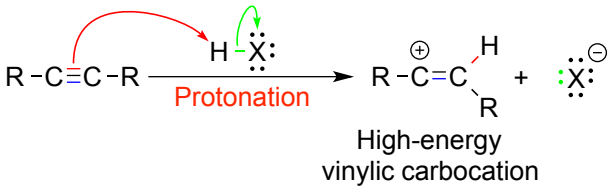
Section 4: Ionic and radical hydrohalogenation

Recall from the previous chapter that hydrohalogenation is the addition of HX across a π bond. The reaction can involve ionic or radical intermediates. These reactions of alkynes are very similar to the hydrohalogenation reactions of alkenes.

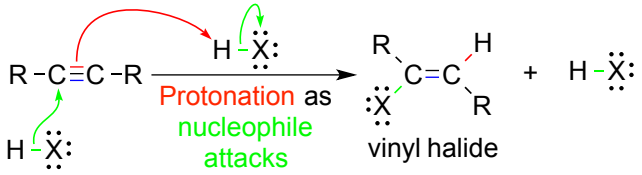
The regioselectivity (Markovnikov or anti-Markovnikov) depends on the conditions used. When HX (HCl, HBr, or HI) is the sole reagent, the reaction proceeds with Markovnikov regioselectivity. When peroxides (ROOR) are added along with HBr, the regiochemistry is reversed, and anti-Markovnikov selectivity is observed.

Since alkynes possess two π bonds, they can undergo the addition of up to two molecules of HX.

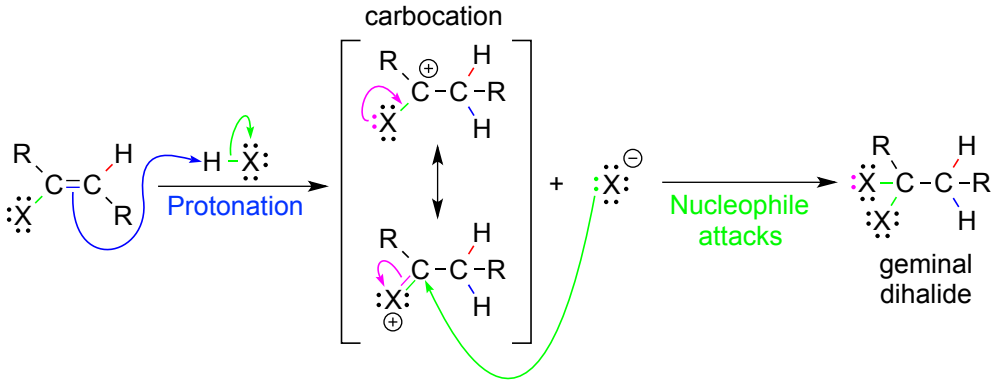
Let's begin with ionic hydrohalogenation of an alkyne. If this mechanism were to begin with a simple protonation of the alkyne π bond, the intermediate would be a vinylic carbocation. However, vinylic carbocations are fairly unstable, so this intermediate is unlikely.



Instead, the carbon of the alkyne that is losing a bond is attacked by a halide from a second molecule of HX at the same time that it is protonated. The net result is still the addition of one molecule of HX across the π bond; however, the high-energy vinylic carbocation was bypassed. The reaction stops with this vinyl halide product if one molar equivalent of HX is used.



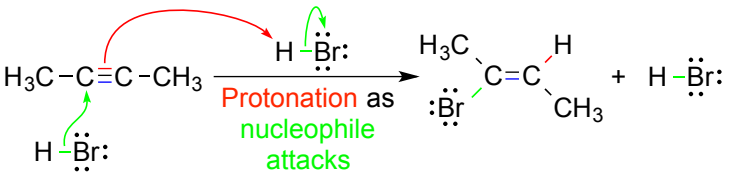
However, if two molar equivalents of HX are used, the remaining π bond can undergo the addition of another molecule of HX. This addition proceeds through protonation of the alkene to yield a carbocation adjacent to the halogen. The reason is that this particular carbocation is resonance stabilized. The subsequent attack of the halide on the carbocation generates a geminal dihalide as the final product.



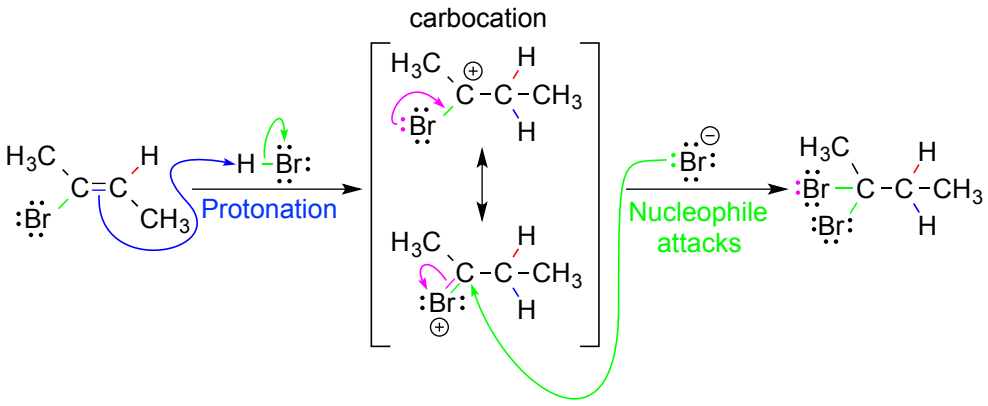
The mechanisms for radical hydrohalogenation of alkenes and alkynes are essentially identical, so you can refer to the corresponding section in the previous chapter to review that mechanism.

Specific examples of hydrohalogenation

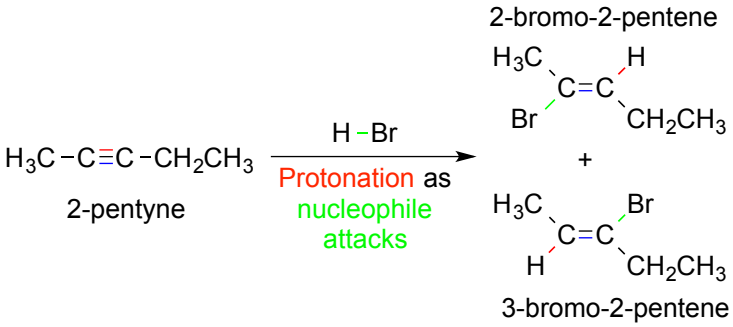
In the following example, the alkyne is symmetrical, so regiochemistry is not an issue during the first addition of HX. Only one regioisomer can be produced due to the molecule's symmetry.



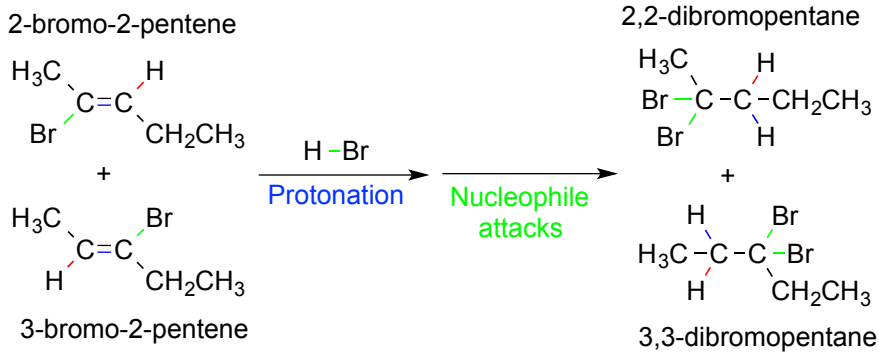
If the vinyl halide generated above is treated with a second equivalent of HBr, only one product will be formed. The vinyl halide is protonated so as to yield the only resonance-stabilized carbocation possible. Attack of bromide on that carbocation affords the geminal dibromide product.



When internal unsymmetrical alkynes are used as substrates, mixtures of products are formed. For instance, in the following example 2-pentyne is the reactant. HBr can add across the π bond of this alkyne in two ways to yield the regioisomeric vinyl halides 2-bromo-2-pentene and 3-bromo-2-pentene. There is no basis for selectivity since both alkyne carbons have the same level of substitution.



If these regioisomeric vinyl halides are treated with a second equivalent of HBr, each will add another equivalent across its remaining π bond so as to form the corresponding geminal dihalide. These geminal dihalides (2,2-dibromopentane and 3,3-dibromopentane) are also regioisomers.



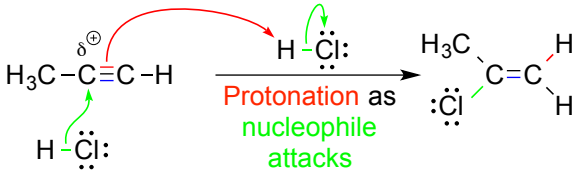
Problem 6. Predict the product of the following hydrohalogenation.

Regiochemical considerations

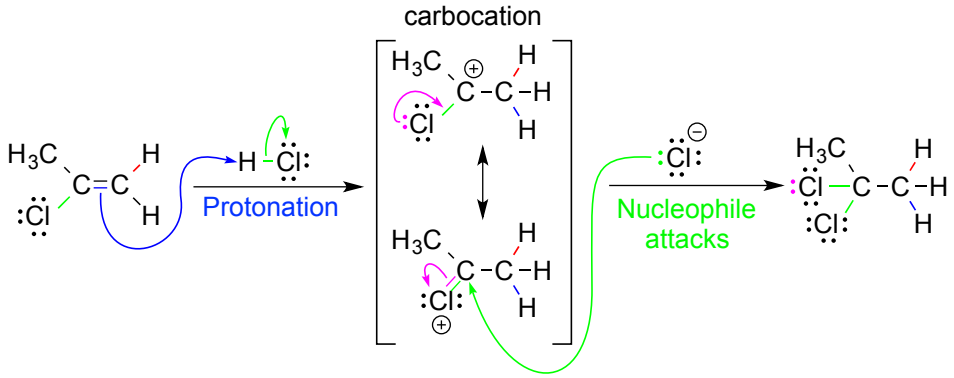
When a terminal alkyne is the substrate, addition of HX follows Markovnikov's rule (i.e., the alkyne carbon possessing more hydrogens acquires the new proton).

In the following example using propyne as the substrate, δ^+ charge can accumulate on a primary or secondary carbon. A δ^+ charge is more stable when it occurs on a more highly substituted carbon, so the primary center acquires the new proton, placing the δ^+ on the

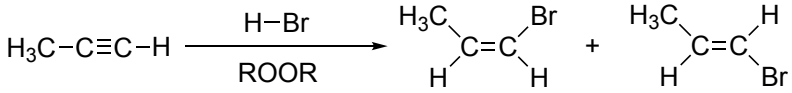
secondary carbon, which is attacked by chloride. This addition affords the Markovnikov vinyl chloride.



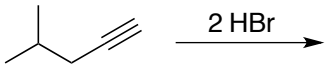
A second addition of HCl would proceed through the resonance-stabilized carbocation intermediate to yield the geminal dichloride product.



As expected, when the same terminal alkyne substrate is treated with HBr and peroxides, the regiochemistry is reversed, and an anti-Markovnikov vinyl bromide is obtained.



Problem 7. Predict the product for the following hydrohalogenation.

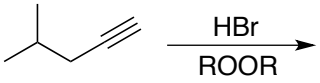


Stereochemical considerations

In ionic hydrohalogenation, the addition of the first equivalent of HX across an alkyne is typically anti. However, if a second equivalent of HX is added, stereochemistry becomes irrelevant since the reactive carbons each acquire two identical new substituents (two hydrogens or two halogens). They cannot be stereocenters as a result.

In radical hydrohalogenation, the addition of HBr across the alkyne often leads to mixtures of *E* and *Z* products.

Problem 8. Predict the product(s) of the following hydrohalogenation.



Carbocation rearrangement

No carbocation rearrangement occurs in ionic hydrohalogenation. The first addition of HX does not proceed through a carbocation intermediate, so no rearrangement is possible. The second addition of HX does proceed through a carbocation intermediate; however, it is resonance stabilized and therefore will not rearrange.

Of course, radical hydrohalogenation doesn't involve carbocation rearrangement either since there are no carbocation intermediates, only radicals.

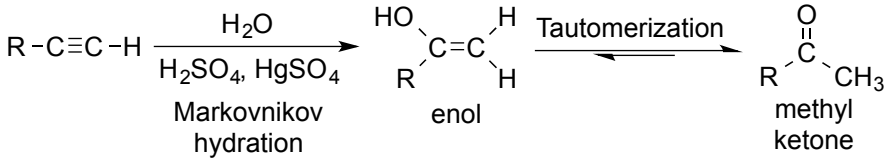
In summary, ionic hydrohalogenation adds HX across an alkyne π bond with Markovnikov regiochemistry to yield a vinyl halide. A second equivalent of HX can be added to afford a geminal dihalide. Stereochemistry is not an issue when two equivalents of HX are added, and carbocation rearrangement does not occur. Use of HBr and peroxides affords anti-Markovnikov selectivity instead.

Section 5: Hydration

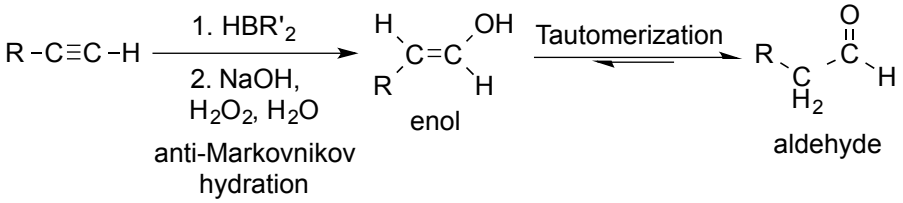
The hydration of alkynes parallels the hydration of alkenes in that there are ways to achieve both Markovnikov and anti-Markovnikov regioselectivity.

When internal alkynes are used as substrates there is no basis for selectivity because both alkyne carbons have the same level of substitution. Symmetrical internal alkynes will therefore yield a single product regardless of the method used, while an unsymmetrical internal alkyne will yield two regioisomeric products regardless of the method used.

However, when terminal alkynes are employed as substrates, the alkyne carbons have different levels of substitution, which provides a basis for selectivity. If the alkyne is treated with mercuric sulfate ($HgSO_4$) in the presence of water and sulfuric acid, Markovnikov hydration occurs and yields an enol (from alk<u>en</u>e and alcoh<u>ol</u>). This enol rapidly undergoes a process known as tautomerization to afford a methyl ketone as the final product.



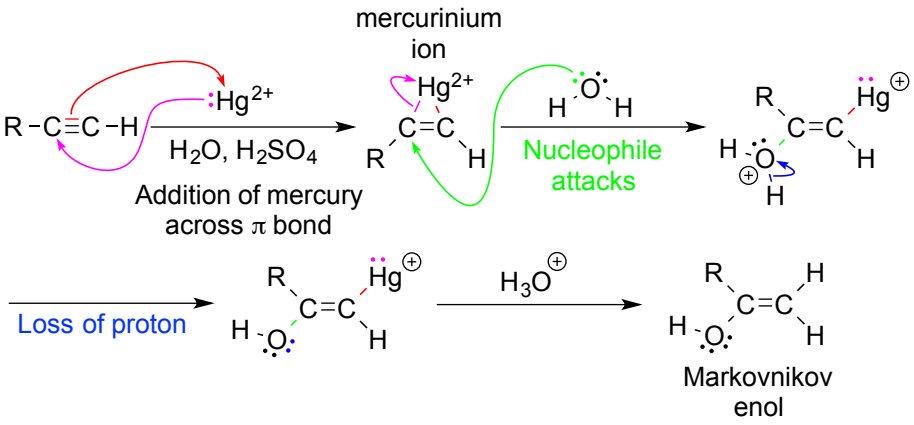
On the other hand, when the terminal alkyne is subjected to hydroboration-oxidation, anti-Markovnikov hydration generates the regioisomeric enol, which also tautomerizes. The final product in this case is an aldehyde.



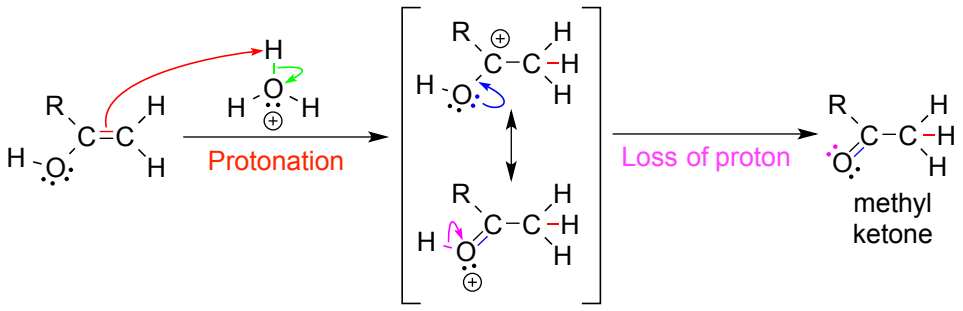
Mechanism for Markovnikov hydration

Markovnikov hydration employs mercuric sulfate ($HgSO_4$) as a source of the mercuric ion (Hg^{2+}). The electrophilic mercuric ion draws the weakly nucleophilic terminal alkyne into reaction. An alkyne π bond attacks the mercury(II) ion, which reciprocates by attacking the carbon of the alkyne that is losing a bond. The results in the formation of a mercurinium ion that is reminiscent of the one seen in the oxymercuration-demercuration of alkenes.

Water then attacks the interior carbon of the mercurinium ion, which bears a more significant δ^+ charge due to its greater substitution. This opens the mercurinium ion. A proton is then lost, and in aqueous acid the mercury ion is exchanged for a proton to yield the Markovnikov enol.

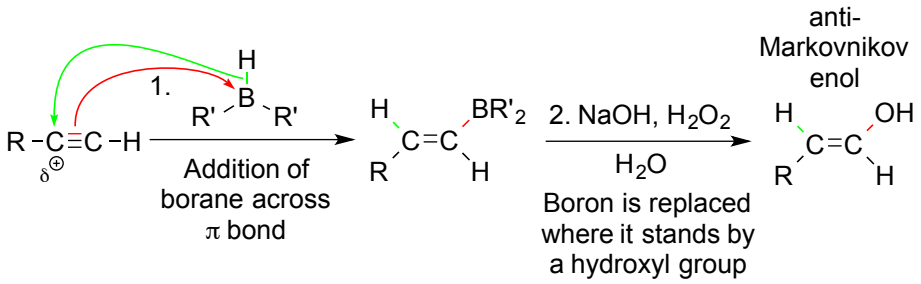


Tautomerization then occurs rapidly in this aqueous acid medium. Tautomerization is the interconversion of constitutional isomers by a reaction that occurs readily: in this case, the migration of a proton and a pi bond. The enol is protonated to make the only resonance-stabilized carbocation possible. The more stable resonance form, in which all atoms possess a complete octet of electrons, contains an oxonium ion. When the oxonium ion loses a proton, tautomerization has occurred, and the final product is a methyl ketone.

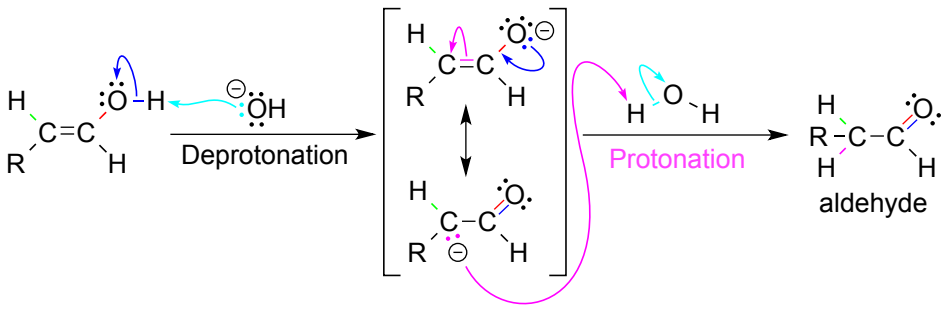


Mechanism for anti-Markovnikov hydration

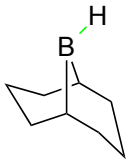
The alternative method for the anti-Markovnikov hydration of an alkyne is hydroboration-oxidation. This very closely mimics the hydroboration-oxidation of an alkene. In step one, a borane is added across an alkyne π bond. This is a concerted, syn addition. The regioselectivity is anti-Markovnikov because the electrophilic boron is added to the terminal alkyne carbon so as to place the developing δ^+ on the more stable secondary position. It is this center that draws in the electrons from the H–B bond. In step two, the boron is replaced where it stands by a hydroxyl group. The mechanism for this step is found in the hydroboration-oxidation section in the Alkenes chapter.



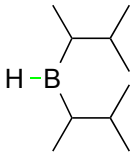
The enol formed in this reaction also rapidly tautomerizes, but this time the medium is aqueous base. Consequently, the mechanism for tautomerization must be different than it was in aqueous acid. In base, the enol is first deprotonated. The conjugate base of the enol is known as an enolate, and it is resonance stabilized. Protonation at the δ^- carbon yields the final reaction product: an aldehyde.



You may have noticed that an organoborane (HBR'_2) was used during the hydroboration step rather than borane (BH_3), which was used in hydroboration-oxidation of alkenes. The reason for the different reagent is the presence of multiple π bonds in the alkyne reactant. To ensure that there is only one addition across the alkyne, an organoborane (HBR'_2) with only a single H–B bond is used. Furthermore, the organoboranes are bulky, which discourages multiple additions. Two commonly used organoboranes are 9-BBN and disiamylborane. Because of their sizable structures, they are often written in the generic form (HBR'_2).



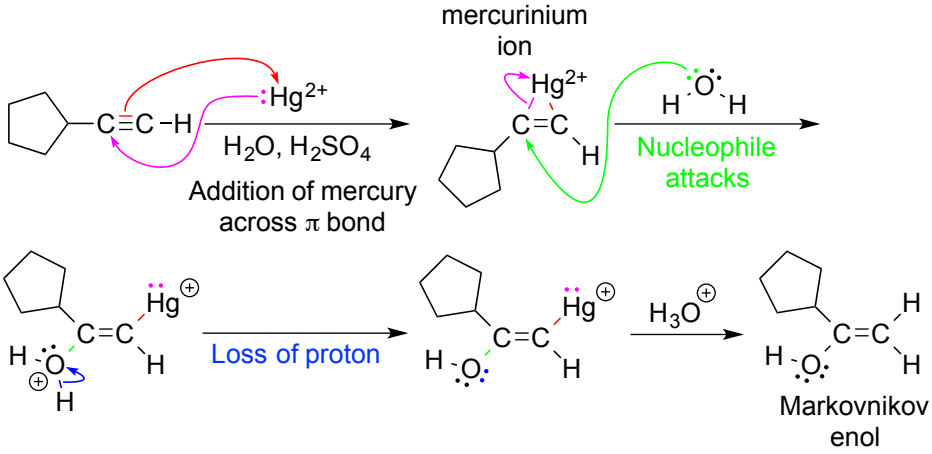
9-borabicyclo[3.3.1]nonane
(9-BBN)



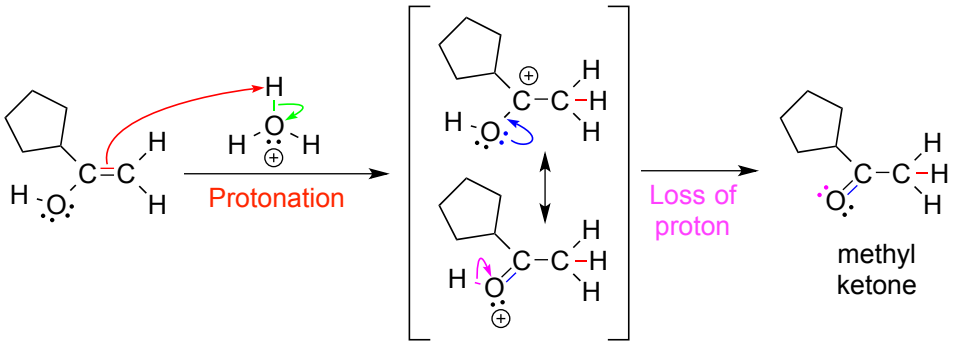
disiamylborane

Specific examples of alkyne hydration

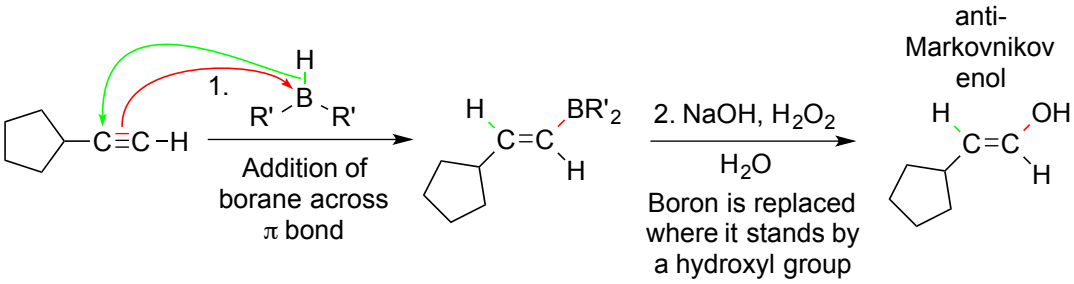
In the following example, cyclopentylacetylene is used as the substrate. This terminal alkyne forms a mercurinium ion upon treatment with mercuric sulfate, and the mercurinium ion is opened by the attack of water at the more δ+ secondary carbon. The end result is the Markovnikov enol.



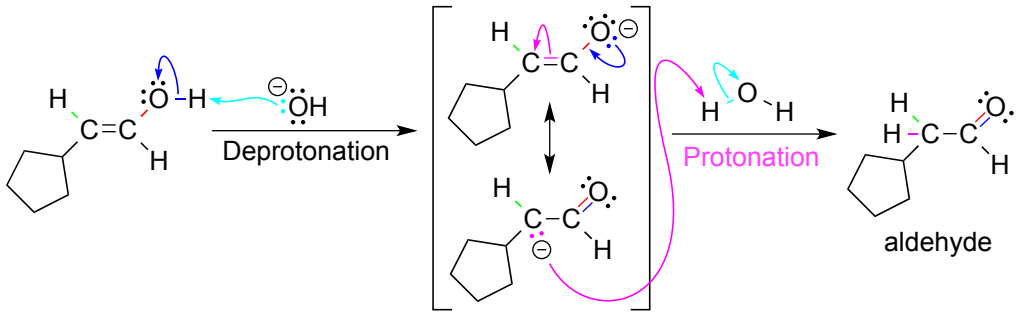
Tautomerization of this enol in aqueous acid yields a methyl ketone as the final reaction product.



The same substrate, cyclopentylacetylene, can be hydrated in an anti-Markovnikov fashion through hydroboration-oxidation.



The anti-Markovnikov enol tautomerizes in aqueous base to afford the final product as an aldehyde.



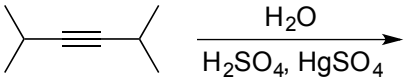
In conclusion, alkynes may be hydrated in multiple ways. Internal alkynes provide no basis for selectivity because both alkyne carbons have the same level of substitution. Therefore, internal symmetrical alkynes will yield a single ketone product regardless of the method used; whereas, internal unsymmetrical alkynes will yield regioisomeric ketone products regardless of the method used.

Terminal alkynes do provide a basis for selectivity because the alkyne carbons have different levels of substitution. Treatment with $HgSO_4$ and H_2SO_4 in water accomplishes Markovnikov hydration to yield an ephemeral enol that rapidly tautomerizes to a methyl ketone product. On the other hand, hydroboration-oxidation achieves anti-Markovnikov hydration. Again, tautomerization is immediate, and the final product is an aldehyde.

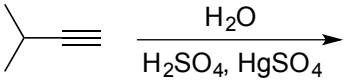
No new stereocenters are formed during these reactions, and neither reaction is subject to carbocation rearrangement.

Problem 9. Predict the products of the following hydration reactions.

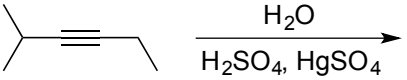
(a)



(b)

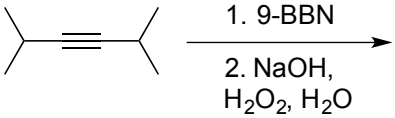


(c)

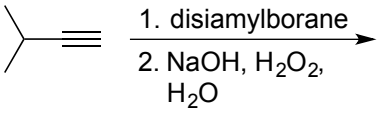


Problem 10. Predict the products of the following hydration reactions.

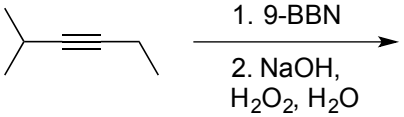
(a)



(b)

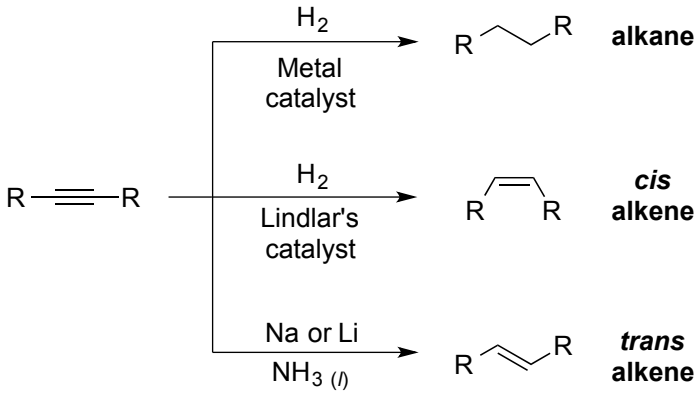


(c)



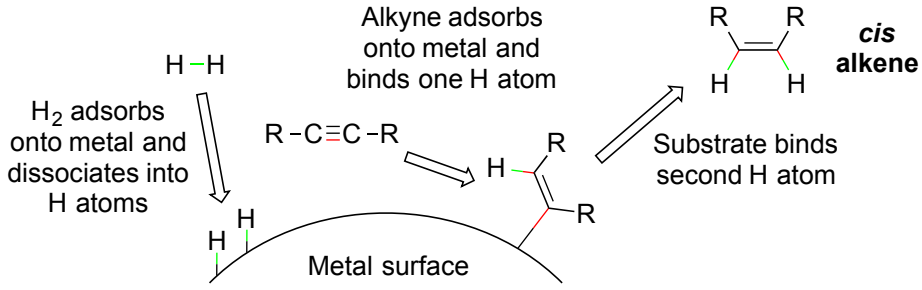
Section 6: Reduction (Hydrogenation and Dissolving Metal Reduction)

Alkynes can be reduced to other hydrocarbons in three different ways. If the alkyne is treated with hydrogen (H_2) and a metal catalyst such as Pd, Pt, or Ni, it is reduced to the alkane through the addition of two molecules of H_2 across its two π bonds. If the alkyne is treated with hydrogen in the presence of a poisoned catalyst, known as Lindlar's catalyst, it is reduced to the *cis* alkene through the addition of one molecule of hydrogen across an alkyne π bond. Alternatively, the *trans* alkene is obtained when an alkyne is treated with sodium or lithium in liquid ammonia. This latter reaction proceeds through a different mechanism and is known as dissolving metal reduction.

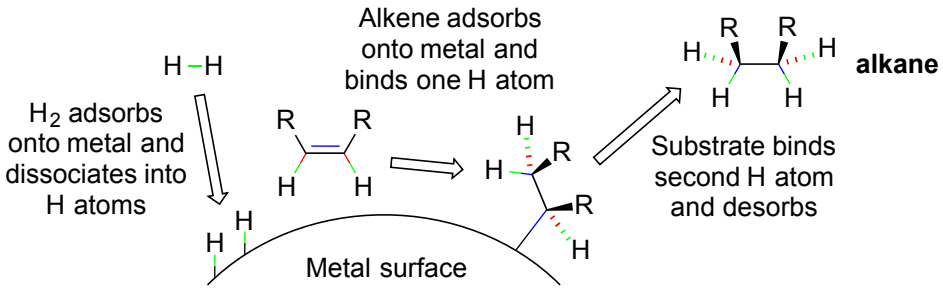


Mechanistic considerations for hydrogenation

Reduction of an alkyne using hydrogen in the presence of a metal catalyst, such as Pd, Pt, or Ni, closely parallels the hydrogenation of alkenes. Although a curved-arrow mechanism is not typically drawn for the process, the mechanism can be described as the following series of steps. Hydrogen adsorbs onto the metal surface and dissociates into hydrogen atoms. The alkyne is adsorbed onto the metal surface as well, and it proceeds to add one hydrogen atom. Upon the addition of a second hydrogen atom, the alkene is formed. This alkene has the *cis* configuration because both hydrogen atoms added to the same side of the alkyne.



However, as we've seen previously (in the hydrogenation section in the alkenes chapter), alkenes are reactive under these conditions as well. So, the *cis* alkene proceeds to add two more hydrogen atoms from the metal surface in the same fashion. Although this addition is also syn, stereochemistry will be irrelevant at the reactive centers, each of which has added two hydrogen atoms.



Lindlar's catalyst is a poisoned catalyst. Its activity is weakened by the treatment of the metal catalyst (Pd) with lead acetate and/or quinoline. This poisoned (or weakened) catalyst is only sufficiently active to catalyze the addition of one molecule of H_2 to an alkyne. It cannot catalyze the second addition, so the reaction is halted at the *cis* alkene.

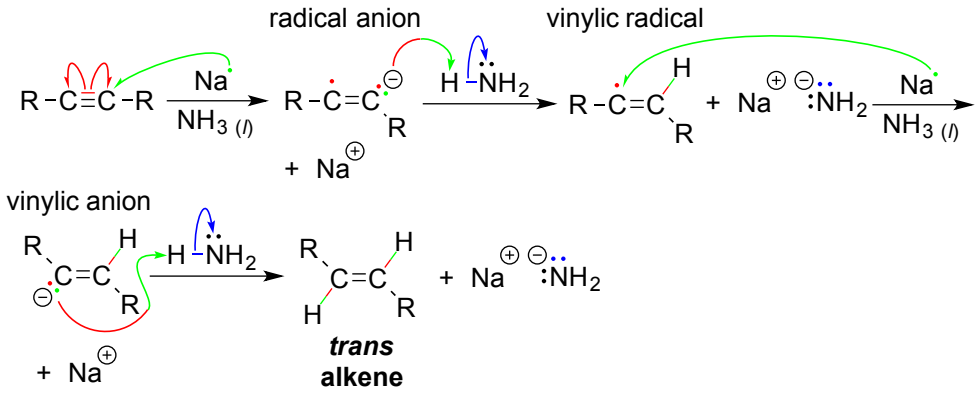
Problem 11. Compound A undergoes hydrogenation in the presence of Lindlar's catalyst to yield Compound B, which has the molecular formula C_8H_{16}. Compound A can also be reduced by hydrogen in the presence of palladium on carbon to provide 2,5-dimethylhexane. What are the structures of Compounds A and B?

Mechanistic considerations for dissolving metal reduction

Dissolving metal reduction proceeds through an entirely different mechanism and ultimately provides the *trans* alkene. An alkyne is treated with sodium or lithium metal in liquid ammonia. To keep the ammonia in the liquid state, it must be cooled, so you'll sometimes see the temperature of -78 °C designated.

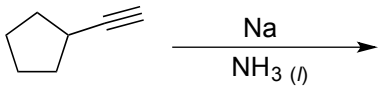
Sodium or lithium metal has one electron in its valence shell that it is anxious to donate so as to achieve the more stable electronic configuration of the preceding noble gas. This electron is freely transferred in liquid ammonia to the alkyne. One of the alkyne π bonds homolyzes in the process, and an intermediate with both an unpaired electron (radical) and a negative charge (anion) is formed. The negative carbon of the radical anion deprotonates ammonia, yielding a vinylic radical.

This radical accepts a second electron from another sodium or lithium atom, forming a vinylic anion. The vinylic anion is more stable in the *trans* configuration, which is the basis for selectivity in dissolving metal reduction. Finally, the anion deprotonates ammonia to provide the final product as the *trans* alkene.

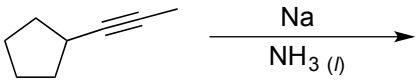


Problem 12. Predict the product for the following reductions.

(a)

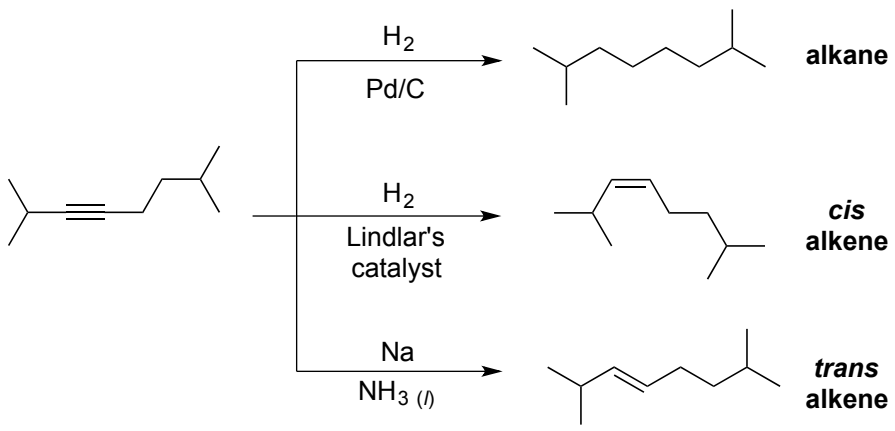


(b)



Specific examples of alkyne reduction

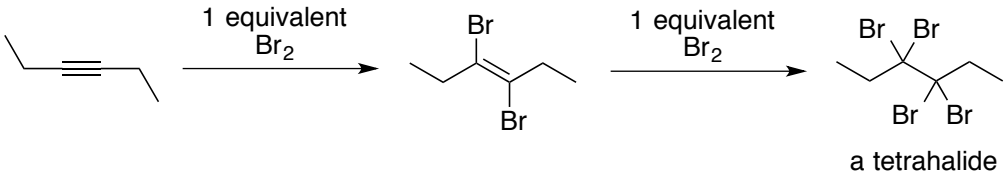
In the following three examples, one alkyne (2,7-dimethyl-3-octyne) is exposed to all three sets of conditions, and three different products result. When the reactant is reduced with hydrogen and palladium on carbon (Pd/C), it is reduced completely to the alkane (2,7-dimethyloctane). Upon reduction with Lindlar's catalyst, the *cis* alkene [(*Z*)-2,7-dimethyl-3-octene] results. Finally, the *trans* alkene [(*E*)-2,7-dimethyl-3-octene] is produced from dissolving metal reduction.



To recap, alkynes may be reduced to alkanes, as well as *cis* or *trans* alkenes. However, each target requires its own unique set of conditions. Simple hydrogenation with hydrogen and a metal catalyst affords the alkane. The substitution of a poisoned catalyst will yield the *cis* alkene. Finally, the mechanistically distinct dissolving metal reduction provides access to the *trans* alkene.

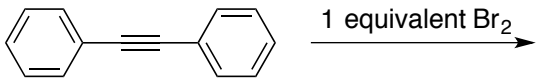
Section 7: Halogenation

Alkynes can undergo halogenation upon treatment with chlorine (Cl_2) or bromine (Br_2). This reaction is directly analogous to the halogenation of alkenes. However, since there are two pi bonds in an alkyne, this reaction can proceed twice if a sufficient amount of the reagent is used. The product of addition of two equivalents of X_2 to an alkyne is a tetrahalide.

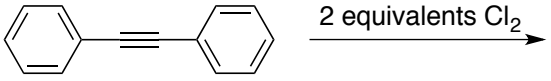


Problem 13. Provide the product for each of the following reactions.

(a)

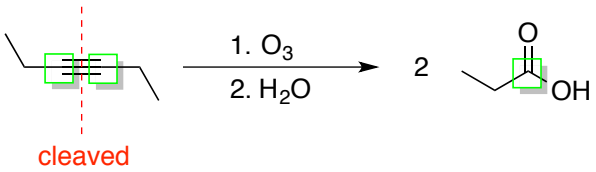


(b)

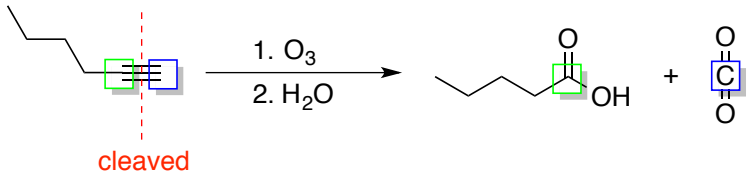


Section 8: Ozonolysis

When alkenes underwent ozonolysis, the two bonds between the alkene carbons were broken and replaced with two bonds to oxygen. When alkynes undergo ozonolysis, the process is similar. The three bonds between the alkyne carbons are cleaved and replaced with three bonds to oxygen. The relevant functional group with three bonds between carbon and oxygen is a carboxylic acid.



The one exception to this trend occurs when the alkyne substrate is terminal. In such a case, the terminal carbon is oxidized to carbon dioxide.

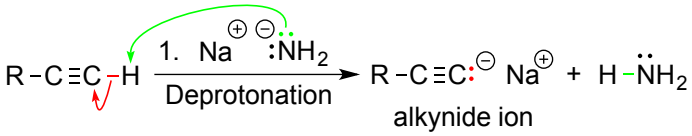


Problem 14. Compound A (C_4H_6) undergoes ozonolysis to yield Compound B and carbon dioxide. What are the structures of Compounds A and B?

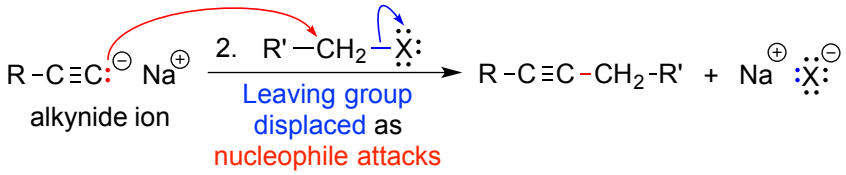
Section 9: Alkylation

Terminal alkynes can be deprotonated with a sufficiently strong base, such as sodamide ($NaNH_2$) or sodium hydride (NaH). The conjugate base of the alkyne can then be alkylated via S_N2 reaction with an unhindered alkyl halide. This is a useful method for extending the length of a carbon chain.

Only terminal alkynes can be used in this process because the alkyne must bear at least one proton (on the sp hybridized carbons themselves) that can be removed. Terminal alkynes have a pK_a value of about 25, so the base used to deprotonate them must be quite strong. Both sodamide ($NaNH_2$) and sodium hydride (NaH) have conjugate acids (NH_3 and H_2, respectively) with a pK_a of about 35, so both are suitable for deprotonation of an alkyne. The conjugate base of an alkyne is known as an alkynide ion.



The alkynide ion is a strong nucleophile, so it can engage in an S_N2 reaction with an unhindered alkyl halide. The alkynide ion attacks the electrophilic carbon as the leaving group is concurrently displaced.

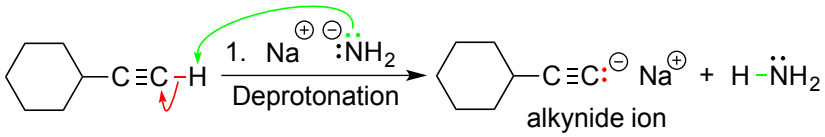


Since this is an S_N2 reaction, it is important for the alkyl halide to be unhindered. Methyl or primary alkyl halides are preferred. Beyond that, elimination (E2) becomes a problematic competing reaction. It is also worth noting that the leaving group could be a sulfonate ($^-$OTs, $^-$OMs, or $^-$OTf) as well as a halide.

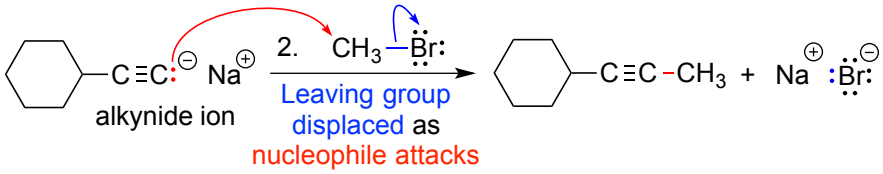
It is very important to designate (using numbers) that the two steps are, in fact, distinct separate steps. Sodamide and the alkyl halide cannot be combined with the alkyne all at once because sodamide can cause the alkyl halide to undergo undesired substitution and elimination reactions.

Specific examples of alkyne alkylation

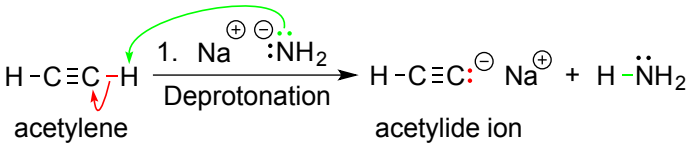
In the following example, cyclohexylacetylene is deprotonated by sodamide to yield the corresponding alkynide ion.



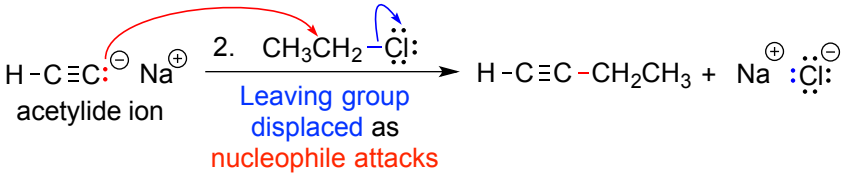
This alkynide ion can then be treated with a variety of electrophiles, such as methyl bromide. Attack of the nucleophilic alkynide ion on the carbon of methyl bromide displaces bromide as a new C–C bond is formed.



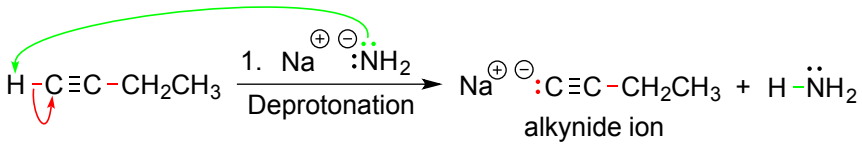
If acetylene is the reactant, two sequential alkylations can be performed because acetylene possesses two alkyne protons. The first deprotonation generates the acetylide ion, which is the name for the specific alkynide ion made from acetylene.



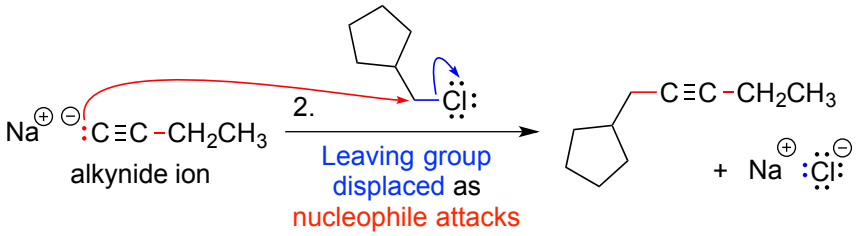
The acetylide ion can be treated with an electrophile such as ethyl chloride. The nucleophilic anionic carbon attacks the electrophilic carbon of ethyl chloride, thereby displacing chloride and forming a new bond between the alkyne and the ethyl group.



Since the product of the above reaction (1-butyne) still possesses an alkyne proton, it can be deprotonated once again to form a new alkynide ion.

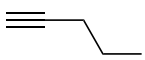


This alkynide ion can be treated with an electrophile like (chloromethyl)cyclopentane, upon which another S_N2 reaction occurs to afford an internal alkyne product.

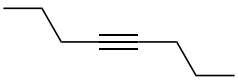


Problem 15. Show how you would prepare the following alkynes from acetylene.

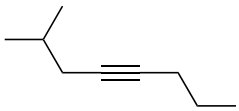
(a)



(b)



(c)

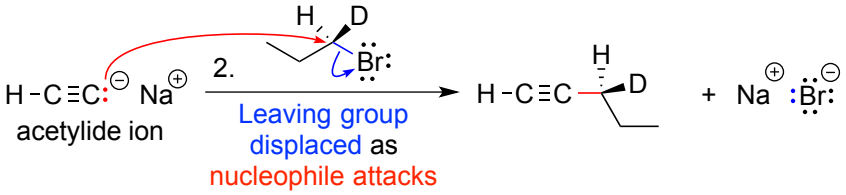


Stereochemical considerations

Since the C–C bond-forming step (step 2) is an S_N2 reaction, it occurs with inversion of configuration at the reactive center. This is rarely evident though because the reaction is typically limited to methyl and primary alkyl halides. Unless isotopic substitution is used, the reactive carbon of these electrophiles will not be a stereocenter.

In the following example, the alkyl bromide bears a deuterium atom (D). Deuterium is an isotope of hydrogen. From the perspective of chemical reactivity, it is nearly the same as hydrogen. However, because deuterium is not identical to hydrogen, they count as different

substituents. Consequently, this primary alkyl bromide does possess a stereocenter at the site of reaction. This stereocenter is inverted during the attack of the acetylide ion.

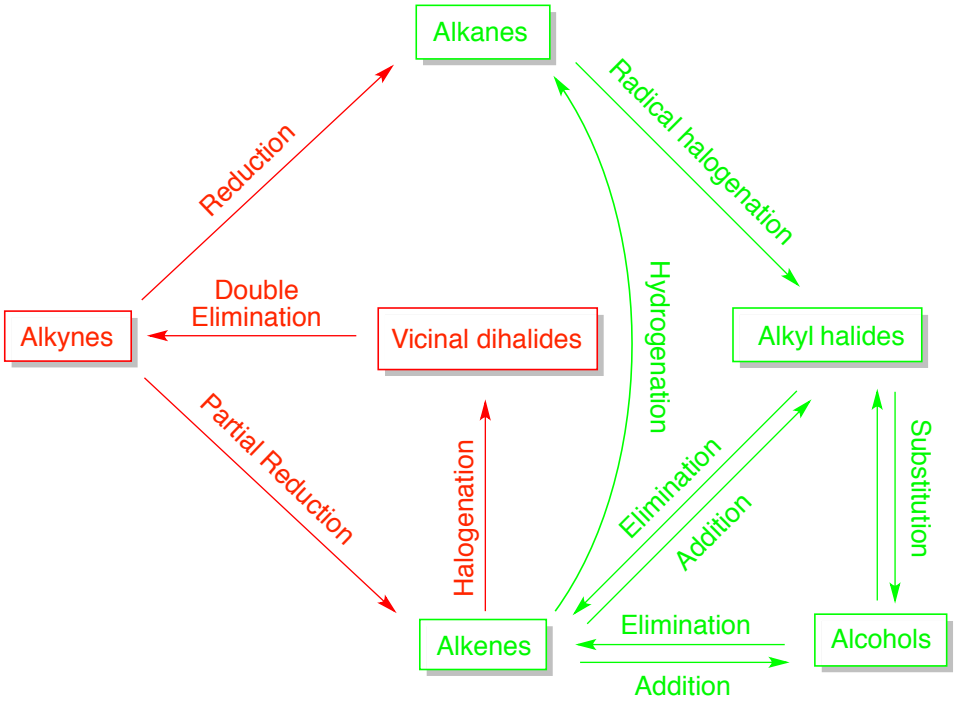


In summary, a terminal alkyne can be deprotonated using a strong base, such as sodamide or sodium hydride. The alkynide ion thus formed is a potent nucleophile that can displace the leaving group from an unhindered alkyl halide in S_N2 fashion to afford a new carbon-carbon bond. Although inversion occurs during this process, it is not usually evident since the alkyl halide substrate is methyl or primary.

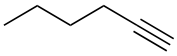
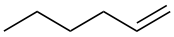
Section 10: Synthesis

Functional group manipulation

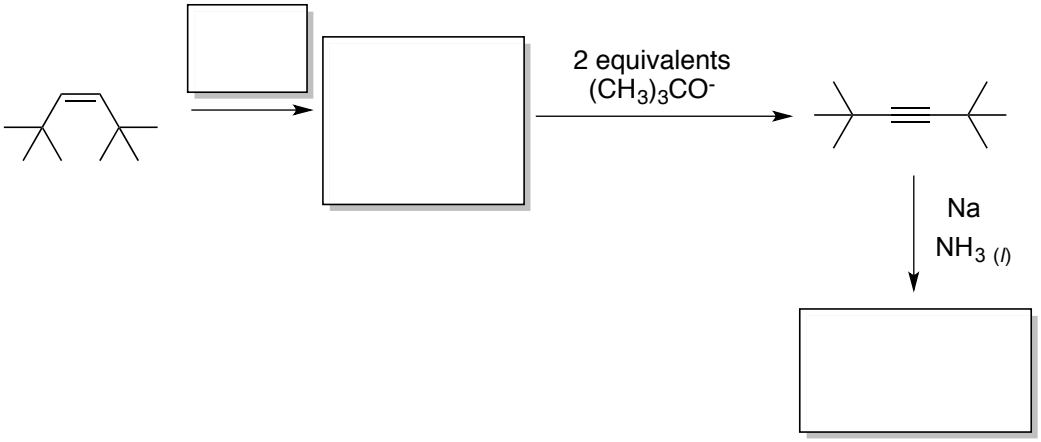
One of the key challenges in synthesis is, of course, interconverting functional groups. As you learn more and more specific reactions, it is useful to map out the "big picture" concepts. In other words, reflect on the types of reactions needed to change one functional group into another. The diagram below contains a great deal of information, but you have seen much of it before in the alkenes chapter. The new portion incorporates the reactions that we've discussed in this chapter. Note that, while there is no method to directly convert an alkene to alkyne, the conversion can be achieved in two steps: (1) halogenation and (2) double elimination. Alkynes may then be partially reduced to alkenes using hydrogenation with Lindlar's catalyst or dissolving metal reduction. Alternatively, alkynes may be fully reduced via hydrogenation to the corresponding alkanes.



Problem 16. Provide reagents and intermediates for the following synthesis.

Synthesize  from 

Problem 17. Fill in the missing intermediates and reagents in the following scheme.

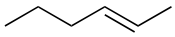


Changes to the carbon skeleton

Perhaps the most significant addition to our repertoire in this chapter has been the ability to use terminal alkynes to forge carbon-carbon bonds. This is accomplished when a terminal alkyne is deprotonated and then treated with a suitable electrophile, such as an unhindered alkyl halide.

When tackling synthesis problems, you should always look for changes to the carbon skeleton. If you need to make carbon-carbon bonds, focus on accomplishing this task first. Once you have the necessary carbon framework in place, you can then turn your attention to manipulating the functional groups.

Problem 18. Provide a means to accomplish the following synthesis.

Convert  into 

End-of-the-Chapter problems

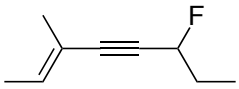
Problem 19. Point out the errors in the following alkyne names.

(a) 3-ethynylhexane

(b) methyl *tert*-butylacetylene

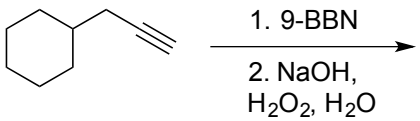
(c) 4-chloro-2-methyl-5-nonyne

Problem 20. If both an alkene and an alkyne are present in a molecule, the molecule can be named by including both suffixes. In other words, the molecule will be called an "enyne" where "en" signifies the alkene and "yne" signifies the alkyne. Additionally, a number is provided for each functional group. Using this information, name the following bifunctional molecule.

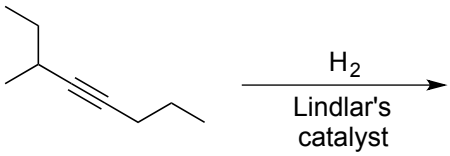


Problem 21. Predict the product(s) of the following transformations.

(a)



(b)



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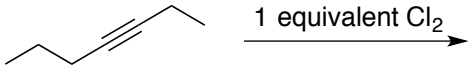
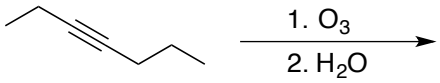
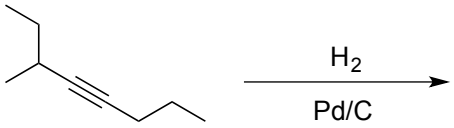


(d)



(e)



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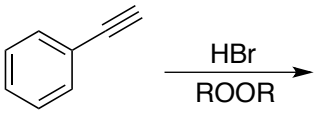
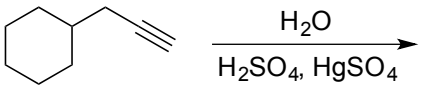
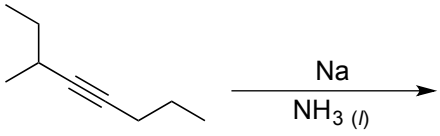


Problem 22. Provide the structures of the major product(s) for each of the following reactions.

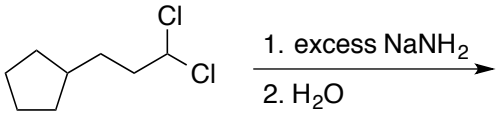
(a)



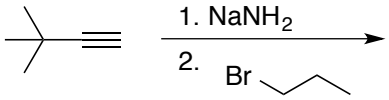
(b)



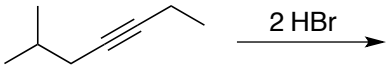
(c)



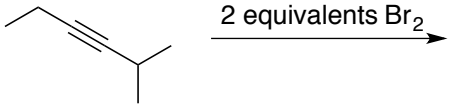
(d)



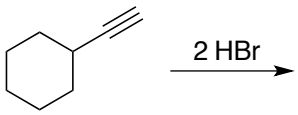
(e)



(f)

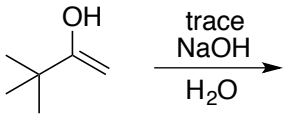


Problem 23. Provide a mechanism for the following transformation.

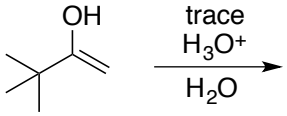


Problem 24. Show a mechanism for each of the following tautomerizations.

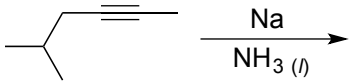
(a)



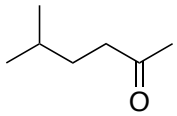
(b)



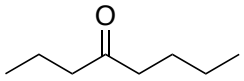
Problem 25. Provide a mechanism for the following reaction.



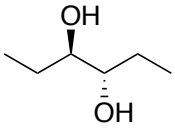
Problem 26. Prepare the following ketone from acetylene.



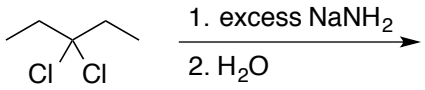
Problem 27. Prepare the following ketone from acetylene.



Problem 28. Show how the following diol can be prepared using acetylene as the *only* source of carbon.

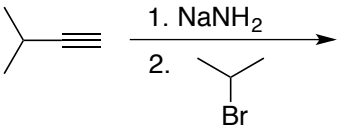


Problem 29. The following reaction was conducted with the expectation that it would provide 2-pentyne, an internal unsymmetrical alkyne.

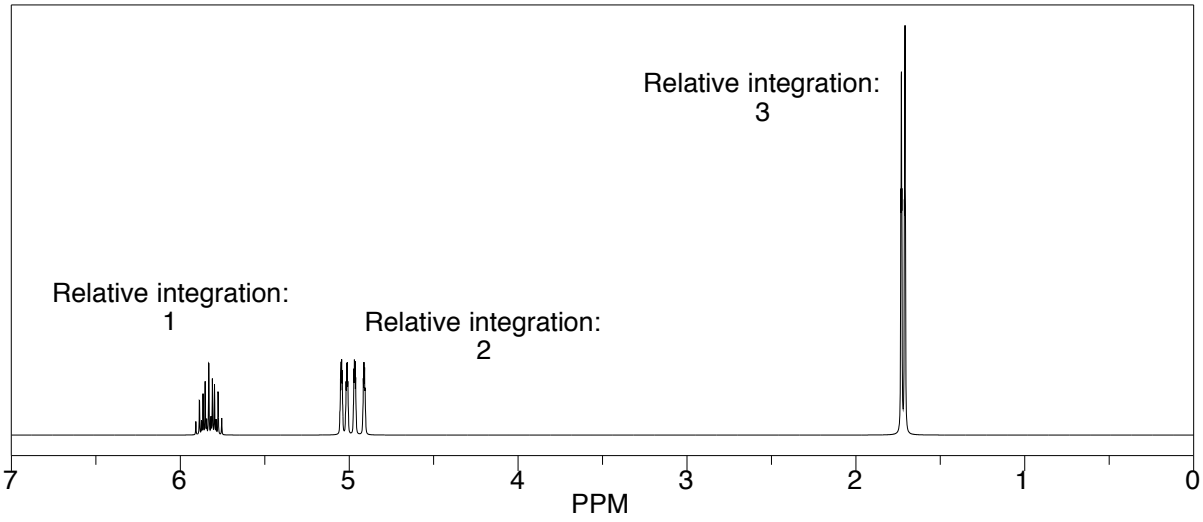


While the mass spectrum did provide the expected signal at *m/z* 68, the IR spectrum revealed a resonance at ~3300 cm^{-1}, which is indicative of a ≡C-H bond. Propose a structure for the actual reaction product, and explain its formation. Hint: Refer to the end of Section 2.

Problem 30. An investigator conducted the following reaction to prepare diisopropylacetylene.



The proton NMR spectrum was expected to exhibit a doublet and a multiplet with relative integrations of 6 : 1. However, one of the isolated products give the following ^1H NMR instead. What actually happened in this reaction and why?

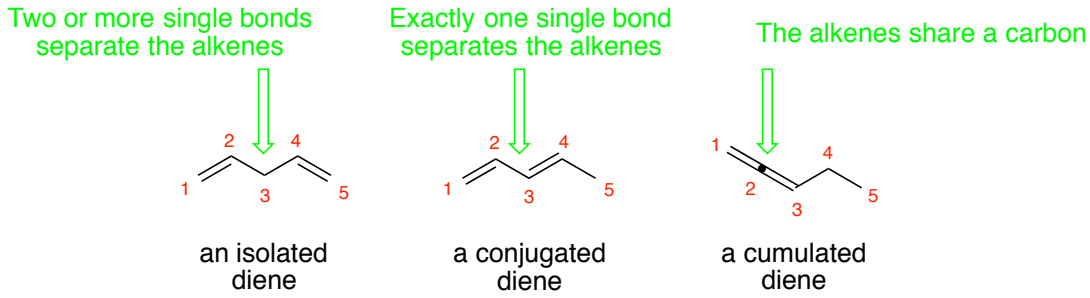

Relative integration:
3
Relative integration:
1
Relative integration:
2
7
6
5
4
3
2
1
0
PPM

Chapter 12: Dienes

Section 1: Types of dienes
Section 2: Molecular orbital theory
Section 3: Ionic hydrohalogenation of conjugated dienes
Section 4: Diels-Alder reaction
Section 5: Cope rearrangement
Section 6: Claisen rearrangement
Section 7: Conjugated systems and light

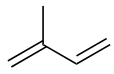
Section 1: Types of dienes

Dienes contain two alkenes. There are three categories of dienes: isolated, conjugated, and cumulated. To illustrate these three types, let's consider placing two pi bonds in a five-carbon chain. They could be placed on opposite ends of the molecule. Or, they could be in closer proximity, namely separated by one or no single bonds. In isolated dienes, the two alkenes are separated by at least two single bonds. In conjugated dienes, the separation between the alkenes is exactly one single bond. And, in cumulated systems, the two alkenes share one carbon in common. That carbon is highlighted by the dot in the cumulated diene shown below.



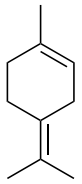
Problem 1. Identify the alkenes in the following molecules as isolated, conjugated, or cumulated.

(a) Isoprene is a common five-carbon building block found in natural products (i.e., compounds found in nature).



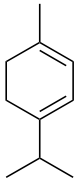
isoprene

(b) Terpinolene is an example of a terpene, which means that it is a compound biosynthetically derived from isoprene [see part (a) above].



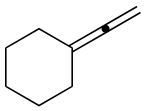
terpinolene

(c) α-Terpinene is also a terpene.

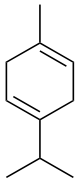


α-terpinene

(d)

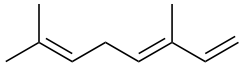


(e) γ-Terpinene is another terpene.



γ-terpinene

(f) *Trans*-β-ocimene is one more example of a terpene.



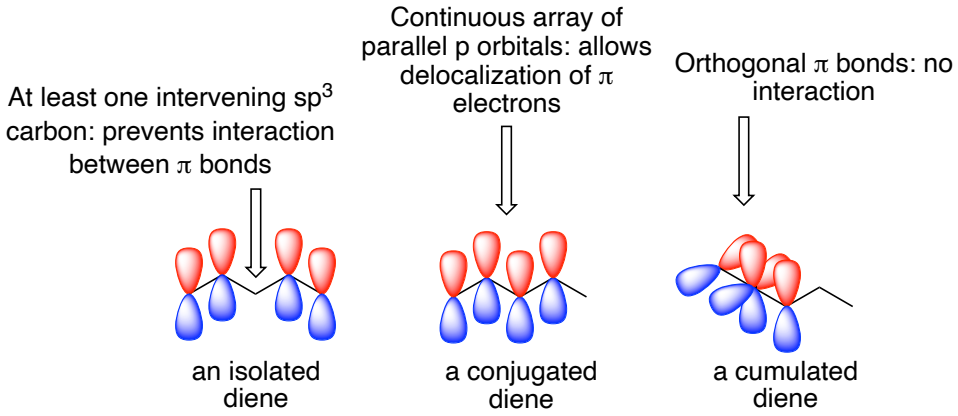
trans-β-ocimene

A very logical question is: Why does the distinction between isolated, conjugated, and cumulated dienes matter?

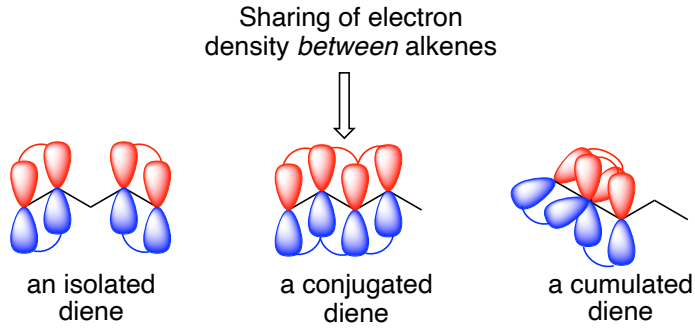
Conjugation and resonance

Conjugated dienes are unlike any other dienes in that the electrons are delocalized. This phenomenon results from the special orientation of the alkenes relative to each other in the

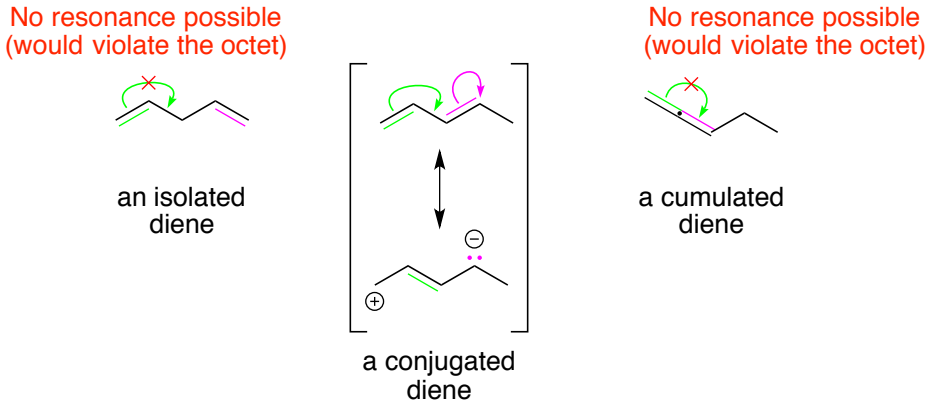
conjugated system. In an isolated diene the two alkenes are separated by at least two single bonds, and this prevents any electronic communication between the two π bonds. In a conjugated diene, however, the four p orbitals of the two alkenes reside on four adjacent carbon atoms. This provides an uninterrupted π cloud throughout which the π electrons can circulate, hence the delocalization of electrons. In the cumulated diene, the two alkenes are actually orthogonal (i.e., perpendicular) to each other. This prevents any electronic communication between them because the p orbitals of the two alkenes only overlap at their nodes, which are sites of zero electron density. Recall that only parallel p orbitals can overlap with each other.



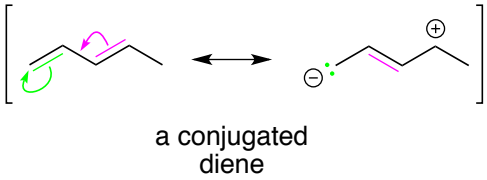
The delocalization of electron density can be represented by the curved lines in the following diagrams. Note that the isolated and cumulated alkenes have delocalization only within the individual alkenes, while the conjugated diene shares electron density not only within the alkenes but also between them.



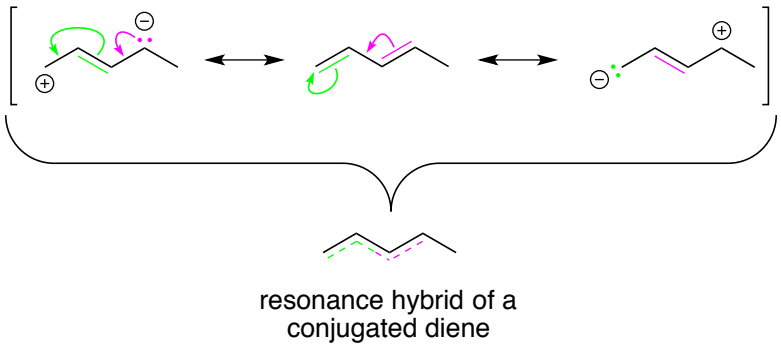
Resonance provides another method for visualizing this effect. In both the isolated and cumulated dienes, it is not possible to draw a resonance structure involving the electrons of *both* alkenes without violating the octet rule. On the other hand, the conjugated diene does have resonance forms, one of which is shown in the diagram below. While the resonance form with charge separation is a minor contributor to the overall resonance hybrid, it nevertheless illustrates the delocalization of electron density within the conjugated diene.



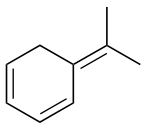
The conjugated diene has another resonance form as well. This one is derived by moving π electrons in the other direction.



Therefore, the actual conjugated diene is a hybrid of all three resonance structures.



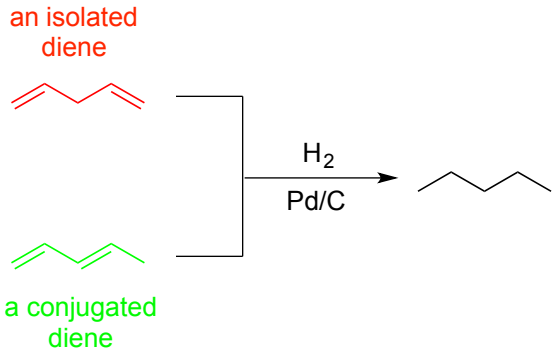
Problem 2. Show all of the resonance forms, as well as the resonance hybrid, for the following conjugated triene.



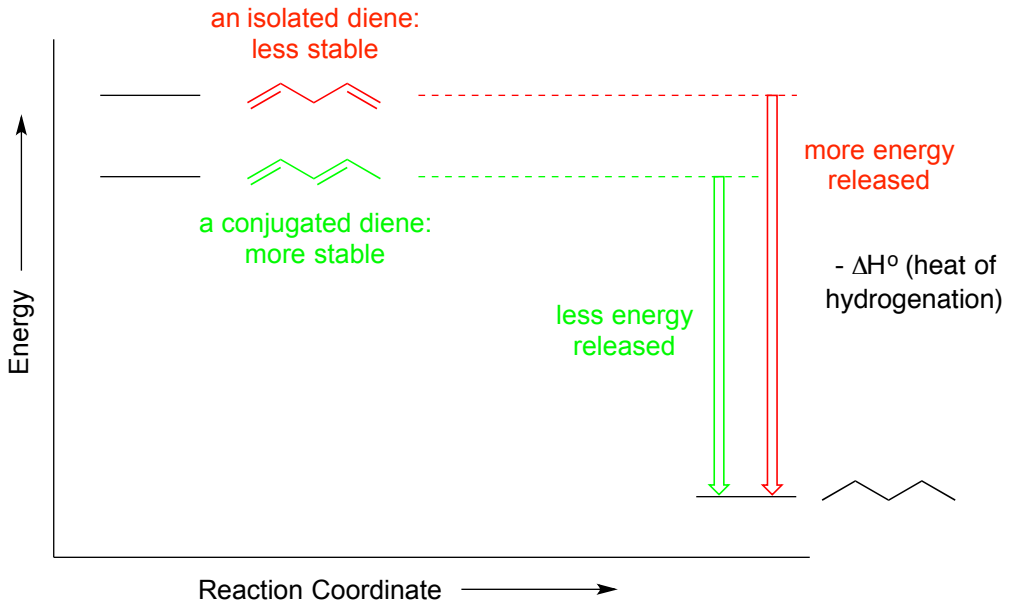
Manifestations of conjugation

You might wonder if there are any practical consequences of conjugation, and indeed there are many. For the moment, let's consider the impact of conjugation on two factors: stability and reactivity.

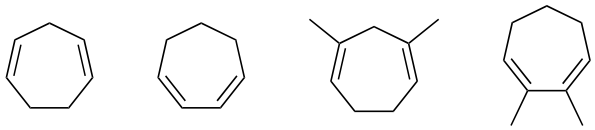
Conjugated dienes are more stable than isolated dienes. As we saw in Chapter 7, hydrogenation data can provide evidence of relative alkene stability. In the diagram below, two isomeric dienes are shown that differ only in the placement of the π bonds so that one is isolated and the other is conjugated. Upon hydrogenation, both dienes yield pentane as the alkane product.



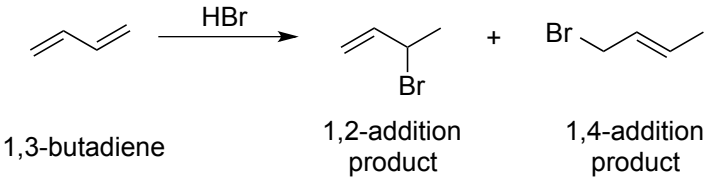
However, these two reactions evolve differing amounts of energy. The hydrogenation of the conjugated diene releases less energy (i.e., has a smaller heat of hydrogenation) than that of the isolated diene. Since both reactions yield the same product, the only way to explain the difference is that the conjugated diene must be lower in energy than its isolated counterpart. Recall that a lower energy molecule is a more stable molecule.



Problem 3. Rank the following dienes in order of decreasing stability.



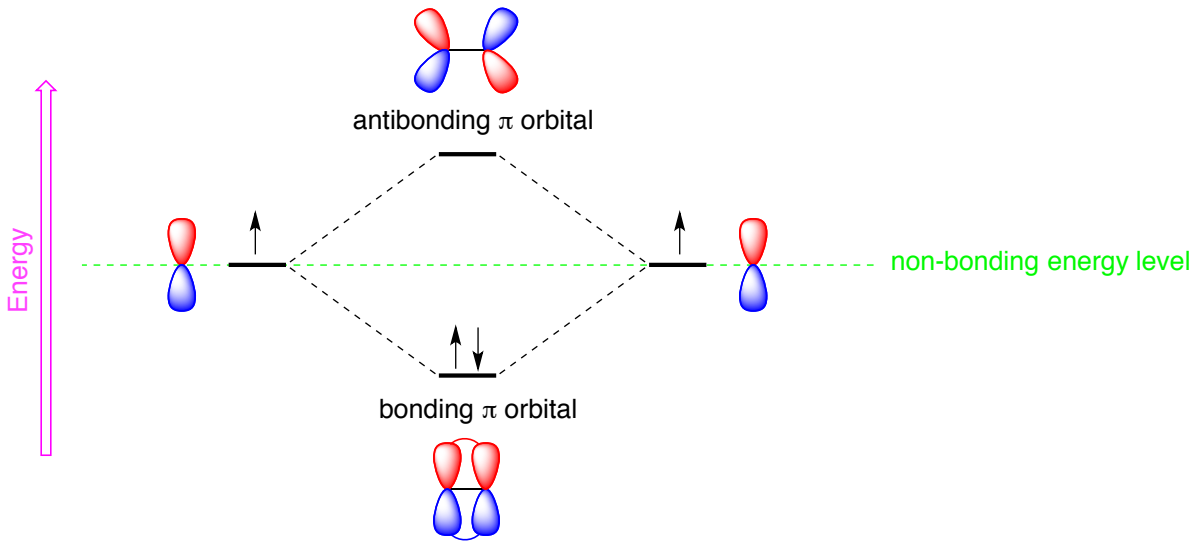
A second manifestation of conjugation is observed in the reactivity of conjugated dienes. Since the two alkenes in a conjugated system are electronically linked, they behave as a single functional group, which can lead to otherwise unexpected reactivity. For instance, in Section 3 we will explore the ionic hydrohalogenation of conjugated dienes. What follows is a preview of this reaction.



The addition of HBr to 1,3-butadiene can yield two products. In the 1,2-addition product, the hydrogen and bromine have added to adjacent carbons; whereas, in the 1,4-addition product, they have added to sites four atoms apart. Based on what we learned about the hydrohalogenation of alkenes in Chapter 10, we would expect the 1,2-addition product, which is simply the result of Markovnikov addition of HBr to one of the two alkenes in the reactant. However, the 1,4-addition product is initially surprising. The π bond in this product is located at a site that had no π bond in the reactant. As we'll learn shortly, this outcome is readily explained by the conjugation of alkenes in the reactant.

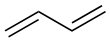
Section 2: Molecular orbital theory

When atomic orbitals interact to form bonds, there are no longer discrete atomic orbitals. Instead, they form molecular orbitals. When you think about it, it is quite logical that *atoms* would have *atomic* orbitals, while *molecules* would have *molecular* orbitals. We learned a bit about this in Chapter 1. Recall, for instance, that we saw how two p orbitals can interact to form bonding and antibonding π orbitals. The bonding orbital forms as a result of constructive interference between the two p orbitals. In other words, like phases overlap. The antibonding orbital, on the other hand, is formed from destructive interference of the two p orbitals. When unlike phases are adjacent, there is no electron density between the two nuclei. The electrons fill the lower-energy bonding π orbital, leaving the higher-energy antibonding π orbital empty.



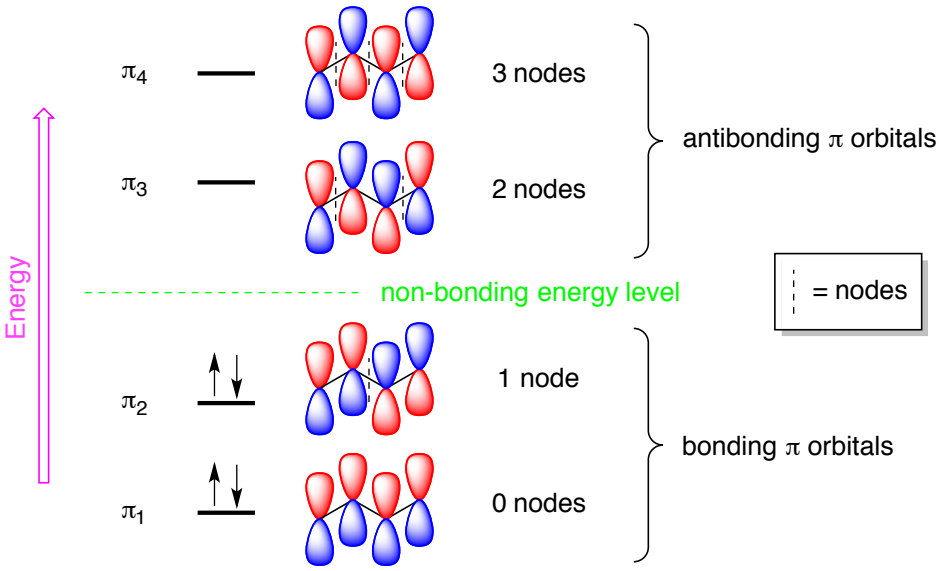
We can draw similar diagrams for larger π systems. Although molecular π orbitals have their own unique shapes that form when the individual p orbitals combine, it is convenient to simplify the rendering of the molecular orbitals by drawing them merely as an accumulation of in-phase or out-of-phase p orbitals. Remember that the number of orbitals is conserved, so there will be as many molecular π orbitals as there are p orbitals from which they are formed.

To illustrate this, let's consider the molecular π orbitals of 1,3-butadiene.

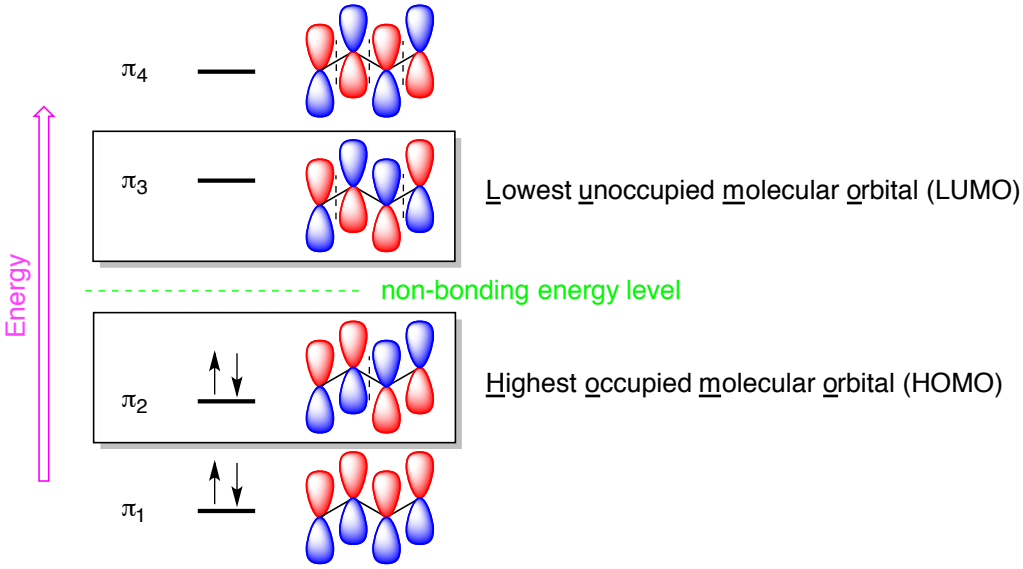


1,3-butadiene

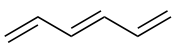
1,3-Butadiene has two π bonds composed of a total of four p orbitals. The four p orbitals are the building blocks for constructing the molecular π orbitals. Furthermore, we know that there will be four molecular π orbitals because we start with four atomic p orbitals. The lowest-energy molecular π orbital (π_1) is the one in which all of the p orbitals experience in-phase interaction (i.e., all like-phase overlap). The energy increases as nodes are introduced. Nodes are locations where an out-of-phase interaction occurs. The next-highest-energy orbital (π_2) occurs when one node is present. This is achieved most symmetrically when the phase switch is in the center of the π system. π_3 contains two nodes, which elevates it in energy, and π_4 has 3 nodes, making it the highest-energy molecular π orbital. These molecular orbitals are symmetrically oriented about the non-bonding energy level. This is due to the conservation of energy; the molecular π orbitals must have the same overall energy as the four non-bonding p orbitals with which we started. The two molecular π orbitals below the non-bonding energy level are bonding orbitals, while those above it are antibonding. Each of the carbon atoms contributes one electron to a π bond, and these four electrons fill the two bonding orbitals.



In reactions, the frontier molecular orbitals are the most important. These are the highest occupied (π_2) and lowest unoccupied (π_3) molecular orbitals. We'll utilize them later when we consider the Diels-Alder reaction in Section 4.



Problem 4. Show the molecular π orbitals for 1,3,5-hexatriene in order of increasing energy. Label the highest occupied and lowest unoccupied molecular orbitals.



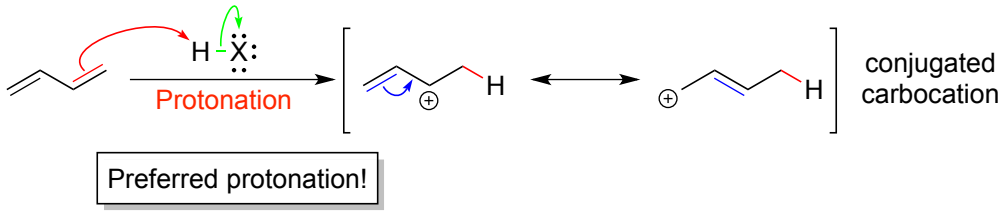
(*E*)-1,3,5-hexatriene

Section 3: Ionic hydrohalogenation of conjugated dienes

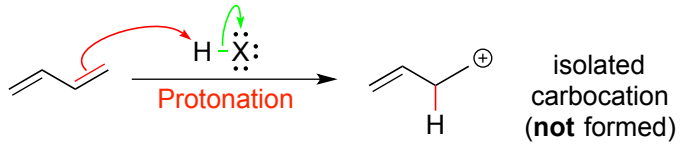
We have seen ionic hydrohalogenation in Chapter 10. However, when the substrate is a conjugated diene, the reaction is a bit different. Conjugated π bonds are not merely two alkenes. The fact that they are conjugated to one another means that they behave as a single functional group. Therefore, the whole functional group must be considered when these conjugated systems undergo ionic hydrohalogenation.

Mechanistic considerations

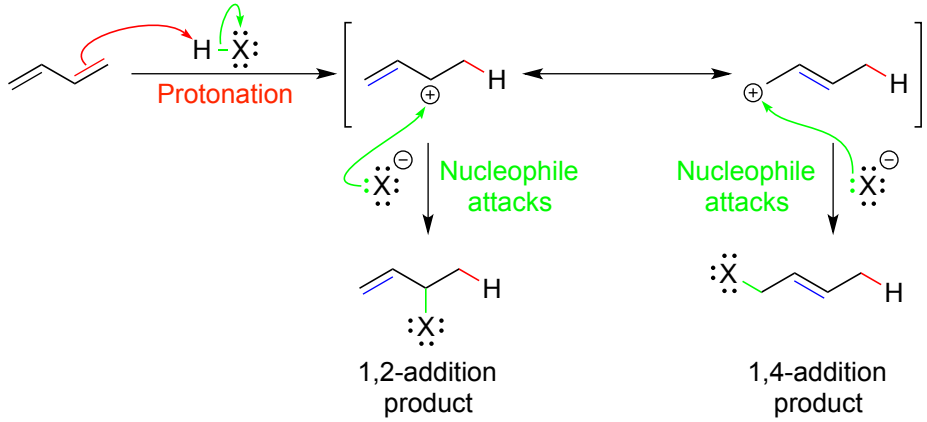
The reaction begins with the protonation of one of the π bonds by HX (usually HCl or HBr), which occurs so as to form the conjugated (allylic) carbocation.



The isolated carbocation would be much higher in energy and is therefore not formed.



There are two resonance forms of the allylic carbocation that spread δ^+ charge over two carbon atoms. Either of these sites can be attacked by the halide, so two products are formed. When the newly added proton and halogen are adjacent to each other, the product is called the 1,2-addition product. When the newly added proton and halogen are separated by four atoms, the product is known as the 1,4-addition product.

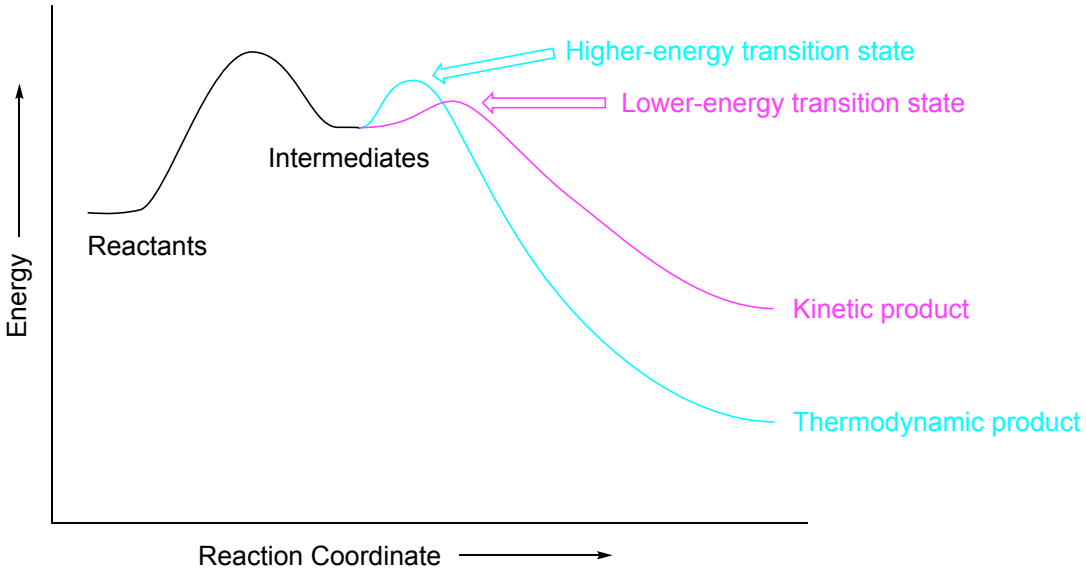


The product distribution can be affected by temperature. Lower temperatures (0 °C or below) favor the 1,2-addition product, which is the kinetically favored (or simply "kinetic")

product. The 1,2-product is formed faster because, once the proton is added to the substrate, the halide is closer to the 2-position than the 4-position. This is sometimes referred to as the proximity effect.

In this reaction, the 1,4-addition product contains the more highly substituted alkene. It has a disubstituted alkene; whereas, the olefin in the 1,2-addition product is only monosubstituted. The 1,4-product is therefore the thermodynamically favored (or simply "thermodynamic") product in this case because it contains the more stable alkene. The thermodynamic product is favored at higher temperatures (typically around 40 °C).

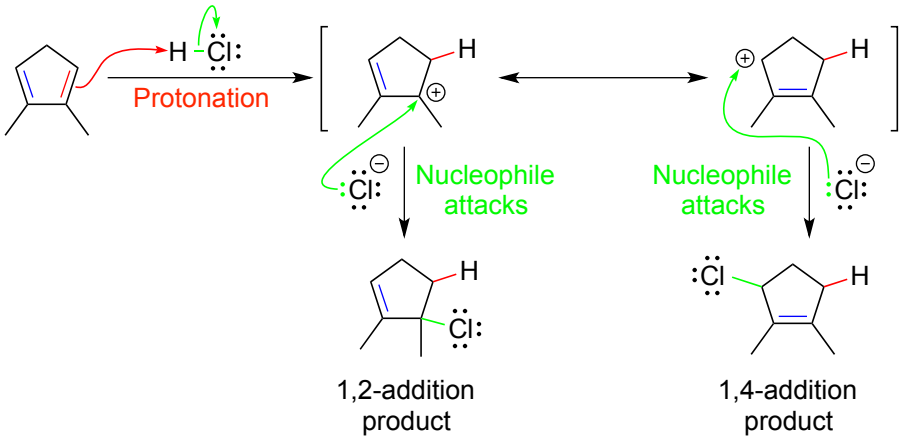
The following energy diagram illustrates why temperature affects the product distribution. The path to the 1,2- and 1,4-addition product is the same up to the stage at which the intermediates are formed. The intermediates include the resonance-stabilized carbocation and the halide. It is at this point that the two paths diverge. The kinetic product is formed through a lower-energy transition state because the halide is already in close proximity to the site where it will add. But, the kinetic product itself contains a less substituted alkene, so it is higher in energy than the thermodynamic product. The thermodynamic product, although it is lower in energy, results from a higher-energy transition state due to the fact that the halide is further from the site to which it must add in order to generate this product.



When energy is limited (at low temperatures), the intermediates will preferentially take the lower energy path to the kinetic product. However, when there is sufficient energy for the system to fully equilibrate, the thermodynamic product will predominate since it has the lowest overall energy.

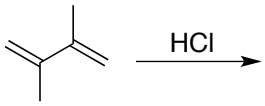
Specific examples of the ionic hydrohalogenation of conjugated dienes

In the following example, 2,3-dimethyl-1,3-cyclopentadiene is treated with HCl. Due to the molecule's symmetry, the two alkenes are completely equivalent, and either can be protonated to yield the same carbocation. Note that the conjugated carbocation is formed, and resonance spreads δ^+ character over two carbon atoms. Chloride then attacks either of these sites to yield the two allylic chloride products.



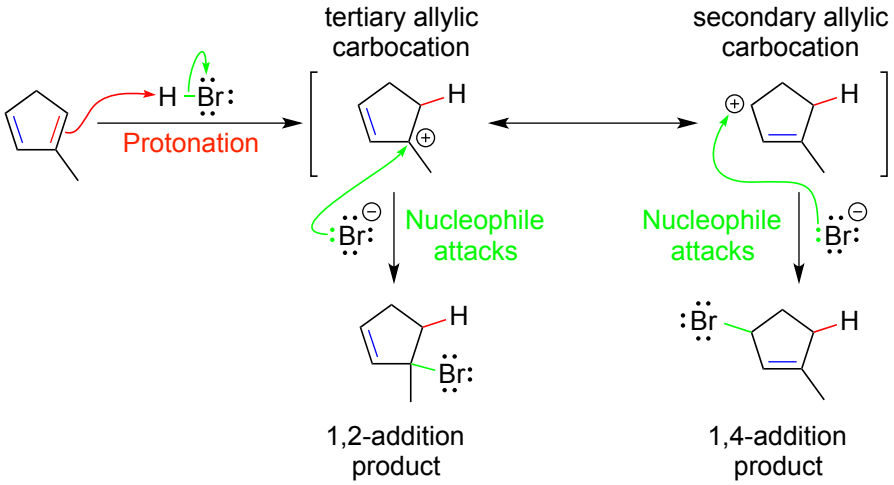
The 1,2-product is the kinetic product and would be favored at lower temperatures. The 1,4-addition product contains a more highly substituted alkene (tetrasubstituted as opposed to trisubstituted), so it is the thermodynamically favored product and predominates at higher temperatures.

Problem 5. Predict the products of the following hydrohalogenation. Which product is favored at lower temperatures? Which product is favored at higher temperatures?



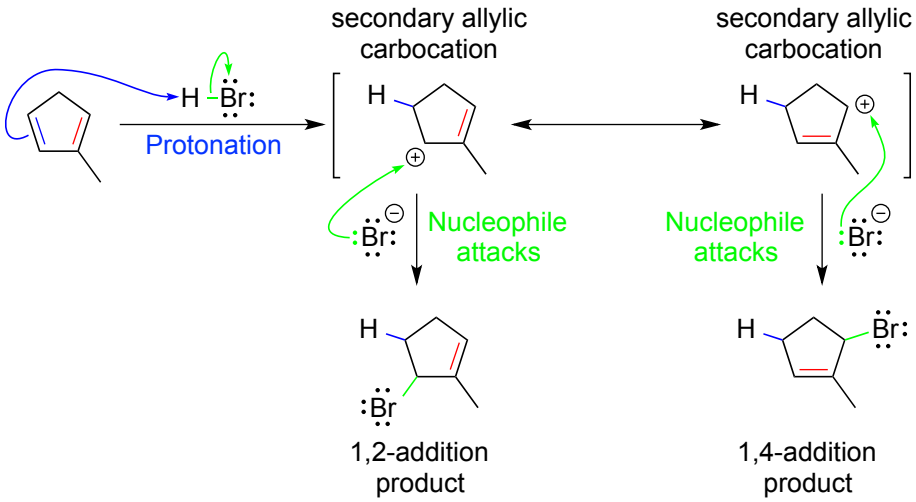
Regiochemical considerations

In the next example, 2-methyl-1,3-cyclopentadiene is treated with HBr. This substrate is unsymmetrical. Therefore, the results will differ depending on which π bond is protonated. Protonation of the red π bond leads to a tertiary allylic carbocation, which is in resonance with a secondary allylic carbocation. Both of the sites bearing δ^+ can be attacked by bromide, yielding two allylic bromides.

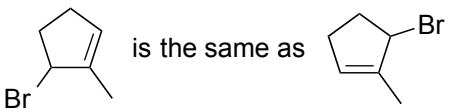


The 1,2-product is the kinetic product and is favored at low temperatures. The 1,4-product contains the more highly substituted double bond (trisubstituted as opposed to disubstituted) and is favored at higher temperatures.

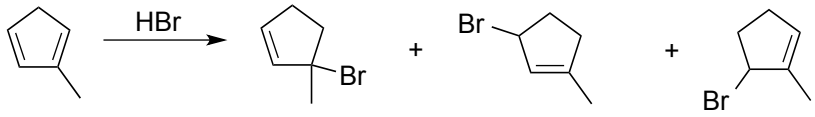
As mentioned at the outset of this example, the lack of symmetry in the reactant means that the outcome will vary depending on which π bond is protonated. If the blue π bond were protonated instead of the red one, a pair of resonance structures, which are both secondary allylic carbocations, result. Attack of bromide at either δ^+ carbon yields an allylic bromide.



In fact, it turns out that these two structures, which may initially appear to be different, are in fact identical. This is more obvious when the hydrogen is not explicitly shown and the colors are omitted, as seen below.



To summarize, the hydrohalogenation of 2-methyl-1,3-cyclopentadiene can yield three allylic bromide products.



The last product results from protonation of the blue π bond and is expected to be a minor product since the carbocations in that pathway are both secondary. The protonation of the red π bond is expected to be preferred because the tertiary and secondary carbocations in that path lead to an overall lower energy resonance hybrid.

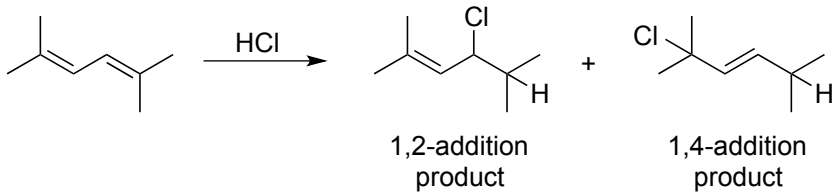
Problem 6. Consider the reaction of 1 equivalent of HBr with 1,3-pentadiene.

(a) Which carbon of the π system is preferentially protonated in the first step of the reaction? Why?

(b) The preferred carbocation formed in part (a) yields only one product. Why?

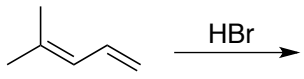
A note about regiochemistry

Although the 1,4-product has been the thermodynamic product in all of the preceding examples, this is not always the case. In the following reaction, the 1,2-product contains a trisubstituted alkene, but the alkene in the 1,4-product is only disubstituted. Therefore, in this case, the 1,2-product is not only the kinetic but also the thermodynamic product.



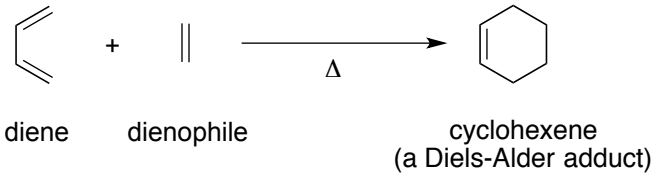
In summary, the hydrohalogenation of conjugated dienes affords two allylic halides: the 1,2- and 1,4-addition products. The product distribution can be affected by temperature. Low temperatures favor the kinetic product, and higher temperatures favor the thermodynamic product. The kinetic product results from nearby addition of both the proton and halide (the proximity effect), leading to 1,2-addition. The thermodynamically favored product contains the more highly substituted alkene.

Problem 7. Provide the two principal products of the following reaction. Which one is favored at lower temperatures? Which one is favored at higher temperatures?



Section 4: Diels-Alder reaction

In the Diels-Alder reaction a conjugated diene and a dienophile ("diene lover") unite to form a cyclohexene ring. The product of this reaction is sometimes referred to generically as the Diels-Alder adduct.

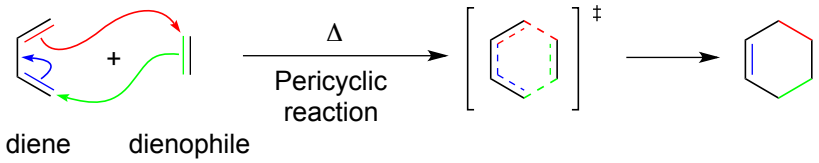


The Diels-Alder reaction is an example of a pericyclic reaction. Pericyclic reactions have a concerted mechanism, meaning that all of the bond making and breaking occurs simultaneously. Pericyclic reactions also have a cyclic transition state. We'll learn more about these features when we examine the mechanism of the reaction.

The Diels-Alder reaction may also be called a cycloaddition. Cycloadditions are pericyclic transformations that make a ring from two unsaturated reactants. This specific reaction is a [4+2]cycloaddition because the reactants have 4 π electrons and 2 π electrons, respectively.

Mechanistic considerations

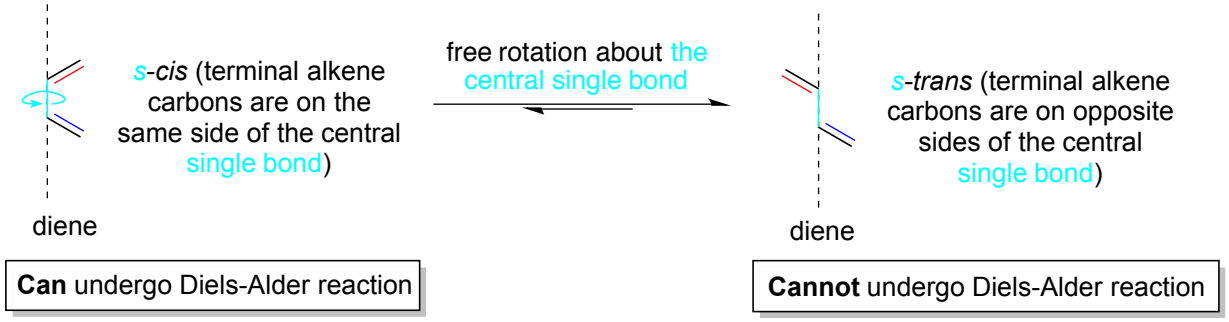
The core elements of a Diels-Alder reaction are shown below. The diene is typically the more electron-rich reactant. As such, you can envision it attacking one of the carbons of the dienophile. The dienophile simultaneously attacks the opposite terminus of the diene, pushing the remaining diene π bond to a new location.



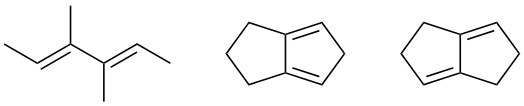
In particular, notice the two features of the mechanism that were mentioned previously: It is concerted, and there is a cyclic transition state.

In this reaction, several important things happen. Two new carbon-carbon σ bonds are formed. A six-membered ring is also formed, which is particularly important because six-membered rings are quite prevalent in natural products that are of synthetic interest. Finally, four carbon atoms are rehybridized from sp^2 to sp^3, meaning that these four carbons could conceivably become stereocenters if they were substituted accordingly. As you can see, the Diels-Alder reaction accomplishes a great deal in a single step. Otto Diels and Kurt Alder were awarded the Nobel Prize in Chemistry in 1950 in recognition of this extraordinarily useful contribution to organic synthesis.

For the Diels-Alder reaction to be possible, the diene must be able to adopt the s-*cis* conformation, in which the terminal alkene carbons reside on the same side of the central single bond. This is accomplished by rotation about that bond. There is an equilibrium between the s-*cis* and s-*trans* conformations. The s-*trans* conformation is typically more stable because it usually minimizes steric hindrance. But, some molecules are nevertheless in the s-*cis* conformation at any moment in time, and these can successfully undergo Diels-Alder reaction.

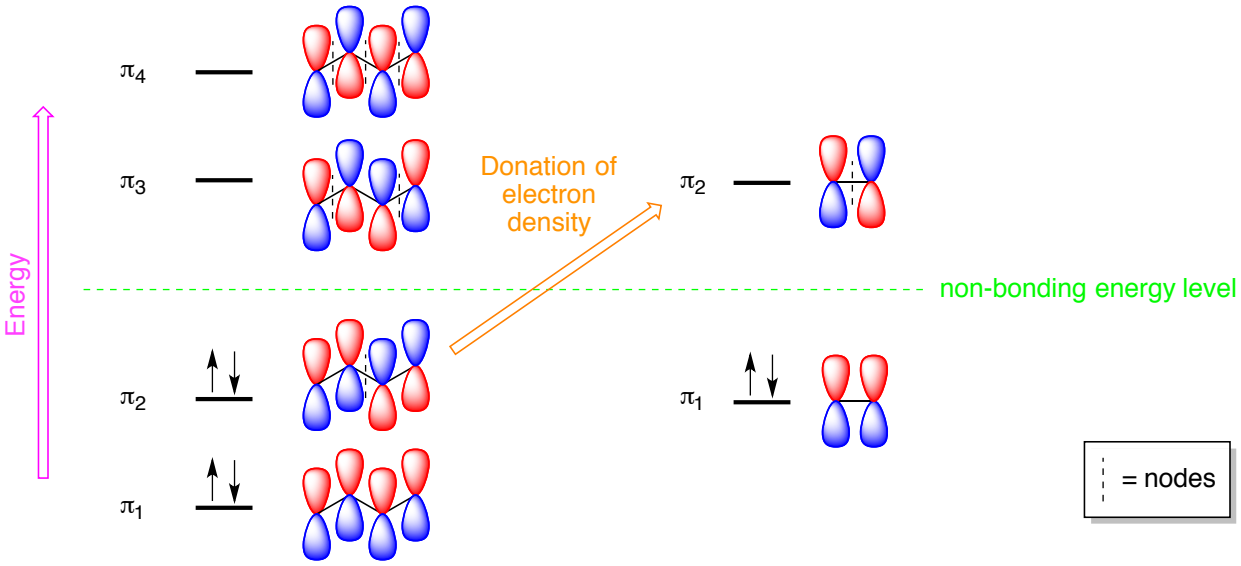


Problem 8. List the following dienes in order of increasing rate of reaction in the Diels-Alder reaction.

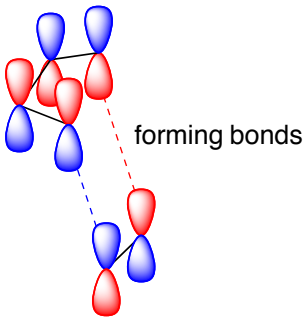


Orbital symmetry

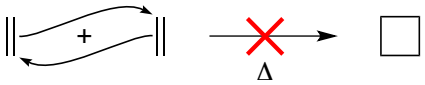
We can better understand the mechanism of the Diels-Alder reaction by considering the interaction between the molecular orbitals of the reactants. In the diagram below, the molecular π orbitals that we've constructed previously for both 1,3-butadiene and ethylene are shown. The interaction between them occurs through the frontier molecular orbitals: the highest occupied and the lowest unoccupied molecular π orbitals. Since the diene is typically the more *electron-rich* reactant, it utilizes its highest *occupied* molecular orbital (π_2), while the dienophile employs its lowest *unoccupied* molecular orbital (π_2).



It is possible for the HOMO of 1,3-butadiene and the LUMO of ethylene to approach one another such that there are in-phase interactions between the termini of their π systems. This allows for constructive interference between the orbitals, resulting in the formation of bonds.



Problem 9. Earlier, we learned that the Diels-Alder reaction can also be called a [4+2]cycloaddition due to the numbers of π electrons utilized by the reactants. Unlike the Diels-Alder reaction, [2+2]cycloadditions do not occur simply upon heating. Use the molecular π orbitals of the ethylene molecules to explain why this is the case.

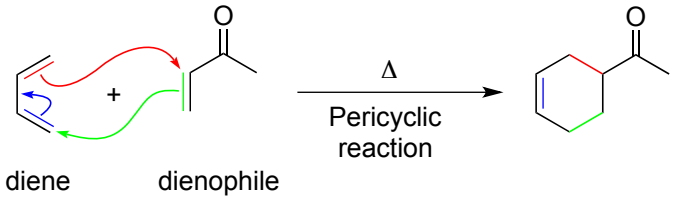


A specific example of the Diels-Alder reaction

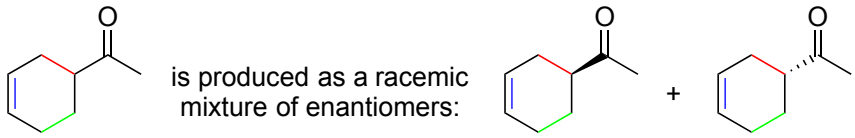
The Diels-Alder reaction works much better with an electron-poor dienophile than it would with ethylene (CH_2=CH_2) as the dienophile. This is because an electron-withdrawing group lowers the energy of the LUMO, thereby lessening the energy gap between the HOMO of the

diene and the LUMO of the dienophile. With a smaller energy gap between the frontier molecular orbitals, the reaction proceeds more readily.

In the following example, 1,3-butadiene (the diene) and 3-buten-2-one (the dienophile) are heated (Δ) to yield a Diels-Alder adduct. The electron-withdrawing ketone substituent renders the dienophile electron poor so that the reaction proceeds more readily. Many different electron-withdrawing groups can be used (e.g., carboxylic acids, esters, nitriles).

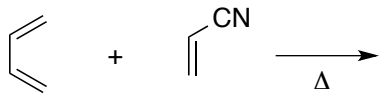


In this reaction, a stereocenter is formed. Since the diene and dienophile are trigonal planar (flat) at the reactive centers, addition can occur from either side of the dienophile to push the ketone up or down. The result is a racemic mixture of enantiomers.

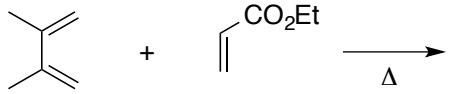


Problem 10. Predict the products of the following Diels-Alder reactions.

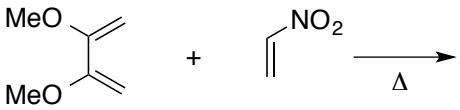
(a)



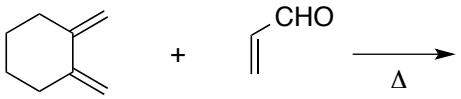
(b)



(c)

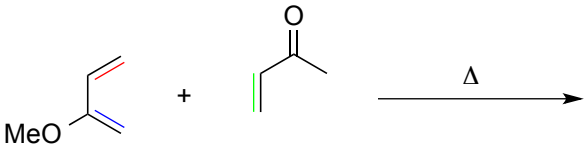


(d)

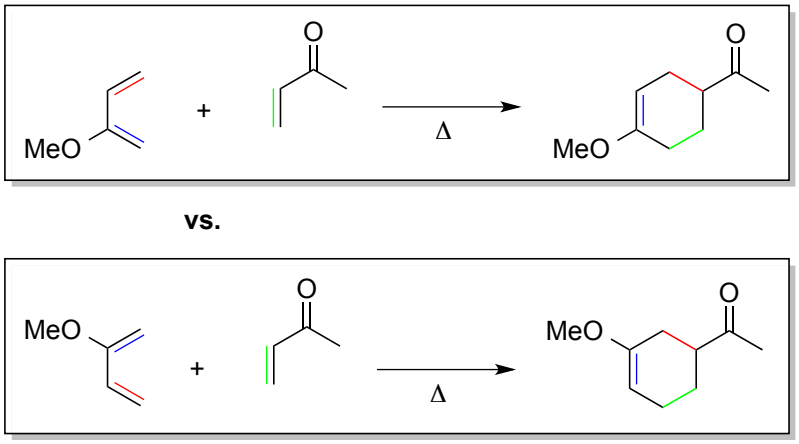


Regiochemical considerations

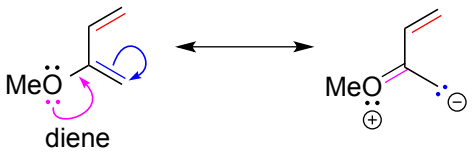
When both the diene and the dienophile are unsymmetrically substituted, regiochemistry becomes an issue. Consider the following reaction.



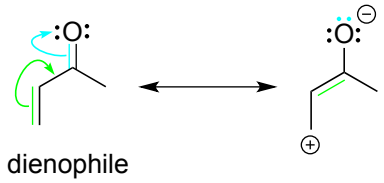
In this transformation, there are two conceivable ways for the diene and dienophile to combine. These two combinations would lead to regioisomeric products.



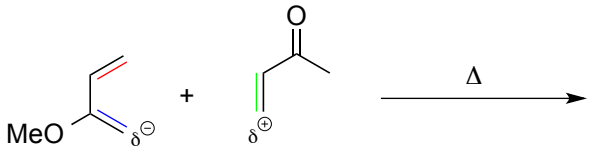
Examining the resonance structures of each reactant will illustrate the preferred combination. The diene has an electron-donating methoxy substituent. A lone pair of electrons from the methoxy group can be pushed into the diene to place δ^- character at one terminus.



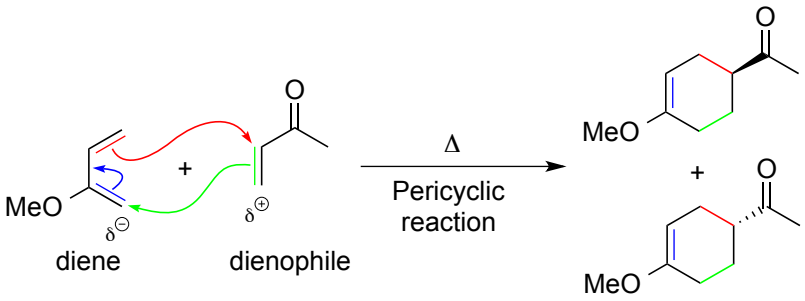
Conversely, the dienophile possesses an electron-withdrawing ketone, which can draw electron density out of the carbon-carbon double bond. This places δ^+ character at one end of the dienophile.



The diene and the dienophile will preferentially approach one another so as to join the termini having complementary polarities. In other words, the δ^- is attracted to the δ^+.

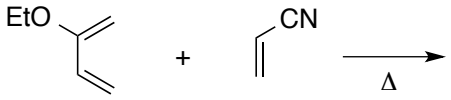


When aligned this way, a single regioisomer results. However, since a stereocenter is formed during the reaction, both configurations are possible, and the product is a racemic mixture of enantiomers.

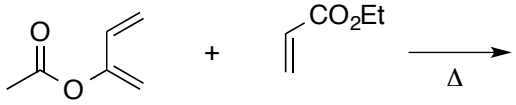


Problem 11. Predict the major product(s) of the following Diels-Alder reactions.

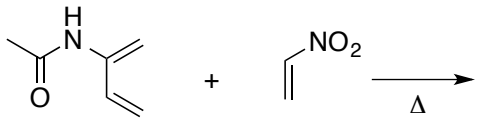
(a)



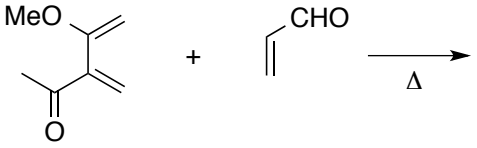
(b)



(c)



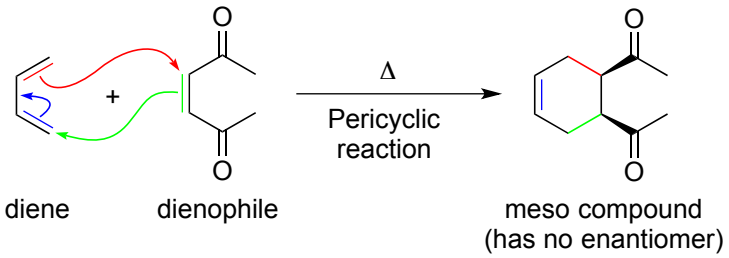
(d)



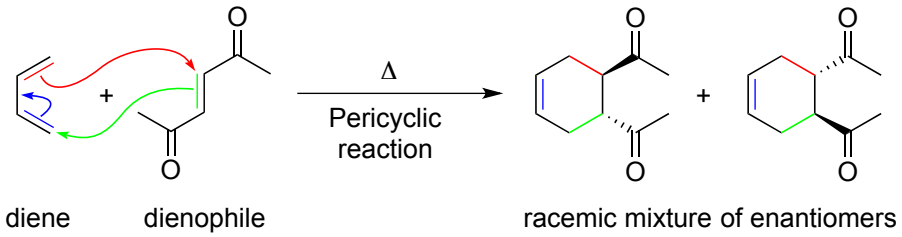
Stereochemical considerations

Since the Diels-Alder reaction is concerted and all bond making and breaking happens at once, the reaction is stereospecific. In other words, a particular configuration of the reactants will lead to a particular configuration of the products.

In the following example, the dienophile has two ketones that are *cis* to one another. That *cis* arrangement is preserved in the product. Since the reaction is concerted, there is no opportunity for any change in the orientation of the ketones relative to one another. This product happens to be a meso compound and therefore has no enantiomer.

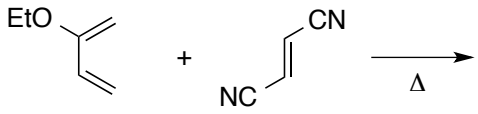


In the next example, the ketones have a *trans* orientation. This is preserved throughout the reaction so that they are *trans* in the product as well. This product has no internal plane of symmetry, so a racemic mixture of enantiomers is formed.

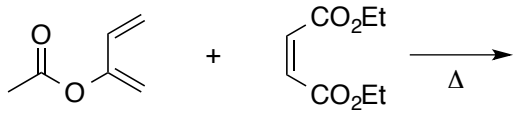


Problem 12. Provide the product(s) of the following cycloadditions.

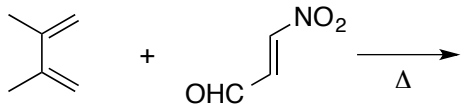
(a)



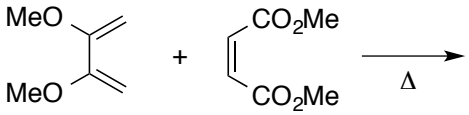
(b)



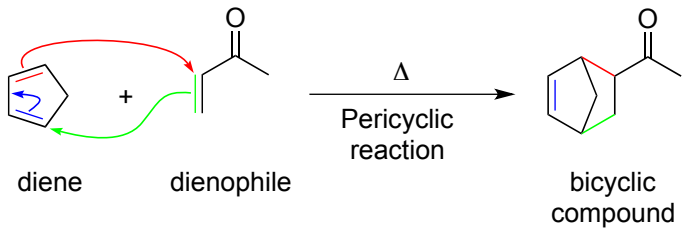
(c)



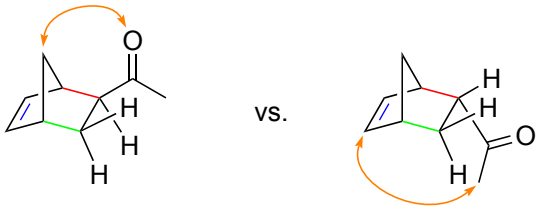
(d)



A second facet of the stereochemistry of the Diels-Alder reaction is the preference for endo addition. In the reaction shown below, a cyclic diene is used, so the product contains not just one ring but two, making it a bicyclic compound.



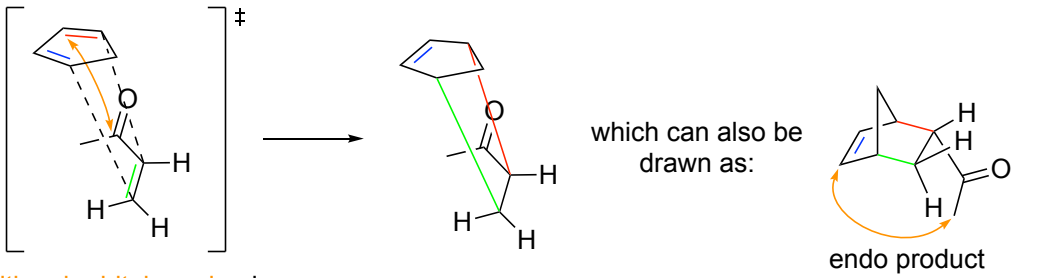
When this bicyclic compound is drawn from a more three-dimensional perspective, it becomes clear that the ketone may be placed closer to the one-carbon bridge or closer to the two-carbon bridge. If the substituent is closer to the shorter bridge, the product is called "exo." When the substituent is closer to the longer bridge, it is termed "endo."



exo product (substituent close to short bridge)

endo product (substituent close to long bridge)

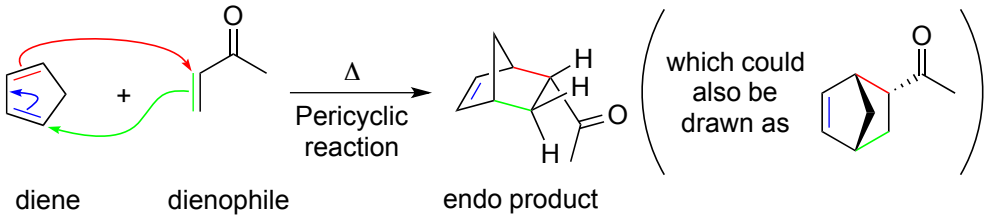
There is an electronic preference for the endo product. This preference results from additional orbital overlap that occurs between the substituent (ketone) and the diene during the transition state of the reaction.



Additional orbital overlap in transition state leading to endo product

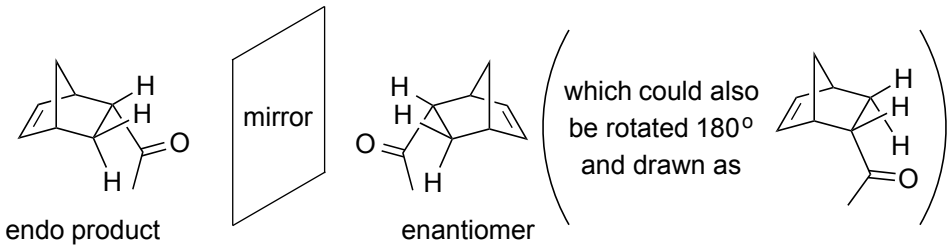
endo product (substituent close to long bridge)

Consequently, this pericyclic reaction can be drawn with more stereochemical detail to illustrate the formation of the endo product.



diene dienophile endo product

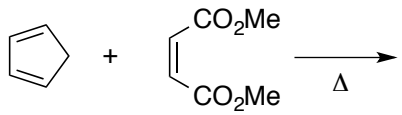
Note that the enantiomer of this endo product is also formed.



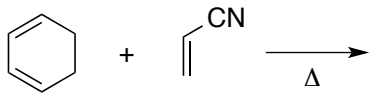
endo product enantiomer

Problem 13. Provide the product(s) of these [4+2]cycloadditions.

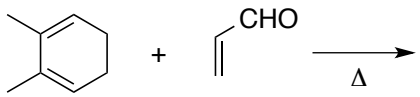
(a)



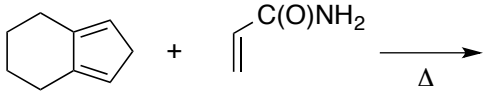
(b)



(c)



(d)

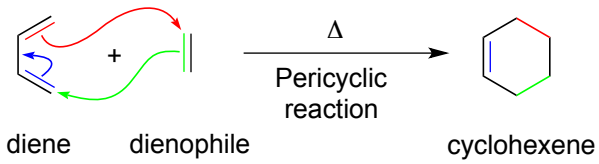


In conclusion, the Diels-Alder reaction is a pericyclic transformation in which a diene and a dienophile are joined to yield a cyclohexene ring. Regiochemistry is determined by complementary polarity of the reactants. The reaction is stereospecific and exhibits a preference for endo addition.

Synthesis using the Diels-Alder reaction

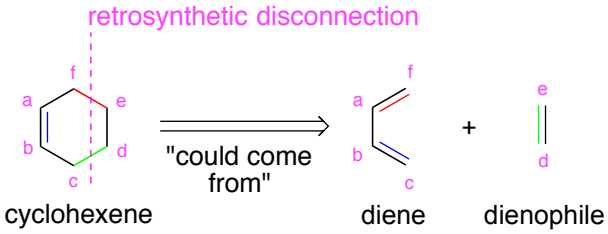
Synthesis problems that utilize the Diels-Alder reaction are actually quite straightforward, provided that you approach them systematically. It is important to have a methodical approach to these synthesis problems because, as we saw in Problem 13, the structures of the Diels-Alder adducts can sometimes be quite complex, which makes them appear daunting at first glance.

It is always useful to reflect back on the simplest possible Diels-Alder reaction.

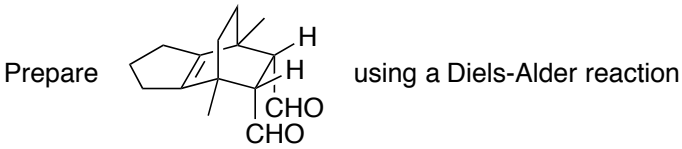


If we were to write this transformation from the retrosynthetic perspective, the cyclohexene adduct would appear first. Recall that the retrosynthetic arrow indicates that

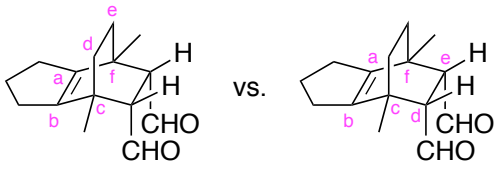
the compound "could come from" suggested reactants. We can then label the carbons (a – f) in both the adduct and its precursors. Additionally, we can show that the retrosynthetic disconnection appears where the new bonds (red and green) are in the cyclohexene ring.



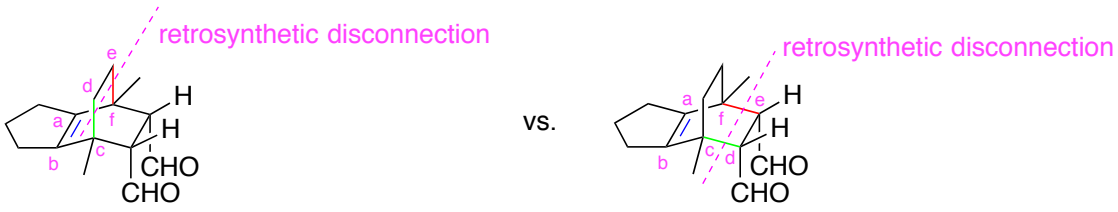
The value of having done this is that we can apply our retrosynthetic labeling to *any* Diels-Alder adduct and use it to guide us through the problem. Consider the following example.



The complexity of this target makes the problem appear more difficult than it actually is. Let's begin by applying the same lettering that we used in the simple case above. To do this properly, it is critical that you start by finding the cyclohexene ring and assigning the letters a and b to the alkene carbons, just as we did in the simple example above. The remaining carbons are lettered accordingly (b is connected to c, c is connected to d, etc.). In this problem, there are two cyclohexene rings, so we can begin by applying labeling for both possibilities.

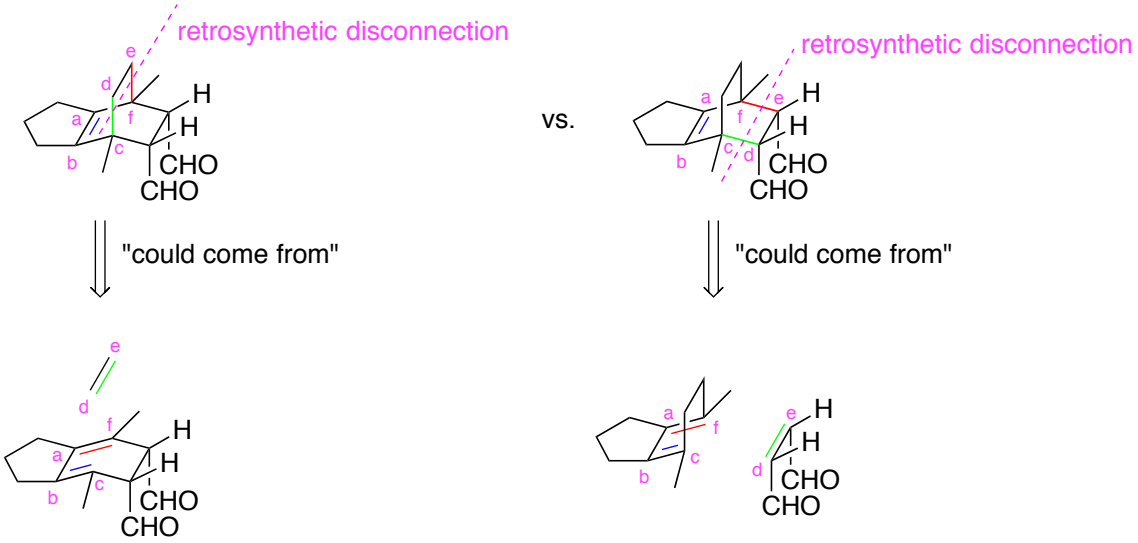


Now, we can apply the color-coding that we've used previously to highlight the bonds formed during the Diels-Alder cycloaddition. The c-d and e-f bonds are those that are made during the reaction, so these are the sites for our retrosynthetic disconnection.



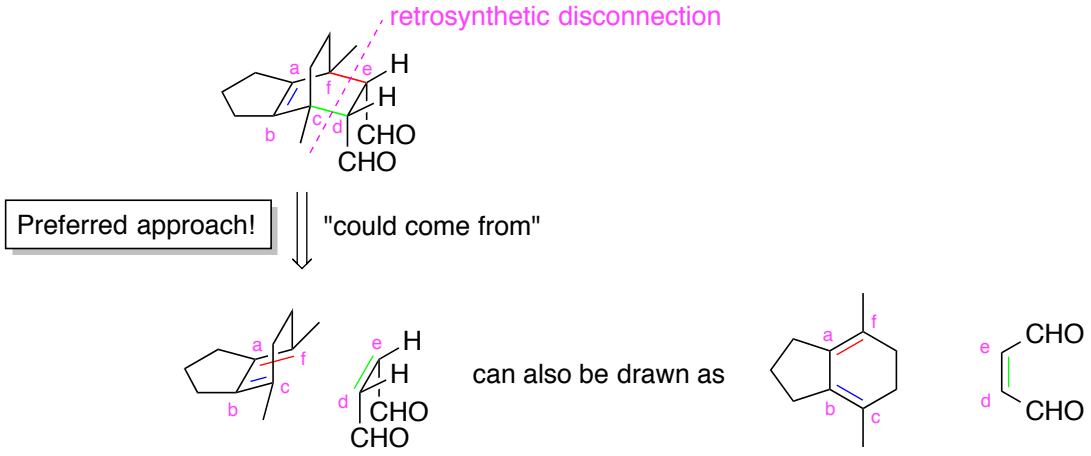
We proceed by simply erasing the c-d and e-f bonds, sliding the resultant fragments apart, and placing the π bonds at the locations indicated by our lettering in the simple example. In

other words, the red π bond appears between carbons a and f of the diene, the blue π bond appears between carbons b and c of the diene, and the green π bond appears between carbons d and e of the dienophile.

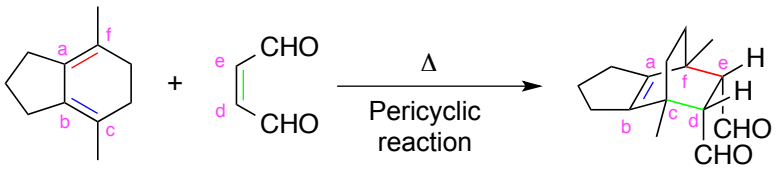


At this point, we can decide which approach is preferable. Recall that the dienophile usually bears electron-withdrawing groups in successful Diels-Alder reactions. In the first retrosynthesis, the dienophile has no electron-withdrawing groups, but in the second retrosynthesis, it has two. Therefore, the latter approach is therefore the preferred one.

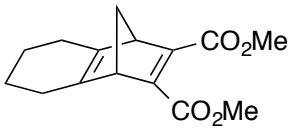
Lastly, we can clean up our drawings to make them look the way we would normally render them. Pay special attention to the *cis* arrangement of the two aldehydes in the dienophile.



All that remains is to draw the reaction in the forward sense to answer the question.



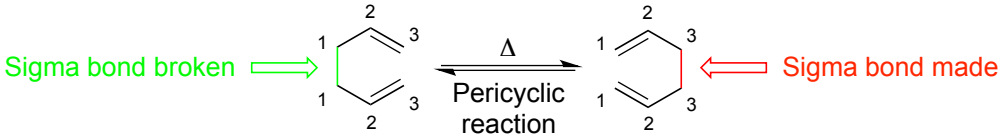
Problem 14. Propose a viable synthesis.

Prepare  using a [4+2]cycloaddition

Section 5: Cope rearrangement

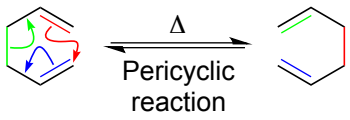
The Cope rearrangement is a reaction of 1,5-dienes. Note that these are isolated dienes, in contrast to the conjugated dienes used in the Diels-Alder reaction. The Cope rearrangement is another example of a pericyclic reaction, meaning that it too has a cyclic transition state in which all bond making and breaking occurs simultaneously. More specifically, the Cope rearrangement is a [3,3]sigmatropic ("sigma bond changing") reaction. It may also be called a sigmatropic shift or rearrangement.

In a sigmatropic reaction, a σ bond in the reactant is broken, and a new σ bond is formed in the product. π electrons also shift during the process. The numbering [3,3] stems from the fact that three atoms separate the site where the sigma bond is broken from the site where the sigma bond is made. This numbering is unrelated to IUPAC nomenclature.

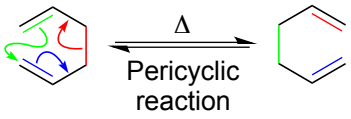


Mechanistic considerations

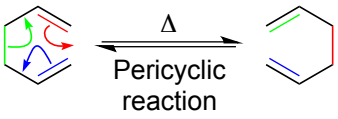
The mechanism can be envisioned as follows. One of the π bonds attacks the carbon six atoms away, thereby forming a new σ bond. This displaces the second π bond, and as that π bond migrates, a σ bond is cleaved and becomes a π bond.



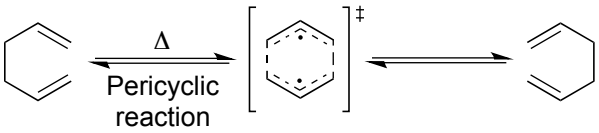
In the reaction shown above, the reactant and the product are the same molecule. Since these compounds have the same energy, the reaction can just as easily proceed in the opposite direction.



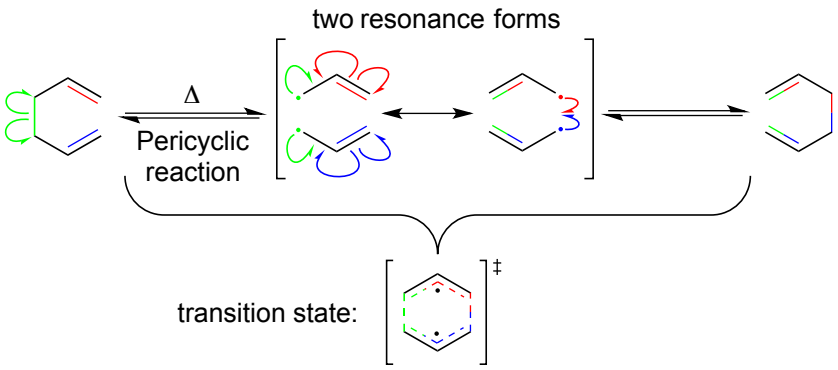
There are two other ways that you may see the mechanism drawn. Sometimes the arrow that forms the new σ bond is drawn not to the carbon six atoms away but in between the two carbons that will be joined by this new bond.



Additionally, you will sometimes see the transition state drawn as a diradical.



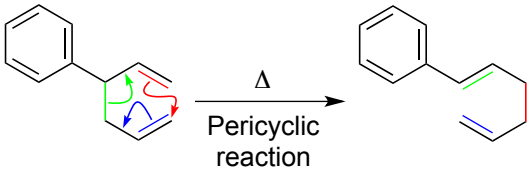
With all of the partially formed and broken bonds represented by dashed lines, this depiction can be difficult to follow. If we imagine a radical process in a stepwise manner, the diradical transition state can be clarified. Imagine the homolysis of the σ bond. This would yield two allylic radicals, both of which can be drawn as an alternate resonance structure. These alternate resonance structures place the two radicals on the opposite sides of the allylic systems. If these centers unite, the product is formed. The diradical transition state captures in one structure all of these events that we imagined as being stepwise. It includes the hybrid of the two resonance forms, as well as the fact that the original σ bond is not completely broken and the new σ bond is not completely formed.



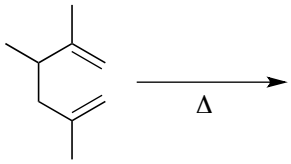
Remember though that the Cope rearrangement is actually a concerted process. All of the bond making and breaking happens at once. Imagining a radical process in a stepwise fashion was merely a tool for clarifying the diradical transition state.

A specific example of the Cope rearrangement

The generic example used above had a reactant and product of equal energy. However, with many substrates this is not the case. When the reactant and product differ in energy, the more stable one is favored at equilibrium. In the following example, Cope rearrangement converts the two monosubstituted alkenes in the reactant to a monosubstituted and a disubstituted alkene in the product. Furthermore, one of the alkenes in the product is also conjugated. The higher level of substitution and the conjugation both make the product more stable than the reactant. The product is therefore favored.

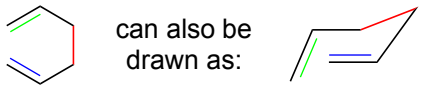


Problem 15. Draw a mechanism for the following Cope rearrangement. Is the reactant or product favored at equilibrium?

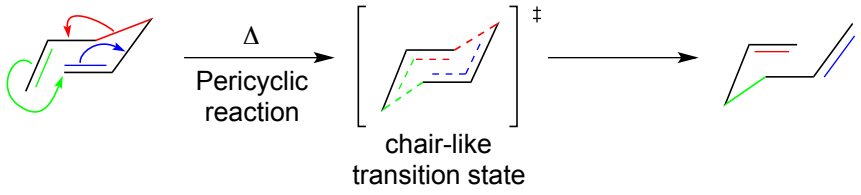


Stereochemical considerations

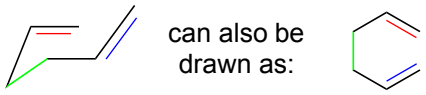
The Cope rearrangement proceeds through a chair-like transition state. This can have stereochemical ramifications. There are six atoms involved in the Cope rearrangement, and these adopt a conformation that approximates the chair conformation of cyclohexane.



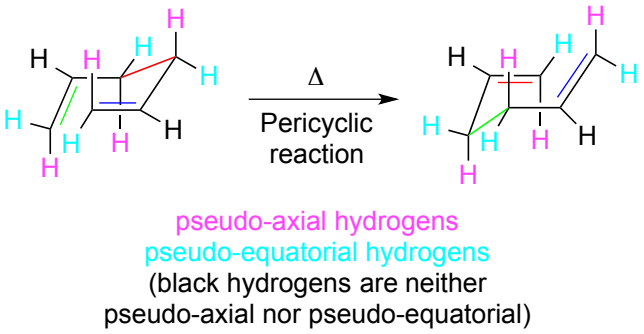
When the Cope rearrangement occurs, the transition state looks much like a chair.



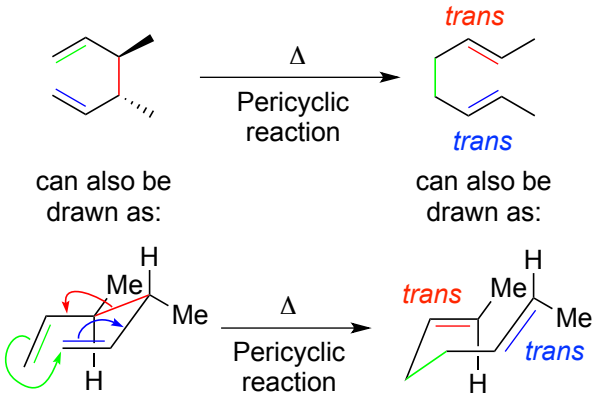
Also, the product initially has a chair-like conformation when it is formed.



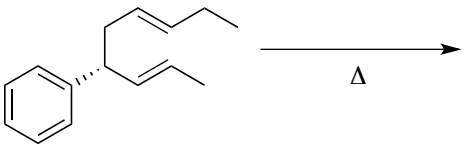
Substituents stemming from this chair-like core are referred to as being in pseudo-axial or pseudo-equatorial positions. The prefix "pseudo" is simply a reminder that there is not an *actual* cyclohexane ring present.



In the following example, the reactant can be drawn in a chair-like conformation. The stereochemistry of the methyl groups has been specified, and this stereochemistry allows them to be placed in pseudo-equatorial positions on the chair-like conformation. After Cope rearrangement, it is apparent that both alkenes have the *trans* configuration.

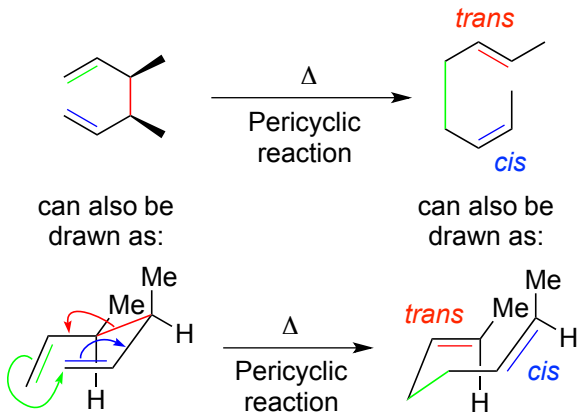


Problem 16. Draw the mechanism for the following [3,3]sigmatropic rearrangement. Use the chair-like transition state to predict the stereochemistry of the product. What is the driving force for this reaction?

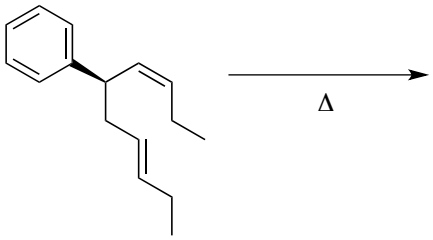


A different reactant stereochemistry will lead to a different outcome. In the next example, the reactant is a meso compound and a stereoisomer of the previously used reactant. When

this compound is drawn in a chair-like conformation, one methyl group can be in the pseudo-equatorial position, but the other must be pseudo-axial. After Cope rearrangement, one of the resultant alkenes is *trans*, but the other is *cis*. Take note of the difference from the previous example in which both alkenes in the product were *trans*.



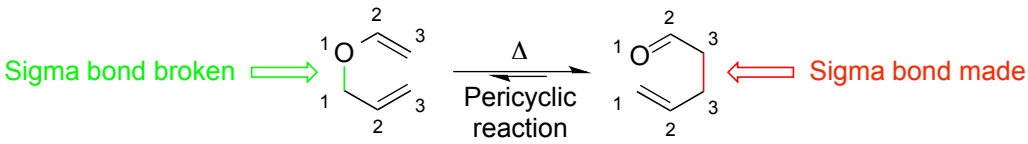
Problem 17. Provide a mechanism for the following Cope rearrangement that explains the stereochemical outcome of the reaction. What drives this reaction?



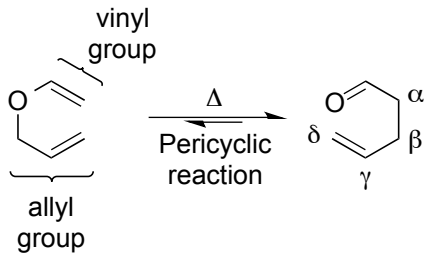
To recap, the Cope rearrangement is a [3,3]sigmatropic rearrangement in which one 1,5-diene is converted to another. The more stable 1,5-diene is favored at equilibrium. The reaction proceeds through a chair-like transition state, which has stereochemical ramifications.

Section 6: Claisen rearrangement

The Claisen rearrangement is a pericyclic reaction much like the Cope rearrangement because it too has a cyclic transition state in which all of the bond making and breaking happens concurrently. Specifically, the Claisen rearrangement is also a [3,3]sigmatropic reaction, meaning that three atoms separate the sites where the original σ bond is broken and the new σ bond is made.

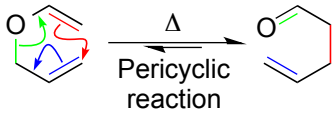


The presence of an oxygen atom in the core of the reactant differentiates the Claisen from the Cope rearrangement. In the Claisen rearrangement, the reactant is an allyl vinyl ether, and after the transformation, a γ,δ-unsaturated carbonyl is formed.

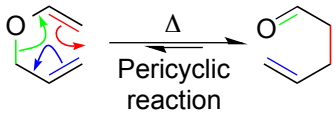


Mechanistic considerations

Analogous to the Cope mechanism, a π bond attacks the carbon six atoms away. This displaces the second π bond, which in turn cleaves the σ bond. The σ bond is transformed into a new π bond of a carbonyl.



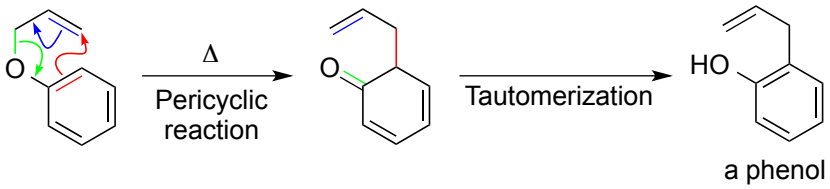
Alternatively, you may see the arrow describing the initial attack of the π bond drawn into the space between the two carbons about to be joined by the new σ bond.



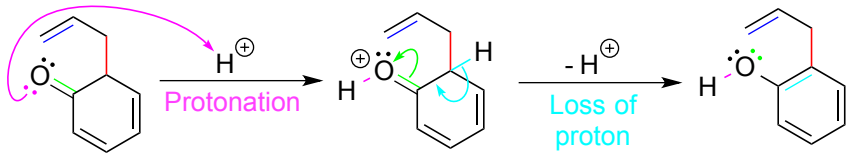
The carbonyl-containing product is typically favored at equilibrium. This is due to the relative strengths (based on bond dissociation energies) of the bonds broken and made in the reaction. A stronger set of bonds is present in the product.

A specific example of the Claisen rearrangement

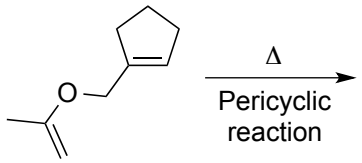
A common example of the Claisen rearrangement is a minor variation on the reaction motif. The reactant contains an allyl phenyl ether (rather than an allyl vinyl ether), where a π bond of the phenyl group plays the same role as the π bond of the vinyl group did in the generic mechanism presented above. In this case, the Claisen rearrangement yields a ketone that tautomerizes rapidly to yield an aromatic ring, affording a phenol as the final product. In the next Chapter, we'll learn more about what makes aromatic rings so stable. For the time being, it is sufficient to know that they are in fact highly stable, and their formation is therefore desirable.



Tautomerization requires only a trace of acid or base. An acid-catalyzed mechanism for tautomerization of the ketone to the phenol is presented below. Protonation of the ketone generates an oxonium ion. Then, loss of a proton from the α carbon restores aromaticity to the ring and pushes electrons onto the carbonyl oxygen to neutralize its charge.

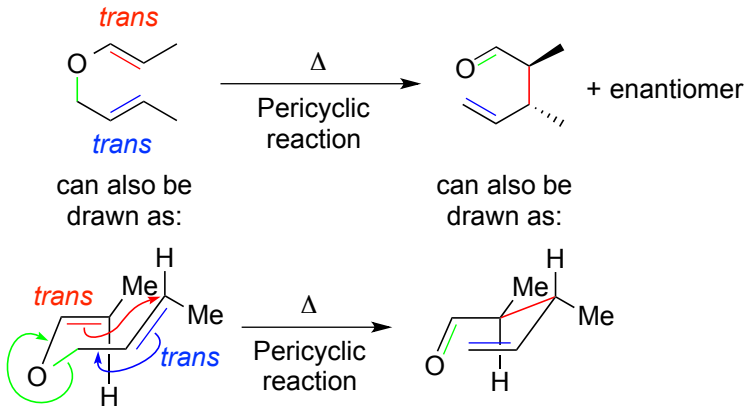


Problem 18. Draw a mechanism for the following Claisen rearrangement.

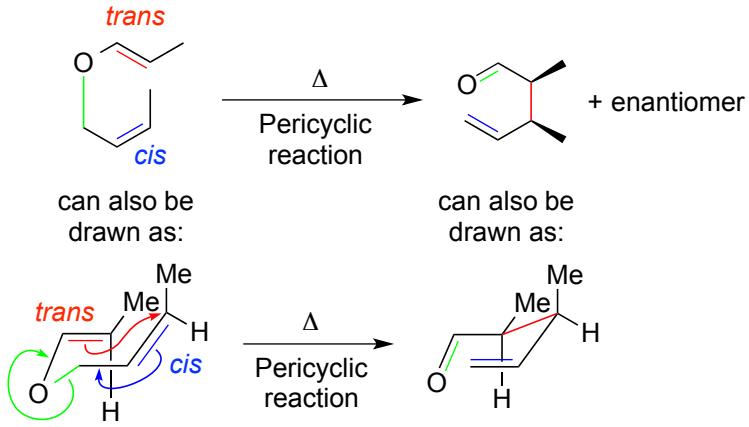


Stereochemical considerations

Much like the Cope, the Claisen rearrangement proceeds through a chair-like transition state, which can have stereochemical consequences. In the reaction below, an allyl vinyl ether with *trans* geometry of both its olefins undergoes Claisen rearrangement. If the reactant is drawn in a chair-like conformation, it becomes apparent that the *trans* configuration of the alkenes allows the methyl groups to be placed in pseudo-equatorial positions. After the pericyclic reaction occurs, the methyl groups are still in pseudo-equatorial positions and occupy opposite sides of this chair-like conformation. An enantiomeric chair-like transition state affords the enantiomeric product as well.



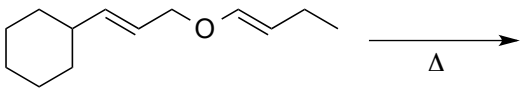
In the next example, the allyl vinyl ether reactant contains one *trans* and one *cis* olefin. In the chair-like transition state, it will only be possible to place one methyl group in the pseudo-equatorial orientation. Therefore, the other methyl group must occupy a pseudo-axial position. The product has both methyl groups on the same side of the chair-like conformation. Again, an enantiomeric chair-like transition state yields the enantiomeric product.



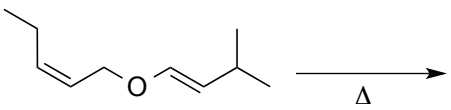
Comparing the previous two examples illustrates the stereochemical ramifications of the chair-like transition state. The different olefin geometries of the stereoisomeric reactants yielded unique stereoisomeric products.

Problem 19. Draw mechanisms for the following Claisen rearrangements. Use the chair-like transition state to predict the stereochemistry of the products.

(a)



(b)

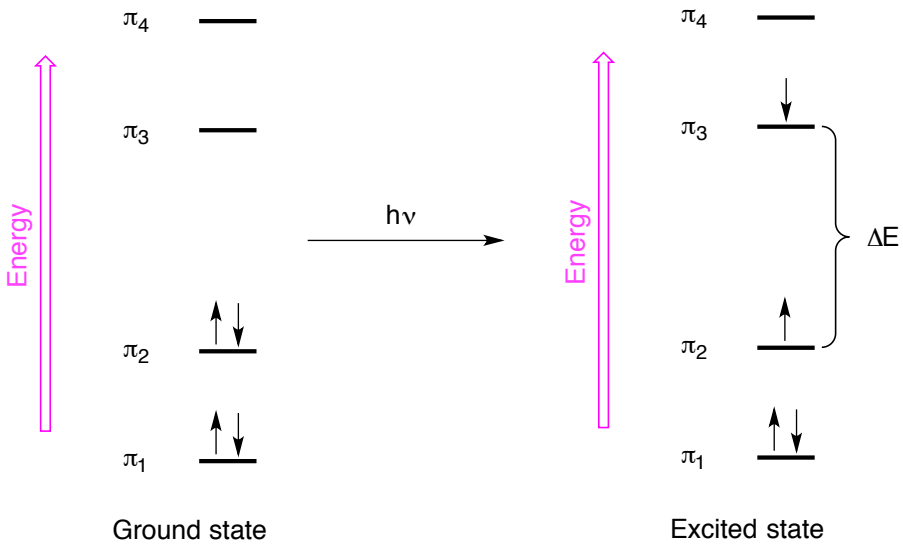


In conclusion, the Claisen rearrangement is a [3,3]sigmatropic reaction of an allyl vinyl ether or an electronically equivalent reactant. The product contains a γ,δ-unsaturated carbonyl. The reaction proceeds through a chair-like transition state, which has stereochemical consequences.

Section 7: Conjugated systems and light

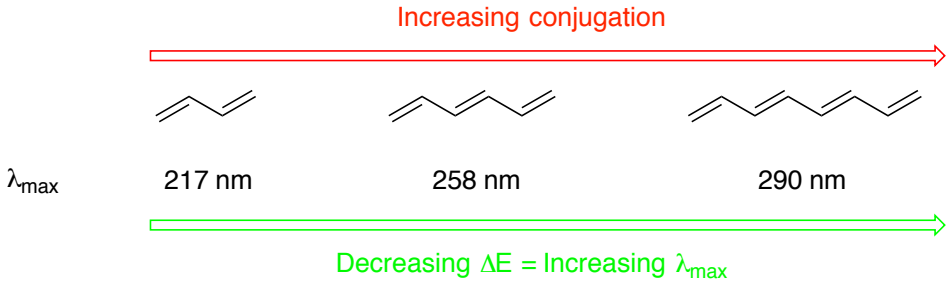
When you think of colored *inorganic* materials, the origin of color is the promotion of an electron in a transition metal's d orbitals. But, with colored *organic* compounds, the origin of color is actually extended conjugation. The absorption of light in the UV-Vis range of the electromagnetic spectrum correlates with the promotion of an electron in the π system to a higher energy state.

The diagram below shows the molecular π orbitals for 1,3-butadiene that we derived in Section 2. Light of the proper energy can promote an electron from the highest occupied (π_2) to the lowest unoccupied (π_3) molecular orbital. It just so happens that light with a wavelength of 217 nm provides the energy needed for this transition (ΔE). This falls in the ultraviolent range (200–400 nm). An isolated diene, on the other hand, would require light outside the UV range (< 200 nm) to similarly promote a π electron to a higher energy level.

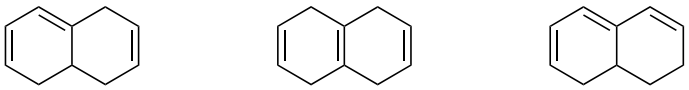


When an electron is promoted to a higher energy state, the molecule is said to be in an excited state. This is in contrast to the ground state, which has the normal electronic configuration.

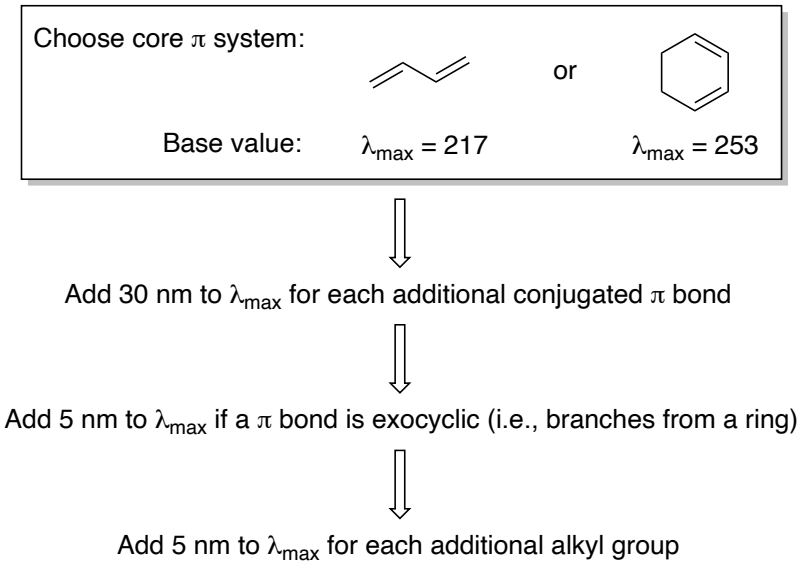
As conjugation increases, the energy gap (ΔE) is reduced. Consequently, a longer wavelength of light with a lower energy is sufficient for the promotion of a π electron. The wavelength at which the maximal absorbance of light occurs is termed the λ_{max}, and in the following series, we see the λ_{max} increase as the conjugation within the molecule is extended one π bond at a time.



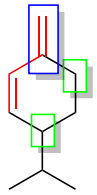
Problem 20. Rank the following compounds in order of increasing λ_{max}.



It is possible to obtain an estimate of the λ_{max} for a conjugated molecule by using the Woodward-Fieser rules. An abbreviated version of the Woodward-Fieser rules encompassing solely hydrocarbons is given in the following diagram. There are additional guidelines for dealing with more complex substances, such as those containing heteroatoms. For simple systems, a base λ_{max} value is assigned depending on whether the core conjugated π system is a 1,3-butadiene moiety or a 1,3-cyclohexadiene group. For each additional conjugated π bond, 30 nm are added to the λ_{max}. If a π bond in the conjugated system includes a ring carbon but is outside the ring, it is known as an exocyclic double bond, and 5 nm are added to the λ_{max}. Also, each alkyl group bonded directly to the conjugated π system increases the λ_{max} by 5 nm.



Let's apply the Woodward-Fieser rules to β-phellandrene, which is shown in the following diagram. The core structure of the π system includes a 1,3-butadiene moiety that gives a base λ_{max} value of 217 nm. This butadiene bears two alkyl groups, and one of the alkenes is exocyclic. Each of these features adds 5 nm to the λ_{max}, resulting in a final value of 232 nm.



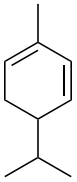
Core structure: 217 nm
Two alkyl groups: 2 x 5 nm
Exocyclic double bond: 5 nm

Expected λ_{max} = 232 nm

β-phellandrene

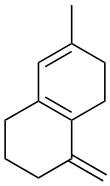
Problem 21. Use the Woodward-Fieser rules to predict approximate λ_{max} values for the following compounds.

(a)

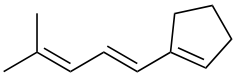


α-phellandrene

(b)



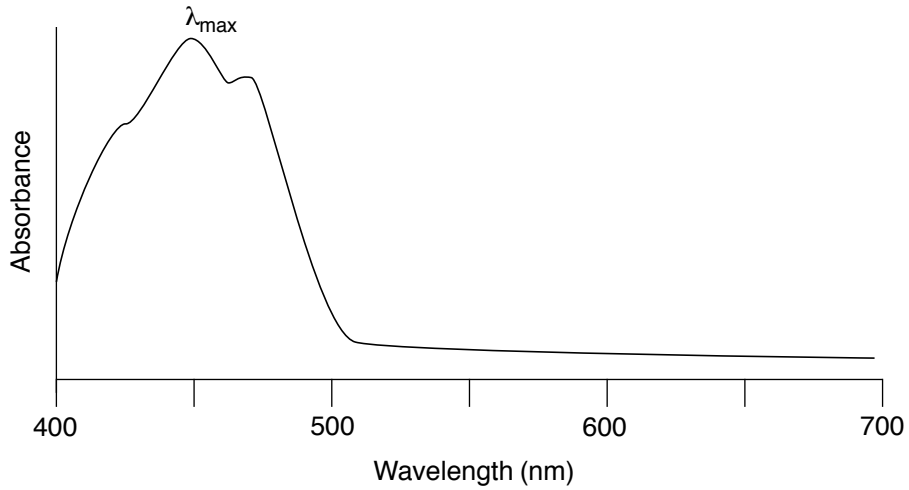
(c)



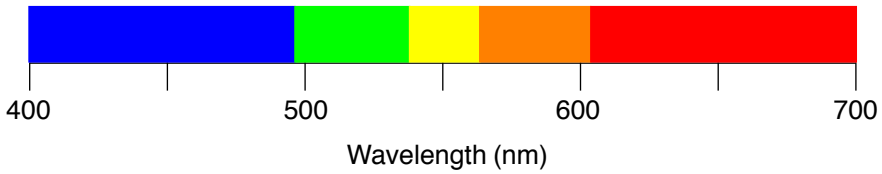
As the conjugation extends further and further, the λ_{max} can become large enough that it actually falls within the visible region (400–700 nm) of the electromagnetic spectrum. This leads to the appearance of color. For instance, β-carotene is the compound responsible for the orange color of carrots. It has an extensive conjugated π system.

β-carotene

β-Carotene has a λ_{max} of 450 nm as seen in the following UV-Vis spectrum.



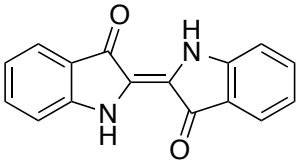
When comparing the λ_{max} to the wavelengths of the colors of light shown in the following diagram, we can see that β-carotene absorbs maximally in the blue region.



A color wheel is a useful tool that places the same information about the wavelengths of different colors of light into a circular format. In this format, the complementary colors appear directly opposite each other on the wheel. Blue's complementary color is orange. Since β-carotene absorbs blue light maximally, we observe it as orange because orange light is reflected from the molecule rather than absorbed by it.

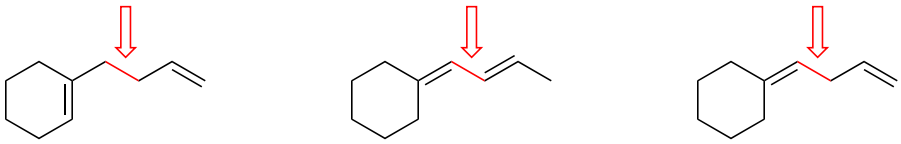
[1]

Problem 22. The following compound has a λ_{max} of 602 nm. What color would you expect it to be?

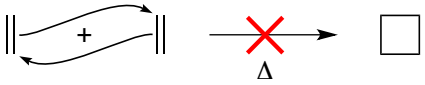


End-of-the-Chapter problems

Problem 23. Consider the indicated bond in each of the following molecules. Rank these compounds in order of decreasing length of this bond.



Problem 24. In Problem 9, we showed why a [2+2]cycloaddition does not occur simply with heating. You'll recall that this was due to a problem with the orbital symmetry.



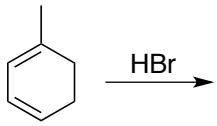
It turns out that the [2+2]cycloaddition does occur under photochemical conditions.

[1] Color wheel image: http://commons.wikimedia.org/wiki/File:BYR_color_wheel.svg

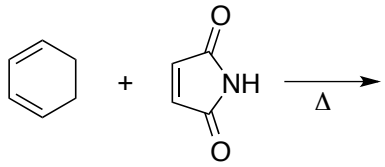
Light promotes an electron of some ethylene molecules from the HOMO to the LUMO, and this newly occupied molecular π orbital then interacts with the LUMO of a ground state ethylene molecule. Using these molecular π orbitals, show how this results in a successful reaction.

Problem 25. Predict the major product(s) of the following reactions.

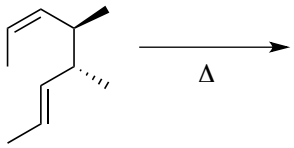
(a)



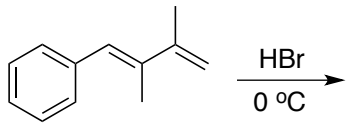
(b)



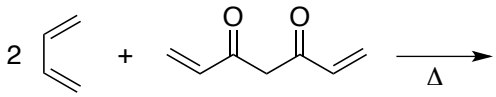
(c)



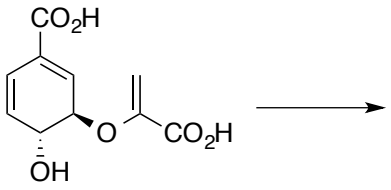
(d)



(e)

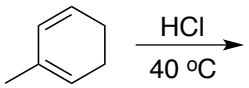


(f) The following is a Claisen rearrangement that occurs in nature during the biosynthesis of the amino acid tyrosine. You need not draw the transition state to determine the stereochemical outcome. Simply note that the vinyl group is on the top face of the molecule, so it must approach the allyl moiety from the top face as well.

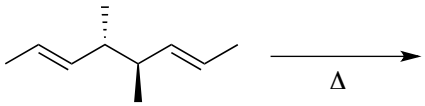


chorismic acid

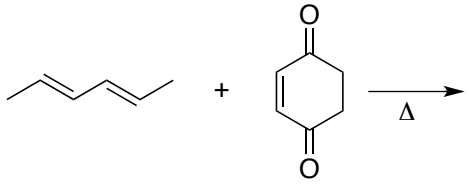
(g)



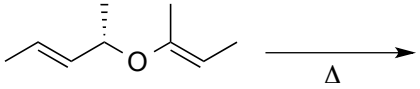
(h)



(i)

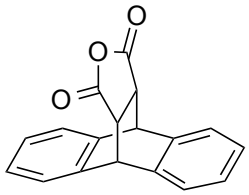


(j)



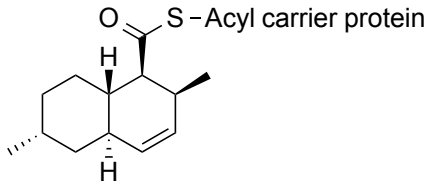
Problem 26. Provide viable syntheses for the following.

(a)

Prepare  using a Diels-Alder reaction

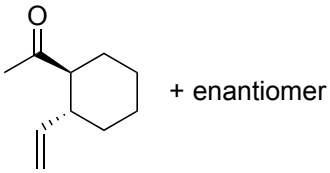
(b) Lovastatin is a drug used for lowering cholesterol levels, but it is also a naturally occurring molecule. Over the years, the notion of an enzyme that could catalyze Diels-Alder

reactions has been a tantalizing and contested idea. Show how a Diels-Alder reaction could be used to prepare the following molecule, which is a precursor of lovastatin.

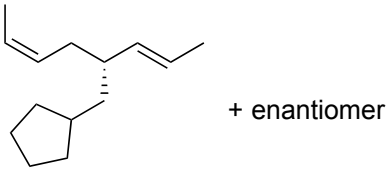


Problem 27. Provide viable syntheses for the following.

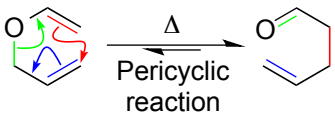
(a) Show how the following molecule can be prepared using a Claisen rearrangement.



(b) Show how the following molecule could be prepared via a Cope rearrangement.

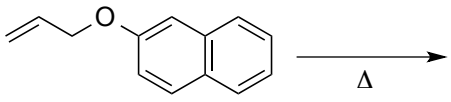


Problem 28. Using the bond dissociation energies provided in the table below, show why the carbonyl-containing product of the Claisen reaction is favored at equilibrium.

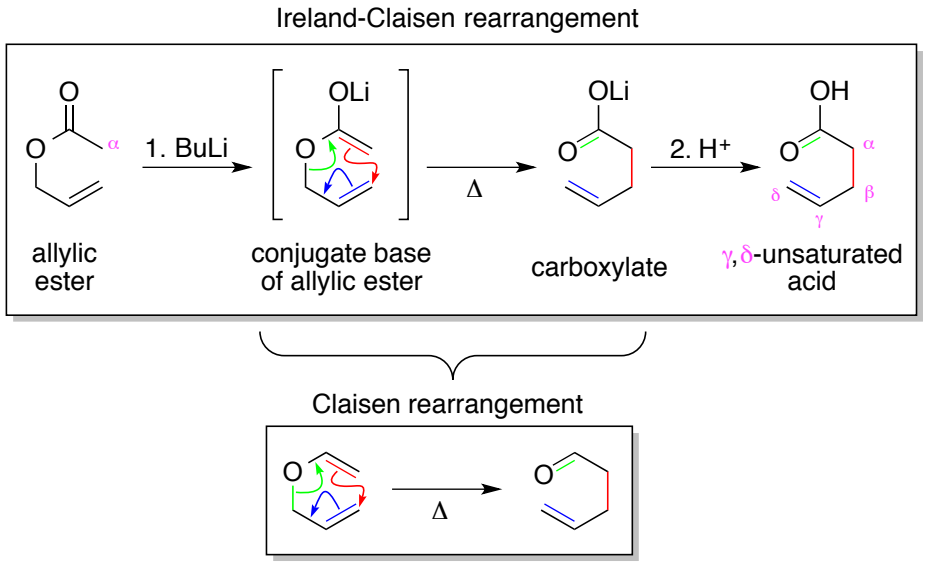


Bond	Bond Dissociation Energy (kcal/mole)
C-C	83
C=C	146
C-O	85.5
C=O	177

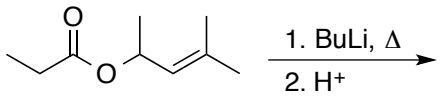
Problem 29. An investigator heated the following ether in the hopes of inciting a Claisen rearrangement. Upon completion of the reaction, she obtained an IR spectrum of the product, which exhibited a broad signal at approximately 3300 cm^{-1}. There were also signals just above and below 3000 cm^{-1} corresponding to sp^2 and sp^3 C-H stretching, respectively. These were the only resonances in the functional group stretching region. What transpired during this reaction?



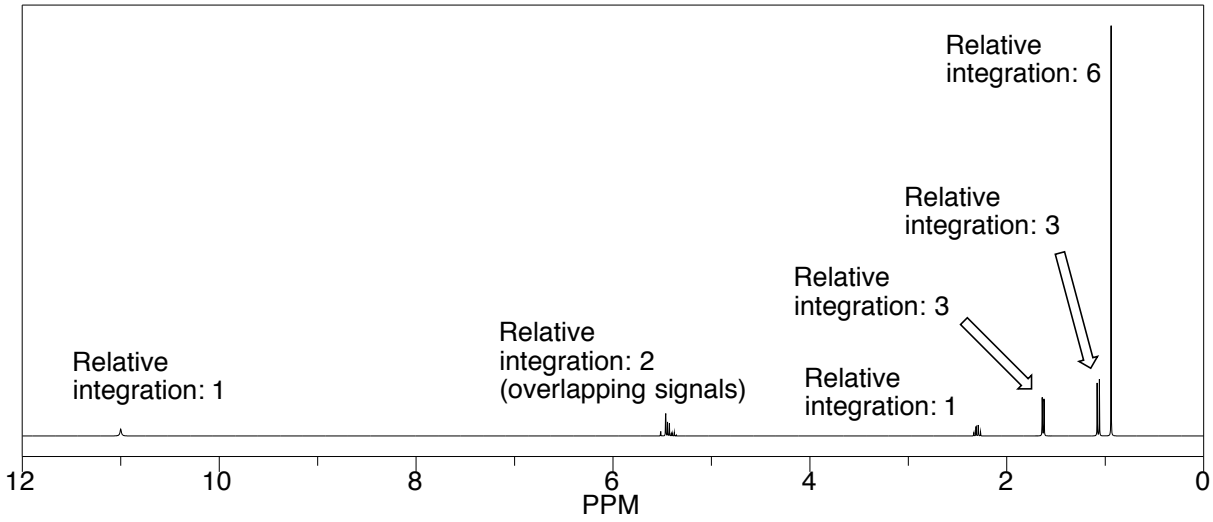
Problem 30. The Ireland-Claisen rearrangement is mechanistically similar to a Claisen rearrangement. An allylic ester is treated with a strong base, such as butyllithium (BuLi). The strong base deprotonates the position next to the carbonyl, which is known as the α position. The conjugate base has a structure very much like that of the allyl vinyl ether used in a Claisen rearrangement. As a result, it undergoes an analogous [3,3]sigmatropic shift. The immediate product of the rearrangement is a carboxylate, which is protonated in a second, separate step to yield a γ,δ-unsaturated carboxylic acid.



Show a mechanism for the following Ireland-Claisen rearrangement. You may ignore stereochemistry.



Then, assign the signals in the ^{1}H NMR spectrum of the product shown below.


Relative integration: 6
Relative integration: 3
Relative integration: 3
Relative integration: 2 (overlapping signals)
Relative integration: 1
Relative integration: 1
12
10
8
6
4
2
0
PPM

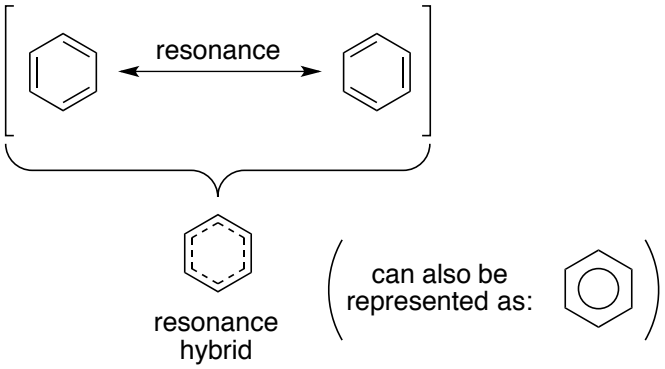
Chapter 13: Aromaticity

Section 1: Benzene
Section 2: Nomenclature of benzene derivatives
Section 3: Hückel's rule
Section 4: Molecular orbitals
Section 5: Annulenes
Section 6: Polyaromatic hydrocarbons
Section 7: Ions and aromaticity
Section 8: Aromatic heterocycles

Section 1: Benzene

The structure of benzene

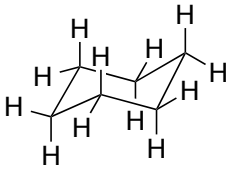
Benzene (C_6H_6) puzzled chemists for quite some time. It was isolated by Michael Faraday in 1825, but it took years for the chemical community to reconcile the presence of only one hydrogen for each carbon in the formula. In 1865, August Kekulé, building on the work of others, proposed the cyclic structure with which we are now quite familiar. Kekulé's initial proposal entailed a rapid interconversion of the Kekulé structures shown below. We now know these to be resonance forms that do not actually interconvert. Instead, we now view them as contributors to a single resonance hybrid, which is the real molecule.



Both drawings of the resonance hybrid reflect the continuous array of parallel p orbitals in the ring. These parallel p orbitals overlap to create a donut-shaped cloud of electron density above and below the plane of the benzene ring itself.

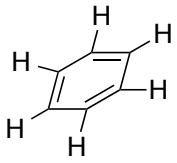
Unlike a cyclohexane ring, a benzene ring is totally flat because all of its carbon atoms are sp^2 hybridized.

Cyclohexane adopts a chair conformation



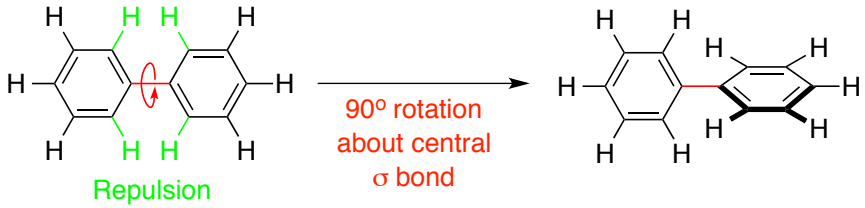
All carbons are sp^3

Benzene is flat



All carbons are sp^2

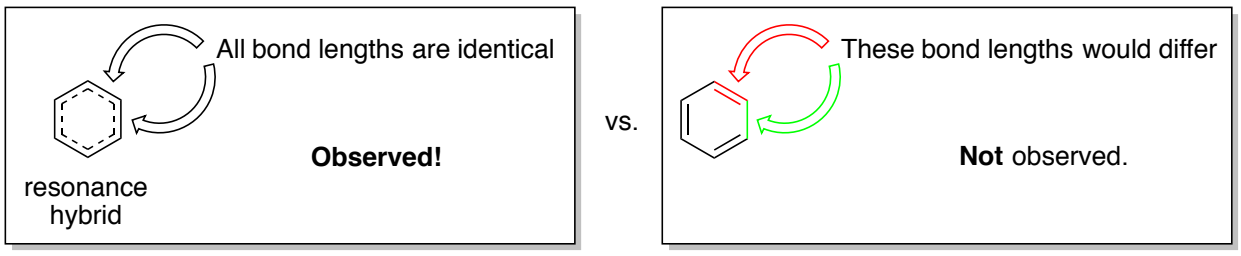
Problem 1. Biphenyl is a compound containing two benzene rings joined by a single σ bond. If the two rings reside in the same plane, there is repulsion of the hydrogen atoms adjacent to the joining σ bond. Rotation about that central bond places the two rings perpendicular to each other and alleviates the repulsion.



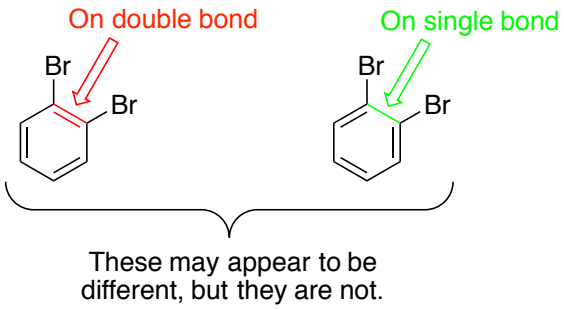
Draw the major resonance forms of biphenyl. In a separate drawing, show the p orbitals of the π system.

Benzene and resonance

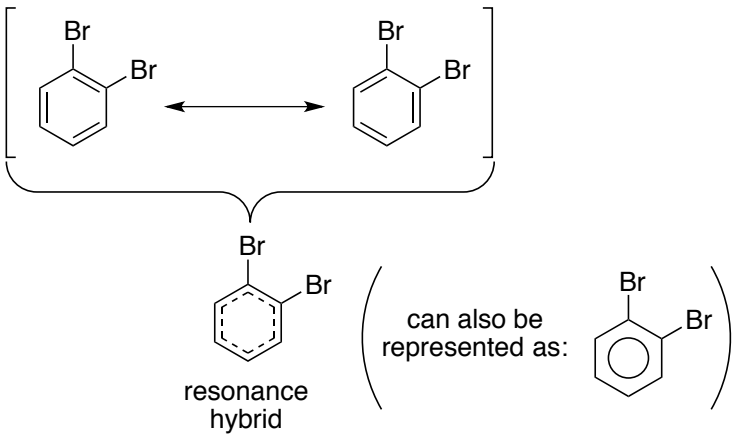
Understanding resonance is integral to appreciating the structure, stability, and behavior of benzene and its derivatives. For instance, all of the bond lengths in benzene are identical. This can only be explained through the resonance hybrid in which all bonds have a bond order between 1 and 2 (i.e., between that of a single and double bond).



Furthermore, all sites on the ring are equivalent. For instance, let's consider a single isomer of a disubstituted benzene, such as 1,2-dibromobenzene. The two Kekulé structures may appear to be different molecules at first glance, but they are not.



In fact, these two structures are merely resonance forms of one another. The resonance hybrid better represents the real molecule and highlights the fact that all sites on the ring are equivalent.



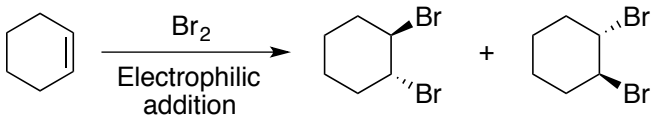
Although the resonance hybrid is the real molecule, electronic bookkeeping (i.e., keeping track of the electrons throughout a reaction) is difficult when using the hybrid. It is therefore convenient to use one of the two Kekulé structures when drawing reaction mechanisms for benzene and its derivatives.

Problem 2. How many isomers of dibromobenzene are there?

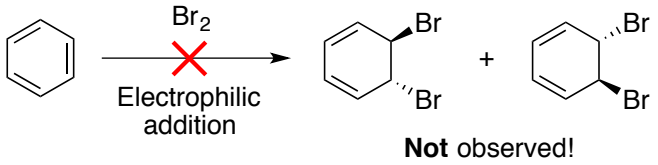
The properties of benzene

You might wonder why we don't just treat benzene as a molecule containing three alkenes, in which case it would have been covered in Chapter 10. It turns out that benzene actually behaves much differently than a typical alkene. As a result, benzene and its derivatives are grouped into a distinct category referred to as aromatic molecules. In this chapter, we'll learn about what makes a molecule aromatic, and in the next chapter, we'll cover the reactions of these aromatic compounds.

Let's begin by highlighting how benzene is very different from a typical alkene. One example is its reactivity. For instance, in Chapter 10 we learned that alkenes undergo electrophilic addition reactions, such as the addition of bromine across the π bond.

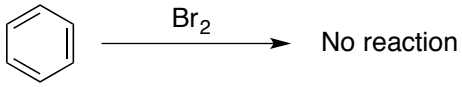


Benzene does not undergo a comparable reaction.

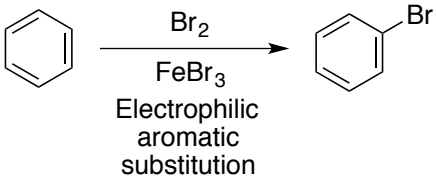


Not observed!

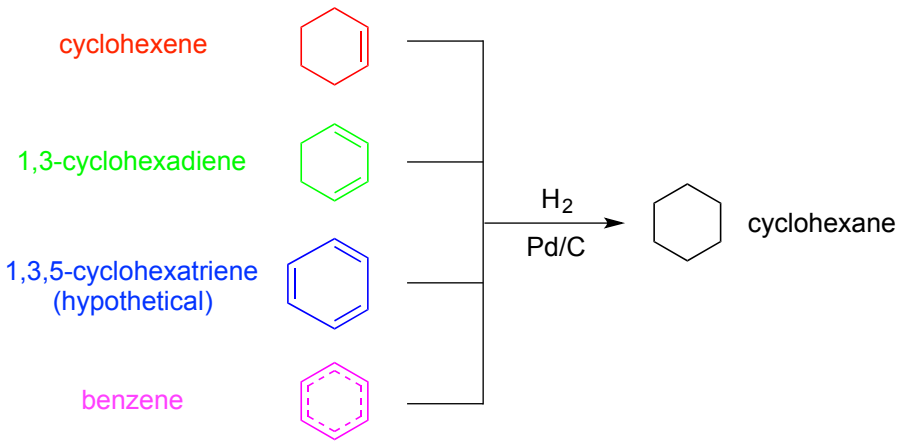
Instead, when it is treated with bromine, no reaction takes place.



If we add a catalyst (e.g., $FeBr_3$), then a reaction does take place, but it is not the anticipated electrophilic addition. Only a single bromine is added to the molecule, and it actually replaces a hydrogen atom. This entirely different reaction paradigm is known as electrophilic aromatic substitution, and it is a primary focus of the next chapter.



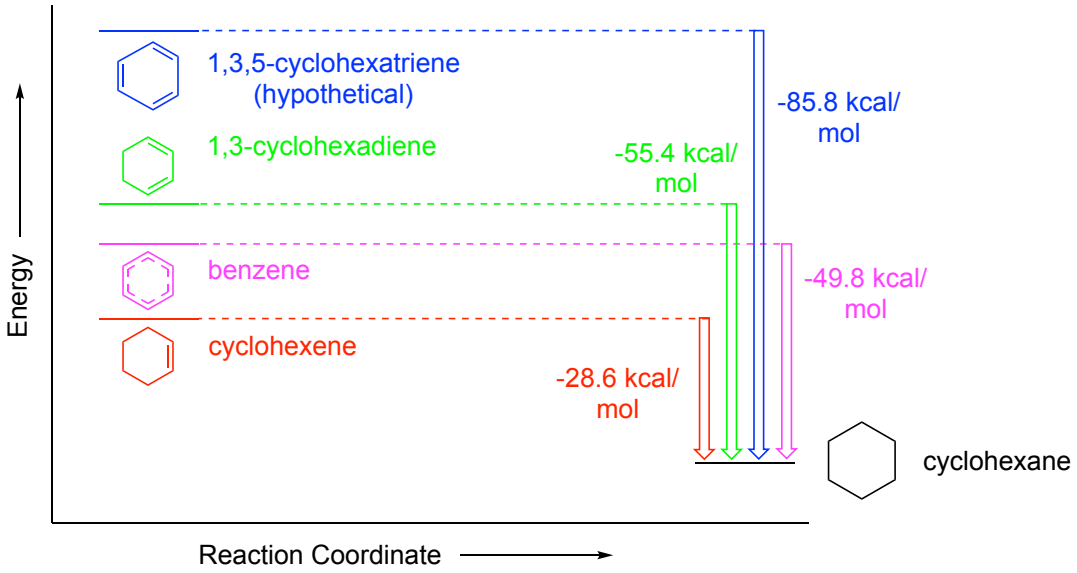
We have now seen that benzene reacts differently than an alkene. Benzene is also much more stable than a comparable alkene would be. In Chapter 7, the notion of using heat of hydrogenation to assess stability was first introduced, and this technique was utilized again in Chapter 12. We'll use it once again now to provide evidence for benzene's unusual amount of stability. To do this, let's consider the hydrogenation of four molecules: cyclohexene; 1,3-cyclohexadiene; 1,3,5-cyclohexatriene (a hypothetical molecule); and benzene itself. The complete hydrogenation of any of these with an appropriate amount of hydrogen would yield cyclohexane.



Our expectations are rather straightforward. Cyclohexene will release a certain amount of energy when it is hydrogenated. Since 1,3-cyclohexadiene contains two alkenes, we expect it to release twice as much energy. 1,3,5-Cyclohexatriene is a hypothetical molecule in which the three alkenes do not enjoy resonance. The three single bonds in this structure are longer to illustrate the imagined isolation of the alkenes. We already know this to be false, so we imagine the existence of such a molecule only to illustrate the expectation that a compound with three isolated alkenes would simply release three times as much energy as cyclohexene when it is hydrogenated. Finally, we will also consider benzene's hydrogenation and compare it to that of the hypothetical 1,3,5-cyclohexatriene.

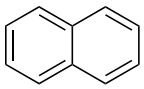
The actual heat of hydrogenation data are plotted below. Cyclohexene releases 28.6 kcal/mole of energy when it is reduced. We therefore expect 1,3-cyclohexadiene to release twice as much energy (2 x 28.6 kcal/mole = 57.2 kcal/mole); however, it only liberates 55.4 kcal/mole upon reduction. The difference can be accounted for by conjugation. As we discussed in the last chapter, a conjugated diene is more stable than its isolated counterpart. Being more stable than expected, 1,3-cyclohexadiene liberates less energy than predicted when it is reduced.

The hypothetical 1,3,5-cyclohexatriene would give off 85.8 kcal/mole (3 x 28.6 kcal/mole) when reduced because we are treating this imaginary compound as though it contains three isolated alkenes. In stark contrast, the real molecule (benzene) releases a mere 49.8 kcal/mole when reduced. This is *much* less energy than the expected 85.8 kcal/mole!



We might have predicted that benzene would give off a little less energy than 1,3,5-cyclohexatriene due to conjugation, much as we saw that 1,3-cyclohexadiene's heat of hydrogenation was a bit smaller than anticipated. But, benzene's heat of hydrogenation is a great deal smaller than we expected. This is compelling evidence that benzene is indeed uniquely stable. The difference between the expected and actual heat of hydrogenation (85.8 kcal/mole – 49.8 kcal/mole) is 36 kcal/mole. This is the resonance energy of benzene, and it is a quantitative measure of benzene's "aromaticity," which is the special stability to which we have continually alluded.

Problem 3. Naphthalene is a polycyclic aromatic (or polyaromatic) hydrocarbon.



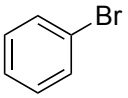
naphthalene

We'll discuss compounds of this type further in Section 6. The heat of hydrogenation of naphthalene is approximately 82 kcal/mole. What is its resonance energy?

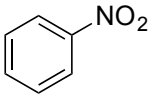
Section 2: Nomenclature of benzene derivatives

Monosubstituted benzene derivatives

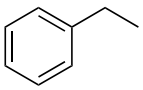
The simplest benzene derivatives are those bearing a single substituent. Many are named by placing the substituent prefix before the word "benzene." No number is needed because all positions on the ring are equivalent, so the substituent may be placed at any location.



bromobenzene

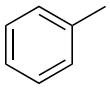


nitrobenzene

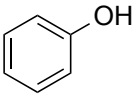


ethylbenzene

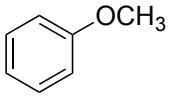
However, certain monosubstituted benzene derivatives have accepted names. For instance, a benzene ring bearing a methyl group is not usually called methylbenzene. Instead, it is known by its accepted name toluene. Similarly, the names hydroxybenzene, methoxybenzene, and aminobenzene are not typically used. Instead, these compounds are known as phenol, anisole, and aniline, respectively. Benzoic acid is a benzene ring with a carboxylic acid substituent, while benzaldehyde is its aldehyde-bearing counterpart.



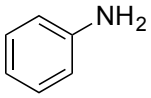
toluene



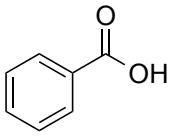
phenol



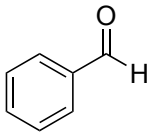
anisole



aniline



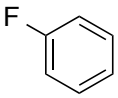
benzoic acid



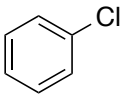
benzaldehyde

Problem 4. Name the following monosubstituted benzene derivatives.

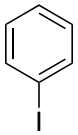
(a)



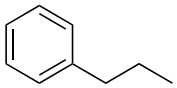
(b)



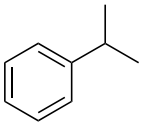
(c)



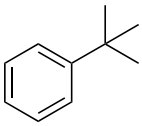
(d)



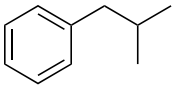
(e)



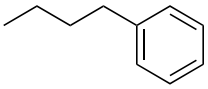
(f)



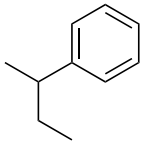
(g)



(h)

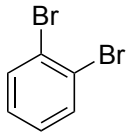


(i)

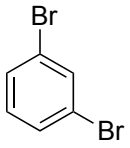


Disubstituted benzene derivatives

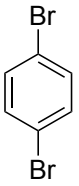
When a benzene derivative has two substituents, it is necessary to indicate the relative locations of these groups. This can be accomplished in two ways. One approach utilizes the terms *ortho*, *meta*, and *para* to denote substituents that are on adjacent carbons, have one intervening unsubstituted carbon, or are on opposite ends of the ring, respectively. These designations can also be abbreviated as *o*, *m*, and *p*.



ortho-dibromobenzene

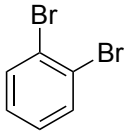


meta-dibromobenzene

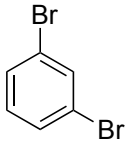


para-dibromobenzene

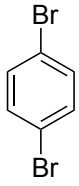
Alternatively, locants can be used to identify the positions of the substituents. When the substituents are identical, one of them receives the locant "1". Then, the ring is numbered so as to give the second substituent the lowest possible number.



1,2-dibromobenzene

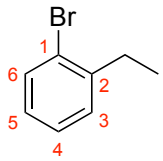


1,3-dibromobenzene

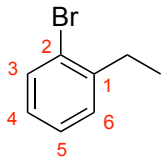


1,4-dibromobenzene

When the two substituents are different, they would receive the same locants regardless of the direction in which the ring is numbered, so the substituent that appears first alphabetically receives the locant "1."

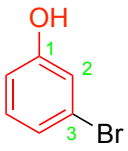


1-bromo-2-ethylbenzene
(**Correct**)



2-bromo-1-ethylbenzene
(**Incorrect**)

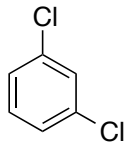
Finally, if a parent larger than benzene can be identified, its accepted name should be used. For instance, phenol is the parent in the following molecule. No number is needed to communicate the location of the hydroxyl group. It is assumed to be at C1. However, a number is needed to indicate where the bromine atom is located relative to the hydroxyl group. The full name is therefore 3-bromophenol, and *meta*-bromophenol is another option.



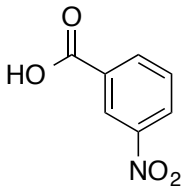
3-bromophenol
(or *meta*-bromophenol)

Problem 5. Provide names for the following disubstituted benzene derivatives.

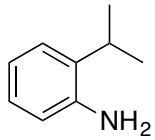
(a)



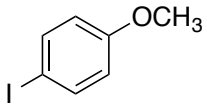
(b)



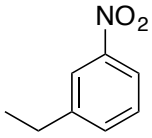
(c)



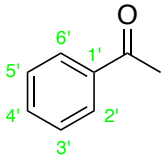
(d)



(e)

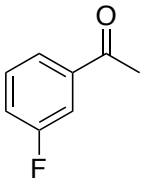


(f) Acetophenone is the accepted name of a benzene ring bearing a methyl ketone. For this compound, the locants on the ring itself are followed by a prime (').

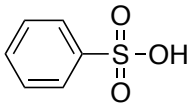


acetophenone

Use this information to name the following compound.

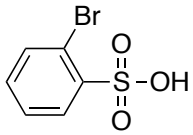


(g) Benzenesulfonic acid is the accepted name of the following molecule.

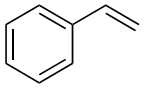


benzenesulfonic acid

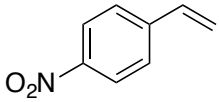
Use this fact to name the structure below.



(h) Styrene is the accepted name of benzene bearing a vinyl group.

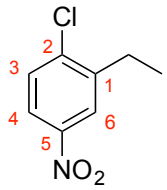

styrene

Use this information in naming the compound below.

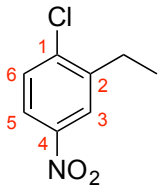


Polysubstituted benzene derivatives

With benzene rings containing more than two substituents, it is no longer feasible to use *ortho*, *meta*, and *para* because these terms describe the relative location of two and only two groups. Instead, we must use locants in the names of these polysubstituted benzene derivatives. One of the substituents must receive the number "1". The ring is then numbered so as to give the second substituent the lowest possible number. In the example below, we can give the first two substituents the numbers "1" and "2" in one of two ways. The final decision is made by giving the third substituent the lowest possible locant.



Incorrect numbering

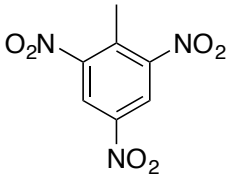


Correct numbering
1-chloro-2-ethyl-4-nitrobenzene

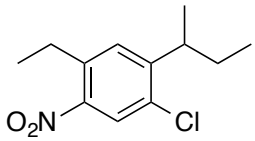
As always, if a parent larger than benzene is present, its name should be used.

Problem 6. Name the following polysubstituted benzene derivatives.

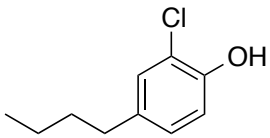
(a)



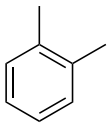
(b)



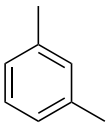
(c)



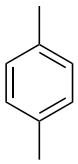
(d) Certain di- and even polysubstituted benzene derivatives have accepted names. For instance, dimethylbenzene is called xylene. Its three isomers are shown below.



ortho-xylene

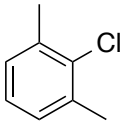


meta-xylene



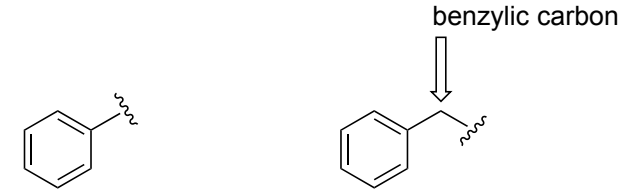
para-xylene

Use this information to name the following molecule.



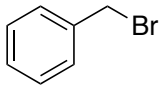
Benzene as a substituent

When benzene is a substituent, it is referred to as a phenyl group. When a benzene ring and a methylene (CH_2) are treated as a substituent, it is known as a benzyl group. The carbon directly bonded to the ring is the benzylic carbon.

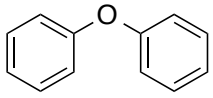


Problem 7. Name the following compounds.

(a)



(b)

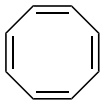


Section 3: Hückel's rule

Given that benzene is aromatic and therefore especially stable, we might expect that other molecules with similar structures will be similarly stable. It turns out that this is not necessarily the case. Cyclic molecules with alternating single and double bonds, like benzene, are called annulenes. The following three molecules are all annulenes, but of the three, only benzene is particularly stable. 1,3,5,7-Cyclooctatetraene is about as stable as a typical alkene, and cyclobutadiene is actually more *unstable* than a regular alkene.

cyclobutadiene:
especially unstable
(antiaromatic)

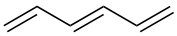
benzene:
especially stable
(aromatic)



1,3,5,7-cyclooctatetraene:
not especially stable or unstable
(non-aromatic)

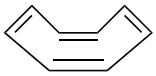
Those compounds that are more stable than expected are called aromatic, while those that are more *unstable* than expected are termed antiaromatic. A compound with no particular stabilization nor destabilization is non-aromatic. In this section, we'll learn how to make the distinction, and in the subsequent section we'll discuss the reasons for these phenomena.

In the early 1930s, Erich Hückel developed guidelines to identify aromatic, antiaromatic, and non-aromatic compounds. These guidelines are sometimes referred to as Hückel's rule in honor of his contribution to science. There are several criteria for an aromatic molecule. If a criterion is not met, then it will result in either antiaromaticity or non-aromaticity. The first criterion is that the molecule must be cyclic. It must also have a p orbital on each and every ring atom, and the ring must be planar so that the p orbitals are all parallel to one another. If you prefer, these three criteria can be condensed into one: To be aromatic, a molecule must contain a continuous, cyclic array of parallel p orbitals. If any of these criteria are unmet, then the molecule is non-aromatic.



not cyclic
(non-aromatic)

cyclic but does not
have a p orbital on
every ring atom
(non-aromatic)



cyclic and has a p orbital
on every ring atom; but
not planar so the p
orbitals are not parallel
(non-aromatic)

The last criterion for aromaticity is a Hückel number of π electrons. Hückel noticed that particular numbers of π electrons resulted in aromaticity, while other numbers of π electrons led to antiaromaticity. Rather than compiling all of these values into a long table, he formulated a simple algebraic expression that allows you to determine whether a molecule has the necessary number of π electrons. That expression is 4n + 2, where n is any integer zero or greater. Some Hückel values are given in the table below.

n	**4n + 2**
0	2
1	6
2	10
3	14
etc.	etc.

The important thing to understand is that n has no physical meaning. It is not derived or predicted from the structure in question. You merely scan through n values until you either reach or pass the number of π electrons in the molecule under consideration. A molecule with a continuous, cyclic array of parallel p orbitals and 4n + 2 π electrons is aromatic. On the other hand, if the molecule has a continuous, cyclic array of parallel p orbitals but possesses 4n π electrons, then it is antiaromatic.

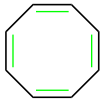
Benzene has a continuous, cyclic array of parallel p orbitals, and it also possesses 6 π electrons in its three π bonds. This is a 4n + 2 value (when n = 1). Consequently, we can accurately predict that benzene is aromatic using Hückel's rule. On the other hand, while cyclobutadiene also has a continuous, cyclic array of parallel p orbitals, it has only 4 π electrons in its two π bonds. This a 4n value (when n = 1), which allows us to predict cyclobutadiene's antiaromaticity.

A continuous, cyclic array of parallel p oribtals and 6 π electrons, a 4n + 2 value (aromatic)

A continuous, cyclic array of parallel p oribtals and 4 π electrons, a 4n value (antiaromatic)

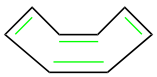
One more point deserves comment. When we were discussing the need for a continuous, cyclic array of parallel p orbitals, one example showed that 1,3,5,7-cyclooctatetraene is not planar. Annulenes that have eight or more carbons are large enough that they *can* bend out of planarity. If 1,3,5,7-cyclooctatetraene were planar, it would be antiaromatic because it has a 4n number of π electrons (8 π electrons). This would make it particularly unstable. Since it is large enough that it can bend out of planarity, it does so in order to avoid antiaromaticity. Bending out of planarity causes 1,3,5,7-cyclooctatetraene to be non-aromatic, and it is better to be non-aromatic, which is neither particularly stable nor unstable, than to be antiaromatic, which is especially unstable.

If 1,3,5,7-cyclooctatetraene were planar:



A continuous, cyclic array of parallel p oribtals and 8 π electrons, a 4n value (antiaromatic)

Since 1,3,5,7-cyclooctatetraene is not planar:

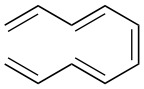


Cyclic and has a p orbital on every ring atom; but not planar so the p orbitals are not parallel (**non-aromatic**)

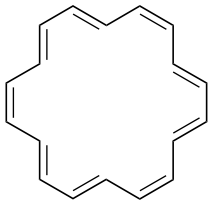
Problem 8. Classify the following molecules as aromatic, antiaromatic, or non-aromatic.

(a)

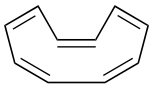
(b)



(c)

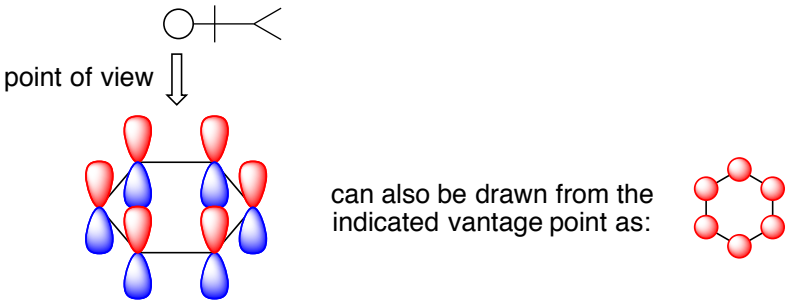


(d)



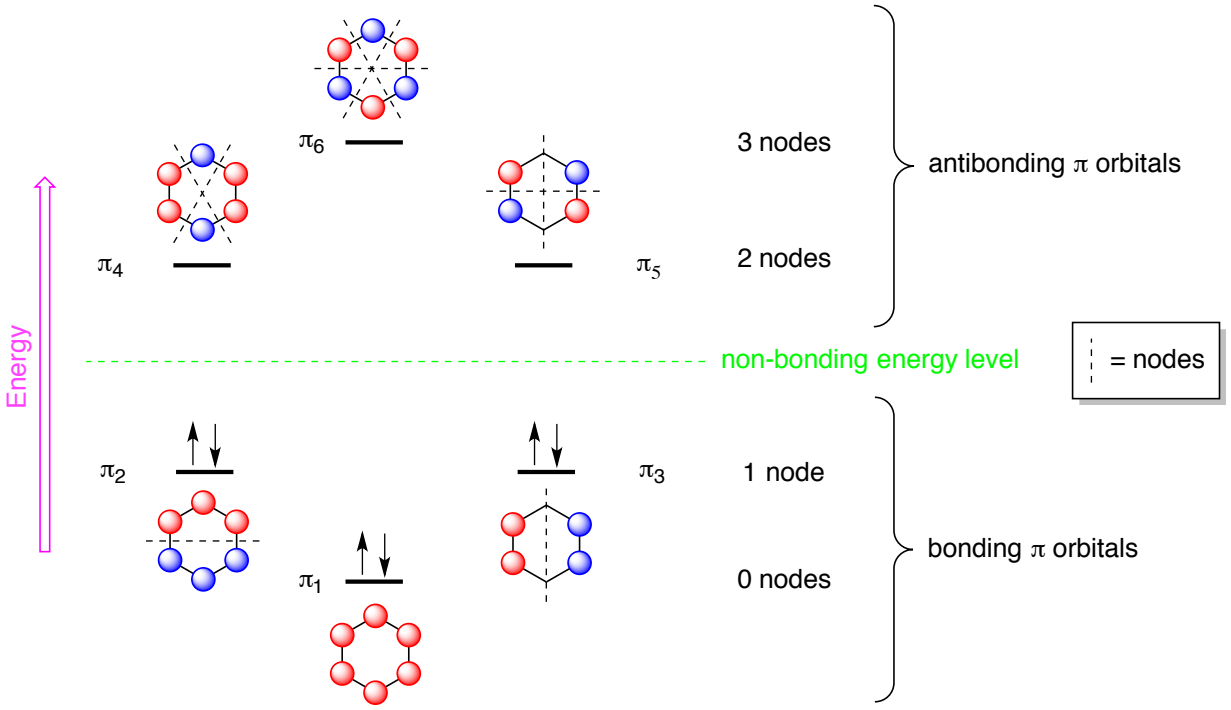
Section 4: Molecular orbitals

To understand the origin of aromatic stability in benzene, we must consider its molecular π orbitals. We'll use the same approach that we did in the previous chapter, namely approximating the molecular π orbitals through the overlap of atomic p orbitals. To keep the diagrams clear and simple, we'll view the ring from above so that only the top lobe of each p orbital will be visible. Furthermore, each p orbital will appear as a circle because of the vantage point.



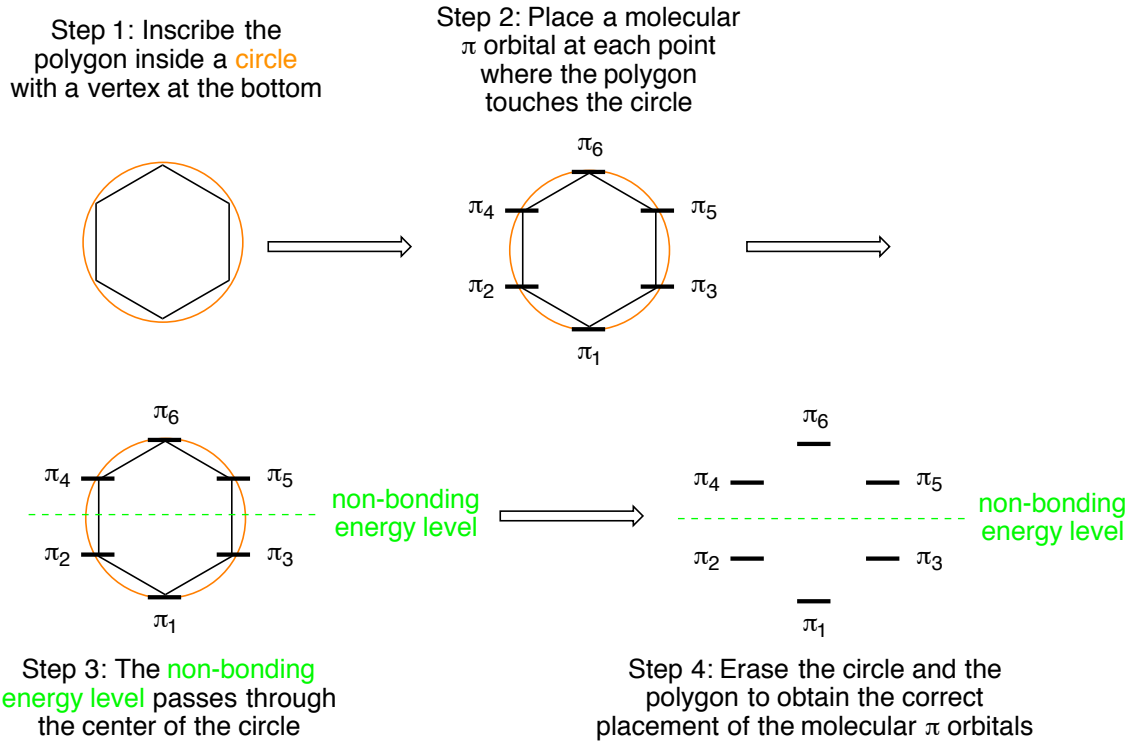
Benzene has six molecular π orbitals (labeled π_1 – π_6), which are formed from the six atomic p orbitals in the π system. The energy increases with the number of nodes, just as we've seen previously. π_1 is the lowest energy molecular π orbital. All of its p orbitals are in phase with one another. Both π_2 and π_3 have a single node. There are two ways to place this single node through the center of the molecule: through bonds or through atoms. Since π_2

and π_3 have the same number of nodes, they also have the same energy, and orbitals with the same energy are called degenerate. The next molecular π orbitals, π_4 and π_5, have two nodes, and once again there are two ways to place them. These orbitals are degenerate as well. Finally, π_6 has three nodes, so all of the p orbitals are out of phase. The molecular orbitals are symmetrically oriented around the non-bonding energy level, which makes π_1 – π_3 bonding orbitals and π_4 – π_6 antibonding orbitals. Benzene's six π electrons are placed into the lowest energy orbitals first, thereby filling π_1 – π_3.

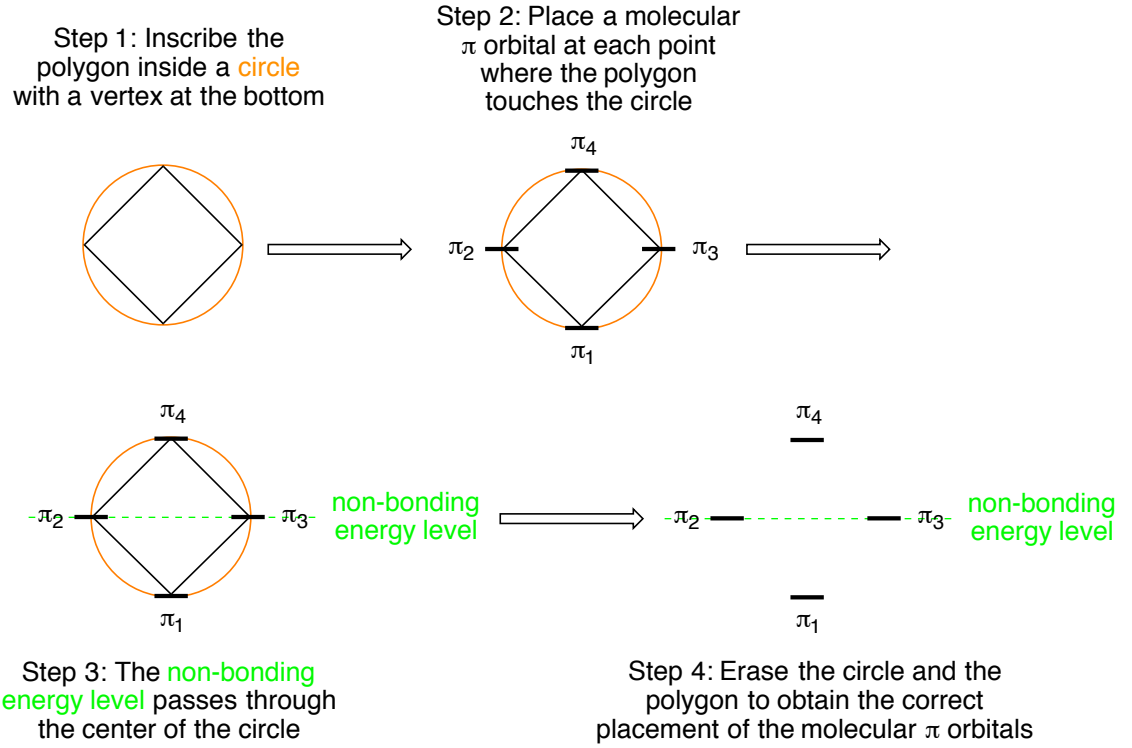


Now that we have constructed the molecular π orbital diagram, consider its meaning. Benzene is very stable because all six of its π electrons reside in bonding orbitals that are lower in energy than they would be at the non-bonding level.

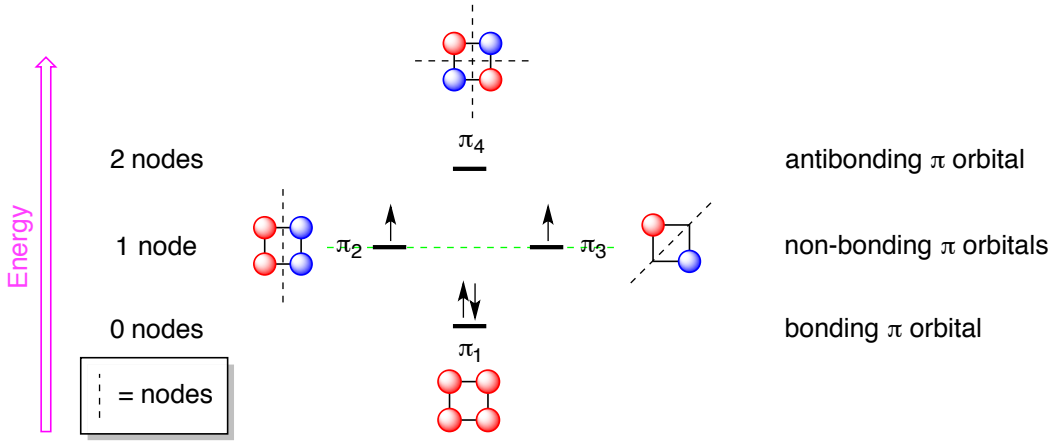
As you no doubt noticed, it is more challenging to place the molecular orbitals for annulenes than it was for conjugated dienes in Chapter 12. As we consider other annulenes, it will be helpful to have a shortcut for the placement of the molecular π orbitals at the proper energy levels. This mnemonic device entails the use of Frost circles. The polygon representing the annulene in question is inscribed inside a circle so that one of the polygon's vertices touches the bottom of the circle. Then, at each point where the polygon touches the circle, a molecular π orbital is placed. The non-bonding energy level passes through the center of the circle. When the polygon and the circle are erased, what remains is the correct number of molecular π orbitals with the correct energies.



Now, let's use this method for cyclobutadiene. Once we have the molecular π orbitals in place, we can determine the origin of its instability.

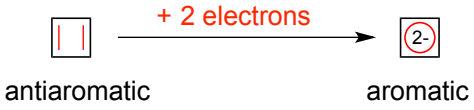


The Frost-circle method has given us the correct number and placement of cyclobutadiene's molecular π orbitals. For the sake of completeness, we can draw them as well. π_1 has all of its p orbitals in phase, so there are no nodes. π_2 and π_3 both have a single node, but this node may pass through bonds (π_2) or through atoms (π_3). Finally, π_4 has two nodes, which necessitates each of its p orbitals being out of phase with its neighbors.



The four π electrons in cyclobutadiene's pi system are placed into these molecular orbitals beginning with the lowest energy orbital (π_1) according to the aufbau principle (i.e., the lowest energy orbitals are filled first). Once π_1 fills, the last two π electrons are placed in π_2 and π_3 following the guideline provided by Hund's rule, which states that the electronic configuration with the maximum number of parallel spins is the most stable. This explains cyclobutadiene's antiaromaticity: It has two unpaired electrons at the non-bonding energy level, which renders it quite unstable.

Problem 9. Although cyclobutadiene is antiaromatic, if two electrons are added to its π system to make a dianion, the resulting compound is aromatic.



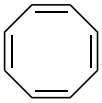
Use the molecular orbital diagram that we've constructed for cyclobutadiene to explain why the addition of two electrons results in an aromatic compound.

Section 5: Annulenes

As noted previously, annulenes are cyclic molecules with alternating single and double bonds. In other words, they are completely conjugated. The number of carbon atoms in the ring is placed in brackets before the word "annulene" when naming these structures. The annulenes that we've considered previously in this chapter include: cyclobutadiene, which can also be called [4]annulene; benzene, which is [6]annulene; and 1,3,5,7-cyclooctatetraene or [8]annulene.

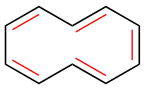
cyclobutadiene
or
[4]annulene

benzene
or
[6]annulene

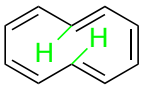


1,3,5,7-cyclooctatetraene
or
[8]annulene

The next annulene in the series is [10]annulene, an isomer of which is shown below. At first glance, this may appear to be an aromatic molecule because it has 10 π electrons (a 4n + 2 value, when n = 2). But, remember that before considering the number of π electrons in the system, we must first ask whether the molecule has a continuous, cyclic array of parallel p orbitals. This compound is certainly cyclic, and there is a p orbital on each and every ring atom. However, it turns out that the ring is not planar.

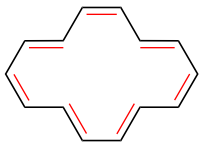


The reason is the repulsion of the hydrogen atoms in the center of the molecule. The central cavity is not large enough to accommodate them, so the ring must bend out of planarity. Since the ring is not planar, this [10]annulene is non-aromatic.



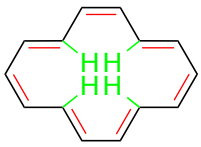
Repulsion

A similar problem arises with [14]annulene, which is the next annulene with a 4n + 2 number of π electrons.



[14]annulene
(14 π electrons =
a 4n + 2 value)

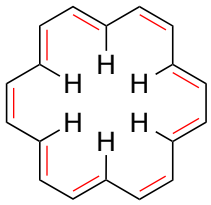
This molecule can achieve planarity, but the repulsion of the hydrogen atoms directed into the relatively small central cavity diminishes the aromatic stabilization.



Repulsion

[14]annulene

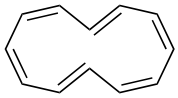
The next annulene with a 4n + 2 number of π electrons is [18]annulene, which has 18 π electrons. This molecule's central cavity is large enough to accommodate the hydrogens that reside inside it, so it can achieve a nearly planar conformation, which allows it to enjoy aromaticity.



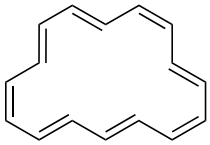
[18]annulene

Problem 10. If you make the assumption that the following compounds are planar, would you expect them to be aromatic, antiaromatic, or non-aromatic.

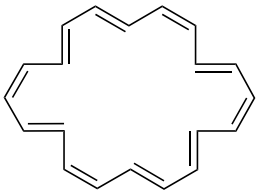
(a)



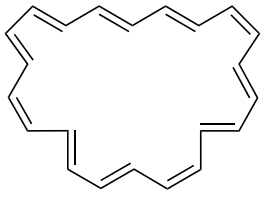
(b)



(c)

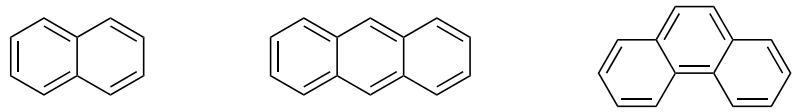


(d)



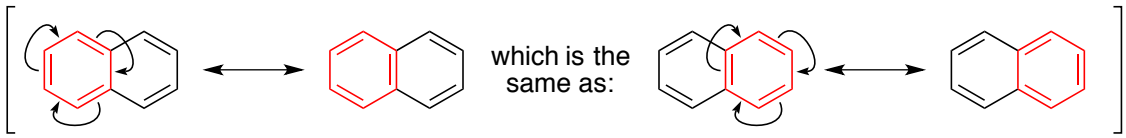
Section 6: Polycyclic aromatic (or polyaromatic) hydrocarbons

Polycyclic aromatic (or polyaromatic) hydrocarbons contain fused aromatic rings. Some examples include naphthalene, anthracene, and phenanthrene.



naphthalene anthracene phenanthrene

Formally, Hückel's rule only applies to monocyclic (one ring) compounds. However, when rings such as benzene that are aromatic are fused together, the resultant compound typically retains at least some aromatic stabilization. Often though, the stabilization is not as great as it would be for a comparable number of individual benzene rings. For instance, naphthalene has a resonance energy of 61 kcal/mole. If we simply added together the resonance energy for two benzene rings (2 * 36 kcal/mole = 72 kcal/mole), we would expect a larger value. The reason for the reduction in resonance energy is that each ring is not fully aromatic in each resonance form.



fully aromatic rings highlighted in red

Similarly, anthracene has resonance energy of 84 kcal/mole, which is much less than what would be expected for three benzene rings (3 * 36 kcal/mole = 108 kcal/mole).

Problem 11. Phenanthrene has a resonance energy of 92 kcal/mole, yet it contains three fused benzene rings just like anthracene, which has a resonance energy of only 84 kcal/mole. Draw the major resonance forms for both anthracene and phenanthrene. Then, compare these resonance forms and use them to propose a reason for the difference in resonance energy.

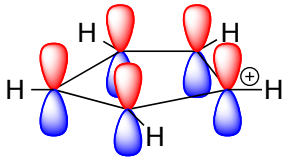
Section 7: Ions and aromaticity

Thus far, we've only encountered aromatic compounds of a particular type. They have all been carbocycles (i.e., rings of carbon atoms), and they have all had alternating single and double bonds through the entire ring. There are other structural motifs that can satisfy Hückel's criteria as well. In this section, we'll consider ions, and in the next section, we'll examine heterocycles, which are rings containing at least one heteroatom.

It is possible for an ion to possess a continuous, cyclic array of parallel p orbitals, in which case it may then be aromatic or antiaromatic. Consider the cyclopentadienyl cation.

the
cyclopentadienyl
cation

It is certainly cyclic. Additionally, it does have a p orbital on each and every ring atom. The carbons involved in π bonds have a p orbital, and the carbocation has an empty p orbital as well.



Due to its small size and the sp^2 hybridization of its atoms, the ring must be planar. Since it has a continuous, cyclic array of parallel p orbitals, we move on to a consideration of its π electrons. There are four π electrons in the cyclopentadienyl cation's two π bonds. The carbocation has an empty p orbital, which therefore contributes no electrons to the π system. With a total of four π electrons (a 4n value), the cyclopentadienyl cation is antiaromatic and particularly unstable.

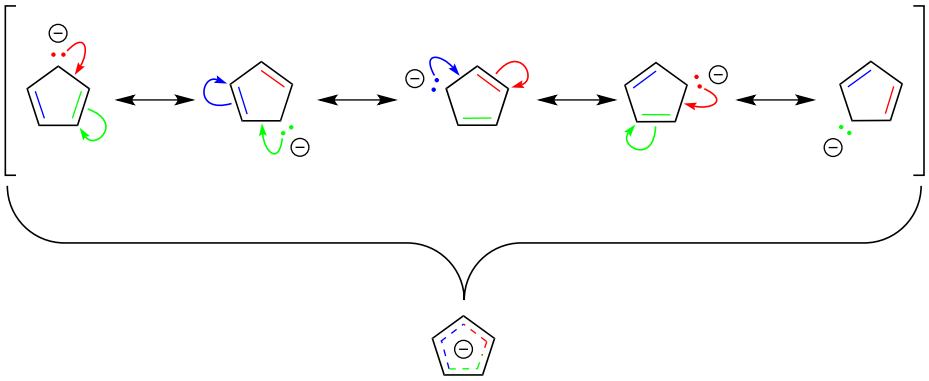
4 π electrons
(a 4n value)

Now, let's consider this compound's anionic counterpart. The cyclopentadienyl anion is also clearly cyclic.

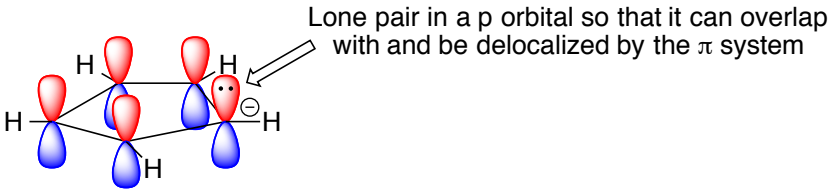
the
cyclopentadienyl
anion

What may initially be less obvious is that it also has a p orbital on each and every ring atom. When we first learned about hybridization, we would have categorized the anionic carbon as sp^3 hybridized because it has four groups around it (two carbons, one hydrogen, and a lone pair). However, that simplistic view neglects to account for the impact of resonance. We now know that the cyclopentadienyl anion is not accurately represented by a single resonance form. Instead, it is a hybrid of all of the resonance forms shown below. Any carbon in this ring is clearly sp^2 hybridized in four out of the five resonance forms. This

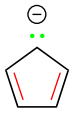
shows that each carbon has predominantly sp^2 character, which in turn means that each carbon has an unhybridized p orbital.



Another way of visualizing this is through an orbital diagram. The only way for the anion to be delocalized is by placing the lone pair into a p orbital, which allows it to overlap with (and therefore be delocalized by) the π system.

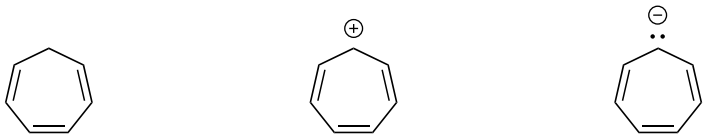


We've now established that this molecule is cyclic and has a p orbital on each and every atom of the ring. It must also be planar due to the small ring size and the sp^2 hybridization of the atoms. Knowing that it has a continuous, cyclic array of parallel p orbitals, we can move to a consideration of the number of π electrons. The cyclopentadienyl anion has a total of six π electrons. There are four π electrons in its two π bonds. Also, we showed through resonance that the lone pair is a part of the π system as well, so it adds two electrons to the π system. Since six π electrons is a 4n + 2 value, this ion is aromatic and is unexpectedly stable.



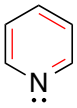
Problem 12. Draw all of the resonance structures for the cyclopentadienyl cation. Then, compare them to the resonance forms of the cyclopentadienyl anion. Does having a resonance-delocalized charge necessarily result in an aromatic compound? Does the extent of resonance delocalization allow us to predict aromaticity?

Problem 13. Classify the following three compounds as aromatic, antiaromatic, or non-aromatic. For the two ions, assume that they are planar molecules.



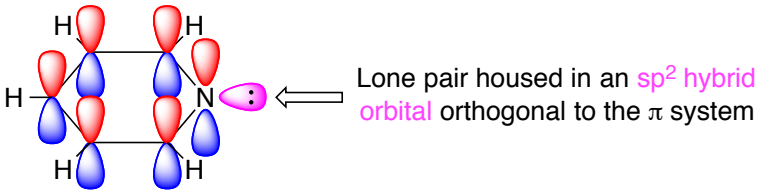
Section 8: Aromatic heterocycles

Heterocycles are rings that contain at least one atom other than carbon. This is a vast category of organic molecules, and some of them meet the criteria for aromaticity. Pyridine, a nitrogen-containing analogue of benzene, is one such example. It is a ring with a p orbital on each and every atom. It must also be planar due to its small size and the sp^2 hybridization of the ring atoms. Furthermore, it has six π electrons in its three π bonds, which is a 4n + 2 value. We therefore expect pyridine to be unusually stable, and indeed it is.

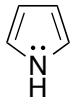


pyridine
6 π electrons
(a 4n + 2 value)

However, we failed to consider the lone pair electrons when analyzing pyridine. Although it will not alter our conclusion in this case, it will impact the decision for many heterocycles, so let's establish the lone pair's relationship to the π system. The nitrogen atom in pyridine is sp^2 hybridized. The three sp^2 hybrid orbitals are used in nitrogen's two σ bonds, as well as to house its lone pair of electrons. Since the lone pair is housed in an sp^2 hybrid orbital, it is orthogonal (or 90°) to the π system. Only the node of the sp^2 hybrid overlaps with the p orbital on nitrogen, and nodes are points of zero electron density. Therefore, the lone pair of electrons is *not* a part of the π system. It does not overlap with the π system and cannot contribute to it in any way. As a result, we were right to ignore the lone pair when counting pyridine's π electrons.

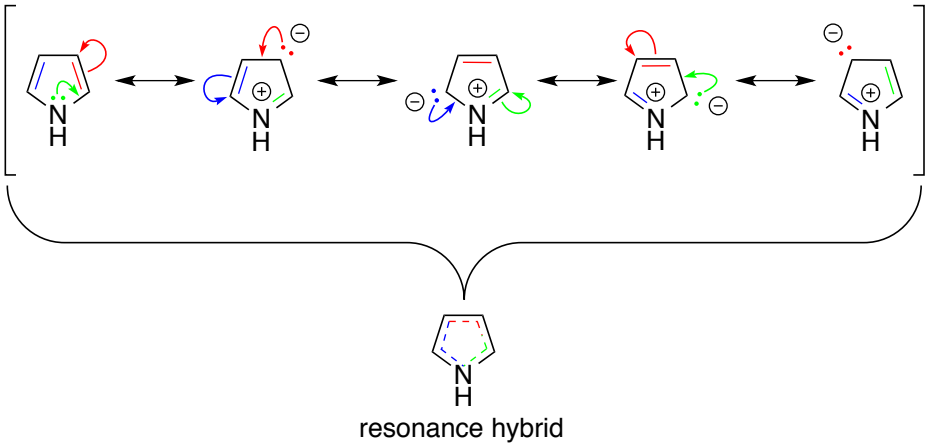


However, this will not always be the case. To illustrate the point, consider pyrrole.



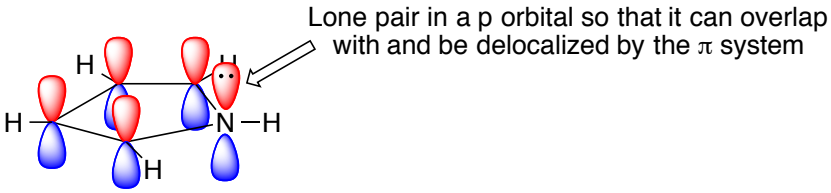
pyrrole

Much as with the cyclopentadienyl anion, it is initially unclear whether or not there is a p orbital on every atom of the ring. Before we knew about resonance, we would have simply considered the nitrogen atom to be sp^3 hybridized, but we now know that pyrrole is actually a hybrid of its five resonance forms. And, in four of those five resonance structures, the nitrogen atom has sp^2 hybridization. This shows us that there is, indeed, significant p orbital character on each and every ring atom.

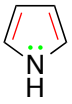


resonance hybrid

If the nitrogen atom were merely sp^3 hybridized (as we would have concluded prior to learning about resonance), the electron-pair repulsion would be minimized, but the lone pair would also be isolated on the nitrogen atom. By adopting sp^2 hybridization and placing the lone pair in an unhybridized p orbital, these electrons are made a part of the π system, which allows them to be delocalized over the entire ring and stabilized as a result.

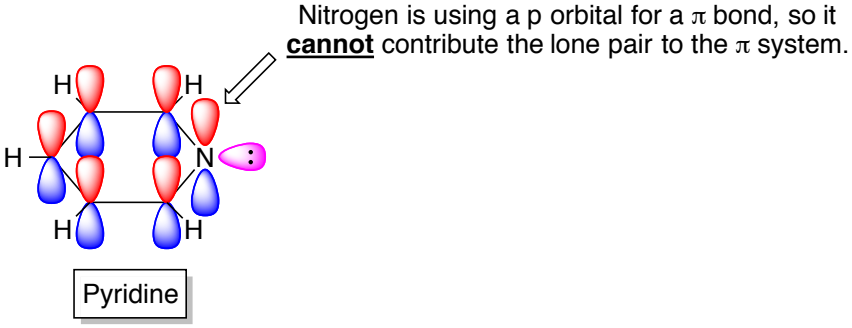


Having shown that pyrrole contains a continuous, cyclic array of parallel p orbitals, we have also illustrated that its lone pair *is* a part of the π system and must therefore be counted when we tally the π electrons. Pyrrole has four π electrons in its two π bonds, as well as two additional π electrons in the lone pair. The total of six π electrons is a 4n + 2 value, meaning that pyrrole is also an aromatic molecule.

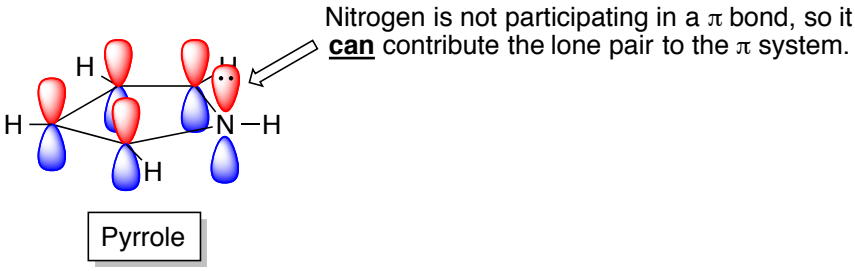


6 π electrons
(4 in π bonds and 2 in the lone pair)
a 4n + 2 value

When comparing the examples of pyridine and pyrrole, it becomes apparent that lone pair electrons may or may not be a part of the π system. If the atom bearing the lone pair is participating in a π bond, it already has a p orbital in the plane of the π system and could not therefore donate the lone pair to the π system.



On the other hand, if the atom bearing the lone pair is not participating in a π bond, then it can contribute the lone pair to the π system by putting it into a p orbital parallel to the others.

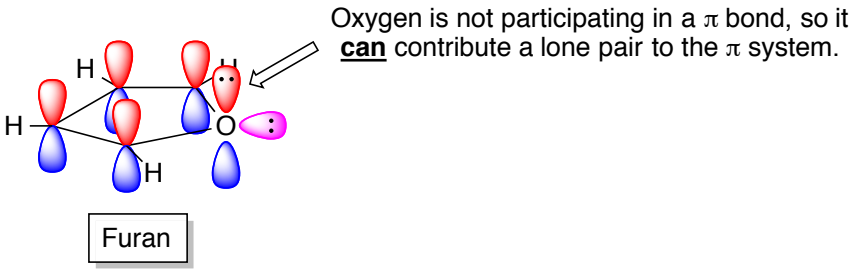


Problem 14. Pyridine is a reasonably basic molecule, but pyrrole is not. What is the basis for this difference in reactivity?

The situation is further complicated by heterocycles that possess atoms with more than one lone pair, such as furan. Now, we have to decide whether oxygen contributes 0, 1, or 2 lone pairs to the π system.

furan

Since oxygen is not participating in a π bond, it can place a lone pair into a p orbital that overlaps with the rest of the π system.



However, it is not possible for oxygen to contribute the second lone pair to the π system. One lone pair can occupy oxygen's only p orbital that is parallel to the π system. Oxygen does not have access to a second p orbital in the valence shell in the same plane. Therefore, the second lone pair resides in an sp^2 hybrid orbital that is orthogonal to the π system. As a result, furan contains a total of only six electrons in its π system: four in the two π bonds and two from one of the lone pairs. Consequently, it is an aromatic molecule as well.

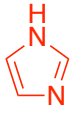
6 π electrons
(4 in π bonds and 2 from one lone pair)
a 4n + 2 value

To summarize, the guidelines for assessing the impact of lone pairs on the π system are as follows:

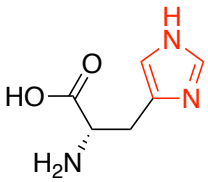
- If the atom bearing the lone pair(s) is participating in a π bond, it cannot donate any lone pair electrons to the π system.

- If the atom bearing the lone pair(s) is not participating in a π bond, it can donate one and only one lone pair to the π system.

Problem 15. Imidazole is a heterocyclic ring found in a wide variety of compounds, including the amino acid L-histidine. Classify imidazole as aromatic, antiaromatic, or non-aromatic.



imidazole

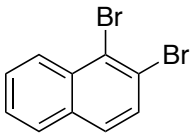


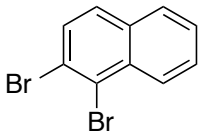
L-histidine

End-of-the-Chapter problems

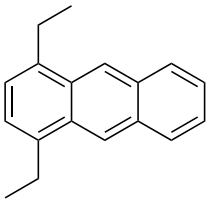
Problem 16. Classify the following as isomers or resonance forms.

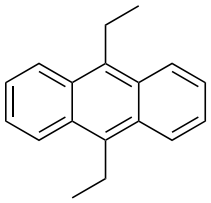
(a)





(b)





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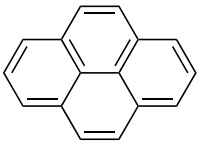
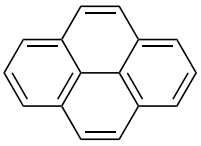
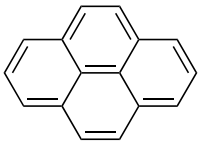
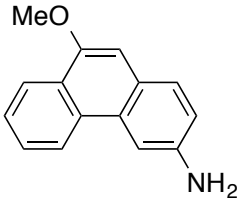
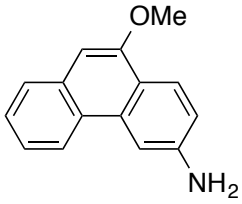






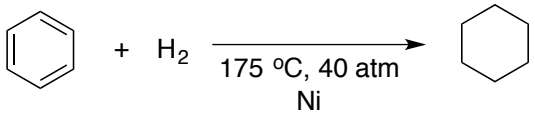
(d)





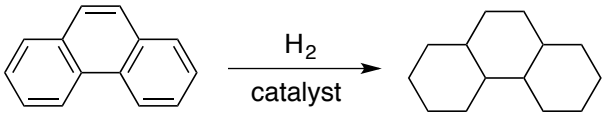
Problem 17.

(a) Benzene's hydrogenation requires forcing conditions. Alkenes can be reduced using hydrogen and a metal catalyst, but benzene's reduction also requires high temperature and high pressure. Why is this the case?



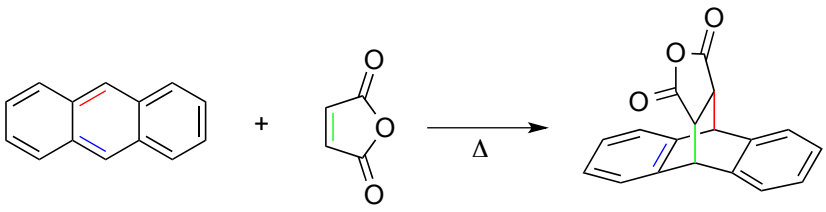
(b) We just saw that benzene is reluctant to undergo reaction. Conversely, cyclobutadiene readily dimerizes via the Diels-Alder reaction, even at low temperature. Explain why this is the case, and draw a mechanism for the reaction in which one molecule of cyclobutadiene acts as the diene while another acts as the dienophile.

Problem 18. As we learned in Problem 11, phenanthrene has a resonance energy of 92 kcal/mole. What is the heat of hydrogenation for the reduction of phenanthrene?



Heat of hydrogenation?

Problem 19. In Problem 26(a) in Chapter 12, the following Diels-Alder reaction was conducted in the course of a synthesis.

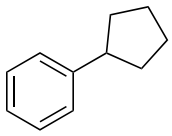


anthracene | maleic anhydride | Diels-Alder adduct

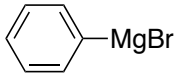
Why did the Diels-Alder reaction take place at the central ring of anthracene as opposed to one of its outer rings?

Problem 20. Provide names for the following compounds.

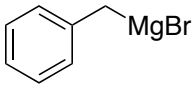
(a)



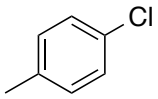
(b) In Chapter 15, we'll learn about Grignard reagents, which are organomagnesium compounds. A Grignard reagent is named as an "alkylmagnesium bromide." Use this information to name the following two compounds.



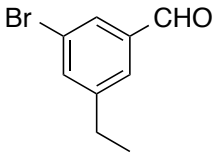
(c)



(d)



(e)



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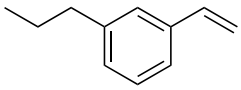
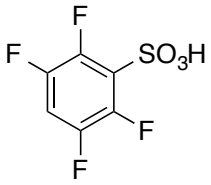
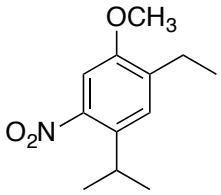


(g)



(h)



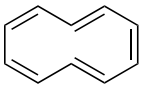
Problem 21.

(a) Classify the following compounds as aromatic, antiaromatic, or non-aromatic.

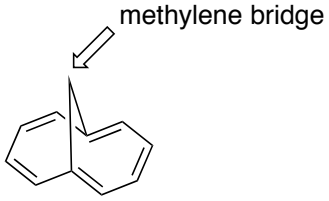
(b) For the cyclopropenyl cation and anion shown above, use the molecular π orbitals to justify your answers in part (a).

Problem 22.

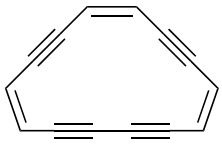
(a) In Section 5, we saw that the following [10]annulene is not planar due to repulsion between the hydrogens directed into the center of the ring.



However, a methylene bridge that spans the ring can hold it in a conformation that is close to being planar. Would you expect this compound to be aromatic, antiaromatic, or non-aromatic?

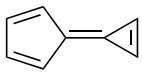


(b) The following annulene contains four alkynes. Would you expect it to be aromatic, antiaromatic, or non-aromatic? Hint: Consider the alkyne π bonds carefully; think about their geometric relationship to the rest of the π system.

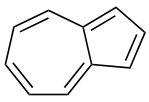


Problem 23. The following molecules display aromatic character, but at first glance it might not appear that they should. Explain this phenomenon. Hints: Remember that Hückel's rule only applies to single rings, and consider charged resonance forms.

(a)

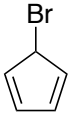


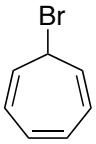
(b)



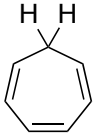
Problem 24.

(a) Which of the following compounds is most reluctant to ionize (i.e., dissociate)?

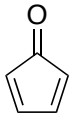


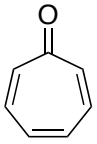


(b) Which of the following compounds has the lowest pK_a value for the indicated hydrogens?

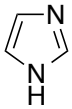


(c) Which of the following compounds is expected to have the smallest dipole?





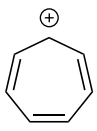
(d) Which site in imidazole is the most basic?



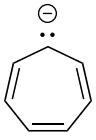
Problem 25.

(a) In Section 7, we saw that the cyclopentadienyl cation is antiaromatic and the cyclopentadienyl anion is aromatic. Reconcile these conclusions with the molecular π orbitals for these ions.

(b) In Problem 13, you concluded that the tropylium ion is aromatic and that its anionic counterpart would be antiaromatic if its lone pair were part of the π system. Reconcile these conclusions with the molecular π orbitals for these ions.

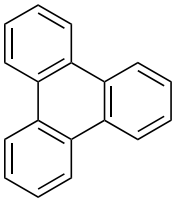


tropylium ion

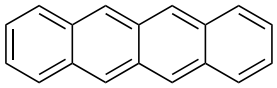


Problem 26.

(a) Triphenylene has a much greater resonance energy than its isomer tetracene. Why is this the case?

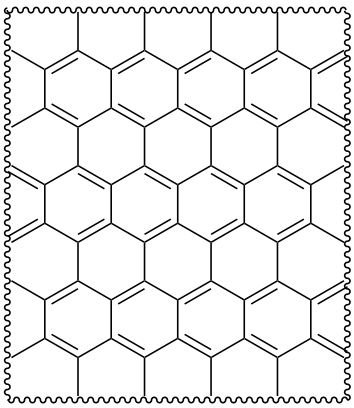


triphenylene



tetracene

(b) Carbon can form a nearly two-dimensional sheet known as graphene. This molecule is only one-atom thick but can extend for great distances within a plane. Graphene is extremely strong and conducts electricity well. As a result, there is tremendous excitement about the possibilities of this material. Would you expect graphene to be aromatic, antiaromatic, or non-aromatic?



a segment of graphene

Problem 27. A series of heterocycles is shown below. Identify each as aromatic, antiaromatic, or non-aromatic.

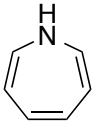
thiophene

oxazole

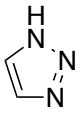
4*H*-pyran

2*H*-azirine

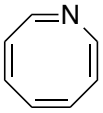
azete



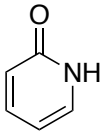
azepine



1,2,3-triazole

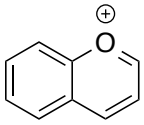


azocine

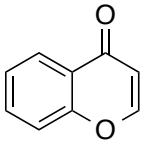


2-pyridone

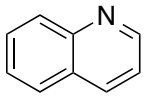
Problem 28. When we studied polycyclic aromatic hydrocarbons, we noted that Hückel's rule formally only applies to single rings. Nevertheless, if rings that are aromatic are fused, the result is an aromatic molecule. Use this guiding principle to determine whether the following heterocycles are aromatic, antiaromatic, or non-aromatic.



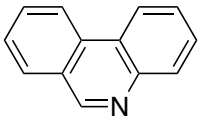
1-benzopyrylium ion



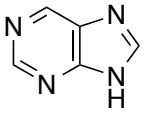
chromone



quinoline

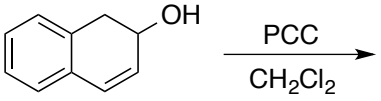


dibenzopyridine

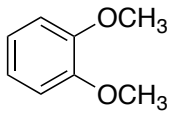


purine

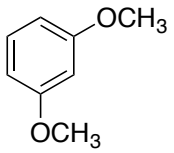
Problem 29. The following alcohol was oxidized with pyridinium chlorochromate (PCC). The IR spectrum of the product showed a broad signal at about 3300 cm^{-1}, peaks just above 3000 cm^{-1}, and *no* signal near 1700 cm^{-1}. What happened in this transformation?



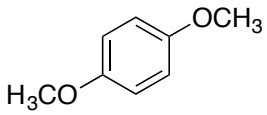
Problem 30. Match the following three dimethoxybenzene isomers with their ^{1}H NMR spectra.



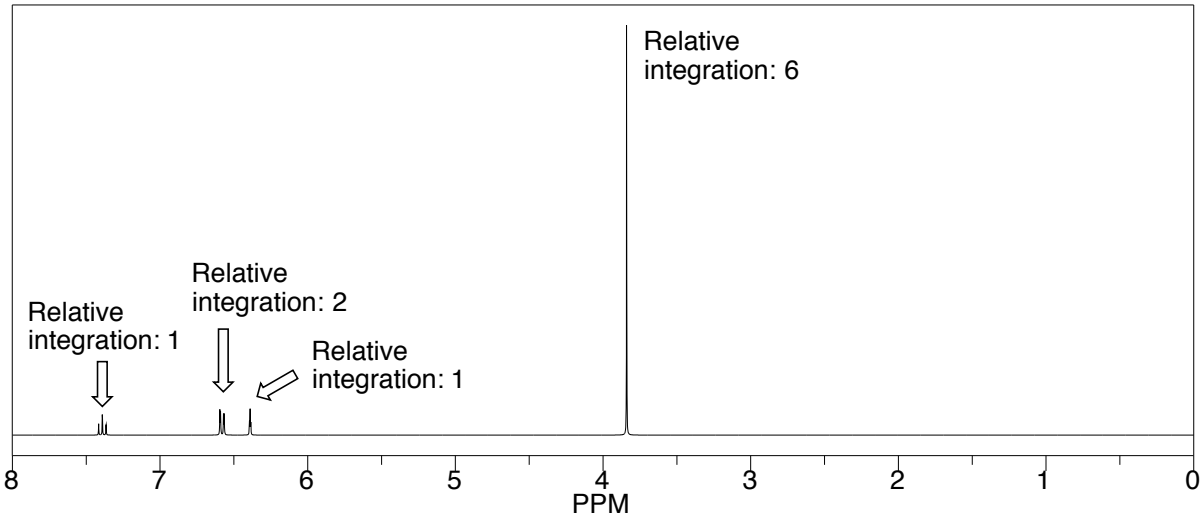
veratrole

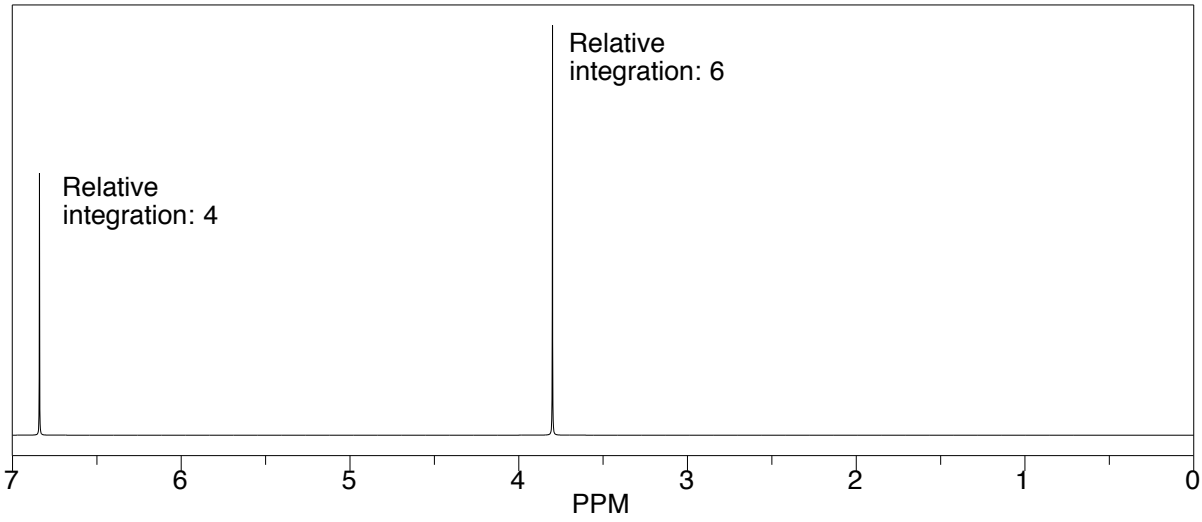


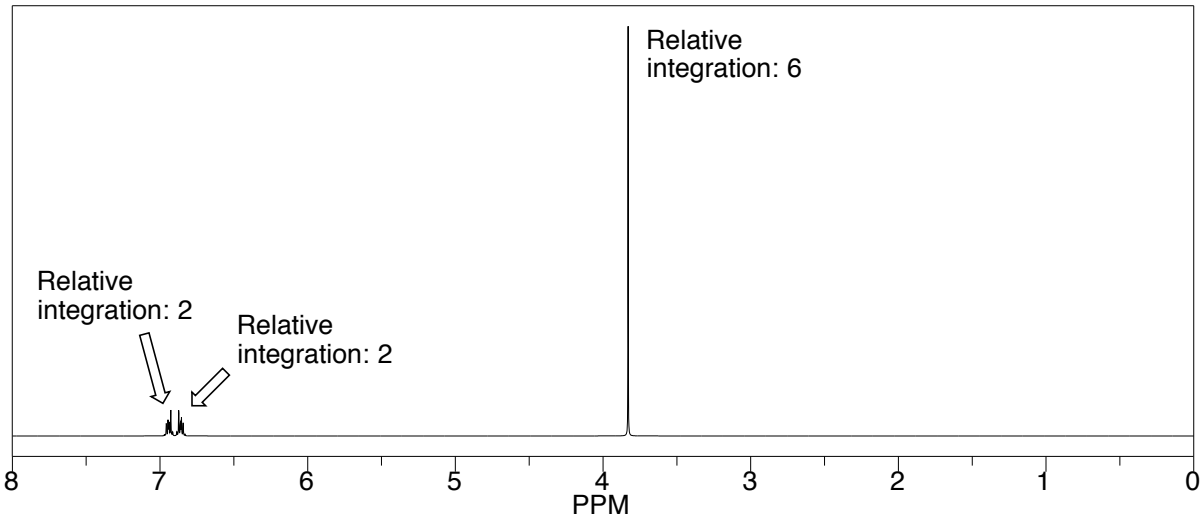
resorcinol dimethyl ether



dimethylhydroquinone





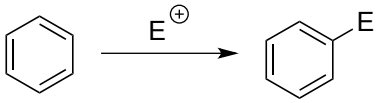

Relative
integration: 6
Relative
integration: 2
Relative
integration: 2
8
7
6
5
4
3
2
1
0
PPM

Chapter 14: Reactions of Aromatic Compounds

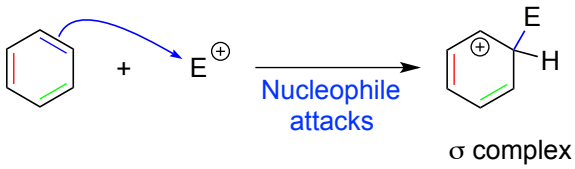
Section 1: Electrophilic aromatic substitution
Section 2: Halogenation
Section 3: Nitration and reduction of the nitro group
Section 4: Sulfonation and desulfonation
Section 5: Friedel-Crafts alkylation
Section 6: Friedel-Crafts acylation
Section 7: The effect of substituents on EAS reactions
Section 8: Synthesis using EAS reactions
Section 9: Benzylic bromination
Section 10: Birch reduction
Section 11: Nucleophilic aromatic substitution (S_NAr)
Section 12: Benzyne (elimination-addition)

Section 1: Electrophilic aromatic substitution

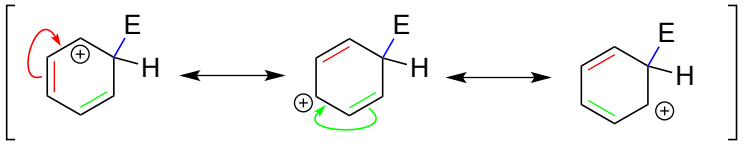
In electrophilic aromatic substitution (EAS), a proton on an aromatic ring is ultimately replaced by a potent electrophile (E^+).



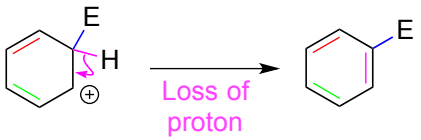
There are several specific EAS reactions, but they all share a common mechanism. The potent electrophile is first attacked by a pi bond of the aromatic ring. Notice that the ring is behaving as a nucleophile during this step. The result of this attack is an intermediate known as the sigma complex, which contains one more sigma bond than the reactant.



The sigma complex is non-aromatic because the conjugation is broken by the sp^3 hybridized carbon bearing the electrophile. Nevertheless, the sigma complex does have resonance delocalization.



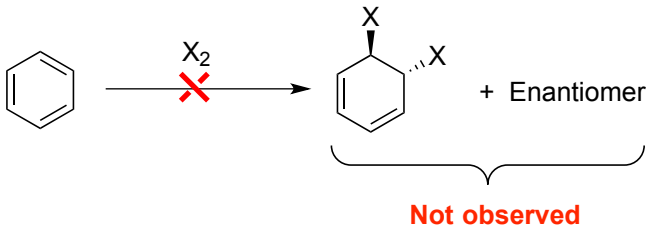
In the last step of the mechanism, the sigma complex loses a proton from the sp^3 hybridized ring carbon. This restores aromaticity to the ring.



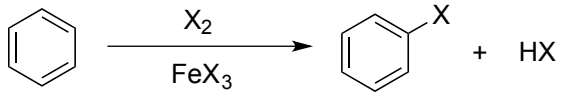
Now let's turn our attention to specific EAS reactions. Over the course of the next few sections, we'll learn about five EAS reactions: halogenation, nitration, sulfonation, Friedel-Crafts alkylation, and Friedel-Crafts acylation.

Section 2: Halogenation

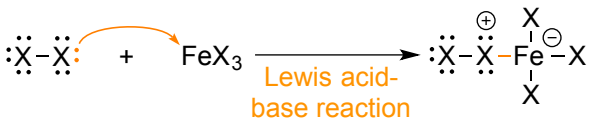
Based on what we've learned about the addition of chlorine or bromine to pi bonds, it would be natural to expect a similar addition to take place with benzene; however, it does not. Such a reaction would result in a non-aromatic product. The loss of aromaticity would be energetically unfavorable.



In the presence of a Lewis acid catalyst, such as iron trichloride ($FeCl_3$), aluminum trichloride ($AlCl_3$), or iron tribromide ($FeBr_3$), the halogenation of the ring can be achieved, but it proceeds differently than expected. This reaction is an example of electrophilic aromatic substitution.

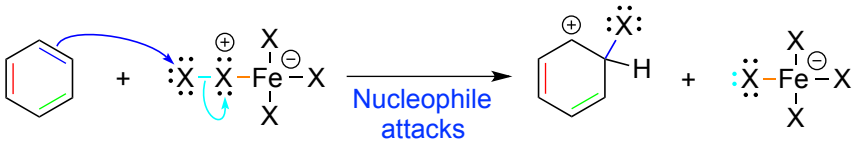


As in all EAS reactions, a potent electrophile is necessary. Chlorine (Cl_2) and bromine (Br_2) can exhibit temporary dipoles, but they are not sufficiently electrophilic to coax the benzene ring into reaction. When a Lewis acid catalyst is added to the mixture, a Lewis acid-base reaction occurs that transforms the halogen into a much stronger electrophile.

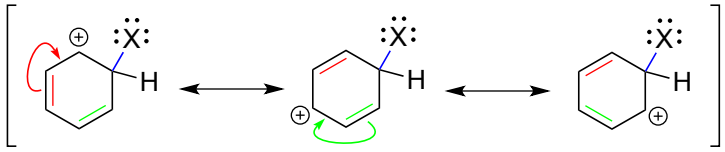


The halogen is now a much better electrophile because the Lewis acid-base complex draws some electron density away. Attack of the benzene ring on the terminal halogen displaces FeX_4^-. It might be tempting to attack the positively charged, internal halogen. However,

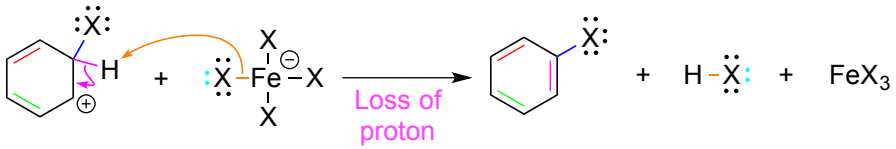
only by attacking the terminal halogen can the internal halogen be returned to its normal valence (i.e., one bond and three lone pairs).



The carbocation intermediate thus formed is stabilized by two additional resonance structures. This intermediate is known as the σ complex.



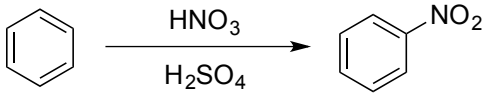
Finally, loss of a proton restores aromaticity to the ring. A halide from FeX_4^- can serve as the base that removes this proton. The Lewis acid catalyst is regenerated, and HX is a byproduct of the reaction.



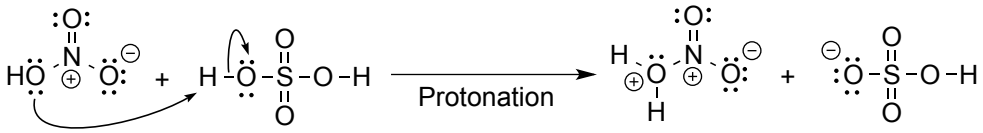
Problem 1. Draw the mechanism for the chlorination of benzene.

Section 3: Nitration and reduction of the nitro group

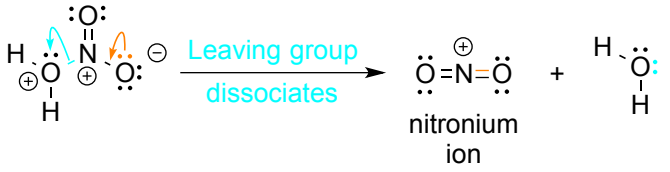
In EAS nitration, a nitro group (NO_2) is installed on the ring. The reaction requires nitric acid (HNO_3) and sulfuric acid (H_2SO_4).



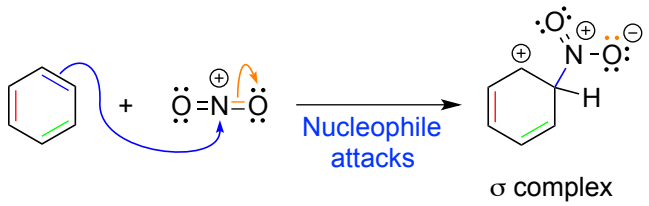
The reaction begins with the protonation of nitric acid by sulfuric acid. It may seem desirable to protonate nitric acid on the negatively charged oxygen atom; however, the adjacent positive charge on nitrogen is stabilized by electrostatic attraction to this neighboring negative charge. Therefore, it is not desirable to neutralize the negative charge. On the other hand, protonation on the hydroxyl oxygen produces a good leaving group (H_2O).



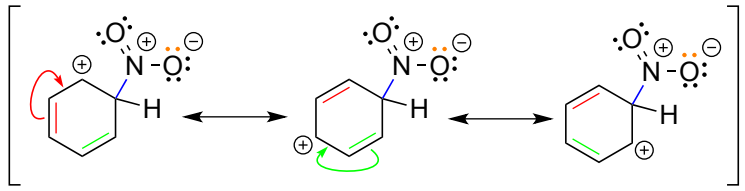
That leaving group dissociates as the nitronium ion ($^{+}NO_2$) is formed.



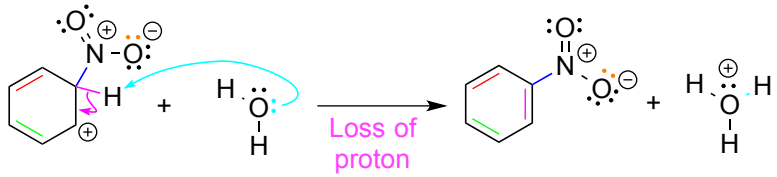
The nitronium ion is the potent electrophile in this EAS reaction. It is attacked by a π bond of the aromatic ring to form the intermediate σ complex. Specifically, the nitrogen atom is attacked. In order to avoid exceeding the octet, nitrogen must give up a bond as it gains a new one, so π electrons are pushed onto oxygen.



The σ complex has two additional resonance forms.

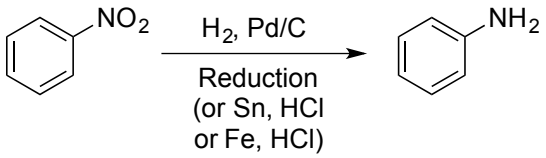


Finally, the loss of a proton from the σ complex restores aromaticity to the ring and yields nitrobenzene as the product.



Reduction of the nitro group

The nitro group, once installed on the ring, can be modified through reduction if desired. Treatment of nitrobenzene with hydrogen in the presence of a metal catalyst, such as palladium on carbon, reduces the nitro group to an amino group (NH_2).

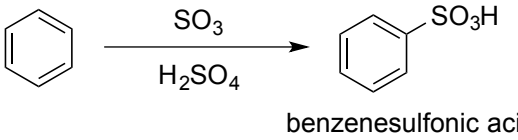


Alternatively, tin and hydrochloric acid or iron and hydrochloric acid can be used to achieve the same transformation.

Problem 2. During the late 1800s, many synthetic dyes were produced, and a number of them were made from aniline and its derivatives. Show how aniline can be produced from benzene in two steps.

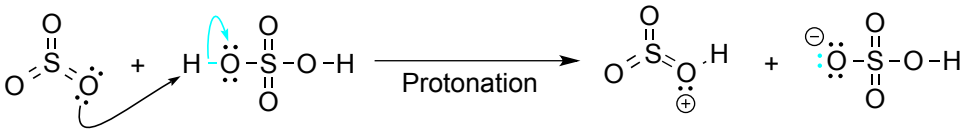
Section 4: Sulfonation and desulfonation

In EAS sulfonation, a sulfonic acid group (SO_3H) is installed on the ring. The reaction requires sulfur trioxide (SO_3) and sulfuric acid (H_2SO_4). This reagent combination is sometimes referred to as "fuming sulfuric acid" (fuming H_2SO_4).

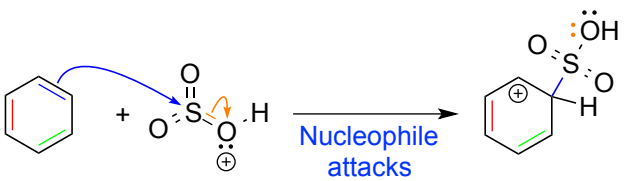


benzenesulfonic acid

The reaction begins with the protonation of sulfur trioxide by sulfuric acid. This generates a potent electrophile for the EAS reaction.

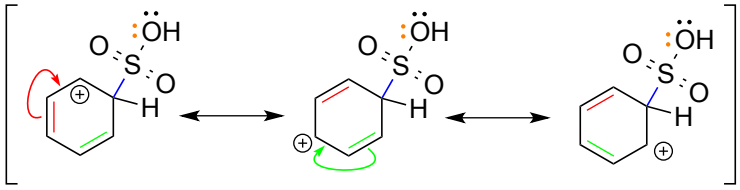


A π bond of the aromatic ring then attacks this potent electrophile, forming the σ complex. The nucleophile attacks sulfur, which allows π electrons to be pushed onto oxygen to neutralize its charge. Note that some texts show direct attack of the aromatic ring on SO_3, rather than on its conjugate acid ($^+SO_3H$). This is also acceptable.

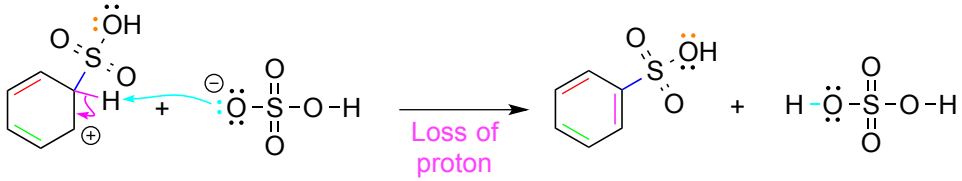


σ complex

The σ complex has a total of three resonance forms.

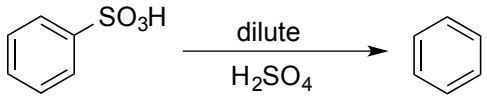


Finally, the loss of a proton from the σ complex restores aromaticity to the ring and yields benzenesulfonic acid.

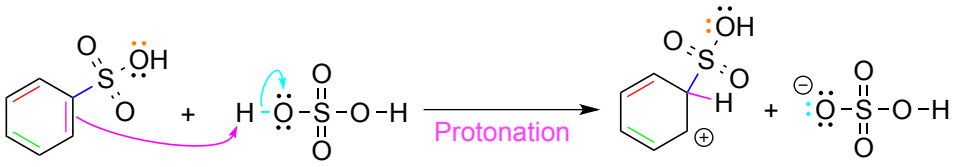


Desulfonation

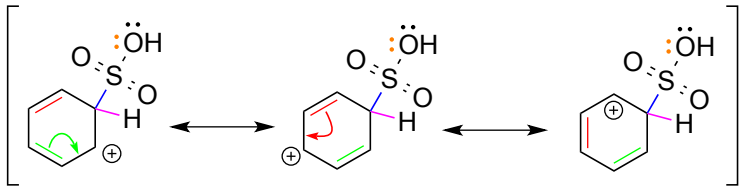
Sulfonation is the only EAS reaction that is readily reversed. For instance, benzenesulfonic acid can undergo desulfonation (loss of the sulfonic acid group) when treated with dilute aqueous sulfuric acid.



The reaction begins with protonation of benzenesulfonic acid to generate a σ complex. The ring can be protonated in any of its six positions; however, only protonation at the carbon bearing the sulfonic acid group will lead to an observable transformation.

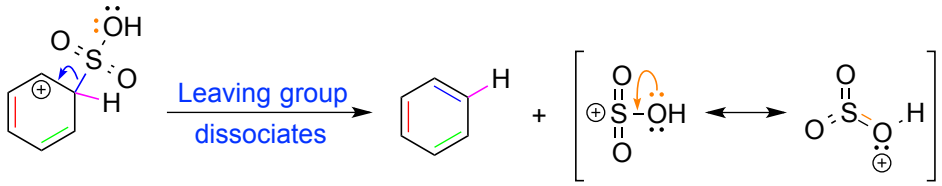


This σ complex has three resonance forms, much like any other simple σ complex.



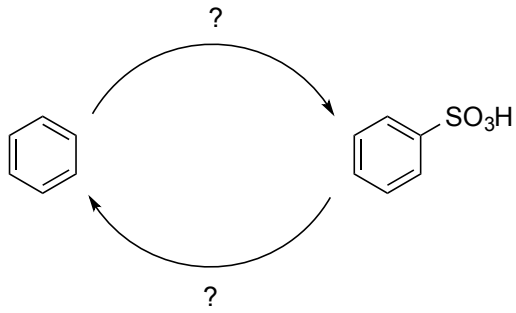
Normally, EAS reaction concludes with the loss of a proton to restore aromaticity to the ring. In this case, it is possible to lose the sulfonic acid group instead. It acts as a leaving group and dissociates. The product is benzene, and the leaving group is the conjugate acid

of sulfur trioxide ($^{+}SO_3H$), which is stabilized by resonance. $^{+}SO_3H$ can then lose a proton to form SO_3 or add water to form H_2SO_4.



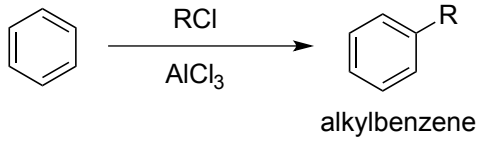
It may seem strange to take the sulfonic acid group off of the ring since we just went through some effort to place it on the ring. When we turn our attention to synthesis, we'll see that the ability to add and then later remove the sulfonic acid group makes it useful in syntheses where it may sometimes be desirable to block one position in order to allow substitution at another.

Problem 3. Fill in the reagents needed to complete this cycle.

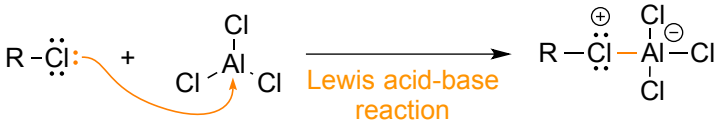


Section 5: Friedel-Crafts alkylation

In Friedel-Crafts alkylation, an alkyl group is installed on the ring. The reaction requires an alkyl chloride and aluminum trichloride ($AlCl_3$).

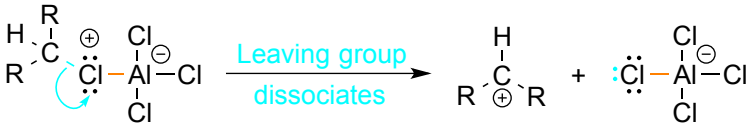


The transformation begins with a Lewis acid-base reaction between the alkyl chloride and aluminum trichloride, which acts as an electron-pair acceptor making it a Lewis acid.

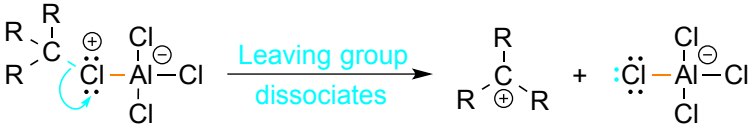


What happens next depends on the structure of the alkyl chloride. When the alkyl chloride is secondary or tertiary, $AlCl_4^-$ dissociates and a carbocation forms.

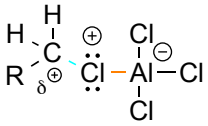
Secondary alkyl chloride:



Tertiary alkyl chloride:

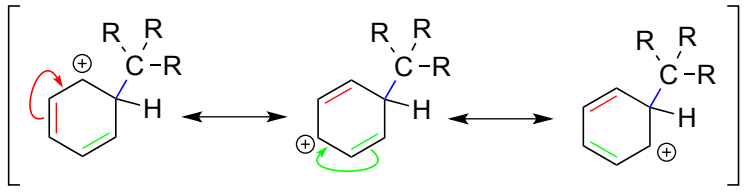


However, when the alkyl chloride is primary, dissociation would lead to a high-energy carbocation, so it does not occur. The primary carbon is nevertheless electrophilic because it bears an intense partial positive charge (δ^+).

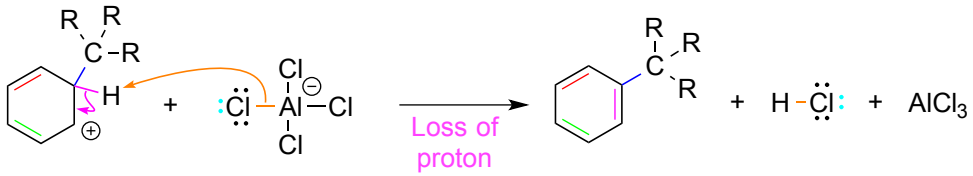


A π bond of the nucleophilic aromatic ring then attacks the electrophile to afford a σ complex. When the alkyl chloride is secondary or tertiary, the electrophile is a carbocation (a tertiary carbocation is shown below).

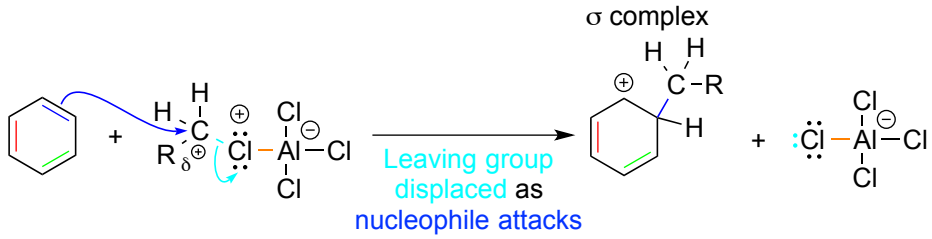
The σ complex has three resonance forms that delocalize the positive charge.



Finally, the loss of a proton from the sp^3 hybridized carbon restores aromaticity to the ring and produces the product. A chloride dissociates from $AlCl_4^-$ and acts as the base to remove the proton. This provides HCl as a byproduct and regenerates aluminum trichloride.



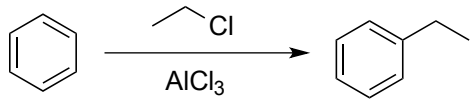
When the alkyl chloride is primary, the electrophile for the EAS reaction is the Lewis acid-base complex. A π bond of the aromatic ring attacks the δ+ primary center and displaces $AlCl_4^-$. This forms the intermediate σ complex that is converted to product as shown above.



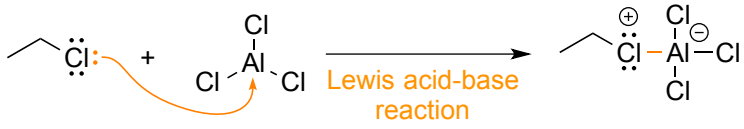
Let's now consider a few specific examples of this reaction.

Installation of an ethyl group

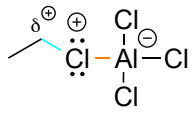
Ethyl benzene can be prepared by treating benzene with ethyl chloride and aluminum trichloride.



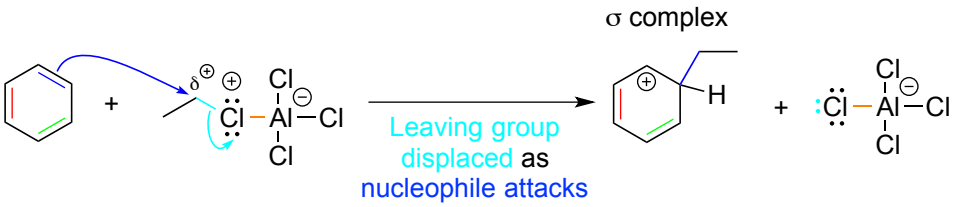
The conversion begins with Lewis acid-base complex formation.



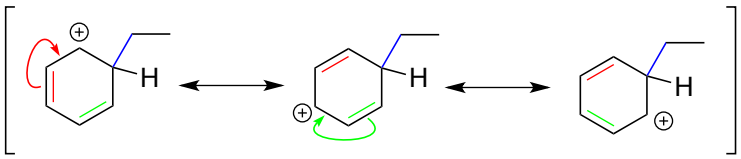
However, in this case, dissociation of $AlCl_4^-$ would yield an unstable primary carbocation. Therefore, no dissociation ensues.



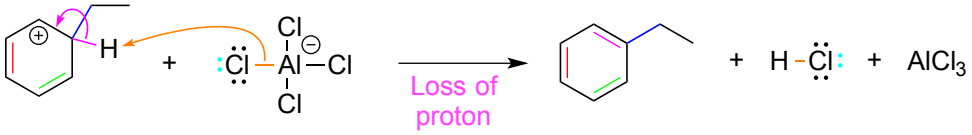
Instead, benzene attacks the δ+ primary carbon directly, displacing $AlCl_4^-$ in the process.



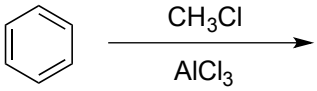
This σ complex is stabilized by two additional resonance forms.



The reaction ends with the loss of a proton from the sp^3 hybridized carbon to produce ethyl benzene.

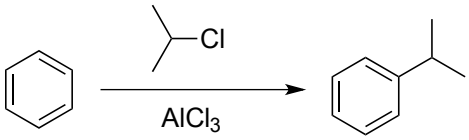


Problem 4. Predict the product of the following Friedel-Crafts alkylation.

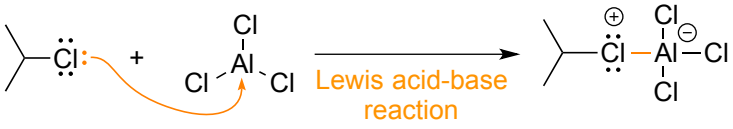


Installation of an isopropyl group

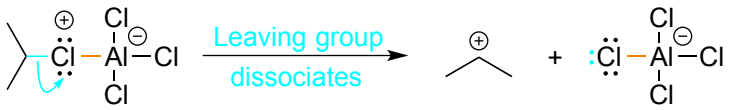
In the following example, benzene is treated with isopropyl chloride (a secondary alkyl chloride) and aluminum trichloride to provide isopropyl benzene.



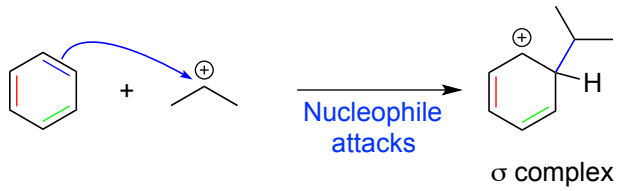
The Lewis acid-base complex is formed as expected.



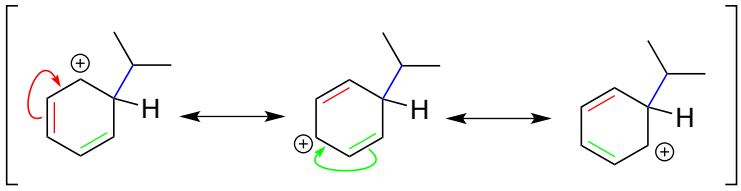
Since this alkyl chloride is secondary, $AlCl_4^-$ dissociates giving a secondary carbocation.



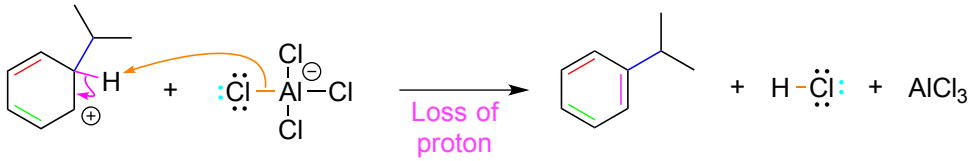
The isopropyl carbocation is the potent electrophile that incites the attack of benzene.



The resulting σ complex is stabilized by a total of three resonance forms.

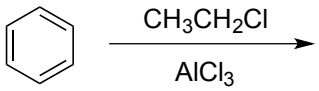


Loss of a proton completes the mechanism, forming isopropyl benzene as the final product.

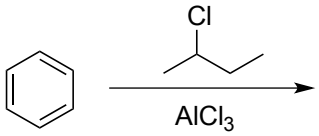


Problem 5. Provide the products of the following alkylation reactions, and for each reaction, indicate whether or not the mechanism involves a carbocation intermediate.

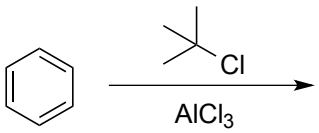
(a)



(b)

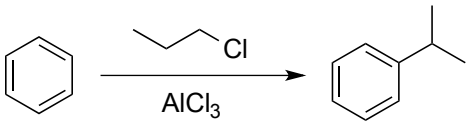


(c)

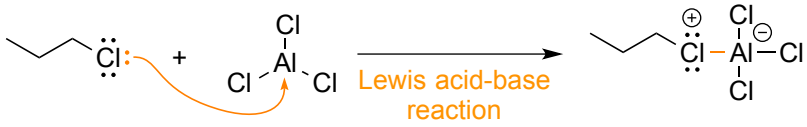


Attempted installation of a propyl group

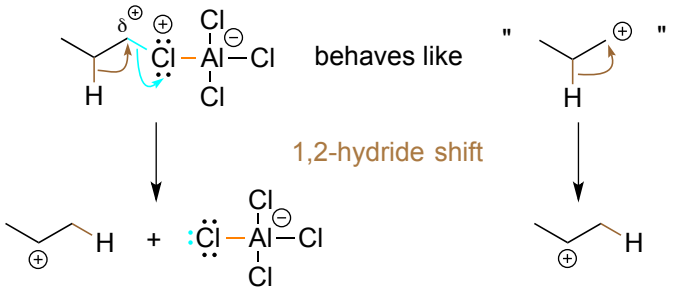
Primary alkyl chlorides other that methyl or ethyl chloride result in rearrangement products as the major products. As shown in the example below, Friedel-Crafts alkylation of benzene with propyl chloride yields not the expected propylbenzene but isopropylbenzene instead.



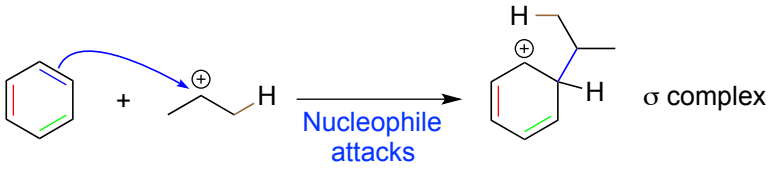
The first step in explaining this result is the formation of a Lewis acid-base complex between propyl chloride and aluminum trichloride.



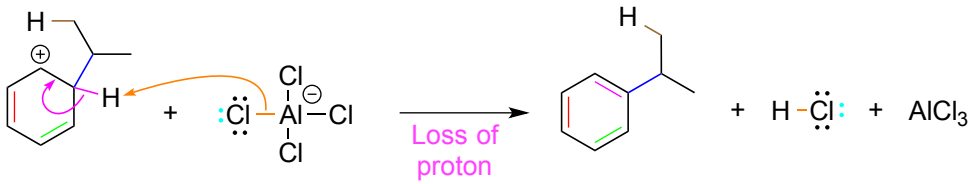
$AlCl_4^-$ will not dissociate from the primary center to form a carbocation because a primary carbocation is high in energy. Nevertheless, there is significant δ^+ character on the primary center, so much so in fact that it behaves as if it were a primary carbocation. If a propyl cation existed, we would certainly expect it to undergo a 1,2-hydride shift to yield a more stable secondary carbocation. A similar shift happens with the Lewis acid-base complex and the migrating hydride displaces $AlCl_4^-$. The result is the formation of the isopropyl carbocation, which serves as the electrophile in the subsequent EAS reaction.



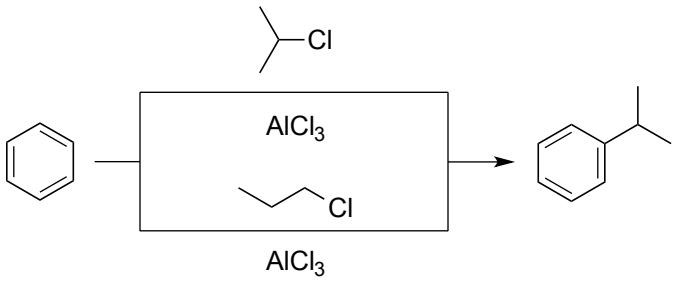
The σ complex is formed through attack of the benzene ring on the electrophilic carbon, which attaches an *isopropyl* group to the ring.



This σ complex enjoys the same kind of resonance stabilization that we've seen in the previous examples. Loss of a proton to chloride completes the formation of isopropyl benzene.



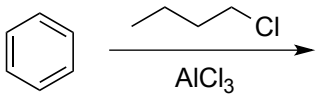
Notice that Friedel-Crafts alkylation of benzene with either isopropyl chloride or propyl chloride yields the same product: isopropylbenzene.



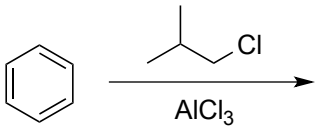
As a result of rearrangement, Friedel-Crafts alkylation is not considered a good way to install primary alkyl groups larger than ethyl on an aromatic ring. In the next section on Friedel-Crafts acylation, we'll see an alternative route for the installation of primary alkyl groups.

Problem 6. What are the products of these Friedel-Crafts alkylations? Pay special attention to whether or not rearrangement is an issue for each reaction.

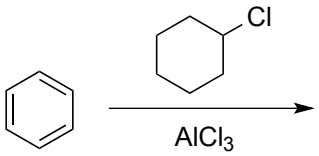
(a)



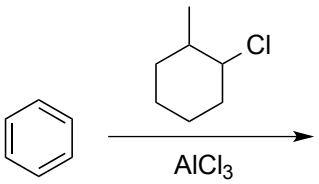
(b)



(c)

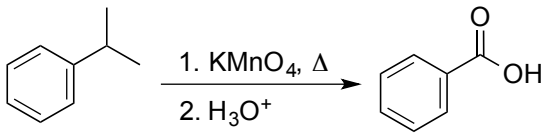


(d)



Benzylic oxidation

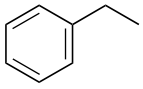
If an alkylbenzene possesses at least one benzylic hydrogen, it can be converted to the benzoic acid using oxidizing agents such as $KMnO_4$ (or $Na_2Cr_2O_7$ and H_2SO_4). The mechanism for this process likely involves radical intermediates, which explains why only the benzylic position reacts since it gives resonance-stabilized radicals. In the process of oxidizing the benzylic carbon, any carbons attached to it are cleaved from the molecule.



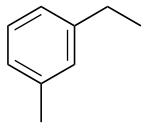
The conditions for step 1 are somewhat basic, so the carboxylate is formed and is protonated to yield the carboxylic acid in step 2. When $Na_2Cr_2O_7$ and H_2SO_4 are used, step 2 is not necessary; the carboxylic acid is obtained directly.

Problem 7. Predict the products when each of the following substrates is treated with potassium permanganate.

(a)



(b)



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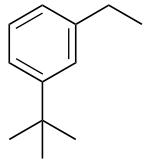
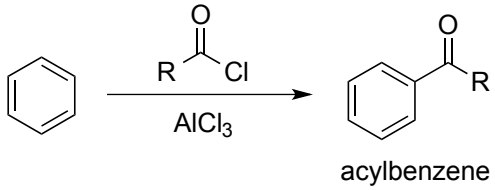
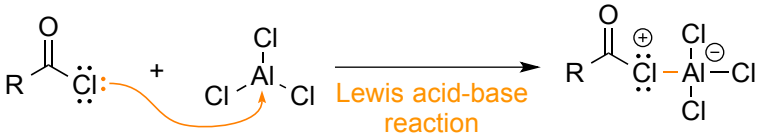


Section 6: Friedel-Crafts acylation

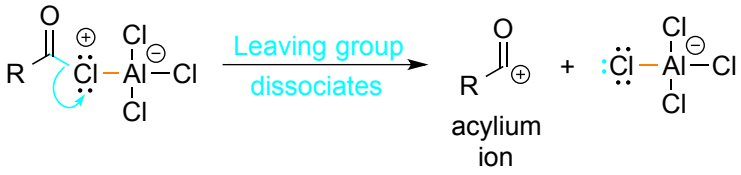
In Friedel-Crafts acylation, an acyl group [RC(O)] is installed on the ring. The reaction requires an acid chloride and aluminum trichloride ($AlCl_3$).



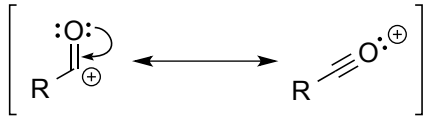
Much like Friedel-Crafts alkylation, the mechanism begins with a Lewis acid-base reaction.



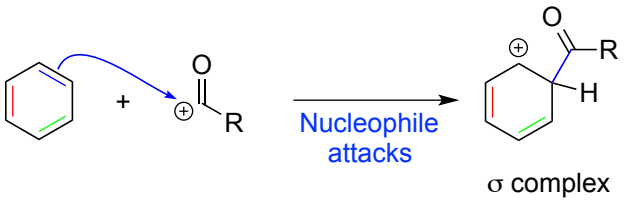
The subsequent dissociation of $AlCl_4^-$ generates a cation known as the acylium ion.



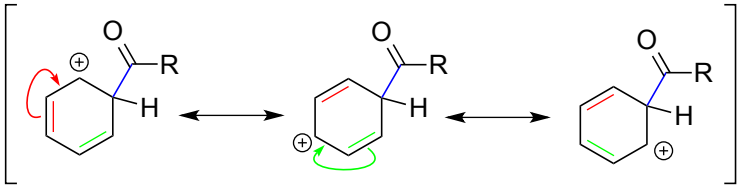
The acylium ion is stabilized by resonance, and it will serve as the potent electrophile in this EAS reaction.



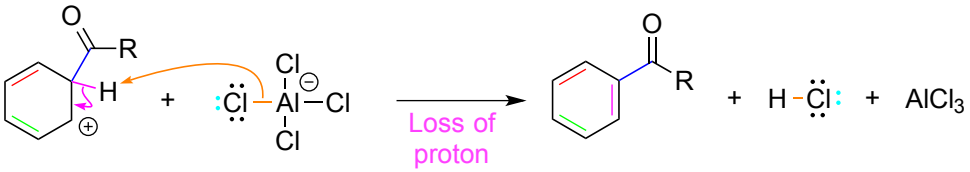
A π bond of the benzene ring attacks the acylium ion to form a σ complex.



The σ complex has the typical resonance forms encountered in EAS reactions, which delocalize the charge around the ring.

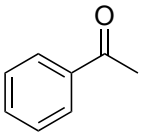


The mechanism ends with the loss of a proton to a chloride that dissociates from $AlCl_4^-$. This yields the acylbenzene product along with HCl as a byproduct and also regenerates $AlCl_3$.

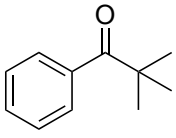


Problem 8. Show how each of the following compounds could be produced by Friedel-Crafts acylation.

(a)



(b)



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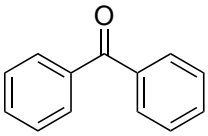
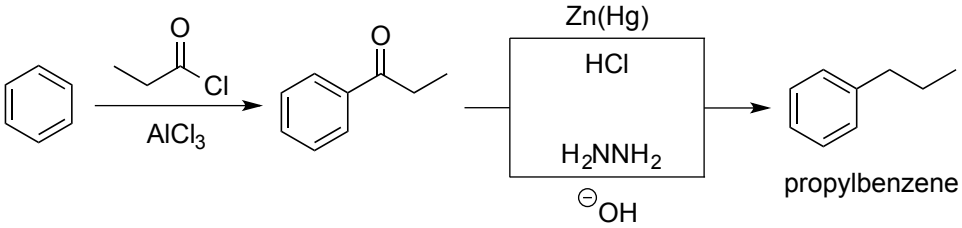


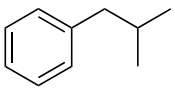
Reduction of the ketone

The ketones of acylbenzenes formed from Friedel-Crafts acylation can be reduced by the Clemmensen [Zn(Hg), HCl] or Wolff-Kishner (H_2NNH_2, ^-OH) reactions. This provides a solution to a problem encountered in Friedel-Crafts alkylation: the inability to efficiently prepare propylbenzene, or similar compounds in which the ring bears a primary alkyl group three or more carbons in length. No rearrangement occurs during Friedel-Crafts acylation because the acylium ion is resonance stabilized.

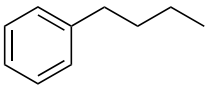


Problem 9. Show how the following alkylbenzenes can be made using a two-step sequence involving Friedel-Crafts acylation followed by reduction. If any of these compounds cannot be made in this way, explain why that is the case.

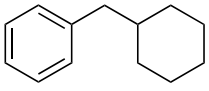
(a)



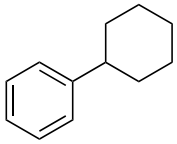
(b)



(c)



(d)

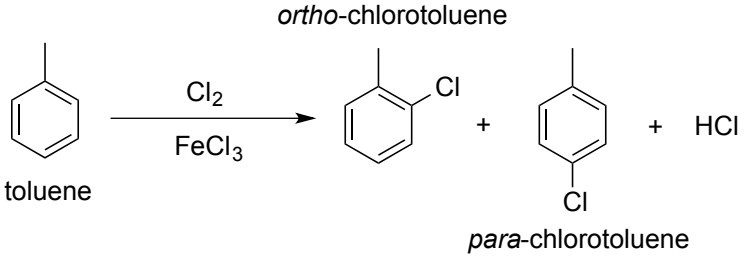


Section 7: The effect of substituents on EAS reactions

When an aromatic ring possesses substituents, those substituents affect the course of an EAS reaction in two important ways: (1) They accelerate or decelerate the reaction, and (2) they impact the regiochemical outcome. Substituents that accelerate EAS reaction are known as activating groups, while those that decelerate the reaction are called deactivating groups. Substituents either direct EAS reaction to the *ortho* and *para* positions or they direct to the *meta* position. Over the course of a few examples, we'll consider why particular substituents exert the effects that they do, and then we'll generalize these effects, showing how you can predict the impact that a substituent will have on an EAS reaction.

Chlorination of toluene

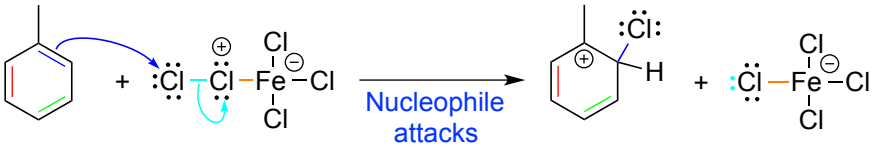
In our first example, toluene is chlorinated to yield a mixture of *ortho*- and *para*-chlorotoluene.



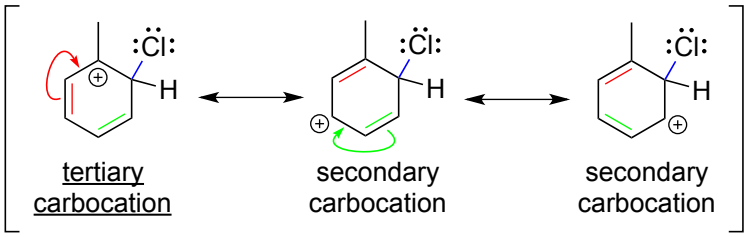
If you were to conduct this reaction in the laboratory, you'd notice that it is faster than the chlorination of benzene. This rate enhancement means that the methyl group is an *activating group*. Since alkyl groups are electron donating, the ring is rendered more electron rich by the presence of the methyl substituent. In EAS reactions, the ring always behaves as a nucleophile, and a more electron-rich nucleophile is a better nucleophile. So, the activating nature of the methyl group can be explained by the fact that it *donates electron density to the ring*, making it a better nucleophile than benzene.

Now, let's turn our attention to the directing effect of the methyl group. The predominant products of this reaction are the *ortho* and *para* isomers. The *meta* isomer is a very minor product. To understand why this is the case, we need to examine the mechanism. The transformation begins with Lewis acid-base reaction between chlorine and iron trichloride.

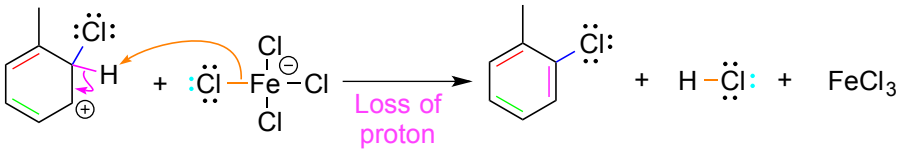
The next step is the attack of toluene on the electrophilic terminal chlorine of the Lewis acid-base complex. This attack could occur so as to place the halogen *ortho*, *meta*, or *para* to the methyl group. The *ortho* and *para* pathways are electronically equivalent, so we will consider only one of the two below. The *ortho* pathway is shown.



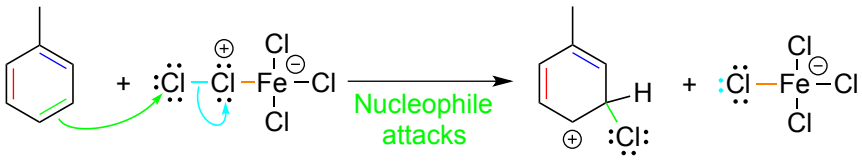
There are two additional resonance forms that stabilize the carbocation intermediate. One of the resonance forms contains a tertiary carbocation, and the other two are secondary. The tertiary carbocation enjoys further stabilization due to the presence of the electron-donating methyl group.



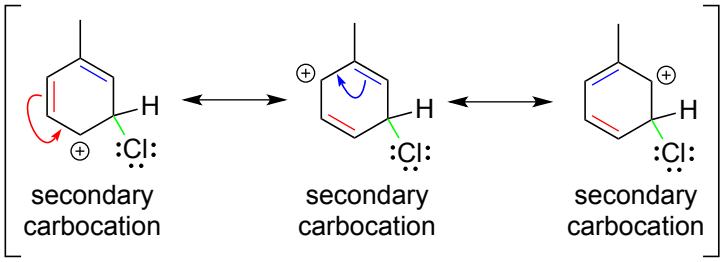
Finally, loss of a proton to chloride generates the *ortho* product. The *para* product is produced through an analogous mechanism.



Now, let's consider the *meta* pathway to illustrate why the *meta* product is not formed in a significant quantity. The initial attack of the ring on the Lewis acid-base complex produces a carbocation as expected.



Notice that, in this case, all of the resonance forms contain secondary carbocations.

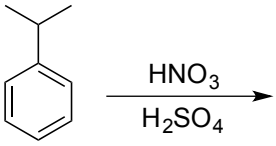


This explains why the *meta* pathway is not as favorable as the *ortho* and *para* pathways. In the *ortho* and *para* pathways, the carbocation intermediate is a resonance hybrid of one tertiary and two secondary cations. In contrast, the *meta* pathway has an intermediate that is a hybrid of three secondary cations. Consequently, the *meta* pathway is higher in energy and less favorable.

Now that we know why the *ortho* and *para* isomers are the major products, you might wonder which one is formed in the greatest amount. In this case, it is the *ortho* isomer that predominates, and the reason is simple. The ring has two *ortho* positions but only one *para* position. Therefore, it is twice as likely that substitution will occur at an *ortho* position. However, with alkyl groups larger than methyl, it is actually the *para* product that predominates. As the substituent grows larger, steric hindrance disfavors attack at the *ortho* position. The sterically uncongested *para* position then becomes the preferred location for substitution.

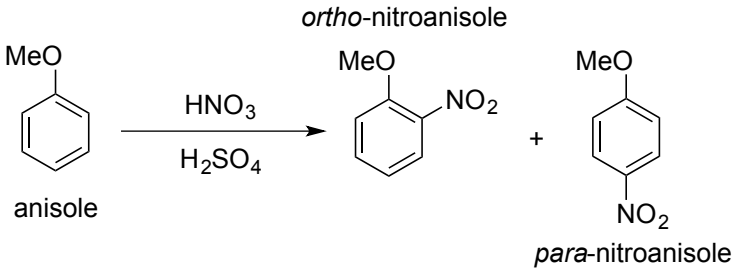
To recap, we have now determined that alkyl groups, such as the methyl group, are activators, as well as *ortho*, *para* directors. These two traits go hand-in-hand. Activating groups will always be *ortho*, *para* directors too. Recall that the activating nature of an alkyl group stems from the fact that it is electron donating. Therefore, we can also expect other electron-donating groups to be activators and *ortho*, *para* directors.

Problem 10. Predict the major product of the following nitration reaction. Draw a mechanism to justify its formation.

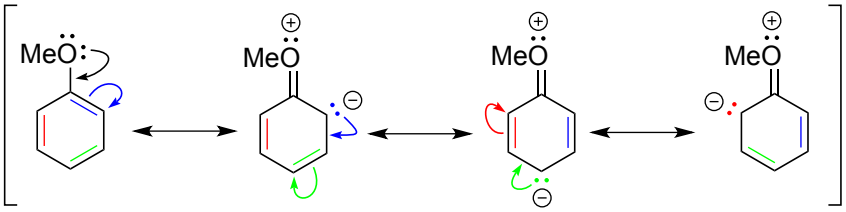


Nitration of anisole

In the following example, anisole is nitrated to yield *ortho*- and *para*-nitroanisole.

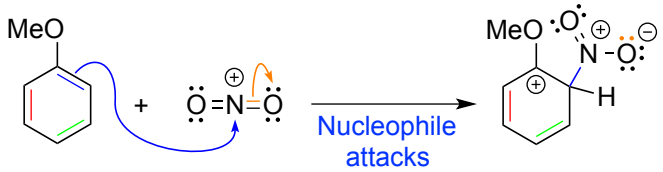


If you were to conduct this reaction in the laboratory, you would find that it is a great deal faster than the nitration of benzene. In fact, it is even faster than the reaction of toluene (a substrate that we considered above). The reason is that the methoxy group donates electron density to the ring via resonance, which is a more powerful effect than induction. The delocalization of a lone pair into the ring makes the ring *significantly* more electron rich. Notice the negative charges on the ring in the following resonance structures, which are evidence of its increased electron density. Remember that a more electron-rich ring is a better nucleophile, which will therefore undergo EAS reaction more rapidly.

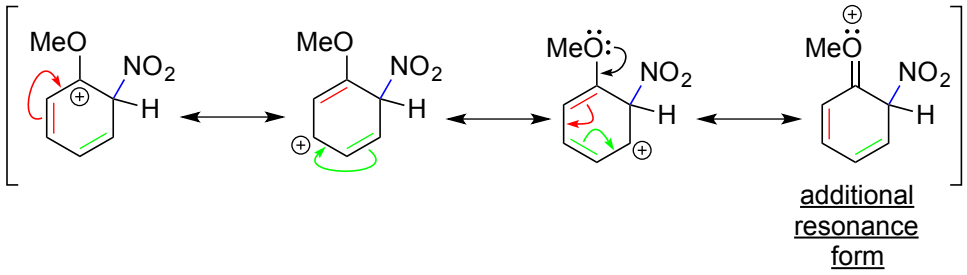


Now that we have established the methoxy group as an activator, we can consider its directing effect. To do so thoroughly, we'll examine the mechanism of the EAS reaction, but before we delve into the full reaction mechanism, notice that you could use the resonance structures above to predict where EAS reaction would take place. Since the ring acts as a nucleophile in EAS, its most nucleophilic sites will be the most reactive. The *ortho* and *para* positions possess negative charges in the above resonance forms, illustrating that they are more nucleophilic than the *meta* position.

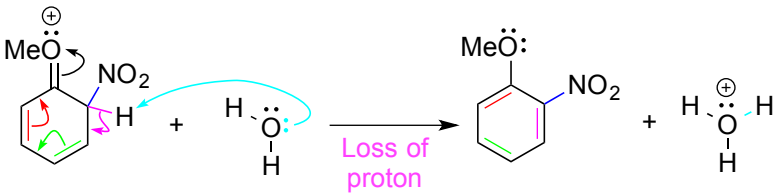
Let's also draw the full mechanism for this reaction to further support the conclusion that the methoxy group is an *ortho*, *para* director. Once the nitronium ion is formed (as illustrated previously in the section on nitration), it is attacked by a π bond of anisole. This attack could place the nitro group in the *ortho*, *meta*, or *para* position. The *ortho* and *para* pathways are electronically equivalent, so we need only examine one of the two. The *ortho* pathway is shown below.



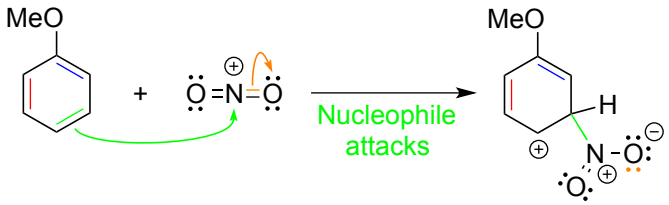
The σ complex for the *ortho* pathway has the three expected resonance forms. Additionally, the methoxy group is electron donating by resonance, and as a result, a fourth resonance structure exists. This last resonance form is particularly stable because all atoms have a complete octet. The *ortho* and *para* pathways are favored because they both possess this additional stabilizing resonance form.



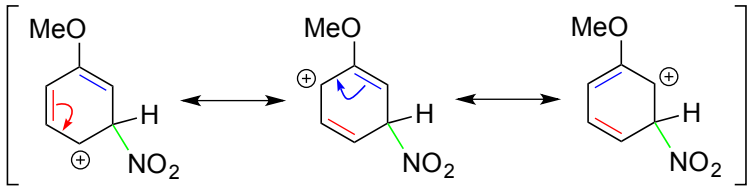
Finally, the loss of a proton from the σ complex affords the *ortho* product. The *para* product is produced through a similar mechanism and can be expected to be the most predominant product due to lesser steric hindrance.



A brief examination of the *meta* pathway will illustrate why it is disfavored with this substrate. The attack of a π bond of anisole on the nitronium ion could yield a *meta* σ complex.



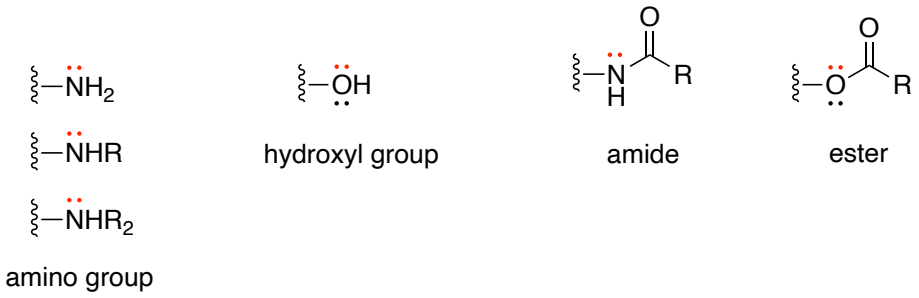
However, this *meta* σ complex has a total of only three resonance structures. There is no way for the methoxy group to further delocalize the positive charge. Consequently, the *meta* σ complex is higher in energy and unfavorable.



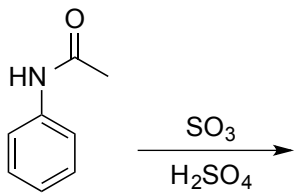
In summary, the methoxy group activates the ring through electron donation by resonance. It also directs substitution to the *ortho* and *para* positions, and we can expect *para* to be the major product since it does not suffer from steric encumbrance.

Generalizations about activating ortho, para directors

We've now seen illustrations of how electron donation via induction or resonance activates the ring toward EAS and directs substitution to the *ortho* and *para* positions. There are other substituents (besides the alkyl and methoxy groups used in the examples above) that donate electron density to the ring. Some examples include the amino group, the hydroxyl group, amides, and esters. Note that each of these groups possesses a lone pair of electrons that can be donated to the ring through resonance. Therefore, these groups also activate the ring toward EAS and direct *ortho* and *para*.

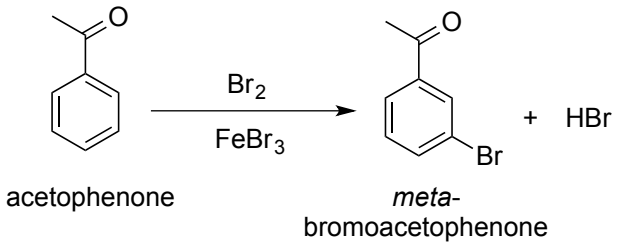


Problem 11. Predict the major product of the following reaction and show a mechanism that justifies its formation.

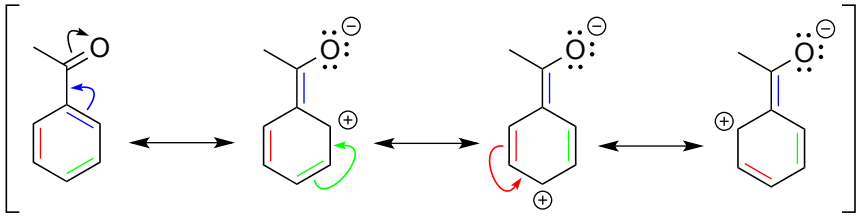


Bromination of acetophenone

In our next case study, acetophenone is brominated to yield *meta*-bromoacetophenone. Notice that, in this example, the *meta* product is now the predominant one.

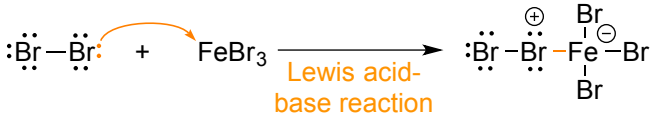


If you were to perform this reaction in the laboratory, you'd discover that acetophenone reacts more sluggishly than benzene. Consequently, the ketone is termed a *deactivating group*. Deactivation of the ring occurs when a substituent is *electron withdrawing*. The withdrawal of electron density from the ring renders it a poor nucleophile, thereby causing EAS reaction to proceed more slowly. In this case, the ketone is conjugated to the ring, so pi electrons from the ring can be delocalized into the carbonyl. This places a positive charge in the ring and clearly illustrates how electron density has been removed.

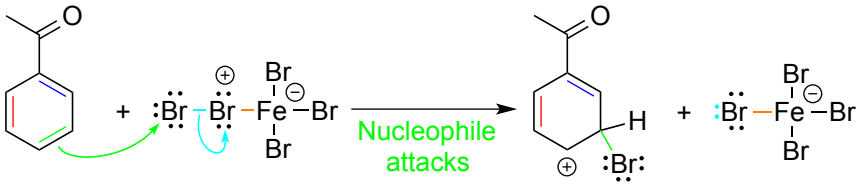


To fully appreciate the *meta*-directing effect of the ketone, we'll examine the mechanism of the reaction in depth. However, the above resonance structures do foreshadow the ultimate outcome. The ring must use its most nucleophilic positions to attack the electrophile. The *ortho* and *para* positions are certainly <u>not</u> nucleophilic since they bear partial positive charges, as illustrated by the resonance forms. Therefore, the only position that can be nucleophilic is the *meta* position.

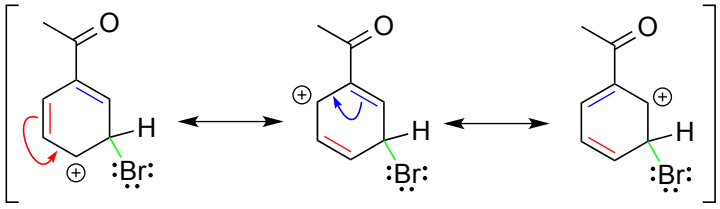
Let's further rationalize the *meta*-directing effect of the ketone by drawing the complete reaction mechanism. The reaction begins with Lewis acid-base complex formation.



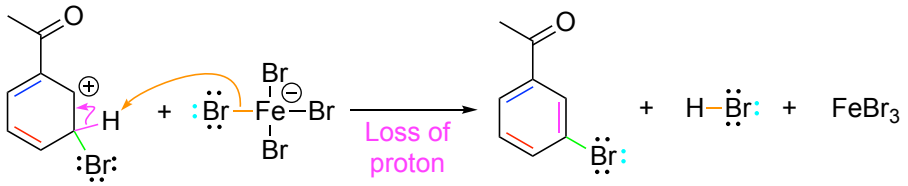
The aromatic ring then attacks the terminal electrophilic bromine atom to form a carbocation intermediate.



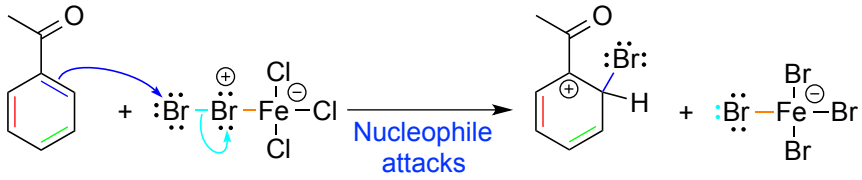
Notice that, in the *meta* pathway, the positive charge is never placed adjacent to the ketone in any of the resonance structures.



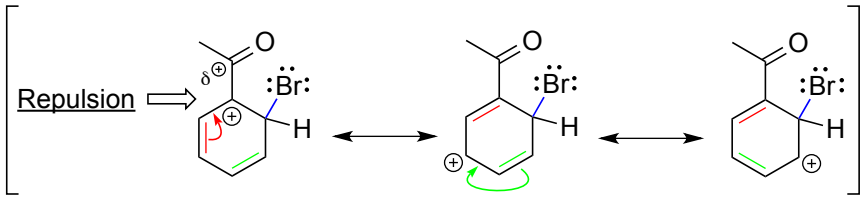
Lastly, loss of a proton restores aromaticity to the ring as the product is formed.



Since the *ortho* and *para* pathways are electronically equivalent, let's consider just one of them below to illustrate why the *ortho* and *para* products are not formed in appreciable amounts in this reaction. If the attack on bromine installs the halogen in the *ortho* position, the positive charge in the intermediate resides on the carbon adjacent to the ketone.



Although this cation also possesses two additional resonance forms, there is repulsion between the positive charge of the carbocation and the partial positive charge (δ^+) of the carbonyl carbon. This raises the energy of the resonance hybrid, thereby disfavoring the *ortho* (and the electronically equivalent *para*) pathway.

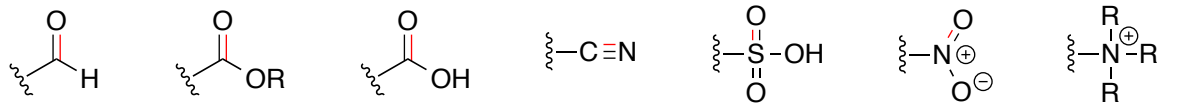


We've now determined that the ketone is both deactivating and *meta* directing due to its electron-withdrawing nature. This trend holds true in most cases. Most (but not all) deactivating groups are *meta* directing. We'll see a notable exception to this trend shortly.

Generalizations about deactivating meta directors

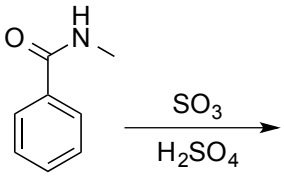
The case study above illustrated the deactivating and *meta*-directing capability of a ketone pendent to the ring. These attributes are the result of the electron-withdrawing effect of the ketone. All groups that withdraw electron density from the ring are deactivating, and most

such groups will also be *meta* directors. Some examples include aldehydes, esters, acids, nitriles, the sulfonic acid group, the nitro group, and quaternary amino groups. Notice that all of these groups, except the quaternary amino group, possess a pi bond into which the ring can donate some of its electron density. This clearly demonstrates why all of these groups are electron withdrawing. The quaternary amino group simply possesses a positively charged nitrogen that withdraws electron density powerfully through induction.



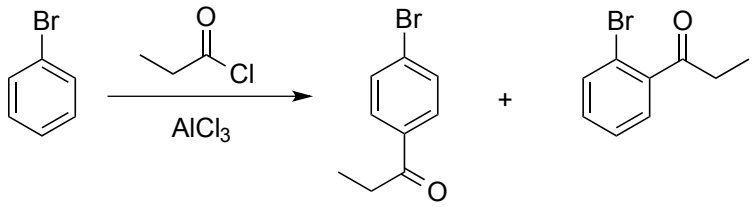
All of these groups are not only deactivators but also *meta* directors. To this point, we have seen that electron-donating groups are activating *ortho*, *para* directors, while electron-withdrawing groups are deactivating and may be *meta* directors. However, there is one type of substituent that does not obey these general trends. The halogens are deactivating *ortho*, *para* directors.

Problem 12. Predict the major product of the following sulfonation reaction and provide a mechanism for its formation.

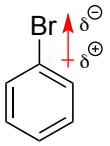


Acylation of bromobenzene

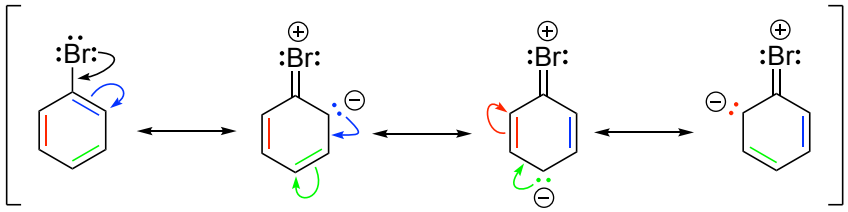
Let's consider another case study that will help us to understand why the halogens exhibit this unexpected behavior. In the following reaction, bromobenzene undergoes Friedel-Crafts acylation with propionyl chloride and aluminum trichloride. *Ortho* and *para* products are produced.



This reaction is slow compared to a comparable reaction with benzene. Therefore, bromine is a deactivating group. The electronegativity of the halogens explains this effect. Halogens inductively withdraw electron density from the ring. The resulting dipole renders the ring electron poor, making it a weaker nucleophile than benzene.

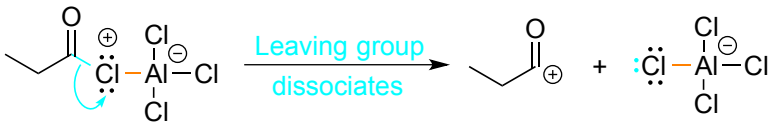


However, resonance is in competition with the inductive effect in this instance, and resonance explains the directing capability of the halogens. If we consider the resonance forms of bromobenzene, it quickly becomes apparent that the *ortho* and *para* positions are the most electron rich and therefore the most nucleophilic. These are the sites that will preferentially undergo EAS reaction.

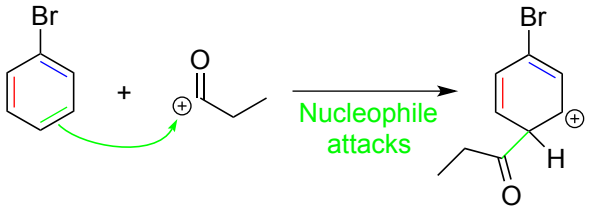


While the resonance structures above foreshadow the directing effect of the halogens, let's also consider the complete mechanism for the reaction in order to further rationalize the effect. Lewis acid-base reaction takes place first.

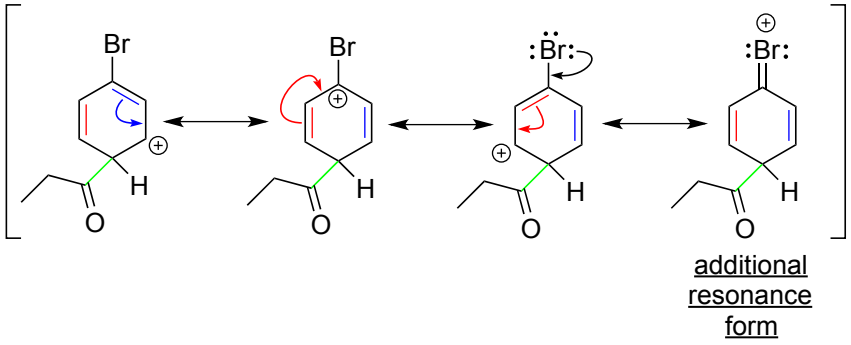
Then, $AlCl_4^-$ dissociates to form an acylium ion.



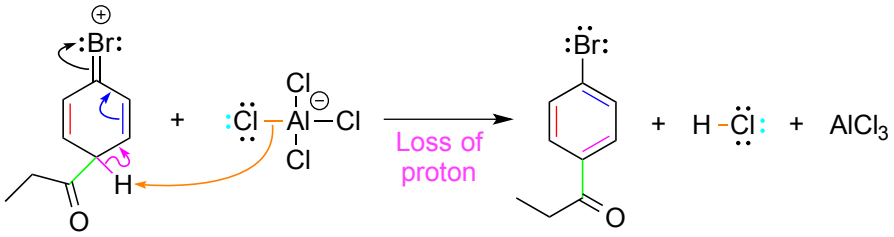
The attack of a π bond of bromobenzene on this electrophile could place the new substituent in the *ortho*, *meta*, or *para* position. Let's examine the *ortho*/*para* pathway first. Since these pathways are electronically equivalent, we need only draw one mechanism. The *para* pathway is shown below.



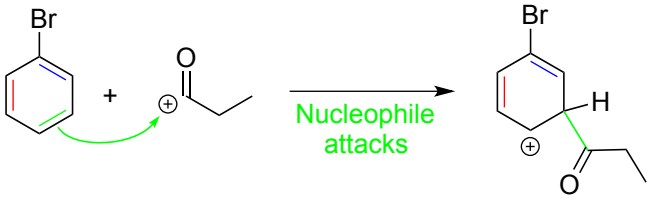
The *para* σ complex has not only the three usual resonance forms that move charge around the ring but also an additional resonance structure in which bromine donates electron density to move the charge outside of the ring. This last resonance form is particularly stabilizing because all atoms possess a complete octet. It lowers the energy of this pathway (as well as that of the *ortho* pathway), thereby favoring it.



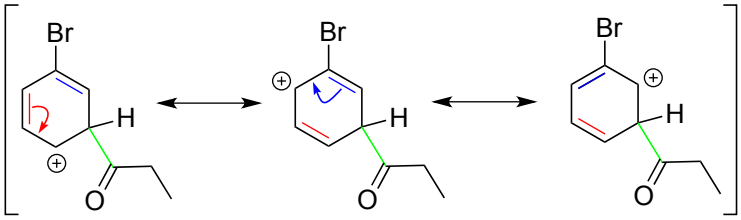
The mechanism concludes with the loss of a proton to a chloride that dissociates from $AlCl_4^-$. This generates the *para* product, and the *ortho* product is formed through an analogous mechanism.



If we examine the *meta* pathway, we can see why it is not favored for this reaction. The formation of the *meta* σ complex is shown below.

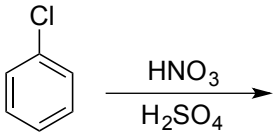


Although this σ complex has resonance, there is no opportunity for the halogen to participate in delocalization of the charge. Consequently, this σ complex is higher in energy than that found in the *ortho*/*para* pathway.



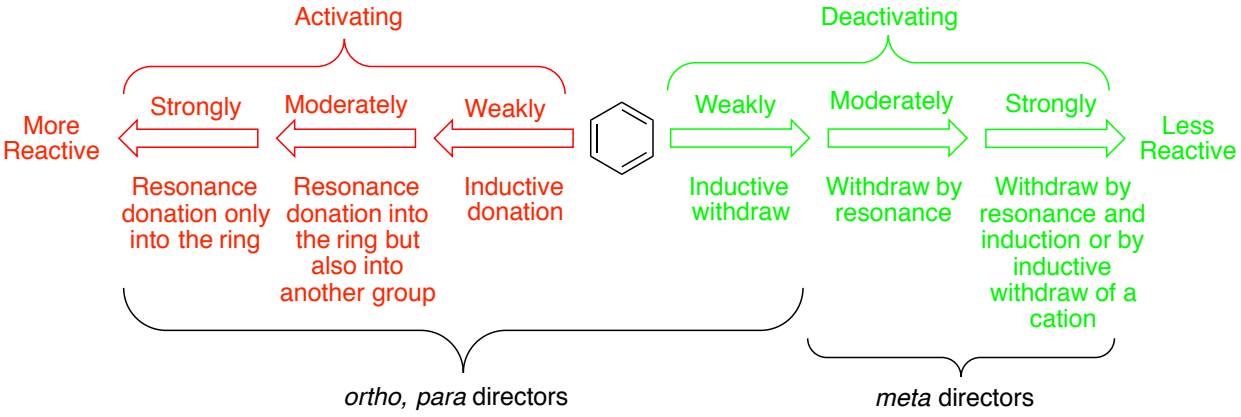
In summary, the halogens present a bit of an anomaly. They deactivate the ring toward EAS reaction by inductively withdrawing electron density. Most groups that withdraw electron density from the ring (and therefore deactivate it toward EAS) also direct further substitution to the *meta* position. The halogens, however, are unique in that they are deactivating toward EAS but direct further substitution *ortho* and *para*.

Problem 13. Predict the products of the following EAS reaction.



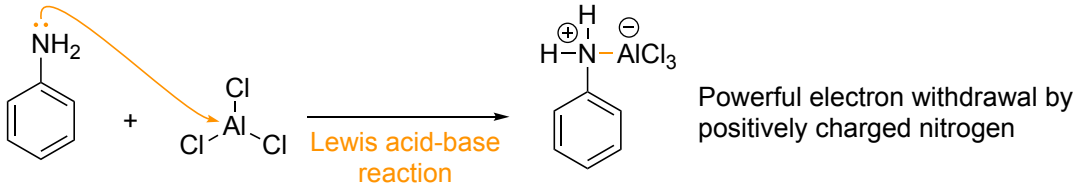
Summary of substituent behavior

The behavior and trends discussed in the preceding sections are summarized in the following diagram. These categorizations apply in most cases.



Problematic Friedel-Crafts reactions

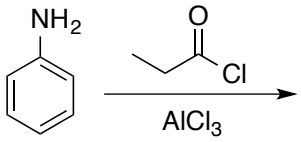
Since we are now delving deeply into EAS reactions of substituted benzene rings, it is important to recognize a few problematic Friedel-Crafts reactions of rings bearing certain types of substituents. Friedel-Crafts reactions do not work with rings bearing nitro (NO_2) or amino (NH_2, NHR, NR_2) groups. Nitro groups withdraw a great deal of electron density from the aromatic ring, making it too weak of a nucleophile for these reactions. Amino groups are Lewis bases, so they will react with $AlCl_3$. This also results in an electron-poor ring that is too weak of a nucleophile for these particular EAS reactions.



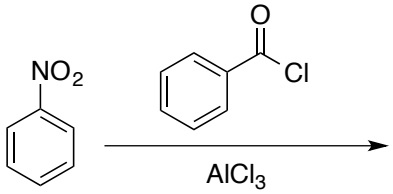
Friedel-Crafts reactions are also problematic with rings bearing carbonyls conjugated to the ring (e.g., aldehydes, ketones, acids, amides, esters) or similar groups (e.g., CN) because $AlCl_3$ likewise complexes with the lone pairs of these functional groups. The resulting Lewis acid-base complex renders the aromatic rings too electron poor to react.

Problem 14. Which of the following EAS reactions will work? For those that do work, provide the structure of major product.

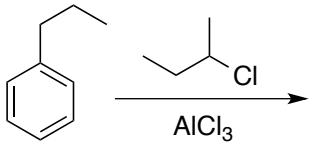
(a)



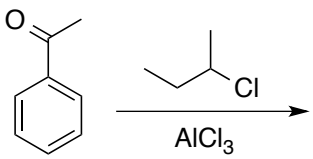
(b)



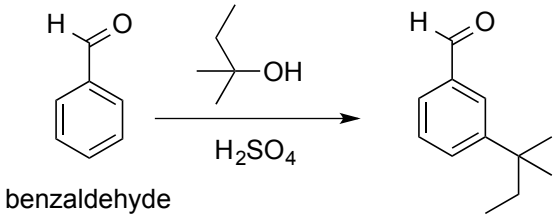
(c)



(d)



Problem 15. A compound such as benzaldehyde will not engage in productive Friedel-Crafts reaction when $AlCl_3$ is used because the carbonyl oxygen complexes with the Lewis acid. However, there are alternative means of generating a potent electrophile for Friedel-Crafts alkylation. Consider the following reaction. Draw a mechanism that explains how this alkylation product is produced. Keep in mind that alcohols can react with sulfuric acid and that an electron-deficient carbon is needed for EAS reaction.

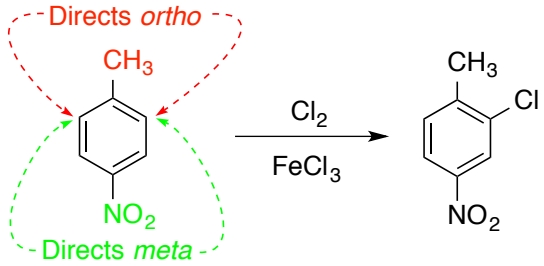


benzaldehyde

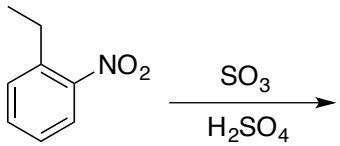
EAS reactions of disubstituted benzene rings

Now that we have established how a single substituent affects an EAS reaction, it is worth asking the question: How will EAS reactions proceed when the benzene ring bears multiple substituents? Let's start by considering the reactions of disubstituted benzene derivatives.

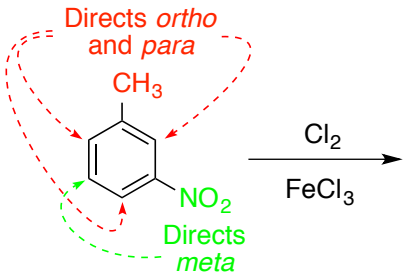
In some instances, the two substituents will both direct EAS reaction to the same location. These are the easier cases because there is no decision to be made. We simply follow the directing trends that we have learned thus far. An example is the chlorination of *para*-nitrotoluene. The methyl group is an activating *ortho*, *para* director, while the nitro group is a deactivating *meta* director. It turns out that both groups direct to the same locations. The methyl group directs only *ortho* to itself because the *para* position is already occupied. This activated site is the same as the positions *meta* to the nitro group. Consequently, the product is 2-chloro-4-nitrotoluene.



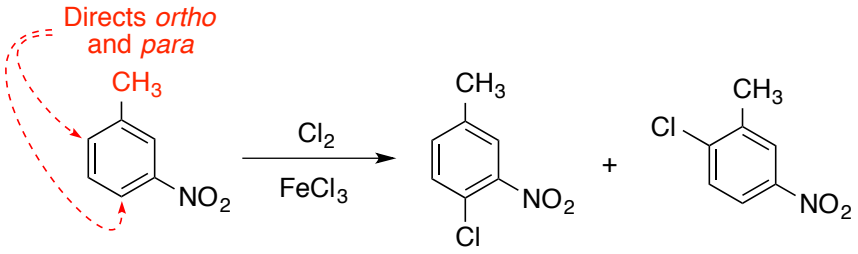
Problem 16. Predict the predominant product of the following sulfonation reaction.



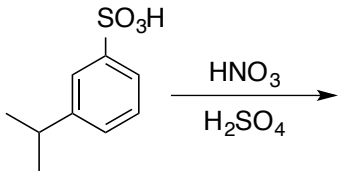
For some substituent patterns, when we compare the directing effects we find that we do need to make a choice. For instance, if we consider the chlorination of *meta*-nitrotoluene (an isomer of our previous substrate), this becomes apparent. The methyl group directs *ortho* and *para* to itself, while the nitro group directs to the only unoccupied position *meta* to itself. In this instance, every location on the ring that doesn't already have a substituent seems to be a candidate for reaction.



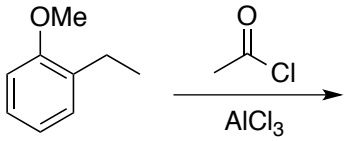
However, we can quickly and easy narrow the choices using two simple guidelines: (1) it is the most activating group on the ring that controls the regiochemistry of EAS, and (2) EAS never occurs between two substituents for steric reasons. Our first guideline renders the nitro group irrelevant. Since the methyl group is activating and the nitro group is deactivating, the methyl group is the more activating group and controls the reaction. The second guideline allows us to disregard the site between the methyl and the nitro groups because it is too sterically encumbered for reaction. This leaves two viable sites for chlorination, and the products are a pair of regioisomers.



Problem 17. What is the major product of the following nitration reaction?

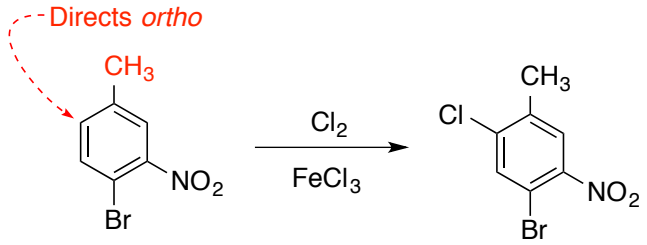


Problem 18. Predict the major product of the Friedel-Crafts acylation below.

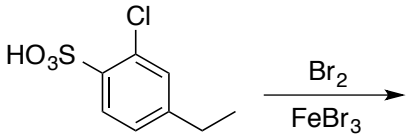


EAS reactions of polysubstituted benzene rings

The same principles apply to predicting the products of EAS reaction using polysubstituted rings. The chlorination of 4-bromo-3-nitrotoluene provides a nice illustration. Knowing that the most activating group will be the one to control EAS, we can streamline our problem solving by first considering each substituent's activating or deactivating potential. While the methyl group is activating, both the halogen and the nitro group are deactivating. Therefore, the methyl group will determine the outcome. The methyl group directs *ortho* and *para*. However, the *para* position already has a substituent, and the *ortho* position that is between two groups is sterically inaccessible. This leaves only one site for chlorination.

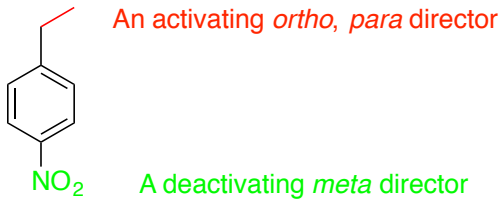


Problem 19. Predict the major product of this EAS reaction.



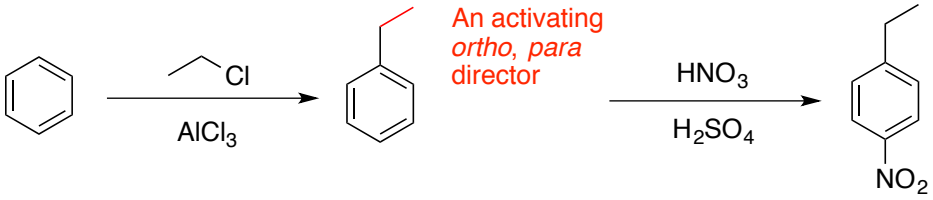
Section 8: Synthesis using EAS reactions

Synthesis problems using EAS reactions fall into two main categories: those that are straightforward and those where the substituent pattern is *seemingly* impossible to achieve. The straightforward synthesis problems are those in which an analysis of the directing effects provides a clear route to the target. For example, if we are asked to prepare 1-ethyl-4-nitrobenzene from benzene, we see that the ring bears both an *ortho*, *para* and a *meta* director.

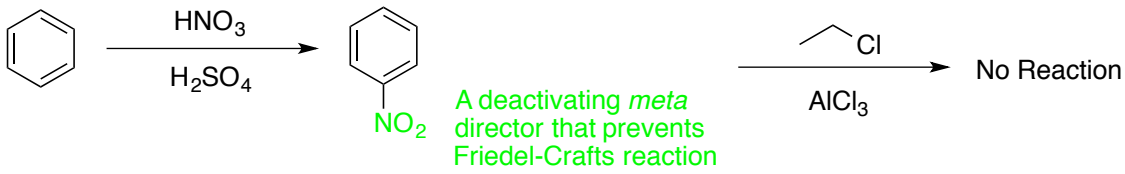


If we were to install the *meta* director first, there would be no hope of placing the second group in the *para* position. Additionally, Friedel-Crafts reaction of nitrobenzene would fail because the ring is too strongly deactivated. Consequently, we would be much better served by first performing a Friedel-Crafts alkylation to install the ethyl group. A

subsequent nitration will be directed mainly to the *para* position by the ethyl group, since it is an *ortho*, *para* director and the *para* position is more sterically accessible.



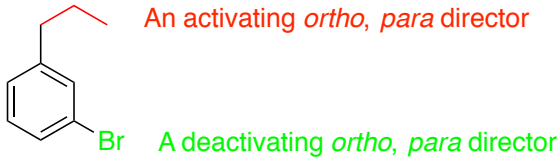
It's very important to remember that selecting the proper reagents is only half the battle. The ordering of the steps can be every bit as important. If we attempt to reverse the two steps used in the successful synthesis above, we are unable to make the target compound because nitrobenzene will not undergo Friedel-Crafts reaction. Furthermore, even if it could undergo alkylation, the new group would be added to the *meta* position instead of the desired *para* position.



The take home message is that a correct synthesis requires that the necessary reactions be performed in the proper order. Neglecting either facet of synthesis will lead to incorrect answers.

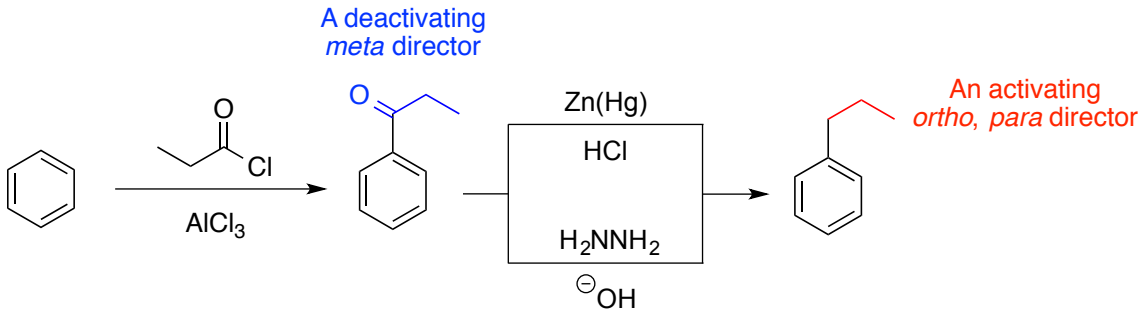
Problem 20. Prepare 1-chloro-3-nitrobenzene from benzene.

Now let's think about a more challenging type of synthesis problem. Sometimes analysis of the directing effects of the substituents makes it seem as though the target couldn't possibly be made. If, for instance, we were asked to prepare 1-bromo-3-propylbenzene from benzene, we might be perplexed by the fact that both substituents are *ortho*, *para* directors. No matter which group is placed on the ring first, it will direct the subsequent reaction to the *ortho* and *para* locations, rather than the desired *meta* position.

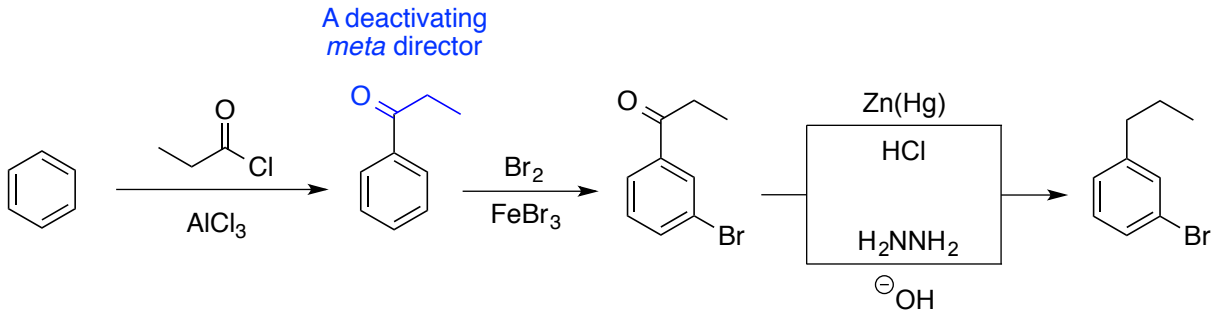


Whenever you encounter this sort of situation, there's always a simple solution. It must be the case that one of the two groups can be installed through a multi-step sequence, and a precursor to the desired substituent will provide the needed directing effect. We know it takes only a single step to install bromine; however, we also know that primary alkyl

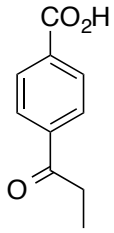
groups larger than two carbons must be added to the ring through a two-step sequence: Friedel-Crafts acylation followed by reduction of the ketone.



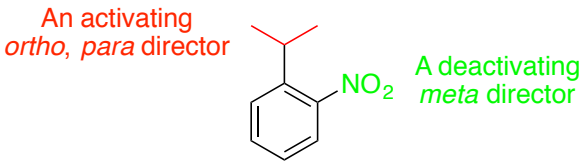
The key to solving this synthesis problem is recognizing that these two steps do not need to be conducted back-to-back. After the initial acylation, the ring bears a *meta* director, providing an opportunity to establish the desired connectivity in this synthesis. Bromination places the halogen in the correct location, and subsequent reduction of the carbonyl yields the target compound.



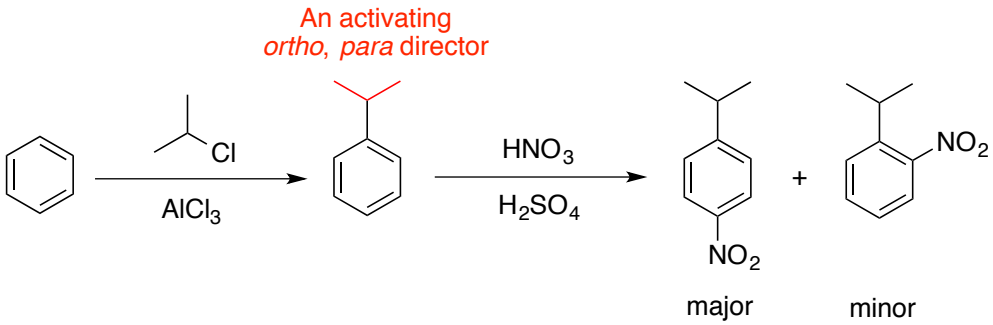
Problem 21. Show how the following molecule can be prepared from benzene.



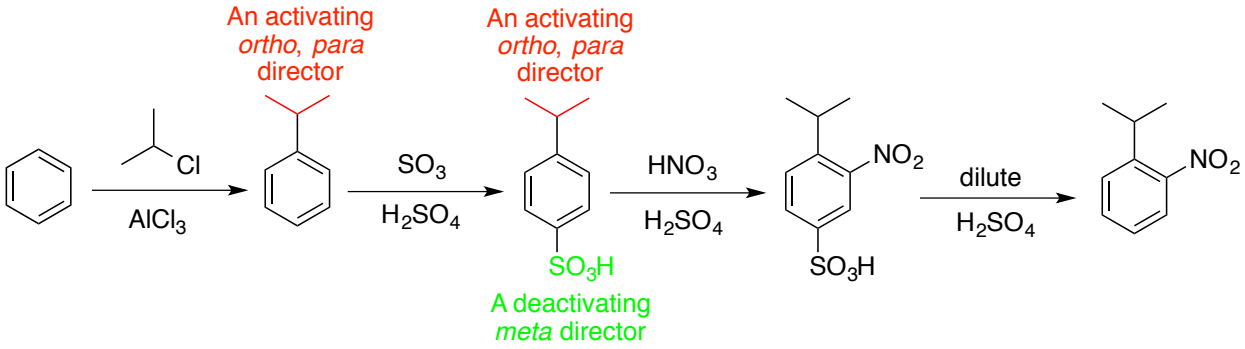
Another example of the seemingly impossible to attain substituent pattern is the synthesis of 1-isopropyl-2-nitrobenzene from benzene. When we consider the directing effects, it becomes clear that the isopropyl group should be added to the ring first so as to direct the nitro group to the desired *ortho* location.



However, given the bulk of the isopropyl group, we expect the major product of nitration to be the *para* product for steric reasons. In this case, the target compound would only be obtained as a minor product, which is undesirable. *Whenever possible, the target of a synthesis should result from the major product of each step.*



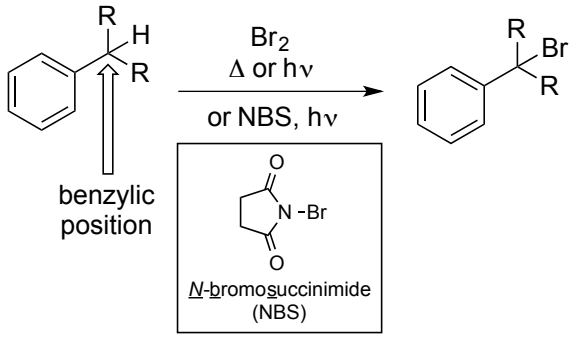
This initially appears to be an intractable problem because the size of the isopropyl group cannot be altered. However, the reversibility of sulfonation provides a solution. The position *para* to the isopropyl group can be blocked with a sulfonic acid group. This forces subsequent nitration to the desired *ortho* location. Then, the sulfonic acid group, having served its purpose, can then be removed upon heating in dilute acid.



Problem 22. Provide a synthesis of 1-chloro-2-propylbenzene, starting with benzene.

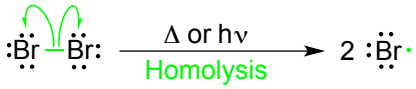
Section 9: Benzylic bromination

Alkylbenzenes bearing at least one hydrogen in the benzylic position can be brominated with bromine (Br_2) and heat (Δ) or light ($h\nu$). Alternatively, NBS and light can be used as a source of a steady, small concentration of bromine. The mechanism entails a radical chain reaction.



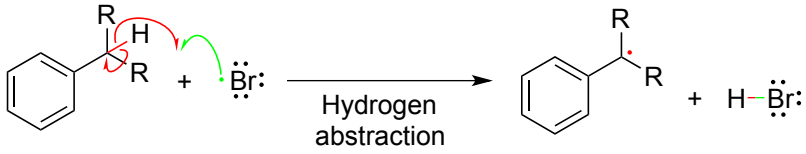
If bromine is used, heat or light initiates the reaction by homolyzing a small number of Br_2 molecules.

Initiation:

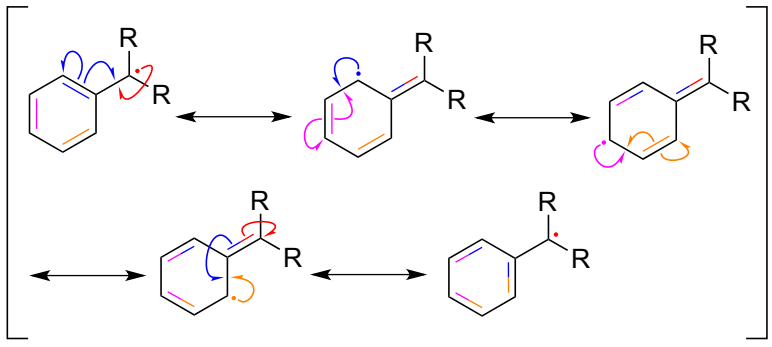


Then, in the first propagation step, a bromine radical abstracts a hydrogen atom from the benzylic position, forming a carbon-centered radical and HBr.

Propagation step 1:

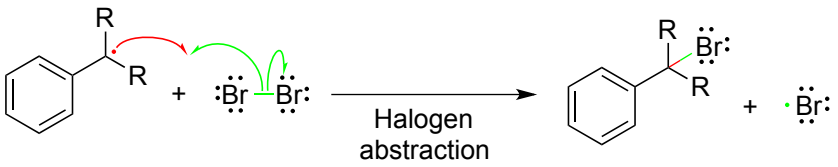


The hydrogen is abstracted specifically from the benzylic position because of the significant resonance delocalization that a benzylic radical has. This is greatly stabilizing.



During the second propagation step, the benzylic radical abstracts a halogen from an unreacted molecule of Br_2. This produces the product as well as a new bromine radical.

Propagation step 2:

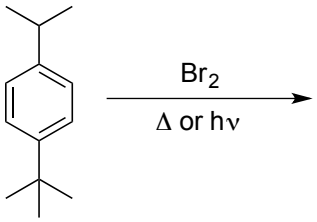


The process is a chain reaction because the bromine radical formed during the second propagation step can enter into a new cycle of propagation.

Termination steps are of little consequence and are therefore not shown. Termination steps explain the fate of the few remaining radicals left over once the reaction has neared completion. However, the vast majority of product is formed during propagation step 2.

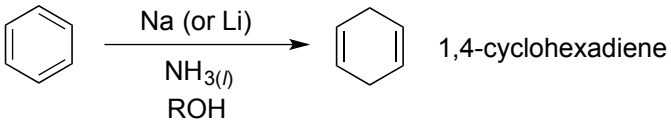
NBS and light can be used as alternative conditions for benzylic bromination. The mechanism for this reaction is very similar to that of allylic bromination (a reaction of alkenes; see Chapter 10 Section 3).

Problem 23. Draw the expected product of the following reaction.

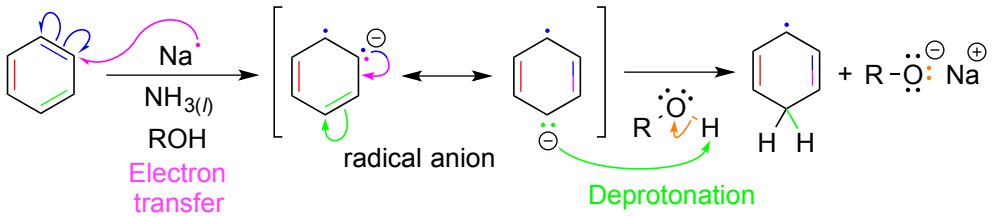


Section 10: Birch reduction

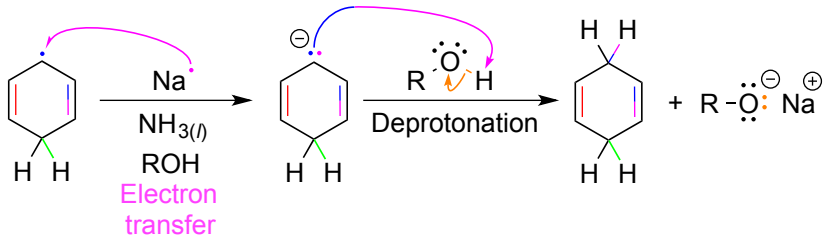
In the Birch reduction, an aromatic ring is reduced to a 1,4-cyclohexadiene by treatment with sodium or lithium in the presence of an alcohol in liquid ammonia.



The metal first donates an electron to the aromatic system. This generates a radical anion (a species with both an unpaired electron and a negative charge) that is resonance delocalized. The resonance form containing a 1,4-diene deprotonates the alcohol to yield a radical intermediate and an alkoxide as a byproduct.



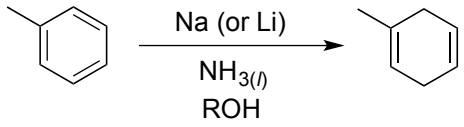
This radical then accepts a second electron from another atom of the metal. The anion thus formed deprotonates another alcohol to form the 1,4-cyclohexadiene product and another molecule of the alkoxide byproduct.



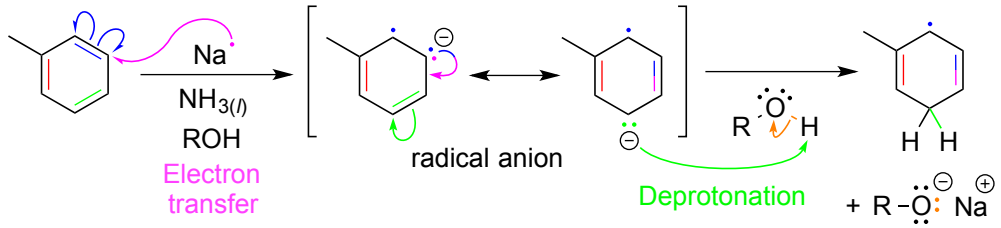
Liquid ammonia ($NH_{3(l)}$) serves as a good solvent to facilitate the transfer of electrons throughout the reaction.

Regiochemistry of the Birch reduction

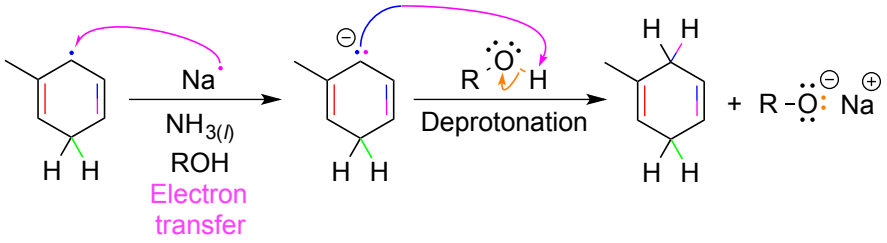
When the aromatic ring is substituted, the nature of the substituent (electron donating vs. electron withdrawing) affects the regiochemical outcome of the reaction. In the following example, toluene is subjected to Birch reduction.



Toluene bears an electron-donating methyl group on the ring. This would destabilize an anion if it appeared on the neighboring carbon. Therefore, the reaction proceeds so as to avoid the placement of negative charge adjacent to the electron-donating methyl group. The initial electron transfer creates a radical anion, whose 1,4-diene resonance form deprotonates the alcohol to afford a radical intermediate.

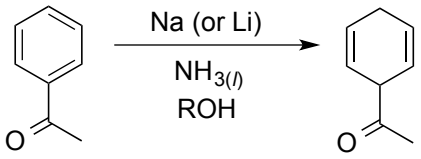


This radical then accepts a second electron, forming an anion that deprotonates another alcohol to yield the 1,4-cyclohexadiene product. Notice that at no point in the mechanism did the negative charge appear on the carbon next to the electron-donating methyl group. Also, note that the electron-donating substituent resides on a double bond in the product.

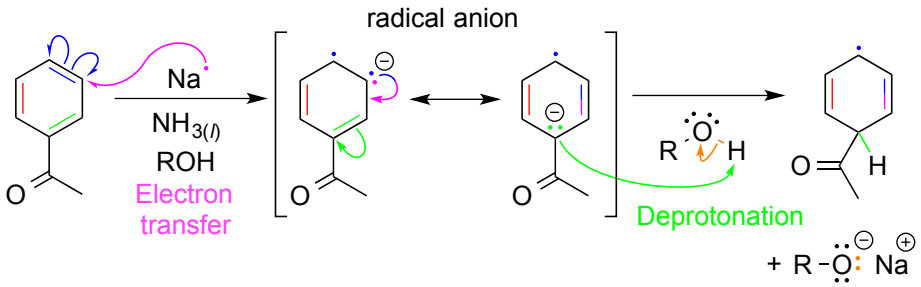


Problem 24. What is the product of Birch reduction of isopropylbenzene?

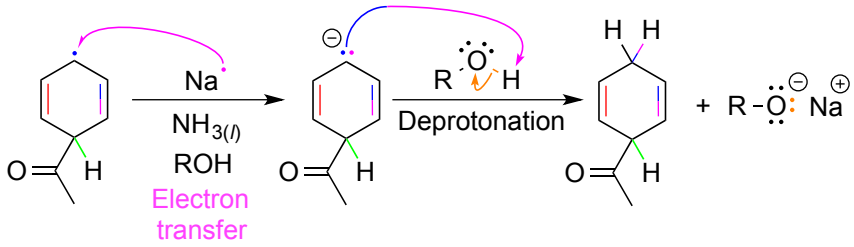
In the next example, acetophenone is reduced. In this case, the substrate has an electron-withdrawing ketone on the aromatic ring. Notice that the substituent is <u>not</u> on a double bond in the product of this reaction. This transformation therefore exhibits the opposite regioselectivity from the previous example.



Since the ketone is electron withdrawing, it will stabilize an anion on the adjacent carbon. Consequently, the reaction progresses so as to place the negative charge at that location. The initial electron transfer generates a radical anion as expected. The 1,4-diene resonance form places the negative charge α (adjacent) to the ketone. This is greatly stabilizing since the charge can then be even further delocalized onto the carbonyl oxygen. Deprotonation of an alcohol yields a radical intermediate.



The radical intermediate subsequently accepts a second electron, and the anion thus formed deprotonates an alcohol to afford the final 1,4-cyclohexadiene product.

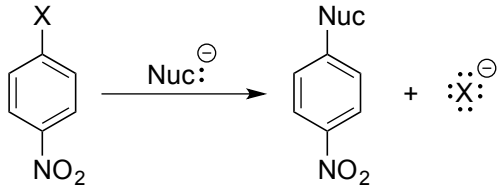


In summary, electron-donating substituents appear on a double bond of the Birch-reduction product, while electron-withdrawing groups do not.

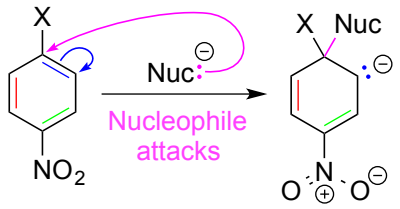
Problem 25. What is the product of Birch reduction of benzoic acid?

Section 11: Nucleophilic aromatic substitution (S_NAr)

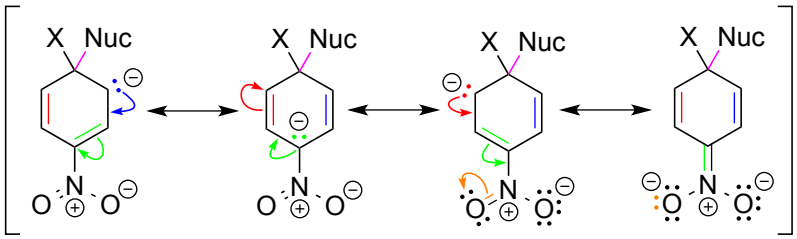
In electrophilic aromatic substitution (EAS) reactions, the aromatic ring always acted as a nucleophile. However, it is also possible for the aromatic ring to react as an electrophile in a reaction called nucleophilic aromatic substitution (S_NAr). This necessitates an electron-poor aromatic ring, which is the result of electron-withdrawing substituents such as the nitro group. The reagent is a nucleophile. In S_NAr reaction, a leaving group (X^-) is ultimately displaced from the aromatic ring.



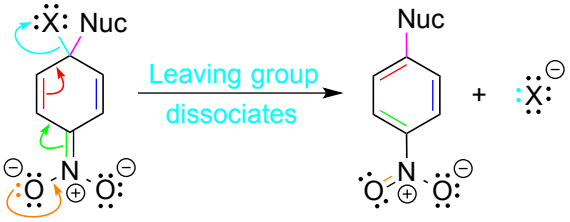
Although this is a substitution reaction, it is important to note that S_N1 and S_N2 reactions do *not* occur on sp^2 hybridized centers. Therefore, this reaction must proceed via a unique mechanism. The S_NAr mechanism begins with the attack of the nucleophile on the electrophilic center bearing the leaving group. Rather than directly displacing the leaving group, the nucleophile pushes a π bond onto the adjacent carbon as a lone pair.



The resulting carbanion is called the Meisenheimer complex, and the negative charge is resonance delocalized around the ring. Electron-withdrawing groups on the ring are important because they provide additional stabilization for the anion. In this case, a nitro group *para* to the leaving group (X) allows the anion to be further delocalized in the final resonance structure.



Finally, the mechanism concludes when the leaving group (X^-) is displaced from the ring. This restores aromaticity as well.

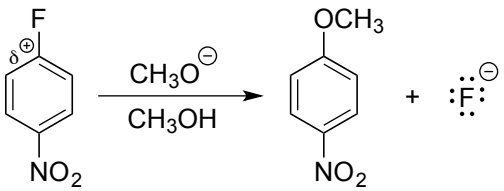


Since the mechanism has two steps in which the nucleophile first adds and the leaving group is then removed, this reaction is also sometimes referred to as addition-elimination.

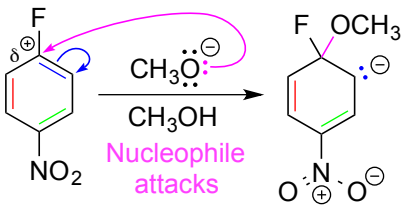
Specific examples

In the following reaction, fluoride will function as the leaving group. This may be surprising because fluoride is not considered to be a particularly good leaving group in S_N1 or S_N2 reactions. Remember that, in both of those reactions, the loss of the leaving group is involved in the rate-determining step, so fluoride's poor leaving group ability matters.

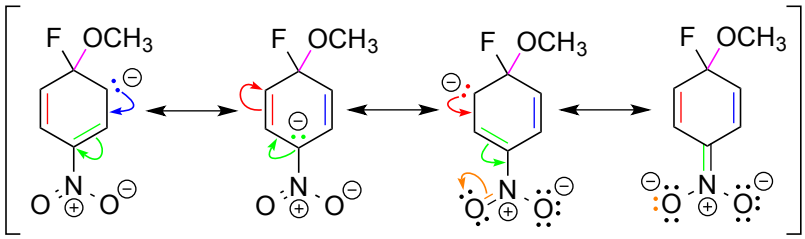
On the other hand, in S_NAr the rate-determining step is the initial attack of the nucleophile on the ring (*not* the loss of the leaving group). This attack occurs more rapidly when the electrophilic site has a strong partial positive (δ^+) charge. Fluorine's powerful electronegativity results in a large δ^+ on the adjacent carbon, which more efficiently attracts the nucleophile. Therefore, fluorine's electronegativity matters more than its leaving group ability in this reaction.



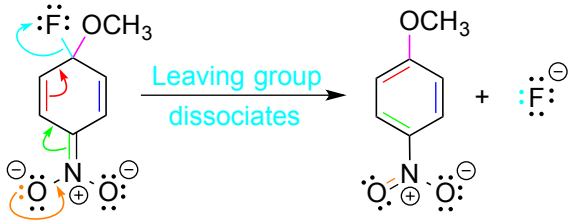
The reaction begins with the attack of methoxide (CH_3O^-) on this intensely δ^+ carbon. A π bond is displaced onto the adjacent atom.



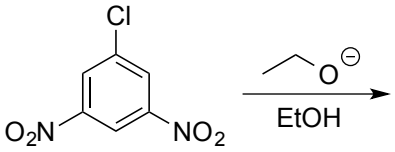
The Meisenheimer complex exhibits significant resonance delocalization of the negative charge. Notably, the last resonance structure places the anion on oxygen, which is a more electronegative atom than carbon. This is especially stabilizing.



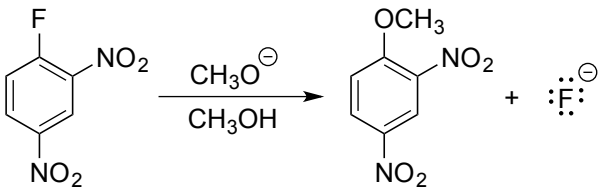
The reaction ends with the loss of fluoride and the restoration of aromaticity.



Problem 26. Predict the product of the following S_NAr reaction.



S_NAr reaction will be more rapid when the ring is more electron poor. Therefore, the following reaction is expected to progress faster than the previous example. The addition of a second nitro group on the ring *ortho* to the leaving group will lead to additional stabilization for the Meisenheimer complex. When the Meisenheimer complex is more stable, the reaction is more facile.

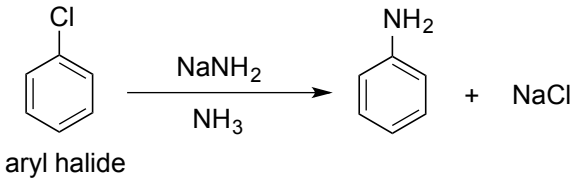


To recap, nucleophilic aromatic substitution (S_NAr) is essentially the reverse of the electrophilic aromatic substitution (EAS) paradigm. In EAS, the ring acts as a nucleophile, and it attacks an electrophile. It does so more efficiently when the ring is electron rich due to the presence of electron-donating substituents. However, in S_NAr, the ring plays the role of the electrophile. It is attacked by a nucleophilic reagent, and this attack proceeds more smoothly when the ring is electron poor due to the presence of electron-withdrawing substituents.

In EAS, a proton on the aromatic ring is replaced by the electrophile. In S_NAr, a leaving group on the aromatic ring is replaced by the nucleophile.

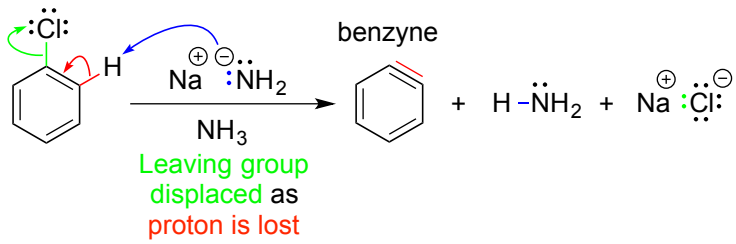
Section 12: Benzyne (elimination-addition)

Benzyne (i.e., benzene containing a triple bond) can be an intermediate in a reaction pathway known as elimination-addition. This mechanism explains the reaction of strong bases/nucleophiles with aryl halides that do not possess electron-withdrawing substituents.



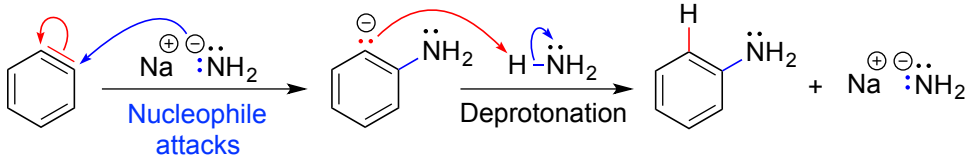
In the previous section on the S_NAr reaction, we saw that a strong nucleophile can add to an aryl halide (an aromatic ring bearing a halogen). However, this requires that the ring also possesses other electron-withdrawing groups to stabilize the intermediate Meisenheimer complex.

When the aryl halide substrate does not possess any additional electron-withdrawing groups, the reaction proceeds through a different mechanism. In this case, elimination occurs first. A strong base (e.g., sodamide) can remove a proton adjacent to the halide leaving group. As the C–H bond breaks, those electrons become a new π bond, and chloride is expelled. The resultant intermediate is known as benzyne.



Another molecule of sodamide serves as a nucleophile, attacking benzyne and displacing the π electrons onto the adjacent atom to yield a carbanion. This portion of the mechanism

is referred to as addition. Finally, the carbanion deprotonates ammonia to yield the product.

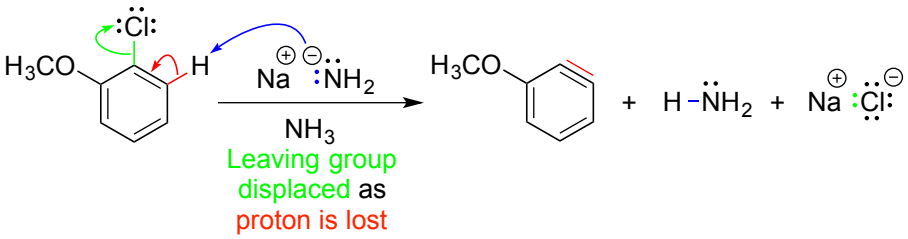


Since elimination is followed by addition in this mechanism, it has the reverse ordering of the key mechanistic steps in S_NAr, which are addition-elimination.

Although two molecules of sodamide were consumed during the reaction, one molecule was also produced in the last step. Therefore, only one equivalent of sodamide is necessary.

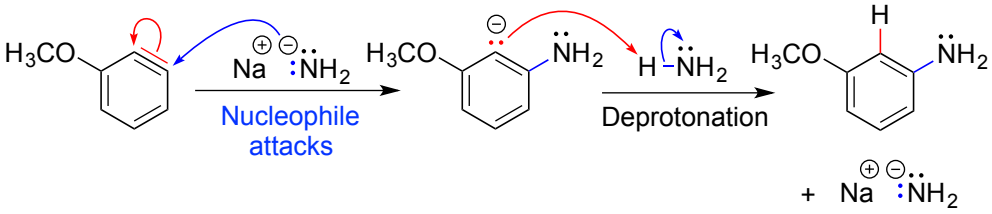
A specific example with regiochemistry

When the aryl halide bears a substituent, regiochemistry becomes a concern. In the following example, the initial elimination affords a benzyne spanning the *ortho* and *meta* positions.

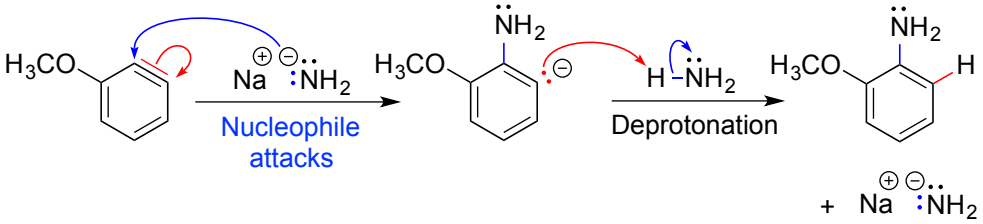


During the addition phase of the mechanism, sodamide can add to either location giving regioisomeric products.

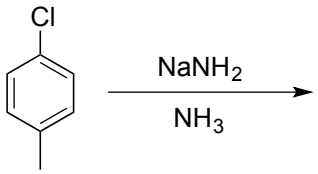
Meta addition:



Ortho addition:

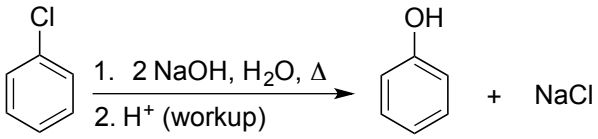


Problem 27. Predict the products of the following transformation.

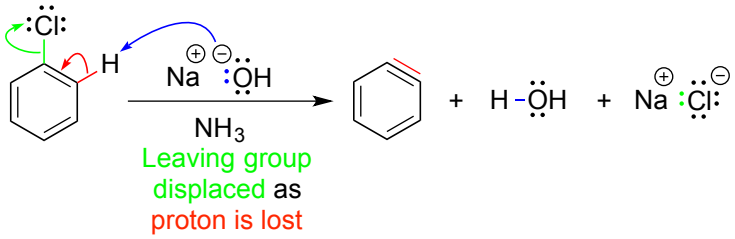


A variation

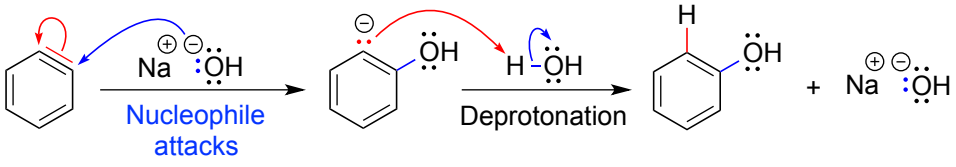
Sodamide is not the only reagent capable of converting an aryl halide to benzyne. Hydroxide can also be used in this capacity and ultimately transforms an aryl halide into a phenol. However, since hydroxide is a much weaker base/nucleophile than sodamide, the reaction requires much higher temperatures. The reaction with sodamide proceeds at -33 °C (at which temperature ammonia is a liquid and can serve as the solvent). On the other hand, reaction with hydroxide can require temperatures in excess of 300 °C.



The mechanism is quite similar, but there is a subtle difference at the end. The reaction begins with hydroxide's removal of a proton adjacent to the leaving group. As a result, a new π bond is formed and the halide is expelled.

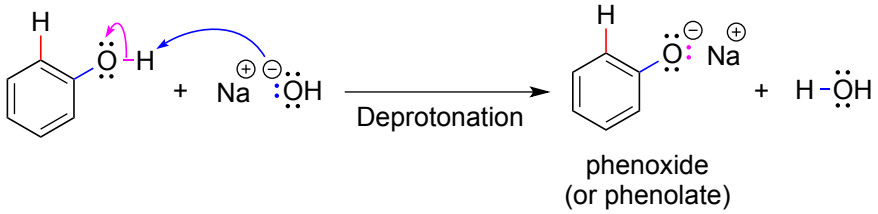


Hydroxide can then add to one of the benzyne carbons during the addition phase of the mechanism. The resulting carbanion deprotonates water to form phenol.



The phenol produced in this transformation is fairly acidic, so hydroxide deprotonates it. As a result, this reaction requires two equivalents of base (as opposed to the single equivalent of base needed when sodamide was used). This also means that, prior to

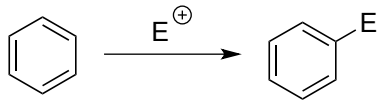
workup, the phenoxide (or phenolate) is the product. During workup, the phenoxide will be protonated to afford phenol.



In conclusion, elimination-addition of an aryl halide proceeds through an intermediate known as benzyne. Benzyne is formed when an aryl halide that has no additional electron-withdrawing groups is treated with a strong base/nucleophile. In such a case, the reaction does not proceed through an addition-elimination pathway (S_NAr) because the Meisenheimer complex would be unstabilized. Addition of the strong nucleophile to benzyne completes the mechanism and can have regiochemical ramifications.

End-of-the-Chapter Problems

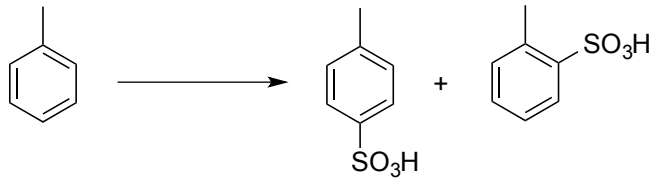
Problem 28. Draw the mechanism for the generic electrophilic aromatic substitution shown below.



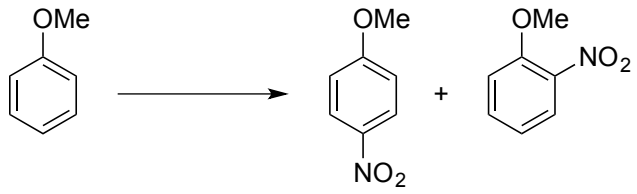
Briefly explain why halogenation, nitration, sulfonation, Friedel-Crafts alkylation, and Friedel-Crafts acylation all follow this same mechanism.

Problem 29. Fill in the missing reagents for the following reactions.

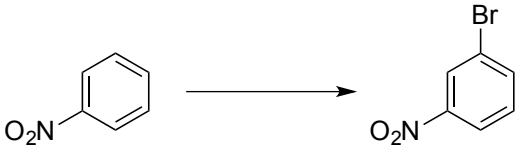
(a)



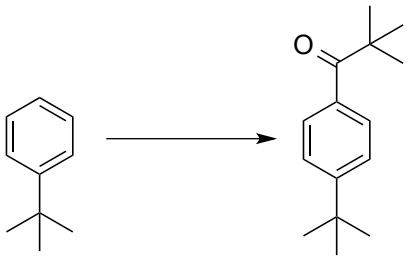
(b)



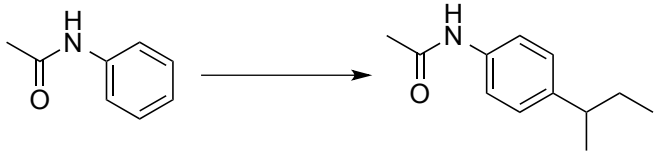
(c)



(d)

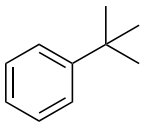


(e)

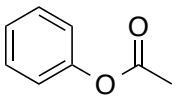


Problem 30. Classify the following benzene derivatives as activated or deactivated toward electrophilic aromatic substitution.

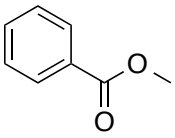
(a)



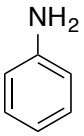
(b)



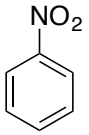
(c)



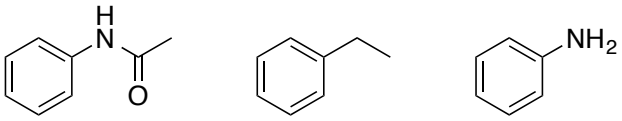
(d)



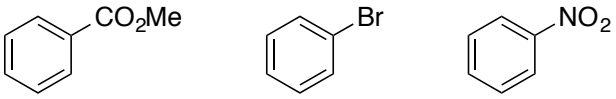
(e)



Problem 31. Rank the following substrates from least activated to most activated toward electrophilic aromatic substitution.

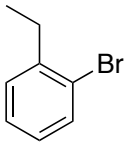


Problem 32. Rank these compounds from most deactivated to least deactivated toward electrophilic aromatic substitution.

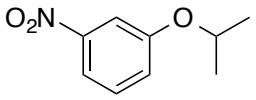


Problem 33. Which positions on the following rings are most likely to undergo electrophilic aromatic substitution?

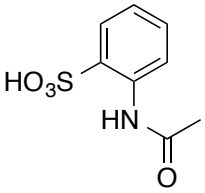
(a)



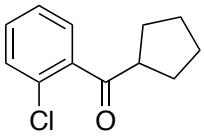
(b)



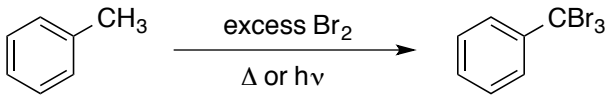
(c)



(d)

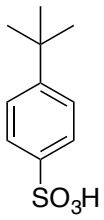


Problem 34. If it is exhaustively halogenated through benzylic bromination, the methyl group of toluene can switch from being an activating to a deactivating group. Why is this the case?

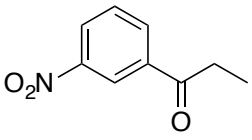


Problem 35. Synthesize the following compounds from benzene.

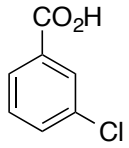
(a)



(b)

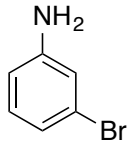


(c)

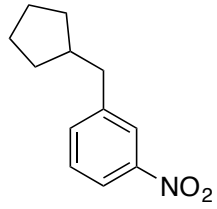


Problem 36. Provide syntheses for the following compounds from benzene.

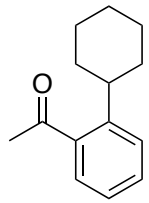
(a)



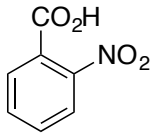
(b)



(c)

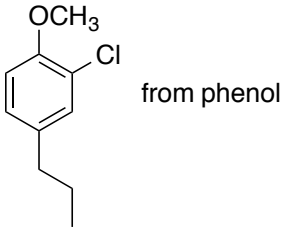


(d)



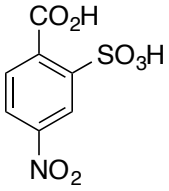
Problem 37. Provide syntheses for each of the following.

(a)



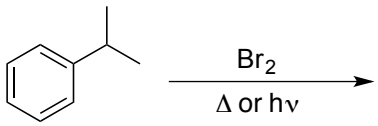
from phenol

(b)



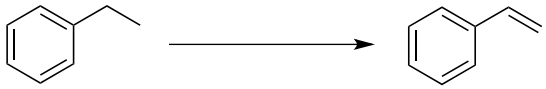
from benzene

Problem 38. Draw a mechanism for the benzylic bromination of isopropylbenzene. Include any relevant resonance forms that help to explain the regiochemistry of the bromination.



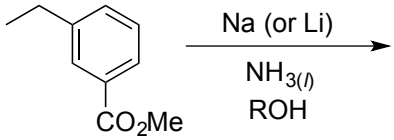
Problem 39. Fill in the reagents needed to accomplish the following transformations. In each case, more than one step may be necessary.

(a)



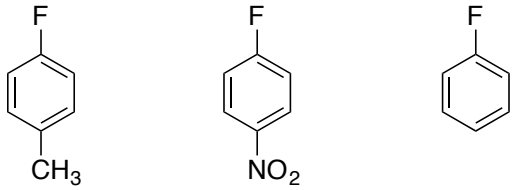
(b)

Problem 40. Predict the product of the following Birch reduction, and draw a mechanism to explain its formation.

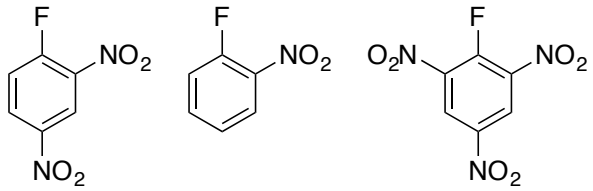


Problem 41. Rank these compounds from most activated to least activated toward nucleophilic aromatic substitution.

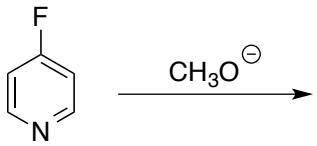
(a)



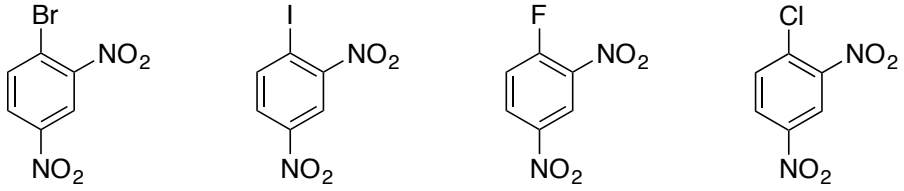
(b)



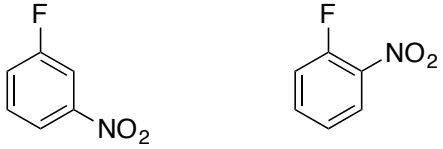
Problem 42. Predict the product of the following S_NAr reaction, and show a mechanism for its formation. Explain how this substrate can undergo S_NAr reaction in the absence of electron-withdrawing substituents, such as nitro groups.



Problem 43. Rank the following compounds from most reactive to least reactive in S_NAr reaction.

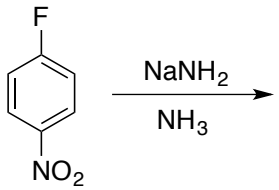


Problem 44. Which of the following compounds is more reactive toward S_NAr reaction and why?

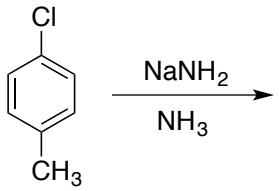


Problem 45. Predict the products of the following reactions.

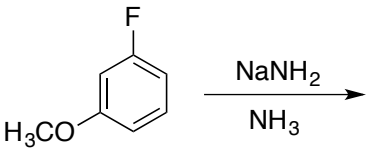
(a)



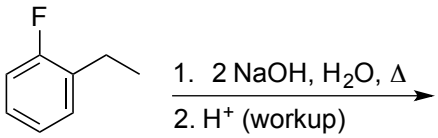
(b)



(c)

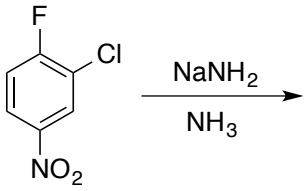


Problem 46. Predict the product(s) of the following transformation.

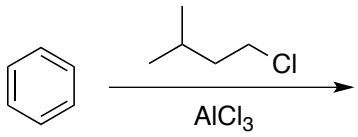


Problem 47. Propose a synthesis of phenol from benzene. Hint: Refer to question 46.

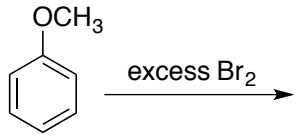
Problem 48. The following reaction yields a product that exhibits M and M+2 peaks in its mass spectrum. The ratio of the M to M+2 peaks is approximately 3:1. What is the reaction product?



Problem 49. The ^{1}H NMR spectrum for the product of the following reaction exhibits the following signals below 2 ppm: a singlet integrating for 6 hydrogens, a quartet integrating for 2 hydrogens, and a triplet integrating for 3 hydrogens. The NMR spectrum also displays a multiplet for 5 hydrogens above 7 ppm. What is the reaction product?



Problem 50. Some strongly activating groups make an aromatic ring nucleophilic enough that it can undergo exhaustive bromination *without* the usual Lewis acid catalyst. The ^{1}H NMR spectrum of the product of the following reaction has only two signals: a singlet integrating for 3 hydrogens at about 4 ppm and a singlet integrating for 2 hydrogens at about 8 ppm. What is the product of this reaction?



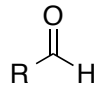
Chapter 15: Aldehydes and Ketones

Section 1: Nomenclature
Section 2: Preparation of aldehydes and ketones
Section 3: Introduction to reactions of aldehydes and ketones
Section 4: Hydrate formation
Section 5: Acetal formation and hydrolysis
Section 6: Imine formation and hydrolysis
Section 7: Enamine formation and hydrolysis
Section 8: Wolff-Kishner reduction
Section 9: Cyanohydrin formation
Section 10: Grignard reaction
Section 11: Hydride reduction
Section 12: Wittig reaction
Section 13: Baeyer-Villiger oxidation
Section 14: Synthesis

Section 1: Nomenclature

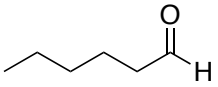
IUPAC nomenclature of aldehydes

Aldehydes are carbonyl-containing functional groups that also have at least one hydrogen on the carbonyl carbon.



aldehyde

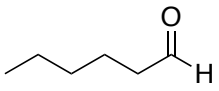
The parent is the longest continuous carbon chain containing the aldehyde. The "e" at the end of the parent alkane's name is removed and replaced with "al" to signify the presence of the aldehyde.



hexanal

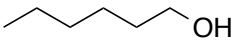
- Six carbon parent = hexane
- Replace "e" of suffix with "al"

Notice how careful and specific we must be with the suffixes. Alcohols end in "ol", while aldehydes end in "al". The difference of a single letter can change the identity of the functional group.



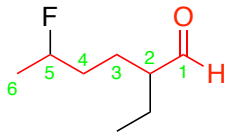
hexanal

vs.



1-hexanol

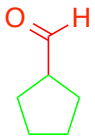
Since there must be at least one hydrogen on the carbonyl carbon, an aldehyde must appear at the terminus of a carbon chain. Consequently, no number is needed to indicate its location on the parent. The aldehyde's carbonyl carbon is assumed to be C1. Substituents still receive numbers as expected though.



2-ethyl-5-fluorohexanal

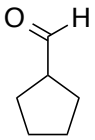
- Six carbon parent = hexane
- Replace "e" of suffix with "al"
- Number the aldehyde carbon as 1
- Add substituent names and numbers

When an aldehyde is pendent to a cycloalkane, the ring's name is followed by the word "carbaldehyde".

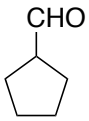


cyclopentanecarbaldehyde

Also, note that the aldehyde functional group is often written in its condensed form as "CHO".

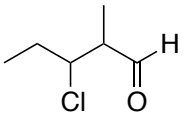


is the same as

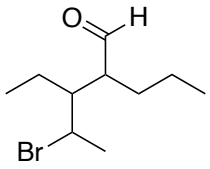


Problem 1. Provide systematic names for the following aldehydes.

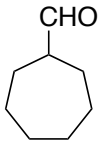
(a)



(b)



(c)

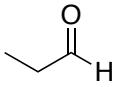


Common nomenclature of aldehydes

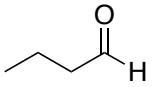
There are a few small aldehydes that are frequently referred to by their common names. In these instances, the word "aldehyde" is preceded by a prefix that indicates the number of carbons in the molecule.

formaldehyde

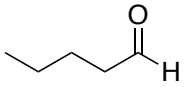
acetaldehyde



propionaldehyde

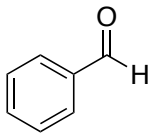


butyraldehyde



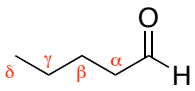
valeraldehyde

We've also seen benzaldehyde previously in the chapter on aromaticity.



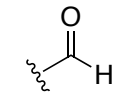
benzaldehyde

Another facet of common nomenclature is that carbons may be labeled with Greek letters to designate their distance from the carbonyl. The position adjacent to the carbonyl is termed the α position. The β position is next to α, and so on and so forth.



valeraldehyde

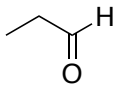
When the smallest aldehyde-containing group is referred to as a substituent, it is called a formyl group.



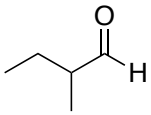
formyl group

Problem 2. Provide common names for the following aldehydes.

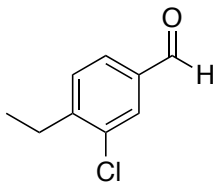
(a)



(b)



(c)

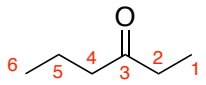


IUPAC nomenclature of ketones

Ketones are also carbonyl-containing functional groups; however, in ketones, the carbonyl carbon bears two R groups.

ketone

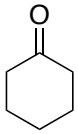
Systematic names for ketones are derived by first identifying the parent, which is the longest continuous carbon chain containing the ketone. The "e" of the suffix is then deleted and replaced by "one" to signify the presence of the ketone. The parent is numbered so as to give the ketone's carbonyl carbon the lowest possible number. Unlike aldehydes, ketones may appear at a variety of locations on a carbon chain, so a number is necessary to identify the functional group's position.



3-hexanone

- Six carbon parent = hexane
- Replace "e" of suffix with "one"
- Number so as to give the ketone's carbonyl carbon the lowest possible number

An exception occurs with the naming of cyclic ketones. Since all carbons on a cycle are identical until the functional group is placed, no number is needed to identify the location of a ketone in a ring. Its carbonyl carbon is assumed to be C1.

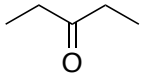


cyclohexanone

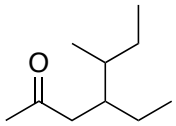
(not 1-cyclohexanone)

Problem 3. Provide IUPAC names for the following ketones.

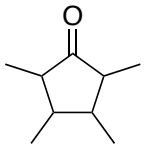
(a)



(b)



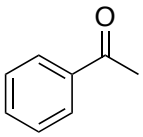
(c)



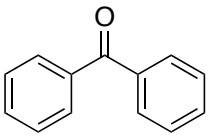
Common nomenclature of ketones

A few small ketones are usually referred to by their common names.

acetone

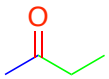


acetophenone



benzophenone

Other small ketones can be assigned common names by placing the names of the alkyl groups attached to the carbonyl before the word “ketone”.

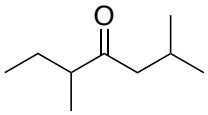


ethyl methyl ketone

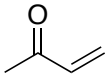
While it is proper to alphabetize the names of the alkyl groups, that convention is sometimes broken. You might recognize MEK as a solvent, where MEK is an acronym for methyl ethyl ketone.

Problem 4. Provide common names for the following ketones.

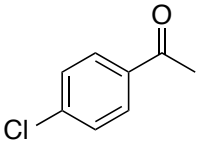
(a)



(b)

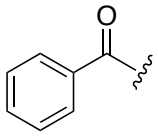


(c)



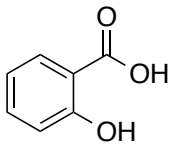
Two common ketone-containing groups are sometimes referred to as substituents. These are the acetyl and benzoyl groups.

acetyl group



benzoyl group

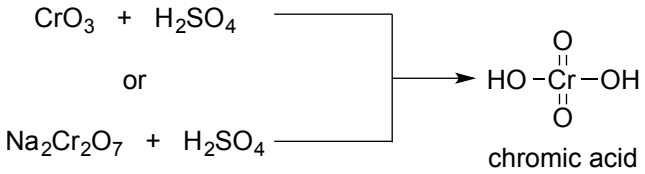
Problem 5. Aspirin is also known as acetylsalicylic acid. The phenol of salicylic acid is acetylated to make aspirin. What is the structure of aspirin?



salicylic acid

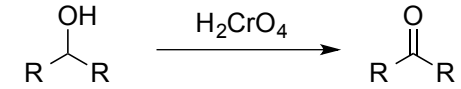
Section 2: Preparation of aldehydes and ketones

In the chapter on alcohols, we saw that aldehydes and ketones may be prepared through oxidation. Chromic acid is prepared from chromium trioxide or sodium dichromate and sulfuric acid.



chromic acid

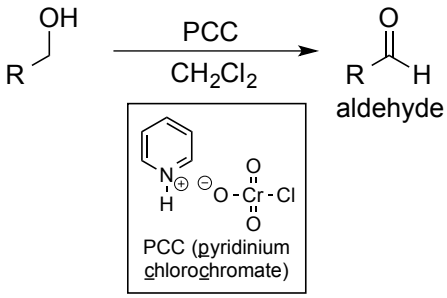
Chromic acid will oxidize a secondary alcohol to a ketone.



secondary alcohol

ketone

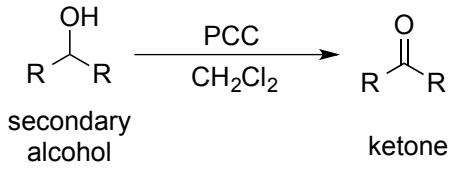
On the other hand, chromic acid will oxidize a primary alcohol to a carboxylic acid, but PCC can be used in its place if we wish to obtain the aldehyde.



aldehyde

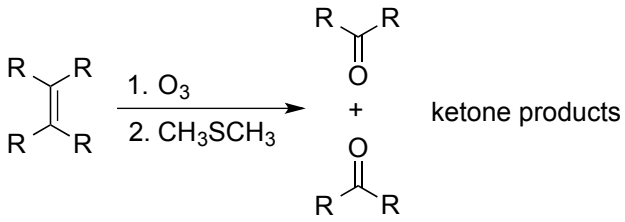
PCC (pyridinium chlorochromate)

This gentler oxidizing agent may also be used to prepare a ketone from a secondary alcohol.

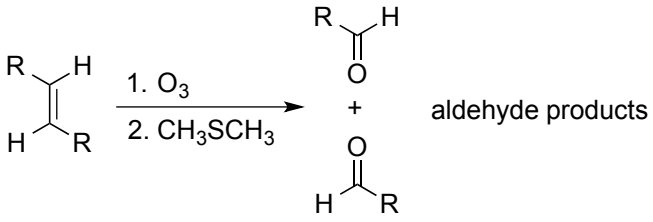


While chromic acid and PCC are essentially interchangeable for the preparation of ketones, PCC must be used to prepare an aldehyde. Otherwise, over-oxidation will lead to the carboxylic acid instead.

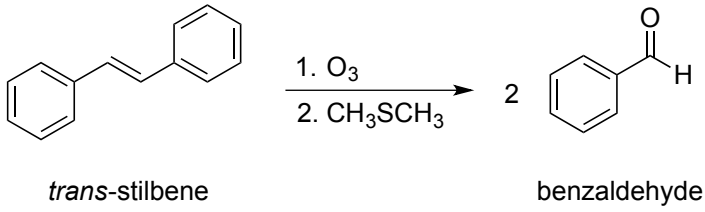
We also learned in the alkenes chapter that ozonolysis of alkenes will give rise to aldehydes and/or ketones. The products obtained depend on the level of substitution of the alkene reactant. For instance, a tetrasubstituted alkene will provide ketone products.



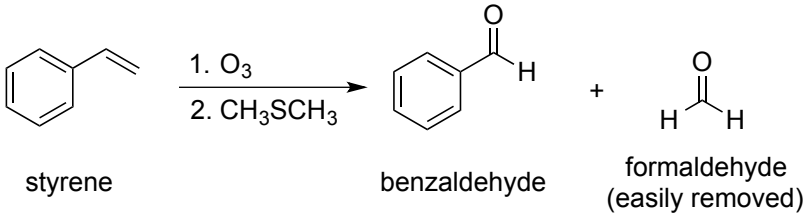
However, a *cis* or *trans* disubstituted alkene will afford aldehyde products.



While the alkene substrate certainly does not have to be symmetrical, if ozonolysis is used to prepare a ketone or aldehyde, a symmetrical substrate provides the highest yield of the target. For instance, ozonolysis of *trans*-stilbene provides two equivalents of benzaldehyde.

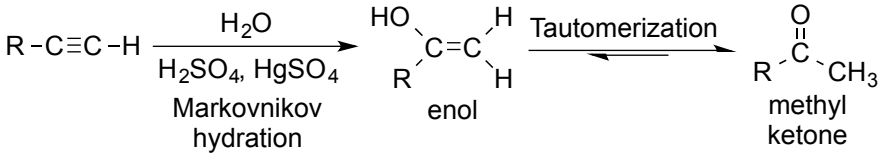


When unsymmetrical alkenes are used in preparative ozonolysis reactions, it is common for one half of the alkene to be small, leading to a small and easily removed ketone or aldehyde byproduct. As an example, the ozonolysis of styrene provides benzaldehyde along with formaldehyde, from which it can be easily separated.

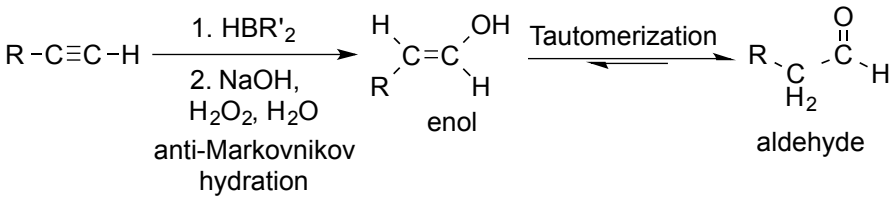


Ozonolysis is unique among methods for the preparation of aldehydes and ketones in that it is accompanied by cleavage of the carbon backbone, and therefore a shortening of the chain.

In the chapter on alkynes, we learned that Markovnikov hydration of a terminal alkyne will afford a methyl ketone.

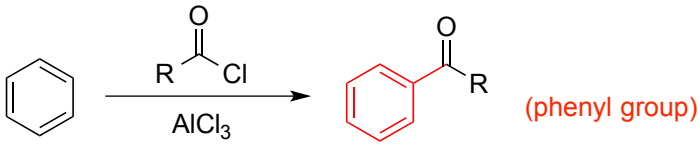


Alternatively, anti-Markovnikov hydration (via hydroboration-oxidation) is a means to prepare aldehydes from terminal alkynes.



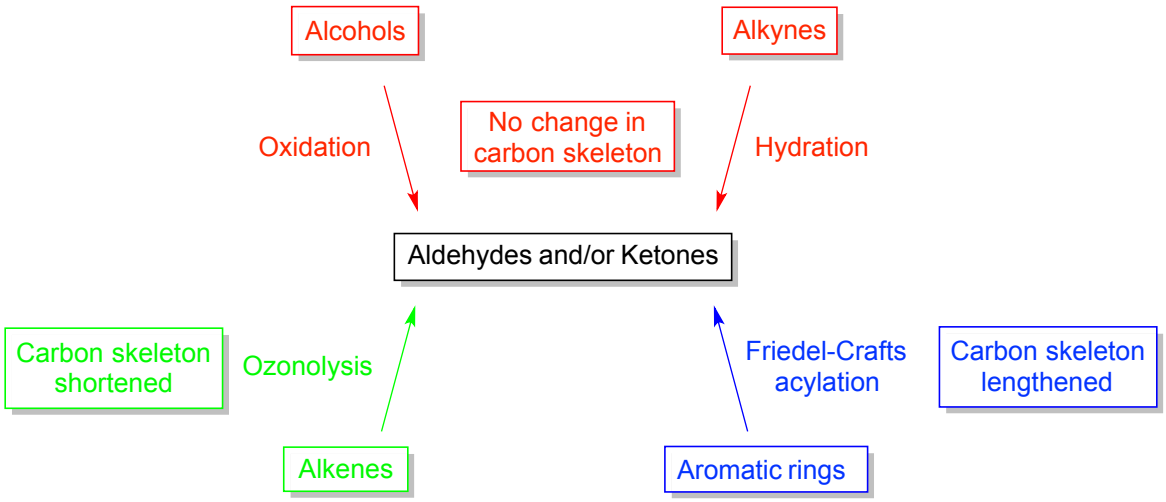
Internal alkynes can be subjected to either method to provide ketone products.

Finally, in the chapter on the reactions of aromatic compounds, we learned that Friedel-Crafts acylation provides ketones bearing a phenyl or aryl (if the ring is substituted) group.



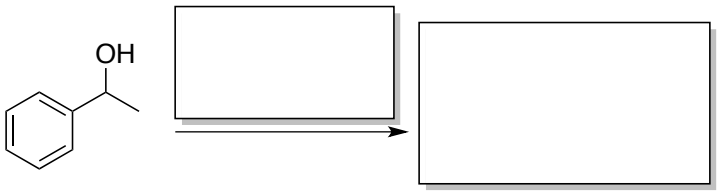
Friedel-Crafts acylation stands out among these preparative methods as one that increases the size of the carbon skeleton.

All of these methods are summarized below according to whether they cause no change in the carbon skeleton, shorten it, or lengthen it.

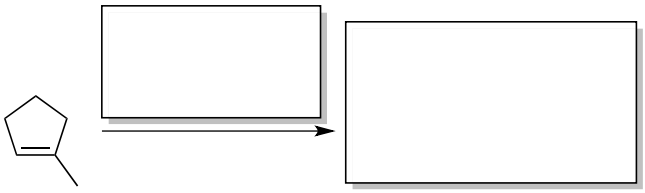


Problem 6. Fill in the missing reagents and/or products in the following reactions, which all prepare ketone and/or aldehyde products.

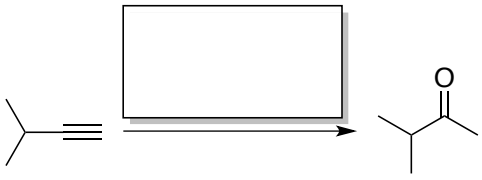
(a)



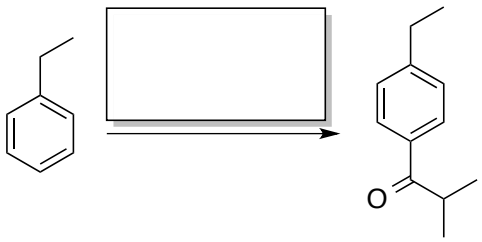
(b)



(c)

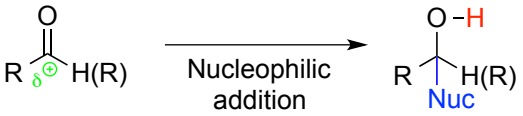


(d)



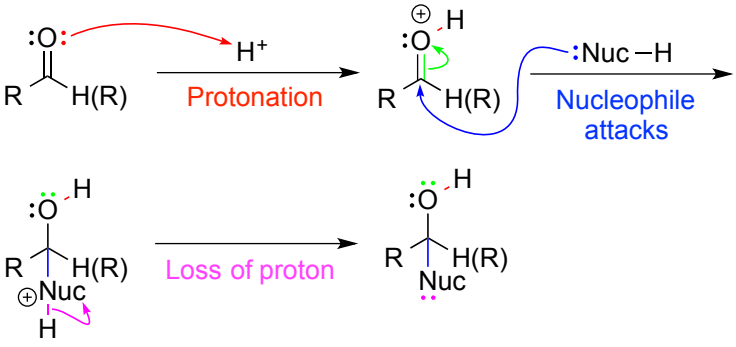
Section 3: Introduction to reactions of aldehydes and ketones

The principal reaction of aldehydes and ketones is known as nucleophilic addition. It amounts to the addition of a nucleophile and a proton across the carbonyl π bond. The nucleophile adds to the carbonyl carbon because of its partial positive charge.

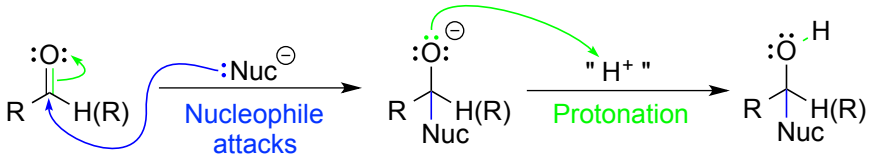


We'll see a number of reactions in this chapter, and the majority will be examples of nucleophilic addition. However, nucleophilic addition can be accomplished in acidic or basic media, and the mechanism varies depending upon the conditions used.

In acidic media, the reaction begins with the protonation of the carbonyl oxygen. This enhances the electrophilicity of the carbonyl carbon because the oxonium ion now has a greater affinity for the electrons shared between them. At this stage, the nucleophile attacks the carbonyl carbon. The nucleophile is typically weak because strong nucleophiles are not compatible with acidic conditions. The weak nucleophile is drawn in by the enhanced electrophilicity of the protonated carbonyl. Finally, a proton is lost from the positively charged nucleophilic atom to afford the nucleophilic addition product.



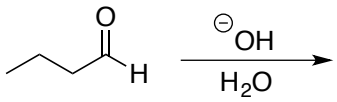
Nucleophilic addition can also take place under basic conditions. In these circumstances, the nucleophile is typically stronger and capable of attacking the carbonyl carbon directly. The resultant anion is neutralized by a proton source ("H^+") of some sort.



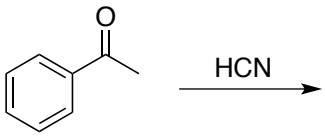
Although the specific identities of the nucleophiles and proton sources will vary in the reactions that follow, keeping these two main mechanistic paradigms in mind will be quite helpful.

Problem 7. Keeping in mind the motif of nucleophilic addition, predict the products of the following reactions.

(a)

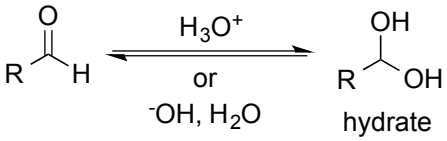


(b)

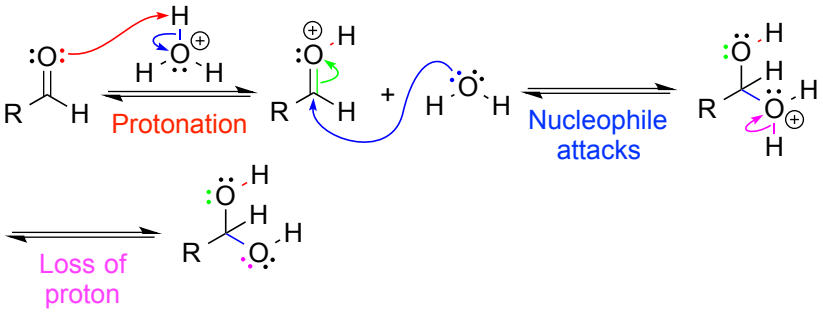


Section 4: Hydrate formation

Ketones and aldehydes can be converted to their corresponding hydrates in water with a trace of acid or base. The position of equilibrium depends on the electrophilicity of the carbonyl carbon and the steric encumbrance around it. As a result, aldehydes are more likely to form hydrates than ketones.

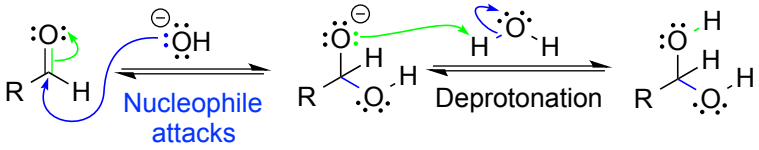


The mechanism is an example of nucleophilic addition across the carbonyl π bond. When a trace of acid is present, the carbonyl oxygen can be protonated. The resulting oxonium ion is more electrophilic and therefore more receptive to the nucleophilic attack of water. This generates a second oxonium ion that readily loses a proton to yield the neutral hydrate.



Notice that, while a proton was consumed in the first step of the mechanism, a proton is also liberated in the final step of the mechanism. Consequently, the acid is catalytic and only a trace amount is necessary.

This reaction can also be catalyzed by base. In the base-catalyzed mechanism, the first step is the nucleophilic attack of hydroxide on the carbonyl carbon. The resultant anion deprotonates water to afford the hydrate.

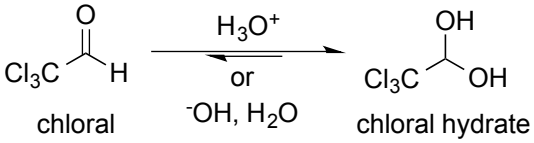


Hydroxide is consumed in the first step but produced in the second step, so the base is also catalytic. Only a trace amount is needed.

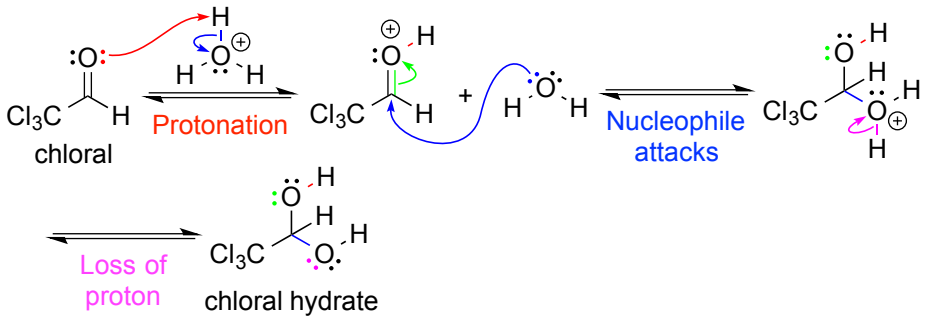
In both instances (the acid- and base-catalyzed reactions), the net result is the addition of water across the carbonyl. A hydroxyl group is added to the carbonyl carbon, while a proton is added to the carbonyl oxygen.

A specific example of hydrate formation

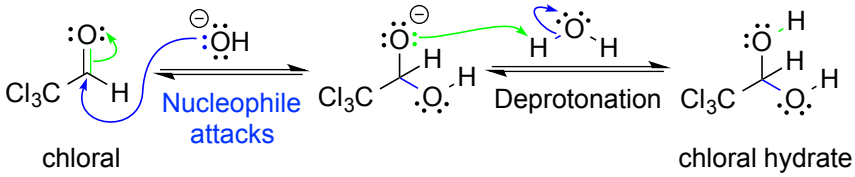
Chloral (shown below) has a very electrophilic carbonyl carbon because of the electron-withdrawing effect of the trichloromethyl group. Consequently, chloral reacts readily with water in trace acid or base to produce chloral hydrate. Chloral hydrate was used as an early sedative but then gained notoriety for its illicit use in knockout drops.



In trace acid, chloral's carbonyl oxygen is protonated. The resulting oxonium ion is subsequently attacked by water. Finally, the loss of a proton yields chloral hydrate.

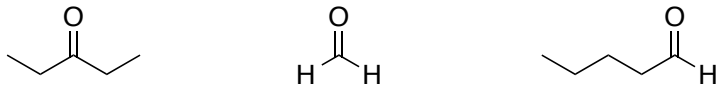


In trace base, chloral's carbonyl carbon is attacked directly by hydroxide. The anion that results then deprotonates water to produce the hydrate.



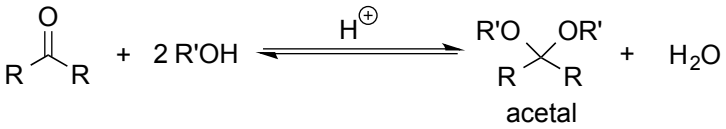
In summary, hydrate formation is the nucleophilic addition of water across the carbonyl π bond of a ketone or aldehyde. The reaction requires a trace of acid or base to act as a catalyst. Particularly electron-poor aldehydes favor hydrate formation. Typical aldehydes equally favor the carbonyl form and the hydrate form; whereas, typical ketones favor the carbonyl form.

Problem 8. Rank the following compounds in order of increasing reactivity in hydrate formation.



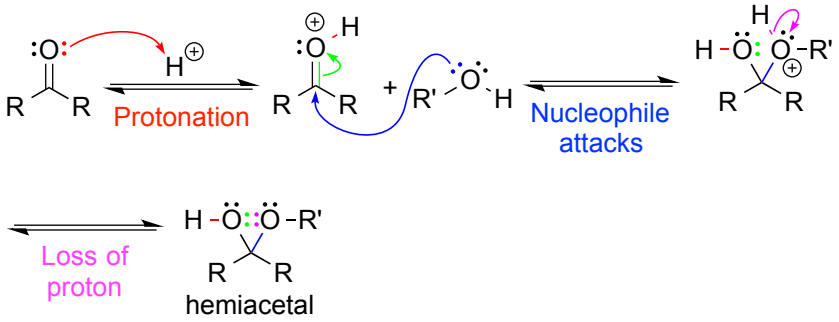
Section 5: Acetal formation and hydrolysis

When treated with two equivalents of an alcohol, a ketone or aldehyde can be converted to the corresponding acetal. Much like hydrate formation, this reaction entails nucleophilic addition across the carbonyl. However, the process occurs twice.

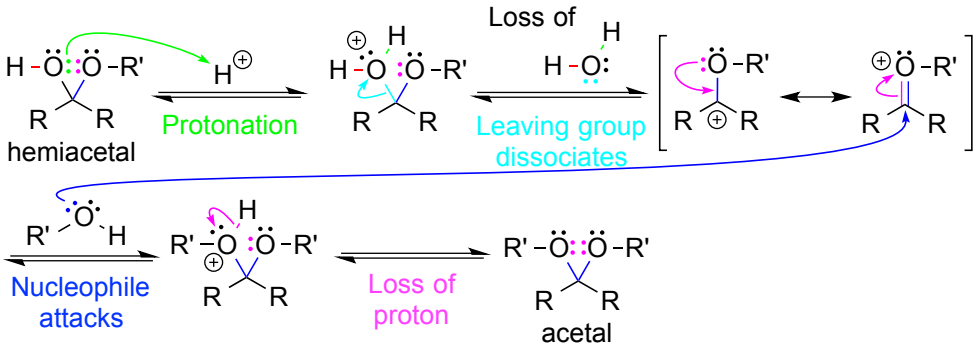


The reaction requires catalytic acid and is freely reversible. The position of equilibrium is often controlled by adding excess alcohol to push the reaction toward the acetal. Alternatively, an acetal can be hydrolyzed using excess water. These are examples of exploiting Le Châtelier's principle to control the position of equilibrium.

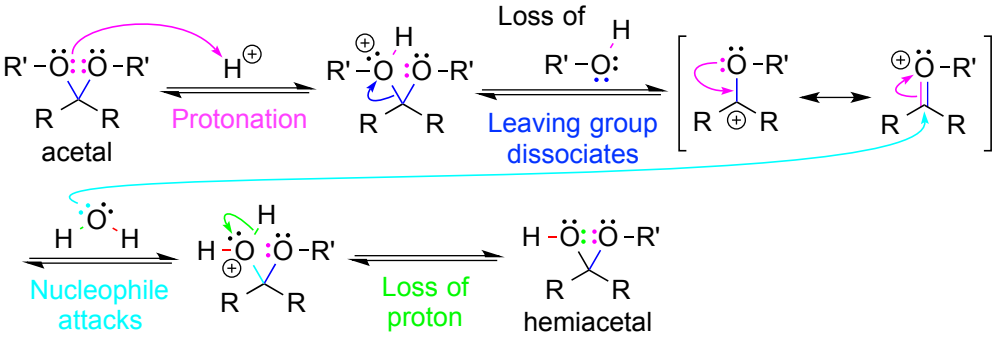
Acetal formation begins with protonation of the carbonyl oxygen. This greatly enhances the electrophilicity of the carbonyl carbon, making it more receptive to the attack of a weak nucleophile, like the alcohol. The oxonium ion formed from this attack readily loses a proton to produce a reaction intermediate known as the hemiacetal.



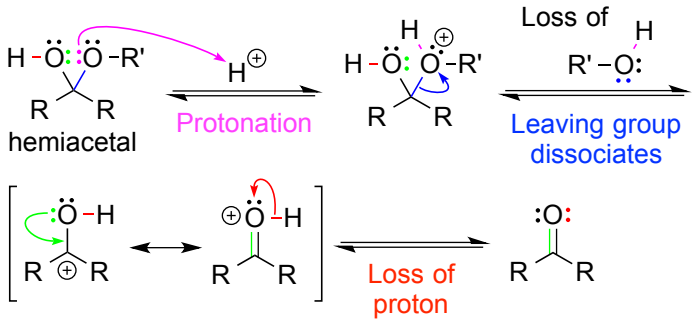
The hemiacetal is susceptible to further reaction. If it is protonated on the hydroxyl oxygen, a good leaving group is produced. Water dissociates from the molecule to form a resonance-stabilized cation. This cation attracts the attack of a second molecule of alcohol, and finally, loss of a proton neutralizes the charge of the oxonium ion to yield the acetal.



Acetal hydrolysis entails the exact same mechanism but in reverse. Protonation of the acetal activates one alkoxy group as a good leaving group. Dissociation of that alcohol affords a resonance-stabilized cation to which water adds. Loss of a proton results in a familiar reaction intermediate: the hemiacetal.

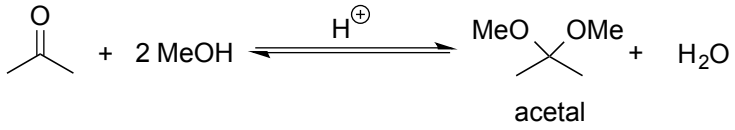


As we saw during the acetal formation mechanism, the hemiacetal is susceptible to further reaction. Its protonation on the alkoxy group makes a good leaving group that dissociates. The resonance-stabilized cation sheds a proton to regenerate the original carbonyl-containing substrate (a ketone in this case).

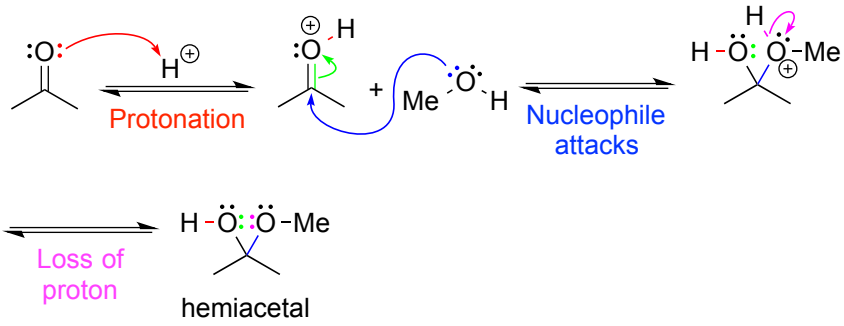


A specific example of acetal formation and hydrolysis

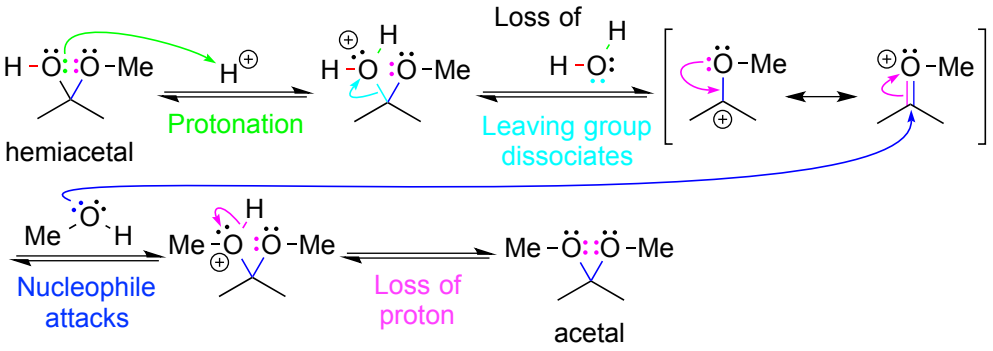
In the following example, acetone is converted to its dimethyl acetal.



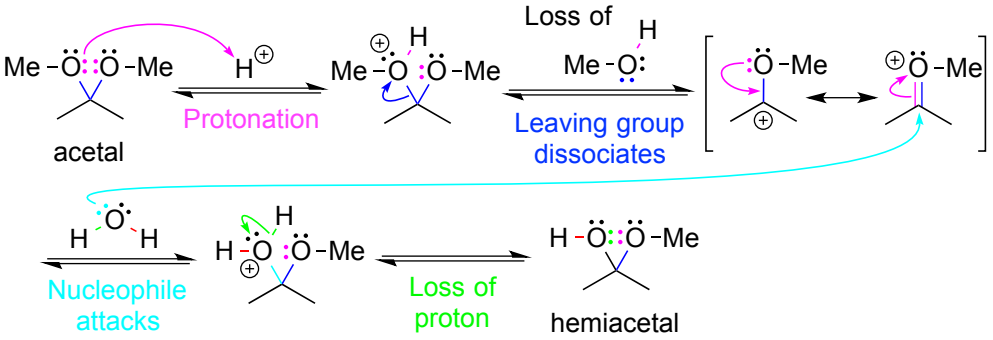
When excess methanol is used, the equilibrium will favor the dimethyl acetal. Protonation on the carbonyl oxygen yields the conjugate acid of acetone. Attack of methanol on the electrophilic carbonyl carbon produces an oxonium ion that easily sheds a proton to form the hemiacetal.



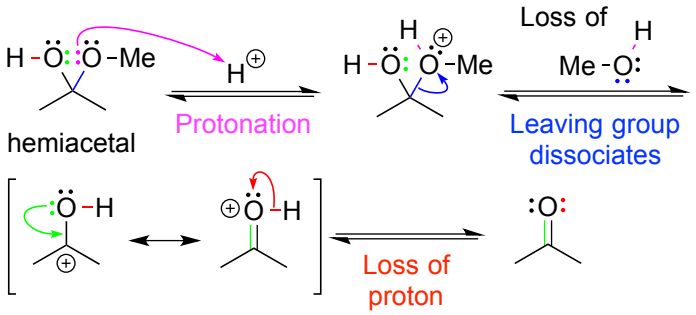
This hemiacetal will react further. When it is protonated on the hydroxyl group, water can then dissociate as a good leaving group. The attack of a second molecule of methanol then yields an oxonium ion that need only lose a proton to become the dimethyl acetal of acetone.



If this dimethyl acetal is treated with catalytic acid and excess water, it can be converted back to acetone. The process begins with protonation. Loss of methanol (a good leaving group) is then followed by attack of water on the electrophilic carbon. Subsequent loss of a proton generates the hemiacetal.

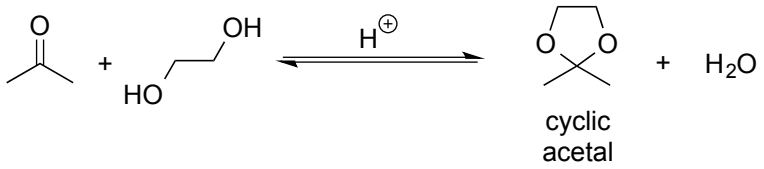


The hemiacetal, when protonated on the methoxy group, can experience the dissociation of a second methanol molecule. Finally, the resonance-stabilized cation sheds a proton to re-form acetone.

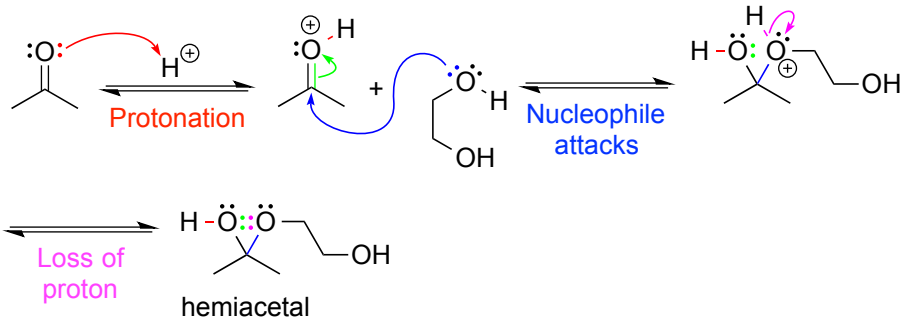


Cyclic acetals

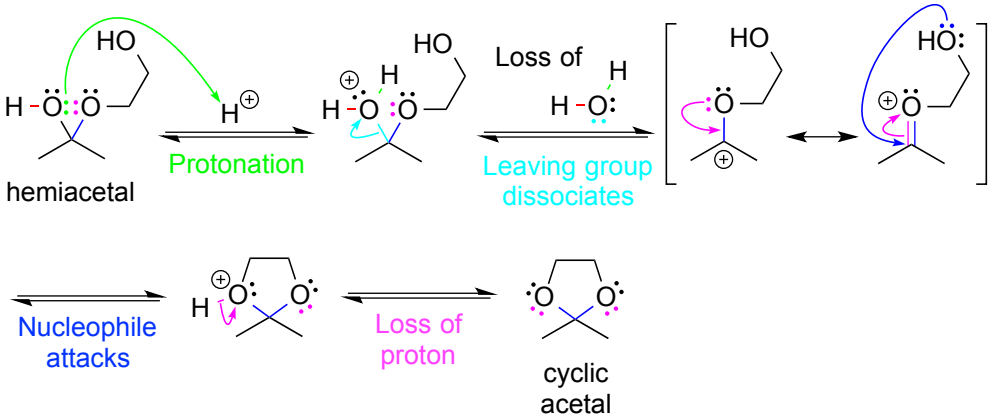
It is also common to encounter cyclic acetals, which are formed from the reaction between ketones or aldehydes and a diol. The mechanism for this reaction is no different. It is merely the fact that the two alcohols are now tethered together that results in a cyclic product.



Acetal formation still begins with protonation of the carbonyl oxygen. With its electrophilicity now enhanced, the carbonyl carbon readily accepts the attack of an alcohol. The oxonium ion thus formed sheds a proton to yield the hemiacetal.

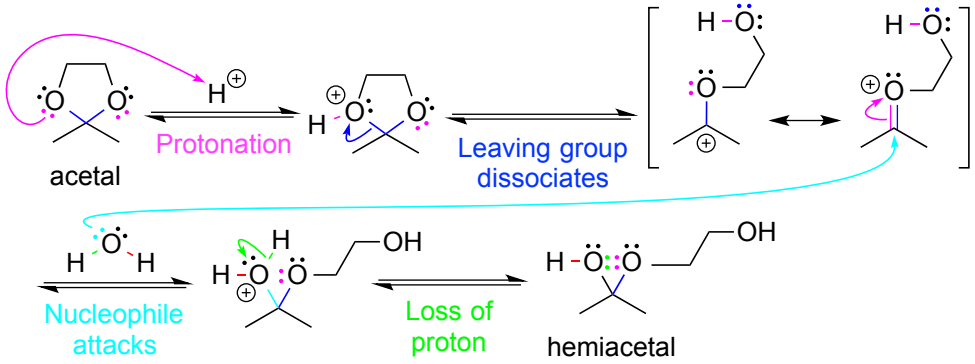


The hemiacetal is protonated on the hydroxyl group, which results in the subsequent dissociation of water as a good leaving group. At this point, the resonance-stabilized cation will be attacked by a second alcohol. In this case though, that alcohol is already tethered to the substrate, and the attack forms a ring as a result. Finally, a proton is lost to afford the cyclic acetal.

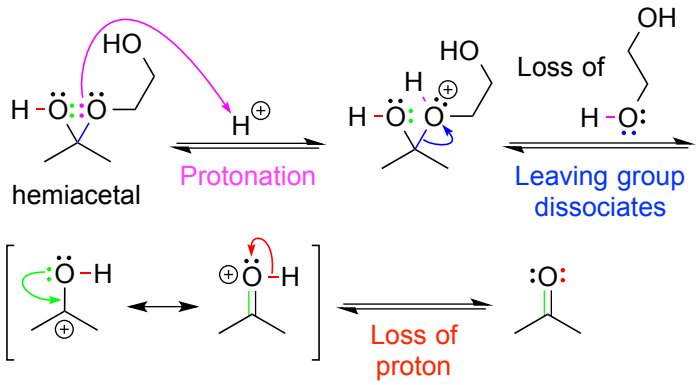


The hydrolysis mechanism is also comparable to that which we have seen previously. Protonation initiates the process. Notice that, now when the leaving group dissociates, the substrate does not break into two molecules. The alcohol that dissociated remains tethered to the substrate. This makes cyclic acetals more robust than their acyclic counterparts because this dissociated hydroxyl group can readily attack again to re-form the cyclic acetal. However, with a sufficient quantity of water present, the hydrolysis mechanism can

move forward with water's attack on the resonance-stabilized cation. A proton is then lost, resulting in the hemiacetal.



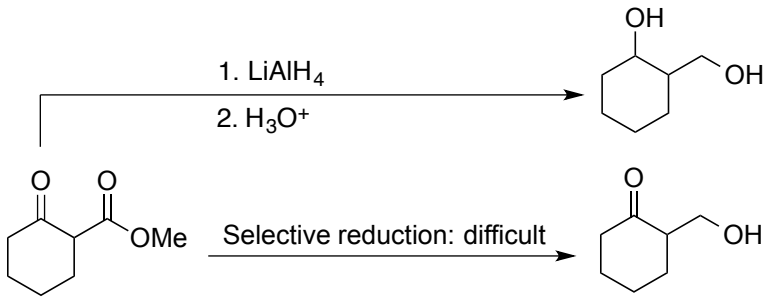
When the hemiacetal is protonated on the alkoxy group, the diol can dissociate. Loss of a proton completes the mechanism and regenerates acetone.



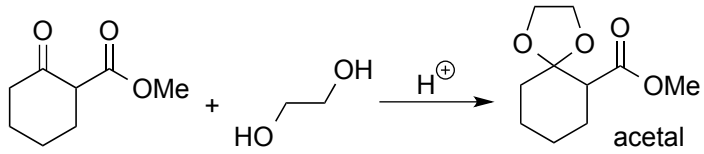
In conclusion, acetals are formed when ketones or aldehydes are treated with catalytic acid and excess alcohol. When the hydroxyl groups are tethered in a diol, a cyclic acetal results. Any acetal can also be hydrolyzed by exposure to catalytic acid and excess water.

Acetals as protecting groups

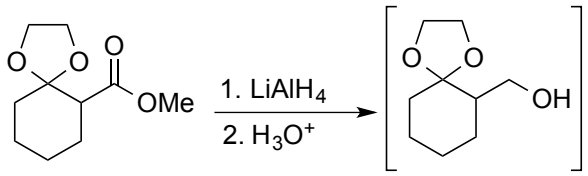
The ability to readily form and remove acetals makes them ideal protecting groups in synthesis. For instance, we will learn in the next chapter that lithium aluminum hydride ($LiAlH_4$) can be used to reduce an ester. However, we'll also see later in this chapter that $LiAlH_4$ reduces ketones and aldehydes too. Consequently, the ester of the following keto ester cannot undergo selective reduction directly.



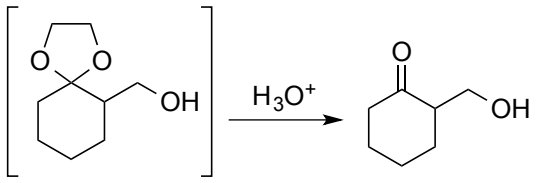
A reducing agent, like $LiAlH_4$, that is powerful enough to reduce the ester will also reduce the ketone. This problem is solved by protecting the ketone as a cyclic acetal.



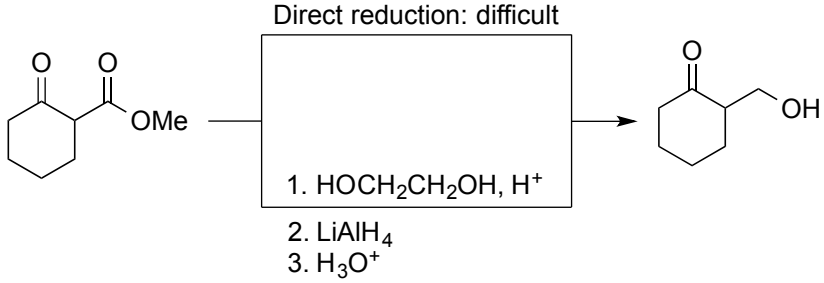
With the ketone thus "masked" and unavailable for reaction, the ester can be reduced to the corresponding alcohol with lithium aluminum hydride.



During the aqueous acid workup of the $LiAlH_4$ reduction (step 2 above), the ketone will also be unveiled through acetal hydrolysis.

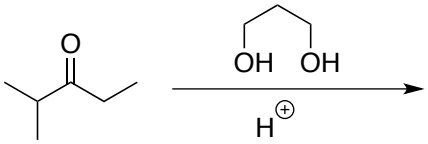


The net result is selective reduction of the ester of the original substrate, a transformation that would have been quite difficult without a protecting group.

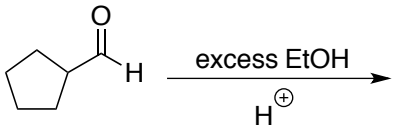


Problem 9. Provide the products of the following reactions. Where reagents or intermediates are missing, provide those as well.

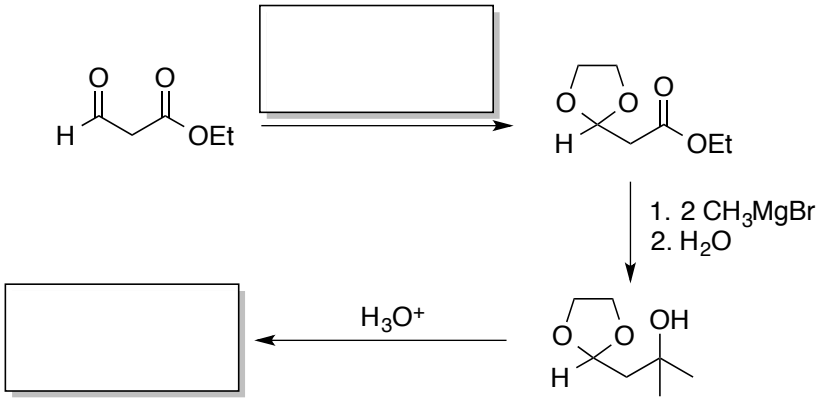
(a)



(b)

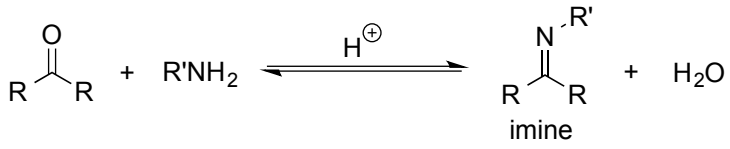


(c) This part involves a reaction (using CH_3MgBr) that we have not yet covered. You'll learn about the reagent later in this chapter and its reaction with esters in the next chapter. The focus of this question is the acetal formation and hydrolysis, so for the moment, you need not worry about the specifics of that intervening reaction.



Section 6: Imine formation and hydrolysis

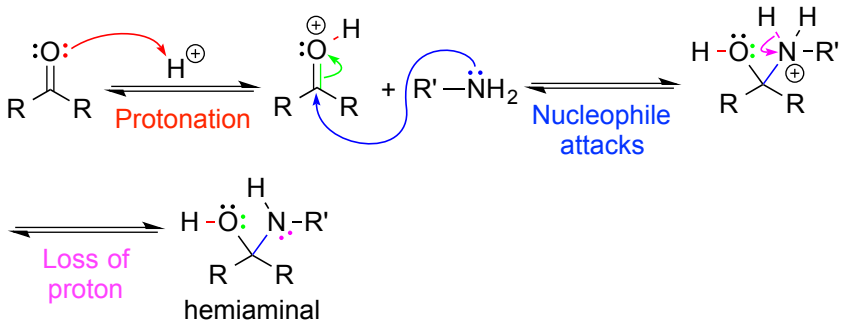
Ketones or aldehydes can condense with ammonia (NH_3) or a primary amine ($R'NH_2$) to yield imines, which contain a carbon-nitrogen double bond. Like hydrate and acetal formation, this reaction relies upon nucleophilic addition across the carbonyl π bond.



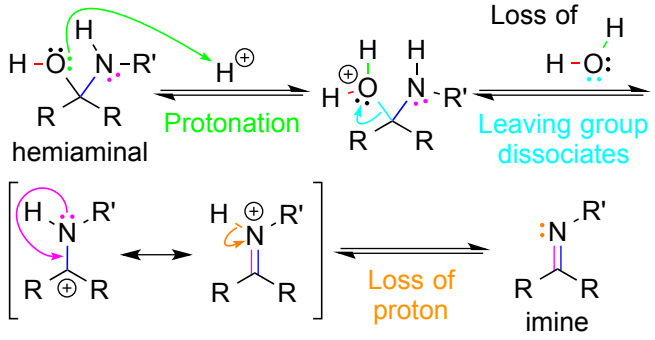
The reaction requires gentle acid catalysis and is freely reversible. The position of equilibrium is often controlled by driving off water to push the reaction toward the imine. Alternatively, an imine can be hydrolyzed using excess water. These are additional examples of exploiting Le Châtelier's principle to control the position of equilibrium.

There is some debate in the chemical literature about the ordering of mechanistic steps in this reaction. The nucleophilic attack may precede protonation. However, for the sake of consistency, the presentation that follows is parallel to the mechanism for acetal formation.

The reaction begins with the protonation of the carbonyl oxygen. Subsequent nucleophilic attack of the amine on the electrophilic carbonyl carbon affords an ammonium ion (positively charged nitrogen). The ammonium ion then sheds a proton to form a mechanistic intermediate known as a hemiaminal. The hemiaminal in this mechanism is comparable to the hemiacetal in the mechanism for acetal formation. Therefore, comparing the two mechanisms is a beneficial exercise.

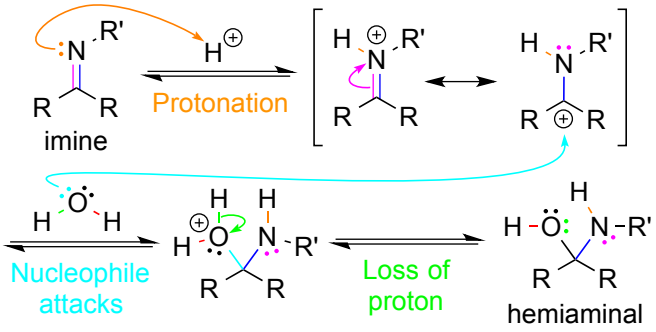


Much like the hemiacetal, the hemiaminal is susceptible to further reaction. Its protonation on the hydroxyl group generates a good leaving group. As such, water dissociates giving a resonance-stabilized cation, which loses a proton to yield the imine product.

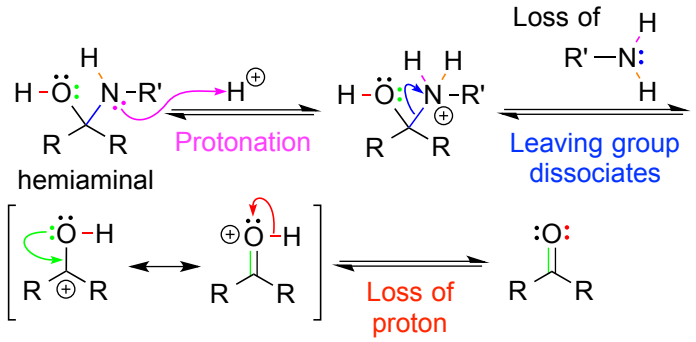


Although the formation of an imine requires acid catalysis, the pH of the medium cannot be too low. If the solution is too acidic, the amine will be protonated, and it is not nucleophilic when protonated. This prevents it from attacking the carbonyl to form the hemiaminal. The optimal pH for imine formation is around 4.5.

The hydrolysis of an imine occurs through the identical mechanism; however, the steps occur in the reverse order. The imine is first protonated. The resonance-stabilized cation thus formed is electrophilic at carbon, so water attacks that site. The resulting oxonium ion loses a proton to produce the hemiaminal.

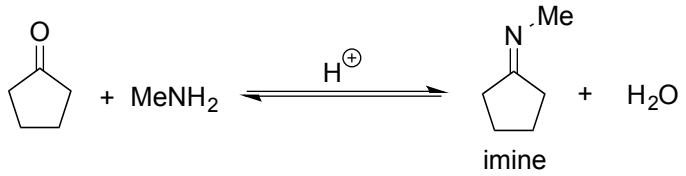


The hemiaminal reacts further when it is protonated on nitrogen to yield an ammonium ion. At this point, the amine dissociates. The resonance-stabilized cation then sheds a proton to re-form the carbonyl-containing compound (a ketone in this case).

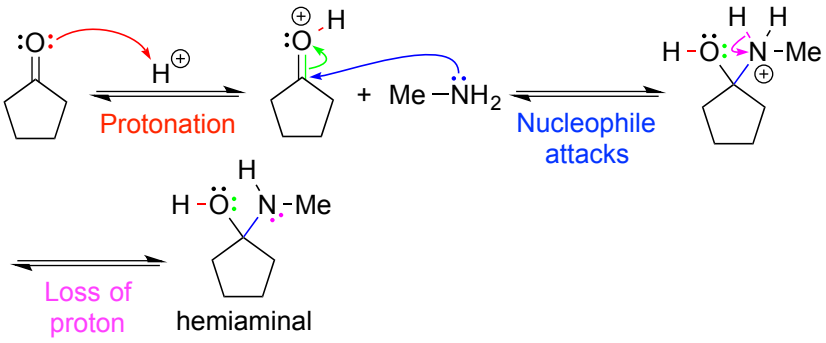


A specific example of imine formation and hydrolysis

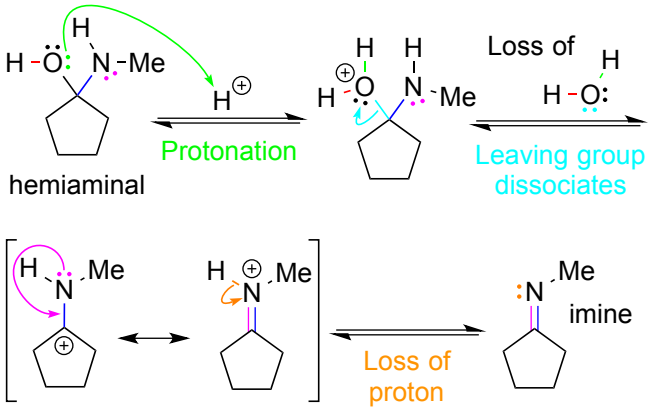
In the following example, cyclopentanone reacts with methylamine to produce an imine product.



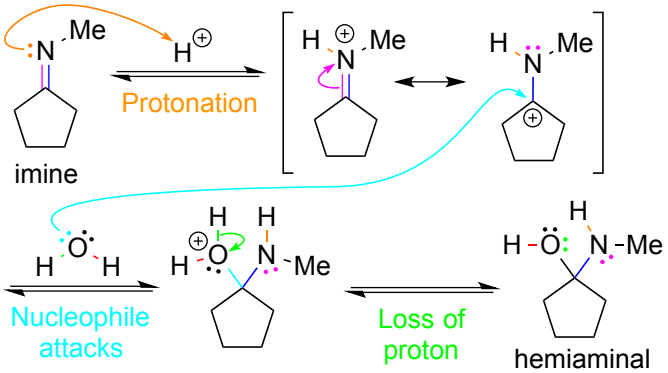
Protonation of cyclopentanone begins the reaction. The nucleophilic attack of methylamine yields an ammonium ion that readily loses a proton, giving the hemiaminal.



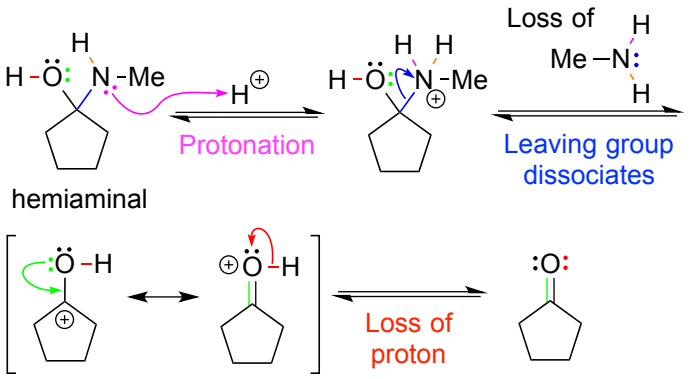
The hemiaminal, when protonated on oxygen, loses water as a good leaving group. The cation thus formed is resonance-stabilized and need only shed a proton to form the imine product.



The imine can be hydrolyzed in aqueous acid if desired, and the mechanism is the reverse of what we saw above. Protonation activates the imine toward the nucleophilic addition of water. The resulting oxonium ion loses a proton to generate the hemiaminal.



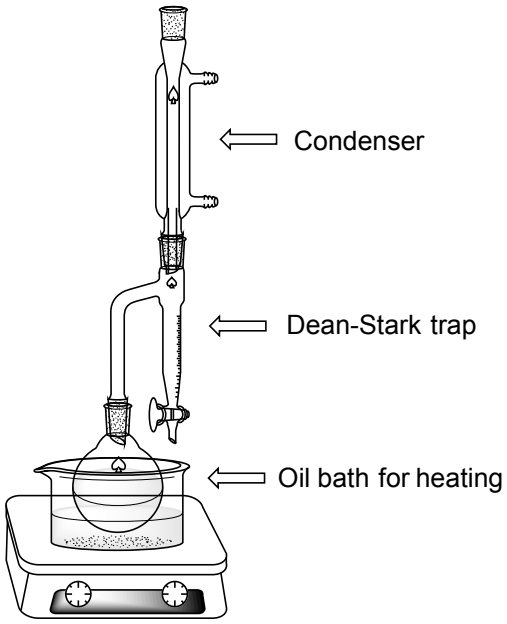
Protonation of the hemiaminal on nitrogen produces a good leaving group. When methylamine dissociates, the resonance-stabilized cation will easily lose a proton to regenerate cyclopentanone.



To recap, imine formation takes place between a ketone or aldehyde and ammonia (NH_3) or a primary amine ($R'NH_2$). Gentle acid catalysis is required. To form the imine, water is driven off to push the equilibrium in the desired direction. When imine hydrolysis is preferred, aqueous acid is used, and the presence of excess water pushes the equilibrium toward the ketone or aldehyde.

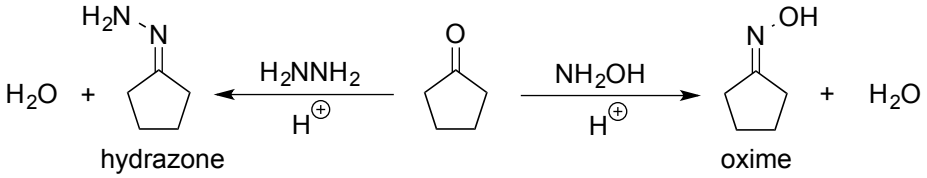
Driving off water

A couple of times in the preceding discussion, there have been references to "driving off water," and you might wonder how that is accomplished. One typical method entails the use of a Dean-Stark trap. The reaction mixture is heated at reflux in a solvent such as toluene that is immiscible with water. A piece of glassware known as a Dean-Stark trap is inserted between the round-bottom flask and the condenser. As solvent condenses, it fills the Dean-Stark trap before returning to the reaction vessel. Furthermore, as water is released, it co-distills with toluene. Since water is more dense than toluene, it settles at the bottom of the trap. The water thus removed can be measured to monitor the reaction's progress. Some Dean-Stark traps also allow for the water to be drained off.



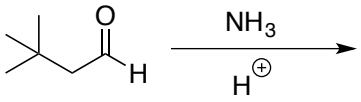
Related reactions

Similar reactions can be performed with hydrazine (NH_2NH_2) or hydroxylamine (NH_2OH) to produce hydrazones or oximes, respectively.



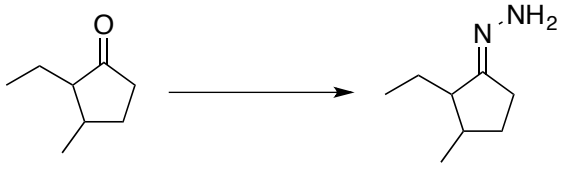
Problem 10. Show the products or the missing reagents in each of the following reaction schemes.

(a)

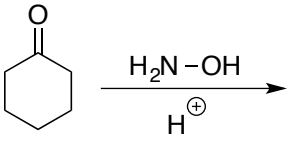


(b)

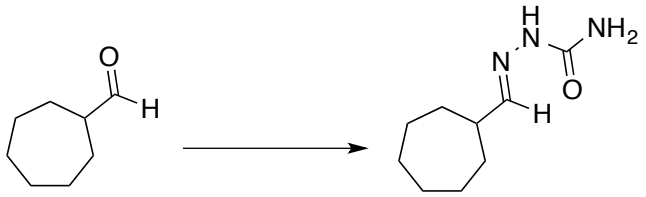
(c)



(d)

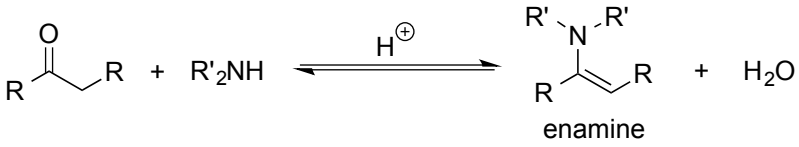


(e)



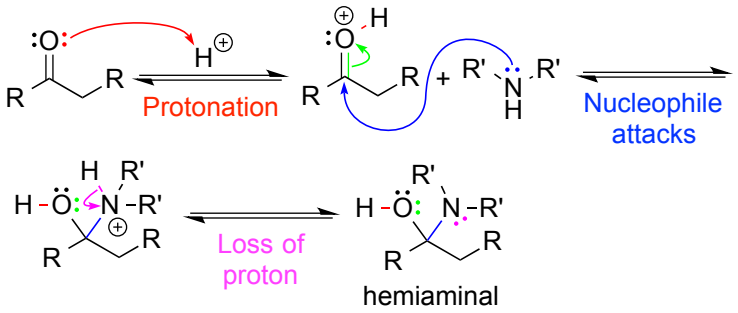
Section 7: Enamine formation and hydrolysis

Ketones or aldehydes can condense with secondary amines (R'_2NH) to yield enamines (a functional group with an amine bonded to an alkene carbon). Like hydrate, acetal, and imine formation, this reaction relies upon nucleophilic addition across the carbonyl π bond. It is worthwhile to compare this reaction closely to imine formation because the presence of one additional R' group on the amine differentiates enamine formation from imine formation in the final mechanistic step only.



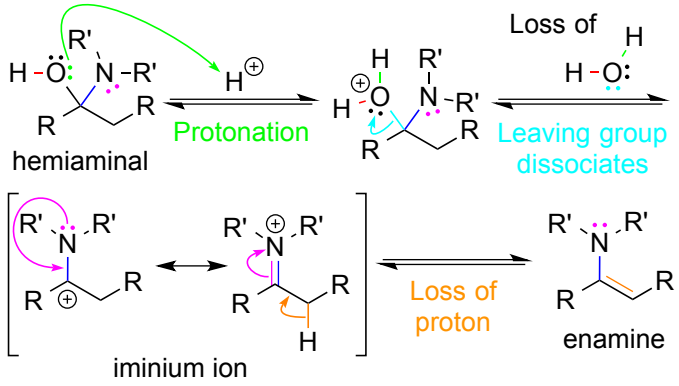
The reaction requires gentle acid catalysis and is freely reversible. The position of equilibrium is often controlled by driving off water to push the reaction toward the enamine. Alternatively, an enamine can be hydrolyzed using excess water. Much as with acetal and imine formation, these are examples of exploiting Le Châtelier's principle to control the position of equilibrium.

The first phase of this reaction is hemiaminal formation, and it is indistinguishable from the first phase of imine formation. Protonation of the carbonyl oxygen activates the carbonyl carbon toward nucleophilic attack of the secondary amine. The ammonium ion thus formed sheds a proton to provide the hemiaminal intermediate.

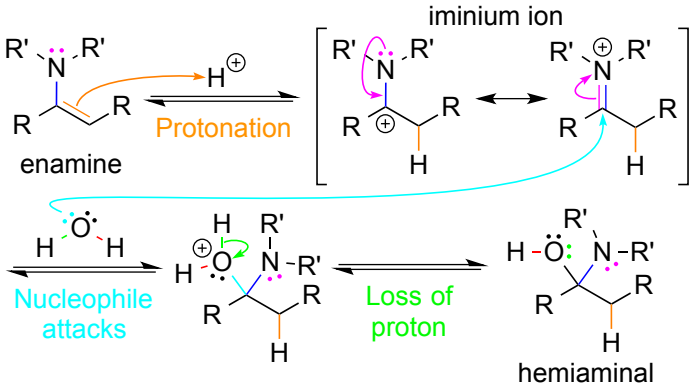


The hemiaminal reacts further, beginning with its protonation on the hydroxyl group. Water is then lost as a good leaving group, and a resonance-stabilized cation results. This cation is called the iminium ion (positively charged imine).

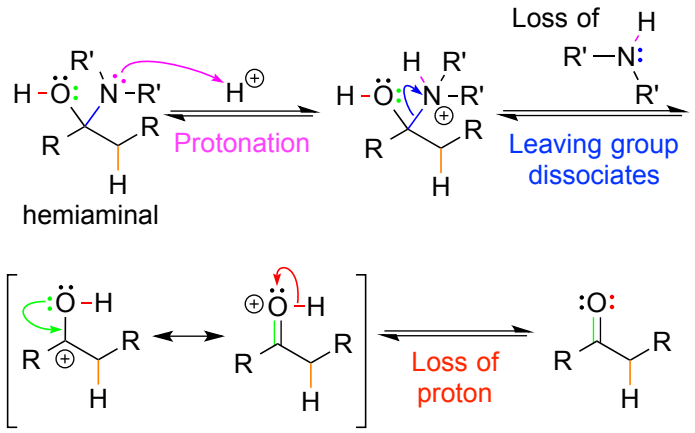
It is only in the last step of the mechanism that this reaction differs from imine formation. In this case, the nitrogen of the iminium ion has no proton to lose, so a proton must be shed from a different location to yield a neutral product. Loss of a proton from a carbon α to the iminium ion allows π electrons to be pushed back onto nitrogen, yielding the neutral enamine.



Enamines, much like acetals and imines, are susceptible to hydrolysis in aqueous acid. The hydrolysis mechanism begins with protonation of the enamine π bond. Protonation occurs so as to form the lower energy, resonance-stabilized cation. Water then attacks the iminium ion, pushing π electrons back onto nitrogen. The hemiaminal is produced when the oxonium ion sheds a proton.

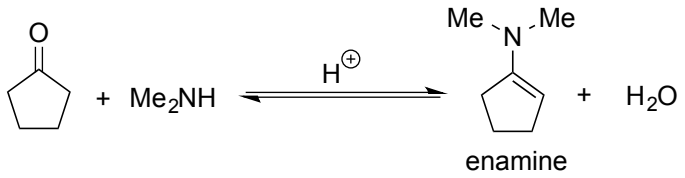


The hemiaminal is still reactive under these conditions. When it is protonated on nitrogen, the secondary amine becomes a good leaving group and dissociates. Another resonance-stabilized cation is formed as a result. Finally, loss of a proton provides the original carbonyl-containing substrate (in this case, a ketone).

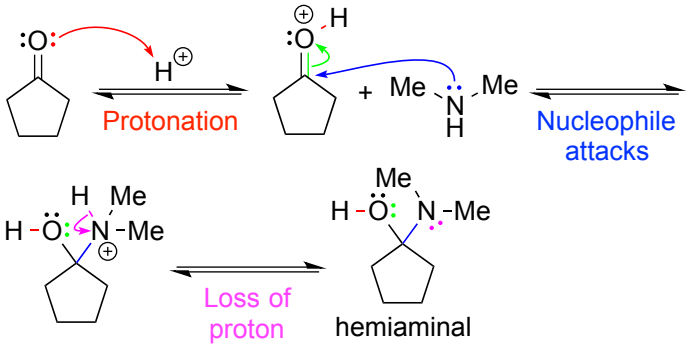


A specific example of enamine formation and hydrolysis

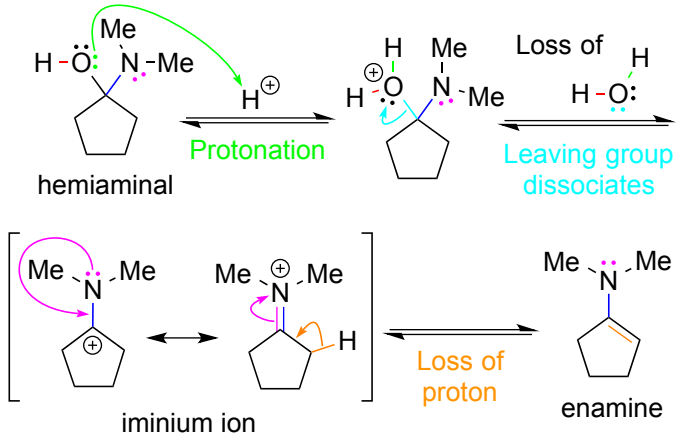
In the following example, cyclopentanone condenses with dimethylamine to yield the corresponding enamine.



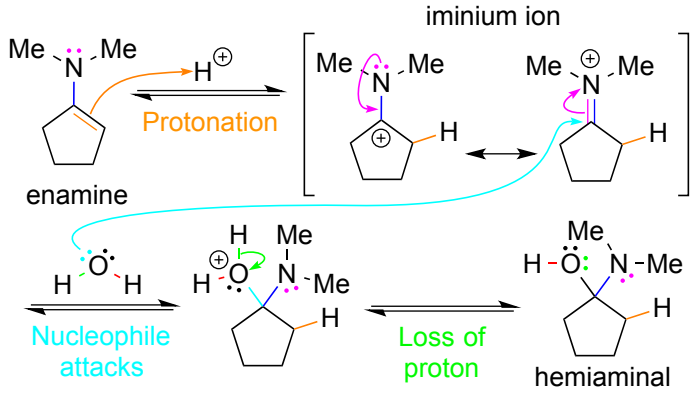
If water is driven off during the reaction, the equilibrium favors the enamine. Enamine formation begins with protonation of cyclopentanone's carbonyl oxygen. Dimethylamine then attacks the electrophilic carbonyl carbon, and a proton is lost from the resulting ammonium ion to form the hemiaminal.



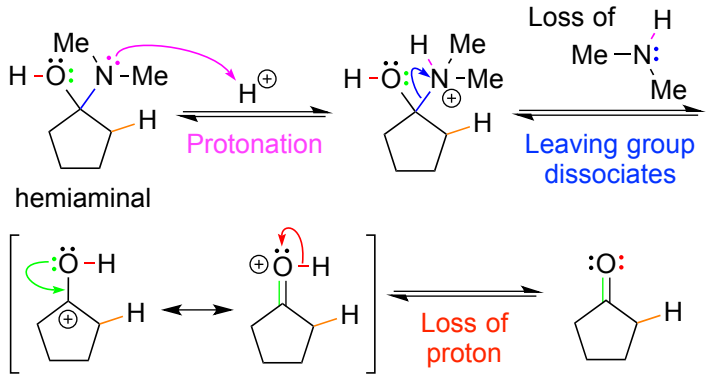
The hemiaminal, when protonated on oxygen, loses water to form the resonance-stabilized iminium ion. In the last step of enamine formation, loss of a proton from the α carbon affords the neutral enamine product.



In aqueous acid, the equilibrium is driven toward the hydrolysis of the enamine. This process is the reverse of the mechanism above and begins with protonation of the enamine π bond so as to form a resonance-stabilized iminium ion. Water adds to the electrophilic carbon, and loss of a proton provides the intermediate hemiaminal.



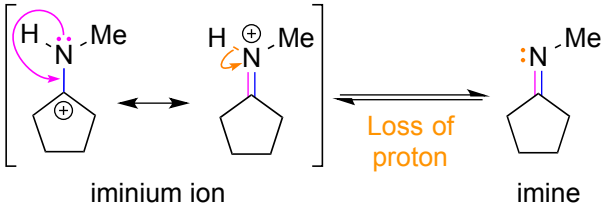
The hemiaminal can then be protonated on nitrogen, which activates the amine as a good leaving group. Dissociation of the secondary amine results in another resonance-stabilized cation, which can easily lose a proton to regenerate cyclopentanone in the final step of enamine hydrolysis.



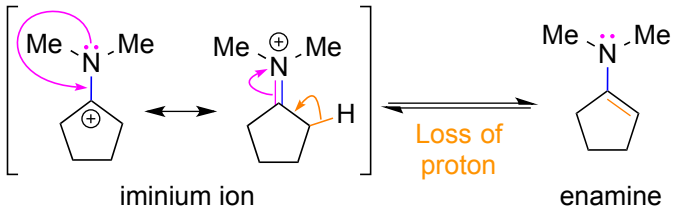
To review, enamine formation takes place between a ketone or aldehyde and a secondary amine (R'_2NH). Gentle acid catalysis is required. To form the enamine, water is driven off to push the equilibrium in the desired direction. When enamine hydrolysis is preferred, aqueous acid is used, and the presence of excess water pushes the equilibrium toward the ketone or aldehyde.

It is very helpful to compare the mechanisms in this section to those in the section on imine formation and hydrolysis. The sole difference between the formation of an imine and an enamine is whether or not the nitrogen atom has a proton to lose in the last step of the mechanism. Seeing the similarities between these mechanisms will make it much easier to learn them.

Final step of imine formation:

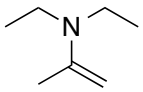


Final step of enamine formation:

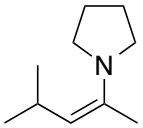


Problem 11. Provide the structures of the ketones or aldehydes and amines needed to prepare each of the following enamines.

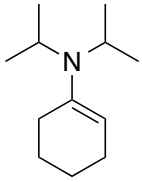
(a)



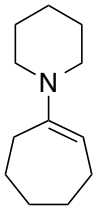
(b)



(c)

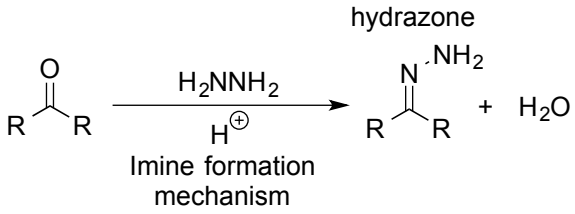


(d)

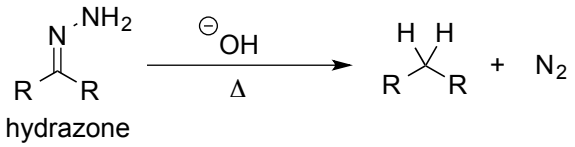


Section 8: Wolff-Kishner reduction

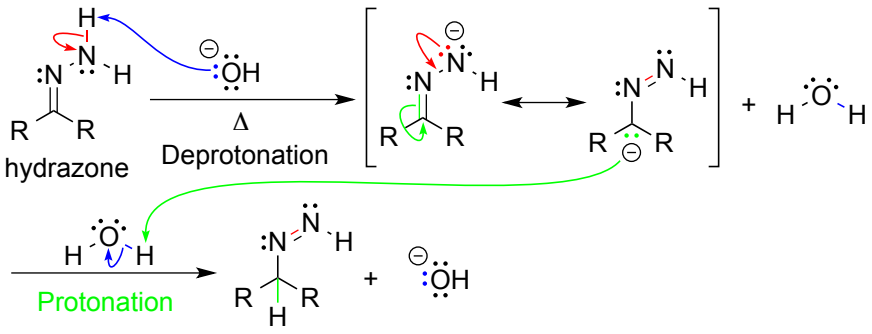
The Wolff-Kishner reaction is a method by which ketones or aldehydes can be reduced to the corresponding methylene (CH_2) via the hydrazone. At the end of the section on imine formation and hydrolysis we saw that reaction with hydrazine (NH_2NH_2) yields a hydrazone, which is similar to an imine.



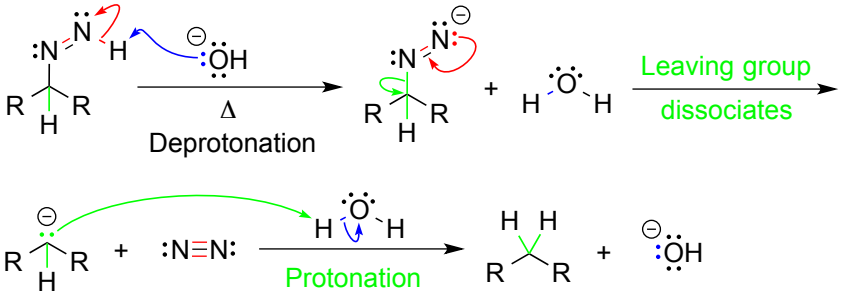
Treatment of the hydrazone with hydroxide at high temperatures results in a methylene where the carbonyl used to be. Nitrogen gas (N_2) is lost in the process.



The mechanism for hydrazone formation is essentially identical to the mechanism for imine formation. When the hydrazone is treated with hydroxide at high temperature, it can be deprotonated. The conjugate base of the hydrazone has a resonance form that places the negative charge on carbon. Protonation of this anion yields a neutral intermediate.

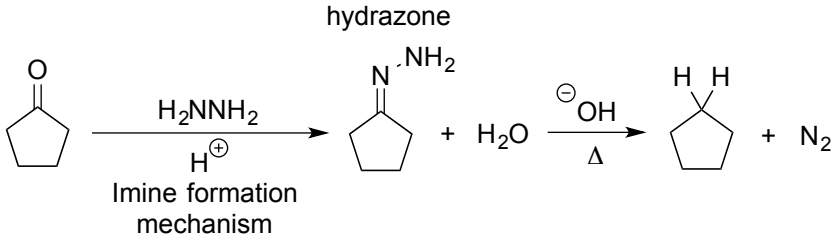


A second deprotonation yields a new anion. As a triple bond is formed between the two nitrogen atoms, a carbanion dissociates as a high-energy leaving group. Although the carbanion is a very poor leaving group, the loss of nitrogen gas, which bubbles out of the mixture, moves the process forward in an irreversible fashion. The carbanion rapidly removes a proton from water to yield the reduced product.

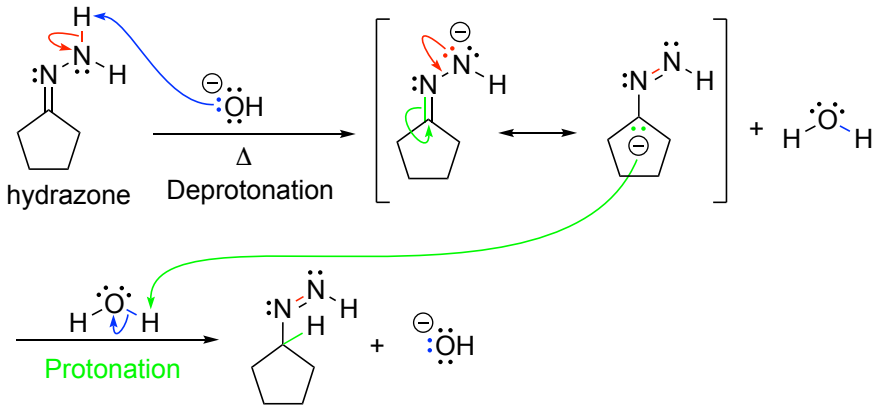


A specific example of the Wolff-Kishner reduction

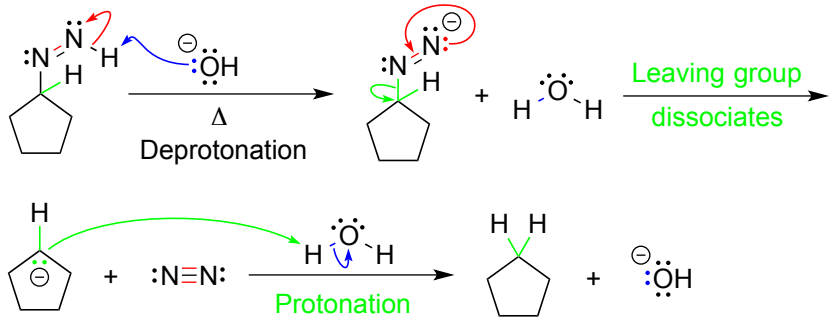
In the following example, cyclopentanone will ultimately be reduced to cyclopentane. The formation of the hydrazone follows the mechanism for imine formation. The hydrazone is then treated with hydroxide at elevated temperatures to effect the reduction.



The mechanism for this reduction follows. The hydrazone is first deprotonated by hydroxide. The resultant anion has a resonance form that places electron density on carbon. This carbanion deprotonates water to form a partially reduced intermediate (one new C–H bond is present).



A second deprotonation affords a conjugate base that can expel a carbanion as the second π bond of nitrogen gas is formed. Although this is energetically costly because the carbanion is unstable, the loss of nitrogen from the system as it bubbles away will ultimately drive the equilibrium toward the product. The carbanion readily deprotonates water to yield cyclopentane.

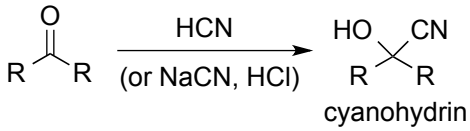


In summary, the Wolff-Kishner reduction converts the carbonyl of a ketone or aldehyde to a methylene (CH_2) group. The transformation proceeds via the hydrazone, which is formed much as an imine is formed. The hydrazone is then reduced to the methylene in base at high temperature through two successive cycles of deprotonation followed by reprotonation.

Problem 12. Compound A is the product of a Friedel-Crafts acylation. It can be reduced using Wolff-Kishner conditions to 1-bromo-4-propylbenzene. What is the structure of Compound A? Show the Friedel-Crafts acylation that formed it.

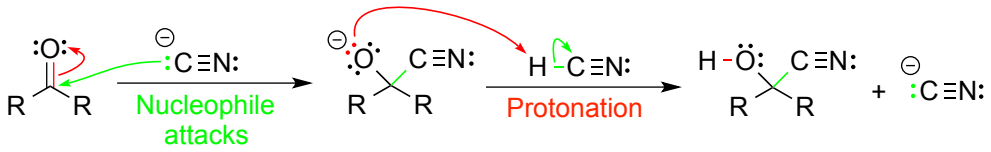
Section 9: Cyanohydrin formation

When a ketone or aldehyde is treated with hydrogen cyanide (HCN), nucleophilic addition across the carbonyl π bond occurs. The result is a compound known as a cyanohydrin.



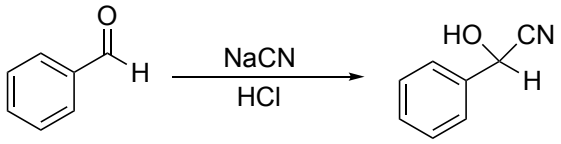
Since hydrogen cyanide is a hazardous gas, safer alternative conditions can be used. For instance, a cyanide salt (such as NaCN or KCN) along with acid achieves the same transformation.

Hydrogen cyanide has a pK_a of approximately 9, making it about as acidic as phenol. Since HCN is reasonably acidic, some of its conjugate base (^-CN) will be present. Cyanide begins the reaction when it nucleophilically attacks the electrophilic carbonyl carbon. The carbonyl π electrons are pushed onto oxygen. The anion thus formed deprotonates a molecule of hydrogen cyanide yielding the cyanohydrin product as well as cyanide.

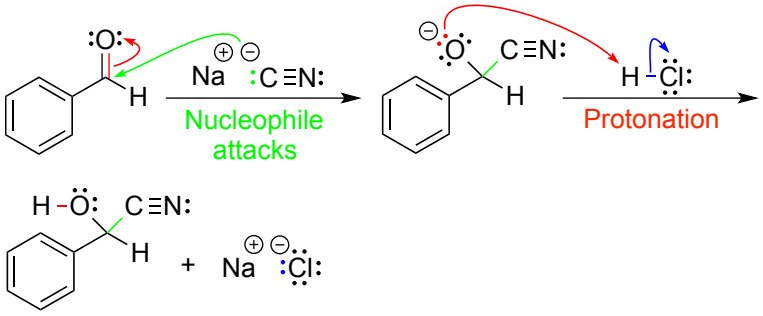


A specific example of cyanohydrin formation

In the following example, benzaldehyde is exposed to the alternate conditions (a cyanide salt and HCl) to produce the cyanohydrin.

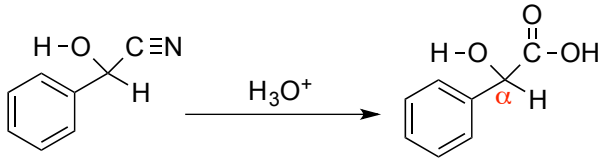


The salt is the source of cyanide in this instance. Nevertheless, it nucleophilically attacks the carbonyl carbon in the exact same manner as before. The anion resulting from the displacement of the carbonyl π electrons acquires a proton from HCl to yield the cyanohydrin product.



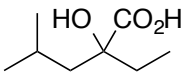
In conclusion, cyanohydrin formation is another example of nucleophilic addition across the carbonyl π bond of a ketone or aldehyde. The reaction requires HCN. Alternatively, a cyanide salt and hydrochloric acid may be used.

Cyanohydrins are versatile because they contain two functional groups, each of which can be further manipulated. For instance, the nitrile can be hydrolyzed to produce an α-hydroxyacid. We'll learn about this reaction in the chapter on carboxylic acids and their derivatives.



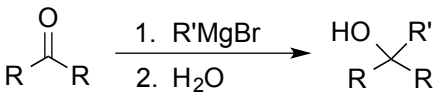
α-hydroxyacid

Problem 13. What ketone could be used to prepare the following α-hydroxyacid?

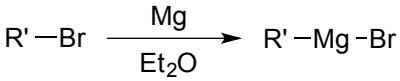


Section 10: Grignard reaction

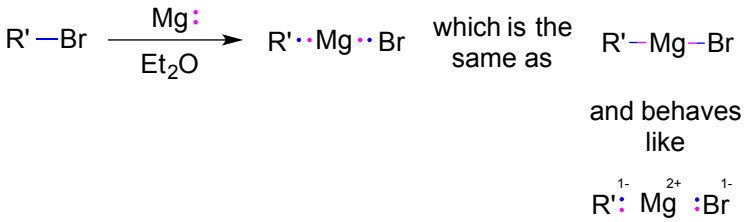
The Grignard reaction is a versatile carbon-carbon bond forming reaction. Aldehydes and ketones react with Grignard reagents via nucleophilic addition across the carbonyl π bond.



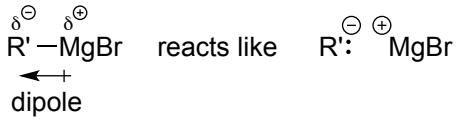
The Grignard reagents, themselves, are prepared from the corresponding alkyl halides by a process known as oxidative insertion. The alkyl halide is treated with neutral magnesium metal in diethyl ether. The magnesium inserts into the carbon-halogen bond and is concurrently oxidized to the +2 state.



To understand this process, it can help to envision the electronics as follows. Neutral magnesium metal has two electrons in its valence shell. It will readily give up these electrons in order to attain the electronic configuration of the preceding noble gas (neon). To that end, magnesium inserts in between the carbon and the halogen, donating one electron to each. The new carbon-magnesium bond has some covalent character, but this reagent, named after Victor Grignard who pioneered its usage, behaves as though a carbanion and bromide are ionically associated with magnesium cation.



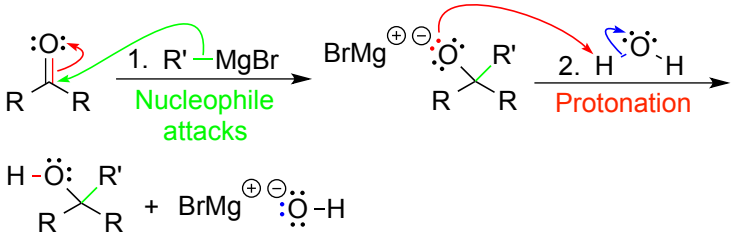
Another way of understanding this behavior comes from focusing on the carbon-magnesium bond. It is polarized toward carbon, which is more electronegative than magnesium. As a result, the carbon bonded to magnesium is electron rich, and it reacts as though it were a carbanion.



Since Grignard reagents behave as though they contain carbanions, they are also strong bases. As a result, they are incompatible with acidic protons in the substrate or the solvent. Consequently, the Grignard reaction is a two-step process in which the proton source (H_2O or H_3O^+) is not introduced until the second step.

The solvent for the first step of the reaction is often diethyl ether, which is free of acidic protons and stabilizes the Grignard reagent through coordination of the lone pairs on oxygen with the metal.

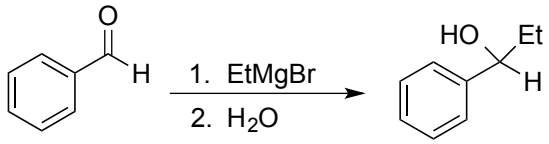
The mechanism of the reaction is very similar to that of cyanohydrin formation. The only difference is that the proton source is not introduced until the second step of this reaction. The electron-rich carbon of the Grignard reagent nucleophilically attacks the electron-poor carbonyl carbon in the first step. This displaces the carbonyl π electrons onto oxygen. The anionic oxygen then removes a proton from water (or H_3O^+) in the second step of the reaction.



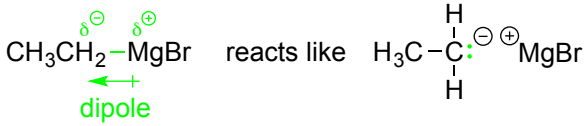
In this generic example, a ketone was used as the substrate, so the product is a tertiary alcohol.

A specific example of the Grignard reaction

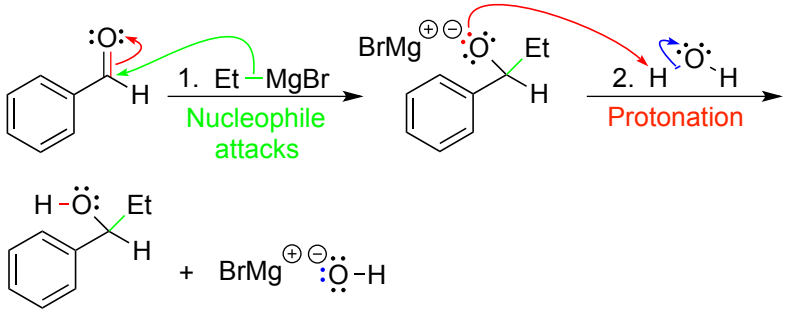
When aldehydes (other than formaldehyde) are used as substrates, secondary alcohols are produced. In the following example, benzaldehyde is treated with ethylmagnesium bromide followed by an aqueous workup. The product is 1-phenyl-1-propanol.



Ethylmagnesium bromide possesses an intense δ^- on the methylene (CH_2) carbon. This carbon atom behaves like a carbanion.

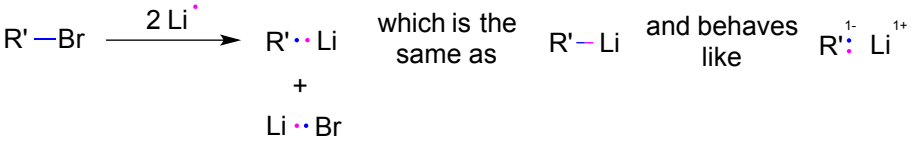


The reaction begins with the attack of the Grignard reagent on the electrophilic carbonyl carbon. Notice that the arrow begins from the carbon-magnesium bond. These are the electrons responsible for the formation of the nascent carbon-carbon bond. The arrow should not begin from the ethyl group itself, or from the magnesium ion. Neither of those sites possesses electrons that are available for new bond formation. As the nucleophilic attack occurs, the carbonyl π electrons are displaced onto oxygen. In the reaction's second step, the oxygen anion is neutralized when it pulls a proton from water.

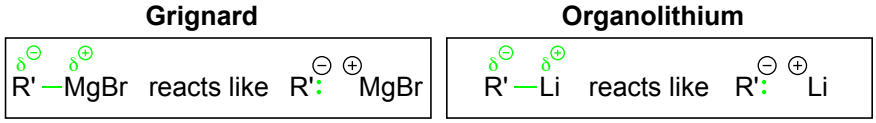


In conclusion, the Grignard reaction is a carbon-carbon bond forming reaction in which an organomagnesium compound (a Grignard reagent) is nucleophilically added to the carbonyl carbon of a ketone or aldehyde. Grignard reagents are basic, so the proton source cannot be introduced until the second step of the reaction. Otherwise, the proton source would quench the Grignard reagent through Brønsted-Lowry acid-base reaction. Similarly, the substrate and the reagent must also be free of acidic protons.

Organolithium reagents behave quite similarly to Grignard reagents and can generally be used in their place. They are prepared when an alkyl halide is treated with two equivalents of neutral lithium metal. Lithium bromide (LiBr) is a byproduct of the reaction. The organolithium species (R'Li) contains a carbon-lithium bond that has some covalent character; however, this reagent behaves as though it contains a carbanion.

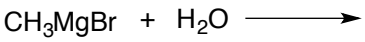


Much like the Grignard reagent's carbon-magnesium bond is polarized toward carbon, the organolithium's carbon-lithium bond is also polarized toward carbon, which is again the more electronegative of the two elements. Both species therefore effectively serve as carbanion sources.

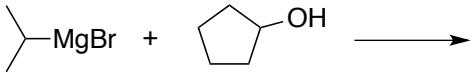


Problem 14. Given that Grignard reagents are strong bases and essentially behave as though they were carbanions, why are they incompatible with acidic protons? In other words, show what happens in each of the following situations.

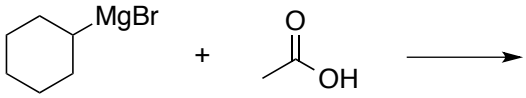
(a)



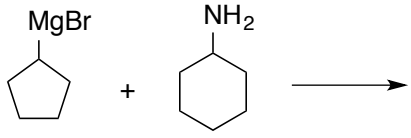
(b)



(c)

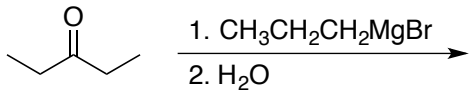


(d)

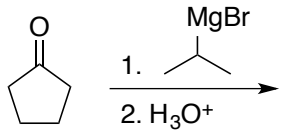


Problem 15. Predict the product of each of the following reactions.

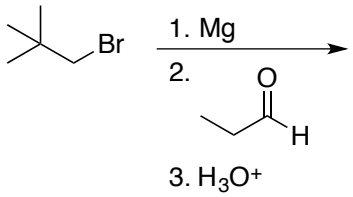
(a)



(b) For this question, note that Grignard reactions are sometimes quenched using aqueous acid (H_3O^+) rather than just water. This does not change the overall reaction.



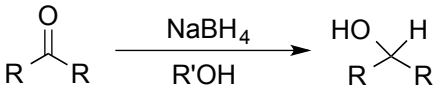
(c)



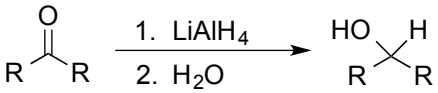
Section 11: Hydride reduction

In the previous section on the Grignard reaction of aldehydes and ketones, we saw the nucleophilic addition of a carbanion ($R:^-$) to the carbonyl carbon. A similar reaction can occur with sodium borohydride or lithium aluminum hydride, two sources of nucleophilic hydride ($H:^-$). Since a new carbon-hydrogen bond is formed in these reactions, the carbonyl is reduced to an alcohol.

Sodium borohydride is a mild hydride source, so it can be used in the presence of a protic solvent (e.g., water or an alcohol).

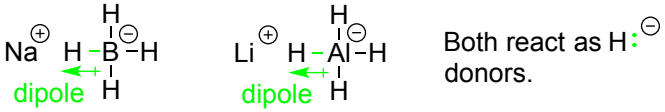


Lithium aluminum hydride is a much more reactive hydride source. It is not compatible with protic solvents. Such solvents would quench the reagent through Brønsted-Lowry acid-base reaction. Consequently, the proton source (usually H_2O or H_3O^+) is typically added in a second, separate step.

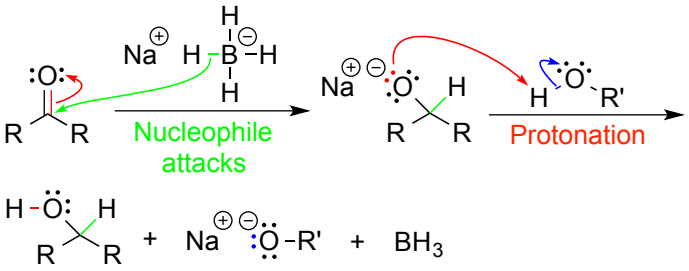


Much like Grignard reagents or organolithium species, $NaBH_4$ and $LiAlH_4$ contain bonds with unusual dipoles. Both the H–B bond of $NaBH_4$ and the H–Al bond of $LiAlH_4$ are

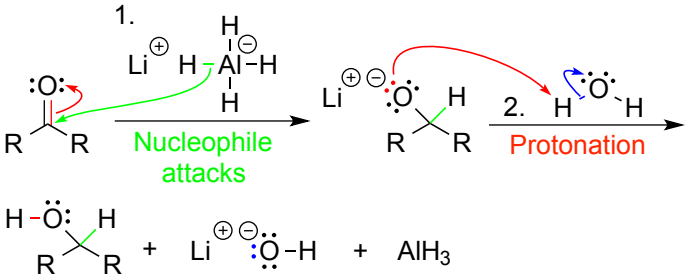
polarized toward hydrogen. Consequently, the hydrogen is electron rich and behaves like hydride ($H:^-$).



When a ketone or aldehyde reacts with sodium borohydride, the first mechanistic step is nucleophilic addition of hydride to the carbonyl carbon. As a result, the carbonyl π electrons are displaced onto oxygen, much as they are during a Grignard reaction. The anion thus formed deprotonates the solvent (water or an alcohol) to yield the product. Since a ketone was used as the substrate in this generic example, the product is a secondary alcohol.



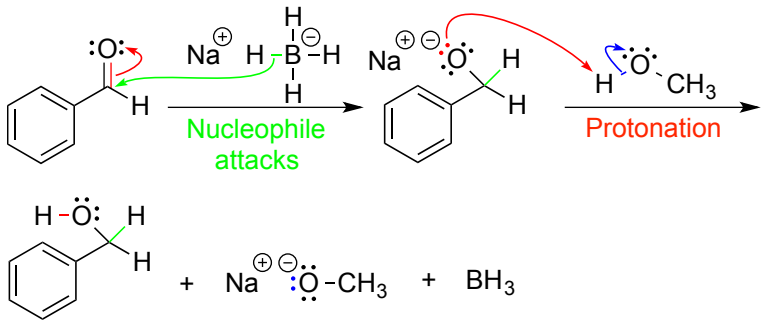
The mechanism is quite similar when lithium aluminum hydride is used. The only notable difference is that the anion formed upon nucleophilic addition of hydride to the carbonyl simply persists until water (or acid) is added during the second step of the reaction. At this point, protonation yields the neutral alcohol product.



A specific example of the reduction of an aldehyde

In the following example, benzaldehyde is reduced through reaction with sodium borohydride. When aldehydes (other than formaldehyde) are reduced in this fashion, the products are primary alcohols.

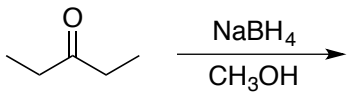
Nucleophilic attack on the carbonyl carbon displaces the carbonyl π electrons onto oxygen and is followed by protonation of the anion by the solvent (methanol in this case) to yield benzyl alcohol.



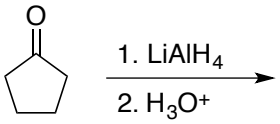
To review, $NaBH_4$ and $LiAlH_4$ are reducing agents that donate hydride to the carbonyl carbon, thereby reducing aldehydes and ketones to the corresponding alcohols. $NaBH_4$ reduction can be conducted in a protic solvent (water or an alcohol). However, $LiAlH_4$ is incompatible with such solvents, so the proton source must be added in the second step of the reaction.

Problem 16. Provide the products of the following transformations.

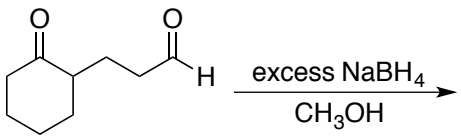
(a)



(b) For this question, note that lithium aluminum hydride reductions are sometimes quenched using aqueous acid (H_3O^+) rather than just water. This does not change the overall reaction.

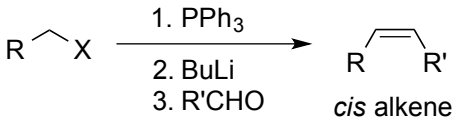


(c)

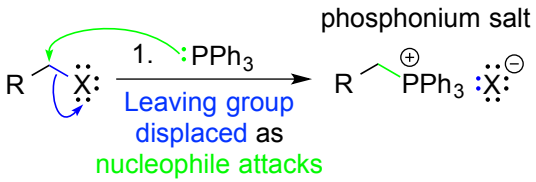


Section 12: Wittig reaction

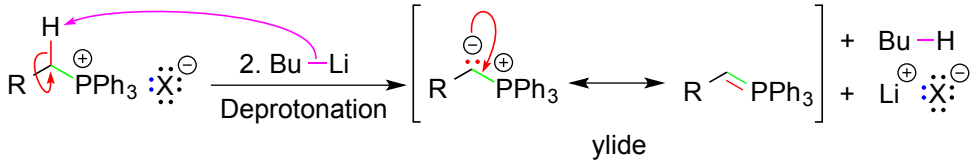
We've seen a number of reactions that can form carbon-carbon single bonds, such as alkylation of alkynes, Friedel-Crafts alkylation and acylation, cyanohydrin formation, and the Grignard reaction. The Wittig reaction is unique in that it unites an alkyl halide with an aldehyde or ketone, and in the process, *both the σ and π bonds of an alkene are formed.*



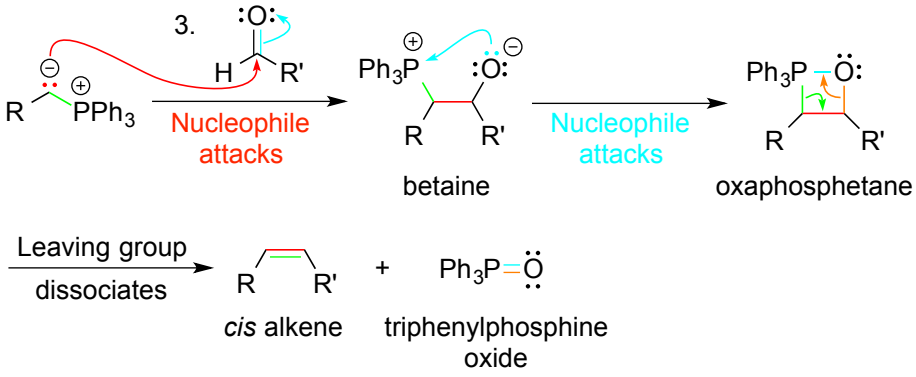
In the first step of the reaction, an unhindered alkyl halide is treated with triphenylphosphine (PPh_3). Phosphorous, much like nitrogen, can possess three bonds and a lone pair of electrons. As a result, it can be nucleophilic and attacks the alkyl halide in S_N2 fashion, thereby displacing the halide leaving group. The product of this step is a phosphonium salt.



In the second step of the reaction, a very strong base (typically butyllithium, BuLi) is introduced. The phosphonium salt is deprotonated at the carbon adjacent to the positive phosphorus. The product is known as an ylide. It is stabilized by adjacent complementary charges, and since phosphorus can possess an expanded octet, there is resonance as well.



In the third and final step of the reaction, the ylide attacks an aldehyde (or ketone). The immediate product is a betaine, but it rapidly forms a four-membered ring due to the attraction of the oxygen anion for the positive phosphorus. The four-membered ring (an oxaphosphetane) then extrudes triphenylphosphine oxide, which can be described by two mechanistic arrows showing that the C–P and C–O bonds are severed. This is driven by the stability of phosphorus-oxygen bonds. The product is a *cis*-alkene in which both the σ and π bonds of the alkene were formed during the reaction.

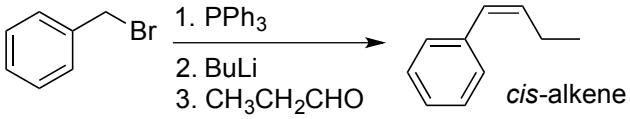


A note on nomenclature

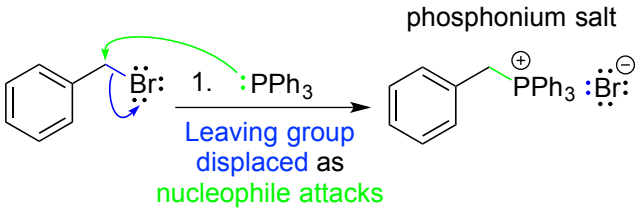
The terms "ylide" and "betaine" were used in the preceding discussion. An ylide is overall neutral but contains a carbanion directly connected to a cationic heteroatom (phosphorus in this case). Both of the charged atoms possess full octets. On the other hand, a betaine, while also overall neutral, contains an anion and a cation that need not be directly connected to each other. The cation does not bear any hydrogens. This differentiates a betaine from a zwitterion, which you may have learned about if you are also studying biology.

A specific example of the Wittig reaction

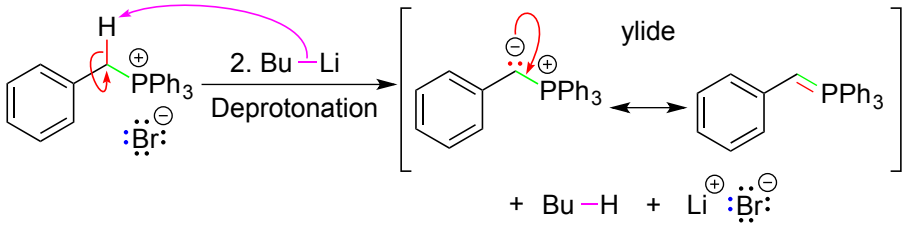
In the following example, benzyl bromide is treated sequentially with triphenylphosphine, butyllithium, and propionaldehyde to afford a *cis*-alkene product.



The reaction begins with S_N2 displacement of bromide from benzyl bromide by the attack of triphenylphosphine.

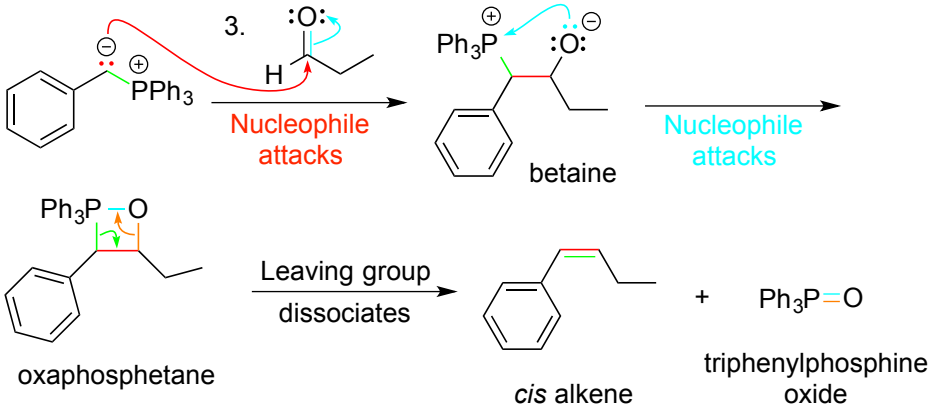


A proton adjacent to the positive phosphorus is then removed by butyllithium to generate an anion at that center. The adjacent complementary charges of the ylide stabilize each other, and a resonance form without any formal charges also exists.



When propionaldehyde is introduced, the ylide attacks the carbonyl carbon, displacing the carbonyl π electrons onto oxygen. The betaine thus formed rapidly closes through intramolecular nucleophilic attack to form a four-membered ring. Finally, the loss of

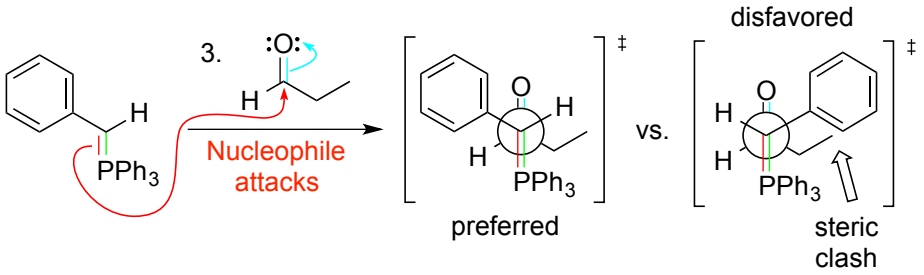
triphenylphosphine oxide through simultaneous cleavage of the carbon-oxygen and carbon-phosphorus bonds yields the *cis*-alkene product.



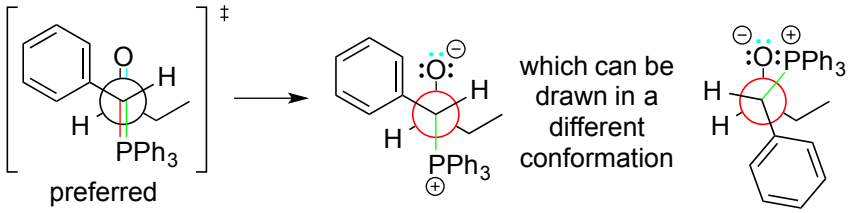
Stereochemical considerations

The preference for the formation of the *cis* alkene rather than the more stable *trans* alkene is certainly not intuitive, but we can explain it if we reexamine the attack of the ylide on the carbonyl in more detail.

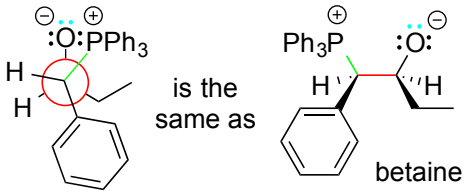
Let's use the other resonance form of the ylide this time, the one that contains a carbon-phosphorous π bond. In the transition state for this attack, the π bonds of the carbonyl and ylide align parallel to one another so that there is overlap of their p orbitals. Given this constraint, there are only two ways to draw the transition state (shown in Newman projections below). The preferred transition state has minimal steric hindrance (i.e., the fewest gauche interactions).



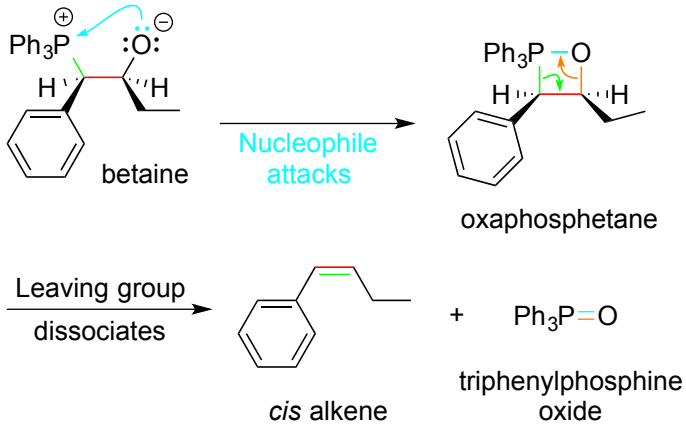
Once the new carbon-carbon σ bond is formed, the molecule can be rotated into other conformations, such as the one shown below.



When viewed from the side, this conformation can also be drawn as a skeletal structure with wedges and dashes.



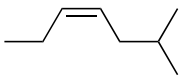
When the betaine closes to form the oxaphosphetane, the two R groups (phenyl and ethyl in this case) are on the same side of the ring. The simultaneous cleavage of the C–P and C–O bonds forms a new carbon-carbon π bond with no opportunity for rotation, so the phenyl and ethyl groups must remain *cis* to one another in the product.



In summary, the Wittig reaction allows the union of an unhindered alkyl halide with an aldehyde or ketone to form a *cis* alkene. The reaction entails sequential treatment of the alkyl halide with triphenylphosphine, butyllithium, and finally the aldehyde or ketone. During the course of these three steps, both the bonds (σ and π) of the alkene are formed. This is rather unique. No other single reaction we've seen accomplishes this.

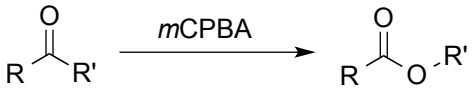
The preference for the *cis* configuration of the product can be explained by examining the transition state for the last step of the Wittig reaction. A transition state with minimal steric hindrance ultimately leads to the *cis* alkene.

Problem 17. Provide two syntheses of the following *cis* alkene using the Wittig reaction.

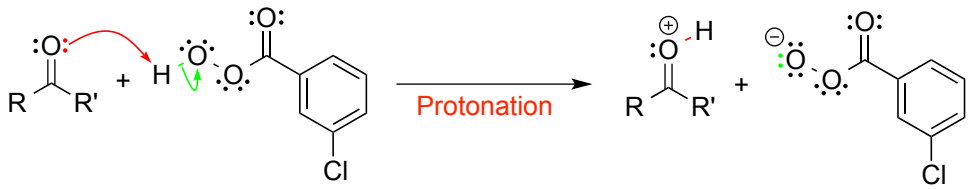


Section 13: Baeyer-Villiger oxidation

The Baeyer-Villiger oxidation is an unusual oxidation in that a carbon-carbon bond is broken during the course of the reaction. Treatment of a ketone with *m*CPBA results in an ester where the R' group has migrated from the carbonyl carbon onto the newly installed carboxyl oxygen (i.e., the sp^3 hybridized oxygen).

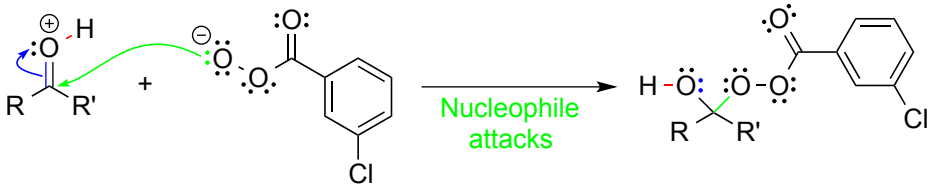


The reagent for the Baeyer-Villiger reaction is a peroxy acid, which is essentially a carboxylic acid with an additional oxygen atom. A commonly used peroxy acid is *meta*-chloroperoxybenzoic acid (*m*CPBA). The mechanism can begin with the protonation of the ketone oxygen by *m*CPBA.

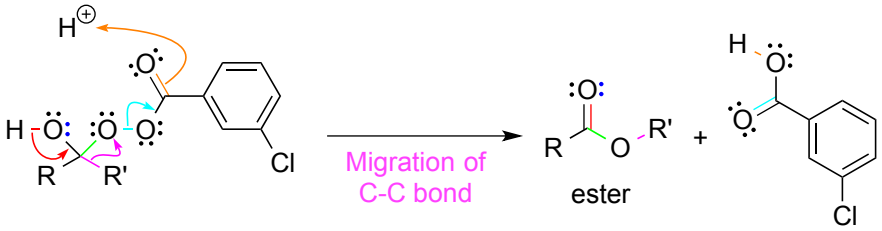


meta-chloroperoxybenzoic acid (*m*CPBA)

The conjugate base of *m*CPBA can then attack the electrophilic carbonyl carbon. The carbonyl π electrons are displaced onto oxygen to neutralize its charge. You may also see the mechanism drawn with direct attack of the peroxy acid on the ketone, followed by proton transfer to reach this same intermediate.

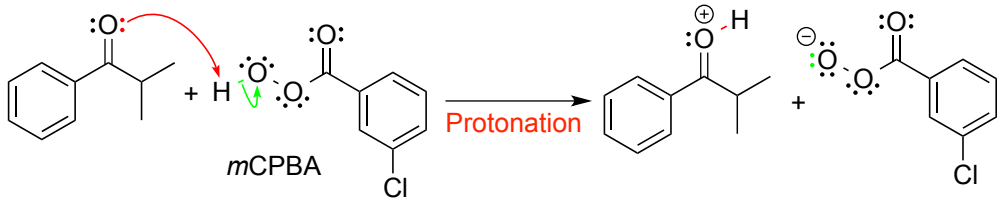


At this stage, the key migration of a carbon-carbon σ bond occurs. The weak oxygen-oxygen bond dissociates as R' migrates to the adjacent oxygen atom. In effect, a carboxylate is being expelled as a leaving group, and it acquires a proton as it dissociates. As R' migrates, the hydroxyl group also loses a proton to form a new carbon-oxygen π bond that replaces the bond carbon is losing. The product of interest is an ester, and it is accompanied by *meta*-chlorobenzoic acid as a byproduct.

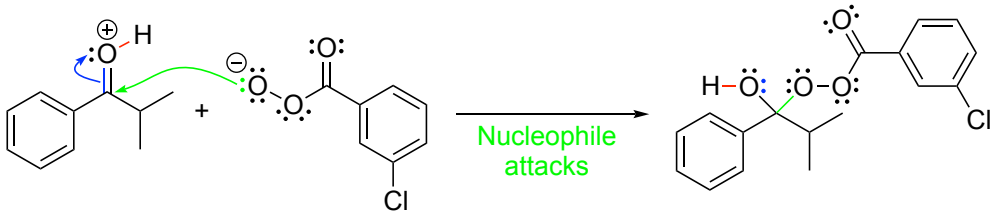


A specific example of the Baeyer-Villiger oxidation

In the following example, isopropyl phenyl ketone is subjected to Baeyer-Villiger oxidation. The reaction begins with the protonation of the ketone's carbonyl oxygen by *m*CPBA.



With the electrophilicity of the carbonyl carbon thus enhanced, the conjugate base of *m*CPBA readily attacks and displaces the carbonyl π electrons onto the oxonium ion.

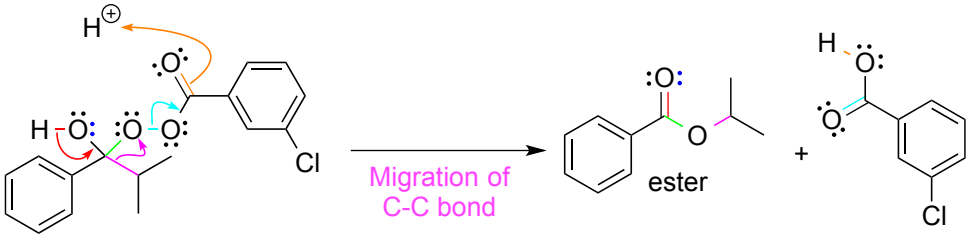


At this point, the key migration will occur. However, there are two groups that could migrate. It is possible for the phenyl or the isopropyl group to migrate onto the adjacent oxygen atom. To make the decision, it is useful to know that the more electron-rich group will be the one to migrate. This makes sense because the migrating group is effectively acting as an internal nucleophile to displace the carboxylate, and we know that more electron-rich nucleophiles are more effective. The order of migratory aptitude is shown below.

Migrates fastest ⟹ Migrates slowest

Tertiary > Secondary > Aryl > Primary > Methyl

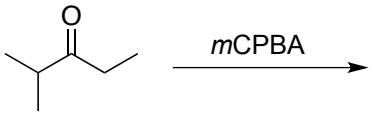
Knowing that the isopropyl group (secondary) will migrate faster than the phenyl group (which is a specific aryl, or aromatic, group), we can complete the mechanism. The isopropyl group migrates to the adjacent oxygen, displacing the carboxylate, which acquires a proton as it leaves. A proton is also lost from the substrate to form a new carbonyl π bond, thereby replacing the bond that carbon lost during the migration. The product of the reaction is an ester known as isopropyl benzoate.



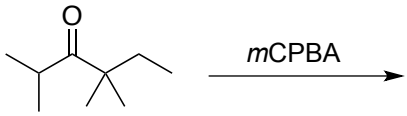
To recap, the Baeyer-Villiger oxidation involves the conversion of a ketone to an ester upon exposure to a peroxy acid, such as *m*CPBA. This oxidation is unusual because a carbon-carbon bond is broken during migration, which is the key step of the mechanism. The more electron-rich R group on the ketone's carbonyl carbon is the one to migrate during the reaction.

Problem 18. Predict the products of the following Baeyer-Villiger oxidations.

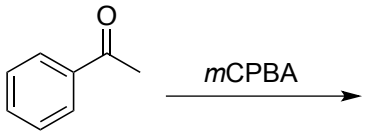
(a)



(b)



(c)



Section 14: Synthesis

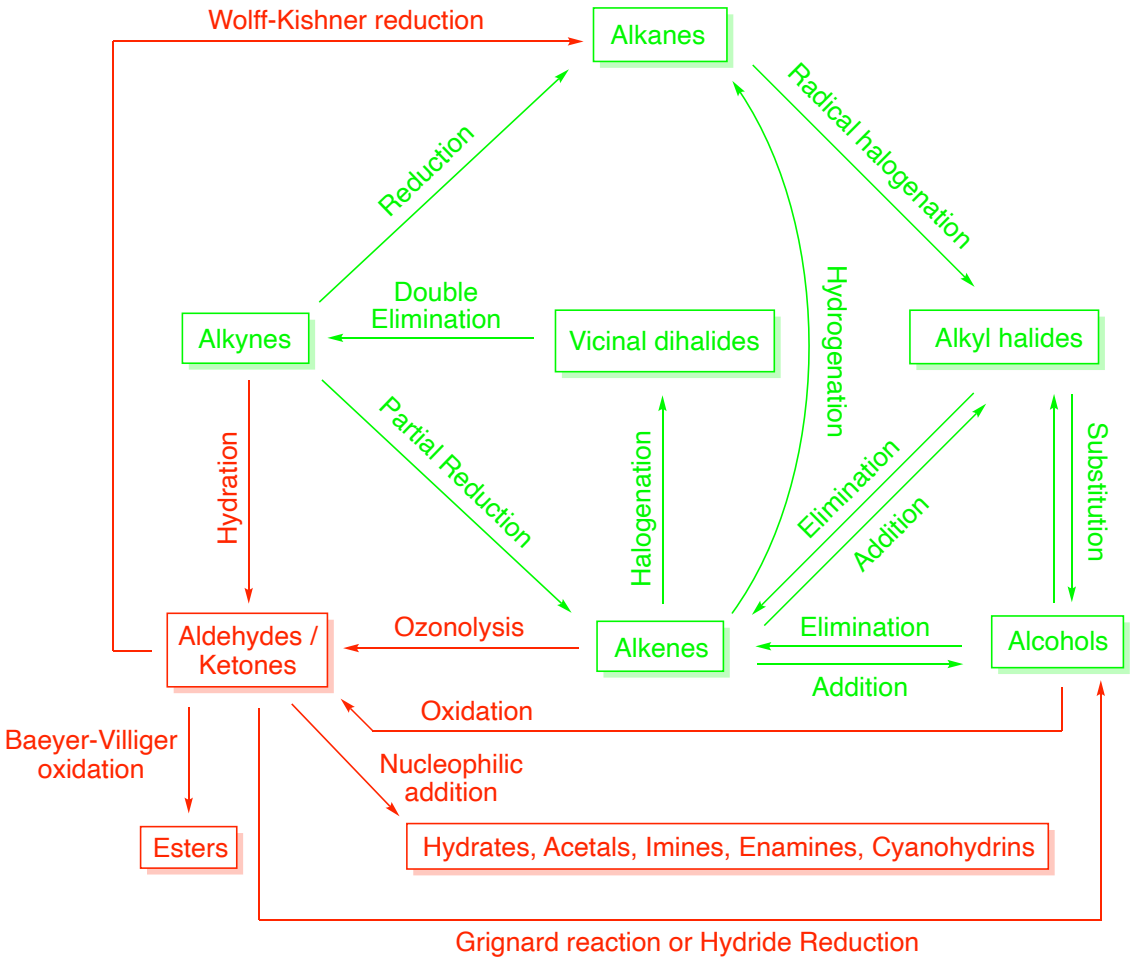
Functional group manipulation

As we've learned more and more reactions, we've seen how it can be helpful to map out some of the ways that the various functional groups can be interconverted. As we continue to build on our diagram of these interconnections, it can start to look a bit intimidating, but remember that you've seen much of this before.

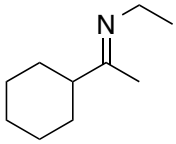
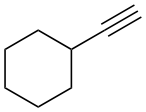
The new connections are highlighted in red below. At the beginning of this chapter, we reviewed the synthesis of aldehydes and ketones from alkynes, alkenes, and alcohols. Those methods have been incorporated into the diagram.

We also saw throughout the chapter a wide variety of nucleophilic additions that can give rise to hydrates, acetals, imines, enamines, or cyanohydrins. The Grignard reaction and hydride reductions are also nucleophilic additions, but they yield alcohols products.

Additionally, we learned about two other redox reactions. The Baeyer-Villiger oxidation allows the production of esters, while the Wolff-Kishner reduction enables aldehydes or ketones to be reduced to alkanes.



Problem 19. Provide a means to achieve the following synthesis.

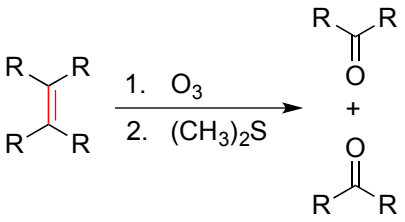
Prepare  from 

Changes to the carbon skeleton

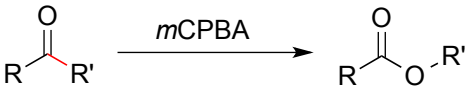
When we discussed synthesis in previous chapters, we often said that changes to the carbon skeleton should be our first synthetic priority, and that guideline continues to be helpful. There are a limited number of ways to alter the carbon framework of a molecule, so if such a change is needed, we should focus on accomplishing it through any means necessary. There are a larger number of ways to manipulate functional groups, so once the carbon framework is in place, we can almost certainly find a way to change the functional groups that we have into those that we need.

Since there are a limited number of ways to alter the carbon skeleton, it is helpful to keep them at your fingertips. These reactions can often be the focal point of a synthesis problem.

Ozonolysis and Baeyer-Villiger oxidation both lead to cleavage of the carbon backbone. Ozonolysis cleaves the σ and π bonds of an alkene. As a result, the chain is broken.

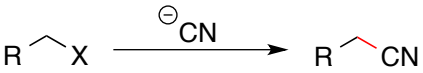


On the other hand, Baeyer-Villiger oxidation cleaves a carbonyl-to-alkyl group bond of a ketone. In this case, a carbon-carbon bond has been broken, but the pieces are still tethered via the ester linkage.

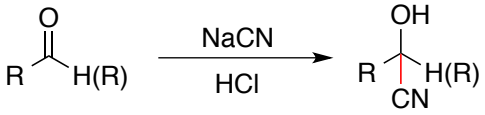


The carbon skeleton can be elongated through a number of techniques, including: (1) the use of cyanide as a nucleophile; (2) alkylation of a terminal alkyne; (3) Diels-Alder reaction; (4) Grignard reaction; or (5) the Wittig reaction. Some of these reactions are more versatile than others.

The use of cyanide leads to the addition of a single carbon to the chain. This can occur through S_N2 reaction.

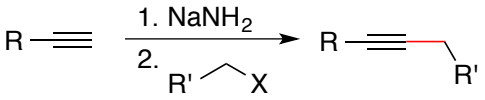


Alternatively, cyanohydrin formation also extends the carbon chain by one.

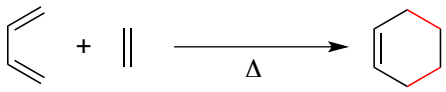


While this homologation is often useful, it is somewhat limiting that only one carbon can be added in this way.

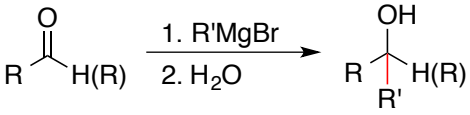
Alkyation of a terminal alkyne can lead to a larger variety of skeletal changes because R and R' can have a wide range of structures. However, this approach is still limited by the need for a *terminal* alkyne and an unhindered electrophile. Consequently, certain substitution patterns will be difficult to attain using this method.



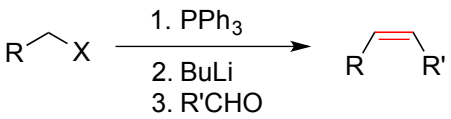
The Diels-Alder reaction leads to a fairly specific change: the formation of a six-membered ring containing a double bond. This is extremely powerful when a cyclohexene ring is needed but less useful for the preparation of acyclic targets.



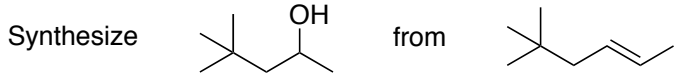
The Grignard reaction is perhaps the most versatile of the methods that we've learned because it can be used to produce a wide variety of carbon frameworks. The R group(s) of the aldehyde or ketone can vary greatly, as can the R' group of the Grignard reagent itself.



The Wittig reaction is also quite versatile, given the constraint that the centers to be joined must be amenable to alkene formation.



Problem 20. Devise a method for the following synthesis.



End-of-the-Chapter problems

Problem 21. Draw the structures of the following ketones or aldehydes.

(a) β-ethylvaleraldehyde

(b) 2,4-dimethyl-3-pentanone

(c) 3-*sec*-butyl-2-ethyl-6-methyloctanal

(d) 1-fluoro-4-methyl-2-hexanone

(e) trichloroacetaldehyde

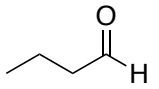
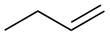
(f) (1*R*,3*S*)-cyclohexane-1,3-dicarbaldehyde

Problem 22. Identify the errors in the following names.

(a) 2-butylpentanal

(b) 3-acetylpentane

Problem 23. Propose two ways to achieve the following synthesis.

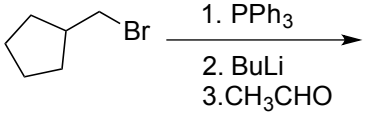
Prepare  from 

Problem 24. Show the mechanism for acid-catalyzed hydrate formation from benzaldehyde.

Problem 25. Provide a mechanism for the acid-catalyzed formation of the diethyl acetal from cyclohexanone.

Problem 26. Provide the products for the following transformations.

(a)



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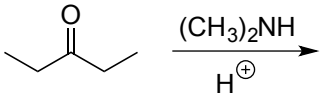

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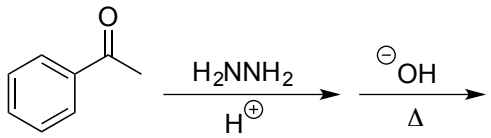

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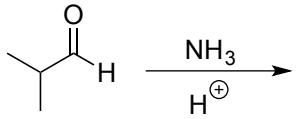

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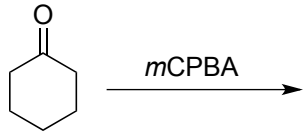

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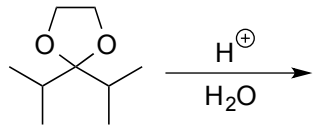
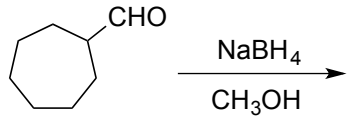
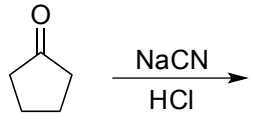


Problem 27. Show the major products of the following reactions.

(a)



(b)



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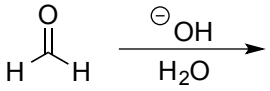

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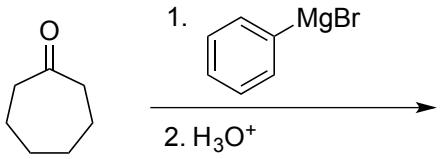

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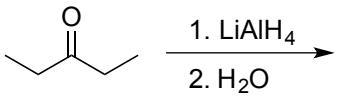

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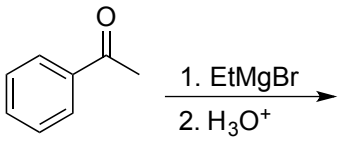
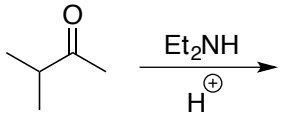
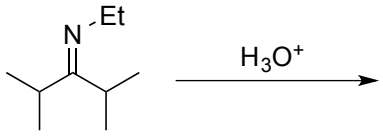


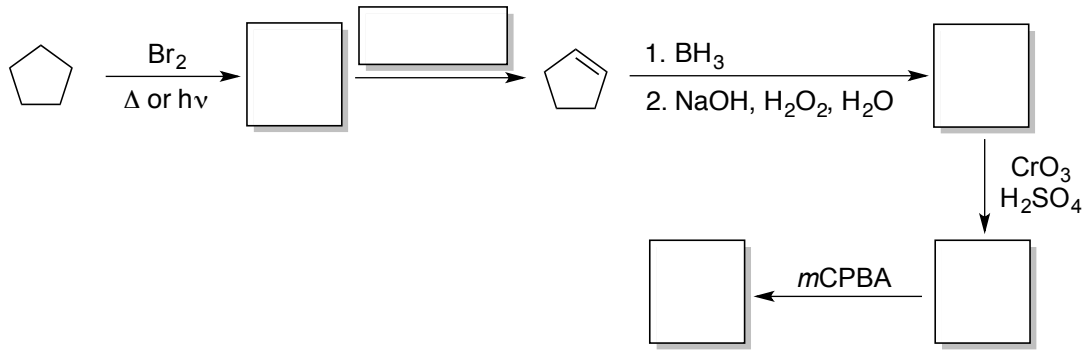
Problem 28. An enamine formed from an unsymmetrical ketone contains predominantly the more stable alkene. Using this fact, predict the major product of the following reaction.



Problem 29. Provide a mechanism for the following transformation.

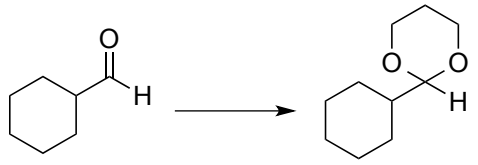


Problem 30. Fill in the missing reagents and intermediates in the scheme below.



Problem 31. Provide the reagents needed to accomplish each of the following transformations.

(a)



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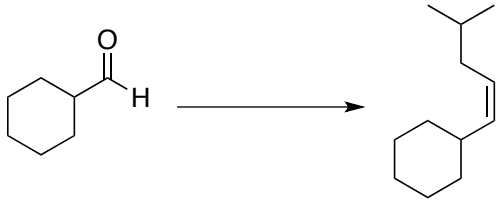

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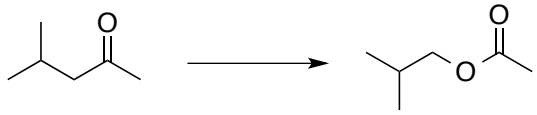
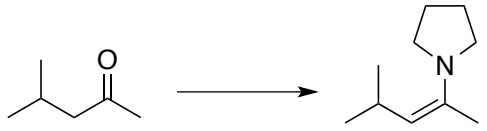
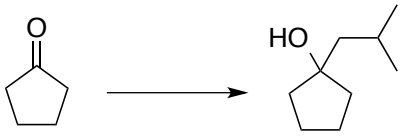


(d)



(e)



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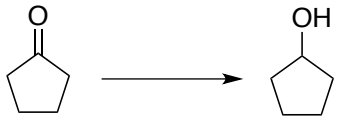
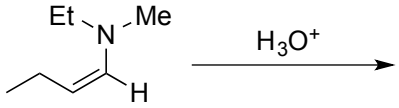
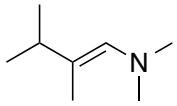


Problem 32. Show a mechanism for the reaction below.

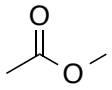


Problem 33. Compound A (C_7H_{14}) undergoes ozonolysis to produce Compound B, as well as a byproduct. Compound B, in turn, can condense with dimethylamine to form the enamine shown below.



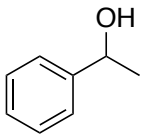
What are the structures of Compounds A, B, and the byproduct formed during ozonolysis?

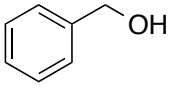
Problem 34. Devise a synthesis of the ester shown below starting with propane.

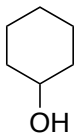


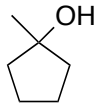
methyl acetate

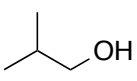
Problem 35. Which of the following compounds cannot be prepared by reduction of a ketone or aldehyde using sodium borohydride in methanol?

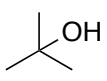


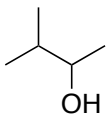


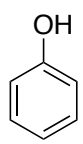






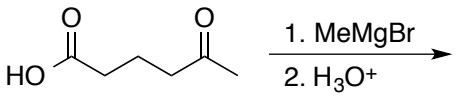




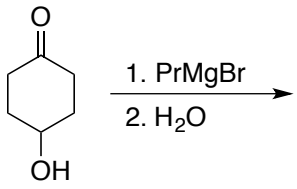


Problem 36. Identify the problem with each of the following Grignard reactions.

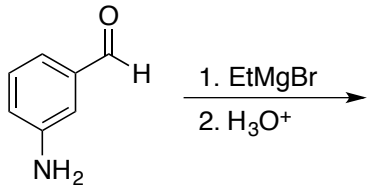
(a)



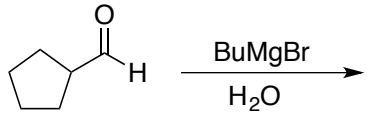
(b)



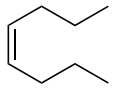
(c)



(d)

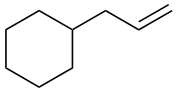
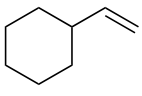


Problem 37. Prepare the following alkene using butane as the *only* source of carbon.

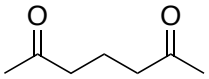
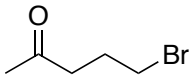


Problem 38. Isobutyl bromide is treated with triphenylphosphine followed by butyllithium to form an ylide. This ylide then undergoes Wittig reaction with 2-methylpropanal. The resulting alkene is subsequently treated with osmium tetraoxide and NMO. What is the structure of the product of this reaction sequence?

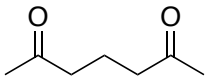
Problem 39. Devise a means to accomplish the following synthesis.

Prepare  from 

Problem 40. Develop a viable synthesis. Hint: Remember that acetals can be used as protecting groups.

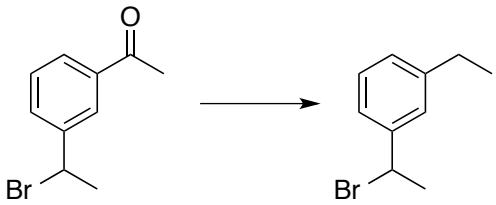
Prepare  from  and 

Problem 41. The diketone shown below was the target compound in Problem 40. In this problem, synthesize it from a reactant having the formula C_5H_8.

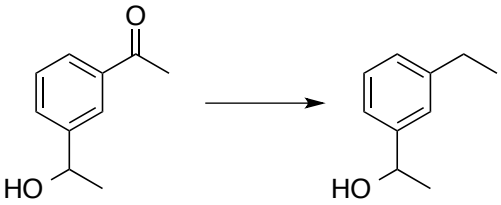


Problem 42. In the chapter on the reactions of aromatic compounds, we learned about two complementary methods to reduce carbonyls to methylene (CH_2) groups: the Clemmensen and Wolff-Kishner reductions. In the previous chapter, we learned that the Clemmensen reduction uses acidic conditions. In this chapter, we've come to more fully appreciate why the Wolff-Kishner reduction uses basic conditions. In the two examples below, one of the two methods is better equipped to give the desired compound *without* side products. In each case, state which method is preferred and explain why.

(a)

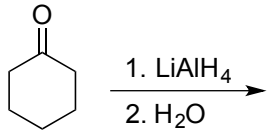


(b)

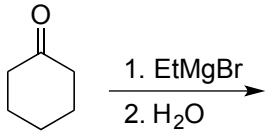


Problem 43. Draw mechanisms for each of the following reactions, and then compare them. Explain how they are similar to one another.

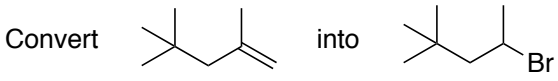
(a)



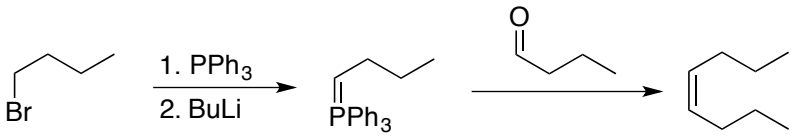
(b)



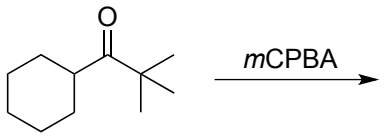
Problem 44. Provide a viable synthesis.



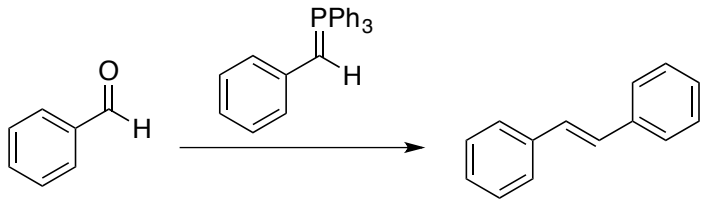
Problem 45. The following Wittig reaction was performed in Problem 37. Provide a mechanism for this transformation.



Problem 46. Provide a mechanism for the following reaction.



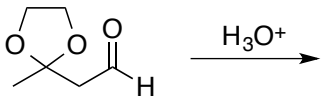
Problem 47. An investigator sets about making *trans*-stilbene using a Wittig reaction as shown below. After the reaction was concluded, mass spectral analysis of the product showed the anticipated molecular ion peak with a m/z ratio of 180.09. However, upon conferring with a colleague, the investigator learned that the reaction product was <u>not</u> actually *trans*-stilbene. What actually happened in the reaction, and how was the investigator led astray by the mass spectral data?



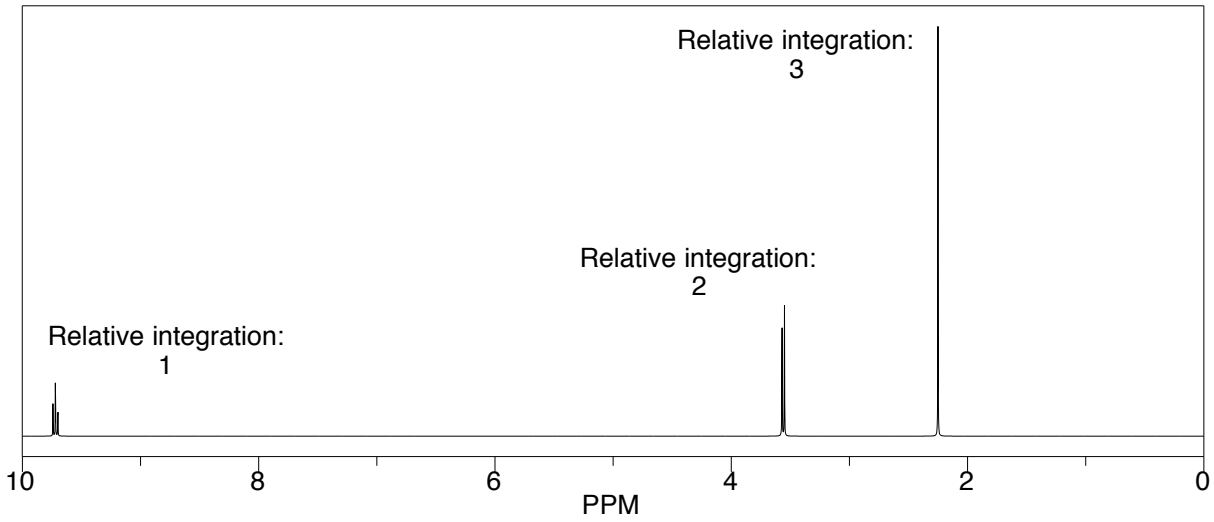
trans-stilbene
Expected

Problem 48. An investigator treats isopropyl phenyl ketone with *m*CPBA. The IR spectrum reveals a carbonyl stretch at approximately 1710 cm^{-1}, which is about 30 cm^{-1} less than the expected resonance for an ester carbonyl. Explain this outcome.

Problem 49. An investigator attempted to use acid-catalysis to form the hydrate of the following aldehyde.

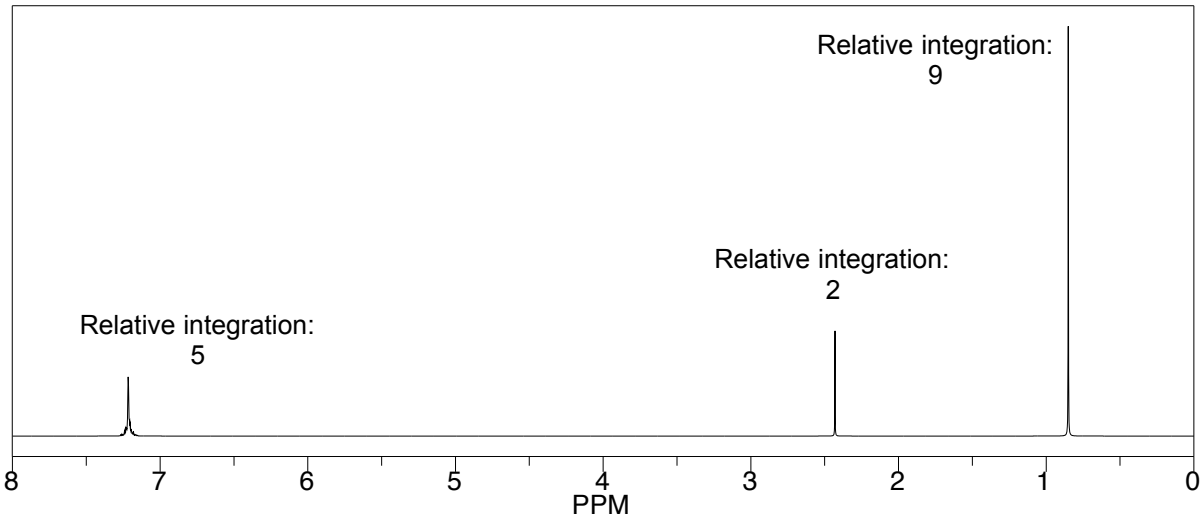


The ^1H NMR of the reaction product follows.



What actually transpired during this reaction? Could the investigator have done anything differently to accomplish the original goal?

Problem 50. Benzyl alcohol was oxidized with PCC and subsequently treated with *tert*-butylmagnesium bromide followed by water. The resulting alcohol was oxidized with chromic acid and then subjected to Wolff-Kishner reduction. The final product of this sequence of reactions exhibited to following ^1H NMR spectrum. What is its structure?


Relative integration:
9
Relative integration:
2
Relative integration:
5
8
7
6
5
4
3
2
1
0
PPM

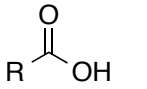
Chapter 16: Carboxylic Acids and Their Derivatives

Section 1: Nomenclature
Section 2: Preparation of carboxylic acids
Section 3: Introduction to reactions of carboxylic acid derivatives
Section 4: Reaction of carboxylic acids with thionyl chloride
Section 5: Nucleophilic acyl substitution of acid chlorides
Section 6: Nucleophilic acyl substitution of anhydrides
Section 7: Nucleophilic acyl substitution of carboxylic acids
Section 8: Nucleophilic acyl substitution of esters
Section 9: Nucleophilic acyl substitution of amides
Section 10: Summary of nucleophilic acyl substitution
Section 11: Dehydration of amides
Section 12: Nitrile hydrolysis
Section 13: Reactions of carboxylic acid derivatives with lithium aluminum hydride or Grignard reagents
Section 14: Synthesis

Section 1: Nomenclature

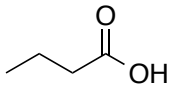
IUPAC nomenclature of carboxylic acids

Carboxylic acids are carbonyl-containing functional groups in which the carbonyl carbon also bears a hydroxyl group.



carboxylic acid

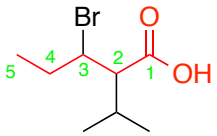
The parent is the longest continuous carbon chain containing the carboxylic acid. The “e” at the end of the parent alkane’s name is removed and replaced with “oic acid” to signify the presence of the carboxylic acid.



butanoic acid

- Four carbon parent = butane
- Replace "e" of suffix with "oic acid"

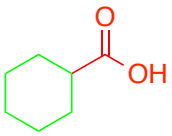
Given its valence, a carboxylic acid must appear at the terminus of a carbon chain. As a result, no number is needed to indicate its location on the parent. The carboxylic acid’s carbonyl carbon is assumed to be C1. Substituents still receive numbers as anticipated though.



3-bromo-2-isopropylpentanoic acid

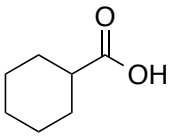
- Five carbon parent = pentane
- Replace "e" of suffix with "oic acid"
- Number the carboxylic acid carbon as 1
- Add substituent names and numbers

When a carboxylic acid is pendent to a cycloalkane, the ring's name is followed by the word "carboxylic acid".

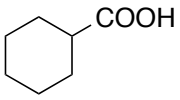


cyclohexanecarboxylic acid

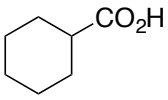
It's also important to remember that the carboxylic acid functional group is often written in its condensed form as "COOH" or "CO_2H".



is the same as

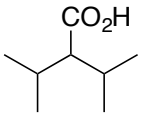


is the same as

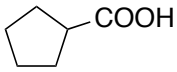


Problem 1. Provide systematic names for the following carboxylic acids.

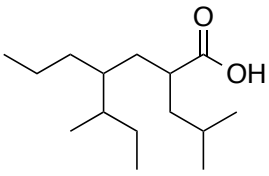
(a)



(b)

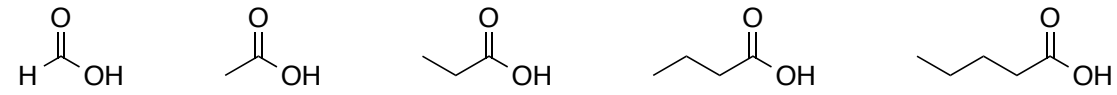


(c)



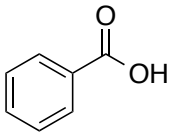
Common nomenclature of carboxylic acids

There are a few small carboxylic acids that are frequently referred to by their common names. In these instances, the suffix "ic acid" is preceded by a prefix that indicates the number of carbons in the molecule. You may recognize these prefixes from the nomenclature of aldehydes in the previous chapter.



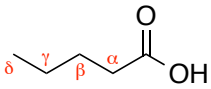
formic acid acetic acid propionic acid butyric acid valeric acid

We've also seen benzoic acid previously in the chapter on aromaticity.



benzoic acid

As we saw with aldehydes in the previous chapter, Greek letters may be used to designate the distance of carbons in the parent chain from the carbonyl.

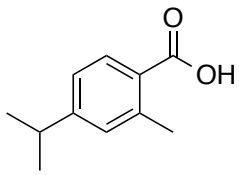


valeric acid

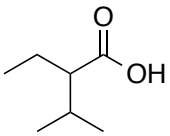
Several functional groups, including acid chlorides, acid anhydrides, esters, amides, and nitriles are considered to be carboxylic acid derivatives. Consequently, their systematic and common names are based on those of the corresponding carboxylic acid.

Problem 2. Provide common names for the acids below.

(a)

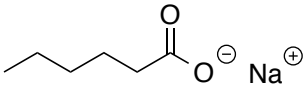


(b)



IUPAC nomenclature of carboxylates

Carboxylates are the conjugate bases of carboxylic acids. Their systematic names are derived from the name of the corresponding acid by removing the "ic acid" suffix and replacing it with "ate". If the counterion has been specified, its name is placed prior to the name of the carboxylate.

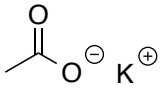


sodium hexanoate

- Six-carbon carboxylic acid parent = hexanoic acid
  - Replace "ic acid" of suffix with "ate"
  - Add counterion's name as a prefix

Common names of carboxylates

Carboxylates are given common names in exactly the same fashion, the only difference being that the common names of the parent acids are used as a foundation for the name.

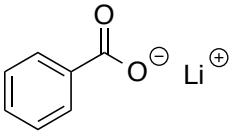


potassium acetate

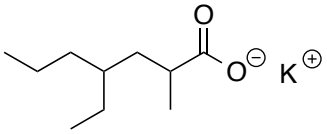
- Two-carbon carboxylic acid parent = acetic acid
  - Replace "ic acid" of suffix with "ate"
  - Add counterion's name as a prefix

Problem 3. Name the following carboxylates

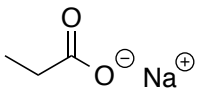
(a)



(b)

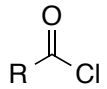


(c)



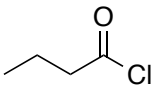
IUPAC nomenclature of acid chlorides

Acid chlorides are also known as acyl chlorides. They are carboxylic acid derivatives in which an acyl group (R plus a carbonyl) is bonded to a chlorine.



acid chloride
(or acyl chloride)

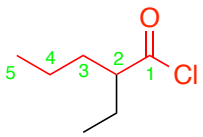
Their names are derived from those of the corresponding carboxylic acids. The "ic acid" suffix of the parent carboxylic acid is removed and replaced with "yl chloride".



butanoyl chloride

- Four-carbon carboxylic acid parent = butanoic acid
- Replace "ic acid" of suffix with "yl chloride"

An acid chloride also must appear at the terminus of a carbon chain. Consequently, no number is necessary to indicate its location. The carbonyl carbon of the acid chloride is assumed to be C1, and substituents are numbered accordingly.

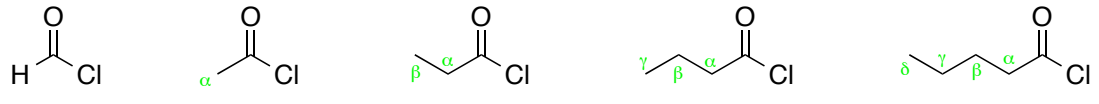


2-ethylpentanoyl chloride

- Five-carbon carboxylic acid parent = pentanoic acid
  - Replace "ic acid" of suffix with "yl chloride"
    - Number the carboxylic acid carbon as 1
      - Add substituent names and numbers

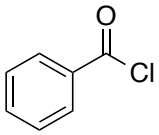
Common names of acid chlorides

The common names of acid chlorides are similarly derived from those of the corresponding carboxylic acids. The method is the same. The "ic acid" suffix is removed and replaced by "yl chloride". The prefixes indicating the length of the carbon chain remain the same. Greek letters may be used to designate the carbons of the parent chain if desired.

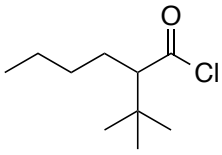


Problem 4. Provide names for the following acid chlorides.

(a)



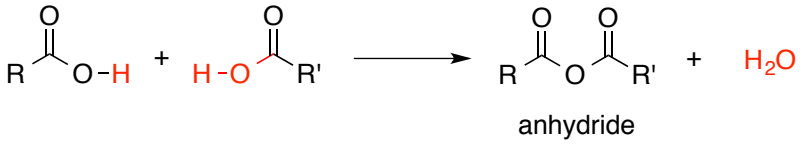
(b)



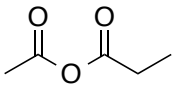
(c)

IUPAC nomenclature of acid anhydrides

Carboxylic acid anhydrides, also known as acid anhydrides or simply anhydrides, are functional groups resulting from the union of two carboxylic acids with the loss of water. The name anhydride literally means "without water". The anhydride can be symmetrical (if R = R') or unsymmetrical (if R ≠ R').

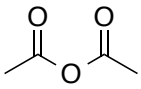


The systematic name of the anhydride is constructed from the name of the acid or acids plus the word "anhydride" to show that they have been linked in this fashion.



ethanoic propanoic anhydride

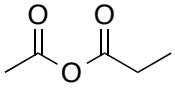
If only a single acid's name is provided, it is assumed that the anhydride is symmetrical.



ethanoic anhydride

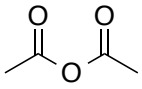
Common nomenclature of acid anhydrides

The method for deriving the common names of anhydrides is identical to the method for constructing systematic names. The only difference is that the common names of the acids are used.



acetic propionic anhydride

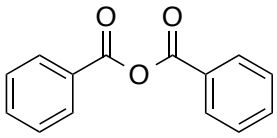
As with systematic names, the appearance of a single acid's name implies a symmetrical anhydride.



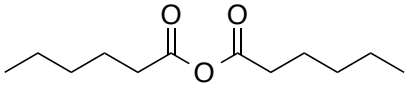
acetic anhydride

Problem 5. Name the following anhydrides.

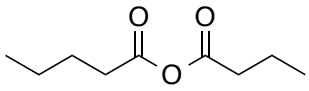
(a)



(b)

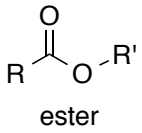


(c)



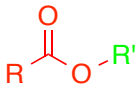
IUPAC nomenclature of esters

Esters are functional groups in which an acyl group is bonded to an alkoxy (OR') group.



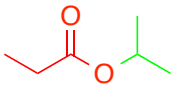
ester

The systematic name is generated from the name of the alkyl group (R') bonded to the carboxyl oxygen and the name of the carboxylate corresponding to the rest of the molecule.



alkyl carboxylate

For instance, the following compound has an isopropyl group on the carboxyl oxygen of the carboxylate known as propanoate.

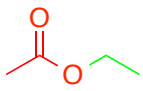


isopropyl propanoate

Common names for esters

The common names of esters are derived in an analogous fashion. The sole difference is that the common names of the carboxylates are used in place of their systematic names.

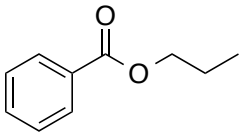
A simple example is ethyl acetate, which is encountered in many nail polish removers.



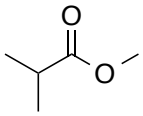
ethyl acetate

Problem 6. Identify the following esters.

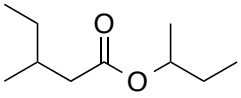
(a)



(b)

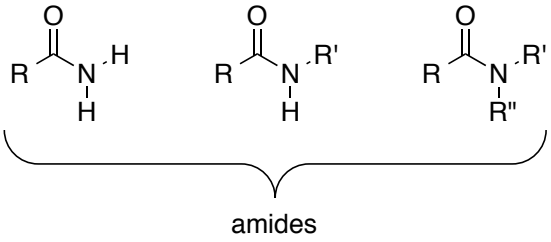


(c)

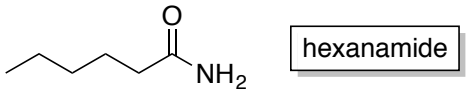


IUPAC nomenclature of amides

Amides are functional groups in which an acyl group is bonded to an amino group.

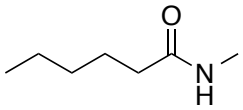


Their systematic names are constructed by removing the "oic acid" ending from the name of the corresponding acid and replacing it with "amide".



- Six-carbon carboxylic acid parent = hexanoic acid
  - Replace "oic acid" of suffix with "amide"

When there are alkyl groups on nitrogen, their location is designated using "*N*" since nitrogen itself it not numbered (only carbon atoms of the parent are numbered).

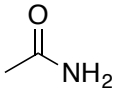


N-methylhexanamide

- Six-carbon carboxylic acid parent = hexanoic acid
  - Replace "oic acid" of suffix with "amide"
- Substituents on nitrogen have location designated using *N*

Common names of amides

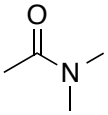
The method for developing common names is quite similar to the systematic approach. The common name of the parent acid is identified, and the "ic or oic acid" suffix is replaced by "amide".



acetamide

- Two-carbon carboxylic acid parent = acetic acid
  - Replace "ic acid" of suffix with "amide"

The location of substituents on nitrogen is designated using the locant "*N*."



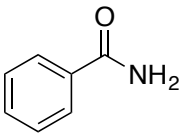
N,*N*-dimethylacetamide

- Two-carbon carboxylic acid parent = acetic acid
  - Replace "ic acid" of suffix with "amide"
- Substituents on nitrogen have location designated using *N*

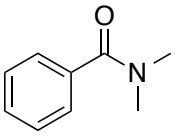
Notice that, regardless of whether the systematic or common method is used, the names of amides end with "amide."

Problem 7. Name the amides below.

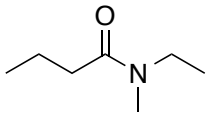
(a)



(b)

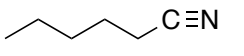


(c)



IUPAC names of nitriles

Nitriles are named by identifying the parent acid and replacing the “oic acid” suffix with “onitrile”.

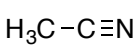


hexanonitrile

- Six-carbon carboxylic acid parent = hexanoic acid
  - Replace "oic acid" of suffix with "onitrile"

Common names of nitriles

To give nitriles common names, the method is extremely similar. The common name of the parent acid is identified. The “ic or oic acid” suffix is then replaced with “onitrile”.



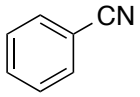
acetonitrile

- Two-carbon carboxylic acid parent = acetic acid
  - Replace "ic acid" of suffix with "onitrile"

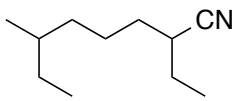
Notice that, regardless of whether the systematic or common method is used, the names of nitriles end with “onitrile.”

Problem 8. Identify the following nitriles.

(a)



(b)



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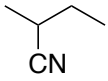
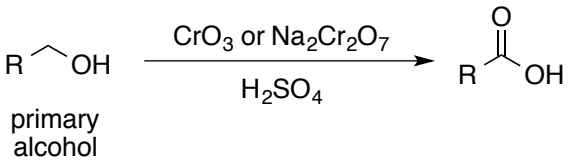
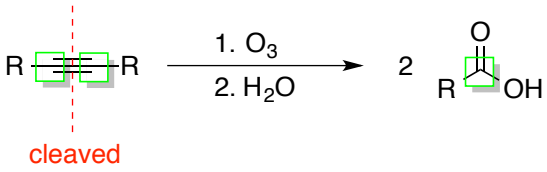


Section 2: Preparation of carboxylic acids

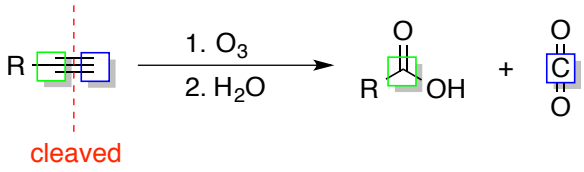
We've encountered a few methods for the preparation of carboxylic acids in previous chapters. By far the most common is oxidation of primary alcohols. This can be accomplished using chromic acid, which is prepared from chromium trioxide or sodium dichromate and sulfuric acid.



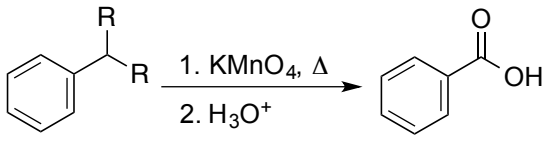
Additionally, the ozonolysis of alkynes provides carboxylic acids. Internal alkynes are cleaved to yield two carboxylic acids. This is most useful as a preparatory method if the alkyne is symmetrical, meaning that two equivalents of the same carboxylic acid would be generated.



Terminal alkynes are cleaved into a carboxylic acid and carbon dioxide.

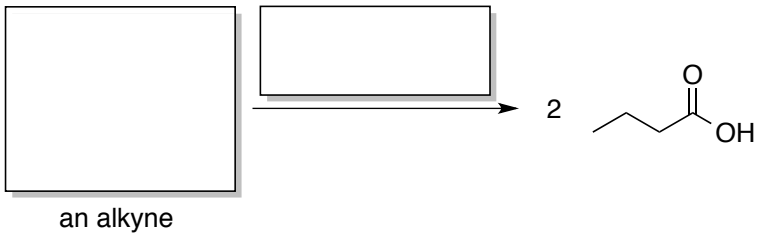


Benzylic oxidation is a method to prepare benzoic acid (or its derivatives) specifically. If the benzylic position possesses at least one hydrogen, that center can be oxidized to the carboxylic acid, and any alkyl groups bonded to the benzylic carbon are cleaved in the process.

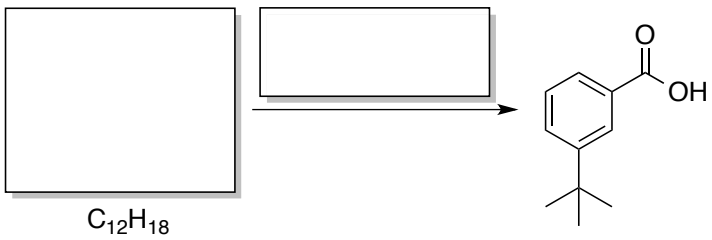


Problem 9. Fill in the missing reactants and reagents needed for the preparation of the following carboxylic acids.

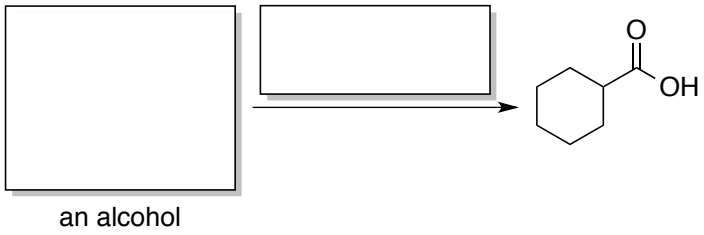
(a)



(b)

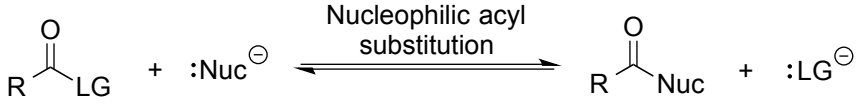


(c)

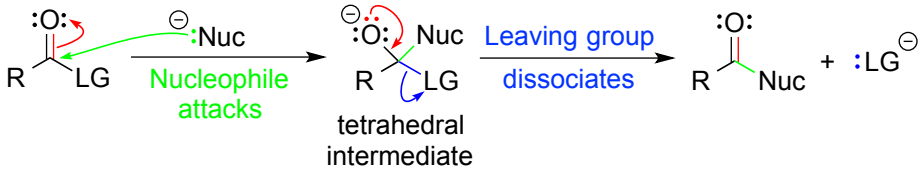


Section 3: Introduction to reactions of carboxylic acid derivatives

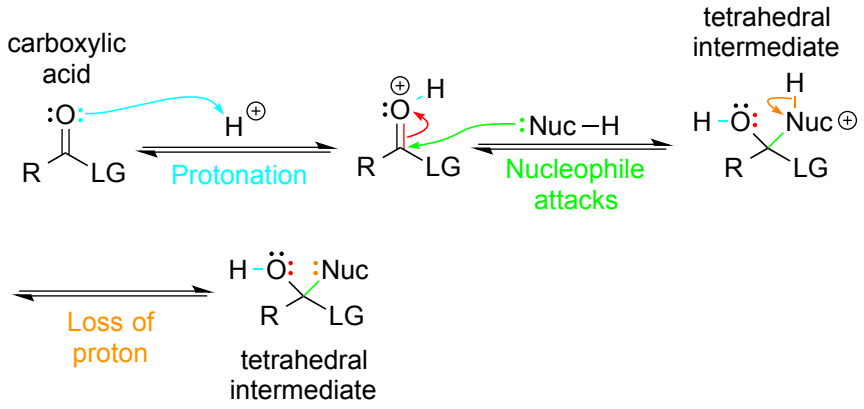
The principal reaction of carboxylic acid derivatives is nucleophilic acyl substitution. The carboxylic acid derivative bears a potential leaving group (LG) on the carbonyl carbon. When treated with a nucleophile (Nuc), the leaving group can be displaced. However, the mechanism is not S_N1 or S_N2, since these reaction pathways do not occur on sp^2 centers. Instead, the displacement occurs via a new mechanism called nucleophilic acyl substitution. The name stems from the fact that a substitution occurs on an acyl group and is incited by a nucleophile. The position of equilibrium is determined by the relative stabilities of the nucleophile ($Nuc:^-$) and leaving group ($LG:^-$). Equilibrium will favor the side with the more stable entities.



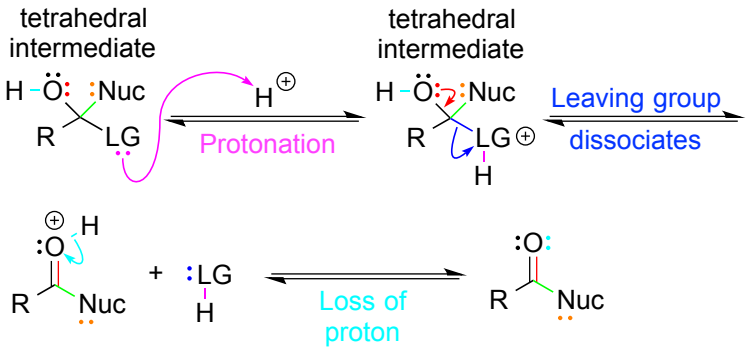
There are two main variants of this mechanism. The reaction conditions determine which one is at play. When the leaving group is particularly good and when the conditions are neutral or basic, the nucleophile attacks the carbonyl carbon directly. The carbonyl π bond is displaced onto oxygen as a lone pair of electrons. The intermediate thus formed is known as a tetrahedral intermediate because the carbonyl carbon rehybridized from sp^2 (trigonal planar or flat) to sp^3 (tetrahedral) due to the addition of the nucleophile. The tetrahedral intermediate then "collapses" to re-form the carbonyl. In the process, the better leaving group is displaced.



Alternatively, when the leaving group is not especially good, acidic conditions are often used. In such cases, the reaction begins with protonation of the carbonyl oxygen. This enhances the electrophilicity of the carbonyl carbon, which is subsequently attacked by the nucleophile. The tetrahedral intermediate thus formed sheds a proton to the medium.

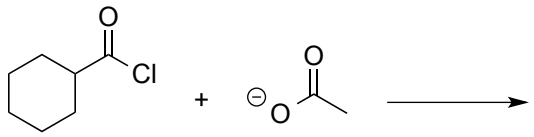


Although the neutral tetrahedral intermediate looks as though it might be a reasonable stopping point, there is more that can happen to it under these reaction conditions. In this acidic medium, protonation of the leaving group can occur. Dissociation is accompanied by the re-formation of the carbonyl π bond. Finally, the loss of a proton neutralizes the oxonium ion and provides the nucleophilic acyl substitution product.



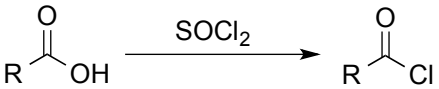
Although the specific reactions covered in the following sections will naturally exhibit slight variations from these generic mechanisms, you'll find a great deal of similarity between these two fundamental reaction paradigms and the mechanisms that we learn in this chapter.

Problem 10. We will see the following reaction in the sections to come. Decide which of the two generic mechanisms above applies to this specific example. Then draw a mechanism for the reaction.

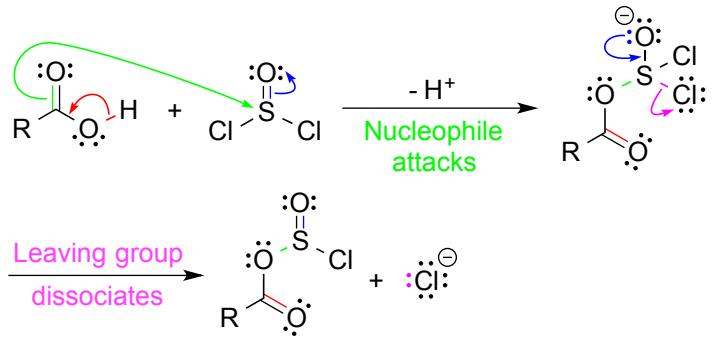


Section 4: Reaction of carboxylic acids with thionyl chloride

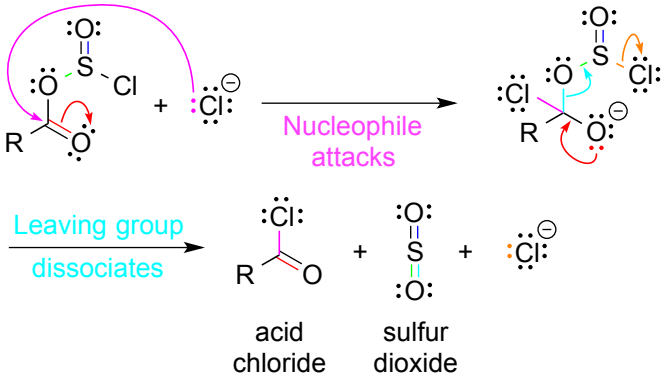
Carboxylic acids are readily available and can be prepared in a variety of ways. However, they possess a poor leaving group ($^-$OH) on the carbonyl carbon. This makes them only modestly reactive in nucleophilic acyl substitution, which is the predominant reaction of carboxylic acid derivatives. Consequently, it is useful to be able to convert carboxylic acids to acid chlorides, which have a much better leaving group (Cl^-) and are therefore much more reactive in nucleophilic acyl substitution. This is accomplished by treatment with thionyl chloride ($SOCl_2$).



The carboxylic acid attacks the electrophilic sulfur of thionyl chloride at the outset of this reaction. As it does so, the carboxylic acid also sheds a proton. The sulfur-oxygen π-bonding electrons are displaced onto oxygen as sulfur acquires a new S–O bond. In the next mechanistic step, the sulfur-oxygen π bond re-forms as chloride dissociates. This portion of the mechanism converts a poor leaving group (the hydroxyl group) into a good leaving group.



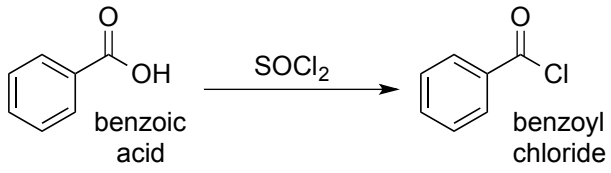
The second half of the mechanism is a nucleophilic acyl substitution. The displaced chloride attacks the carbonyl carbon, pushing the π electrons onto oxygen. In the final mechanistic step, the carbonyl π bond re-forms as a leaving group dissociates. This particular leaving group is somewhat unusual in that it fragments as it dissociates. The electrons from the breaking C–O bond form a sulfur-oxygen π bond, and chloride is displaced as a leaving group.



The fragmentation of the penultimate compound into three pieces during the last mechanistic step is entropically favored. Additionally, sulfur dioxide bubbles out of the reaction mixture, thereby driving the reaction to completion.

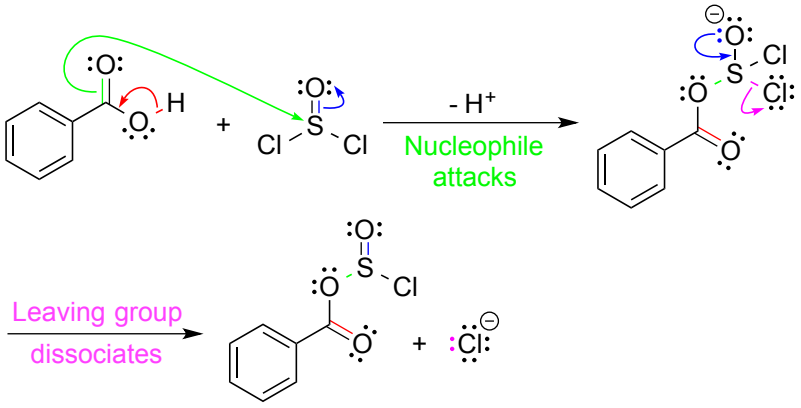
A specific example of the reaction of a carboxylic acid with thionyl chloride

In the following example, benzoic acid is converted to benzoyl chloride by reaction with thionyl chloride.

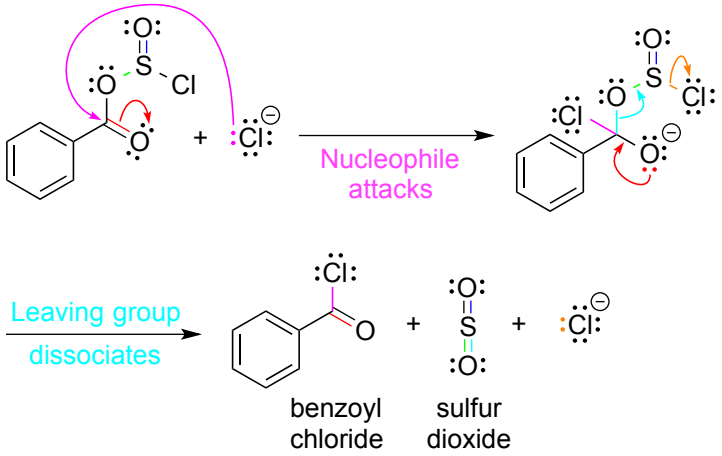


The transformation begins with the attack of benzoic acid on thionyl chloride. A proton is lost during the process so that a new carbonyl can be formed, thereby maintaining the

desired valence at the carbonyl carbon. The sulfur-oxygen π electrons are pushed onto oxygen. The anion thus formed then collapses to re-form the sulfur-oxygen π bond during the second step of the mechanism. As this occurs, chloride dissociates from sulfur. The carbonyl carbon now bears a good leaving group that can be replaced by chloride as the mechanism progresses.

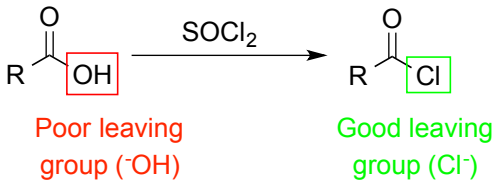


During the nucleophilic-acyl-substitution segment of the mechanism, the chloride that was previously displaced then attacks the carbonyl carbon. The π electrons are pushed onto oxygen, but the anion that is formed will then collapse to regenerate the carbonyl π bond. As it does so, the leaving group dissociates, and sulfur dioxide is formed along with chloride.



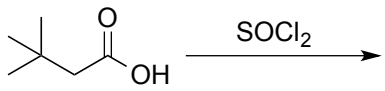
In summary, carboxylic acids can be converted to acid halides through exposure to thionyl chloride. The mechanism involves two stages. In the first stage, the hydroxyl group is transformed into a good leaving group. In the second stage, this good leaving group is replaced by chloride via nucleophilic acyl substitution.

This reaction is significant because it converts a poor leaving group on the carbonyl ($^{-}$OH) into a good leaving group (Cl^{-}). As a result, the reactivity of the substrate is greatly enhanced through conversion to the acid chloride.



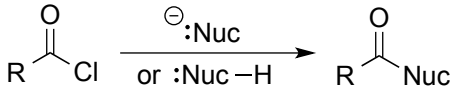
The significance of having a good leaving group on the carbonyl carbon will become even more apparent in the next section.

Problem 11. Draw the mechanism for the following reaction.



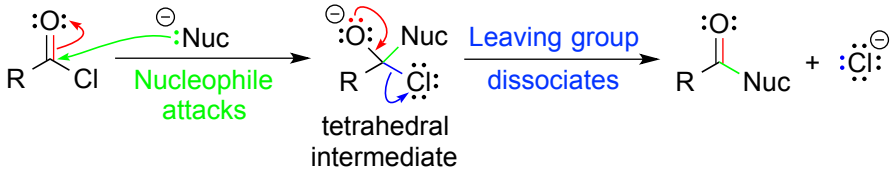
Section 5: Nucleophilic acyl substitution of acid chlorides

We saw in the previous section how acid chlorides can be prepared from carboxylic acids. In this section, we'll examine the reactions of acid chlorides. These reactions follow the paradigm of nucleophilic acyl substitution, in which a leaving group on a carbonyl is replaced by a nucleophile.



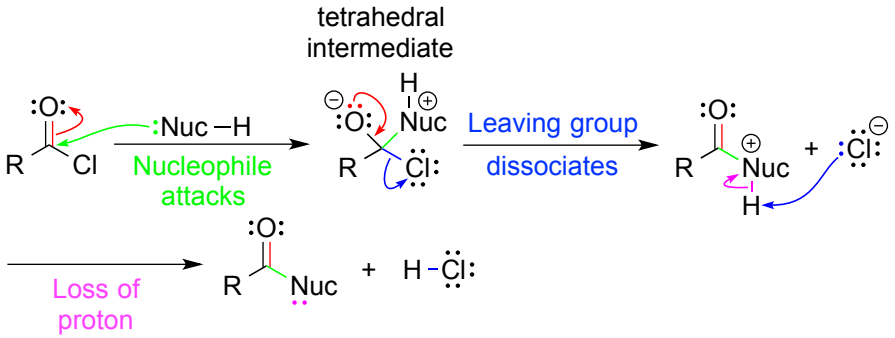
The nucleophile may be negative or neutral. The mechanism is nearly the same in either case, except that neutral nucleophiles require one additional step. Let's first examine the mechanism when a negatively charged nucleophile is used.

The mechanism begins with nucleophilic attack on the electrophilic carbonyl carbon. This displaces the carbonyl π electrons onto oxygen. The tetrahedral intermediate then "collapses" to re-form the carbonyl. As it does so, the best leaving group is displaced from the tetrahedral center. Chloride is an excellent leaving group, so it is the entity that gets displaced.



Very little changes when the nucleophile is neutral. The initial nucleophilic attack still generates a tetrahedral intermediate, but in this case as the neutral nucleophile acquires a new bond, it becomes positively charged. The leaving group dissociates as the carbonyl is

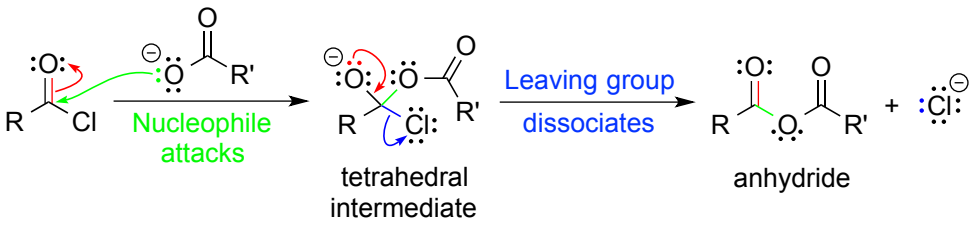
re-formed. And, finally, one additional step is used to show the loss of a proton from the nucleophile to generate a product without any formal charge.



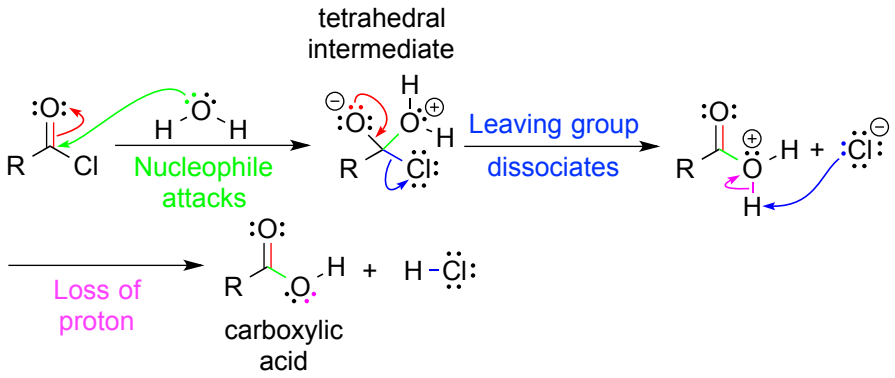
Specific examples of the nucleophilic acyl substitution of acid chlorides

Since acid chlorides are so reactive (due to their excellent leaving group), they can undergo nucleophilic acyl substitution with a variety of nucleophiles.

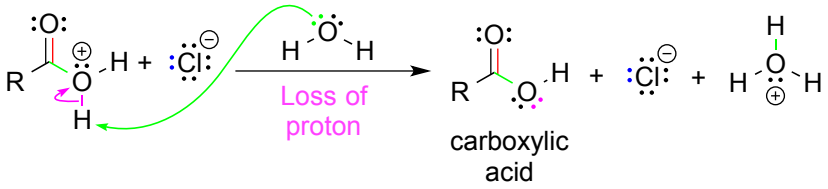
• Reaction with carboxylates: Recall that carboxylates are the conjugate bases of carboxylic acids. A carboxylate is a negative nucleophile that reacts with an acid chloride according to the first generic mechanism described above. The carboxylate attacks the carbonyl carbon, displacing the π electrons onto oxygen to form a tetrahedral intermediate. The tetrahedral intermediate then collapses to expel chloride, and an anhydride is formed as a result.



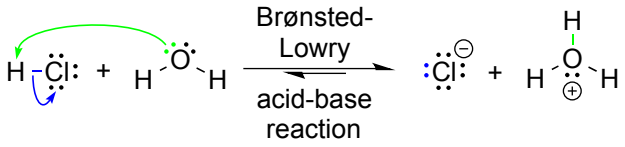
• Reaction with water: Water is a neutral nucleophile, so its reaction with an acid chloride follows the paradigm of the second generic mechanism outlined above. Water initially attacks the carbonyl carbon and pushes the carbonyl π electrons onto oxygen. The tetrahedral intermediate then collapses to re-form the carbonyl as chloride dissociates. Finally, a proton is lost to provide the neutral carboxylic acid as the final reaction product. In this instance, chloride is shown as the base that removes the acidic proton.



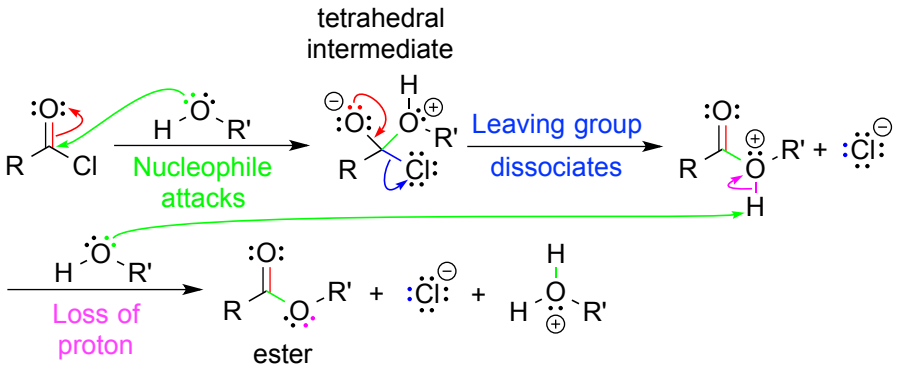
Sometimes, in the last step of the preceding mechanism, you will see another molecule of water used as the base that removes the acidic proton. In this case, the byproducts are chloride and the hydronium ion, rather than HCl.



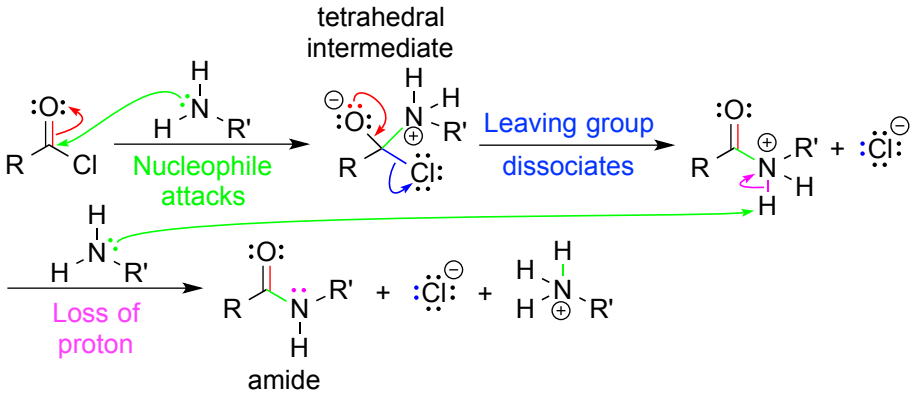
This difference is not as significant as it may initially appear to be. When water is used as a reactant or reagent, it also often serves as the solvent. If HCl is formed in water, Brønsted-Lowry acid-base reaction yields chloride and the hydronium ion. So, whether the base that removes the acidic proton is chloride or water, the end products will ultimately be the same in either case: the carboxylic acid, chloride, and hydronium ion.



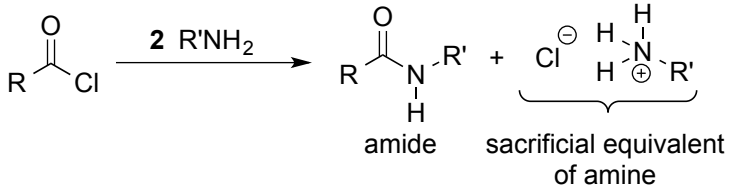
• Reaction with alcohols: Whenever a reaction uses water as a reactant or reagent, the chances are good that the use of an alcohol instead will provide a similar product through a nearly identical mechanism. The reaction between an acid chloride and an alcohol is therefore very similar to the reaction between an acid chloride and water. The reaction begins with the nucleophilic attack of the alcohol on the carbonyl carbon. The tetrahedral intermediate thus formed loses chloride in the process of restoring the carbonyl. Finally, a proton is lost to form a neutral ester. In this depiction of the mechanism, another alcohol molecule was used to remove the proton, leading directly to the ultimate byproducts: chloride and the conjugate acid of the alcohol.



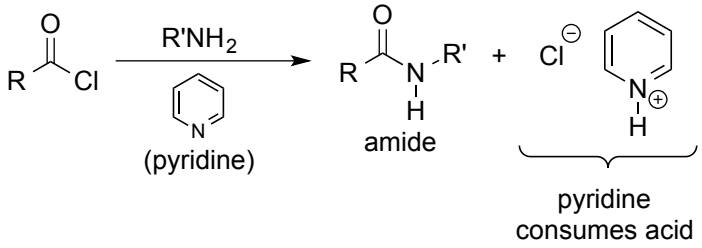
• Reaction with amines: An acid chloride can also react with ammonia (NH_3), primary amines ($R'NH_2$), or secondary amines (R'_2NH) to provide an amide product. In the example below, a primary amine is used. The amine first attacks the carbonyl carbon, pushing electrons onto oxygen to form the tetrahedral intermediate. As the tetrahedral intermediate collapses, chloride dissociates. The reaction concludes with the loss of a proton to yield the neutral amide.



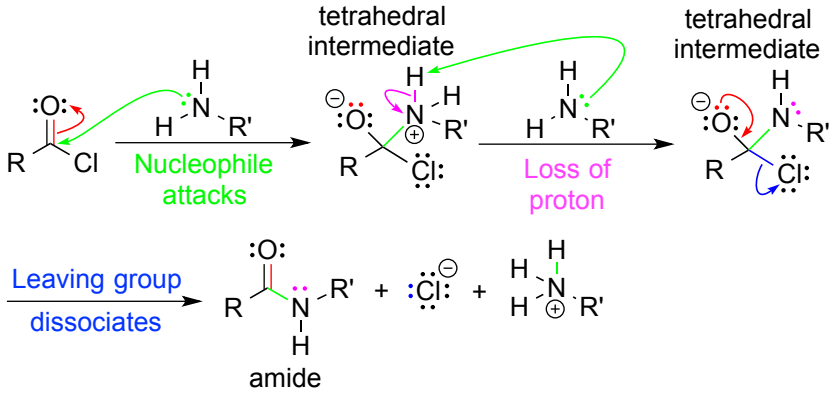
Since amines are fairly basic, it is important to use *two equivalents* of amine in this reaction. One equivalent is incorporated into the amide, and the other reacts with the acid liberated during the reaction to form an ammonium salt as a byproduct. The second equivalent of amine can be termed "sacrificial" because it is incorporated into a byproduct rather than the desired product. Since amines are rarely used as reaction solvents (meaning that they are rarely used in great excess, as water and alcohols may be), chemists consider it significant to note that two equivalents of amine are needed.



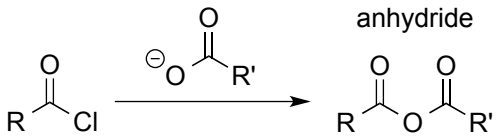
If the amine in question is expensive or difficult to prepare, an alternative option is to use one equivalent of the amine along with one equivalent of pyridine. Pyridine functions as a non-nucleophilic base and reacts with the acid produced during the reaction. It therefore takes the place of the sacrificial equivalent of amine.



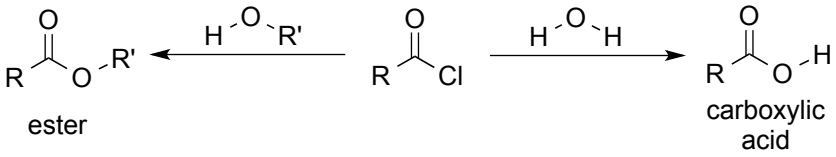
• A final note on mechanistic variations: The mechanisms above were presented in a highly parallel fashion so as to make learning them more manageable. Sometimes the loss of proton and dissociation of the leaving group are shown in the reverse order, particularly when the conditions are more basic. The net result is the same, but the second and third mechanistic steps are reversed in this variation.



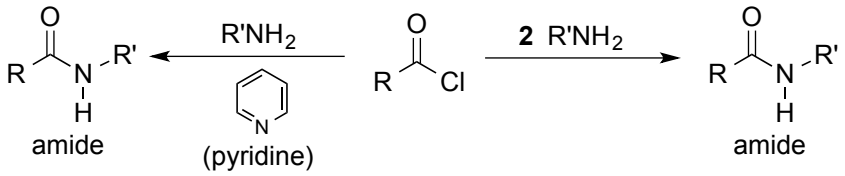
In conclusion, acid chlorides react readily via nucleophilic acyl substitution. They can react with carboxylates to yield anhydrides.



Reaction with water affords carboxylic acids, while the analogous reaction with alcohols provides esters.

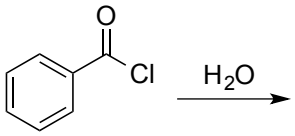


Reaction with amines produces amides. This last reaction requires either two equivalents of amine (one of which is sacrificial) or one equivalent of an amine with one equivalent of pyridine to consume the acid produced during the reaction.

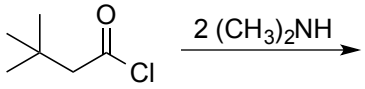


Problem 12. Predict the products of the following reactions.

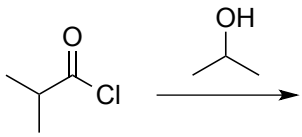
(a)



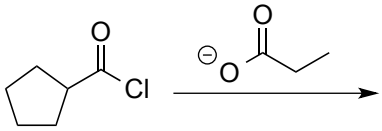
(b)



(c)

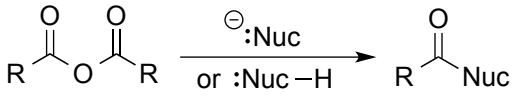


(d)

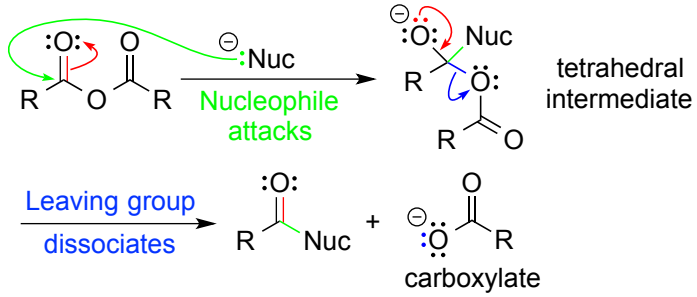


Section 6: Nucleophilic acyl substitution of anhydrides

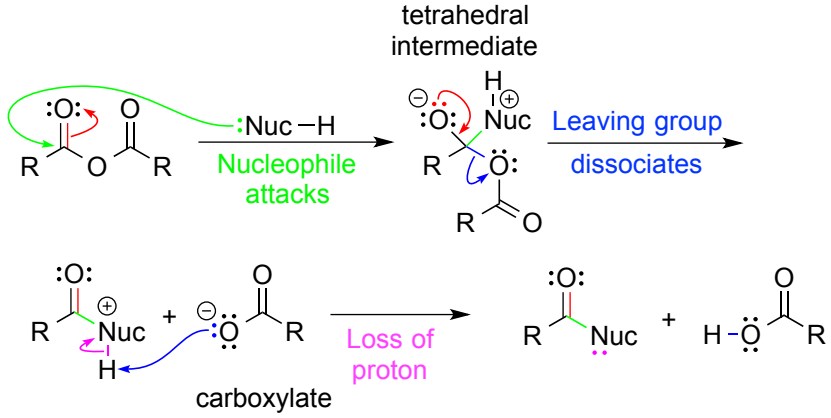
Anhydrides are nearly as reactive as acid chlorides in nucleophilic acyl substitution reactions. They too can be attacked by negative or neutral nucleophiles; however, in practice it is much more common for anhydrides to react with neutral nucleophiles, such as water, alcohols, or amines.



An anhydride can be treated with a negative nucleophile. The nucleophile's attack on one of the carbonyl carbons pushes the π electrons onto oxygen, thereby forming a tetrahedral intermediate. The carbonyl re-forms as the tetrahedral intermediate collapses. During this process the best leaving group is displaced from the incipient carbonyl. The displacement of a carboxylate is shown below.



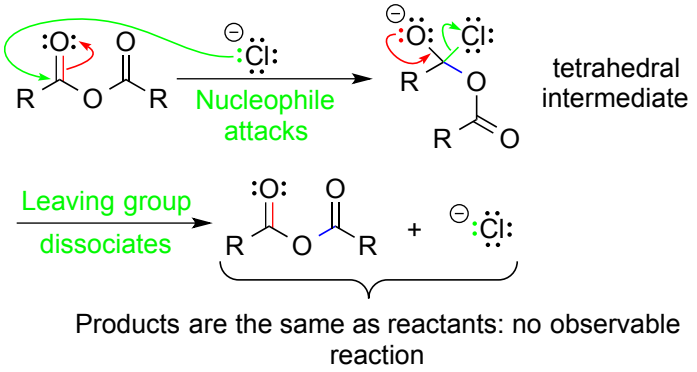
As noted above, while anhydrides can react with negative nucleophiles in nucleophilic acyl substitution, their most common reactions involve neutral nucleophiles. The reaction begins with the attack of the nucleophile on one of the two carbonyl carbons. The carbonyl π electrons are displaced onto oxygen as a result, forming a tetrahedral intermediate. The tetrahedral intermediate then collapses to re-form the carbonyl π bond. As this occurs, the best leaving group is displaced. The carboxylate is a very good leaving group, so it will usually be displaced. Finally, the loss of a proton yields a neutral product of nucleophilic acyl substitution.



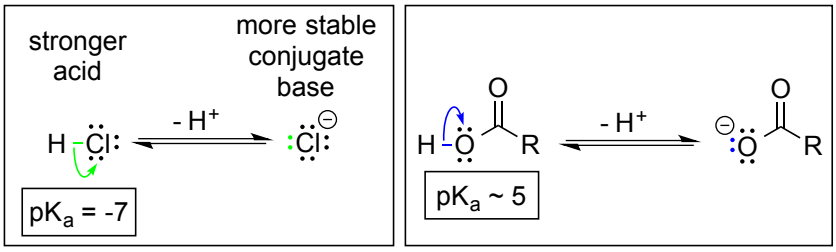
Specific examples of the nucleophilic acyl substitution of anhydrides

As with acid chlorides (see the previous section), there are several possible nucleophiles that can react with anhydrides. One notable option fails to produce a reaction though.

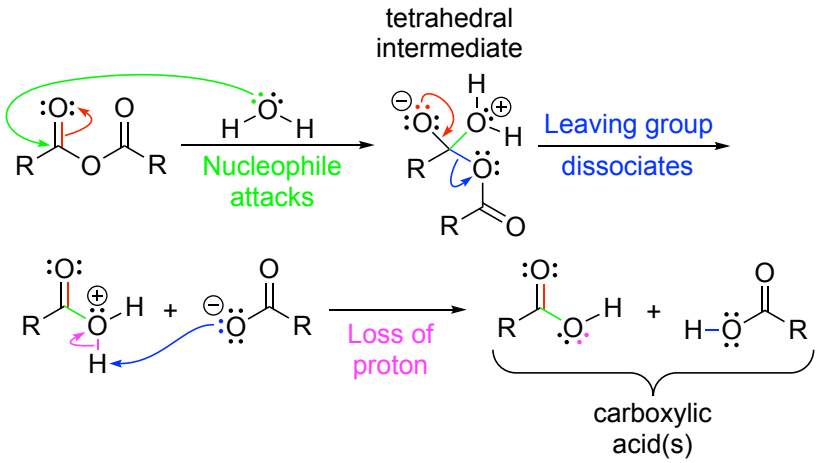
• Reaction with chloride: The reaction of anhydrides with chloride fails. Chloride, a negative nucleophile, can attack the carbonyl carbon to form a tetrahedral intermediate. When the tetrahedral intermediate collapses, the best leaving group is displaced. In this instance though, chloride is a better leaving group than the carboxylate, so it is ejected from the molecule to re-form the original anhydride. *No net change has occurred.*



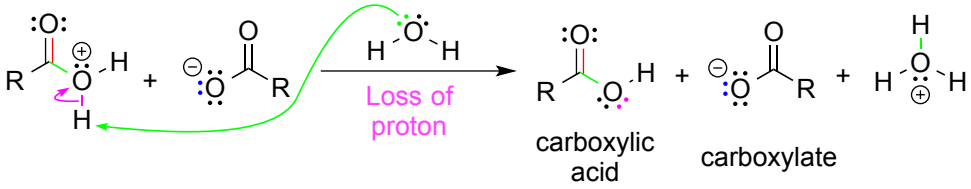
To understand why chloride is a better leaving group than the carboxylate, we can compare the pK_a values for their conjugate acids. The pK_a of HCl is about -7; whereas, the pK_a of a carboxylic acid is around 5. Consequently, HCl is the stronger acid. Since both of the acid-base reactions shown below simply involve the loss of a proton, the difference in acidity must be due to the stability of the conjugate bases. HCl is more acidic, so its conjugate base (chloride) is more stable. Once we have identified that chloride is more stable than a carboxylate, this fact can be applied to any reaction (e.g., nucleophilic acyl substitution). This explains why chloride was expelled in the preceding reaction rather than the carboxylate. Chloride is the more stable entity and therefore the better leaving group.



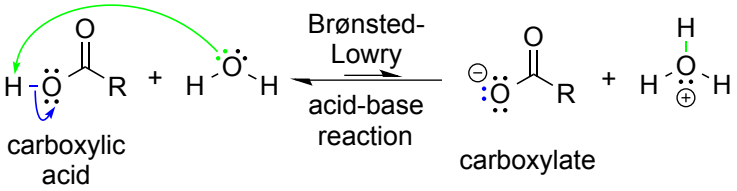
• Reaction with water: While reaction with chloride failed, many other reactions of anhydrides with nucleophiles will be successful. For instance, anhydrides can be treated with water to form carboxylic acids. Water is a neutral nucleophile. It attacks one of the carbonyl carbons and pushes the π electrons onto oxygen. When the tetrahedral intermediate collapses, the carboxylate is displaced. Transfer of a proton results in two carboxylic acids. If the anhydride substrate is symmetrical, then two equivalents of the same carboxylic acid are produced.



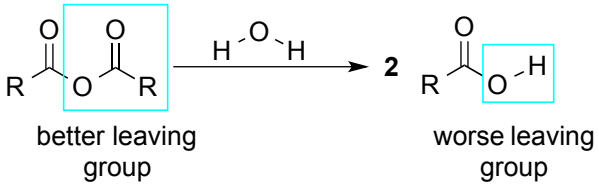
You may also sometimes see a second water molecule used as the base that removes the proton in the final step of the mechanism.



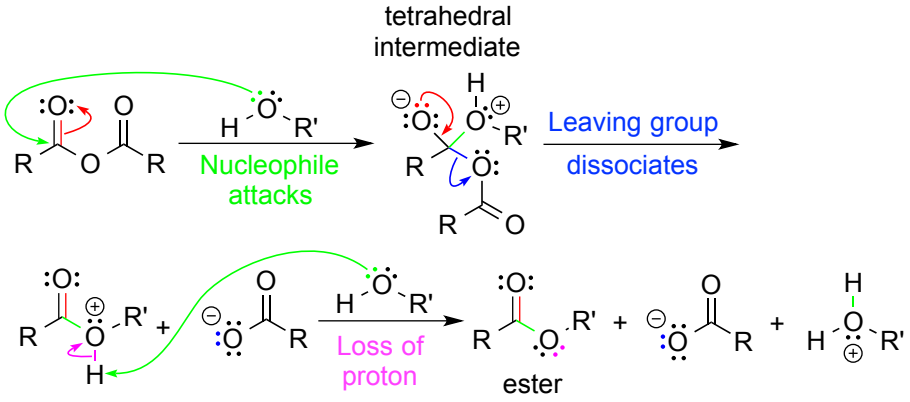
Although this may appear to result in a different outcome, it is important to keep in mind that, when a carboxylic acid is produced in water, some of it dissociates to create the carboxylate and hydronium ion. Consequently, both ways of drawing the final step actually have the same outcome.



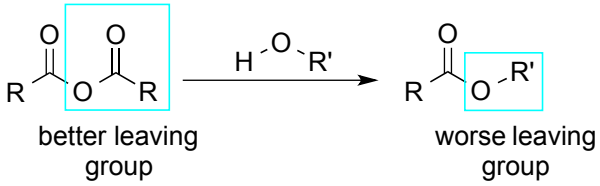
To understand why this reaction was successful (as opposed to the reaction with chloride that failed), we can examine the leaving groups on the carbonyl of the reactant and product. The carboxylate is a better leaving group than hydroxide ($^-$OH). This means that the anhydride is more reactive than the acid toward nucleophilic acyl substitution, and the products are therefore favored at equilibrium.



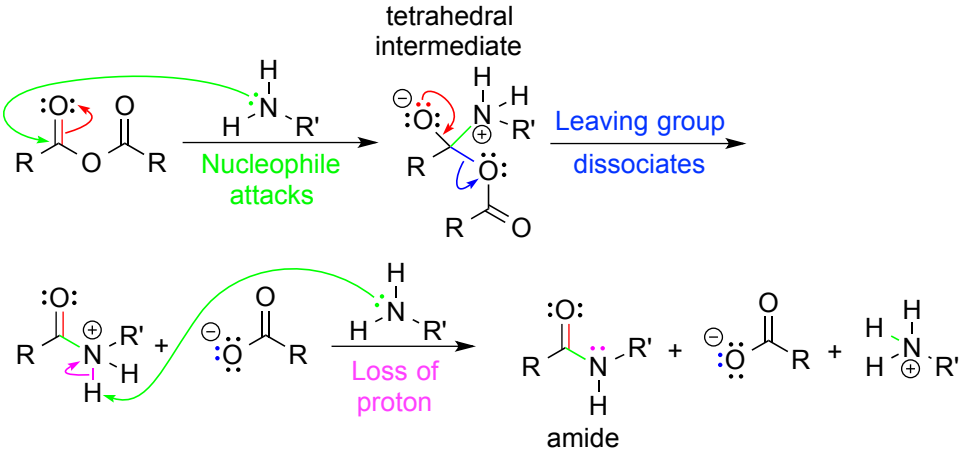
• Reaction with alcohols: As we saw in the previous section on acid chlorides, the reaction with alcohols is similar to the reaction with water. An alcohol can also serve as a neutral nucleophile, attacking the carbonyl to form a tetrahedral intermediate as the π electrons are displaced. The re-formation of the carbonyl is accompanied by the loss of the carboxylate. Finally, a proton is lost (to either the carboxylate or a second alcohol molecule) to yield an ester.



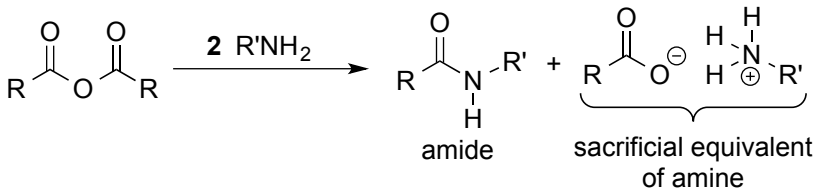
Again, this reaction's success can be rationalized by comparing the leaving groups on the reactant and product carbonyls. This reaction was successful because the carboxylate is a better leaving group than the alkoxide (⁻OR').



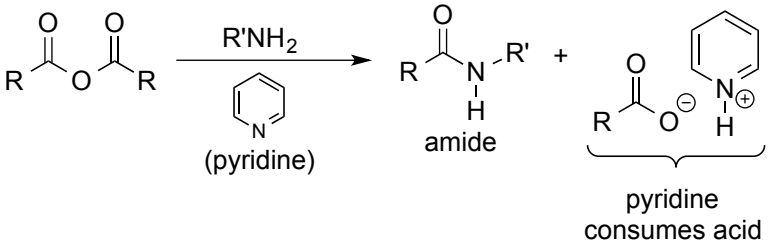
• Reaction with amines: Anhydrides can also react with ammonia (NH_3), primary amines ($R'NH_2$), or secondary amines (R'_2NH) to yield amides. A primary amine is used in the following reaction. It attacks the carbonyl, and the π electrons are pushed onto oxygen. The collapse of the tetrahedral intermediate occurs concurrently with loss of the carboxylate leaving group. A proton is then lost to form the neutral amide.



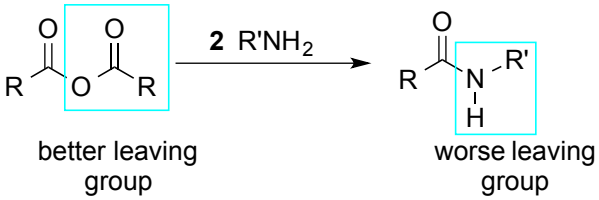
Much as with acid chlorides, this reaction requires two equivalents of amine. One equivalent is sacrificed to acid-base reaction with the acid produced during this transformation.



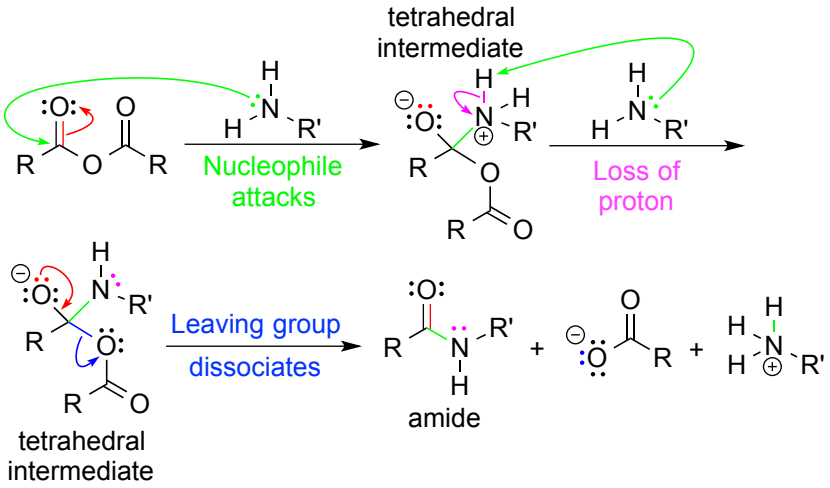
If the amine is expensive or hard to prepare, one equivalent can be used along with one equivalent of pyridine. Pyridine again acts a non-nucleophilic base that reacts with the acid liberated as the reaction progresses, thereby freeing the amine to react with the anhydride and generate the amide product.



Leaving group ability justifies the reaction once again. This reaction was successful because the carboxylate is a better leaving group than that found on the amide (¯NHR').



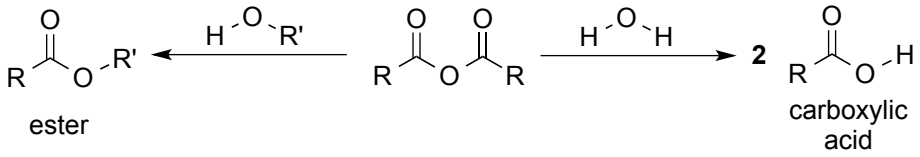
• A final note on mechanistic variations: As discussed in the previous section on reactions of acid chlorides, the order of dissociation of leaving group and loss of proton can be reversed. You will sometimes see either ordering of these two steps. If the last two mechanistic steps are reversed, the tetrahedral intermediate loses a proton to a second molecule of amine prior to the dissociation of the carboxylate. The end result is the same.



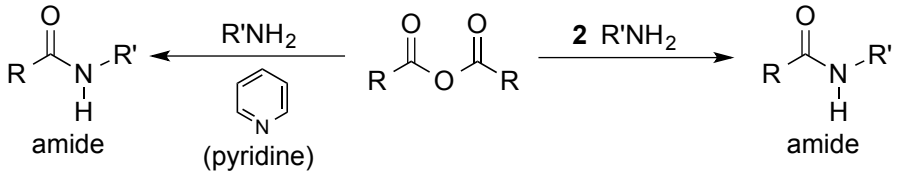
Regiochemical considerations

Symmetrical anhydrides are typically preferred because attack at either carbonyl carbon generates the same product. If an unsymmetrical anhydride is used, multiple products may result. This is usually undesirable because a mixture of products is harder to deal with in the laboratory than a single product would be.

To recap, anhydrides are reactive in a variety of nucleophilic acyl substitution reactions. They can react with water or alcohols to yield carboxylic acids or esters, respectively.

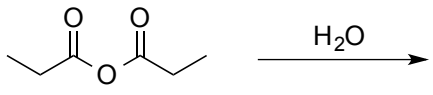


Reaction with amines yields amides. However, the acid produced during this reaction must be trapped by either a sacrificial equivalent of amine or an equivalent of pyridine.

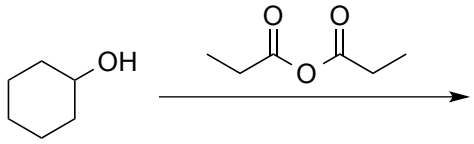


Problem 13. Predict the product for each of the following reactions. If the reactants are favored at equilibrium, state that there is no reaction.

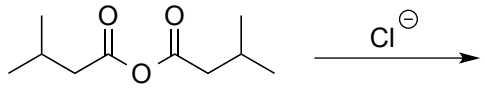
(a)



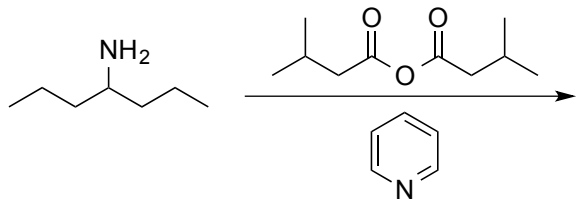
(b)



(c)

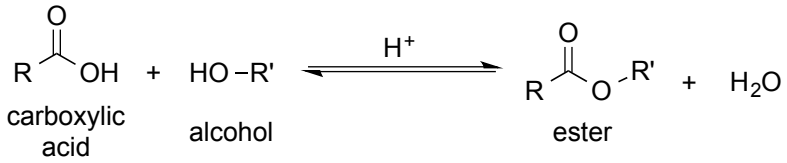


(d)



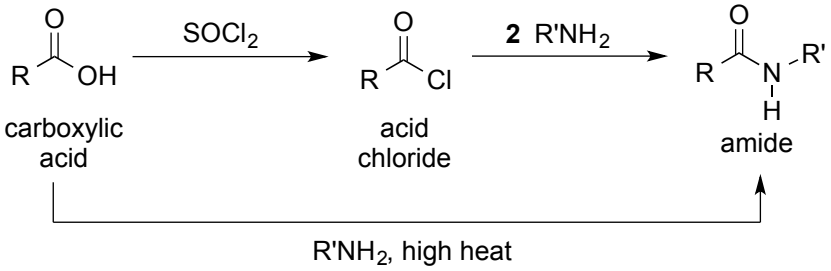
Section 7: Nucleophilic acyl substitution of carboxylic acids

In nucleophilic acyl substitution, carboxylic acids have more limited reactivity than acid chlorides and anhydrides. This is due to the poor leaving group ($^-$OH) on the carbonyl carbon of a carboxylic acid. One prominent reaction of carboxylic acids that circumvents this problem is Fischer esterification. In Fischer esterification, a carboxylic acid and an alcohol are united to form an ester in the presence of catalytic acid.



Carboxylic acids can also be converted to amides by heating to high temperatures with amines. This method is harsh and therefore rarely useful, so it is much more common to convert the carboxylic acid to its acid chloride. The acid chloride then easily reacts with an

amine to form an amide. We learned about both of these transformations in the preceding sections.

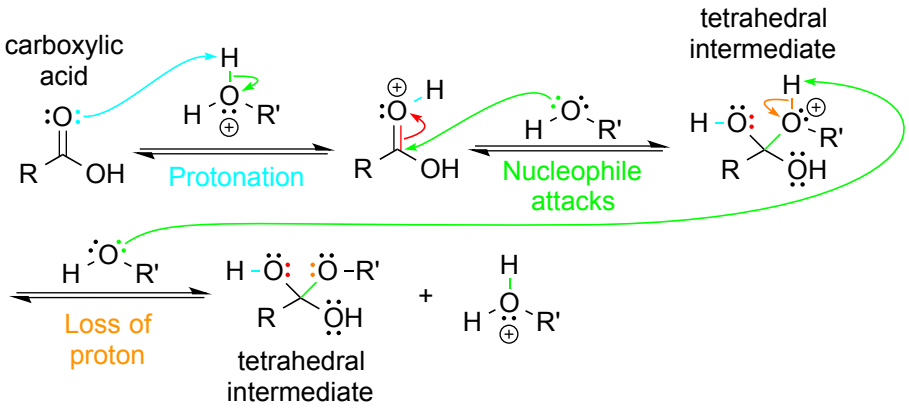


Mechanistic considerations

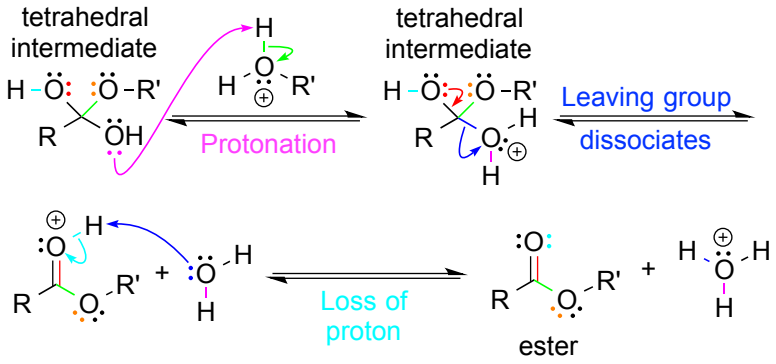
• Fischer esterification begins with the protonation of the carbonyl oxygen. *Protonation always occurs on the carbonyl oxygen (as opposed to the carboxyl oxygen) because the oxonium ion that results is resonance stabilized.*

The proton source can be written in three slightly different ways. The proton source may simply be designated as "H^+". Alternatively, the proton may come from whichever specific acid is added to the mixture (usually H_2SO_4). When sulfuric acid is mixed with an alcohol, the alcohol will be protonated, so you may also see the conjugate acid of the alcohol used as the proton source (as shown below).

Once protonated, the carboxylic acid is more electrophilic at the carbonyl carbon. The alcohol now attacks this center, pushing the π electrons onto oxygen. The first of several tetrahedral intermediates is formed in this way. The oxonium ion of the first tetrahedral intermediate then loses a proton to yield a neutral tetrahedral intermediate.



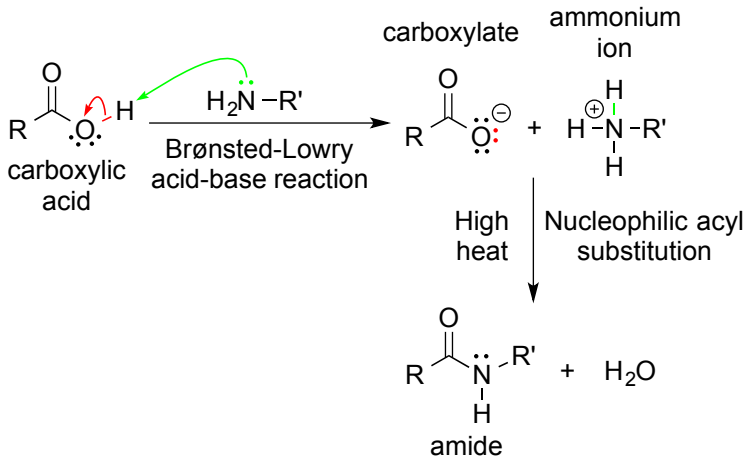
This neutral tetrahedral intermediate could be protonated on any of its three oxygen atoms. Protonation of the alkoxy group would merely be a reversal of the previous step. However, protonation of either hydroxyl group allows the reaction to move forward by generating a new good leaving group (H_2O). Water dissociates as the carbonyl is re-formed. Finally, a proton is shed to yield the neutral ester as the reaction product.



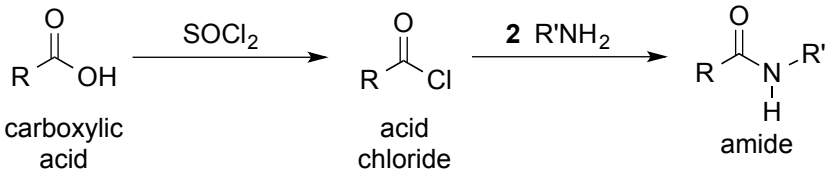
Notice that the acid is catalytic. Although two protons are consumed during the reaction (in the first and fourth steps), two protons are liberated as well (in the third and sixth steps).

Fischer esterification is freely reversible. We'll see the reverse reaction (hydrolysis of an ester) in the next section on the nucleophilic acyl substitution of esters. In this case though, the position of equilibrium is controlled by using excess alcohol to drive the reaction toward the ester. This is an example of using Le Châtelier's principle to push a reaction to completion.

• Conversion of an acid to an amide can be achieved through reaction of a carboxylic acid with an amine; however, this reaction is rarely practical. Since amines are fairly basic and carboxylic acids are acidic, they readily undergo Brønsted-Lowry acid-base reaction. The resulting salt is unreactive in nucleophilic acyl substitution. The negative charge of the carboxylate repels nucleophiles, and the ammonium ion is non-nucleophilic because it lacks a lone pair of electrons. Only through heating at very high temperatures can the reaction be pushed forward through dehydration. This approach is harsh and therefore rarely used.

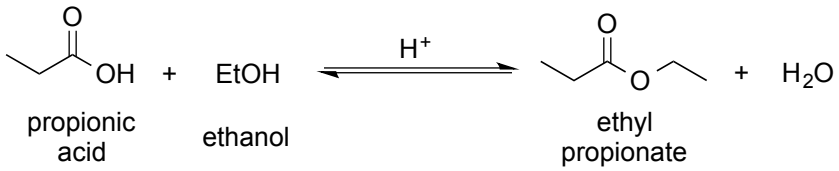


Instead, it is much easier to convert the acid to the acid chloride through treatment with thionyl chloride. The acid chloride then readily reacts with an amine to yield an amide.

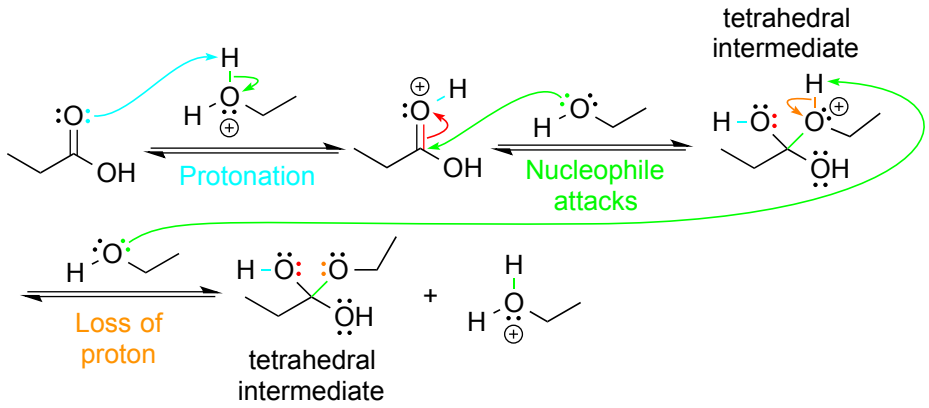


Specific examples of the nucleophilic acyl substitution of carboxylic acids

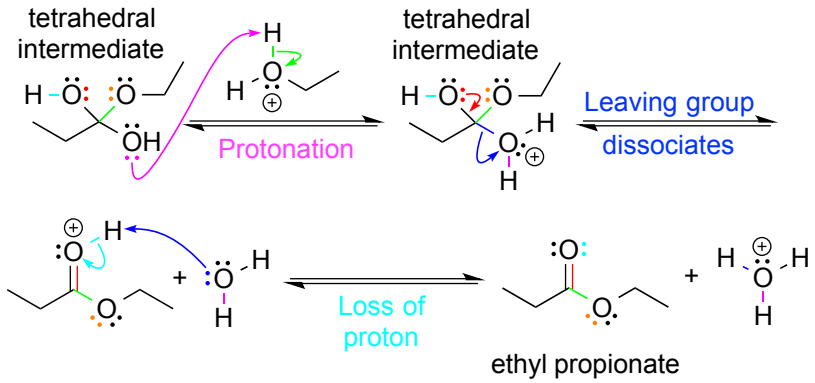
• Fisher esterification: In the following reaction, propionic acid is treated with ethanol in the presence of catalytic acid to produce ethyl propionate.



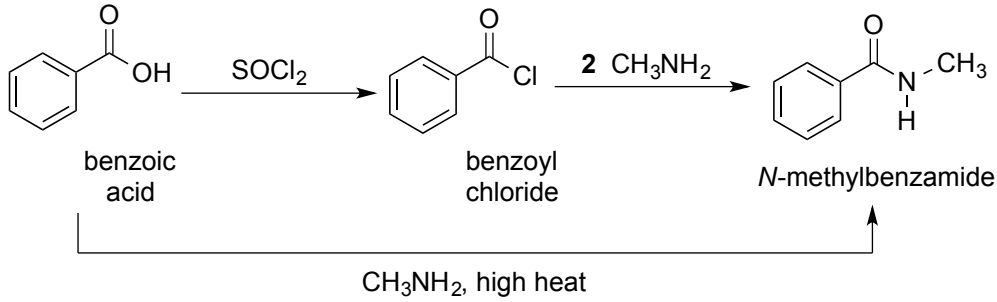
The reaction begins with the protonation of propionic acid by the conjugate acid of ethanol. The electrophilic carbonyl carbon is then attacked by ethanol, which leads to the formation of a tetrahedral intermediate as the π electrons are displaced onto oxygen. Loss of a proton from the oxonium ion neutralizes the charge on the ethoxy group.



The neutral tetrahedral intermediate can be reprotonated on one of its hydroxyl groups. When this happens, water is ejected as the tetrahedral intermediate collapses. Finally, a proton is lost to yield ethyl propionate as the final product.



• Amide formation: When benzoic acid and methylamine (CH_3NH_2) are combined, an acid-base reaction ensues. While high heat can push the reaction toward amide formation through dehydration, an alternative approach is typically preferable. Benzoic acid can be converted to benzoyl chloride through treatment with thionyl chloride. Subsequent reaction with two equivalents of methylamine yields *N*-methylbenzamide.

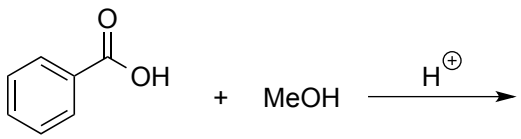


To summarize, carboxylic acids, although less reactive than acid chlorides and anhydrides, can still engage in nucleophilic acyl substitution. In Fischer esterification, a carboxylic acid reacts with an alcohol in the presence of catalytic acid to yield an ester and water. The mechanism follows the nucleophilic acyl substitution motif, and the equilibrium can be pushed toward the ester by using excess alcohol.

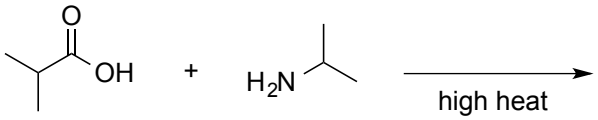
For other conversions of carboxylic acids, the most straightforward method is to convert the acid to its corresponding acid chloride using thionyl chloride. Then, the acid chloride can be converted into any carboxylic acid derivative via nucleophilic acyl substitution.

Problem 14. Identify the products of the following transformations.

(a)



(b)



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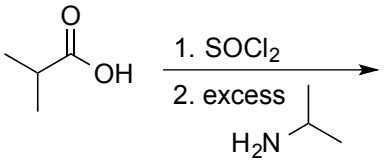
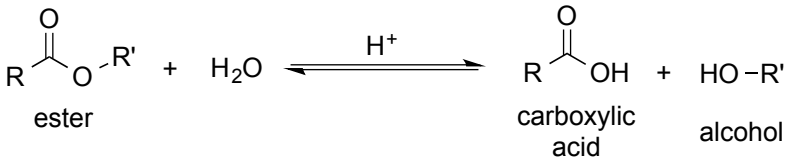


Section 8: Nucleophilic acyl substitution of esters

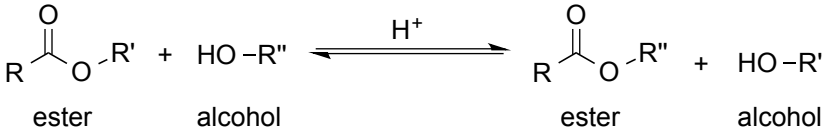
Esters, much like carboxylic acids, have poor leaving groups ($^-$OR) on the carbonyl carbon, so their reactivity in nucleophilic acyl substitution is limited. The principal nucleophilic acyl substitution reactions of esters are hydrolysis (acidic and basic), transesterification (acidic and basic), and aminolysis.

Acid-catalyzed hydrolysis:

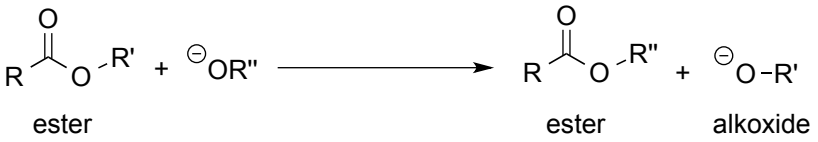


Basic hydrolysis (saponification):

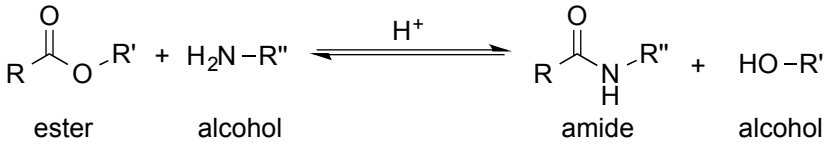
Acid-catalyzed transesterification:



Basic transesterification:



Aminolysis:



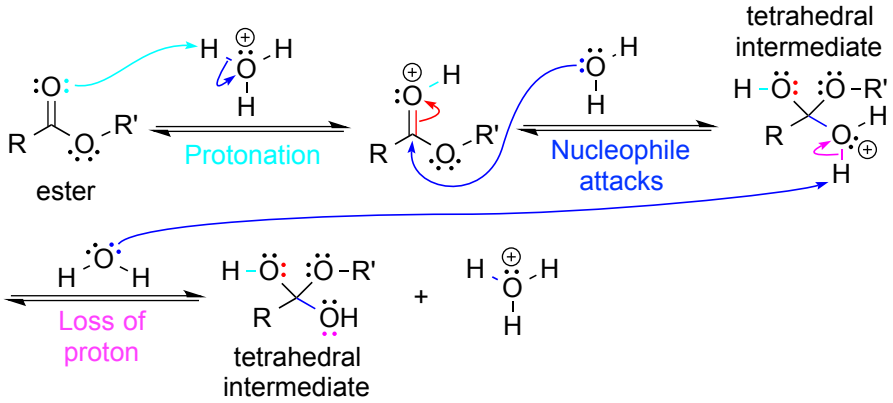
Although this seems like a large number of potential mechanisms, we'll soon see that acid-catalyzed hydrolysis is just the reverse of Fischer esterification and that it is also nearly identical to acid-catalyzed transesterification. Additionally, basic hydrolysis is almost the same as basic transesterification.

Mechanistic considerations

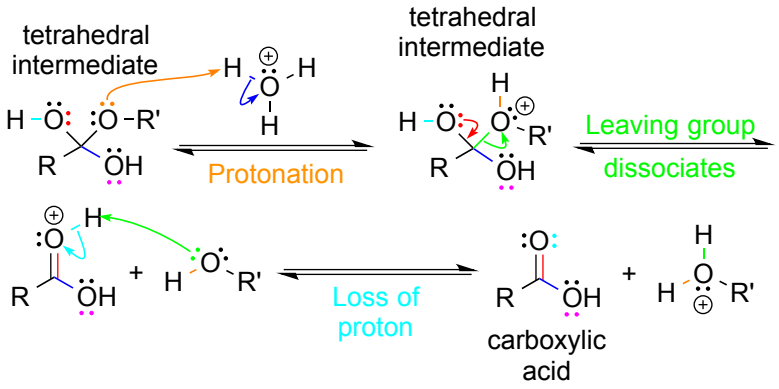
• Acid-catalyzed hydrolysis is merely the reverse of Fischer esterification. An ester is combined with water in the presence of catalytic acid to yield the carboxylic acid and alcohol fragments. Excess water is used to drive this freely reversible process toward the hydrolysis products.

The reaction begins with the protonation of the ester. As with Fischer esterification, the proton source may be written in one of three slightly different ways: H^+, H_2SO_4 (a commonly used acid), or hydronium ion (formed from sulfuric acid in water).

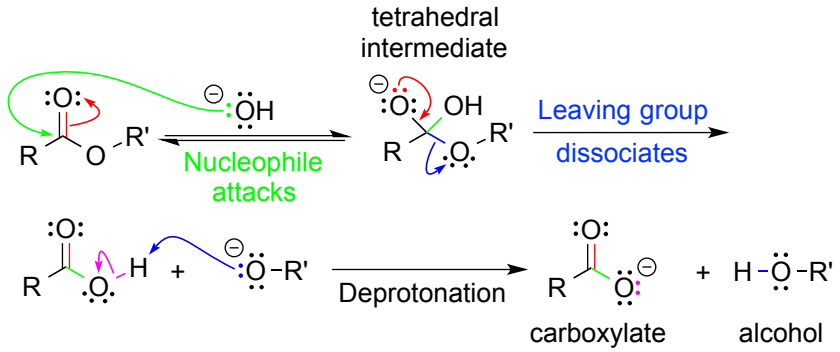
Once protonated, the carbonyl carbon is a great deal more electrophilic. As a result, it is attacked by water, and a tetrahedral intermediate is formed as the carbonyl π electrons are pushed onto oxygen. The oxonium ion then loses a proton, giving a neutral tetrahedral intermediate.



The protonation of this neutral tetrahedral intermediate on the alkoxy group generates a new good leaving group (R′OH). The alcohol then dissociates as the carbonyl π bond re-forms, and the loss of a proton yields the carboxylic acid as the final reaction product.



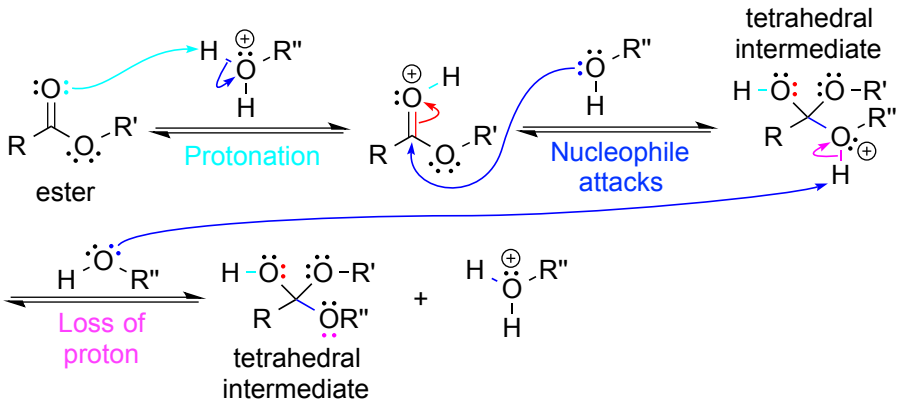
• Basic hydrolysis is also called saponification because it can be used in soap making. In this reaction, hydroxide attacks the carbonyl carbon directly since it is a more powerful nucleophile. The tetrahedral intermediate thus formed collapses to displace either hydroxide or the alkoxide, both of which are comparable leaving groups. When hydroxide is displaced, the reaction reverts to starting material. However, when the alkoxide is displaced, a subsequent acid-base reaction between the carboxylic acid and the basic alkoxide renders the reaction irreversible. This acid-base reaction eventually drives the reaction toward the hydrolysis products.



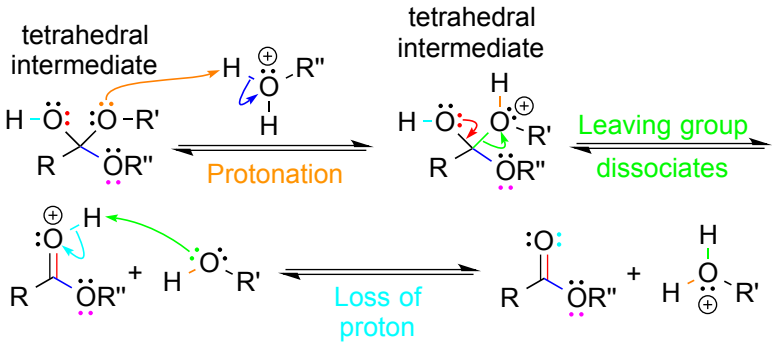
If the carboxylic acid is desired rather than the carboxylate, an acidic workup can be performed to protonate the carboxylate.

• Acid-catalyzed transesterification is nearly identical to acid-catalyzed hydrolysis. The only difference is that the nucleophile is a new alcohol (R"OH) rather than water. This new alcohol can be used in excess to drive the reaction toward a new ester that incorporates the R" group.

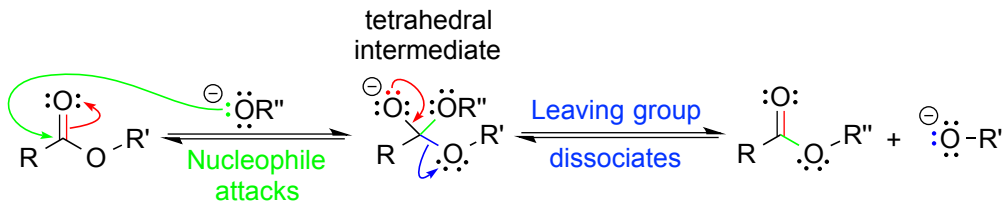
Protonation affords an electrophilic carbonyl. The attack of the new alcohol pushes π electrons onto oxygen and forms a tetrahedral intermediate. Loss of a proton from the oxonium ion then neutralizes the charge on the tetrahedral intermediate.



This neutral tetrahedral intermediate can be protonated on any of its oxygen atoms. When it is protonated on the alkoxy group bearing R', the reaction can move forward. Loss of the original alcohol moiety (R'OH) as the carbonyl re-forms is followed by loss of a proton to generate the new ester.

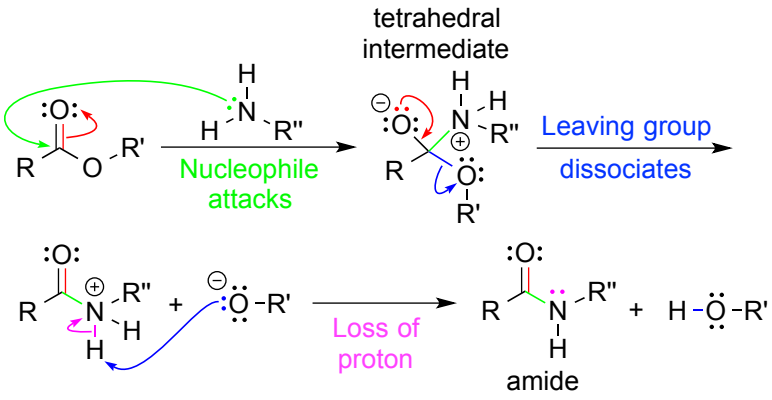


• Basic transesterification is very similar to saponification (basic hydrolysis). The new alkoxide ($R''O^-$) attacks the carbonyl carbon. The tetrahedral intermediate can collapse to displace either of the two comparable leaving groups, $R'O^-$ or $R''O^-$. Unlike basic hydrolysis, no acid-base reaction is possible at this stage, so the equilibrium must be driven using an excess of the new alkoxide ($R''O^-$).

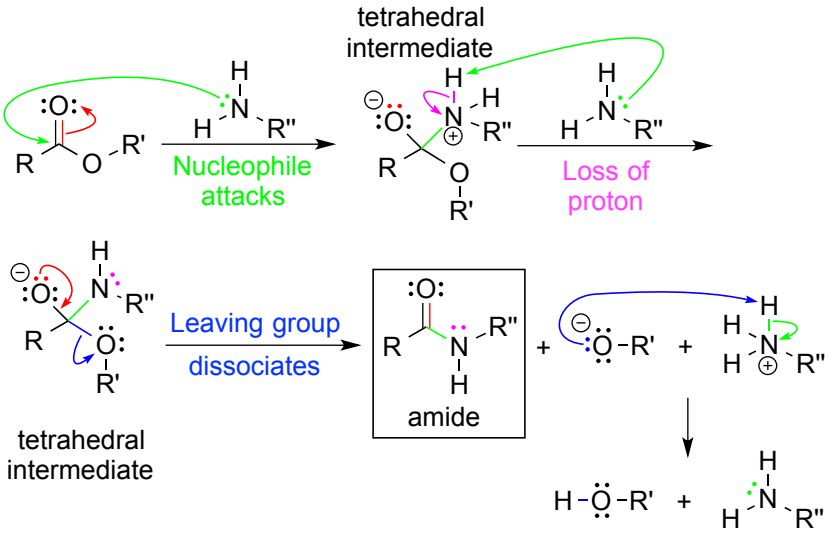


• Aminolysis is the cleavage of an ester using an amine. Ammonia (NH_3), a primary amine ($R''NH_2$), or a secondary amine (R''_2NH) could be used. The following example uses a

primary amine, which attacks the carbonyl to form a tetrahedral intermediate. The collapse of the tetrahedral intermediate displaces the alkoxide, which then readily removes a proton from nitrogen. The neutral amide results as the final product.

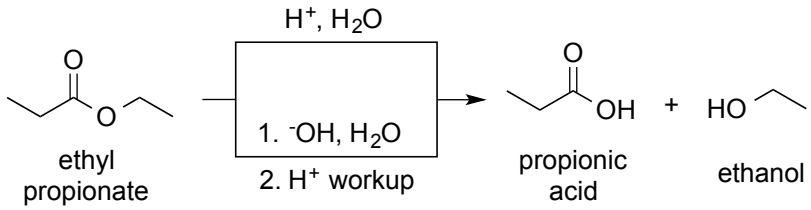


An alternate version of this mechanism is also encountered. In the alternate version, the order of the last two steps is reversed. The tetrahedral intermediate can lose a proton to another amine molecule. Then the alkoxide, although not a very good leaving group, is clearly a better leaving group than ¯NHR" would be. As the alkoxide dissociates, the carbonyl re-forms. The amide is the product of interest, but we can also note that the displaced alkoxide will remove a proton from the conjugate acid of the amine that was formed during the second step of this mechanism.

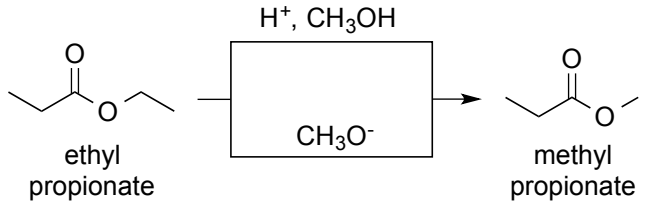


Specific examples of the nucleophilic acyl substitution of esters

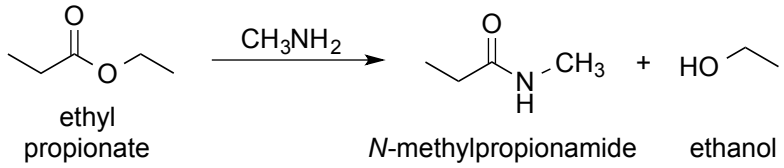
In the following two examples, ethyl propionate is hydrolyzed to yield propionic acid and ethanol. This can be achieved with aqueous acid. Alternatively, aqueous base can be used, followed by an acidic workup to protonate the carboxylate formed under these conditions.



In the next two examples, ethyl propionate is transesterified to produce methyl propionate. This can be accomplished with methanol and acid catalysis or with methoxide (CH_3O^-). In the first instance, ethanol would be liberated, but in the second, ethoxide ($CH_3CH_2O^-$) would be the other reaction product.



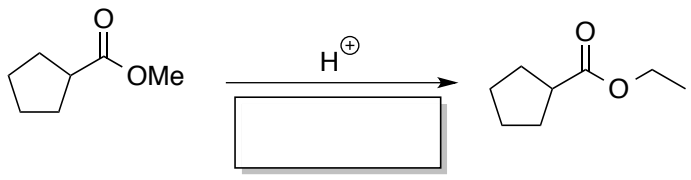
In the last example, aminolysis of ethyl propionate with methylamine yields *N*-methylpropionamide and ethanol.



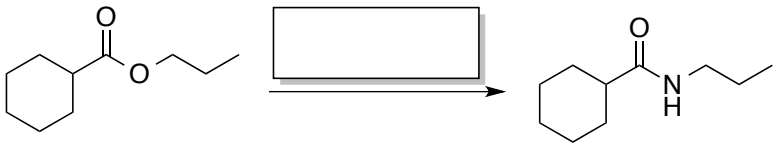
In conclusion, esters, like carboxylic acids, have a fairly poor leaving group bonded to the carbonyl carbon. As a result, their nucleophilic acyl substitution reactions are limited to hydrolysis, transesterification, and aminolysis. Both hydrolysis and transesterification can be conducted under acidic or basic conditions.

Problem 15. Fill in the missing reactants or reagents needed to achieve the following transformations.

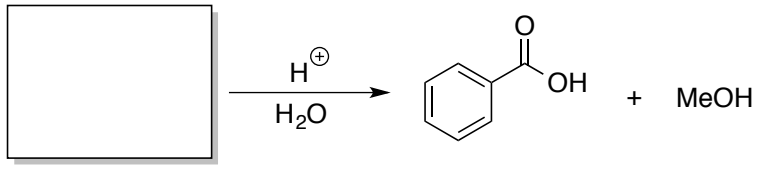
(a)



(b)



(c)



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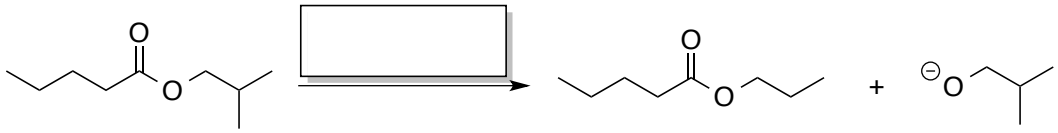
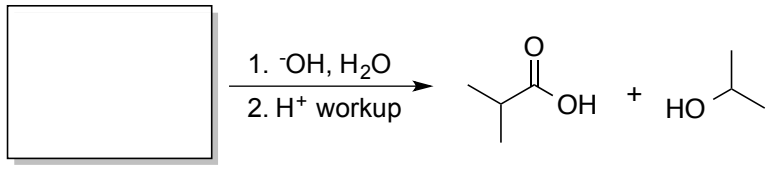


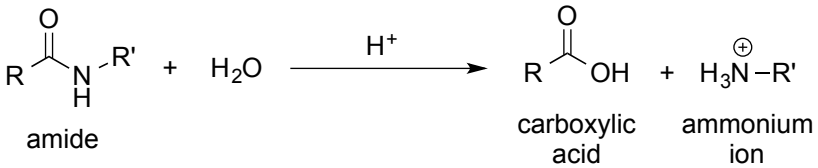
(e)



Section 9: Nucleophilic acyl substitution of amides

Of all the carboxylic acid derivatives, amides have the worst leaving group bonded to the carbonyl carbon. Consequently, amides have the most limited reactivity in nucleophilic acyl substitution. Their principal reaction is hydrolysis, which can be achieved in aqueous acid or base. This reaction typically requires strong acid or base, along with heating.

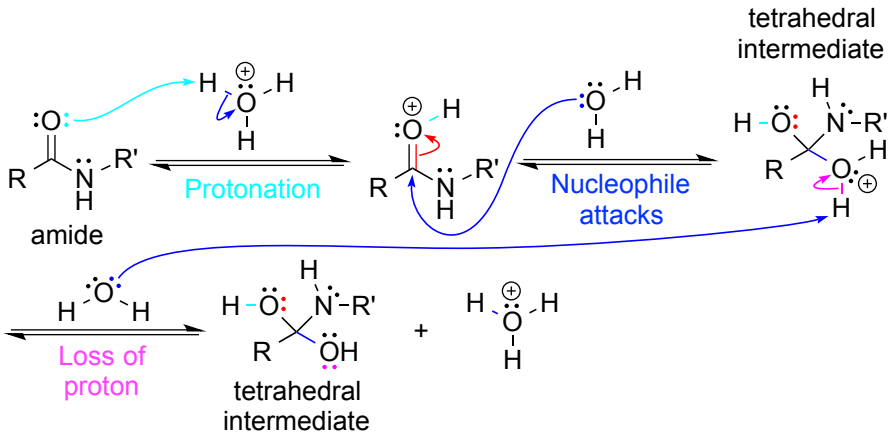
Acidic hydrolysis:



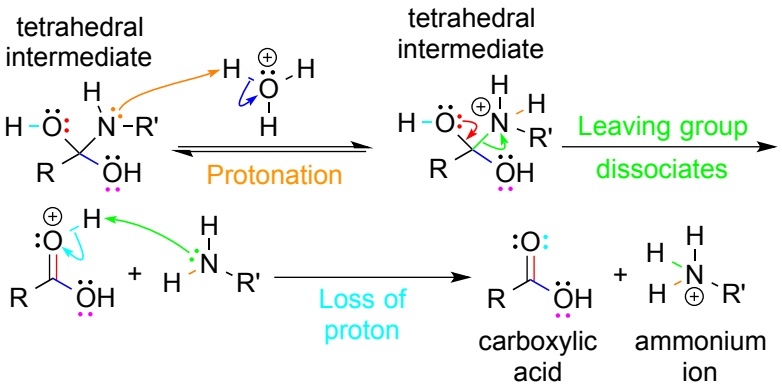
Basic hydrolysis:

Mechanistic considerations

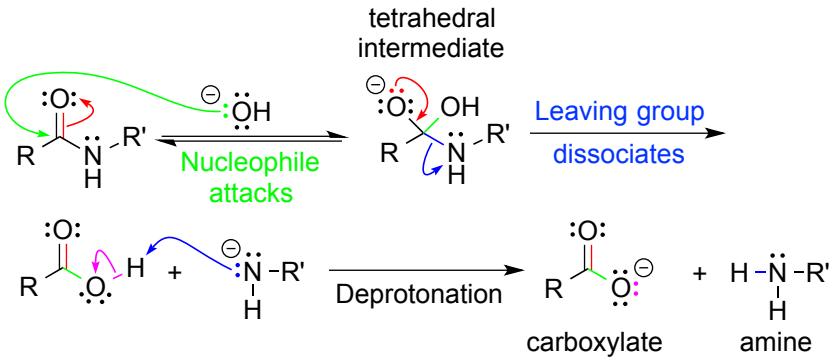
• Acidic hydrolysis begins with the protonation of the carbonyl oxygen. Although it might be tempting to protonate the nitrogen instead, *the carbonyl oxygen is always the correct location for protonation because it leads to a resonance-stabilized cation*. With the electrophilicity of the carbonyl carbon thus enhanced, water attacks and pushes the π electrons onto oxygen. A tetrahedral intermediate results, and it sheds a proton to neutralize the charge on the oxonium ion.



The neutral tetrahedral intermediate can be protonated on either hydroxyl group or on the amino group. When protonation occurs on the hydroxyl groups, the tetrahedral intermediate reverts to reactants. On the other hand, protonation on the amino group makes it a good leaving group. This allows the reaction to move forward as the amine dissociates upon collapse of the tetrahedral intermediate. The amine, once liberated, will readily become protonated. This renders it non-nucleophilic, so at this point, a reversal of the reaction is improbable.

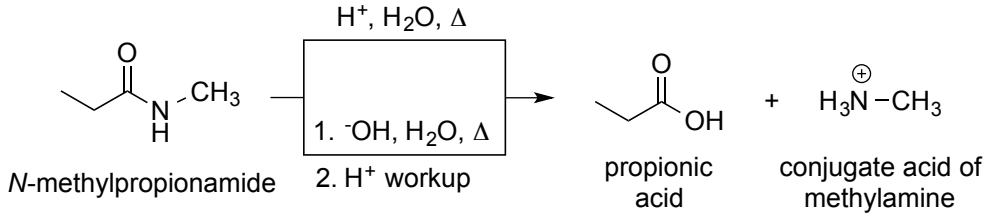


• Basic hydrolysis starts with the direct attack of hydroxide on the carbonyl carbon. Since hydroxide is a more powerful nucleophile than water, no prior activation of the carbonyl is necessary. The tetrahedral intermediate thus formed will collapse. Most of the time, the collapse will be accompanied by the dissociation of hydroxide, which is the better leaving group. This will cause the reaction to go backwards (toward the reactants). However, occasionally the amino group will be displaced. When this happens, the very strong base ($^-$NHR') will immediately remove a proton from the carboxylic acid. This acid-base reaction is very favorable, and it renders the process irreversible because: (1) the carboxylate is now shielded from nucleophiles by its negative charge and (2) the neutral amine also has significantly reduced nucleophilicity (as compared to its anionic form). As a result of the essentially irreversible final step, the equilibrium eventually shifts toward the products.



A specific example of the nucleophilic acyl substitution of amides

In the following examples, *N*-methylpropionamide is hydrolyzed. When aqueous acid is used, the products are propionic acid and the conjugate acid of methylamine. When aqueous base is used, the immediate products would be the carboxylate and the neutral amine. However, the carboxylic acid is often the product of interest in such reactions, so it is common to employ an acidic workup to provide the carboxylic acid, as well as the conjugate acid of methylamine.

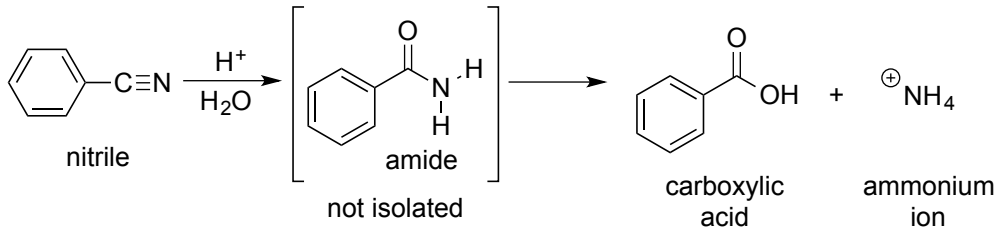


To recap, amides, although they have limited reactivity in nucleophilic acyl substitution, are subject to hydrolysis upon heating with strong aqueous acid or strong aqueous base.

In aqueous acid, the amide is cleaved into a carboxylic acid and the protonated form of an amine. In aqueous base, the initial cleavage products are the carboxylate and the amine;

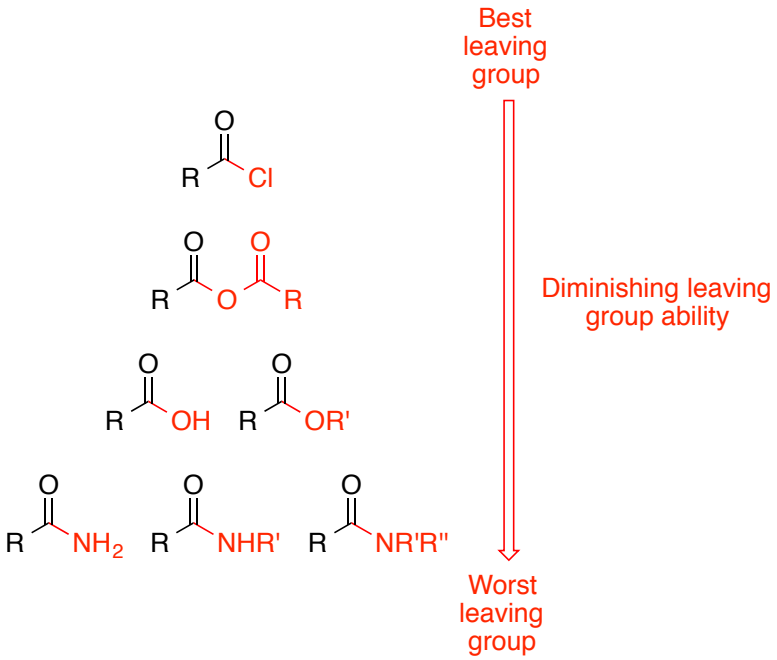
however, an acidic workup will also provide the carboxylic acid and the protonated form of the amine.

Problem 16. Later in this chapter, we'll learn about the hydrolysis of nitriles. We'll see that nitriles are first hydrated to give amides, and that those amides are then hydrolyzed to yield carboxylic acids under the conditions used for the reaction. Provide a mechanism for the second half of the reaction below (i.e., the hydrolysis of the amide).



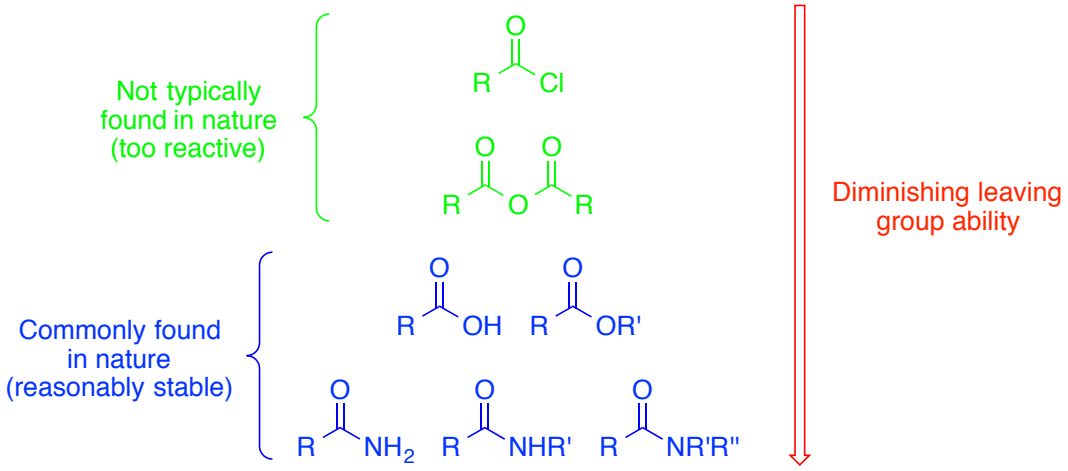
Section 10: Summary of nucleophilic acyl substitution

We've seen quite a number of nucleophilic acyl substitution reactions in the preceding sections. Organizing all of this knowledge may seem overwhelming at first. One of the most efficient ways of conceptualizing this topic is by ranking the leaving groups of the various carboxylic acid derivatives. Acid chlorides have the best (i.e., most stable) leaving group. Anhydrides also have fairly good leaving groups; however, their carboxylate leaving groups are not quite as good as chloride. Acids and esters have fairly poor leaving groups (hydroxide or alkoxides, respectively), and amides have quite poor leaving groups.



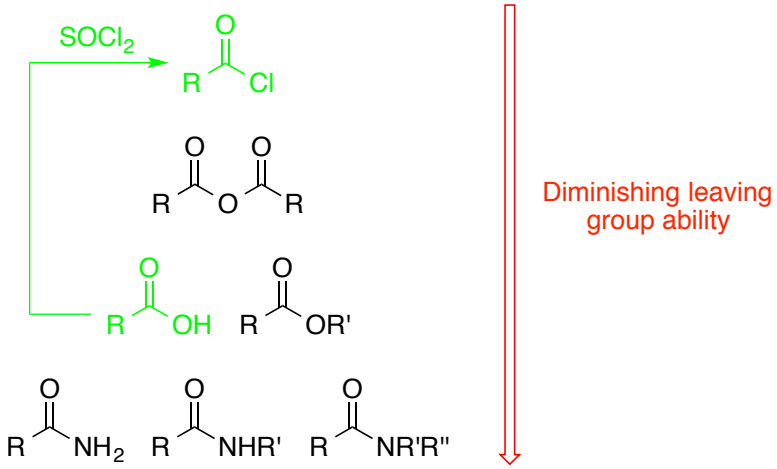
The two most reactive carboxylic acid derivatives are those with the best leaving groups: acid chlorides and anhydrides. In fact, these compounds are so reactive that they can

undergo spontaneous hydrolysis in the presence of water. As a result, acid chlorides and anhydrides are not typically found in natural products (i.e., those compounds that naturally occur in living systems). The water that is present in living organisms would lead to the spontaneous hydrolysis of such functional groups. However, esters and amides, which have poor leaving groups, are reasonably stable. They can be hydrolyzed, but their hydrolysis requires acidic or basic conditions. Consequently, they are stable enough to be found in natural products.



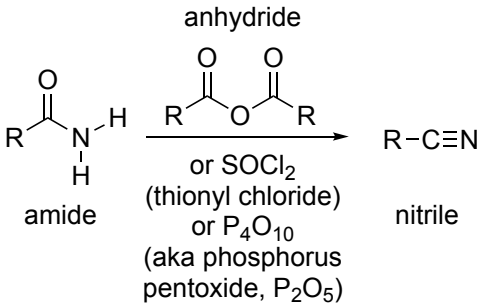
From a synthetic standpoint, it is easiest to move down this "reactivity ladder." In other words, any carboxylic acid derivative can be made from an acid chloride. Acid chlorides can be directly and easily transformed into anhydrides, acids, esters, and amides. As you move down the ladder, the options become more limited. Anhydrides can be converted into acids, esters, and amides, but they cannot be converted into acid chlorides. Acids can be converted into esters or amides, although the conversion to amides requires harsh conditions. Esters can be converted into acids or amides. Finally, amides can only be hydrolyzed to acids using strongly acidic or basic conditions.

Due to the continually decreasing synthetic options as you move down the reactivity ladder, it is common for acids to be converted to acid chlorides using thionyl chloride. Carboxylic acids are among the most widely available of these compounds, so they are common substrates. Since their reactivity is limited, conversion to the acid chloride opens up a great many possibilities.



Section 11: Dehydration of amides

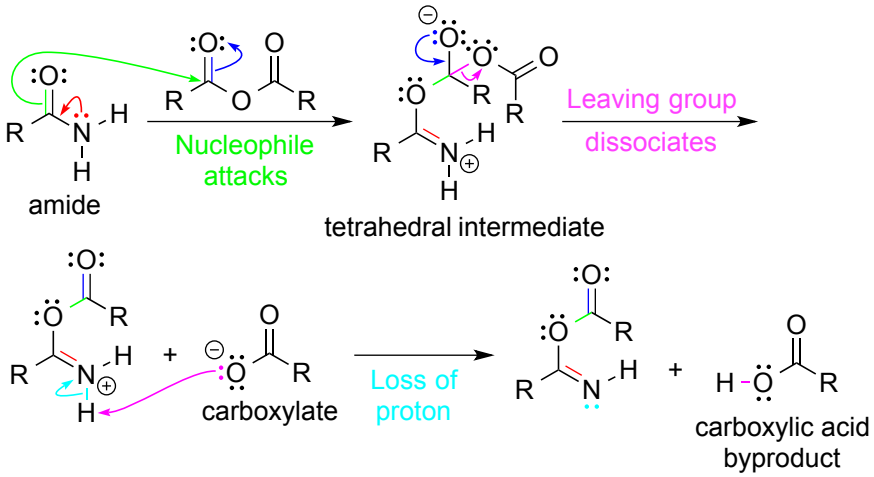
Primary amides (those bearing two hydrogens on nitrogen) can be dehydrated to yield nitriles through exposure to one of several reagents. The dehydrating agent may be an anhydride, thionyl chloride, or phosphorus pentoxide. The mechanisms for two of the three methods follow.



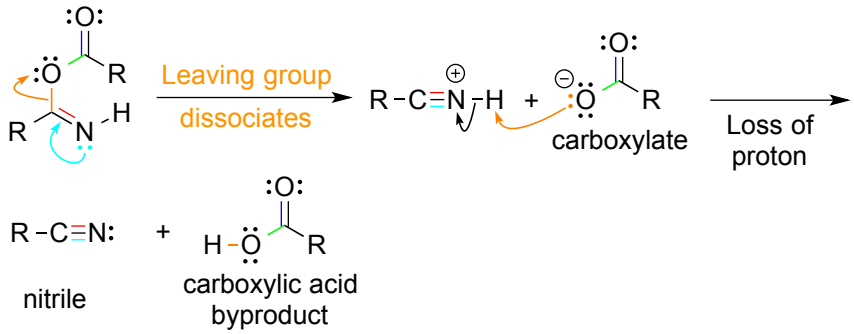
Mechanistic considerations

• Dehydration using an anhydride begins with the attack of the amide on one of the two carbonyl carbons of the anhydride. Much like protonation occurs on the carbonyl oxygen, addition of the electrophile occurs on the carbonyl oxygen as well because the resulting positive charge on nitrogen is resonance stabilized.

This step amounts to the beginning of a nucleophilic acyl substitution on the anhydride. The anhydride has simply been treated with a nucleophile that we have not used before. As such, a tetrahedral intermediate results. The loss of the carboxylate occurs as the tetrahedral intermediate collapses, and the displaced carboxylate then acquires the proton lost from the positive nitrogen.

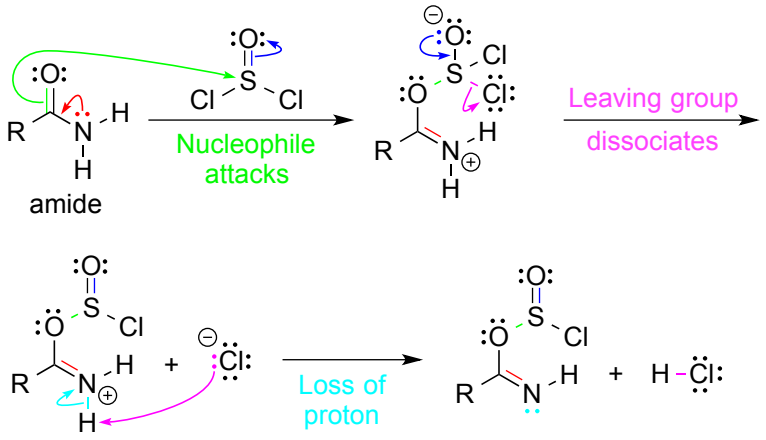


The first three steps of the mechanism have converted the carbonyl oxygen into a good leaving group. This second carboxylate now dissociates as the third bond of the nitrile functional group is formed. The displaced carboxylate again acquires the proton lost from nitrogen. The nitrile is the ultimate reaction product, and it is accompanied by two molecules of carboxylic acid as byproducts.

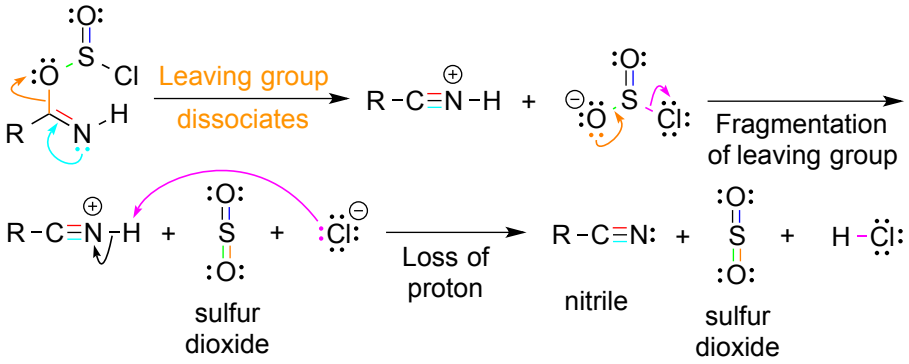


• Dehydration using thionyl chloride follows the same general motif. The basic strategy of both dehydration mechanisms is to convert the carbonyl oxygen into a good leaving group as the π bonds of the nitrile are formed through sequential loss of protons from nitrogen.

In this reaction, the first step also entails the attack of the nucleophilic amide carbonyl oxygen on an electrophile. This time the electrophile is the electron-poor sulfur atom of thionyl chloride. A compound akin to a tetrahedral intermediate is formed, and it then collapses, displacing chloride. A proton is lost from nitrogen to complete the first phase of the mechanism.

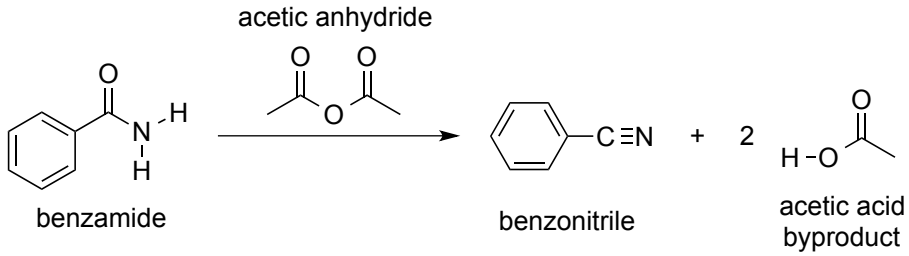


Now that the carbonyl oxygen has been converted to a good leaving group, it dissociates as the third bond of the nitrile is formed. It might be useful to compare this to the reaction of carboxylic acids with thionyl chloride, in which an oxygen atom is also converted into a good leaving group by $SOCl_2$. Finally, the leaving group fragments into sulfur dioxide and chloride, which removes a proton from the substrate to yield the nitrile.



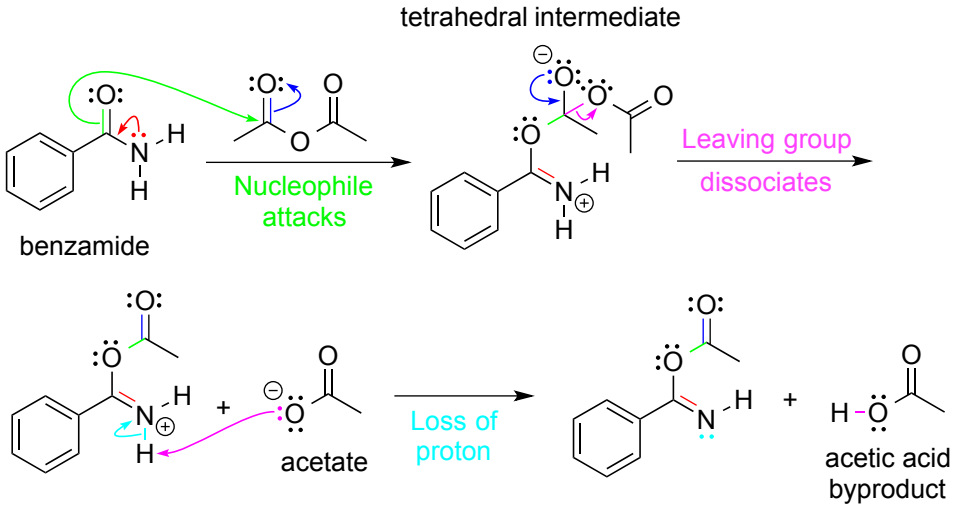
A specific example of the dehydration of amides

In the following example, benzamide is converted into benzonitrile by treatment with acetic anhydride.

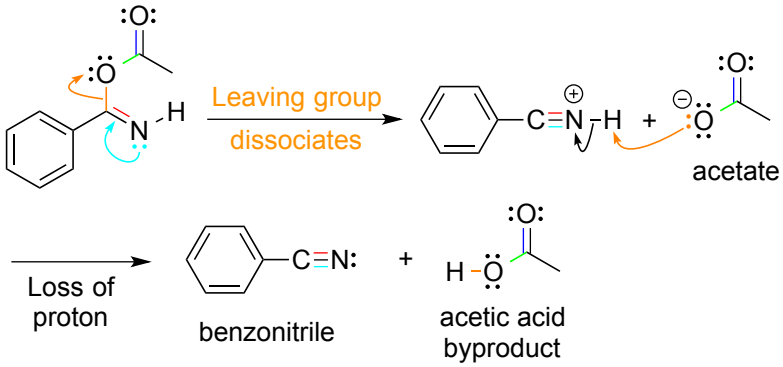


The reaction begins with the attack of benzamide's nucleophilic carbonyl oxygen on either of the two identical carbonyl carbons of acetic anhydride. This pushes the π electrons onto oxygen, forming a tetrahedral intermediate. The tetrahedral intermediate then collapses

and forces acetate off of the molecule as a leaving group. Nitrogen loses a proton to acetate to complete the first half of the mechanism.



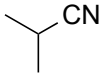
In the last half of the mechanism, the carbonyl oxygen dissociates as part of acetate (a good leaving group), and the positive nitrogen sheds a proton to afford benzonitrile.



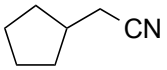
In summary, primary amides [$RC(O)NH_2$] can be dehydrated to generate nitriles. This can be accomplished using an anhydride, thionyl chloride, or phosphorus pentoxide. The mechanism entails the conversion of the carbonyl oxygen into a good leaving group as successive hydrogens are lost from nitrogen to form the π bonds of the nitrile.

Problem 17. Provide the structure of the amide that could be dehydrated to prepare each of the following nitriles.

(a)

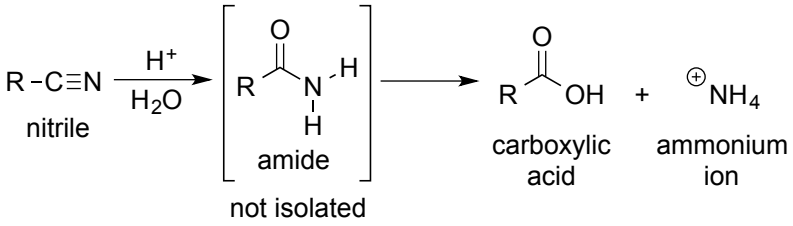


(b)

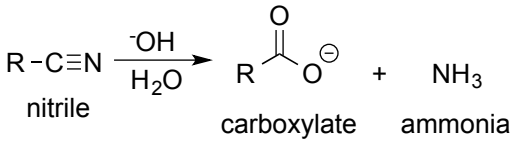


Section 12: Nitrile hydrolysis

In the previous section, we saw that amides can be dehydrated to yield nitriles. A nitrile can be hydrolyzed in strong acid or strong base to yield a carboxylic acid. In the case of acidic hydrolysis, this reaction proceeds via the amide, but the amide is not typically isolated.

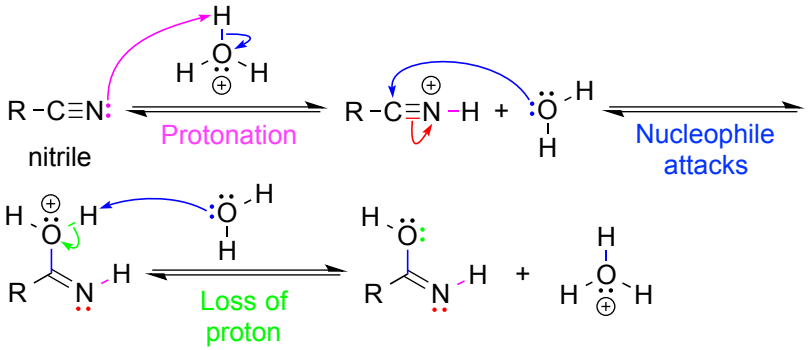


In the case of basic hydrolysis, the carboxylate is produced in the alkaline medium used for the reaction. However, an acidic workup could be used to provide the neutral carboxylic acid if desired.



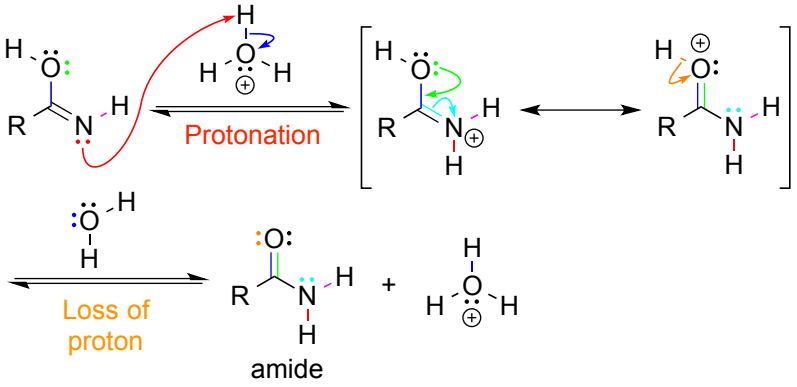
Mechanistic considerations

• In strong acid, a nitrile will be protonated on nitrogen. This enhances the electrophilicity of the adjacent carbon, which is subsequently attacked by water. The oxonium ion thus formed sheds a proton to yield a neutral intermediate.

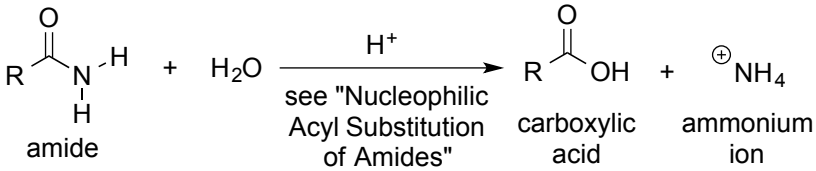


This neutral intermediate happens to be the tautomer of an amide. Tautomers are constitutional isomers that can readily interconvert, in this case through the relocation of a single proton, which is accompanied by the migration of a π bond as well. In acid,

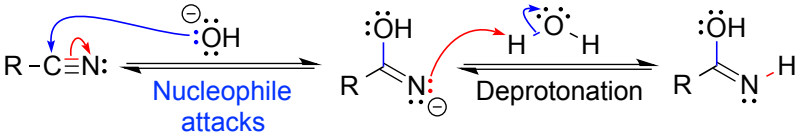
tautomerization occurs via protonation on nitrogen. The cation that results is resonance stabilized and loses a proton from oxygen to afford the amide.



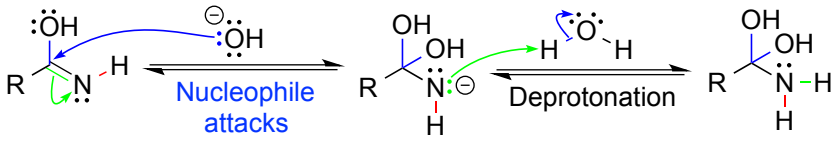
The amide, however, is not usually the product of this reaction. Under strongly acidic conditions, it *cannot* be isolated because hydrolysis follows.



• Nitriles can also be hydrolyzed in strong base. Under these conditions, hydroxide directly attacks the nitrile carbon, pushing π electrons onto nitrogen. The resulting anion then deprotonates water. Notice that the intermediate thus formed is again the tautomer of an amide.

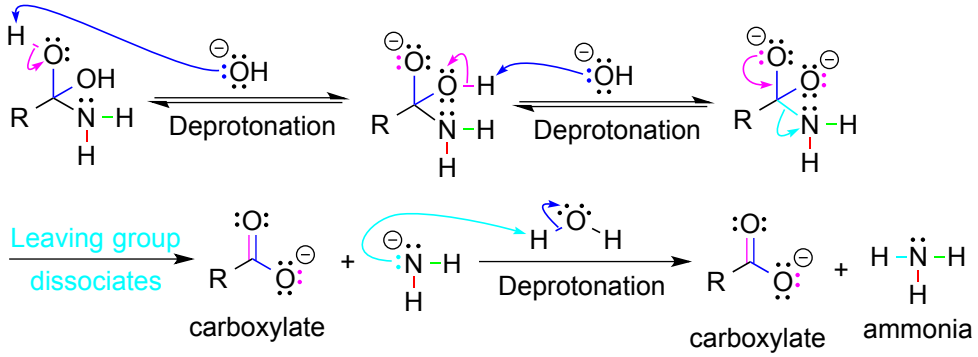


We may tautomerize to form the amide, and then proceed with basic hydrolysis of that amide, or the tautomer shown can be attacked again by hydroxide, displacing another pair of π electrons onto nitrogen. The anion is neutralized through acid-base reaction with water.



This tetrahedral intermediate is deprotonated twice under the strongly basic conditions needed for this reaction. Both hydroxyl groups lose a proton in the process. At this point, neither oxygen can serve as a leaving group because O^{2-} would be too high in energy.

Instead, amide ($^-NH_2$) is displaced as a leaving group. Although it is a poor leaving group, there is no other choice. Amide rapidly removes a proton from water to yield ammonia as a byproduct. The carboxylate is the organic product of this reaction.

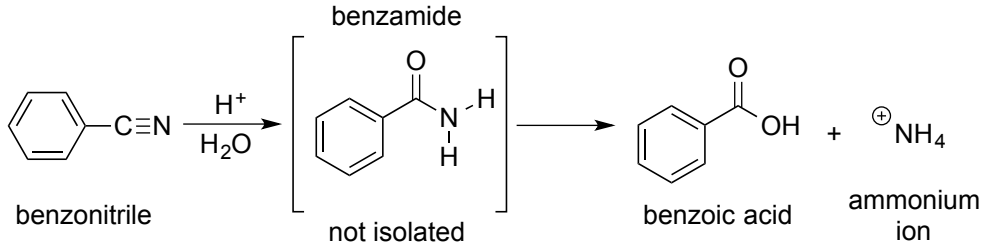


A note on nomenclature

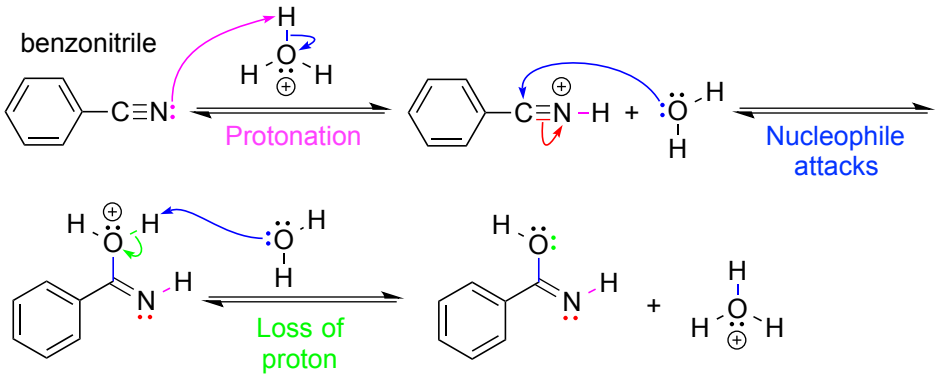
"Amide" has two meanings. In the paragraph above "amide" is used to refer to the conjugate base of ammonia ($^-NH_2$). "Amide" of course also denotes a particular carboxylic acid derivative [e.g., $RC(O)NH_2$]. However, in this instance, the former definition is the one of interest.

Specific examples of nitrile hydrolysis

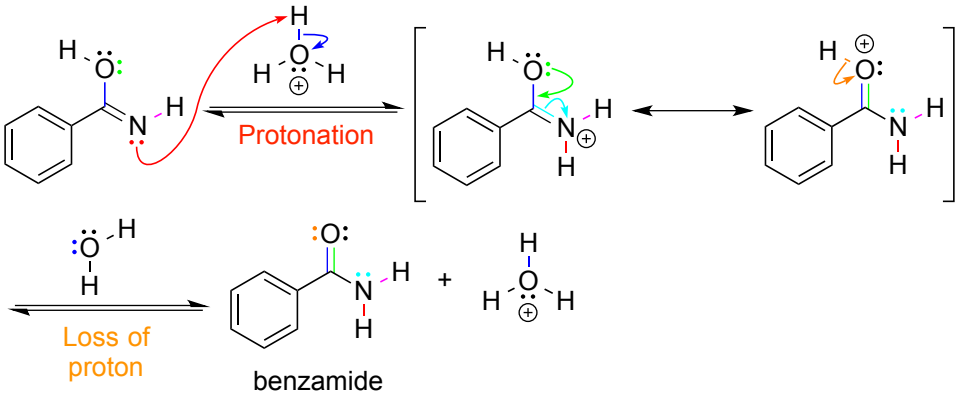
• In the following example, benzonitrile is hydrolyzed in strong acid to afford benzoic acid via benzamide as an intermediate.



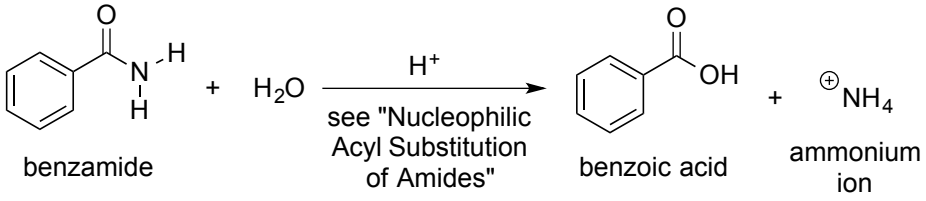
The reaction begins with the protonation of the nitrile, followed by attack of water on the nitrile carbon. The resultant oxonium ion loses a proton to yield the tautomer of an amide.



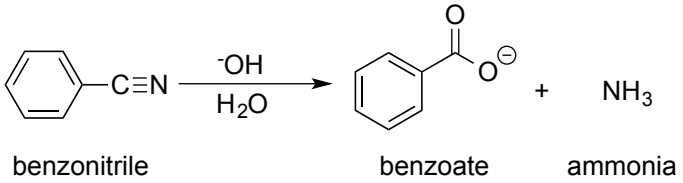
Tautomerization in acid proceeds through protonation of nitrogen to yield a resonance-stabilized cation. When this cation sheds a proton from oxygen, benzamide results.



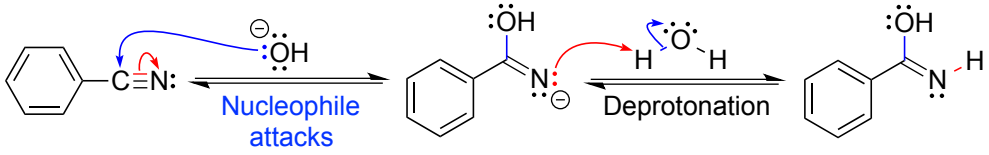
Benzamide is then hydrolyzed to yield benzoic acid and the ammonium ion as the final reaction products.



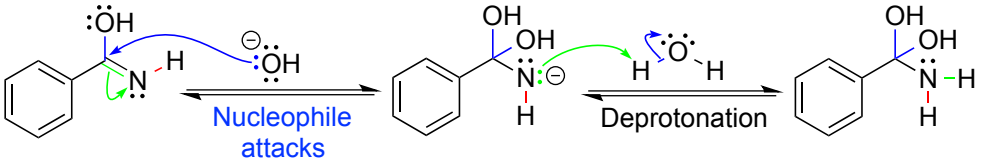
On the other hand, benzonitrile can also be hydrolyzed in base. Benzoate and ammonia are the reaction products under these conditions. However, if benzoic acid is desired, an acidic workup can be performed.



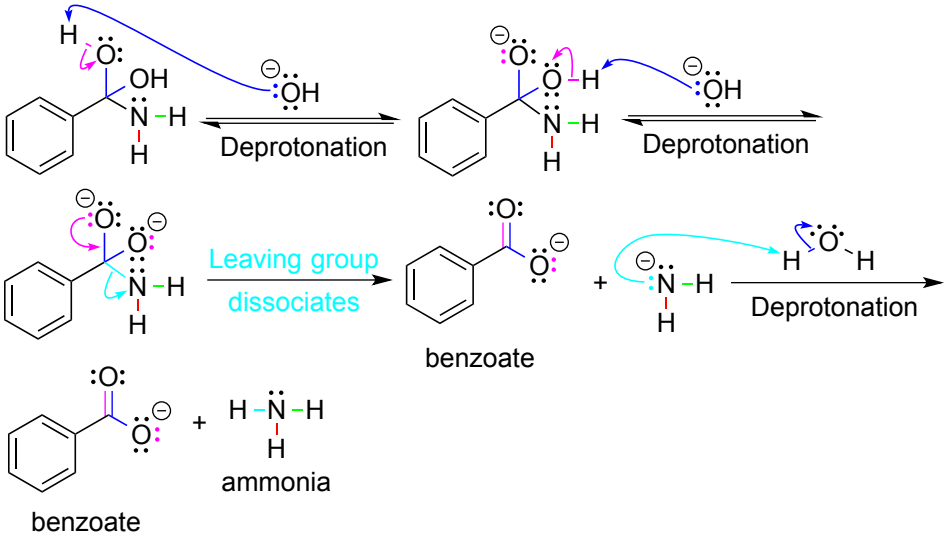
This reaction begins with the attack of hydroxide on the nitrile carbon. A π bond is displaced onto nitrogen, and the anion is neutralized by removing a proton from water.



The tautomer of an amide results. We could tautomerize this to the amide and consider the basic hydrolysis of that amide. Alternatively, we can consider the attack of a second hydroxide ion on this tautomer. The resulting anion deprotonates water to yield a tetrahedral intermediate.

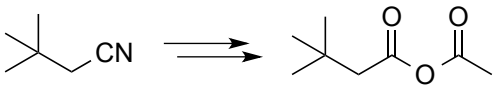


The tetrahedral intermediate can be deprotonated twice in strong base. When this happens, there is only one reasonable leaving group (albeit a poor one). Amide ($^-NH_2$) dissociates as the tetrahedral intermediate collapses to form benzoate. Amide is then neutralized when it removes a proton from water.



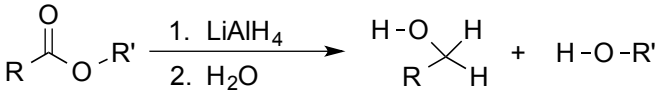
In conclusion, nitriles can be hydrolyzed in strong acid or base. Both reactions proceed through the amide (or its tautomer); however, the amide is not typically isolated. Instead, it is hydrolyzed to afford the carboxylic acid (or carboxylate) as the final reaction product.

Problem 18. Using your knowledge of nitrile hydrolysis, show how it would be possible to achieve the following conversion in three steps.

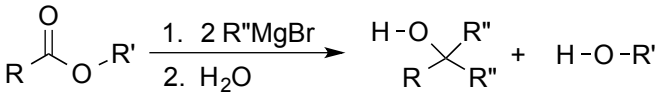


Section 13: Reactions of carboxylic acid derivatives with lithium aluminum hydride or Grignard reagents

We've seen previously that aldehydes and ketones can react with reducing agents (e.g., $NaBH_4$ and $LiAlH_4$) or Grignard reagents. Carboxylic acid derivatives can also engage in some of these reactions. Sodium borohydride ($NaBH_4$) is too weak of a hydride source to reduce carboxylic acid derivatives. However, lithium aluminum hydride ($LiAlH_4$, also abbreviated as LAH) is a strong hydride donor and can reduce these compounds. For example, esters may be reduced to alcohols by treatment with LAH.



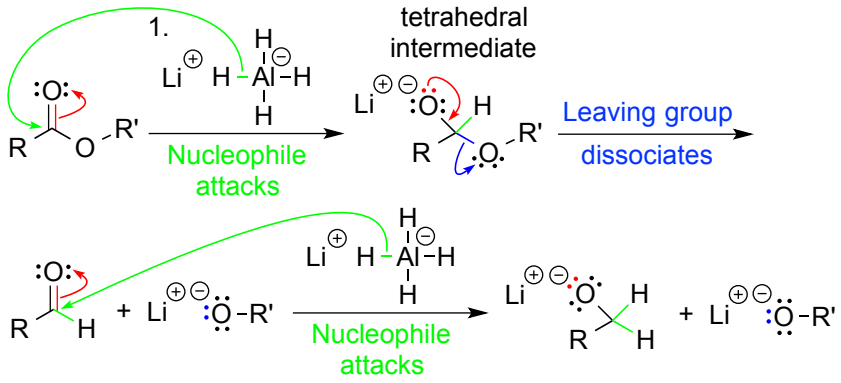
The reaction with Grignard (or organolithium) reagents is very similar. Instead of adding two equivalents of hydride to the carbonyl carbon, two equivalents of a carbanion are added to the carbonyl carbon. This yields a tertiary alcohol with two identical alkyl groups (R").



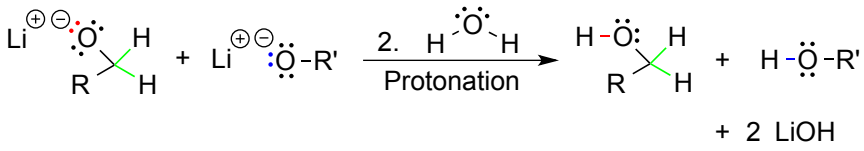
Mechanistic considerations

• The reduction of esters with LAH begins with the nucleophilic attack of hydride on the carbonyl carbon. For a review of why the hydride is nucleophilic, you may wish to refer back to the previous chapter. During the nucleophilic attack, the π electrons are displaced onto oxygen, thereby forming a tetrahedral intermediate. The collapse of the tetrahedral intermediate expels an alkoxide ($^-OR'$) and yields an aldehyde.

The aldehyde is not, however, the final reaction product because it can be further reduced by LAH, as we learned in the last chapter. The addition of a second hydride to the carbonyl creates a tetrahedral intermediate that has no reasonable leaving groups and therefore must simply persist until workup.



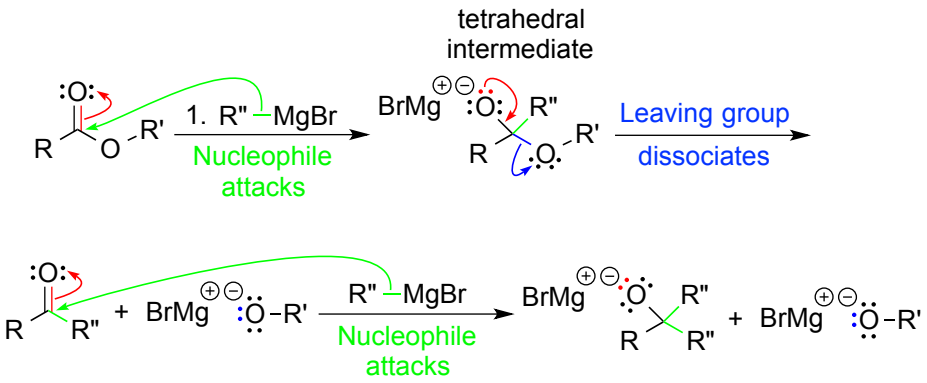
The workup involves adding either water or aqueous acid. In either case, both alkoxides are protonated yielding two alcohols (RCH_2OH and R'OH) as the final reaction products.



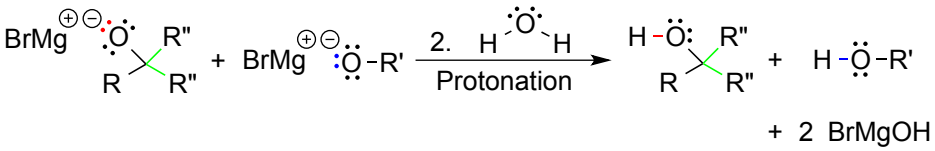
• The reaction of esters with Grignard reagents is nearly identical. The only difference is that, instead of adding hydride to the carbonyl carbon, a carbanion is added to the carbonyl carbon. For a review of why Grignard reagents act like carbanions, refer back to the previous chapter.

The reaction begins with the nucleophilic attack of the Grignard reagent on the carbonyl carbon. The π electrons are pushed onto oxygen, and a tetrahedral intermediate is formed. The collapse of the tetrahedral intermediate expels an alkoxide leaving group, and a ketone is formed as a result.

The reaction does not stop at this point though. Recall from the previous chapter that ketones are reactive with Grignard reagents as well, so a second equivalent of Grignard reagent attacks the ketone. This yields a tetrahedral intermediate bearing only extremely poor leaving groups. Consequently, the intermediate persists until workup.

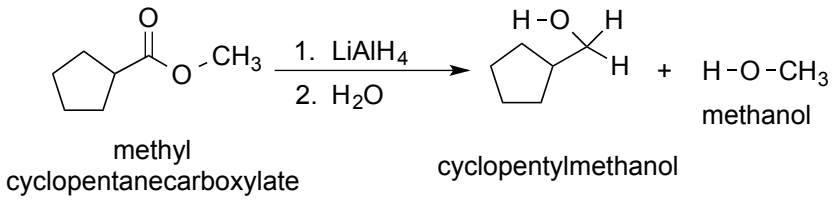


The workup entails treatment with water or aqueous acid. In either case, both alkoxides are protonated, and two alcohols result. The tertiary alcohol is usually the product of interest in such reactions.

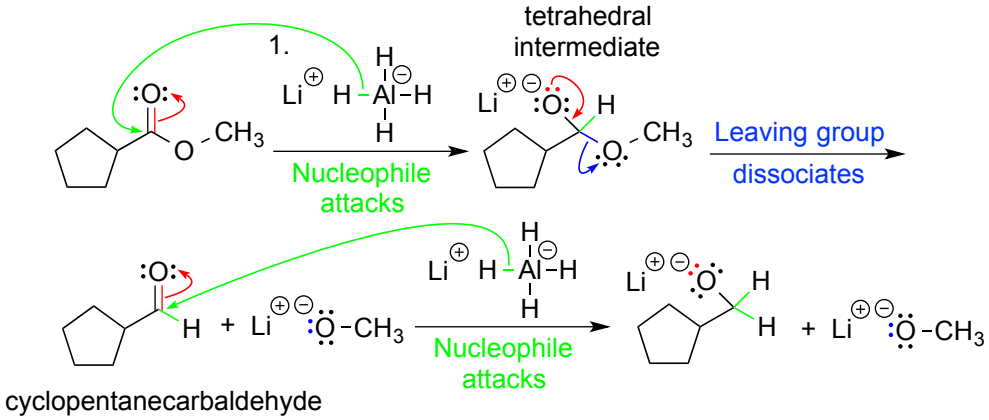


Specific examples of the reaction of carboxylic acid derivatives with lithium aluminum hydride or Grignard reagents

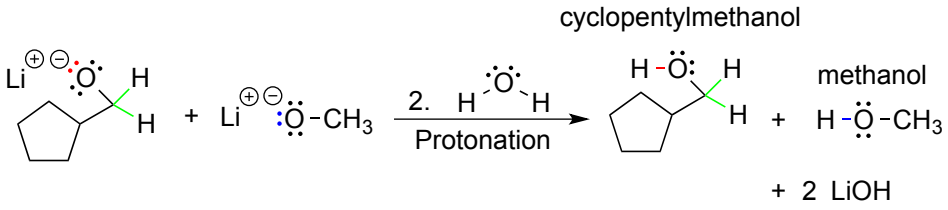
• In the following example of reduction, methyl cyclopentanecarboxylate is reduced by LAH to cyclopentylmethanol. Methanol is also produced as a byproduct.



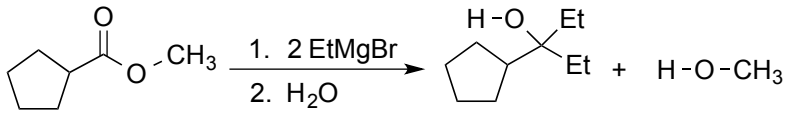
The reaction begins with the attack of hydride on the carbonyl carbon. The tetrahedral intermediate thus formed collapses as methoxide dissociates to yield cyclopentanecarbaldehyde, which is attacked by another equivalent of hydride. The resultant alkoxide persists until workup.



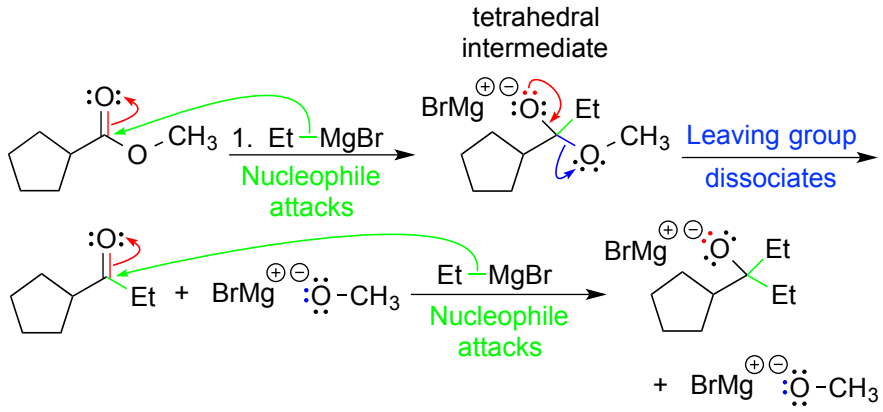
The workup leads to protonation of both alkoxides, yielding the two alcohol products, cyclopentylmethanol and methanol.



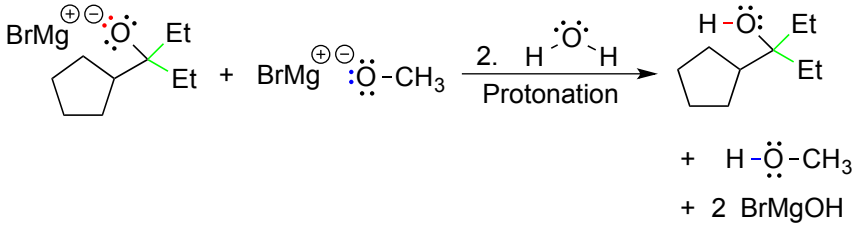
• In the example Grignard reaction that follows, methyl cyclopentanecarboxylate is treated with two equivalents of ethylmagnesium bromide to produce a tertiary alcohol after workup.



The reaction begins with the attack of ethylmagnesium bromide on the carbonyl carbon. The resulting tetrahedral intermediate collapses and expels methoxide in the process. A ketone is formed, but the ketone is subject to further reaction with the Grignard reagent. After the second nucleophilic attack on the carbonyl, the tetrahedral intermediate bears no viable leaving groups and therefore persists until workup.

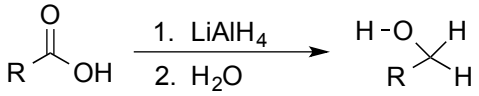


During workup, both alkoxides are protonated. The product of interest is the tertiary alcohol bearing two ethyl groups, and it is accompanied by methanol as a byproduct.

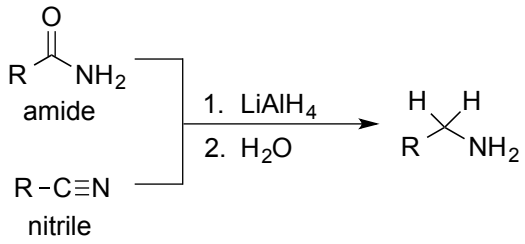


Related reductions

Carboxylic acids may be reduced to primary alcohols by LAH in much the same fashion as esters were.

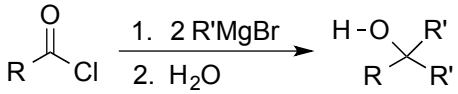


Amides and nitriles are similarly reduced; however, they yield amines instead of alcohols.

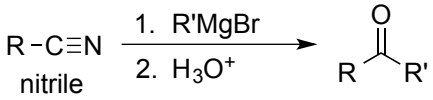


Related Grignard reactions

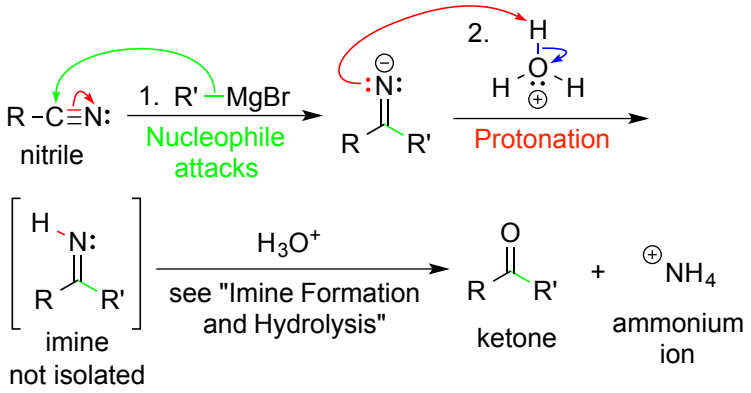
Acid chlorides (or anhydrides for that matter) can also undergo the addition of two equivalents of a Grignard reagent. The mechanism is directly comparable to that seen with esters.



Nitriles, on the other hand, yield ketones when treated with Grignard reagents.



This process deserves further comment, so the mechanism is shown below. The Grignard reagent attacks the nitrile carbon and pushes a pair of π electrons onto nitrogen. This anion is resistant to the addition of any additional Grignard reagent, so the reaction stops at this point. During workup with aqueous acid, the anion is protonated to afford an imine. The imine is then hydrolyzed to form the final product, which is a ketone. The complete mechanism for the hydrolysis of the imine is found in the previous chapter.



In conclusion, carboxylic acid derivatives are subject to reduction by LAH. Esters and acids are reduced to primary alcohols; whereas, amides and nitriles are reduced to amines.

Esters, acid chlorides, and anhydrides can also undergo reaction with Grignard reagents. Two equivalents of Grignard reagent are added to yield a tertiary alcohol with two identical alkyl groups. When nitriles are treated with Grignard reagents, a single addition occurs, and a ketone is formed during the workup (via hydrolysis of the intermediate imine).

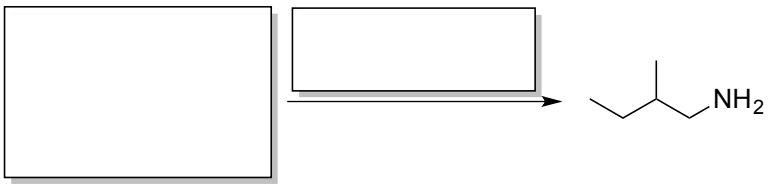
The reduction and Grignard reactions differ only in whether $H:^-$ or $R:^-$ adds to the carbonyl carbon.

Problem 19. Select appropriate reactants and reagents to prepare the following compounds.

(a)

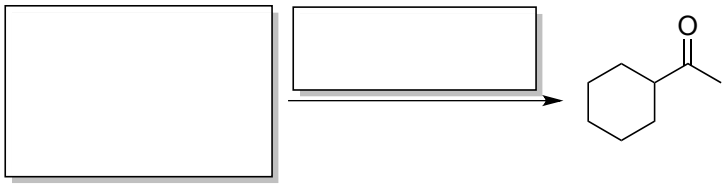
an ester

(b)



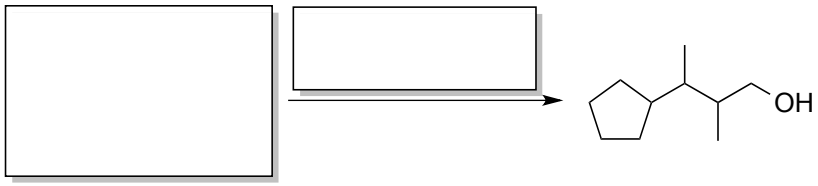
(C_5H_9N)

(c)



a reactant containing 7 carbons

(d)



($C_{11}H_{20}O_2$)

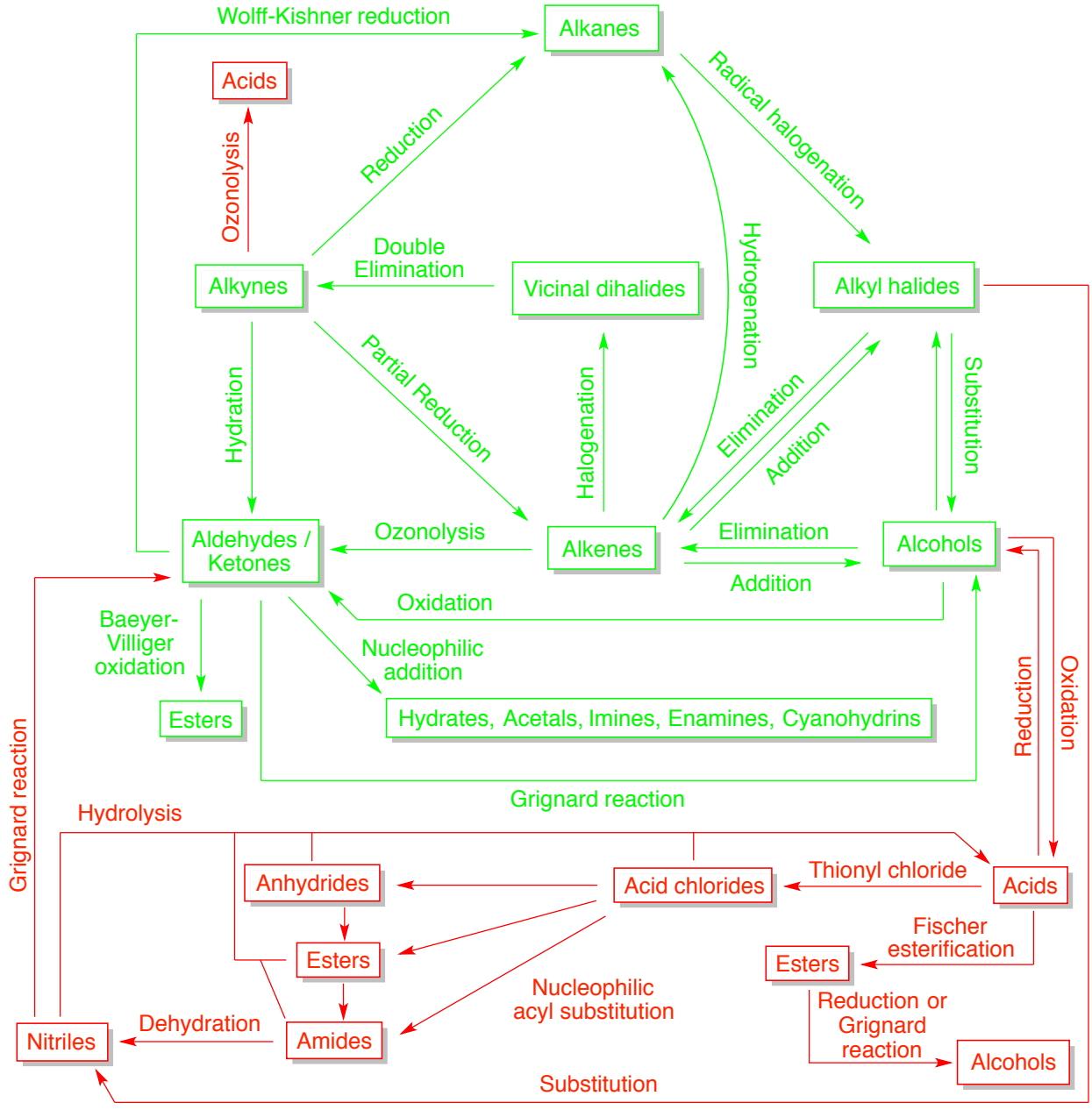
Section 14: Synthesis

Functional group manipulation

In previous chapters, we've mapped out some of the connections between functional groups that arise from the transformations we've learned. Let's continue to flesh out that diagram. When you know an increasing number of reactions, you also know an increasing number of ways to make connections between functional groups. Rather than allowing this to be overwhelming, view it as an advantage. There is likely more than one feasible path from a substrate to a target, so you have options from which to choose. Therefore, if you forget one of the conversions, you can probably circumvent that gap using other reactions. The connections that you've seen before are in green below. Those that we've added in this chapter are in red. While this diagram isn't exhaustive, it captures a great deal of the methods you've mastered.

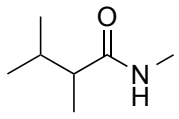
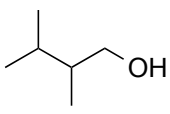
We know that acids can be produced from alcohols by oxidation and from alkynes through ozonolysis. Once prepared, carboxylic acids may be converted to esters through the Fischer esterification. Alternatively, acids can be transformed into acid chlorides, which can serve as precursors to a wide range of functional groups through nucleophilic acyl substitution. Acid chlorides can be converted into anhydrides, esters, or amides using this method. Amides can be dehydrated to yield nitriles, which are also accessible from alkyl halides through substitution reactions employing cyanide ($^{-}$:CN). To come full circle, nitriles can be hydrolyzed to afford carboxylic acids once again.

Nitriles and esters can undergo Grignard reactions to yield, ketones and alcohols respectively. Both of these transformations are also accompanied by changes to the carbon skeleton.

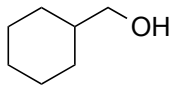
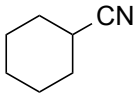


Problem 20. Provide viable syntheses.

(a)

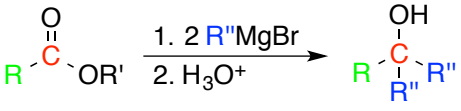
Prepare  from 

(b)

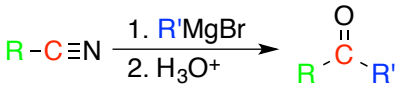
Convert  into 

Changes to the carbon skeleton

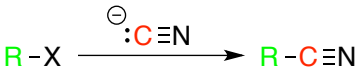
As noted above, the Grignard reactions of esters and nitriles result in changes to the carbon framework of the molecule. Esters undergo the successive addition of two equivalents of Grignard reagent. As a result, one of the R groups bonded to the product's alcohol carbon comes from the original ester, while the two identical alkyl groups (R'') bonded to that same carbon come from the Grignard reagent. The alcohol carbon itself corresponds to the original ester's carbonyl carbon.



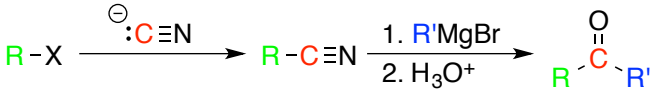
On the other hand, when nitriles undergo Grignard reactions, one of the R groups connected to the carbonyl of the ketone product comes from the original nitrile, while the other (R') comes from the Grignard reagent. The carbonyl carbon itself corresponds with the original nitrile's carbon.



It's also worth recalling that, when nitriles are prepared from alkyl halides through S_N2 reaction with cyanide, a single carbon is added to the original substrate.



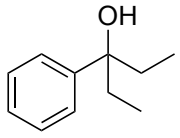
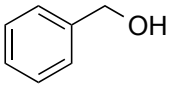
Consequently, when using both of the preceding reactions to prepare ketones, cyanide can serve as a linchpin for the connection of the R group of an alkyl halide and the R' group of a Grignard reagent.



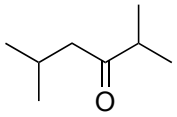
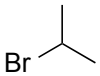
Also, remember that ozonolysis of alkynes degrades the carbon skeleton, while providing a carboxylic acid product.

Problem 21. Provide feasible methods to achieve each of the following conversions.

(a)

Synthesize  from 

(b)

Prepare  from 

End-of-the-Chapter problems

Problem 22. Draw the structures corresponding to the following compound names.

(a) α-methylbutyryl chloride

(b) *sec*-butylbenzoate

(c) cyclobutanecarboxylic acid

(d) 3-ethyl-4-methylpentanonitrile

(e) *N*,*N*-diethylvaleramide

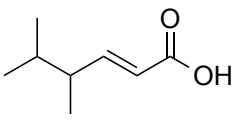
Problem 23. Each of the following names contains an error in nomenclature. Identify the error, and assign the correct name.

(a) β-isopropylvaleronitrile

(b) *N*-dimethylbenzamide

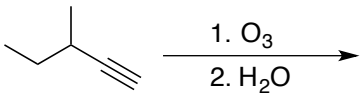
(c) α-propylbutyric acid

Problem 24. In bifunctional molecules, carboxylic acids have priority over other functional groups. For instance, if a molecule contains both an alkene and a carboxylic acid, it is named by removing the "e" from the suffix of the alkene's name and replacing it with "oic acid" to indicate the presence of the carboxylic acid. The molecule is numbered so as to give the carboxylic acid, which has the higher priority, the number 1. Using this information, name the following bifunctional molecule.

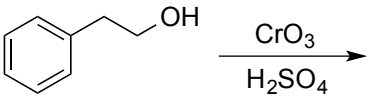


Problem 25. Predict the products of the following transformations.

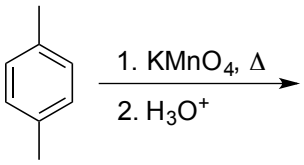
(a)



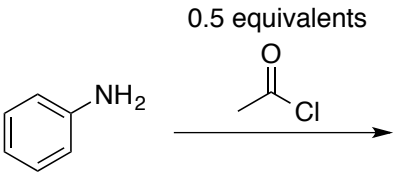
(b)



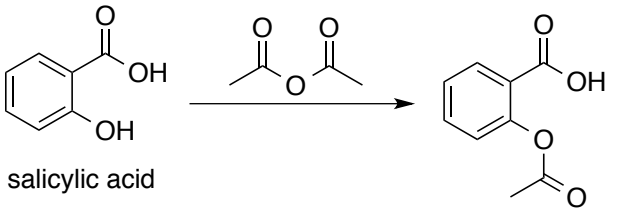
(c)



Problem 26. Draw a mechanism for the following transformation.



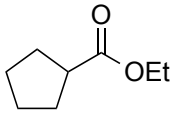
Problem 27. Aspirin is prepared by treating salicylic acid with acetic anhydride. This reaction initially appears to be a bit more complex than those covered in this chapter; however, if you focus only on the reactive portion of salicylic acid, this transformation becomes no more complicated than any other nucleophilic acyl substitution of an anhydride. Provide a mechanism for the acetylation of salicylic acid.



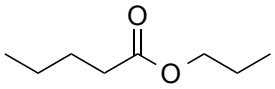
salicylic acid

acetylsalicylic acid
(aspirin)

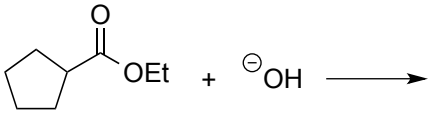
Problem 28. Draw a mechanism for the Fischer esterification that would be needed to form the following ethyl ester.



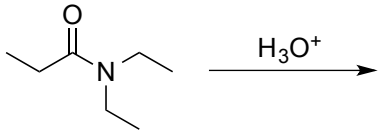
Problem 29. Provide *four* one-step methods for the preparation of the following ester.



Problem 30. In Problem 28, we examined the formation of the ester shown below. Now, draw a mechanism for its saponification.

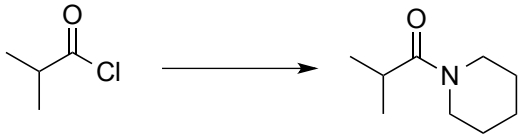


Problem 31. Provide a mechanism for the acidic hydrolysis of the following amide.

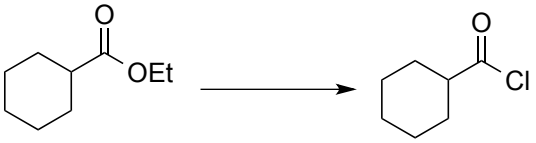


Problem 32. Which of the following transformations can be achieved in a single step?

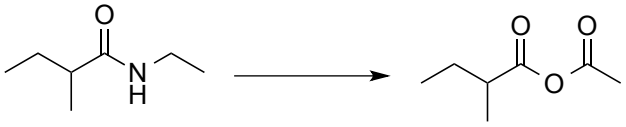
(a)



(b)

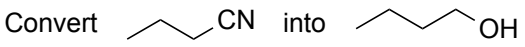


(c)

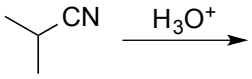


Problem 33. Provide a mechanism for the reaction of butyramide with thionyl chloride.

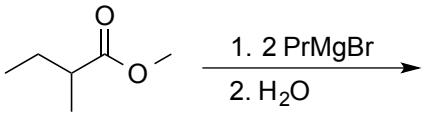
Problem 34. Provide a means to accomplish the following synthesis.



Problem 35. Provide a mechanism for the following transformation.

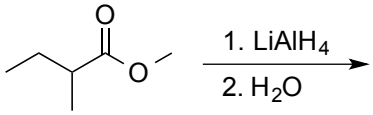


Problem 36. Draw a mechanism for the following Grignard reaction.



Problem 37. Compound X has the molecular formula C_2H_3N. It is treated with ethylmagnesium bromide followed by an aqueous acid workup to yield Compound Y, which has the molecular formula C_4H_8O. What are the structures of Compounds X and Y?

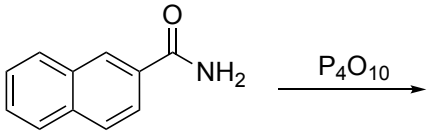
Problem 38. Provide a mechanism for the following LAH reduction.



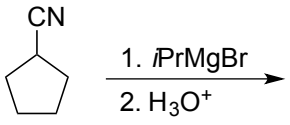
Then, compare this mechanism to that in Problem 36.

Problem 39. Predict the products of the following reactions.

(a)



(b)



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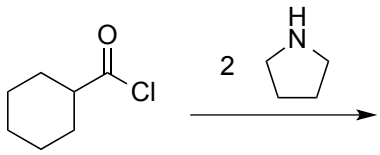
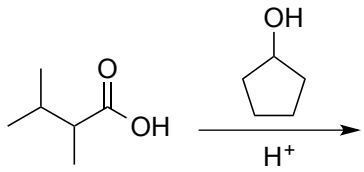
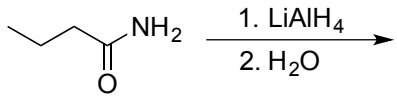


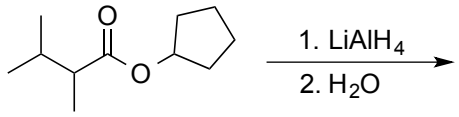
(d)



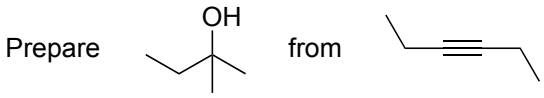
(e)



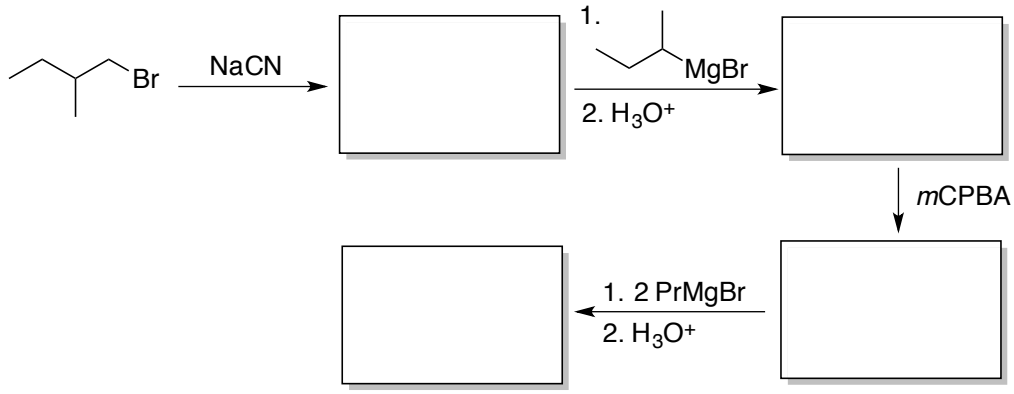
(f)



Problem 40. Provide a viable synthesis.

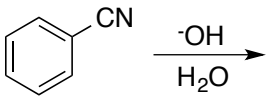


Problem 41. Fill in the missing compounds in the scheme below.

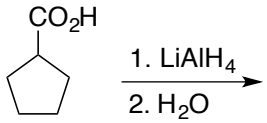


Problem 42. Predict the products of the following reactions.

(a)



(b)



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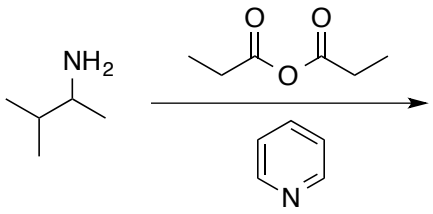
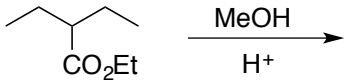


(d)



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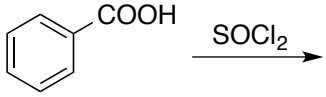

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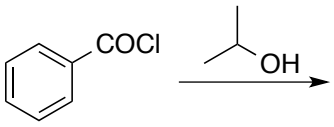
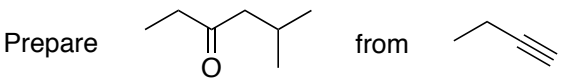
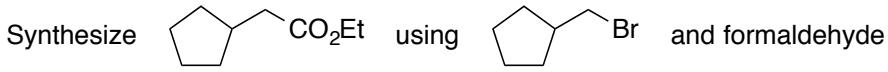


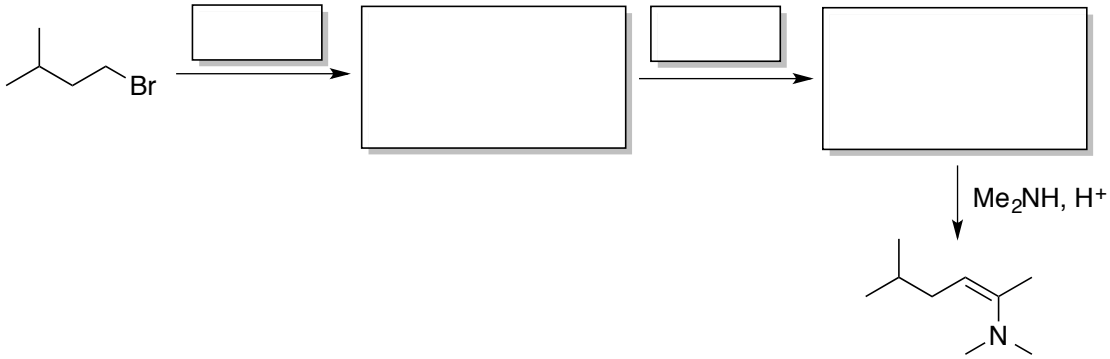
Problem 43. Devise a synthesis.



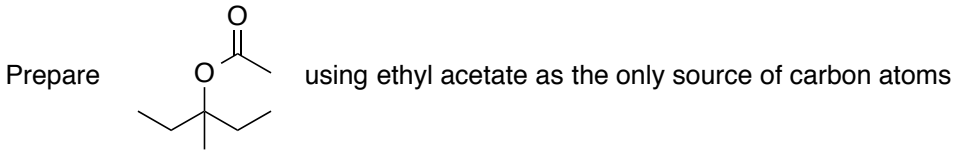
Problem 44. Develop a synthesis for the following.



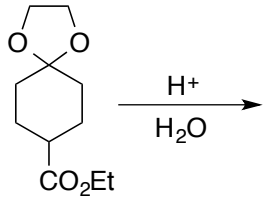
Problem 45. Fill in the missing reagents and intermediates in the scheme below.



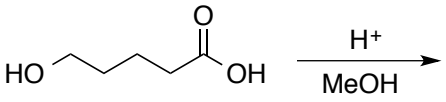
Problem 46. Devise a viable synthesis for the following.



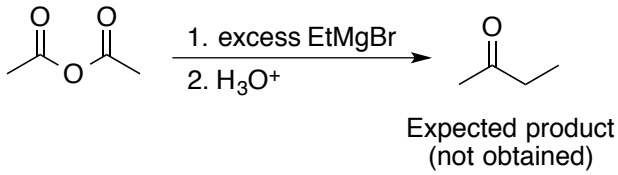
Problem 47. An investigator conducted the following reaction with the goal of hydrolyzing the ethyl ester. The intended carboxylic acid product would exhibit a molecular ion peak having a m/z ratio of 186.09. The mass spectrum of the product obtained from this reaction showed a molecular ion peak with a m/z ratio of 142.06. What actually transpired during this reaction?



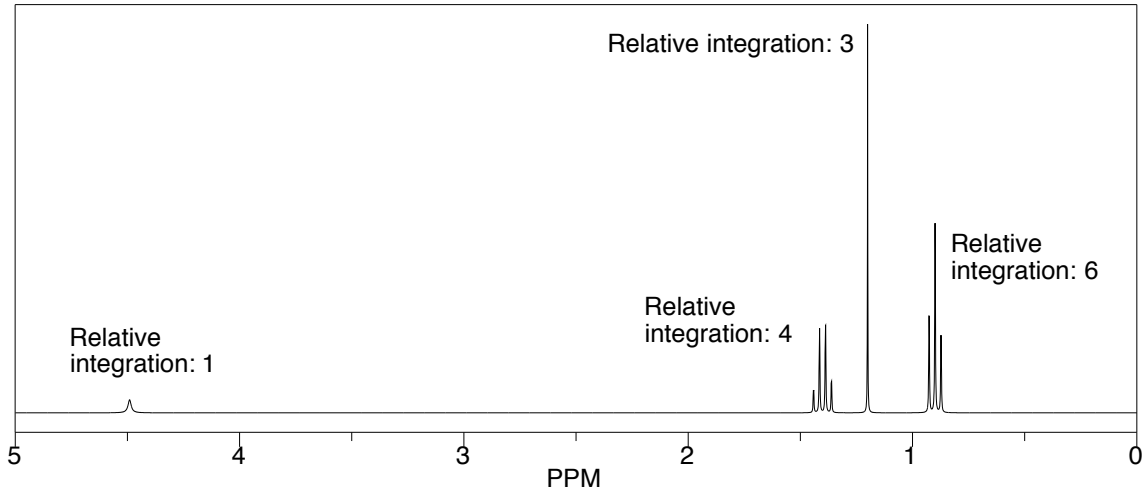
Problem 48. An investigator conducted the following reaction in an attempt to prepare the methyl ester from the carboxylic acid. However, upon inspection of the product's IR spectrum, there was no sign of the expected alcohol O-H stretch. The only significant signals were sp^3 C-H stretching below 3000 cm^{-1} and an ester C=O stretch at about 1740 cm^{-1}. What actually happened during this reaction? Draw a mechanism to explain the outcome.



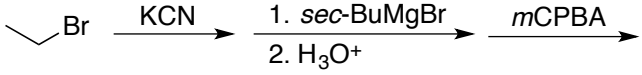
Problem 49. An investigator conducted the following Grignard reaction in an effort to prepare ethyl methyl ketone. An excess of the Grignard reagent was used because the glassware was not thoroughly dried, and the investigator wanted to ensure that there was sufficient Grignard reagent for the reaction, even if some of it was quenched by small amounts of moisture on the glassware.



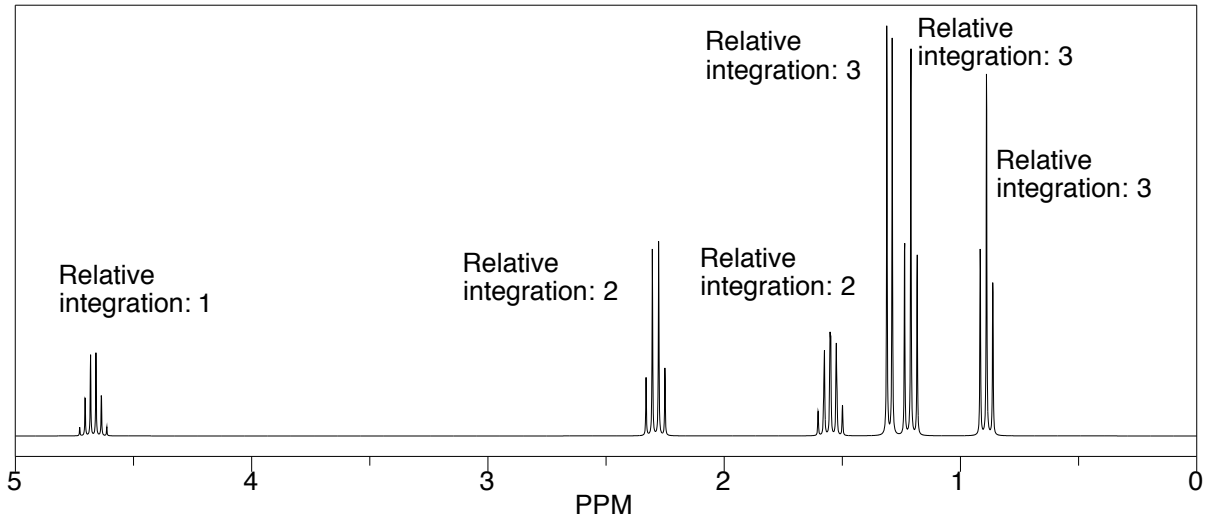
Upon workup, the product was isolated, and its ^{1}H NMR spectrum (shown below) did not display the anticipated signals. What actually transpired during this reaction? Draw a mechanism to explain the outcome.



Problem 50. Ethyl bromide was subjected to the following series of reactions.



The product exhibits the following ^{1}H NMR spectrum. Identify the structure of the product.

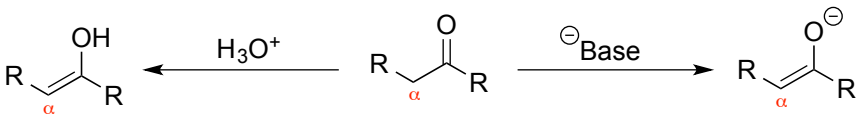

Relative integration: 1
Relative integration: 2
Relative integration: 2
Relative integration: 3
Relative integration: 3
Relative integration: 3
5
4
3
2
1
0
PPM

Chapter 17: Reactions of Carbonyl Compounds at the Alpha Carbon

Section 1: Introduction to reactions of carbonyl compounds at the alpha carbon
Section 2: Acidity of alpha protons
Section 3: Alpha bromination
Section 4: Haloform reaction
Section 5: Aldol reaction
Section 6: Claisen condensation
Section 7: Alpha alkylation
Section 8: Malonic ester synthesis
Section 9: Acetoacetic ester synthesis
Section 10: Michael reaction
Section 11: Stork enamine reaction
Section 12: Robinson annulation
Section 13: Synthesis

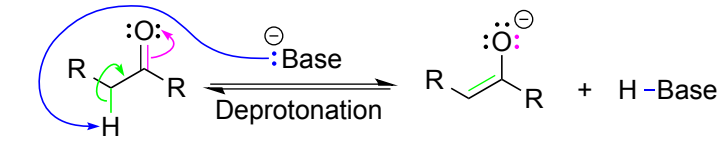
Section 1: Introduction to reactions of carbonyl compounds at the alpha carbon

In the two previous chapters, we've learned quite a bit about the reactivity of carbonyl-containing compounds. However, most of that chemistry has focused on reactions of the carbonyl carbon. We saw that ketones and aldehydes engage in nucleophilic addition, while carboxylic acid derivatives frequently react through nucleophilic acyl substitution. The carbonyl carbon is not the only reactive site in such compounds though. In fact, the α-carbon is also a highly reactive center. It can be rendered nucleophilic in contrast to the carbonyl carbon, which is electrophilic. Carbonyl-containing compounds can be converted to their enol forms in acid or to their conjugate bases, known as enolates, in base. Both of these entities are nucleophilic at the α center for reasons that we'll explore momentarily.



enol form | carbonyl-containing compound | enolate

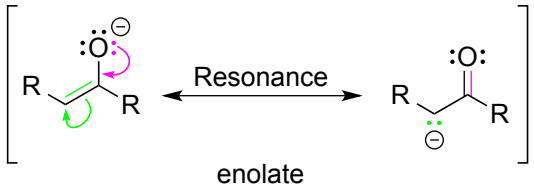
Enolates are more obviously nucleophilic due the negative charge, so let's examine them first. When treated with a base, the carbonyl-containing compound can be deprotonated at the α-carbon. It is most common to show the electrons from the breaking C-H bond flowing directly into the adjacent carbonyl because this places the negative charge on oxygen, thereby creating the most stable resonance form possible.



carbonyl-containing compound

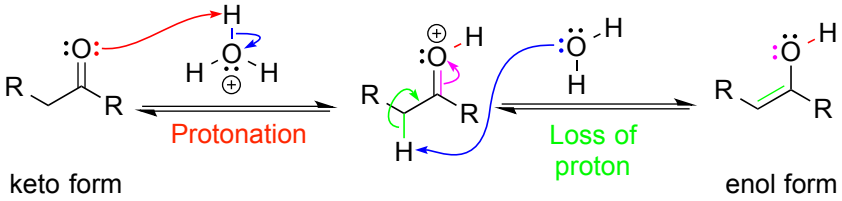
enolate

As noted above, the resonance structure with the negative charge on oxygen is the most stable resonance form of the enolate. There is a second resonance contributor to the hybrid that has the negative charge on the α-carbon, which illustrates that this center is also electron rich.



enolate

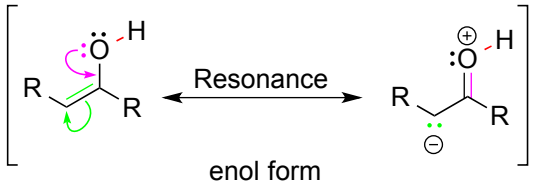
Alternatively, carbonyl-containing compounds can be converted to the corresponding enols in acidic media. While the carbonyl-containing compound (often known as the keto form of the molecule) is typically predominant at equilibrium, a small amount of the enol form is still produced. This happens through protonation of the carbonyl oxygen followed by the loss of a proton from the α center, which allows electrons to flow onto oxygen and neutralize its charge.



keto form

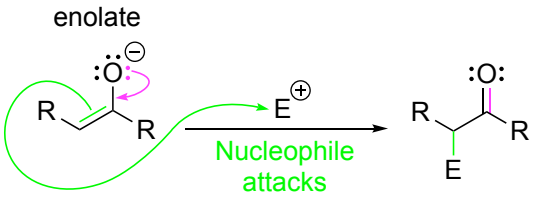
enol form

The enol also possesses a second resonance structure that places a negative charge on the α-carbon. While this is a minor resonance contributor, it nevertheless shows that the α center is nucleophilic.

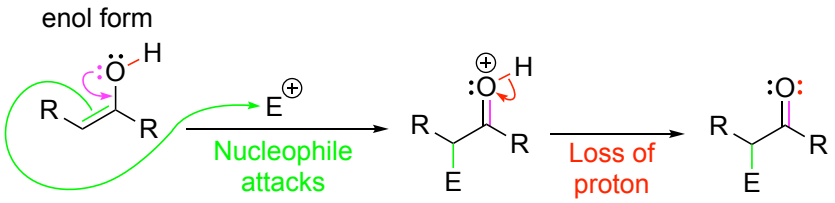


enol form

The reactions that are the focus of this chapter are those of the α-carbon. Once the enolate or enol has been generated, the α-carbon is nucleophilic enough that it will react with an electrophile. When an enolate attacks an electrophile, the carbonyl π bond is concurrently re-formed, and the immediate product is neutral.

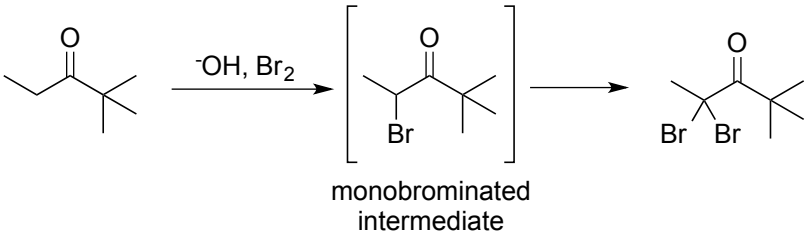


When an enol attacks an electrophile, the carbonyl π bond is similarly re-formed, but the immediate product is an oxonium ion. In a subsequent step, it sheds a proton to the medium, yielding the same product as an enolate.



Over the course of this chapter, we'll see how the choice of electrophile allows a variety of compounds to be prepared.

Problem 1. Later in this chapter, we'll learn about a reaction known as α-halogenation. An example of α-bromination is shown below. Which of the generic mechanisms presented in this section more accurately describes this transformation? Using that generic mechanism as a guide, draw a mechanism for the formation of the monobrominated intermediate.



Section 2: Acidity of alpha protons

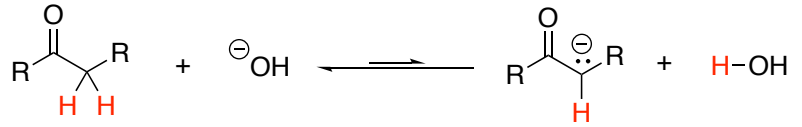
In the previous section, we alluded to the acidity of α-protons. When enolates are formed through the deprotonation of the α-carbon, a Brønsted-Lowry acid-base reaction is taking place in which the α-carbon is the proton donor. The acidity of α-carbons is much greater than that of alkanes or alkenes because of the electron-withdrawing nature of the adjacent carbonyl. The carbonyl allows the negative charge of the conjugate base to be resonance delocalized, which is greatly stabilizing. The specific type and number of carbonyl-containing functional groups impacts the acidity of the α position, and the relative acidity of α-protons is relevant because it impacts the choice of base.

The α-protons of aldehydes and ketones have pK_a values around 20, while the α-protons of esters have pK_a values of approximately 25.

aldehydes / ketones
pK_a ~20

esters
pK_a ~25

This is significant because it illustrates that, when treated with hydroxide (or an alkoxide), these substrates will be only partially deprotonated. In other words, equilibrium favors the reactants in such cases (by about 10^5).

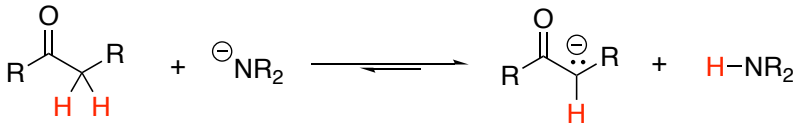


ketones
pK_a ~20

water
pK_a ~15

Equilibrium favors the side with the weaker acid (i.e., the higher pK_a value)

On the other hand, treatment of an aldehyde, ketone, or ester with a much stronger base, such as the conjugate base of an amine, can lead to more complete deprotonation. In this case, the products are favored by approximately 10^{15}.



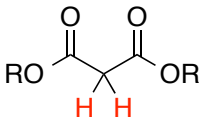
ketones
pK_a ~20

amine
pK_a ~35

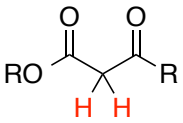
Equilibrium favors the side with the weaker acid (i.e., the higher pK_a value)

Problem 2. Esters have a higher pK_a value than ketones or aldehydes. Propose a reason for this. Hint: consider all of the possible resonance of the corresponding enolates.

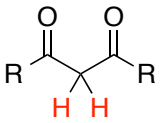
The acidity enhancement provided by carbonyls is cumulative. One carbonyl-containing functional group makes the adjacent carbon a suitable proton donor. Multiple carbonyl-containing functional groups connected to the same α-carbon make it even more acidic. Diesters, ketoesters, and diketones all have pK_a values less than that of water.



diesters
pK_a ~13

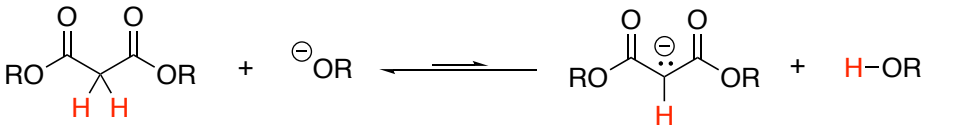


ketoesters
pK_a ~11



diketones
pK_a ~9

This is significant because the addition of a second carbonyl-containing functional group makes the α-carbon acidic enough that it can be deprotonated effectively using merely hydroxide or an alkoxide (as shown below).



diesters
pK_a ~13

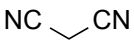
alcohols
pK_a ~15

Equilibrium favors the side with the weaker acid (i.e., the higher pK_a value)

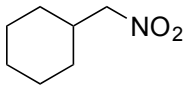
In some of the upcoming sections, we'll be selecting bases to deprotonate various α-carbons. Keep these acidity values in mind because they will justify our choices of base.

Problem 3. Carbonyl-containing functional groups are not the only ones that enhance the acidity of the α-protons. Show how the following compounds have conjugate bases that enjoy resonance stabilization much like traditional enolates.

(a)

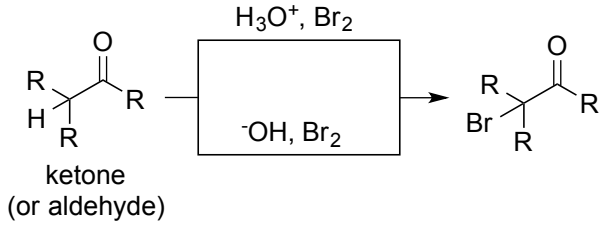


(b)

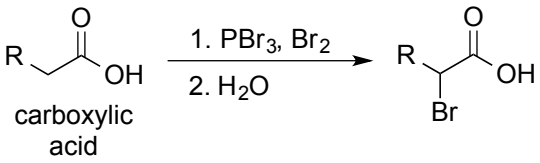


Section 3: Alpha bromination

In the previous sections, we've established the nucleophilicity of the α-carbon. As a result of this attribute, the α-carbon can react with electrophiles, such as bromine. This leads to α-bromination, which can occur in acid or base via distinct mechanisms.

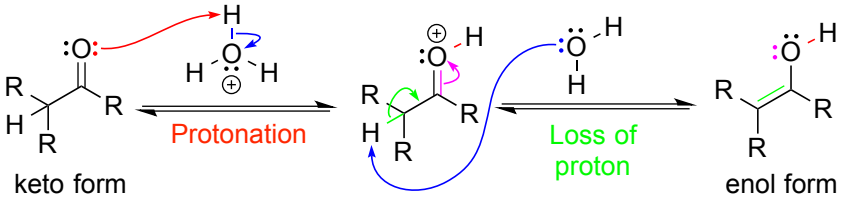


Carboxylic acids can also be brominated in the α position under slightly different conditions employing phosphorus tribromide (PBr_3) and bromine (Br_2). Sometimes phosphorous (P) is simply mixed with Br_2 instead, which generates PBr_3 *in situ*. The net result of the reaction is the installation of a bromine atom on the α-carbon.

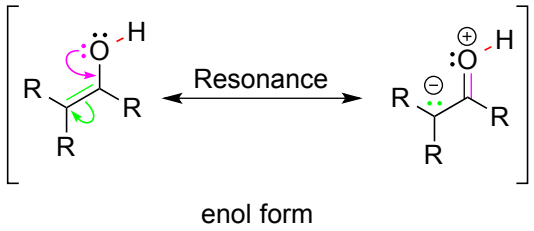


Mechanistic considerations

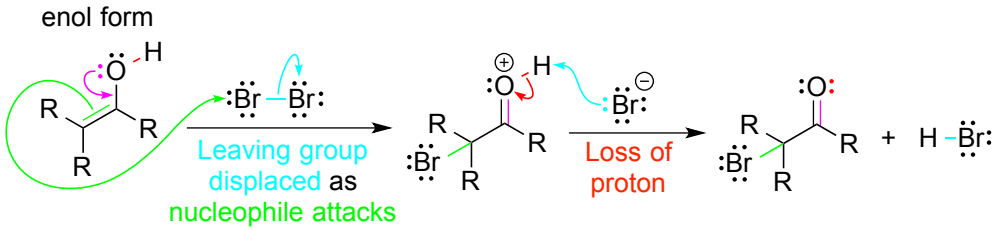
• The acidic α-halogenation of ketones or aldehydes begins with tautomerization to the enol. This occurs via a two-step mechanism in acid (as shown in Section 1). First, the carbonyl oxygen is protonated. Then, a proton is lost from the α-carbon, and electrons flow onto the carbonyl oxygen.



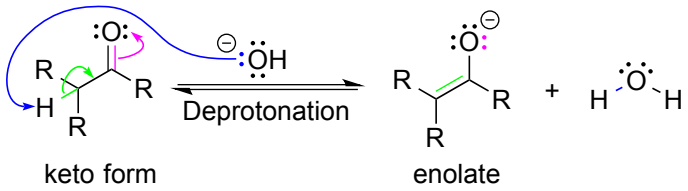
Recall that to understand why the enol is nucleophilic on the α-carbon, we need only examine the resonance structures of the molecule. Electron density can be pushed onto the α center, which means that this center bears a δ^- in the resonance hybrid.



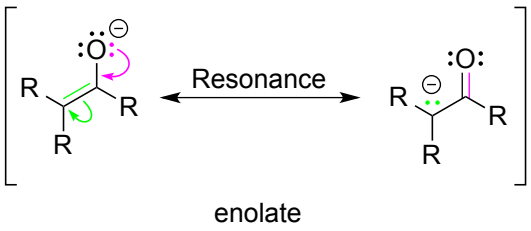
The attack of the α-carbon on bromine breaks the bromine-bromine bond. The displaced bromide then removes a proton from the oxonium ion, and the α-brominated ketone (or aldehyde) results as the final reaction product.



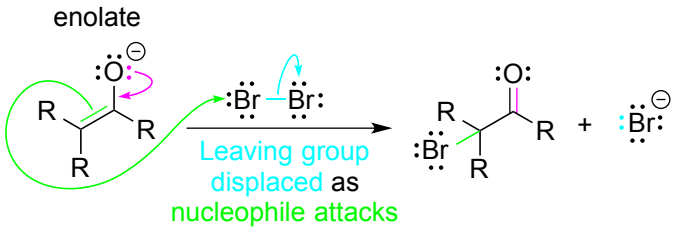
• The basic halogenation of ketones or aldehydes begins with formation of the enolate (as described in Section 1). Hydroxide removes a proton from the α-carbon, and electrons ultimately flow onto the carbonyl oxygen.



Recall that the enolate also has resonance that shows the nucleophilic (δ^-) character of the α-carbon.

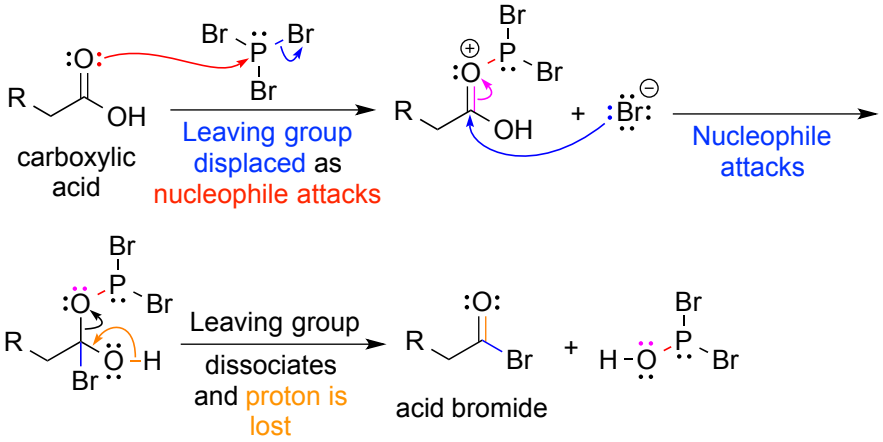


Attack of the enolate on Br_2 installs the α-bromine and displaces bromide.

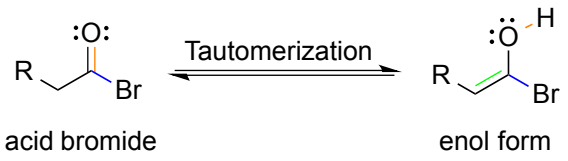


• The α-bromination of carboxylic acids involves different conditions. This reaction is sometimes referred to as the Hell-Volhard-Zelinsky (HVZ) reaction. It begins with the attack of the carbonyl oxygen on the electron-poor phosphorus of phosphorus tribromide. A bromide is displaced in the process, and it subsequently attacks the carbonyl carbon, pushing the π electrons onto oxygen. The resulting tetrahedral intermediate collapses to displace the good leaving group ($^-OPBr_2$). To shorten the mechanism, the loss of a proton is shown concurrently, rather than in a separate mechanistic step. The result is an acid

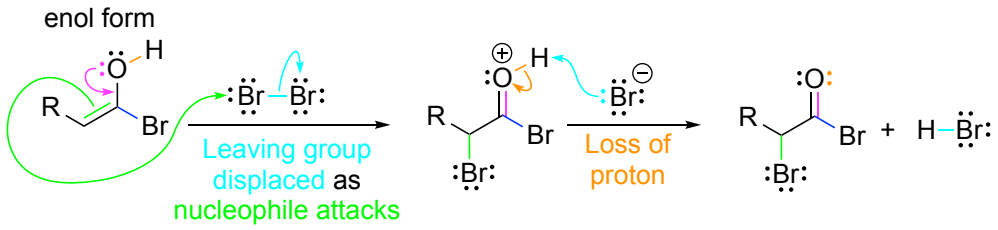
bromide, which is similar to the acid chlorides that we have learned about in the previous chapter.



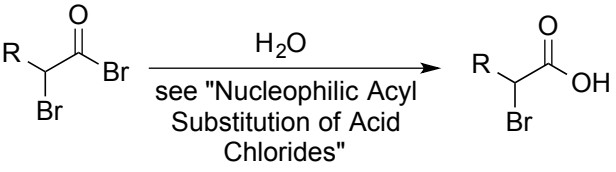
The acid bromide tautomerizes more readily than the original carboxylic acid. This is important because it is the enol tautomer that is reactive at the α center.



The enol form has nucleophilic (δ^-) character at the α-carbon and can therefore attack bromine. After loss of a proton to the displaced bromide, the α-halogenated acid bromide results.

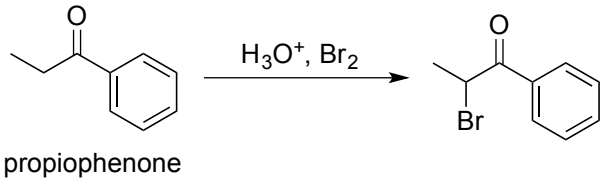


During the second step of the reaction, water is added. This hydrolyzes the acid bromide in much the same way that an acid chloride reacts with water (refer to the section on "Nucleophilic Acyl Substitution of Acid Chlorides" in the previous chapter). The final reaction product is the α-halogenated carboxylic acid.



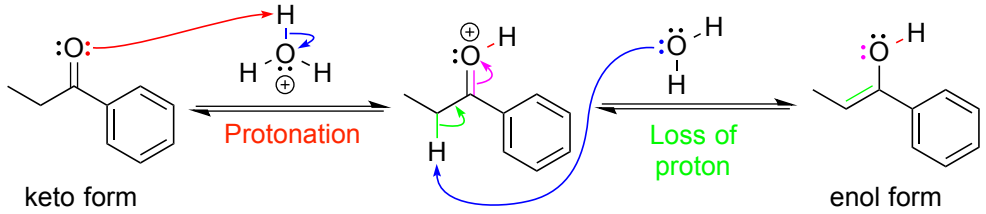
Specific examples of alpha halogenation

• In the following example, propiophenone is treated with bromine and acid to achieve α-bromination.



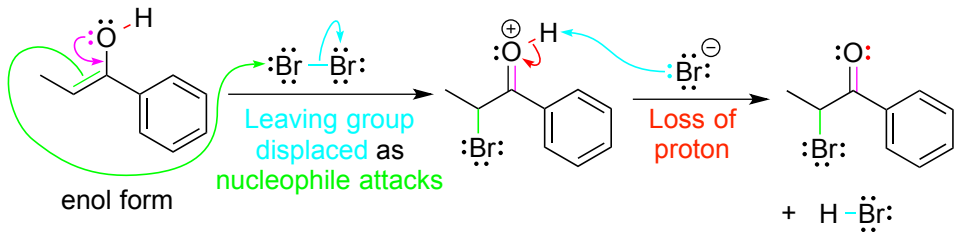
propiophenone

The reaction begins with protonation of the carbonyl oxygen. This enhances the acidity of the α-protons because loss of an α-proton will allow electrons to be pushed onto the oxonium ion thereby neutralizing its charge. The enol results from this tautomerization.



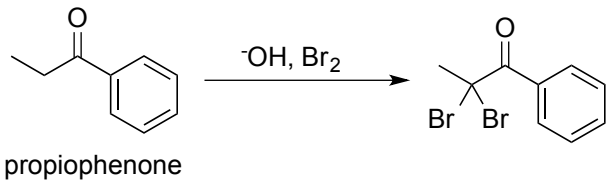
keto form enol form

The enol then attacks bromine, which installs the α-halogen. The oxonium ion subsequently loses a proton to complete the reaction.



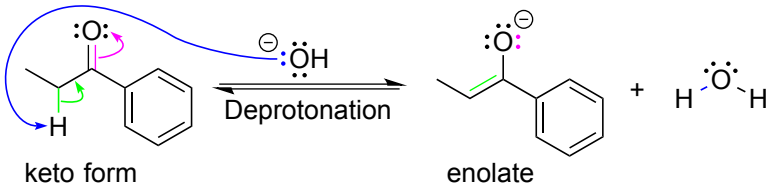
enol form

• In the next example, propiophenone is treated with bromine and base. This reaction proceeds a bit differently than the previous one. In base, it is difficult to stop after a single bromination. As a result, the dibrominated product is obtained.

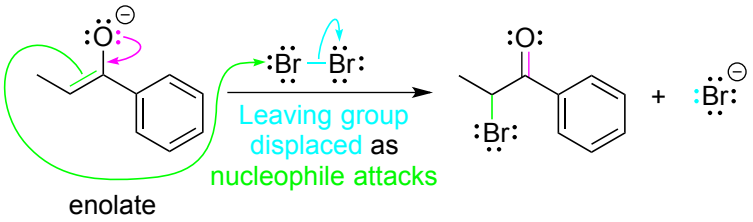


propiophenone

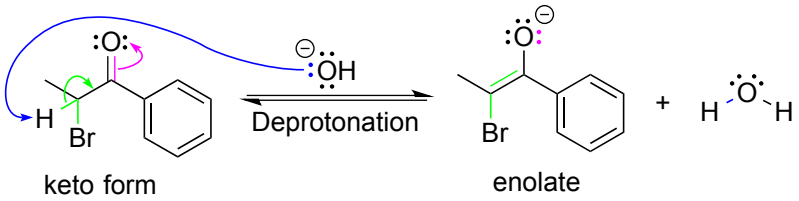
The reaction begins with deprotonation of the α position.



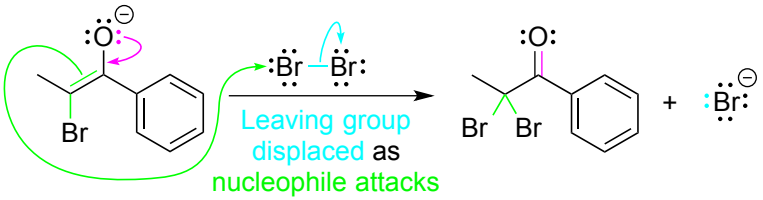
The enolate thus formed nucleophilically attacks bromine to install the first halogen at the α-carbon.



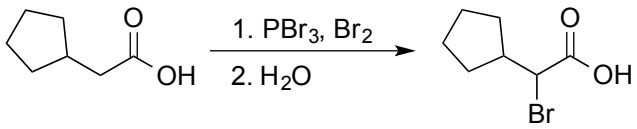
The α center is now more acidic than it was originally due to the electron-withdrawing effect of the bromine atom, which weakens the remaining C–H bond. Consequently, a second deprotonation proceeds even more readily.



This new enolate will also attack bromine to install the second α-halogen. At this point, no additional α-protons remain, so the reaction must come to a halt.

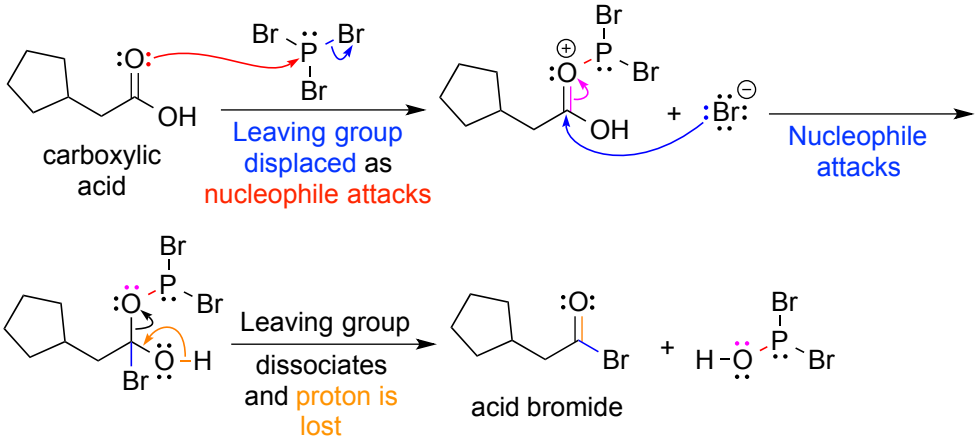


• The final example is Hell-Volhard-Zelinsky reaction of a carboxylic acid.

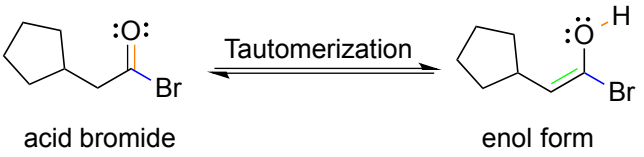


The carbonyl oxygen attacks PBr_3, which is the first step toward activating the carbonyl oxygen as a good leaving group. The bromide that is expelled during the first mechanistic

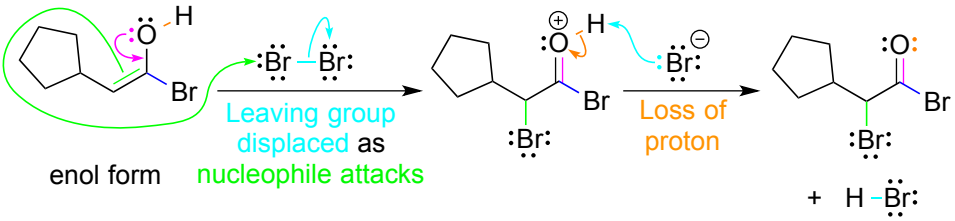
step then attacks the carbonyl carbon in the second mechanistic step. The tetrahedral intermediate thus formed then collapses to expel $^{-}OPBr_2$ as a leaving group.



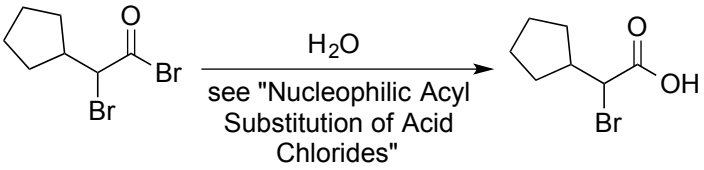
The acid bromide that was generated in the first phase of the mechanism now readily tautomerizes, yielding some of the enol form.



Attack of the enol on bromine installs the halogen adjacent to the carbonyl, and a proton is then lost to afford a neutral product.



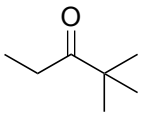
Finally, the acid bromide is hydrolyzed during the second step of the reaction when water is added to the mixture. This generates the ultimate reaction product, an α-brominated carboxylic acid.



In summary, ketones or aldehydes can be brominated in the α position under acidic or basic conditions. When there is only a single α-proton, both reactions provide the same product. When more than one α-proton exists, acidic bromination will yield a monobrominated product, while basic conditions lead to exhaustive bromination at the α position.

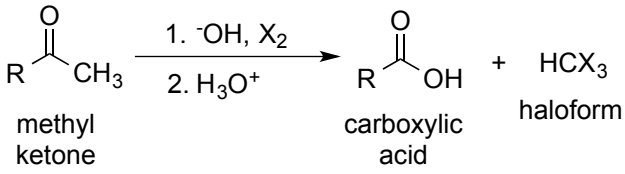
Carboxylic acids can engage in a similar reaction, but the conditions are slightly different. Known as the Hell-Volhard-Zelinsky reaction, this process entails treatment of the carboxylic acid with PBr_3 and bromine. Phosphorus tribromide converts the carboxylic acid to its acid bromide. The acid bromide then tautomerizes more readily, allowing for subsequent reaction with bromine. Upon aqueous workup, the acid bromide is hydrolyzed, and the product is the α-halogenated carboxylic acid.

Problem 4. In Problem 1, you provided a mechanism for the α-bromination of the following ketone in base. Now show a mechanism for its bromination under acidic conditions.

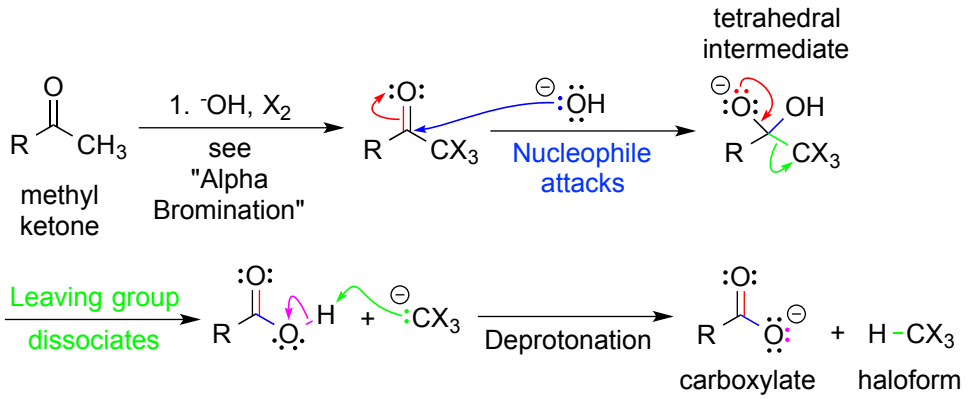


Section 4: Haloform reaction

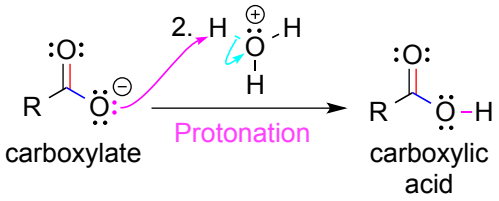
The haloform reaction converts a methyl ketone into a carboxylic acid that is one carbon shorter in length. The reaction is named as such because a haloform (i.e., chloroform, bromoform, or iodoform) is produced as a byproduct of the reaction.



The reaction begins with exhaustive halogenation at the α position under basic conditions, which we saw in the previous section. This process converts the methyl group into a trihalomethyl (CX_3) group. Hydroxide then attacks the carbonyl carbon, pushing the π electrons onto oxygen as a tetrahedral intermediate is formed. The tetrahedral intermediate subsequently collapses as $^-CX_3$ dissociates. Although we would not normally consider a carbanion to be a reasonable leaving group, this carbanion is stabilized by the cumulative electron-withdrawing effect of its three halogens. A proton exchange completes the first step of the reaction, yielding the haloform and a carboxylate as products.

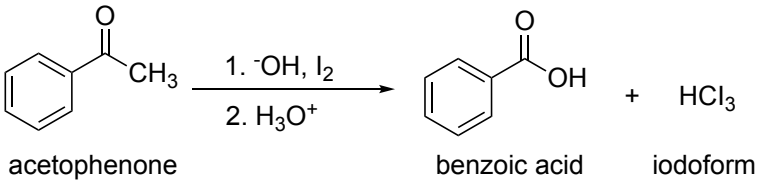


In the second step of the reaction, aqueous acid is added. This leads to protonation of the carboxylate, affording the corresponding carboxylic acid as the final reaction product.

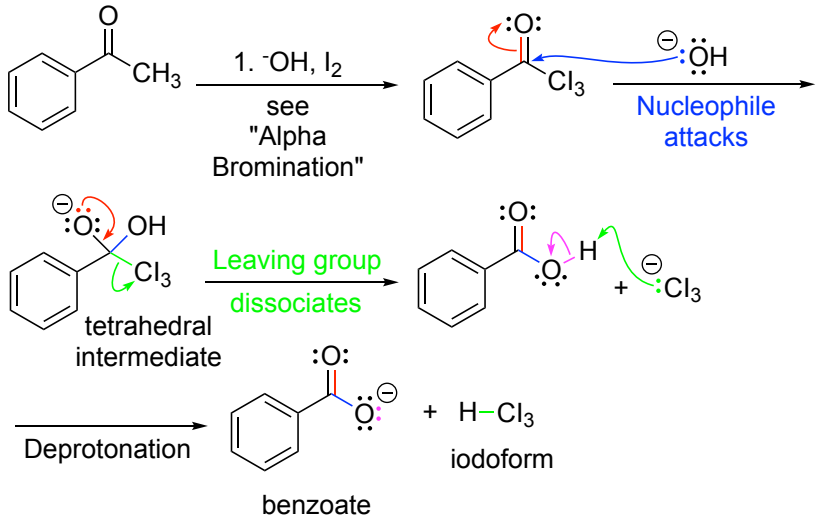


A specific example of the haloform reaction

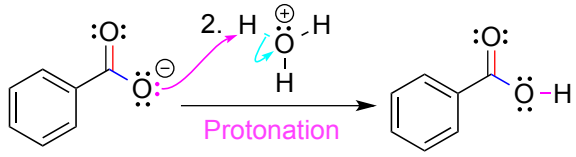
In the following example, acetophenone is subjected to the iodoform reaction to produce benzoic acid.



The first phase of the mechanism involves exhaustive iodination of the α-carbon. This occurs via the same mechanism as exhaustive bromination (refer to the previous section). All that differs is the specific halogen used. Hydroxide subsequently attacks the carbonyl carbon. A tetrahedral intermediate is formed in the process. When it collapses, $^-CI_3$ is expelled. A proton transfer provides benzoate and iodoform and completes the first step of the reaction.

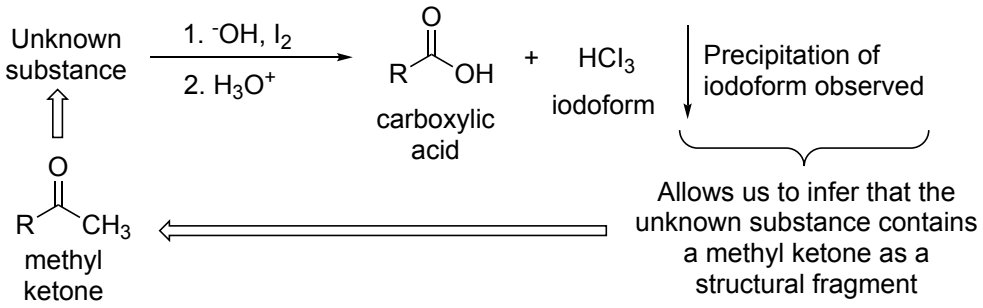


In the reaction's second step, aqueous acid is added. This leads to the protonation of benzoate. Benzoic acid is formed as the ultimate reaction product. Notice that it contains one fewer carbon than acetophenone, the reactant. That carbon was lost as iodoform.



Additional uses of the haloform reaction

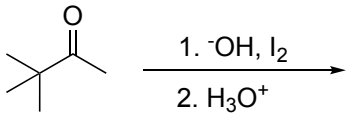
The iodoform reaction is sometimes also known as the iodoform test because it can be used as a qualitative test for methyl ketones. Iodoform is a yellow solid that is insoluble in water and is therefore produced as a precipitate if a methyl ketone is a structural component of an unknown substance.



In conclusion, the haloform reaction transforms a methyl ketone into a carboxylic acid with one fewer carbon. The reaction is unusual in that it cleaves a carbon atom from the substrate in the form of the haloform byproduct.

The iodoform reaction is a useful qualitative test for methyl ketones due to the precipitation of the insoluble iodoform byproduct.

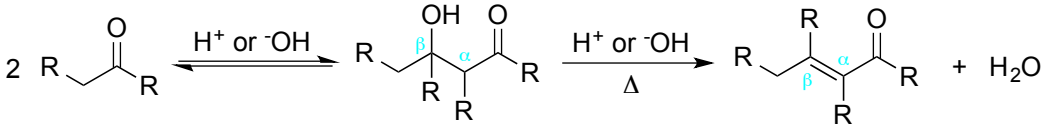
Problem 5. Predict the products of the following reaction. Would there be any visual evidence of the reaction having taken place?



Section 5: Aldol reaction

In the aldol reaction, two equivalents of a ketone or aldehyde unite to form a β-hydroxy carbonyl-containing compound. The reaction proceeds with acid or base catalysis and involves the formation of a new C–C bond. The reaction is called the aldol reaction because the product contains an aldehyde (or ketone) and an alcohol.

The aldol reaction is freely reversible, so sometimes the β-hydroxyaldehyde or ketone is dehydrated through heating. The loss of water drives the reaction due to the accompanying increase in entropy. This variation is referred to as the aldol *condensation* because a small molecule (in this case, water) is lost. The aldol condensation yields an α,β-unsaturated compound.



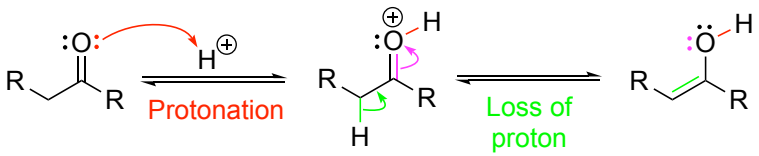
ketone or aldehyde

aldol product (β-hydroxyketone or aldehyde)

aldol condensation product (α,β-unsaturated ketone or aldehyde)

Mechanistic considerations

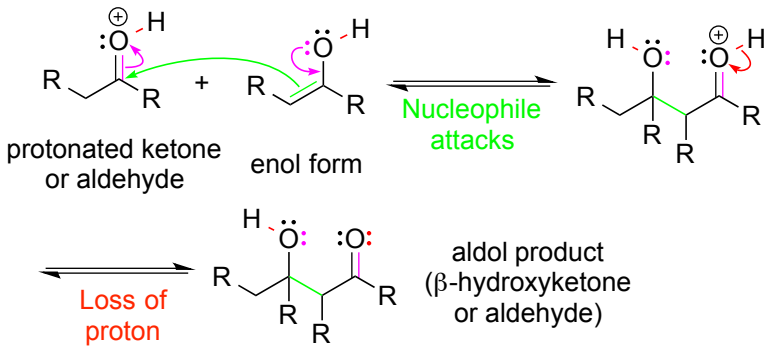
• An acid-catalyzed aldol reaction begins with tautomerization, which occurs exactly as we saw earlier in this chapter. In acid, tautomerization involves protonation of the carbonyl oxygen followed by loss of a proton from the α-carbon. The result is the enol form of the substrate.



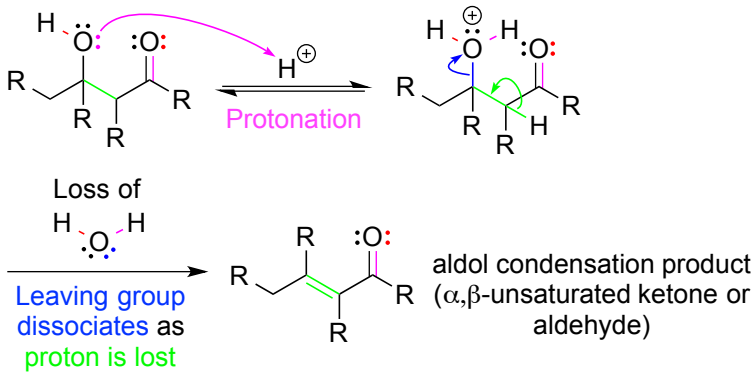
protonated ketone or aldehyde

enol form

This enol can then nucleophilically attack another molecule of aldehyde or ketone that has been protonated (and is therefore quite electrophilic). This installs the new carbon-carbon σ bond. The oxonium ion then merely sheds a proton to the medium, resulting in the neutral aldol product.

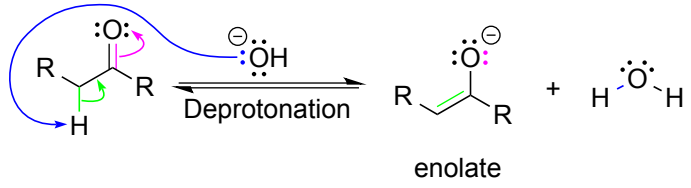


The reaction can halt at this stage, or if it is heated, dehydration will follow. This occurs through protonation of the hydroxyl group. The good leaving group (water) then dissociates as a proton is lost from the α-carbon. Dehydration results in an increase in entropy because the aldol product (a single molecule) has been broken into two fragments: the α,β-unsaturated ketone or aldehyde and water.

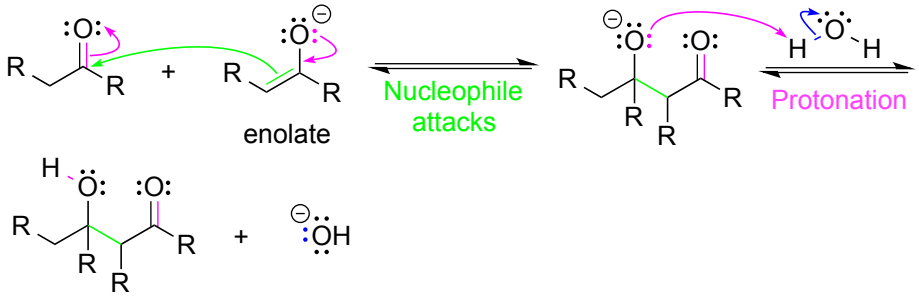


Notice that, for every proton consumed in the reaction, a proton has also been liberated. The acid is therefore catalytic.

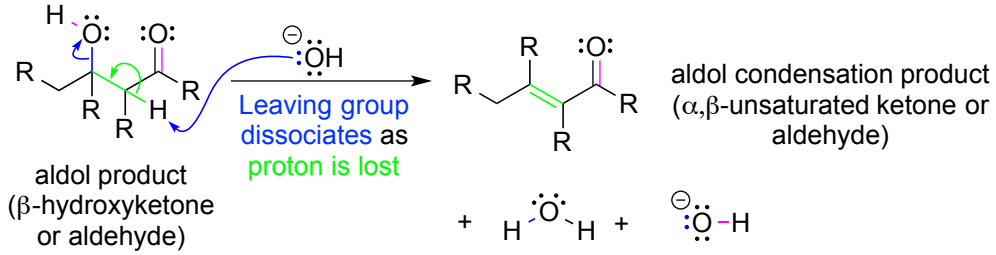
• The base-catalyzed aldol reaction begins with the removal of a proton from the α position by hydroxide. Electrons can flow toward the carbonyl oxygen to show the enolate in its more stable resonance form.



The α position of a ketone or aldehyde has a pK_a of approximately 20; whereas, water has a pK_a of 15.7. Consequently, when hydroxide is used as the base, only a small amount of the ketone or aldehyde is deprotonated. Most of the substrate remains in its original form. Therefore, attack of the enolate on one of the many unreacted molecules of ketone or aldehyde generates the new C–C σ bond. The alkoxide thus formed removes a proton from water to afford the neutral aldol product.



When the reaction is heated, the aldol product is dehydrated. Hydroxide removes a proton from the α-carbon, forming a carbon-carbon π bond as hydroxide is expelled as a leaving group. Although we do not usually consider hydroxide to be a suitable leaving group, this dehydration trades one hydroxide ion for another while simultaneously increasing the entropy of the system through fragmentation of the aldol product into two molecules: the α,β-unsaturated ketone or aldehyde and water.

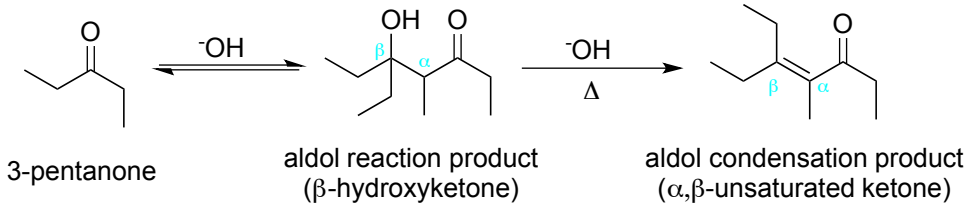


Throughout the mechanism, a hydroxide ion is produced for every one that is consumed. Therefore, the base is catalytic.

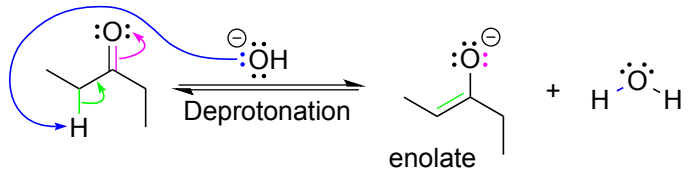
It is worth noting that both the acid and the base-catalyzed aldol reactions are merely examples of nucleophilic addition to a ketone or aldehyde. We saw many examples of this in the chapter on the reactions of aldehydes and ketones. The only difference is that now a new nucleophile (the enol or enolate) is being used.

Specific examples of the aldol reaction

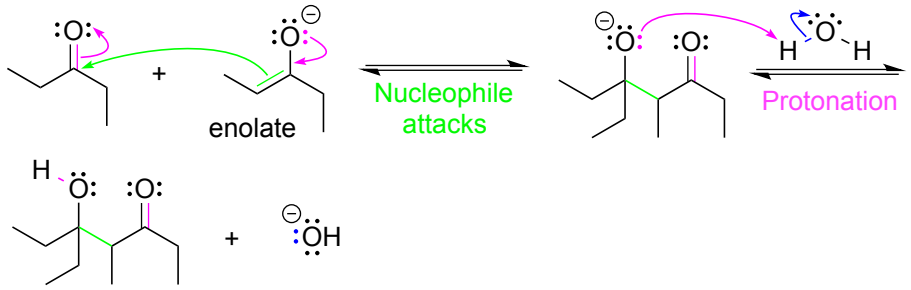
• In the example below, 3-pentanone undergoes base-catalyzed aldol reaction with heating to yield an α,β-unsaturated ketone. Notice that, although two equivalents of 3-pentanone are consumed to yield a single molecule of the aldol product, the stoichiometry is not always written.



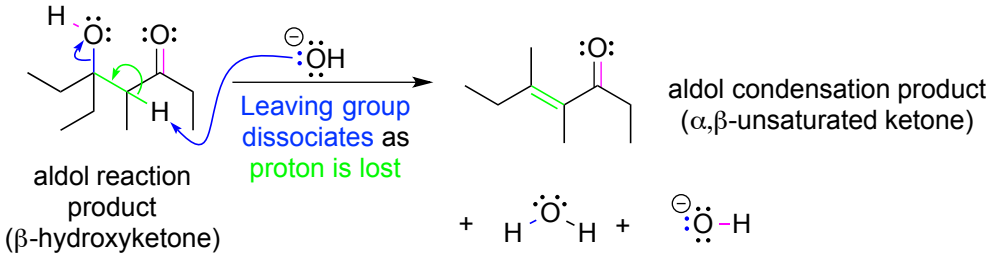
The reaction begins with the deprotonation of a small amount of 3-pentanone by hydroxide. Since this molecule is symmetrical, it does not matter which α-carbon is deprotonated.



The enolate thus formed attacks an unreacted molecule of 3-pentanone, pushing the carbonyl π electrons onto oxygen. In this way, the new carbon-carbon bond is generated. The alkoxide intermediate then removes a proton from water to yield the aldol product.

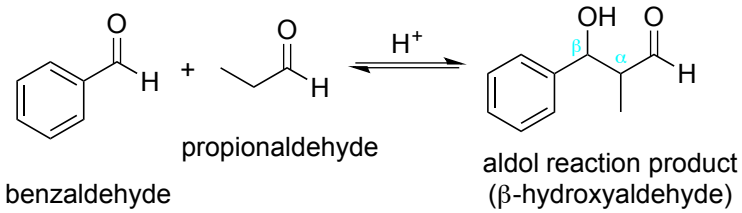


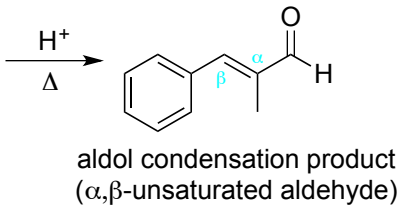
When heated, deprotonation of the α position forms the new carbon-carbon π bond as hydroxide dissociates from the β-carbon.



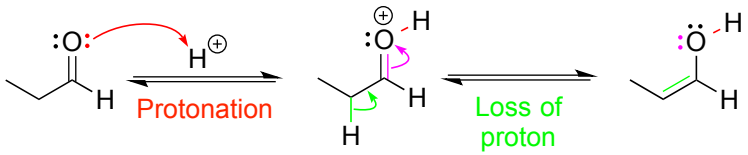
• So far, we have only considered self-condensation reactions, but crossed-aldol (or mixed-aldol) reactions are also possible. In a crossed-aldol reaction, two different reactants are used. However, in order to avoid product mixtures, it is common to select one substrate that has no α-protons. This simplifies the reaction because that substrate cannot form the

enol (or enolate). In the next example, propionaldehyde condenses with benzaldehyde in a crossed-aldol condensation.

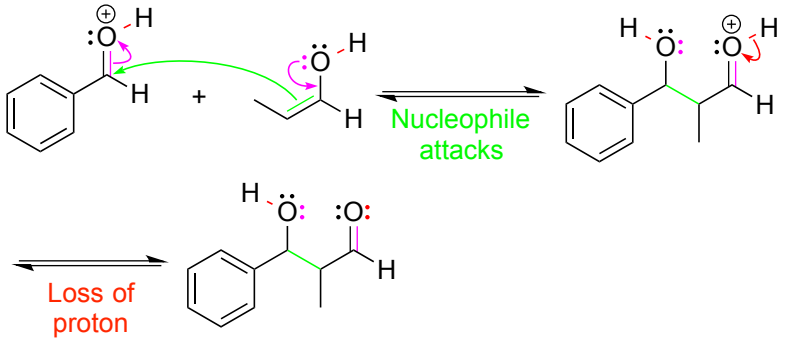




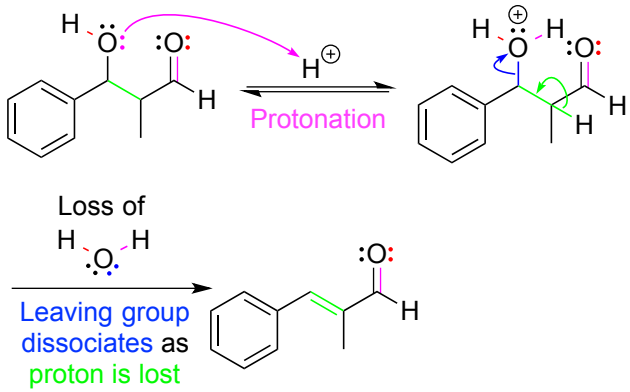
The reaction begins with the tautomerization of the "enolizable" aldehyde (i.e., the aldehyde that has α-protons and can therefore form the enol). Protonation of the carbonyl oxygen is followed by loss of an α-proton to afford the enol tautomer.



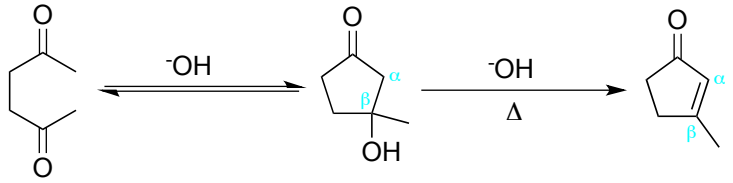
The enol then attacks a protonated molecule of benzaldehyde, pushing the carbonyl π electrons onto oxygen to neutralize its charge. Loss of a proton from the resulting oxonium ion completes the formation of the aldol product.



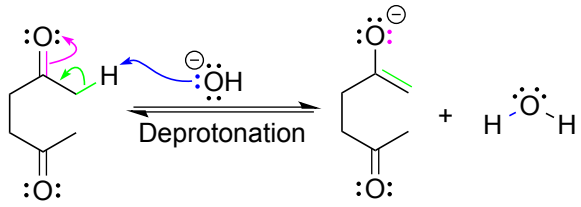
When the reaction is heated, dehydration follows. The β-hydroxyl group is protonated, and water then dissociates as an α-proton is lost. The final aldol condensation product is therefore the α,β-unsaturated aldehyde.



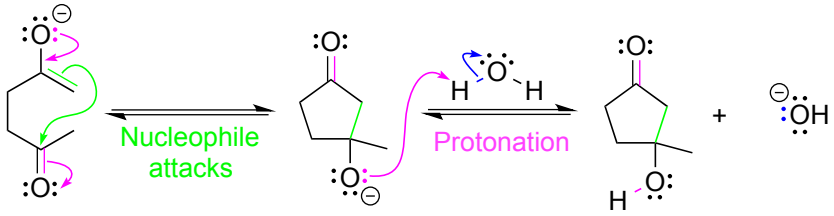
• It is also possible to perform *intramolecular* aldol reactions, which yield rings. In the following example, 2,5-hexadione undergoes intramolecular aldol condensation in base to yield a cyclopentenone product.



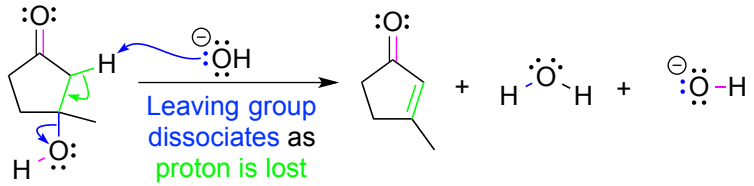
The reaction begins with the deprotonation of an α-carbon. The molecule is symmetrical, so there are only two types of α-carbons to be considered. The α-methyl group is five atoms away from the other carbonyl, while the α-methylene (CH_2) is only three atoms away from the other carbonyl. Given that five-membered rings are less strained than three-membered rings, we would expect this freely reversible process to favor the formation of a five-membered ring. Therefore, while the α-methylene can be deprotonated, it is the loss of a proton from the α-methyl group that is of greater interest in explaining the formation of product.



The enolate that was formed through deprotonation attacks the electrophilic carbonyl to which it is tethered. This not only installs a new carbon-carbon bond but also generates a ring. The alkoxide then removes a proton from water to afford the cyclic aldol product.



When heated, the aldol product is dehydrated via removal of an α-proton, which leads to the dissociation of hydroxide as the new π bond is formed.



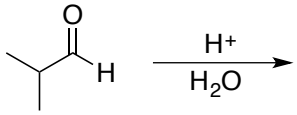
To recap, ketones or aldehydes with α-protons can self-condense via the aldol reaction to yield products with a β-hydroxyl group. The reaction requires acid or base catalysis. When the reaction is heated, it is referred to as the aldol condensation because water is lost in the process of forming the α,β-unsaturated product.

Crossed-aldol reaction/condensation is possible, but the substrates must be carefully chosen to avoid product mixtures. Typically, one substrate lacks α-protons, which prevents it from enolizing and acting as a nucleophile.

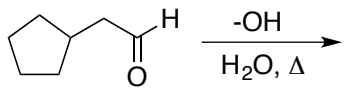
Intramolecular aldol reaction/condensation is also possible when a reactant with two carbonyls is employed.

Problem 6. Predict the product of each of the following aldol reactions/condensations.

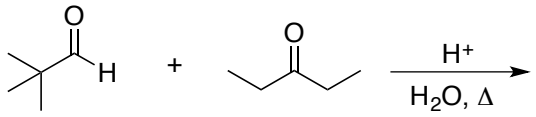
(a)



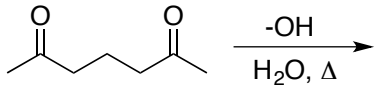
(b)



(c)

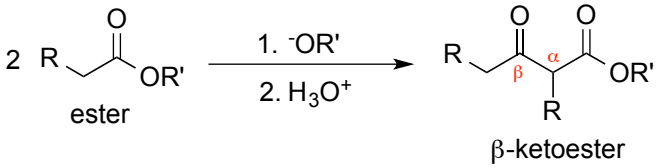


(d)

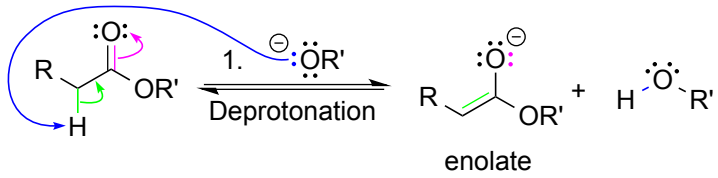


Section 6: Claisen condensation

The Claisen condensation entails the base-promoted union of two esters. It relies upon the reactivity of both the α-carbon and the carbonyl carbon. The reaction consists of two steps: (1) treatment with an alkoxide followed by (2) acidic workup. The result is a β-keto ester.



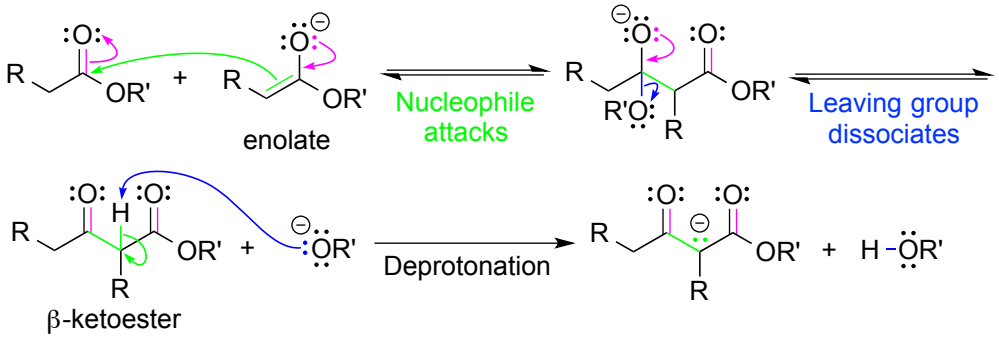
The reaction begins with deprotonation of the α-carbon by the alkoxide. This generates an ester enolate.



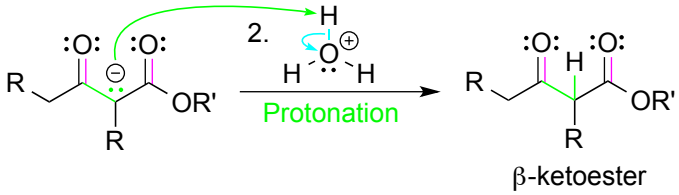
Instead of using hydroxide as in the aldol reaction, the Claisen condensation employs an alkoxide. The reason is that hydroxide would saponify the ester rather than deprotonate the α-carbon (for a review of saponification, see the section on the nucleophilic acyl substitution of esters in the previous chapter). Furthermore, it is important that the alkoxide bears the same R' group as the carboxyl oxygen of the ester. Otherwise, transesterification will take place (again, refer to the section on nucleophilic acyl substitution of esters in the preceding chapter).

The α position of an ester has a pK_a of approximately 25, while alcohols have pK_a values around 15. Therefore, when an alkoxide is used as the base, only a small amount of the ester enolate is formed. The majority of the ester is unaltered. Consequently, the enolate will readily encounter an unreacted ester molecule. When it does, it nucleophilically attacks the carbonyl carbon, displacing π electrons onto oxygen and forming a new carbon-carbon σ bond in the process. When the tetrahedral intermediate collapses, an alkoxide leaving group is displaced. As a result, a β-ketoester is formed, but only transiently. The α position

of this β-ketoester is much more acidic (pK_a ~10) because it is now activated by two adjacent carbonyls. Consequently, the displaced alkoxide easily removes a proton from this center, yielding an alcohol and a new enolate. It is this final deprotonation step that drives the equilibrium toward the products.



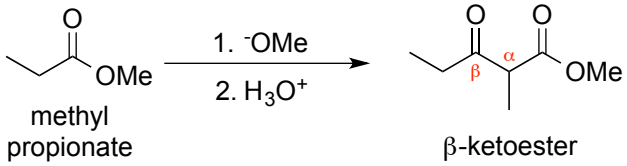
The enolate of the β-ketoester persists until workup. When acid is added at this stage, protonation yields the β-ketoester in its neutral form.



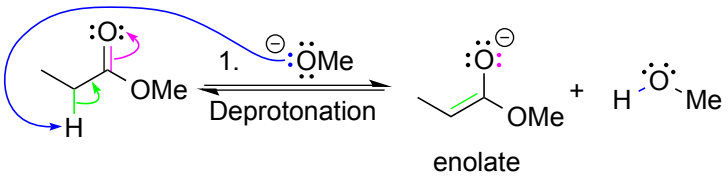
The reaction is called the Claisen *condensation* because a small molecule (this time an alcohol) is liberated as the two esters unite. It is also worth noting that the Claisen condensation is nothing more than a nucleophilic acyl substitution of an ester. We are simply using a new nucleophile (an ester enolate) in this reaction.

Specific examples of the Claisen condensation

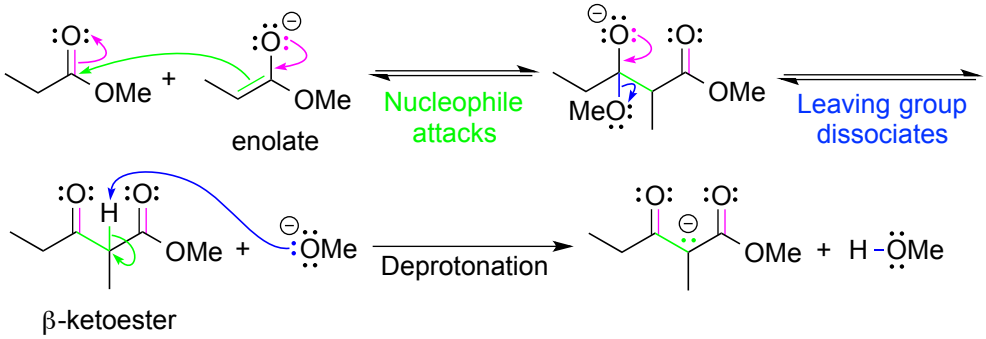
• In the following example, methyl propionate is treated with methoxide, followed by an aqueous acid workup, to yield a β-ketoester. Although two molecules of methyl propionate do unite to form the product, that stoichiometry is not necessarily written.



The reaction begins with deprotonation of a relatively small number of ester molecules by methoxide to provide the ester enolate. Notice that, if methoxide were to attack the carbonyl carbon, no observable transformation would take place because the alkyl group of methoxide matches the alkyl group on the ester's carboxyl oxygen.

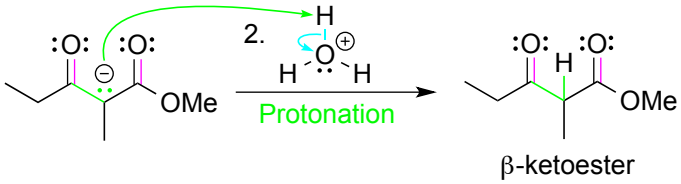


The ester enolate now attacks an unreacted ester molecule. The tetrahedral intermediate thus formed collapses and displaces methoxide in the process. The equilibrium is driven as the resultant β-ketoester is deprotonated by methoxide at the most acidic position (between the two carbonyls).

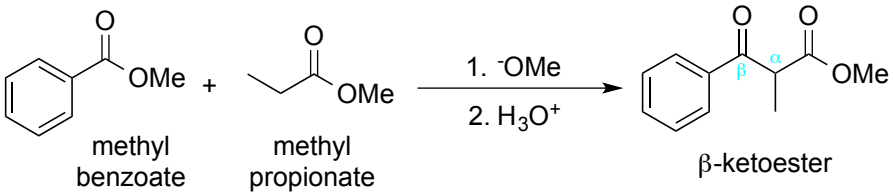


Notice that, unlike the base-*catalyzed* aldol reaction, the Claisen condensation is base *promoted*. In other words, it requires at least one full equivalent of alkoxide. Two methoxide ions are consumed during the reaction (in forming the ester enolate and in deprotonating the β-ketoester); however, only one methoxide ion is produced (when the tetrahedral intermediate collapses). Therefore, there is a net consumption of one equivalent of methoxide.

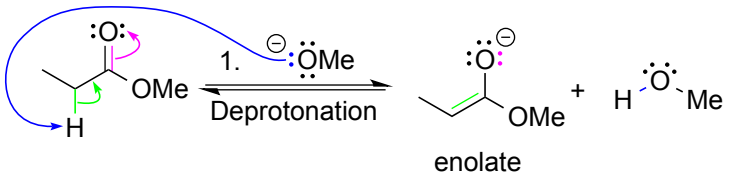
During the workup with aqueous acid, the enolate of the β-keto ester is protonated to afford the neutral product.



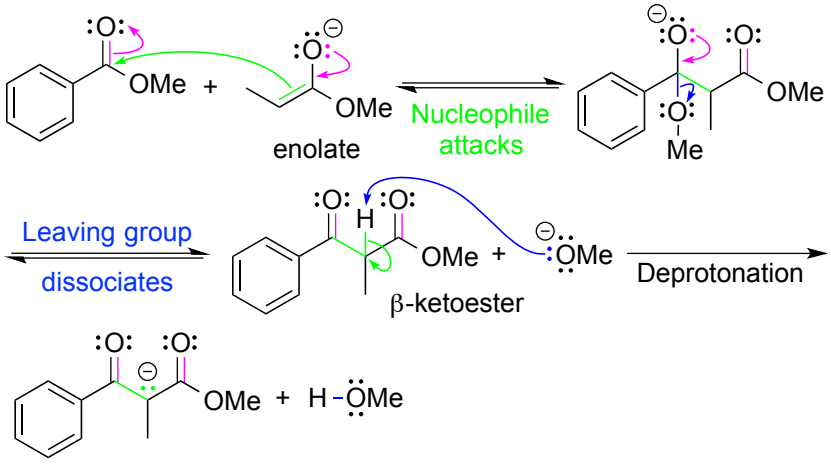
• Much like crossed-aldol reactions are possible, so are crossed-Claisen (or mixed-Claisen) condensations. It is still useful to select one reactant that lacks α-protons in order to avoid complex product mixtures. In the following example, methyl benzoate and methyl propionate undergo crossed-Claisen condensation upon treatment with methoxide.



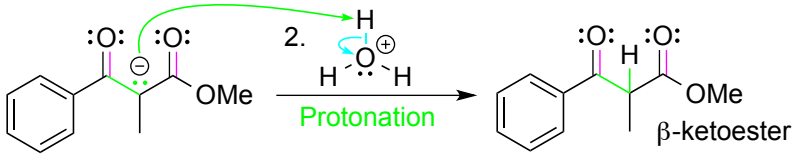
The reaction begins with the deprotonation of the only enolizable ester, methyl propionate.



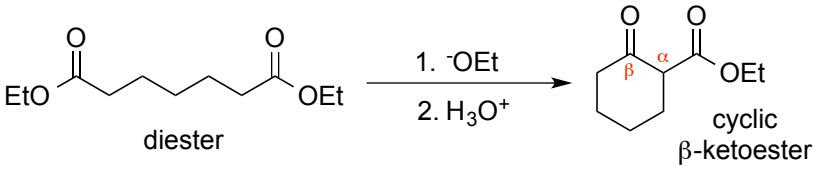
The ester enolate then attacks methyl benzoate's carbonyl carbon to yield a tetrahedral intermediate. The collapse of this intermediate re-forms the carbonyl as methoxide is expelled. The reaction is driven by methoxide's removal of the especially acidic proton α to two carbonyls.



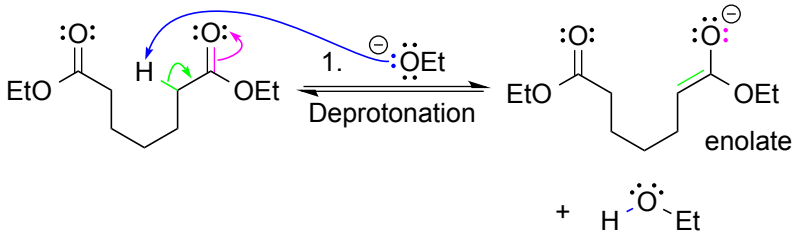
Upon workup, the enolate is protonated to afford the β-keto ester.



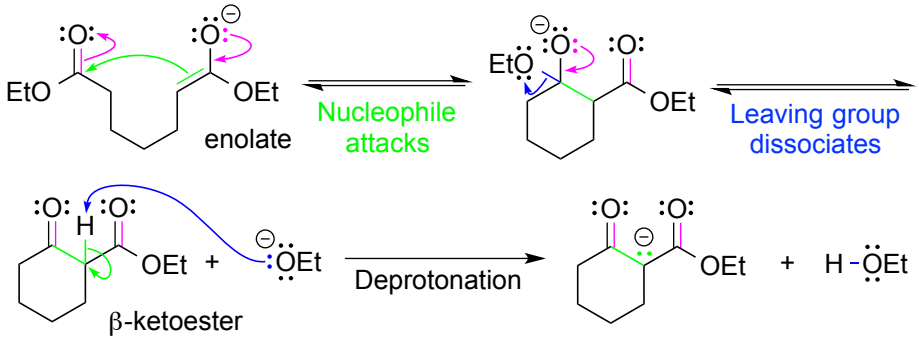
• In the previous section, we saw that aldol reactions can take place intramolecularly to generate cyclic products. The same is true here. The intramolecular variation of the Claisen condensation is known as the Dieckmann condensation. In the following example, diethyl pimelate (a diester) is treated with ethoxide to produce a cyclic β-ketoester.



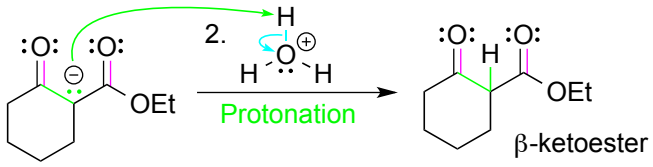
The deprotonation of one of the α-carbons affords an ester enolate that is tethered to an electrophile.



Since the electrophilic carbonyl carbon is a mere six atoms away from the nucleophilic α-carbon, intramolecular attack ensues. This generates not only a new carbon-carbon σ bond, but also a six-membered ring. When the tetrahedral intermediate collapses to reinstall the carbonyl, ethoxide is displaced. This ethoxide ion readily removes the acidic proton that is α to both carbonyls, thereby driving the reaction to completion.



Workup serves to restore the α-proton and yields the final product.



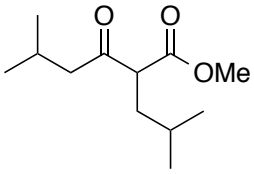
To summarize, Claisen condensation is the base-promoted union of two esters. It is driven by the deprotonation of the β-ketoester product, which possesses the most acidic hydrogen in the system. Acidic workup returns a proton to this center.

The crossed-Claisen condensation utilizes two different ester substrates. This reaction is most efficient when one ester possesses no α-protons and cannot, therefore, enolize to become a nucleophile.

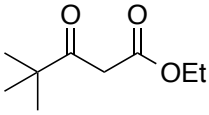
The intramolecular version of the Claisen condensation is known as the Dieckmann condensation. It too produces β-ketoesters, but since this variation is intramolecular, a ring is also introduced.

Problem 7. Provide the structures of the esters needed to prepare each of the following compounds through Claisen condensation.

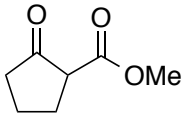
(a)



(b)

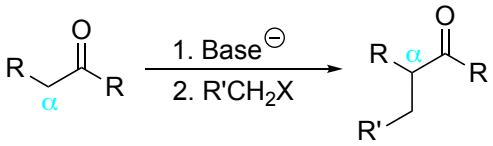


(c)

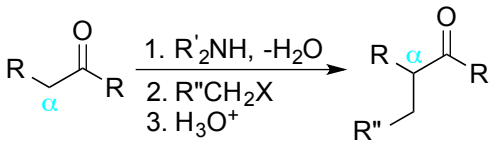


Section 7: Alpha alkylation

In the previous entries, we have seen that the α position can be deprotonated and rendered nucleophilic upon treatment with base. If the enolate is then treated with an alkyl halide (or a comparable electrophile), the α position will be alkylated.

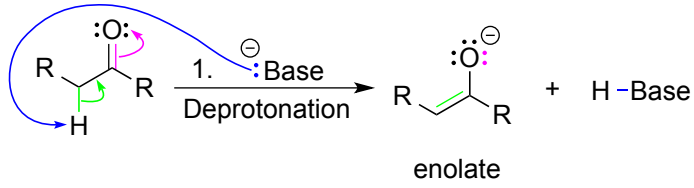


This transformation can also be achieved via the intermediacy of an enamine.

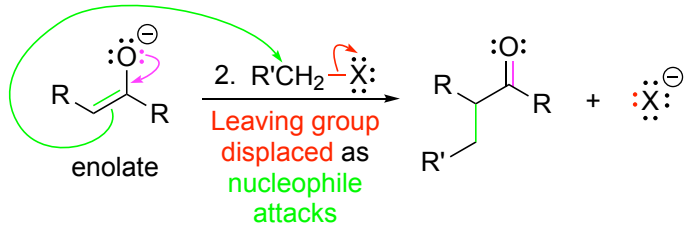


Mechanistic considerations

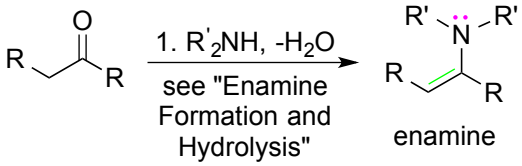
• When treated with base, the α-carbon can be deprotonated to afford the enolate.



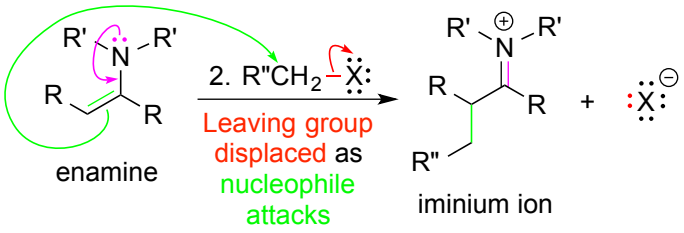
The enolate can then attack an unhindered alkyl halide to install the new substituent at the α position. This is merely an S_N2 reaction of an alkyl halide in which an enolate is acting as the nucleophile that displaces the good leaving group. Recall that alkyl halides must be unhindered to participate in S_N2 reactions.



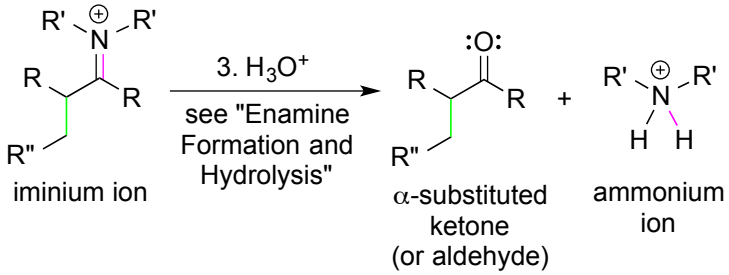
• A mild alternative to the method presented above entails the use of an enamine to achieve α-alkylation. In the first step of this process, the enamine is formed by condensation of a ketone or aldehyde with a secondary amine. The complete mechanism for this conversion is shown in the section on enamine formation and hydrolysis in the chapter on the reactions of aldehydes and ketones.



The enamine is also nucleophilic at the α-carbon, so when treated with an alkyl halide, it can attack and displace the leaving group. This results in an iminium ion bearing a new substituent on the α position.

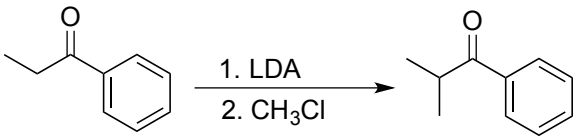


The iminium ion is then hydrolyzed during the final step of the reaction when aqueous acid is added. A complete mechanism for this reaction is also found in the section on enamine formation and hydrolysis in Chapter 15. The hydrolysis unveils the α-alkylated ketone (or aldehyde) and releases the secondary amine in its protonated form.

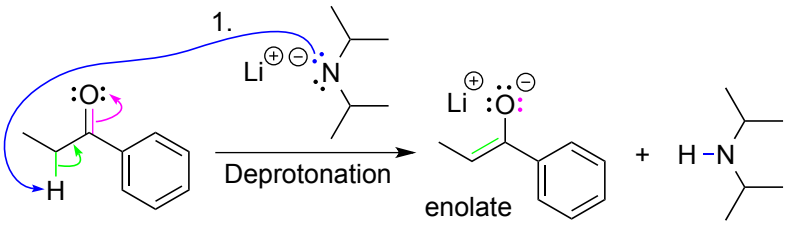


Specific examples of alpha alkylation

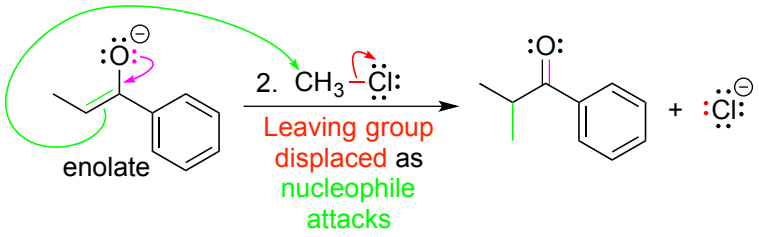
• In the following example, propiophenone is alkylated in the α position using methyl chloride.



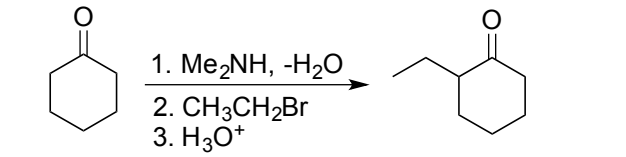
In the first step of the reaction, it is common to treat the substrate with a strong, non-nucleophilic base to completely deprotonate the α-carbon. During the aldol and Claisen condensations, fairly weak bases were used because both the enolate and the unmodified substrate were needed for the reaction to move forward. In α-alkylation however, it is desirable to convert all of the substrate to its corresponding enolate. Strong, non-nucleophilic bases used for this purpose include reagents such as lithium diisopropylamide (LDA) and sodium hydride (NaH). In this specific example, LDA is used. It forms the enolate, and the equilibrium significantly favors the products. This can be rationalized by examining the pK_a values of the ketone (~20) and diisopropylamine (~35), which shows that the products are favored by approximately 10^{15}.



The enolate is then treated with methyl chloride. Attack of the enolate displaces chloride and yields the α-alkylated product.

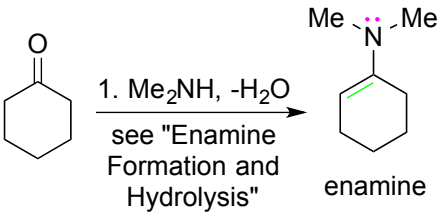


• In the next example, an enamine is employed to achieve the α-alkylation of cyclohexanone.

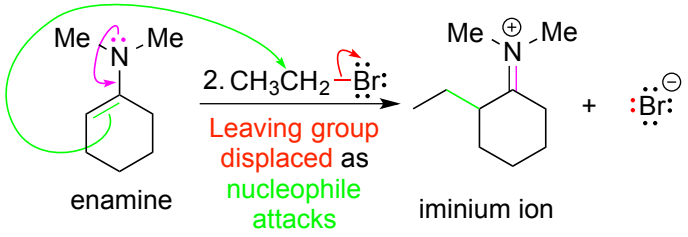


cyclohexanone 2-ethylcyclohexanone

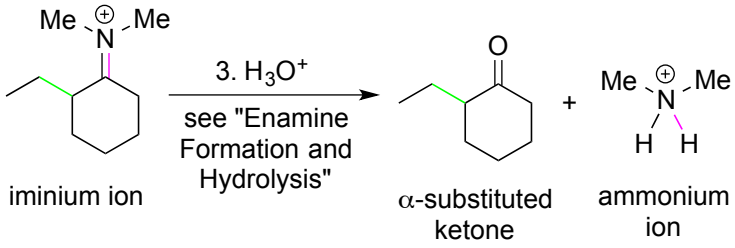
In the first step of the sequence, dimethylamine condenses with cyclohexanone to afford the enamine.



The enamine then attacks ethyl bromide, displacing Br^- and installing the new bond to the ethyl group.

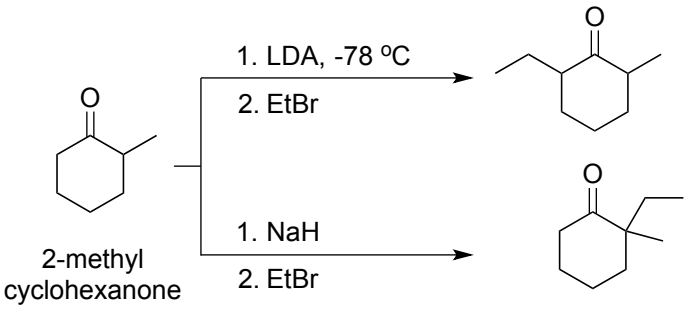


Finally, the iminium ion is hydrolyzed when aqueous acid is added.

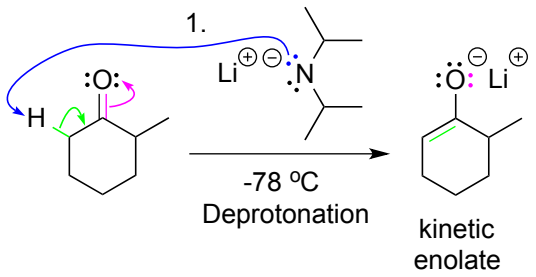


Regiochemical considerations

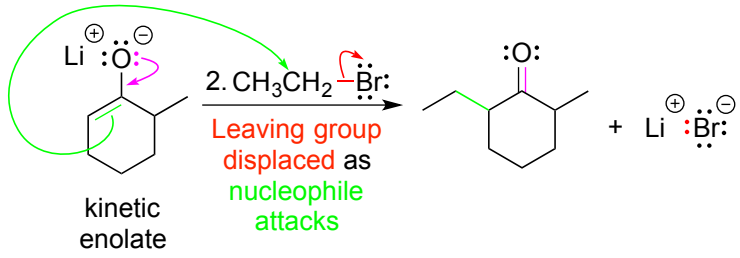
In the preceding examples, there was no question of where alkylation would occur. There was either just one α-carbon with protons, or the molecule was symmetrical. However, some substrates may have two different α-carbons whose alkylation would lead to different products. Such is the case with 2-methylcyclohexanone. The choice of base and temperature allows for selective alkylation at a single location.



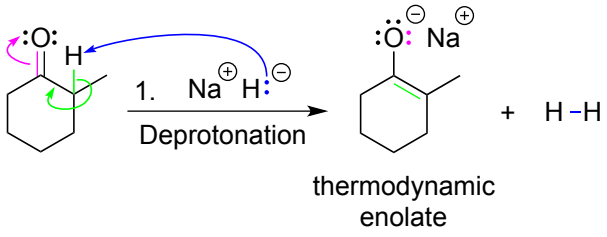
LDA is a hindered base due to its bulky isopropyl groups. When LDA is used at low temperature, the more accessible α-proton is removed. This forms what is known as the kinetic enolate. The removal of this proton proceeds through a transition state with minimal steric hindrance. Deprotonation at the other α center would have a higher-energy transition state due to greater steric encumbrance. The enolate formed under these conditions (LDA, low temperature) is termed the kinetic enolate since it is formed more readily.



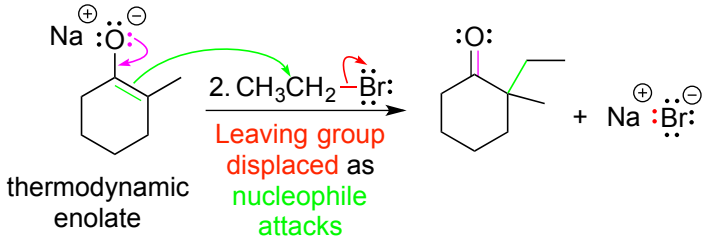
The kinetic enolate then attacks ethyl bromide to yield 2-ethyl-6-methylcyclohexanone.



If alkylation is desired at the other α-carbon, an unhindered strong base, such as sodium hydride (NaH) is used at room temperature. Under these conditions, either α-carbon may be deprotonated. Consequently, the thermodynamically favored enolate predominates at equilibrium. This is the enolate with a more highly substituted carbon-carbon double bond, and it results from deprotonation of the more highly substituted α position.



When the thermodynamic enolate is treated with ethyl bromide, the regioisomeric α-alkylation product is obtained.

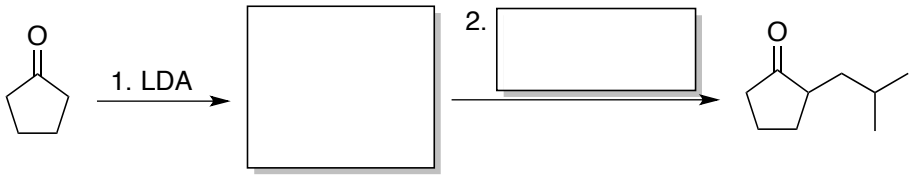


To conclude, alkylation at the position α to a carbonyl can be achieved through the enolate or the enamine. In either case, the α-carbon is rendered more nucleophilic so as to facilitate its attack on the electrophilic alkyl halide.

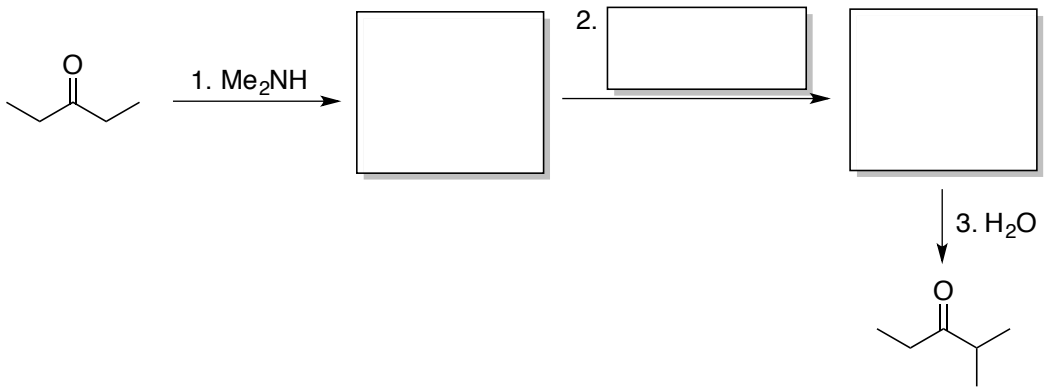
When two unique α positions are present, the choice of base and temperature will determine which enolate is formed. Deprotonation with LDA at low temperatures proceeds through a lower-energy transition state when it occurs at the less hindered site. This results in the kinetic enolate. On the other hand, deprotonation with sodium hydride affords the more stable (and therefore thermodynamically favored) enolate.

Problem 8. Fill in the missing intermediates and reagents in the following schemes.

(a)



(b)



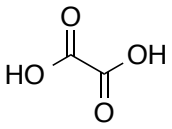
(c)

(d)

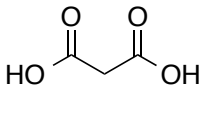
Section 8: Malonic ester synthesis

The malonic ester synthesis employs the reactivity of the α-carbon in the preparation of mono or disubstituted acetic acid derivatives. The reaction is named for the substrate, which is a diester formed from malonic acid.

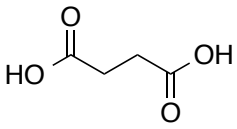
To appreciate the nomenclature, you need to be aware of the names given to the common dicarboxylic acids, which are also called diacids. The following diacid names may be easier to remember using the mnemonic "Oh my, such good apple pie," where the first letter of each word corresponds with the first letter in the names of the diacids. If you merely recall that the smallest possible diacid contains two carbons, you can quickly reconstruct the entire homologous series using this mnemonic device.



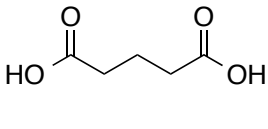
oxalic acid



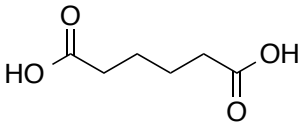
malonic acid



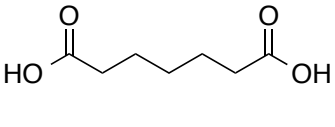
succinic acid



glutaric acid

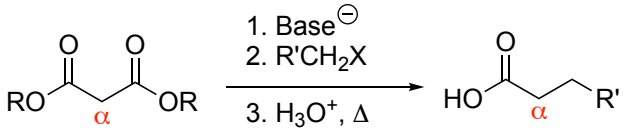


adipic acid



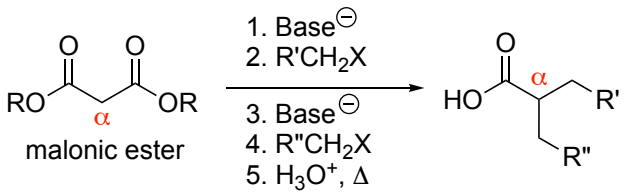
pimelic acid

The malonic ester synthesis utilizes a diester derived from the three-carbon diacid, malonic acid. The preparation of monosubstituted acetic acid derivatives is a three-step process involving: (1) formation of the enolate; (2) alkylation; and finally (3) hydrolysis and decarboxylation.



malonic ester

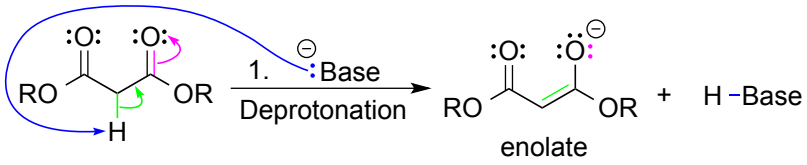
The synthesis of disubstituted acetic acid derivatives is quite similar. It simply incorporates an additional round of deprotonation and alkylation.



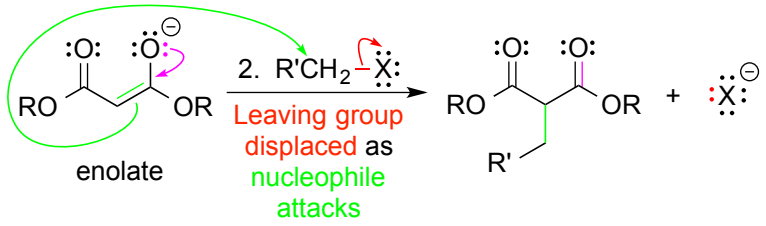
malonic ester

Mechanistic considerations

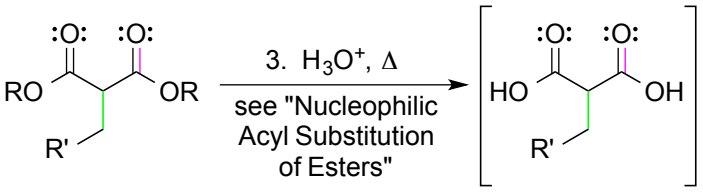
• Let's examine the mechanism for the formation of monosubstituted acetic acid derivatives first. The α position of malonic ester is adjacent to two ester carbonyls, which renders it fairly acidic (pK_a ~13). Consequently, it can be deprotonated readily to yield an enolate.



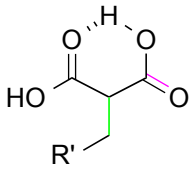
In the next step of the reaction, an electrophile, such as an alkyl halide, is added to achieve α-alkylation as discussed in the previous section. The enolate attacks the electrophilic carbon bearing the leaving group and displaces the halide.



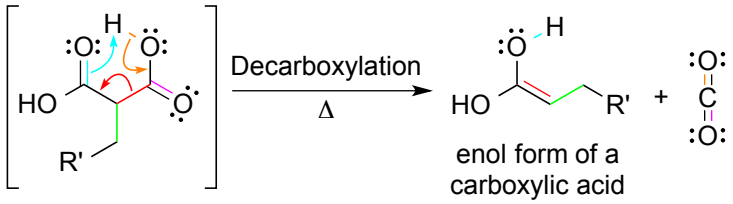
Since the critical new C–C bond has now been installed, one of the two ester groups can be removed. The malonic ester starting material was chosen because of its doubly activated α position, which made deprotonation facile under mild conditions. Now that the second activating group has served its purpose, it can be dispensed with. This happens upon heating in aqueous acid. The esters are first hydrolyzed to the corresponding carboxylic acids. See the section on the nucleophilic acyl substitution of esters in Chapter 16 for the full mechanism of this hydrolysis.



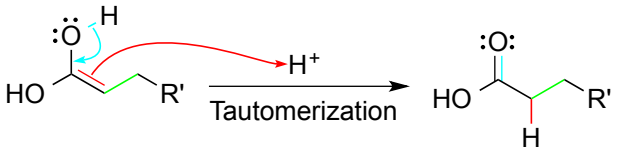
Decarboxylation then follows at the elevated temperatures used for this step. The proton of one carboxylic acid can participate in six-membered hydrogen bonding with the carbonyl oxygen of the other carboxylic acid. The diacid is drawn below so as to highlight that association.



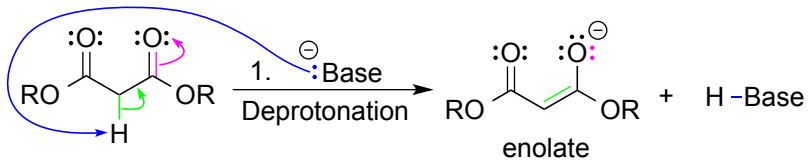
As the hydrogen bond becomes stronger, the carbonyl π electrons can be used to remove the carboxylic acid proton. This frees the H–O σ bonding electrons, which collapse between oxygen and carbon to form the second π bond of carbon dioxide. Finally, the carbon-carbon bond tethering the carboxyl group to the molecule breaks, yielding the enol form of a carboxylic acid.



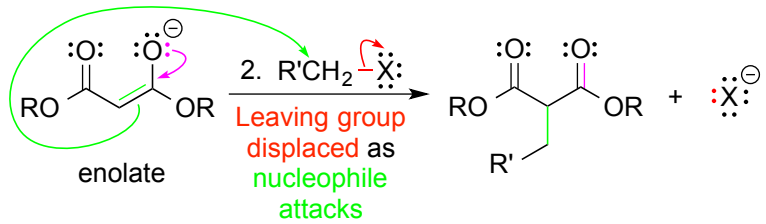
The enol spontaneously tautomerizes through protonation at the α center and loss of an enol proton. The final monosubstituted acetic acid product is thus obtained.



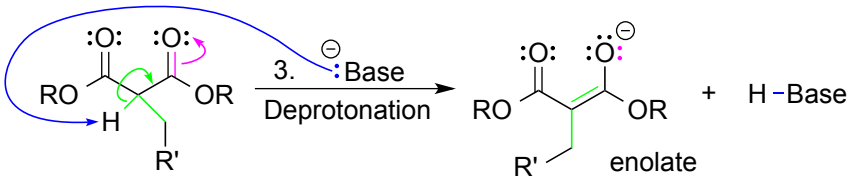
• The preparation of disubstituted acetic acid derivatives follows the same pattern. The reaction begins with enolate formation.



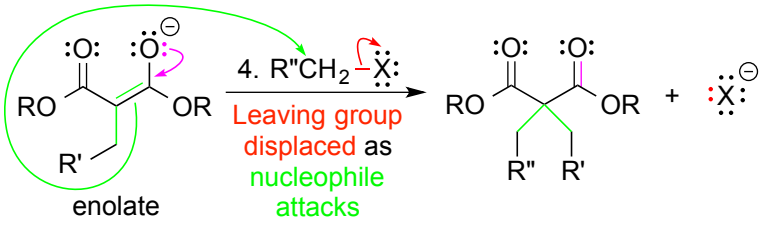
Alkylation follows, just as before.



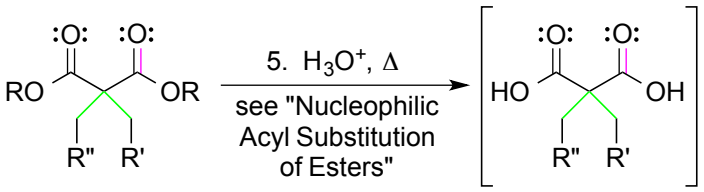
One proton is left on the α-carbon after the first alkylation. Additionally, the acidity of this position remains high because both activating carbonyls are still present. Therefore, if desired, the remaining α-proton can be removed to form another enolate.



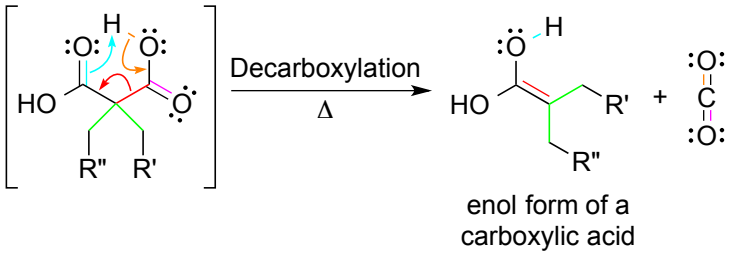
This enolate can then be alkylated using another alkyl halide.



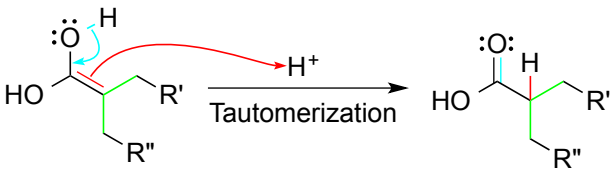
Finally, the endgame of the synthesis is the same as before. The esters are both hydrolyzed in aqueous acid.



At elevated temperatures, the diacid then spontaneously decarboxylates to afford the product in its enol form.

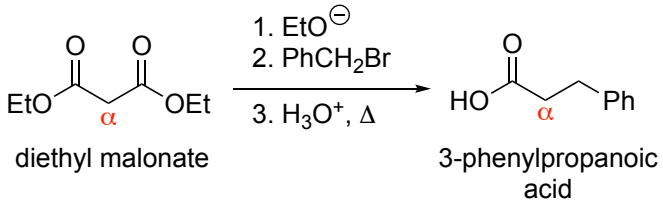


Tautomerization yields the disubstituted acetic acid derivative.



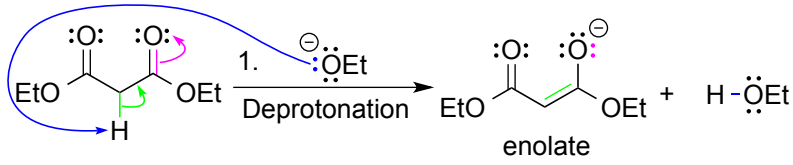
Specific examples of the malonic ester synthesis

• In the example below, diethyl malonate is converted to 3-phenylpropanoic acid through sequential treatment with ethoxide, benzyl bromide, and aqueous acid.

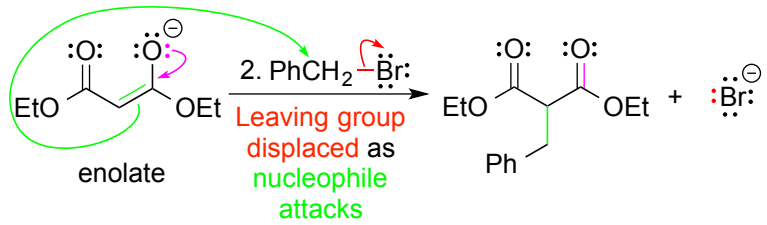


diethyl malonate — 3-phenylpropanoic acid

Since the α position of diethyl malonate is doubly activated giving it a pK_a of approximately 13, it is acidic enough to be efficiently deprotonated by ethoxide, whose conjugate acid (ethanol) has a pK_a of about 16. Notice that the alkoxide was chosen so that its alkyl group matches those of the esters. This prevents transesterification from being a complicating factor.

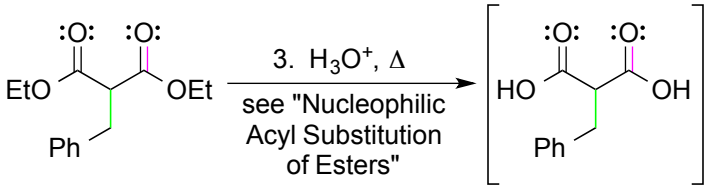


The resulting enolate can be alkylated by an unhindered alkyl halide. Remember from the previous section on alpha alkylation that this step is an S_N2 reaction in which the enolate acts as a nucleophile and attacks benzyl bromide to displace Br^-. Since it is an S_N2 reaction, the alkyl halide must be unhindered.

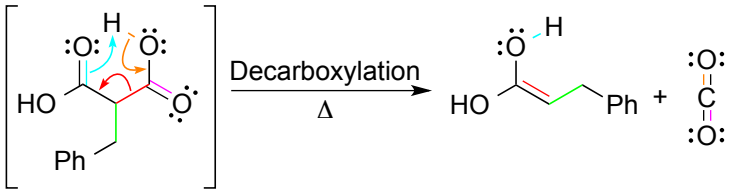


enolate

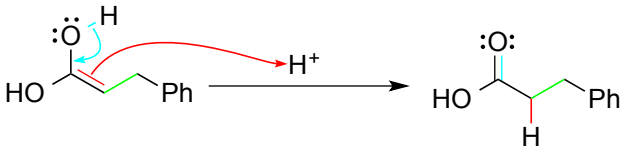
The two ethyl esters can now be hydrolyzed to form the diacid.



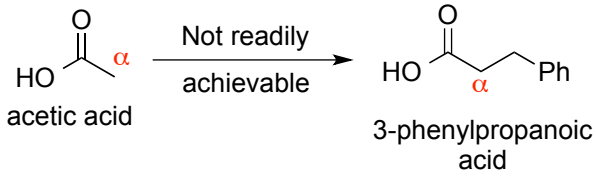
This diacid subsequently decarboxylates through: exchange of one carboxylic acid proton, formation of the second π bond of carbon dioxide, and cleavage of a carbon-carbon bond.



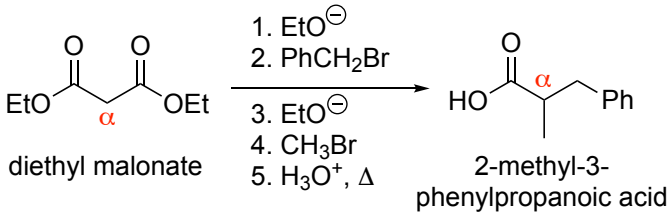
The resulting enol tautomerizes to afford 3-phenylpropanoic acid.



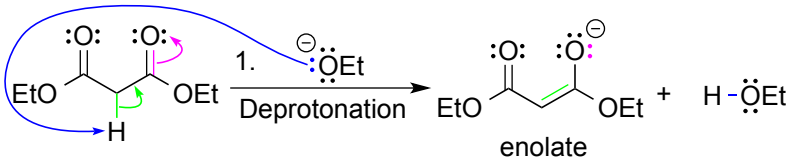
It is important to step back and appreciate the overall strategy behind the malonic ester synthesis. It allows us to generate acetic acid derivatives that we could not easily make from acetic acid itself. A direct synthesis from acetic acid suffers from two fatal flaws. First, the most acidic proton of acetic acid is the carboxylic acid proton, not the proton at the α position. And, secondly, once the carboxylate is formed through deprotonation of the carboxylic acid, it would be difficult to deprotonate the same molecule a second time at the α position. The malonic ester synthesis circumvents these two problems by masking the acid as an ester and by adding a second, removable activating group to enhance the acidity of the α center.



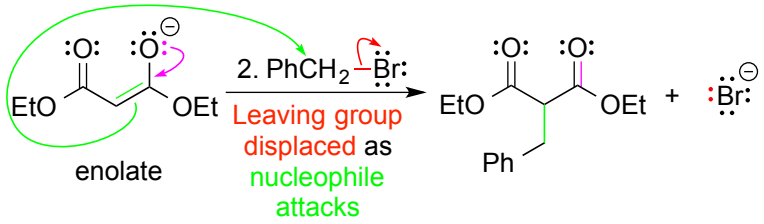
• In the next example, diethyl malonate is used to prepare 2-methyl-3-phenylpropanoic acid. This synthesis requires two rounds of alkylation prior to hydrolysis and decarboxylation.



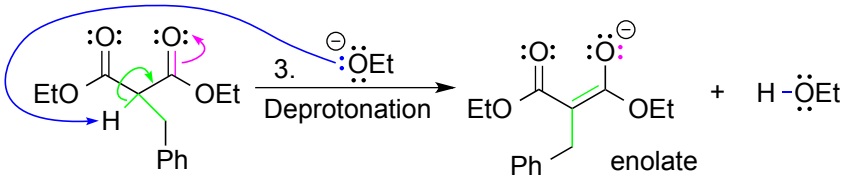
The reaction begins with enolate formation.



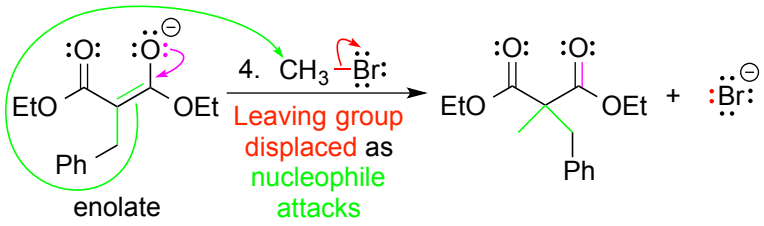
The first alkylation employs benzyl bromide, just as in the last example.



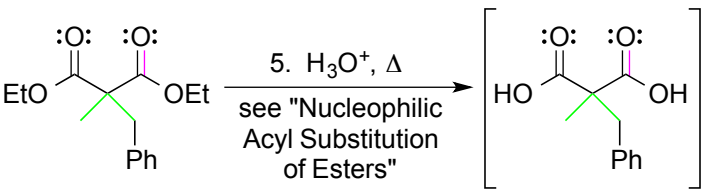
Since an α-proton remains after the first alkylation, it can now be removed to afford a new enolate.



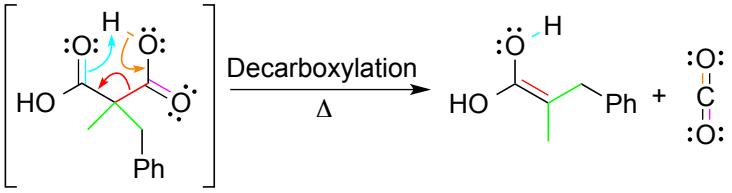
Alkylation of this second enolate with bromomethane installs a methyl group on the α-carbon.



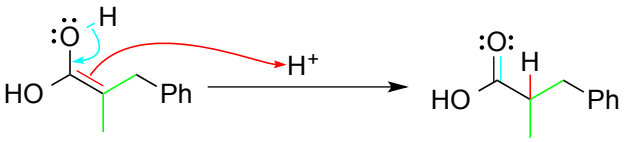
It is worth noting that the order of the two alkylation events does not matter. Interchanging steps 2 and 4 would result in the same doubly alkylated product. This diester is now hydrolyzed to yield the diacid.



Decarboxylation follows, releasing carbon dioxide and generating the product in its enol form.



Finally, tautomerization of the enol yields 2-methyl-3-phenylpropanoic acid.

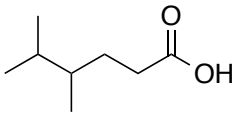


In conclusion, the malonic ester synthesis provides access to mono or disubstituted acetic acid derivatives. These compounds would be difficult to access through direct alkylation of acetic acid. The use of a malonic ester masks the problematic carboxylic acid and allows for mild deprotonation conditions due to the second carboxyl group that enhances the acidity of the α position.

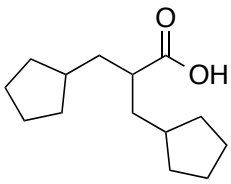
The reaction has a few stages. It begins with enolate formation and alkylation. These are the two steps of α-alkylation (as seen in the previous section). If a disubstituted product is desired, these two steps can be repeated. After α-alkylation is complete, heating with aqueous acid results in hydrolysis of both esters and decarboxylation to afford the final product.

Problem 9. Use the malonic ester synthesis to prepare the following carboxylic acids.

(a)



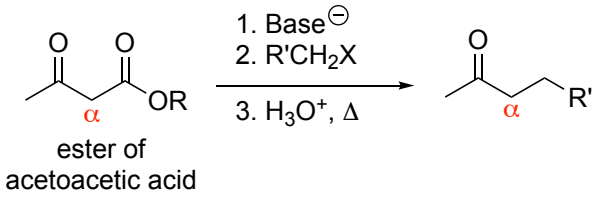
(b)



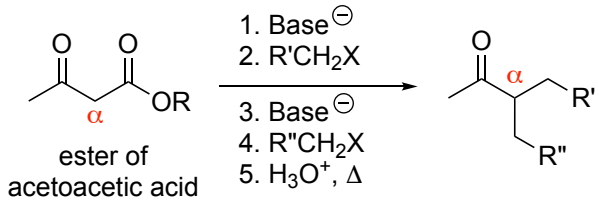
Section 9: Acetoacetic ester synthesis

The acetoacetic ester synthesis is very similar to the malonic ester synthesis. This procedure also utilizes the reactivity of the α-carbon but in the preparation of mono or disubstituted acetone derivatives. The reaction is named for the substrate, which is an ester of acetoacetic acid.

The preparation of monosubstituted acetone derivatives involves three-steps: (1) formation of the enolate; (2) alkylation; and finally (3) hydrolysis and decarboxylation.

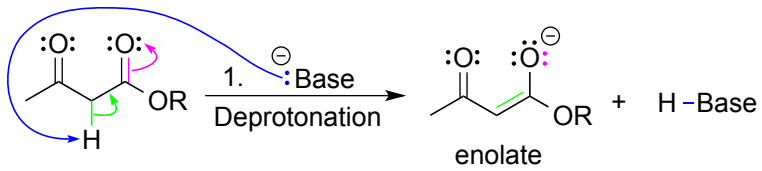


Disubstituted acetone derivatives are prepared in an analogous fashion, but a second iteration of α-alkylation occurs prior to hydrolysis and decarboxylation.

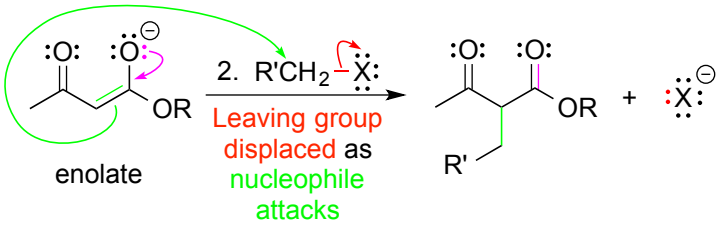


Mechanistic considerations

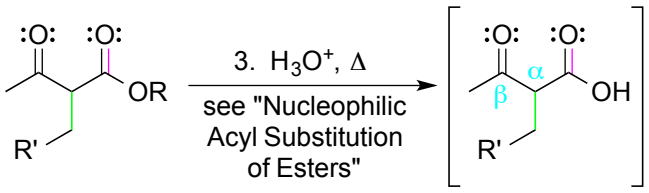
• The preparation of a monosubstituted acetone derivative begins with enolate formation. A base removes one of the two most acidic protons in the molecule, which are those α to both carbonyls (pK_a ~11). The electrons from the broken C–H σ bond can be delocalized into both the ketone and ester carbonyls, providing a great deal of stabilization for the enolate.



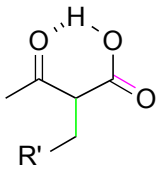
The enolate is alkylated when it attacks an alkyl halide (or a comparable electrophile) and displaces the good leaving group. Since this is an S_N2 reaction, the alkyl halide must be unhindered.



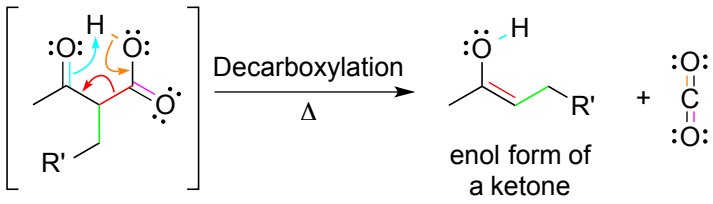
Upon heating with aqueous acid, the ester is hydrolyzed to a β-ketoacid. The complete mechanism for this transformation is provided in the section on the nucleophilic acyl substitution of esters in Chapter 16.



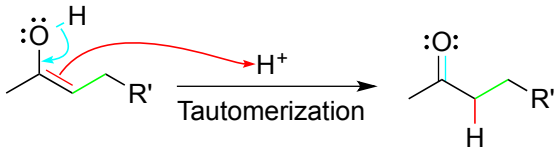
Drawing the β-ketoacid in a different conformation makes it more apparent that it can engage in intramolecular hydrogen bonding.



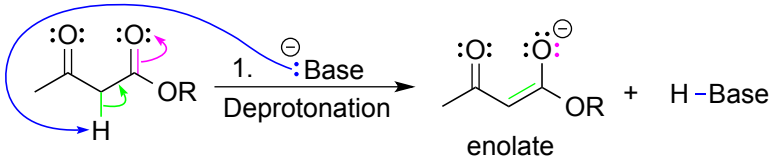
As the hydrogen bond grows stronger, the ketone π-bonding electrons can be used to remove the labile carboxylic acid proton. As a result, a new carbon-oxygen π bond is formed while a carbon-carbon σ bond is cleaved. This leads to the loss of the carboxylic acid as CO_2 and provides the product as its enol tautomer.



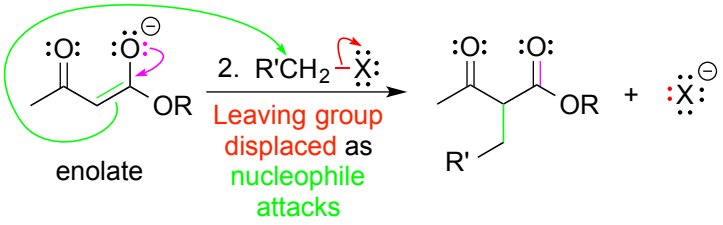
Tautomerization occurs spontaneously through protonation at the α position and loss of the enol proton. This generates the monosubstituted acetone derivative in its keto form.



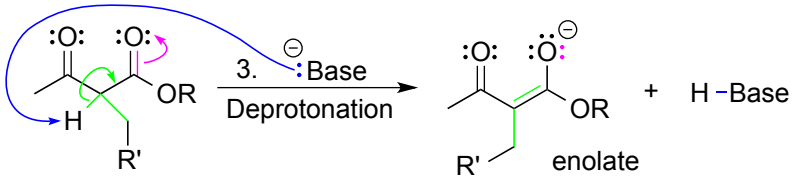
• The synthesis of disubstituted acetone derivatives is quite similar. The process begins with enolate formation.



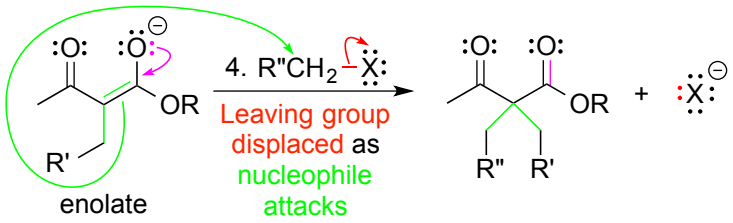
The first α-alkylation is completed when an alkyl halide is added in step 2.



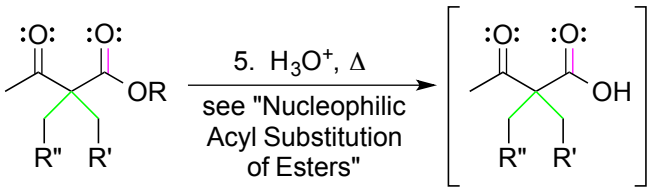
Since the doubly activated α-carbon still bears one proton, it is possible to deprotonate a second time to form a new enolate.



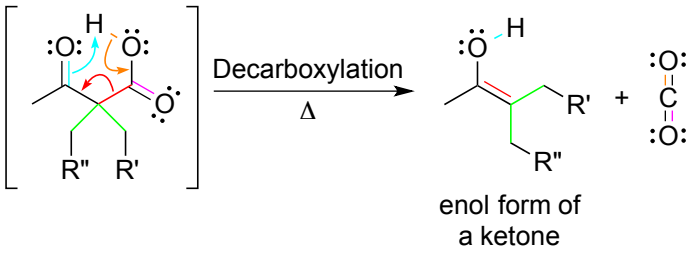
The second α-alkylation occurs when an alkyl halide is added to this enolate in step 4.



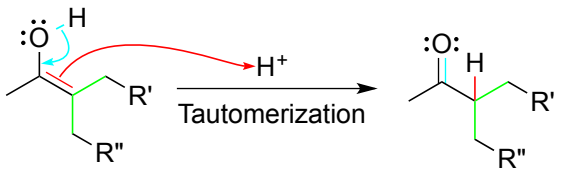
At this point, no highly acidic protons remain on the carbon between the ester and the ketone. Therefore, no further alkylation is possible at this center. Hydrolysis and decarboxylation can be initiated by heating in aqueous acid. The hydrolysis occurs first giving the β-ketoacid.



The β-ketoacid then decarboxylates to yield the product in its enol form.

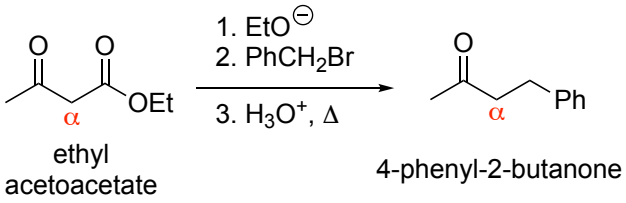


Tautomerization affords the disubstituted acetone derivative as the favored keto tautomer.

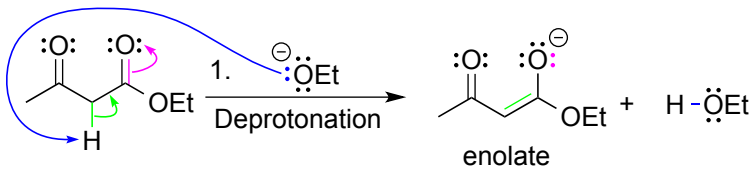


Specific examples of the acetoacetic ester synthesis

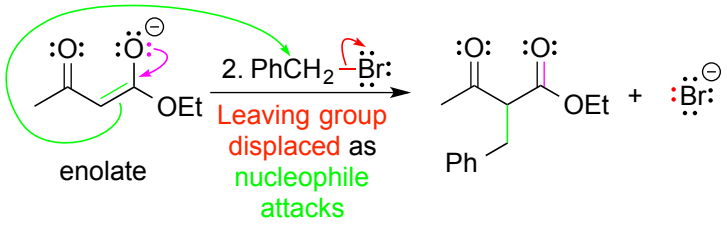
• In the following example, ethyl acetoacetate is used in the preparation of 4-phenyl-2-butanone, a monosubstituted acetone derivative.



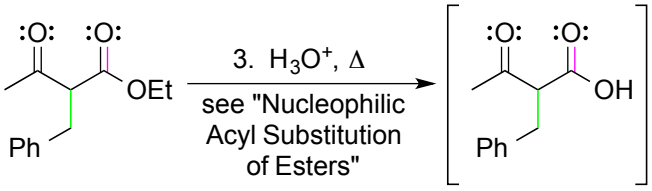
The synthesis begins with enolate formation. Ethyl acetoacetate is fairly acidic (pK_a ~11) at the position between the ketone and the ester. Consequently, mild bases can be used to deprotonate this substrate. Notice how the base chosen (ethoxide) has an alkyl group that matches the alkyl group of the ester. This prevents transesterification from becoming a complicating factor.



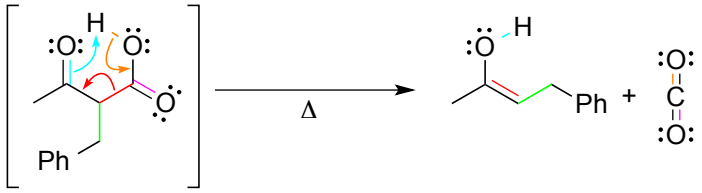
Addition of an alkyl halide—in this case benzyl bromide—completes the α-alkylation.



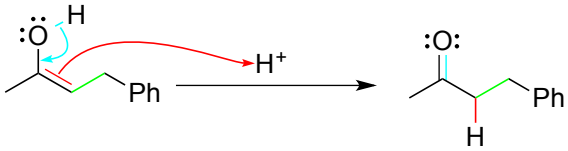
Acidic hydrolysis converts the ethyl ester to the corresponding carboxylic acid.



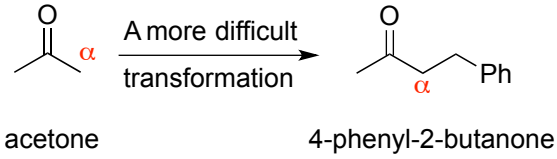
Since this particular carboxylic acid possesses a carbonyl in the β position, it is susceptible to decarboxylation when heated. This cleaves one carbon from the substrate in the form of carbon dioxide. The product is also produced in this step in its enol form.



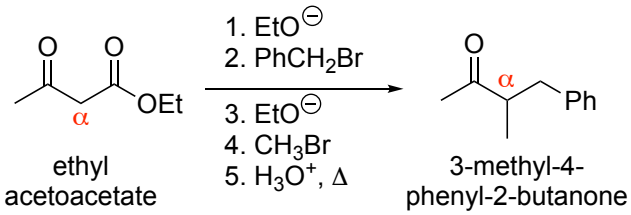
Tautomerization rapidly converts the product from its enol form to the favored keto form.



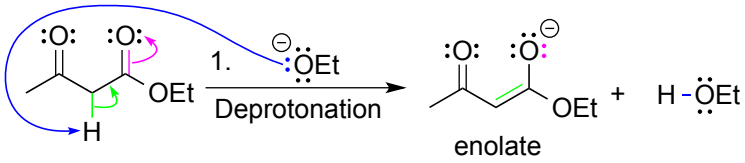
It is useful to consider the overall strategy behind the acetoacetic ester synthesis. This approach to the preparation of the target compound (4-phenyl-2-butanone) allowed for the use of a mild base because ethyl acetoacetate possesses two carbonyls that enhance the acidity of its α-carbon. The direct alkylation of acetone would have been more difficult. One reason is that a stronger base is needed to fully deprotonate its less acidic α-position. A second problem is that acetone tends to polymerize in base.



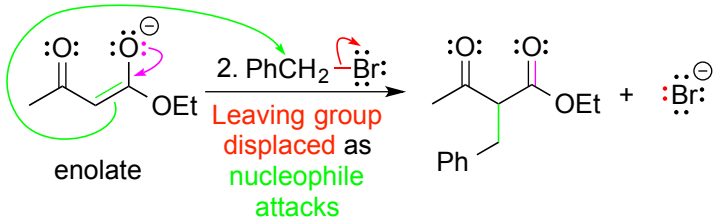
• In the next example, a disubstituted acetone derivative (3-methyl-4-phenyl-2-butanone) is prepared through two rounds of α-alkylation followed by hydrolysis and decarboxylation.



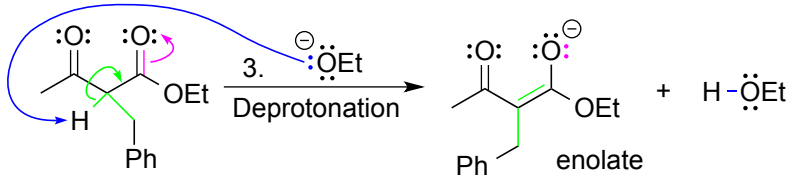
Enolate formation occurs when ethoxide is used to deprotonate the α-carbon of ethyl acetoacetate.



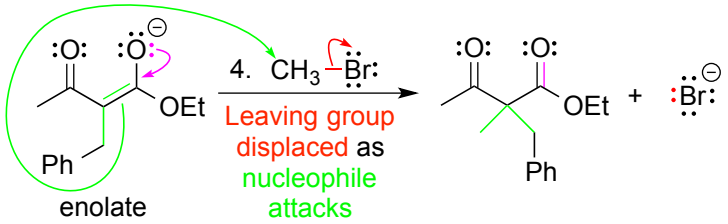
The first α-alkylation concludes with the addition of an alkyl halide bearing one of the two alkyl groups that we wish to install at the α position. The order of the two alkylations does not matter. We could install either the benzyl or the methyl group first. Benzyl bromide has been used below.



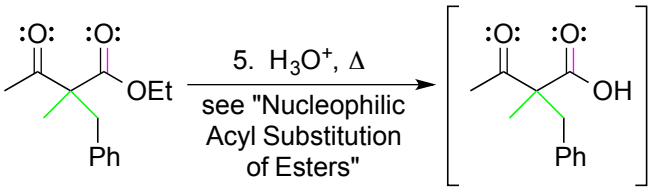
With one acidic proton remaining at the position between the two carbonyls, we can deprotonate yet again through treatment with ethoxide.



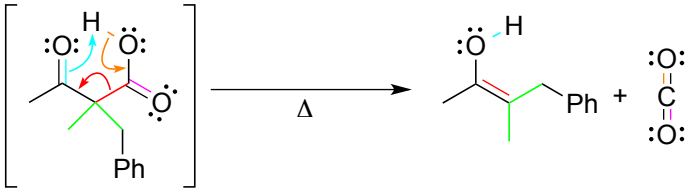
The newly formed enolate attacks methyl bromide in the fourth step of the reaction. This installs the second and last alkyl group that is needed at the α position.



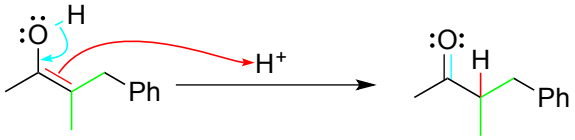
At this point, hydrolysis and decarboxylation will remove the ester from the substrate to afford the desired product. Hydrolysis occurs first and converts the ethyl ester to the carboxylic acid.



This β-ketoacid decarboxylates when heated. The enol tautomer of the product is obtained first.



Tautomerization occurs rapidly and spontaneously, giving the target compound.

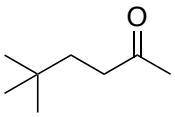


In summary, the acetoacetic ester synthesis allows us to produce mono or disubstituted acetone derivatives more conveniently than we could through direct α-alkylation of acetone itself. The ester in the substrate serves as a removable activating group that enhances the acidity of the α-protons, enabling deprotonation under mild conditions. When it is no longer needed, the ester is cleaved off through hydrolysis and decarboxylation.

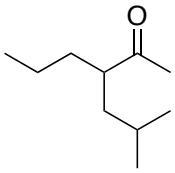
The reaction has a few stages that are directly comparable to those of the malonic ester synthesis. It begins with enolate formation and alkylation. These are the two steps of α-alkylation. If a disubstituted product is desired, these two steps can be repeated. After α-alkylation is complete, heating with aqueous acid results in hydrolysis of the ester and decarboxylation to afford the final product.

Problem 10. Use the acetoacetic ester synthesis to prepare each of the following ketones.

(a)

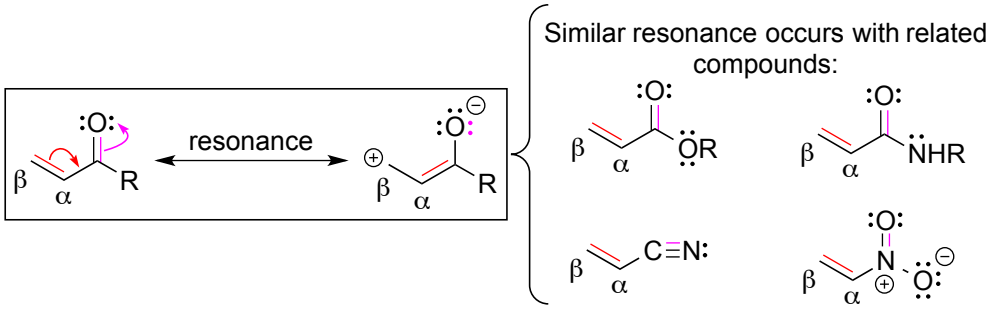


(b)

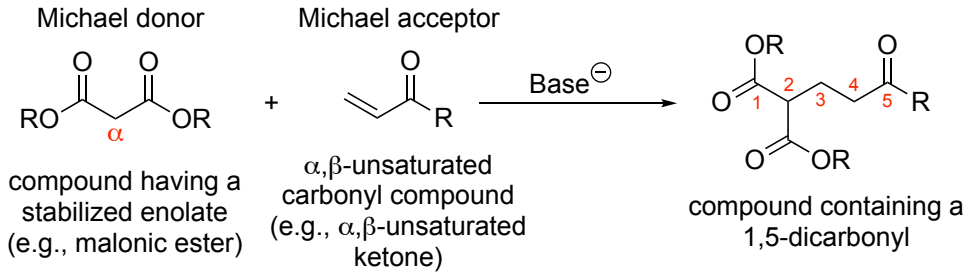


Section 10: Michael reaction

The Michael reaction is a specific type of conjugate addition to an α,β-unsaturated carbonyl compound (or its equivalent, such as an α,β-unsaturated nitrile). Conjugate addition is the result of nucleophilic attack at the β position. This can occur because the β-carbon is electron poor, as highlighted through resonance.

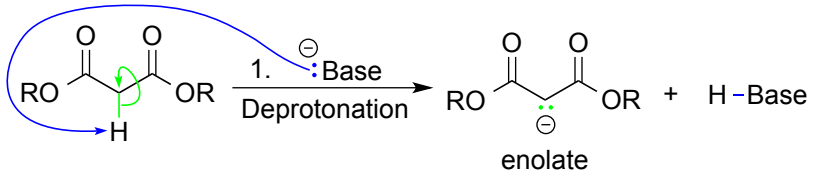


While powerful nucleophiles add directly to the carbonyl carbon (for examples, see the Grignard reaction sections in Chapters 15 and 16), weaker nucleophiles add to the β position. One type of weaker nucleophile is an enolate that is stabilized by resonance involving two electron-withdrawing groups, such as carbonyls. When such a nucleophile adds to the β position of an unsaturated compound, a new carbon-carbon bond is formed. This process is referred to as the Michael reaction.

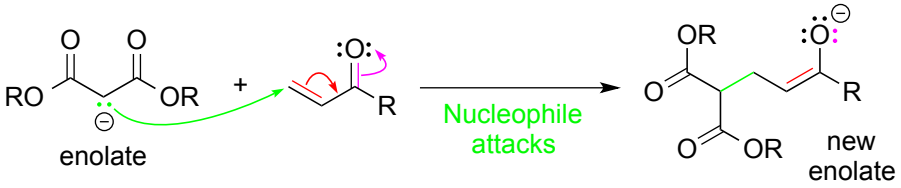


The nucleophile is termed a Michael donor, while the unsaturated compound is called a Michael acceptor. The product of this reaction is a 1,5-dicarbonyl compound.

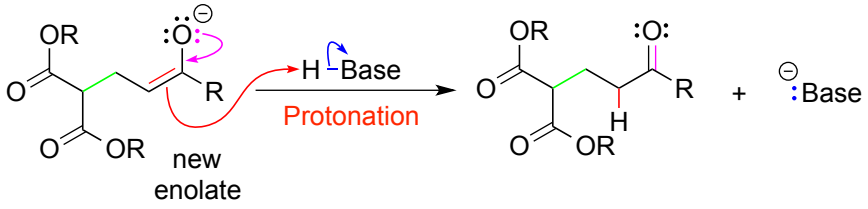
The reaction begins with the removal of the most acidic proton in the system by the base. While there may be more than one α position among the substrates used, there is typically only a single α position that is activated by two carbonyls. That center will be significantly more acidic than the others because deprotonation there yields an enolate with extended resonance delocalization.



This enolate, due to its resonance stabilization, is a milder nucleophile than those that add directly to the carbonyl carbon. Consequently, it is drawn to the β position of the α,β-unsaturated ketone used in this generic example. The alkene π bond is pushed toward the carbonyl, and the carbonyl π bond is displaced onto oxygen.

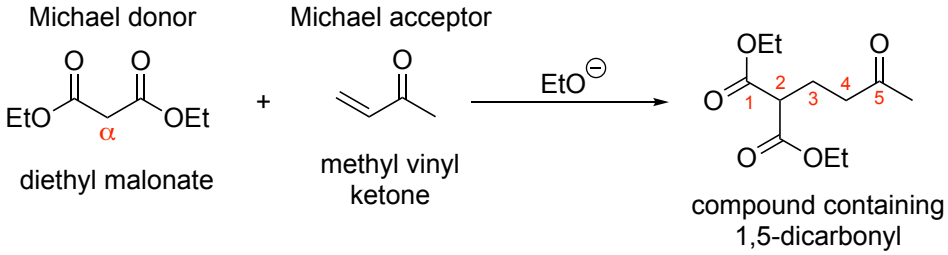


The new enolate formed from this addition is more basic due to lesser resonance stabilization, so it readily acquires a proton to yield the product.

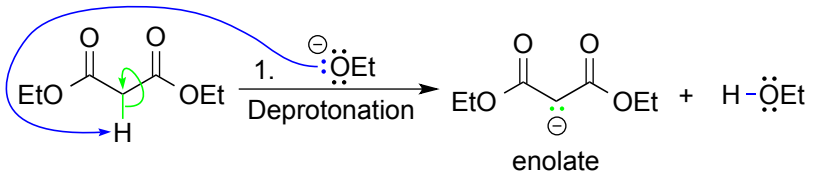


Specific examples of the Michael reaction

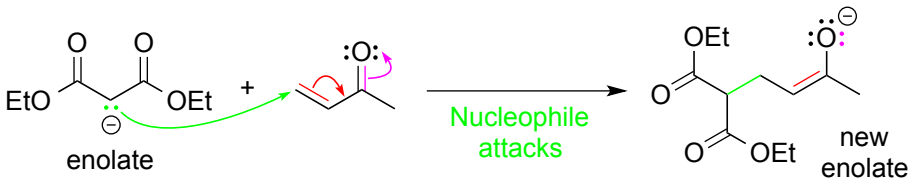
• In the following example, diethyl malonate (which was used in the malonic ester synthesis) was chosen as the Michael donor, and methyl vinyl ketone acts as the Michael acceptor.



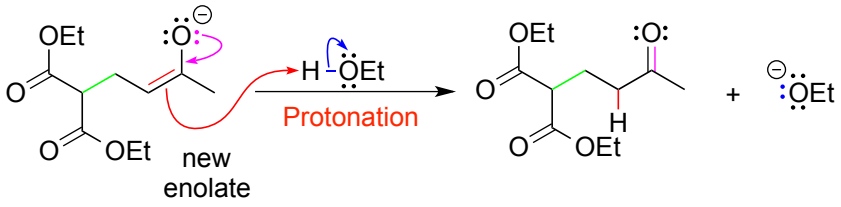
Although both methyl vinyl ketone and diethyl malonate have α-protons, only those of diethyl malonate are α to two carbonyls. These are therefore the most acidic protons in the system and can be removed by ethoxide. Notice that the alkoxide base has an alkyl group that matches that of the esters so that transesterification is not a complicating factor.



The resonance-stabilized enolate that results adds to the β-carbon of methyl vinyl ketone, forming a new carbon-carbon σ bond. The α,β-unsaturation is displaced, as is the carbonyl π bond.

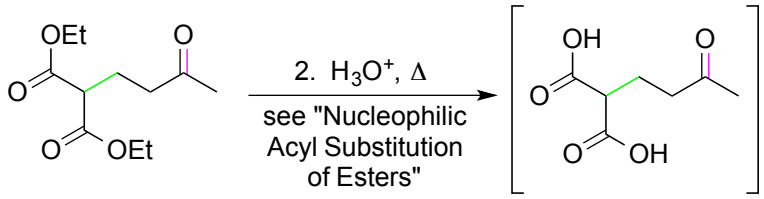


The new enolate that results is more basic since it has one fewer stabilizing carbonyl. Consequently, it readily deprotonates ethanol to afford the Michael reaction product.

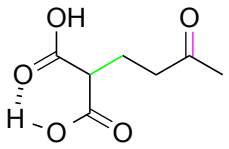


We can stop at this point if desired, but another option is to hydrolyze and decarboxylate the diethyl malonate moiety. If we choose to do this, a separate step will be used in which

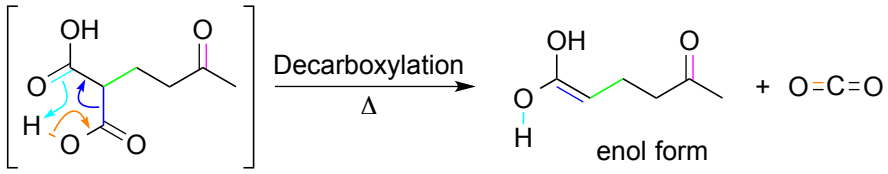
the Michael reaction product is heated with aqueous acid. This first hydrolyzes both of the esters.



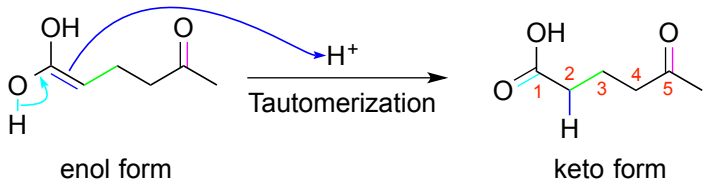
The diacid that results exhibits intramolecular hydrogen bonding, as highlighted in the following diagram.



As the intramolecular hydrogen bond grows stronger, the carbonyl π bond can be used to deprotonate the neighboring acid. This results in the formation of a new carbon-oxygen π bond, as well as the cleavage of a carbon-carbon bond.

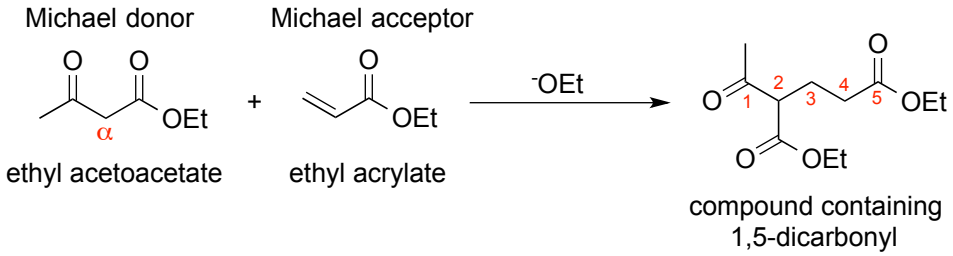


The resulting enol tautomerizes spontaneously to yield the final decarboxylation product, which still possesses a 1,5-dicarbonyl. This product could also be referred to as a δ-ketoacid because C-2 is the α position, C-3 is β, C-4 is γ, and C-5 is δ.

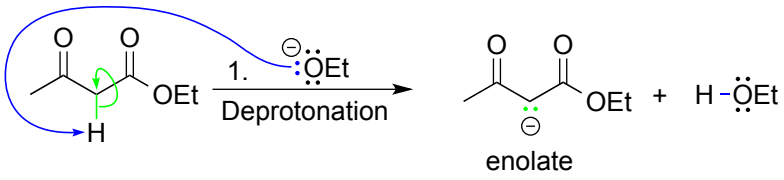


Note that this hydrolysis-decarboxylation sequence is reminiscent of the endgame of the malonic ester synthesis.

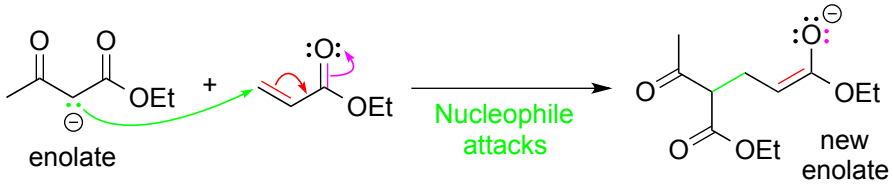
• In the next example, ethyl acetoacetate is used as the Michael donor, and the acceptor is ethyl acrylate.



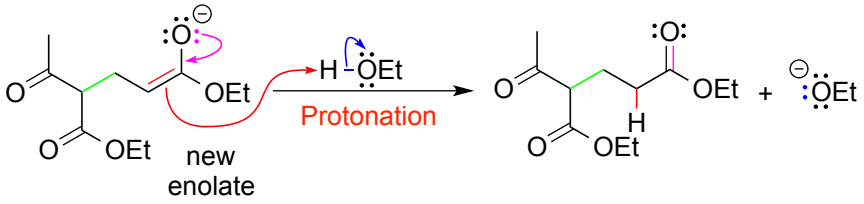
The reaction begins with deprotonation of the most acidic position, which is the only position between two electron-withdrawing carbonyls.



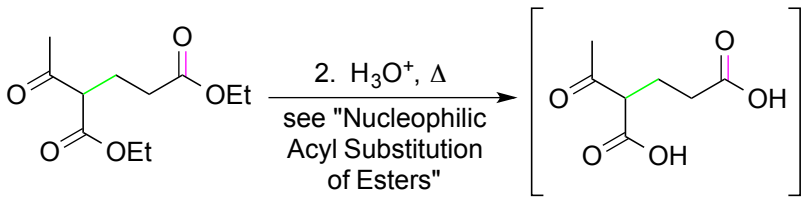
The stabilized enolate thus formed undergoes conjugate addition to the α,β-unsaturated carbonyl to yield a new enolate.



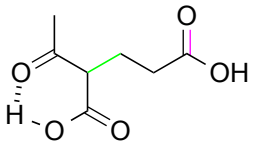
This newly formed enolate is of much greater basicity, so it deprotonates ethanol to conclude the Michael reaction.



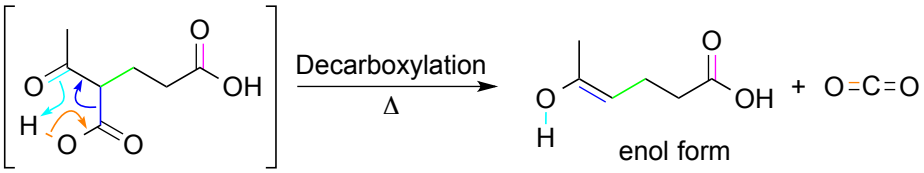
Again, we have the choice of stopping here at the end of the Michael reaction or proceeding to a second, separate step in which hydrolysis and decarboxylation will occur. If we choose the latter, heating in aqueous acid first hydrolyzes both ethyl esters.



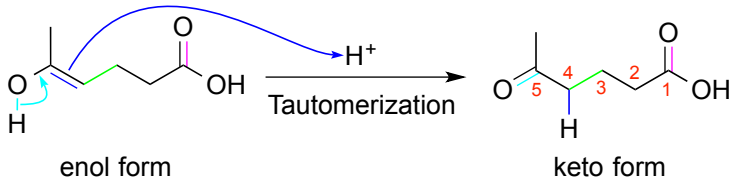
While the resulting hydrolysis product does contain two acids, only one can undergo decarboxylation. The acid with the β-keto group engages in six-membered intramolecular hydrogen bonding.



This is the acid that can decarboxylate. Decarboxylation requires a β-carbonyl so that the electrons from the breaking carbon-carbon bond can be funneled into that electron-withdrawing group.



The enol that is formed tautomerizes to provide the product in its keto form. This product still contains the 1,5-dicarbonyl that is the hallmark of Michael reaction. As in the last example, this product could also be termed a δ-ketoacid.



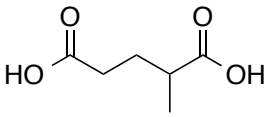
Note that this hydrolysis-decarboxylation sequence is reminiscent of the endgame of the acetoacetic ester synthesis.

To recap, the Michael reaction is a carbon-carbon bond forming reaction that occurs through conjugate addition of a stabilized enolate to an α,β-unsaturated compound. The stabilized enolate is the nucleophilic Michael donor, while the α,β-unsaturated compound is the electrophilic Michael acceptor. The reaction results in a 1,5-dicarbonyl.

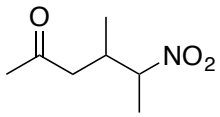
With certain Michael donors (those containing at least one ester), it is possible to hydrolyze and decarboxylate after the Michael reaction is complete. This entails a separate step, which is not formally a part of the Michael reaction, but it does provide additional synthetic versatility.

Problem 11. Prepare the following compounds using the Michael reaction.

(a)

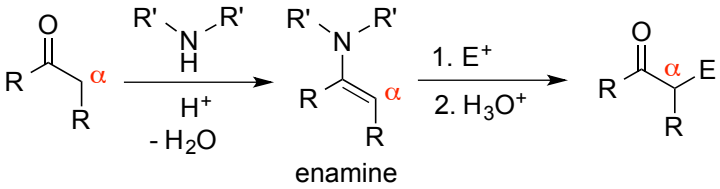


(b)



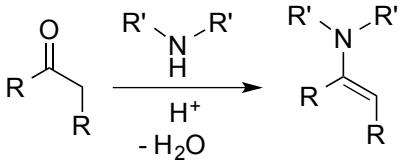
Section 11: Stork enamine reaction

Stork enamine reactions utilize the nucleophilicity of enamines at their α-carbon in order to form new carbon-carbon bonds under mild conditions. A ketone or aldehyde is first converted to the corresponding enamine through condensation with a secondary amine. That enamine then reacts with an electrophile (E^+), and the resulting iminium ion is hydrolyzed upon workup to afford the ketone or aldehyde bearing a new group at the α center.



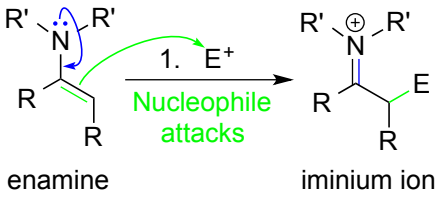
We have already seen an example of this in the alpha alkylation section when enamines were treated with alkyl halides. In this section, we will consider electrophiles other than alkyl halides, namely Michael acceptors which are the electrophiles in the Stork enamine reaction.

The first step is conversion of the ketone or aldehyde into an enamine. The mechanism for this transformation is covered in detail in the section on enamine formation and hydrolysis in Chapter 15.

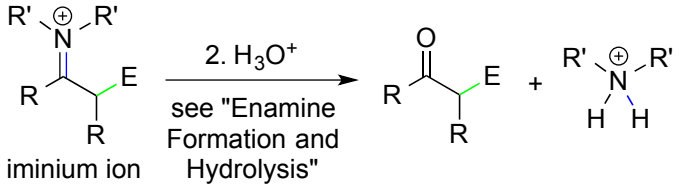


see "Enamine Formation and Hydrolysis"

The enamine is then treated with an electrophile. As the enamine π bond attacks, lone pair electrons from nitrogen form an iminium ion.

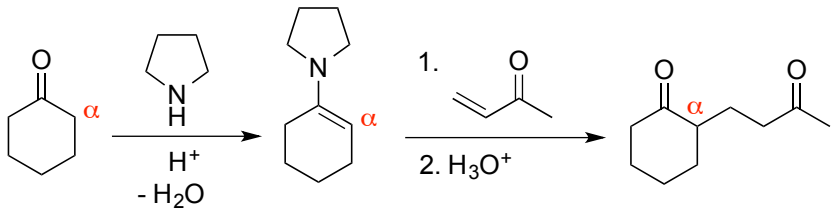


Subsequent treatment of the iminium ion with aqueous acid leads to hydrolysis, which unveils the original ketone or aldehyde. This mechanism is also described in Chapter 15. The ketone or aldehyde now bears a new substituent (E) on the α-carbon.

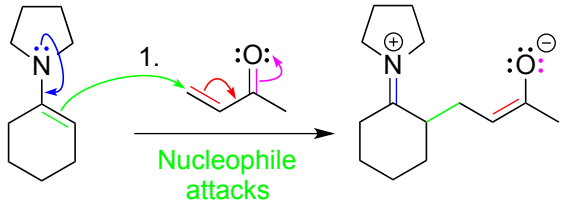


Specific examples of the Stork enamine reaction

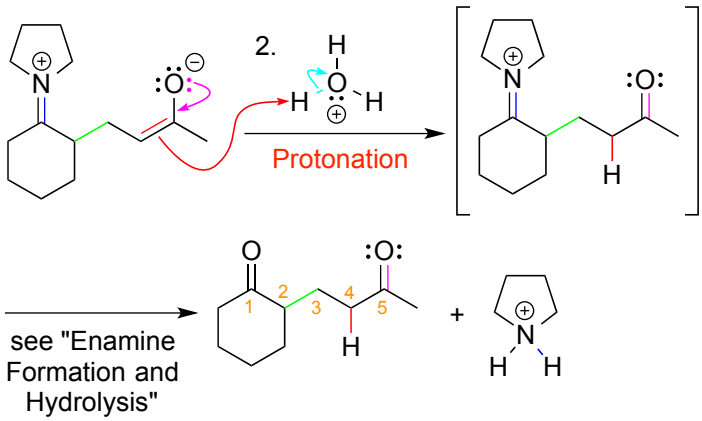
• In the following example, cyclohexanone undergoes a Michael reaction via the intermediacy of an enamine. The Michael acceptor is methyl vinyl ketone.



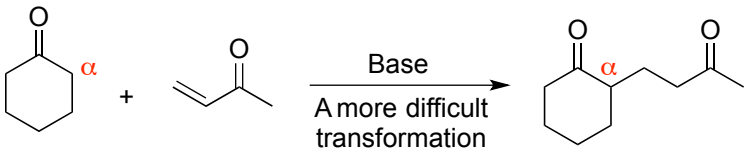
Once formed, the enamine, which is a mild nucleophile, attacks the β position of methyl vinyl ketone. The alkene π-bonding electrons are displaced toward the carbonyl, and the carbonyl π electrons are pushed onto oxygen.



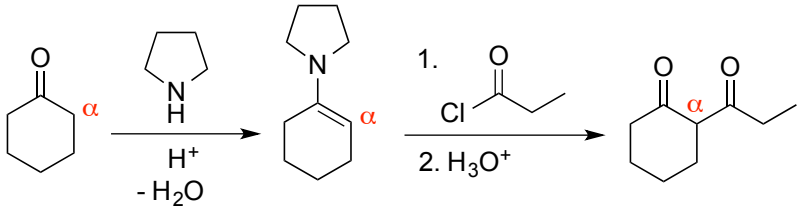
During the workup with aqueous acid, the enolate is protonated, and the iminium ion is hydrolyzed. The product contains a 1,5-dicarbonyl, which is also the hallmark of a Michael reaction.



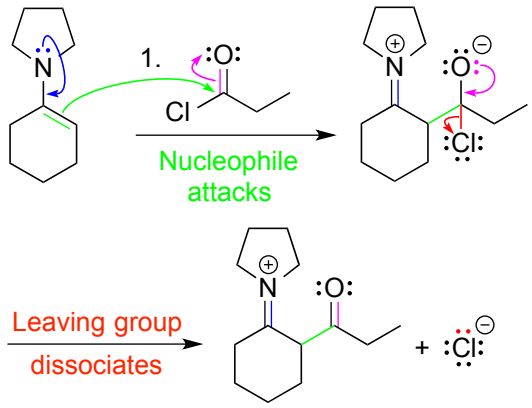
The strategic value of the Stork enamine reaction is that it allows us to accomplish a Michael addition that would have been challenging if we didn't proceed through the enamine. Recall that Michael reactions require stabilized enolates having two electron-withdrawing groups on the α-carbon. Cyclohexanone possesses only a single electron-withdrawing ketone, so it would not make a sufficiently stabilized enolate. Therefore, the Michael addition shown below would be problematic. However, the Stork protocol allowed us to circumvent this problem by using the enamine as the nucleophile rather than the enolate.



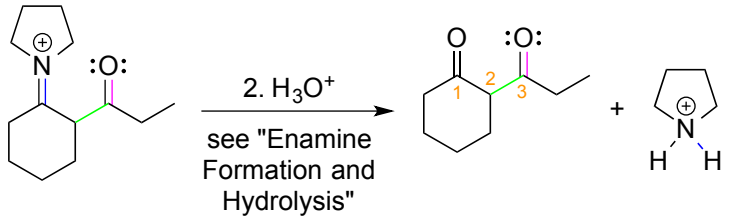
• Stork enamine reactions can utilize a variety of electrophiles. In the following example, an acid chloride serves as the electrophile in the preparation of a 1,3-dicarbonyl compound.



The enamine plays the role of the nucleophile in a nucleophilic acyl substitution on the acid chloride. To see the analogy, it may be helpful to refer back to the section on the nucleophilic acyl substitution of acid chlorides in Chapter 16. As the enamine attacks the acid chloride's electrophilic carbonyl carbon, the carbonyl π electrons are displaced onto oxygen. The resulting tetrahedral intermediate collapses to re-form the carbonyl as chloride dissociates.



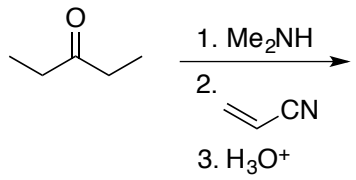
The iminium ion is then hydrolyzed upon treatment with aqueous acid to afford the 1,3-dicarbonyl.



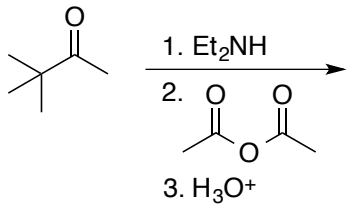
In conclusion, the Stork enamine reaction utilizes an enamine as a neutral (and therefore mild) "enolate equivalent" in reactions where unstabilized enolates would be problematic. The enamine attacks an electrophile (e.g., an alkyl halide, an α,β-unsaturated carbonyl compound, an acid chloride), and the iminium ion that results is hydrolyzed upon workup. The product is an aldehyde or ketone bearing a new α substituent.

Problem 12. Predict the products of the following Stork enamine reactions.

(a)

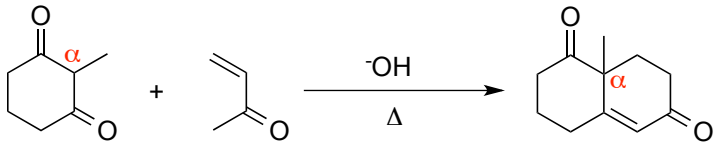


(b)



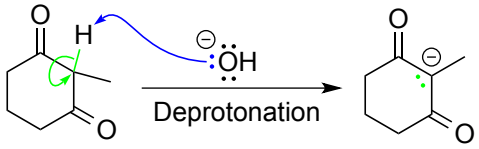
Section 12: Robinson annulation

An annulation is a ring-forming reaction. The Robinson annulation involves tandem Michael addition and intramolecular aldol condensation. The process begins with the union of a Michael donor and a Michael acceptor. The Michael donor is a stabilized enolate resulting from the deprotonation of a compound bearing two electron-withdrawing groups on its α center. The particular Michael acceptor shown below is methyl vinyl ketone, although other similar substrates may be used.

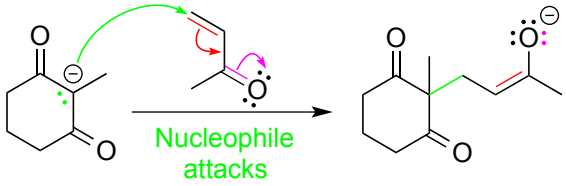


Mechanistic considerations

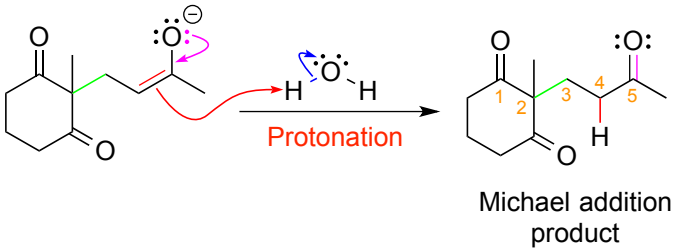
• The first phase of the reaction is a Michael addition, which begins with the deprotonation of the most acidic α position in the system. This is the center α to two carbonyls.



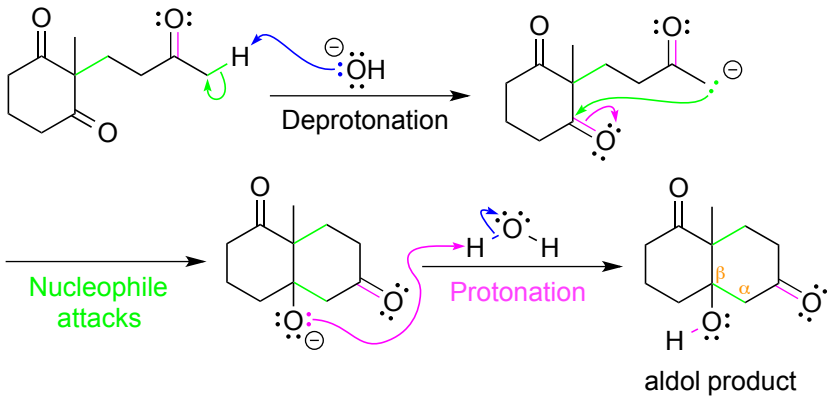
The resultant enolate is a Michael donor that undergoes conjugate addition to the Michael acceptor. As the enolate adds, the alkene π electrons are pushed toward the carbonyl, and the carbonyl π electrons are displaced onto oxygen.



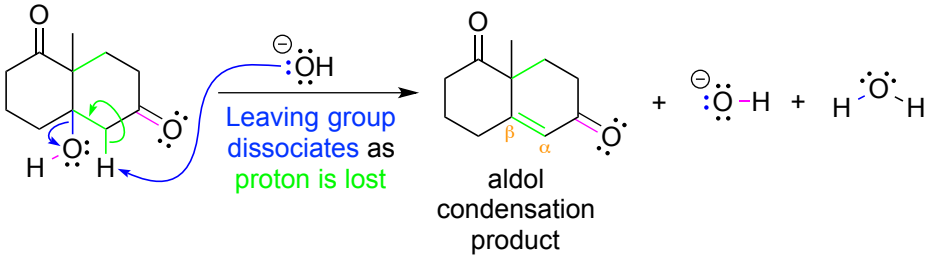
A carbon-carbon σ bond was formed in this step, and a new, less stable enolate results as well. Since it is less stable (and therefore more basic), the enolate readily acquires a proton from water to form the Michael addition product, which contains a 1,5-dicarbonyl as expected.



• In the second phase of the reaction, intramolecular aldol condensation occurs. While there are multiple α-protons in this molecule, one particular α position can form an unstrained six-membered ring when it is deprotonated and adds to a nearby carbonyl carbon. Protonation of the resulting alkoxide affords the aldol product.

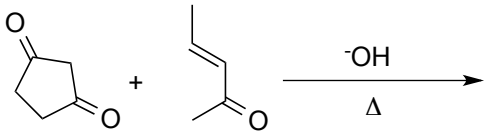


When warmed, this initial aldol product undergoes dehydration. An α-proton is removed by hydroxide, and a hydroxide leaving group dissociates as an α,β-unsaturation is generated. This aldol condensation completes the mechanism with the formation of the ultimate reaction product: a six-membered cyclic α,β-unsaturated ketone.



In summary, the Robinson annulation employs tandem Michael addition and intramolecular aldol condensation in the formation of a six-membered ring containing an α,β-unsaturated ketone. While the substituent pattern around the rings may vary, this structural core always exists.

Problem 13. Provide the product of the following Robinson annulation and show a mechanism for its formation.



Section 13: Synthesis

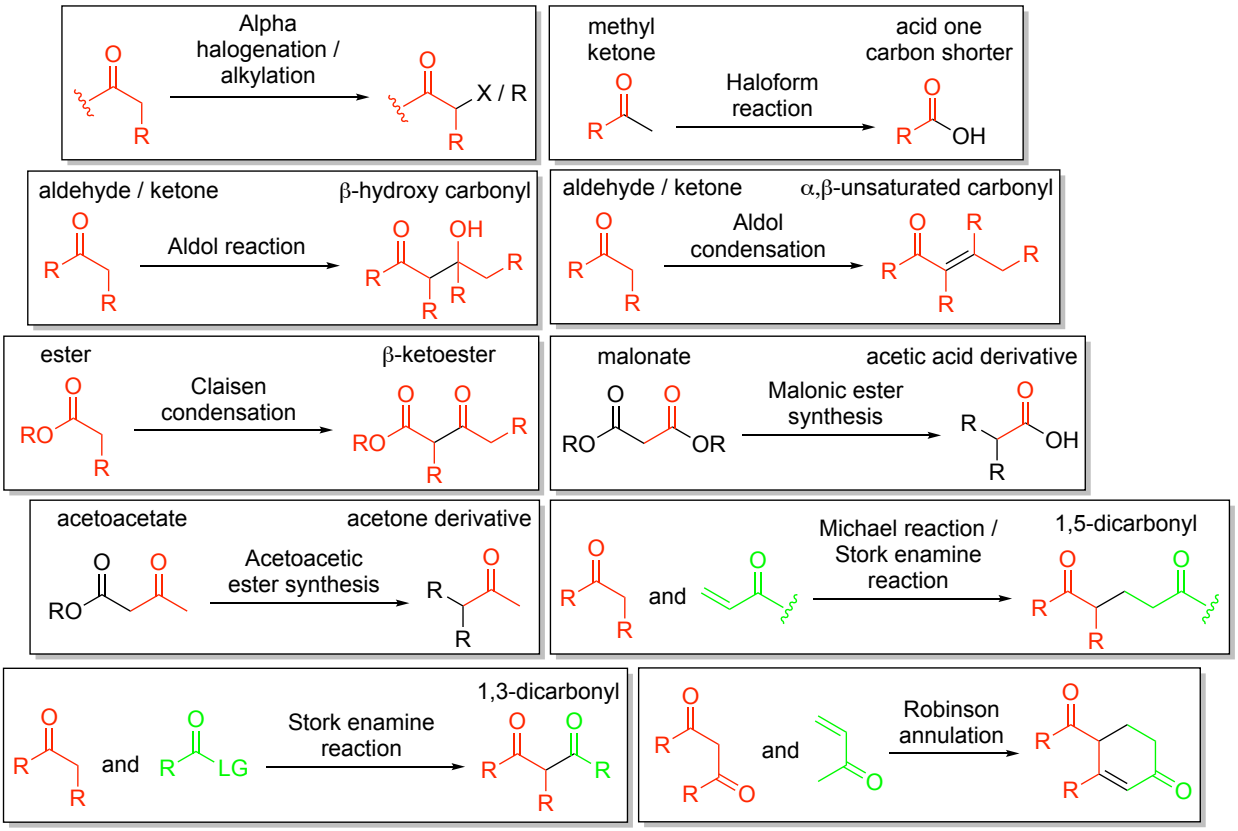
The reactions of the α-carbon are typically more closely associated with changes to the carbon skeleton than they are with functional group interconversions. While these reactions entail alterations to functional groups, the more significant change in most instances is a shortening or lengthening of the carbon framework of the substrate. As you master these transformations, it will be helpful to associate the names of the products with the reactions themselves. This will enable you to describe a target molecule and then immediately discern the most useful reaction for the preparation of that substance.

The following figure allows you to compare all of the reactions of the α-carbon at a glance. Alpha halogenation and alkylation are among the simplest reactions. They merely add a halogen or an alkyl group to the carbonyl's α position. The haloform reaction shortens the carbon skeleton by one, providing a carboxylic acid as the product. These are relatively small changes to the architecture of a molecule.

More comprehensive alterations occur with the other reactions covered in this chapter. The aldol reaction unites two aldehydes or ketones, yielding a product with a hydroxyl group β to the carbonyl. On the other hand, the aldol condensation yields an α,β-unsaturated system. The Claisen condensation joins to esters to afford a β-ketoester.

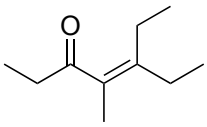
The malonic ester and acetoacetic ester syntheses are targeted at very specific sorts of products. The malonic ester synthesis provides access to mono or disubstituted acetic acid derivatives. The analogous acetoacetic ester synthesis produces monosubstituted or geminally disubstituted acetone derivatives.

The Michael reaction, Stork enamine reaction, and Robinson annulation can all provide 1,5-dicarbonyls but of varying types. The Michael reaction uses stabilized enolates to provide access to 1,5-dicarbonyls, which may or may not possess other electron-withdrawing groups as well. The Stork enamine reaction may produce 1,5-dicarbonyls or 1,3-dicarbonyls depending on the reagents used. Finally, the Robinson annulation appends a new ring to the existing molecular framework.



Problem 14. Describe each of the following targets, and state which of the methods described above could most readily provide access to the desired structure. Note that you don't actually have to devise a synthesis yet. We'll do that in subsequent problems.

(a)



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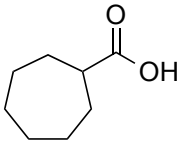

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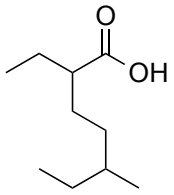

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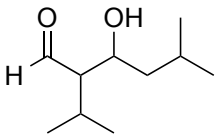

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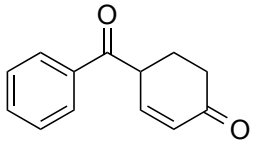

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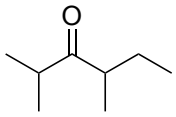

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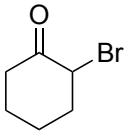

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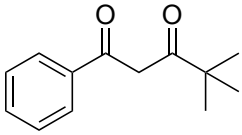
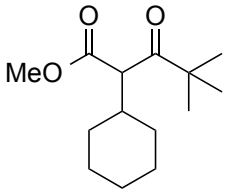


(i)



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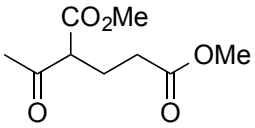

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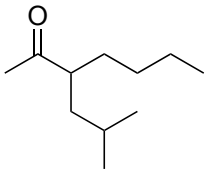
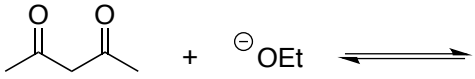


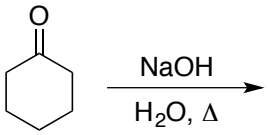
End-of-the-Chapter problems

Problem 15. For the following reaction, predict the products. Then state which side is favored at equilibrium and by how much.

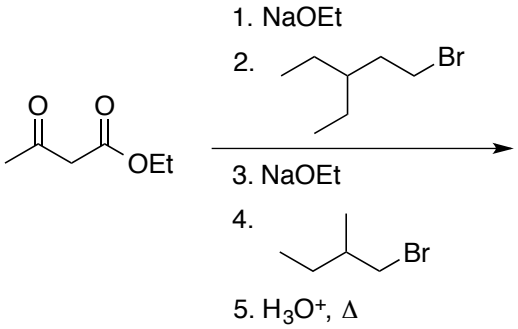


Problem 16. Predict the products of the following reactions.

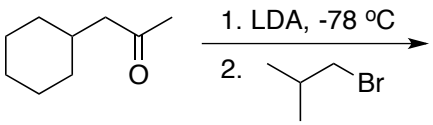
(a)



(b)



(c)



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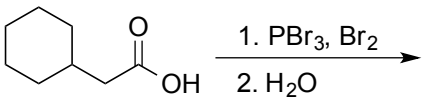

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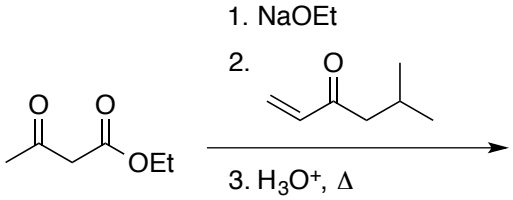

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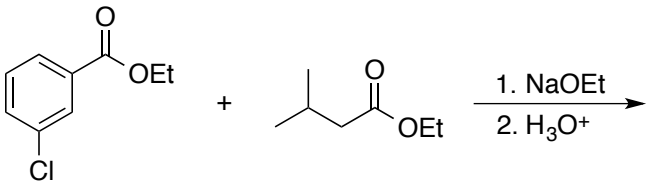
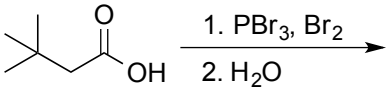
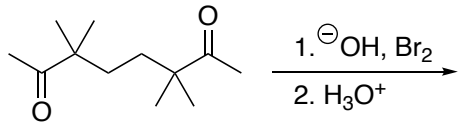


Problem 17. Provide the product of the following reaction as well as a mechanism to explain its formation.



Problem 18. Predict the products of the following reactions.

(a)



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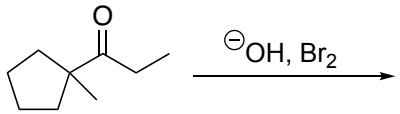

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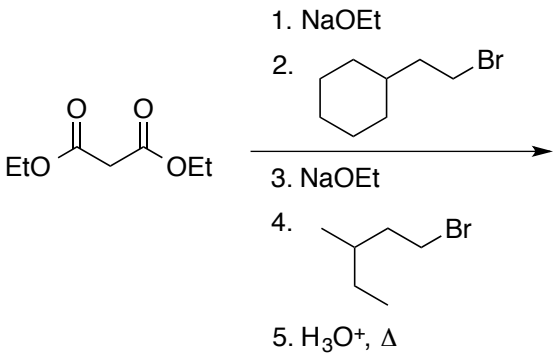

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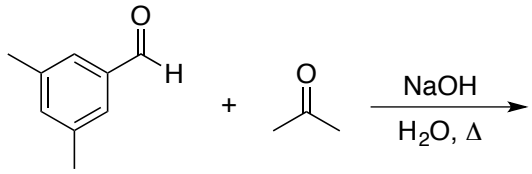

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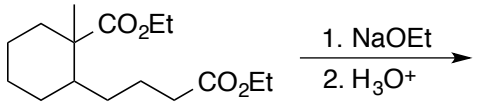

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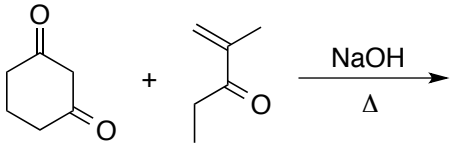
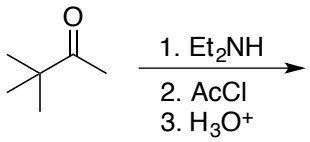
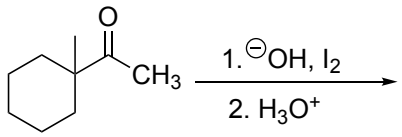


(g)

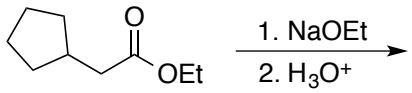


Problem 19. Provide a mechanism for the transformation below.

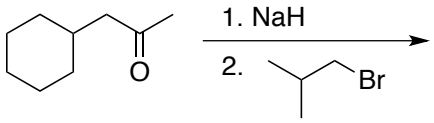


Problem 20. Predict the products of the reactions below.

(a)



(b)



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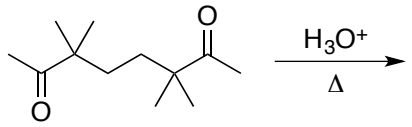

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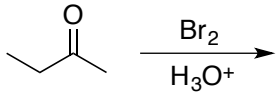
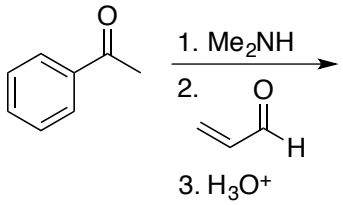
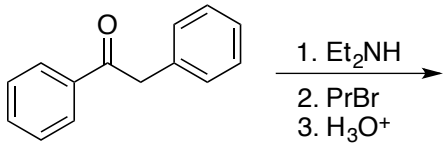


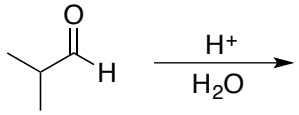
(e)



(f)

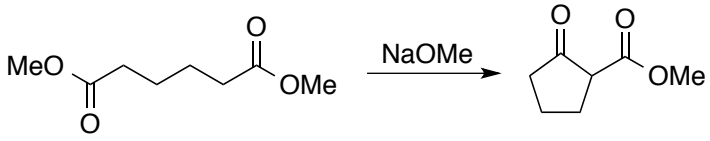


Problem 21. In Problem 6(a), you predicted the product of the following transformation. Now, provide a mechanism for its formation.

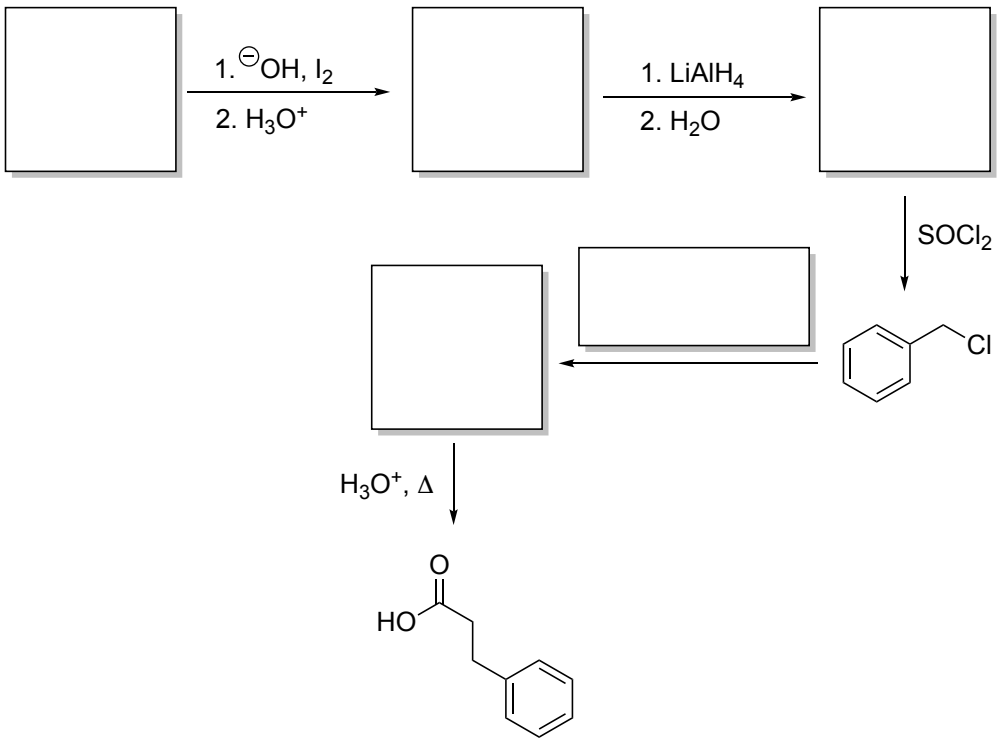


Problem 22. Compound X ($C_7H_{12}O_2$) undergoes reaction with iodine in base, followed by aqueous acid workup, to yield 2,2-dimethylmalonic acid. What is the structure of Compound X?

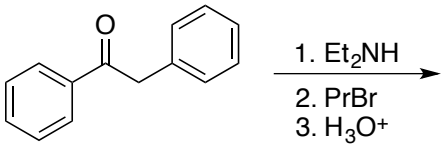
Problem 23. In Problem 7(c), you deduced that the following diester would undergo Dieckmann condensation (i.e., intramolecular Claisen condensation) to afford a product containing a five-membered ring. Now, provide a mechanism for this conversion.



Problem 24. Fill in the missing reactant, intermediates, and reagents in the scheme below.

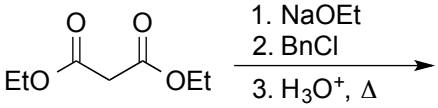


Problem 25. In Problem 20(f), you predicted the product of this α-alkylation. Now, show a mechanism for step 2 of this reaction.

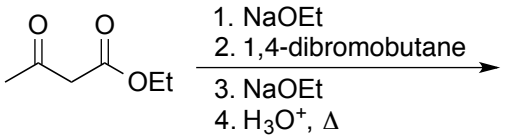


Problem 26. Compound A is a symmetrical ketone with the molecular formula $C_5H_{10}O$. It is treated with bromine in aqueous acid to yield Compound B (C_5H_9BrO). Compound B is then treated with *tert*-butoxide to generate Compound C (C_5H_8O). Finally, Compound C is exposed to the conjugate base of diethyl malonate in ethanol to produce Compound D ($C_{12}H_{20}O_5$). What are the structures of Compounds A – D?

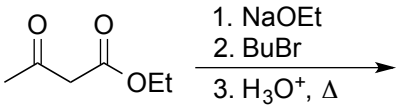
Problem 27. Provide a mechanism for the reaction shown below.



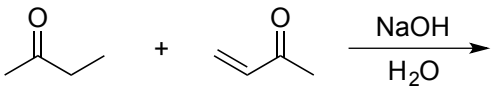
Problem 28. Predict the product of the following sequence.



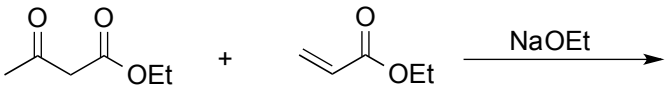
Problem 29. Provide a mechanism for the following reaction.



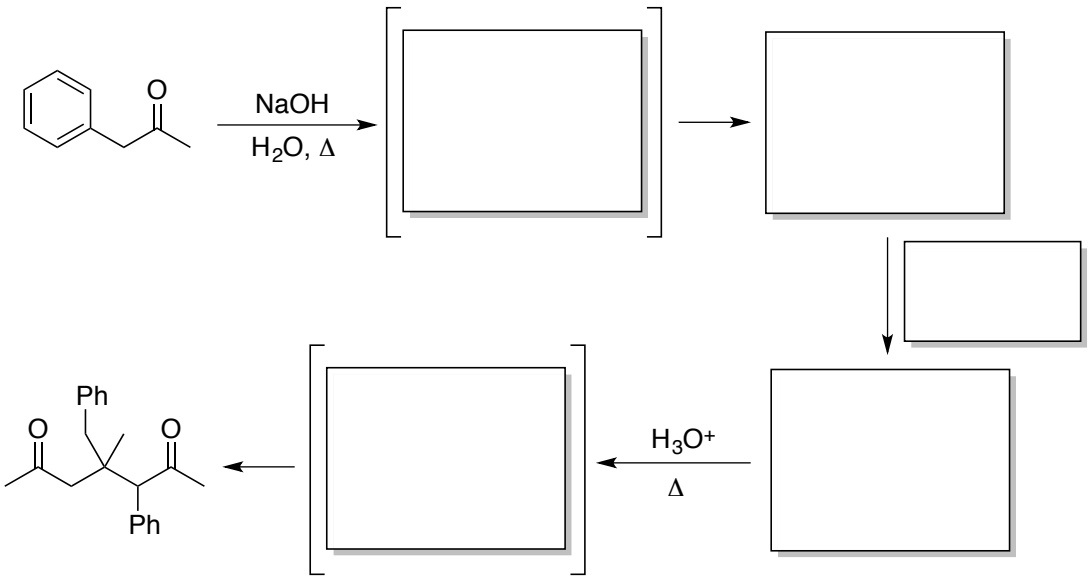
Problem 30. It has been mentioned that Michael reactions require stabilized enolates. Provide some reasons why the following attempted Michael reaction, which lacks a stabilized enolate, would be problematic.



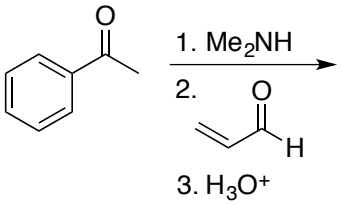
Problem 31. Provide a mechanism to explain the following reaction.



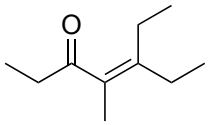
Problem 32. Complete the following scheme by filling in the missing intermediates and reagents.



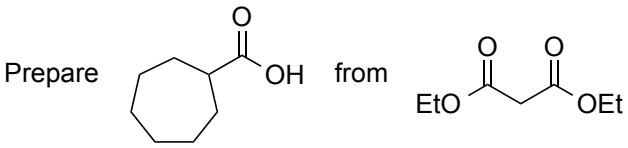
Problem 33. In Problem 20(e), you predicted the product of the following transformation. Now, provide a mechanism for step 2 of the process.



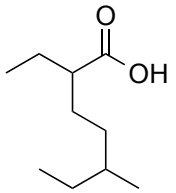
Problem 34. In Problem 14(a), you identified the reaction most likely to produce the following compound. Now, devise a synthesis for this molecule.



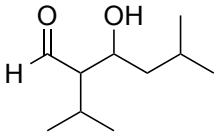
Problem 35. In Problem 14(b), you considered the reactions most likely to yield the following acid. Now, devise a viable synthesis of this target from diethyl malonate.



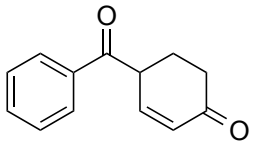
Problem 36. In Problem 14(c), you thought about those reactions best suited to the preparation of the following carboxylic acid. Now, devise a synthesis of this molecule from reactants having no more than six carbons.



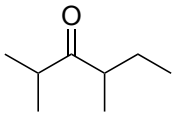
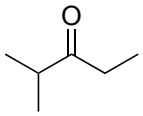
Problem 37. In Problem 14(d), you decided upon the best method to prepare the compound below. Now, devise a synthesis of this compound.



Problem 38. In Problem 14(e), you considered the following target. Now, devise a synthesis of this molecule from reactants having nine carbons or less.

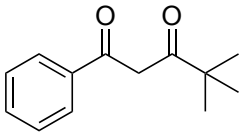


Problem 39. In Problem 14(f), you analyzed the target shown below. Now, devise a viable method for its preparation.

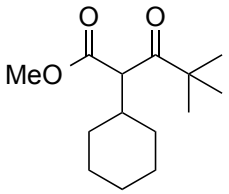
Prepare  from 

Problem 40. Devise a synthesis of 2-bromocyclohexanone, which you considered in Problem 14(g), starting with cyclohexanone.

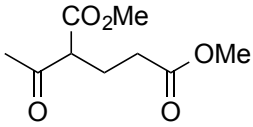
Problem 41. In Problem 14(h), you suggested an efficient way to make the following 1,3-diketone. Now, propose a viable synthesis of this molecule starting with acetophenone.



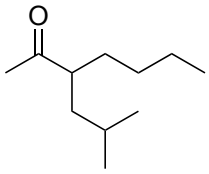
Problem 42. Provide a synthesis for the following molecule [encountered in Problem 14(i)] beginning with reactants containing no more than nine carbons.



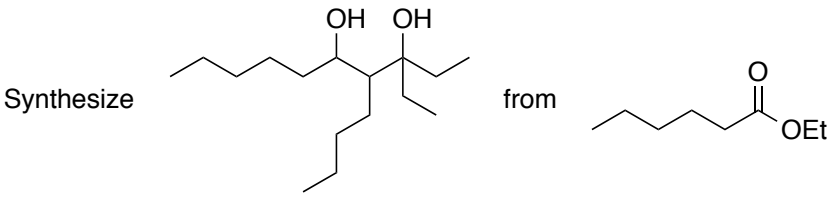
Problem 43. In Problem 14(j), we encountered the following molecule. Devise a viable synthesis of this target using reactants having five carbons or fewer.



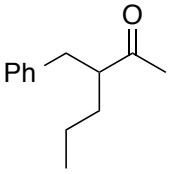
Problem 44. We saw the ketone below in Problem 14(k). Synthesize this compound from reactants having six carbons or fewer.



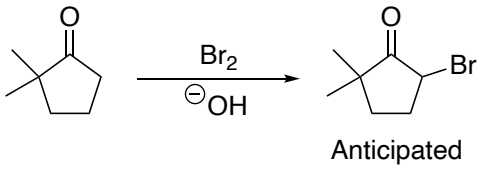
Problem 45. Propose a viable method to accomplish the following synthesis.



Problem 46. Propose a synthesis of the following molecule from diethyl malonate.

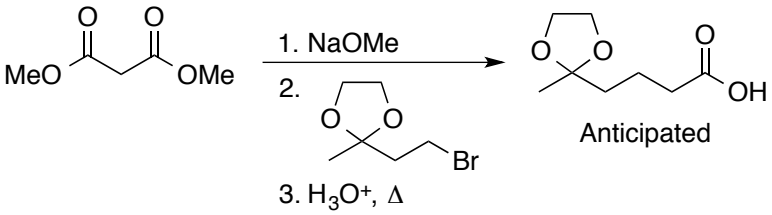


Problem 47. In an attempt to prepare the brominated derivative shown below, an investigator treated 2,2-dimethylcyclopentanone with bromine in aqueous base.



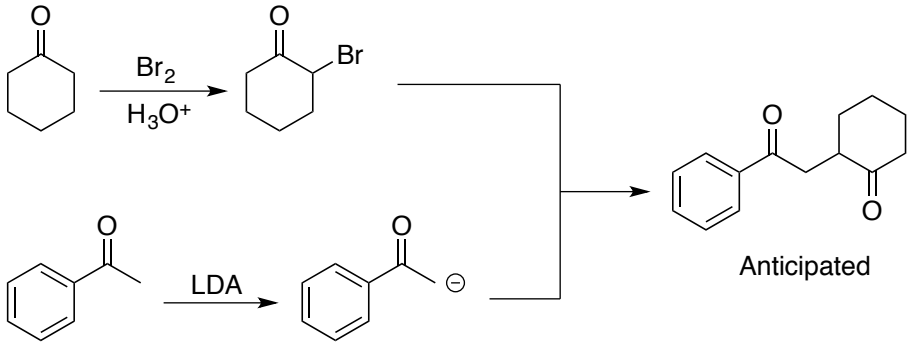
However, upon analyzing the product by mass spectrometry, the expected M and M+2 isotope pattern was not observed for the molecular ion peak. Instead, M, M+2, and M+4 peaks were present in a ratio of 1:2:1. What actually happened during this transformation?

Problem 48. An investigator conducted the following malonic ester synthesis in the hopes of obtaining the product shown.

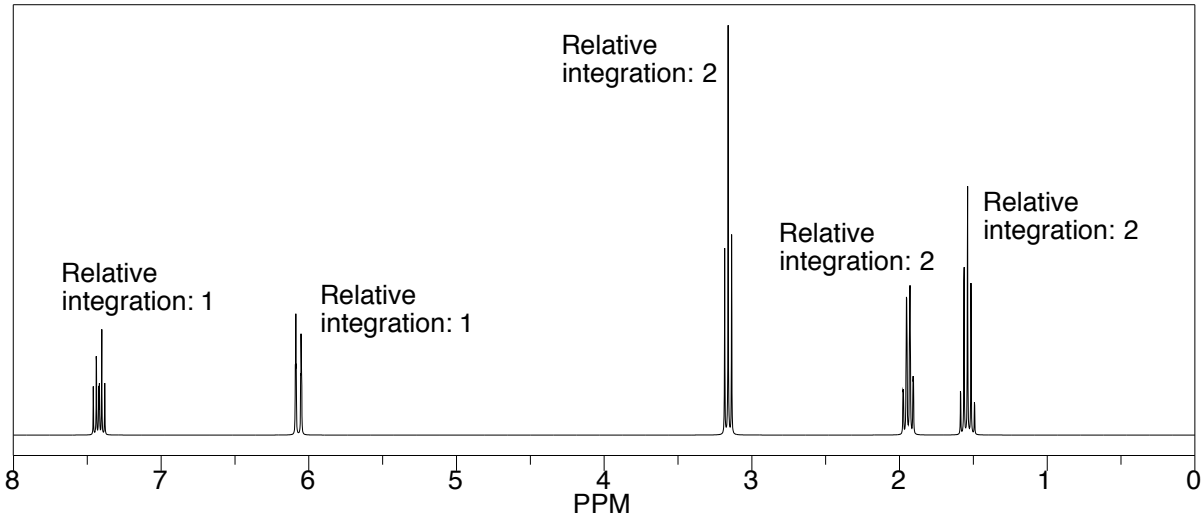


However, upon examination of the IR spectrum, not just one but two carbonyl resonances were observed. What actually happened during this transformation?

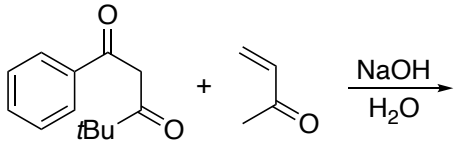
Problem 49. A researcher conducts the following sequence in the hope of obtaining the product shown below. Cyclohexanone is brominated in the α position. Acetophenone is deprotonated using LDA. Then, the enolate of acetophenone is combined with 2-bromocyclohexanone to ultimately achieve an α-alkylation of acetophenone.



The ^{1}H NMR spectrum of one of the products obtained from this sequence is shown below. Identify the product isolated, and explain its formation.



Problem 50. The following Robinson annulation results in two products. Explain why that is the case, and provide the structures of the two products.



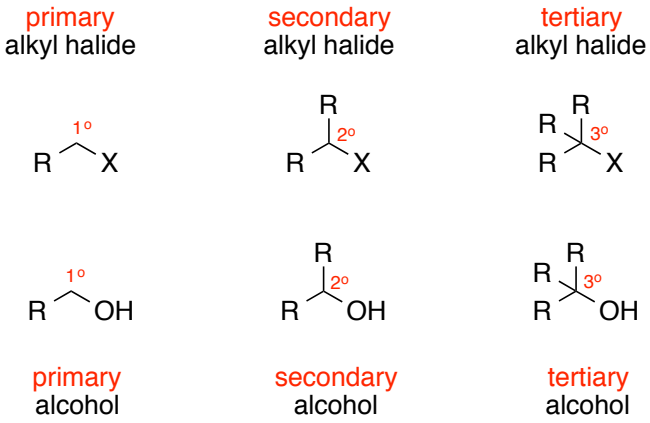
Chapter 18: Amines

Section 1: Nomenclature
Section 2: Properties
Section 3: Amines as bases and nucleophiles
Section 4: Preparation of amines via direct alkylation
Section 5: Gabriel synthesis
Section 6: Reductive amination
Section 7: Hofmann elimination
Section 8: Diazotization
Section 9: Synthesis

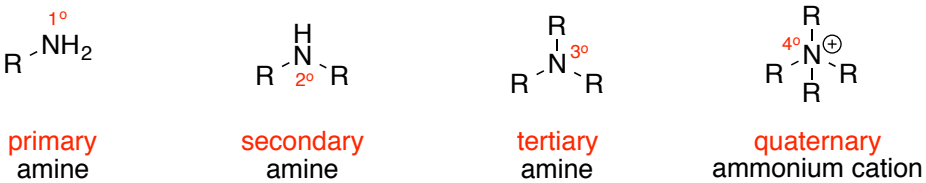
Section 1: Nomenclature

Classification

The classification strategy for amines varies slightly from that used with alkyl halides and alcohols. Halogens and hydroxyl groups are monovalent and will only ever have a single alkyl group directly bonded to the X or OH. Consequently, we classify them by the number of R groups bonded to the carbon bearing the halogen or hydroxyl group.

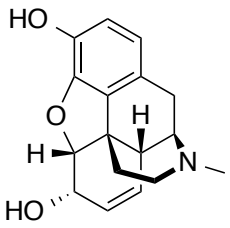


In contrast, the nitrogen of an amine can have one to four R groups directly bonded to it. Therefore, amines are classified as primary, secondary, tertiary, or quaternary based on the number of alkyl groups *directly* connected to nitrogen.



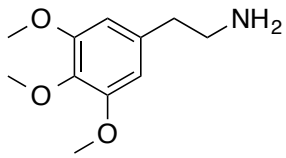
Problem 1. Alkaloids are nitrogen-containing organic bases that are found primarily in plants. Classify the aliphatic (i.e., non-aromatic) amines in the following alkaloids.

(a)



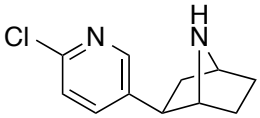
morphine (a powerful pain reliever isolated from opium)

(b)



mescaline (a psychoactive compound occurring in the peyote cactus)

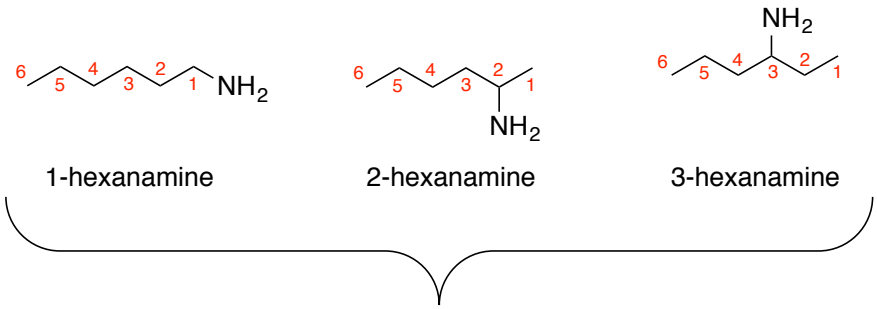
(c)



epibatidine (found on the skin of certain poison dart frogs)

IUPAC nomenclature of amines

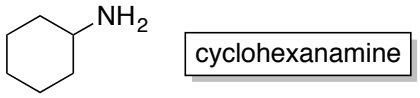
Amines are given systematic names by identifying the longest continuous carbon chain containing the functional group. The suffix "e" is removed from the name of the parent alkane and is replaced by "amine" to signify the presence of the functional group. A number is also needed in most instances to identify the location of the functional group.



- Six carbon parent = hexane
- Replace "e" of suffix with "amine"
- Number so as to give the amine the lowest possible number

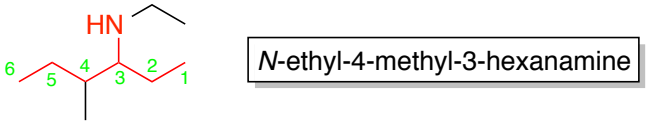
Occasionally, a number may not be necessary to indicate the amine's position. This is only the case when there can no ambiguity about where on the parent chain the amine resides. Such is the case with extremely small chains (i.e., one or two carbons) and rings.

- Two carbon parent = ethane
- Replace "e" of suffix with "amine"



- Six carbon, cyclic parent = cyclohexane
- Replace "e" of suffix with "amine"

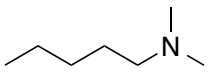
Substituents are handled in the usual way. When substituents appear on nitrogen itself, the locant *N* is used to indicate their position.



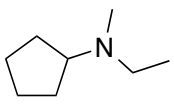
- Six carbon parent = hexane
- Replace "e" of suffix with "amine"
- Number so as to give the amine the lowest possible number
- Add substituent names and numbers

Problem 2. Provide IUPAC names for the following amines.

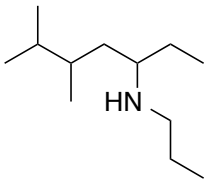
(a)



(b)

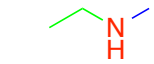


(c)

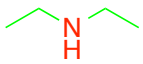


Common nomenclature of amines

In common parlance, amines are named by placing the names of the alkyl groups bonded to nitrogen before the word "amine."



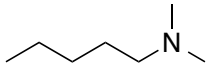
ethylmethylamine



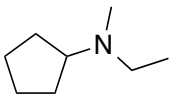
diethylamine

Problem 3. Give common names for the amines below.

(a)



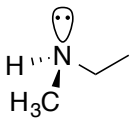
(b)



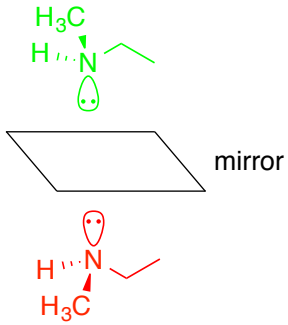
Section 2: Properties

Chirality

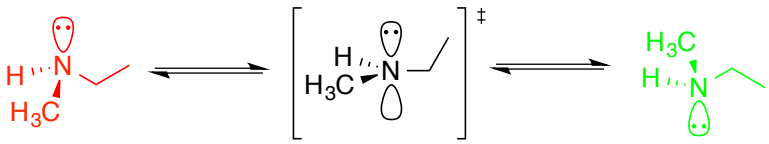
Depending on the nitrogen's substituents, it is possible for an amine to be chiral. For instance, ethylmethylamine contains a nitrogen surrounded by four different groups: ethyl, methyl, hydrogen, and a lone pair.



Such an amine has a nonsuperimposable mirror image. That is to say that amines like this have an enantiomer.

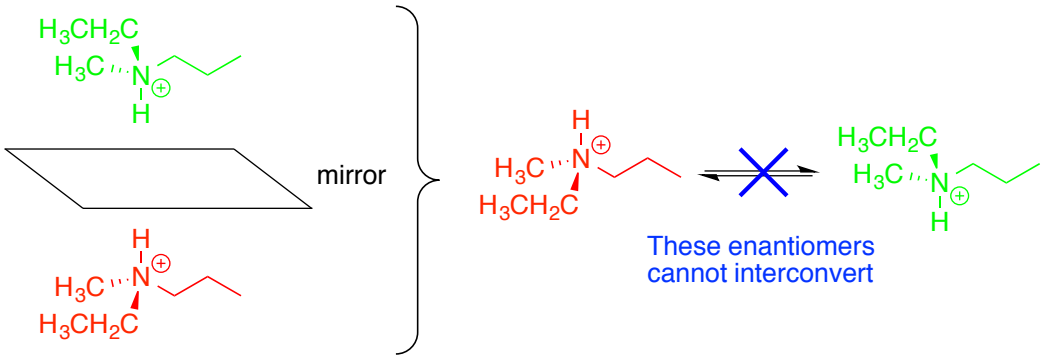


However, when nitrogen is a chiral center, a phenomenon known as pyramidal inversion allows it to convert freely from one configuration to the other at room temperature. The configuration inverts through a trigonal planar (sp^2) transition state.



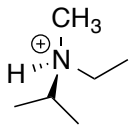
Since the two configurations freely interconvert at room temperature, a single enantiomer *cannot* be readily isolated. Racemic mixtures are formed from any such sample, and as a consequence, it is optically inactive.

However, a quaternary ammonium cation does not possess a lone pair and cannot therefore undergo pyramidal inversion. Consequently, the configurations of quaternary ammonium cations do *not* interconvert, and the enantiomers are separable.

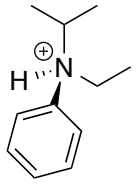


Problem 4. Assign a configuration to both of the quaternary ammonium cations below.

(a)

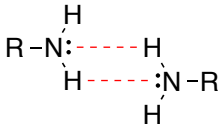


(b)

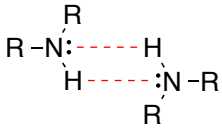


Hydrogen bonding

The ability to hydrogen bond, when present, exerts a great influence on the properties of molecules. Primary and secondary amines contain both hydrogen bond donors and acceptors, allowing them to hydrogen bond even within a neat (i.e., pure) sample. This strong intermolecular attraction is expected to elevate their boiling points.

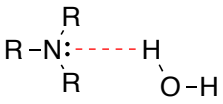


example of hydrogen bonding
(primary amine)



example of hydrogen bonding
(secondary amine)

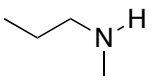
Tertiary amines lack a hydrogen bond donor, so they are unable to hydrogen bond in a neat sample; however, they can hydrogen bond with other compounds that possess a donor, such as water.

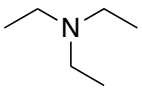


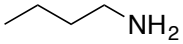
example of hydrogen bonding
(tertiary amine)

The powerful intermolecular attractions between amines and water allow small amines (i.e., those having 5 or fewer carbons) to be miscible with water or highly water soluble. The hydrocarbon portion of the molecule [i.e., the R group(s)] is hydrophobic, so as its size increases, the water solubility diminishes.

Problem 5. Rank the following compounds in order of decreasing water solubility.



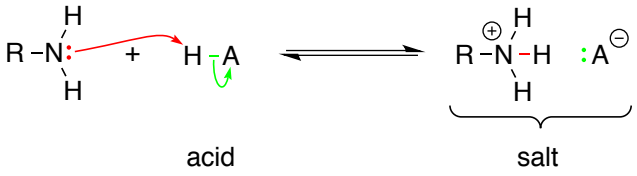




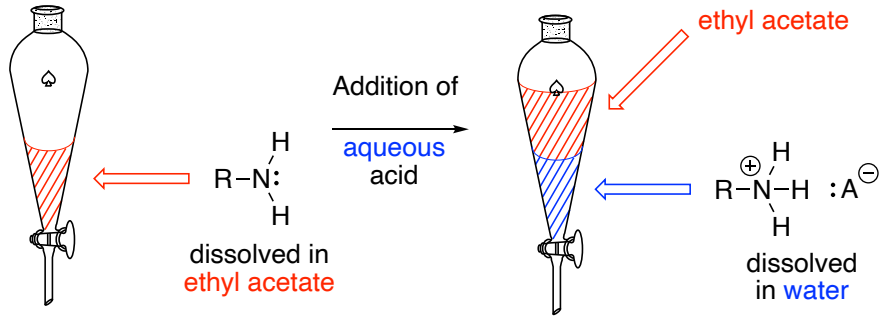
Section 3: Amines as bases and nucleophiles

Amines as bases

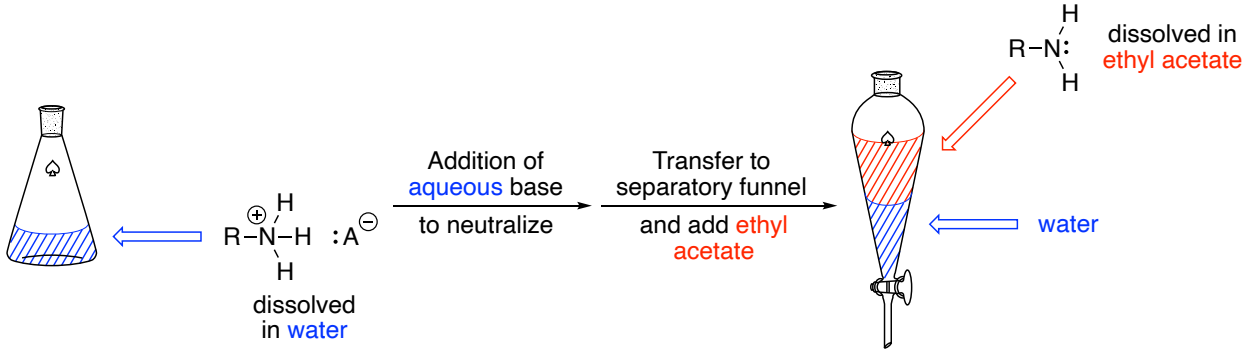
As we've seen many times previously, amines frequently behave as bases.



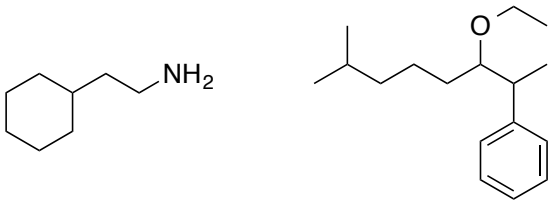
The ability to readily protonate an amine, thereby forming the corresponding salt, is commonly exploited in laboratory settings. The unprotonated amine is likely to be more soluble in organic media, given an R group of a reasonable size. On the other hand, the protonated amine will have increased water solubility. The difference in solubility before and after the acid-base reaction enables us to move an amine from an organic layer to an aqueous layer or vice versa. If we need to remove an amine from organic media, a wash with aqueous acid will protonate the amine, and the salt will preferentially migrate into the aqueous layer.



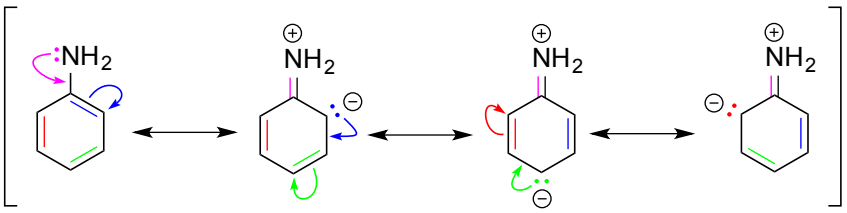
Conversely, if we need to extract an ammonium ion from aqueous media, treatment with base will deprotonate it and yield the free amine. When an organic solvent is added, the amine will preferentially migrate into that layer.



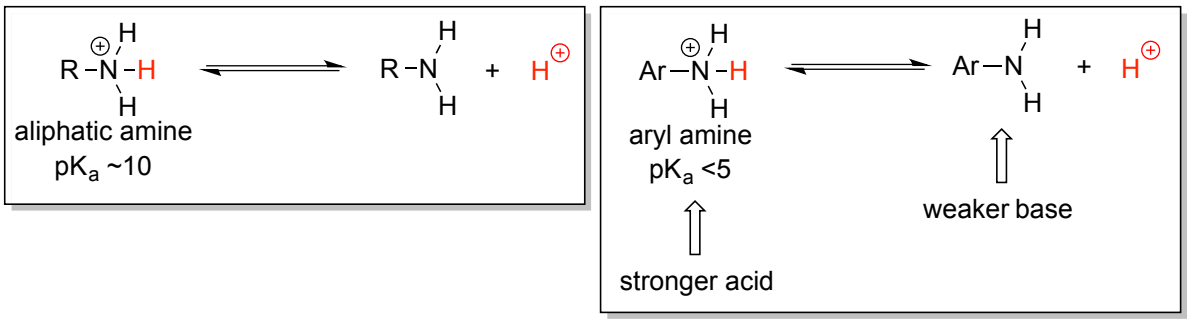
Problem 6. Explain how a mixture of the following amine and ether could be separated using acid-base chemistry.



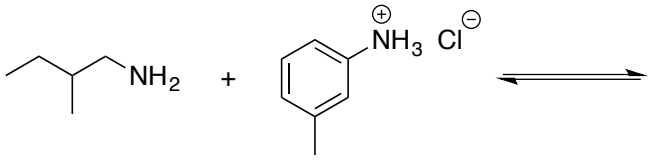
The basicity of amines can by impacted by a variety of factors. A particularly important one is resonance. Arylamines, or those amines directly bonded to aromatic rings, experience resonance delocalization of their lone-pair electrons. For instance, aniline has the resonance structures shown below. These highlight the fact that the electron density of the lone pair is spread around the aromatic ring. With the electron density of the lone pair diffused in this way, the amine becomes much less basic.



Resonance explains why arylamines are, in general, a good deal less basic than aliphatic amines. The pK_a of a typical protonated aliphatic amine is approximately 10, while the pK_a of a typical protonated arylamine is less than half that value. These pKa values allow us to make inferences about the strength of the conjugate bases and confirm that arylamines are indeed the weaker bases.

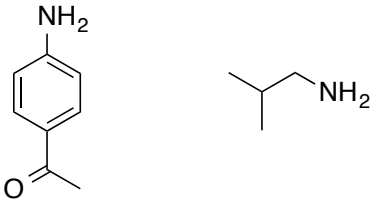


Problem 7. Predict the products of the following acid-base reaction. Then, state which side of the reaction is favored at equilibrium and by how much.



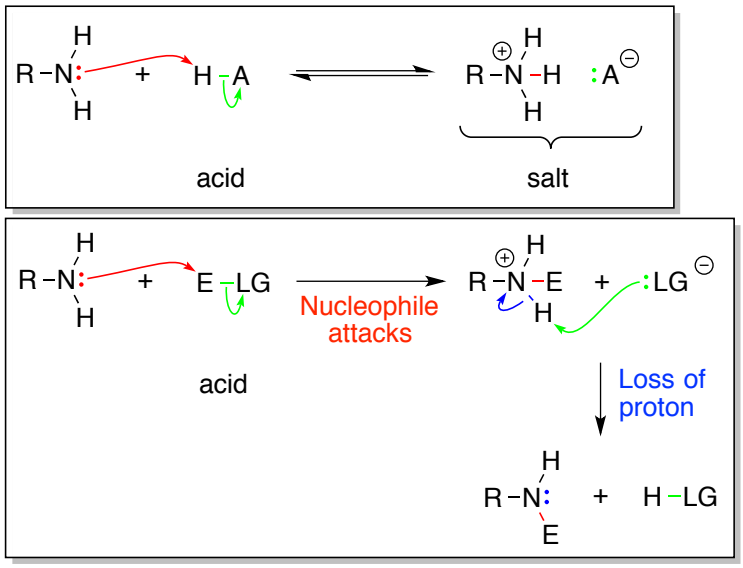
Recall that nucleophilicity parallels basicity. Therefore, the trends described above apply to the nucleophilicity of amines as well. Arylamines are weaker nucleophiles than their aliphatic counterparts due to delocalization of nitrogen's lone pair.

Problem 8. Which of the following two amines is expected to be more nucleophilic and why?

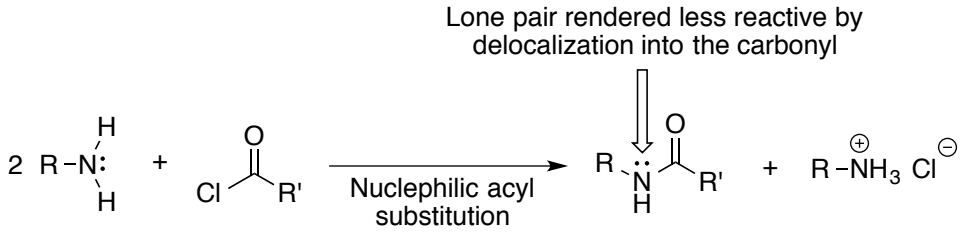


Amines as nucleophiles

We've previously seen amines behave as nucleophiles. This is directly analogous to the behavior of amines as bases. While the acid-base reaction begins with the attack of the amine on a labile proton, nucleophilic behavior begins with the attack of the amine on an electrophilic center (E). In the acid-base reaction, the conjugate base ($A:^-$) dissociates from the proton. When an amine acts a nucleophile, a leaving group ($LG:^-$) dissociates from the electrophile. Nucleophilic attack tends to be followed by the loss of a proton from nitrogen to yield a neutral product.



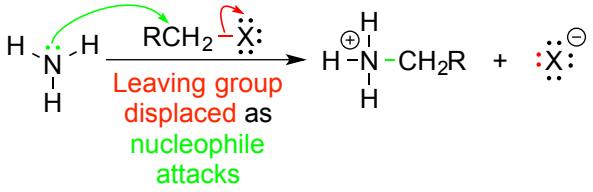
As we saw in Chapter 16, the nucleophilicity of an amine can be leveraged to add an acyl group to it. This occurs through treatment with an acid chloride or anhydride and follows the nucleophilic acyl substitution mechanism. Once installed, the presence of the electron-withdrawing group on nitrogen makes its lone pair of electrons less reactive, effectively bringing the reaction to a halt.



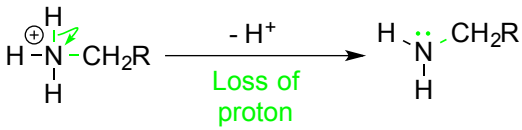
As we'll soon see though, some reactions (like alkylation) add electron-donating groups to nitrogen. In such cases, the amine becomes more nucleophilic. As a consequence, further reaction may take place, and this can be a complicating factor.

Section 4: Preparation of amines via direct alkylation

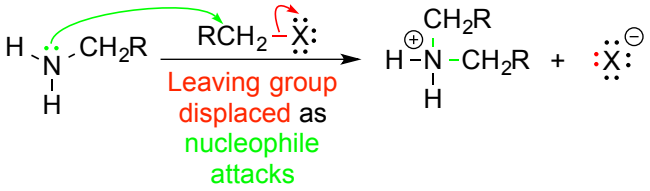
The synthesis of monosubstituted amines via simple S_N2 reaction between ammonia and an alkyl halide is problematic. The initial nucleophilic attack and displacement of the leaving group proceeds as expected.



The resulting ammonium ion can then shed a proton to the medium, thereby reinstalling the lone pair on nitrogen. This monosubstituted amine is, however, more nucleophilic than ammonia due to the electron-donating nature of the alkyl group.

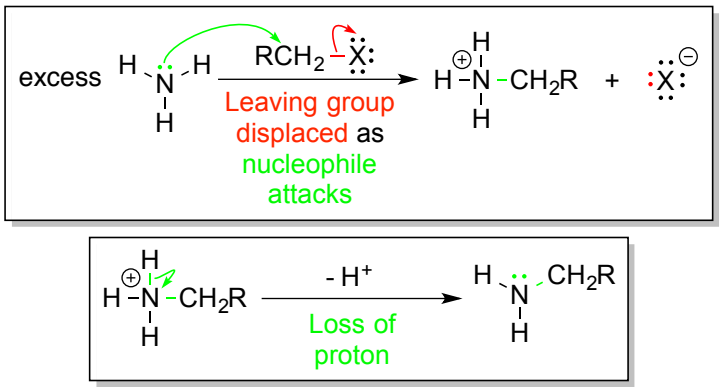


Consequently, the first molecules of monosubstituted amine that are formed will react with the remaining alkyl halide faster than ammonia will. This results in a second alkylation of the nitrogen atom.



The addition of yet another alkyl group makes the nitrogen even more nucleophilic once it loses a proton. As a result, alkylation continues to occur until the nitrogen can be alkylated no further. A quaternary ammonium salt is generated in this way.

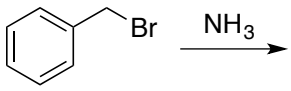
If our goal was to prepare a monosubstituted amine, then this is an undesirable result. One way to circumvent overalkylation is to use a large excess of ammonia. This decreases the probability of the initial primary amine product encountering another molecule of alkyl halide before ammonia does. As a result, the primary amine becomes the predominant product.



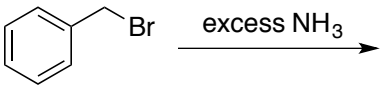
In the coming sections, we'll see some additional solutions to this problem that are more elegant.

Problem 9. Do the following reactions have different outcomes? If so, why the difference?

(a)

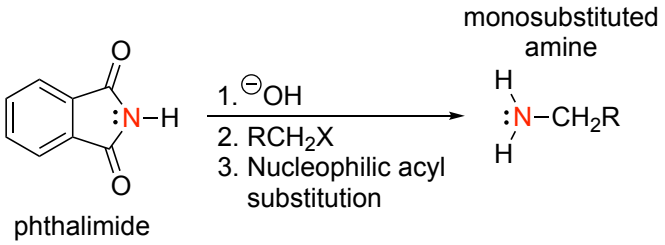


(b)

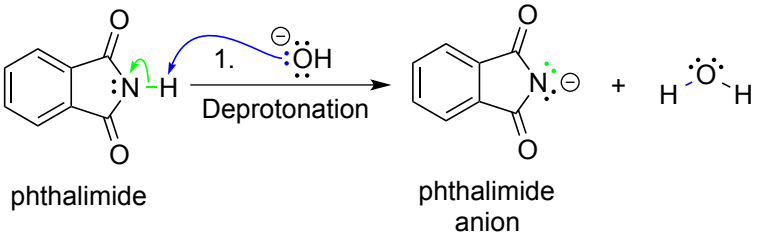


Section 5: Gabriel synthesis

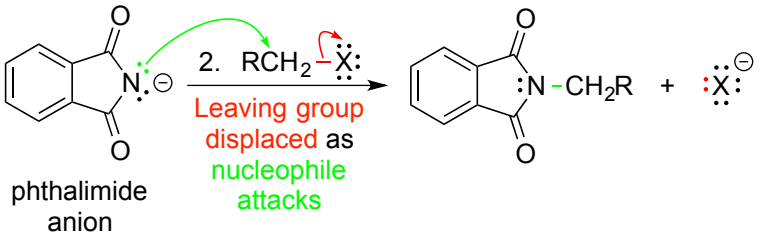
The Gabriel synthesis provides an alternative solution to the problem of overalkylation. Phthalimide is used as the source of the nitrogen atom in the product. Phthalimide is deprotonated and alkylated. Then, the undesired portion of the reactant is cleaved off using nucleophilic acyl substitution. The end result is selective synthesis of a monosubstituted amine.



The first step of the reaction is deprotonation of phthalimide. This can be accomplished with a moderate base, such as hydroxide, because phthalimide is fairly acidic (pK_a < 10). Phthalimide's acidity results from the fact that its conjugate base (the phthalimide anion) has resonance stabilization provided by two adjacent carbonyls.

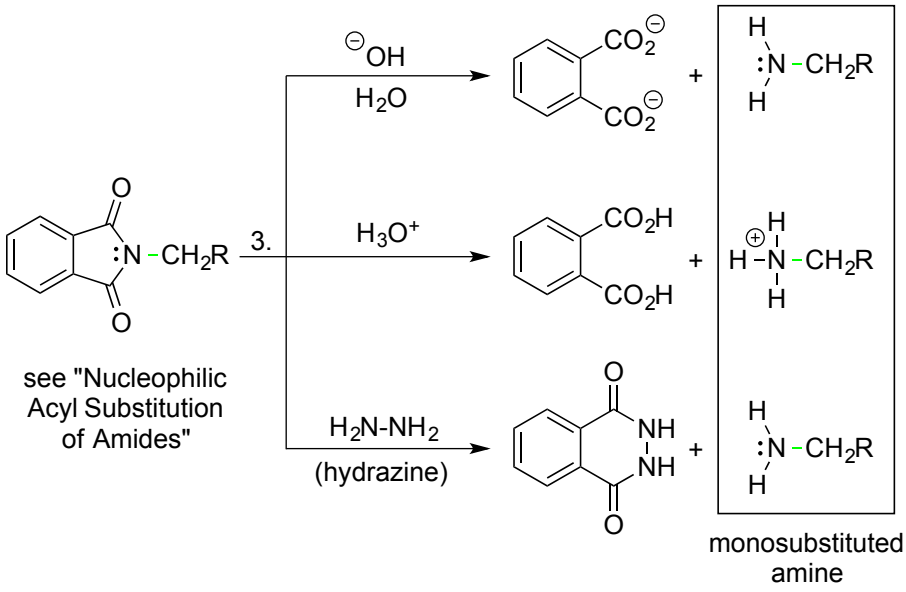


The phthalimide anion is nonetheless electron rich, so it can serve as a nucleophile for S_N2 reaction with an unhindered alkyl halide. It attacks the electrophilic carbon and displaces a halide leaving group.



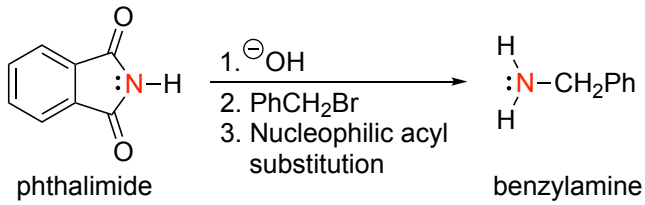
No further alkylation occurs because the lone pair on nitrogen is delocalized into the two electron-withdrawing carbonyls, making it fairly unreactive.

In the final step of the Gabriel synthesis, the aromatic ring and its two carbonyls are cleaved from nitrogen to liberate the desired monosubstituted amine. There are multiple ways to achieve this goal, but they all entail nucleophilic acyl substitution. Basic or acidic hydrolysis can be used. These reactions are extremely similar to the hydrolysis reactions that we saw in the section on nucleophilic acyl substitution of amides in Chapter 16. The only difference is that the nucleophilic acyl substitution occurs twice (once at each carbonyl). Basic hydrolysis yields the amine in its neutral form, and the byproduct is the dicarboxylate, phthalate. On the other hand, acidic hydrolysis provides the amine in protonated form and the byproduct as the dicarboxylic acid phthalic acid. Another option for this cleavage is the use of hydrazine, which also performs double nucleophilic acyl substitution to afford the neutral monosubstituted amine and 2,3-dihydrophthalazine-1,4-dione, a cyclic diamide, as the byproduct.

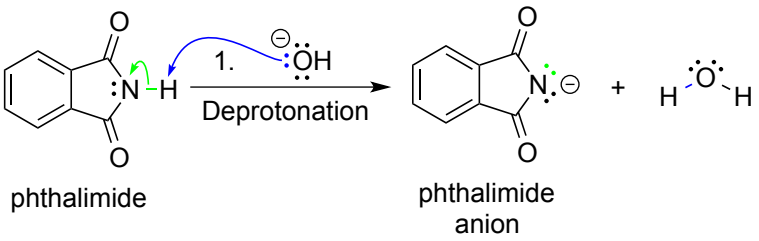


A specific example of the Gabriel synthesis

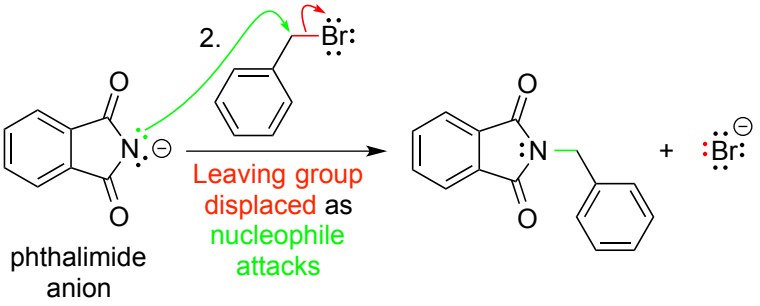
In the following example, benzylamine is prepared from phthalimide by deprotonation, alkylation, and nucleophilic acyl substitution. Phthalimide is the source of the nitrogen atom in the product.



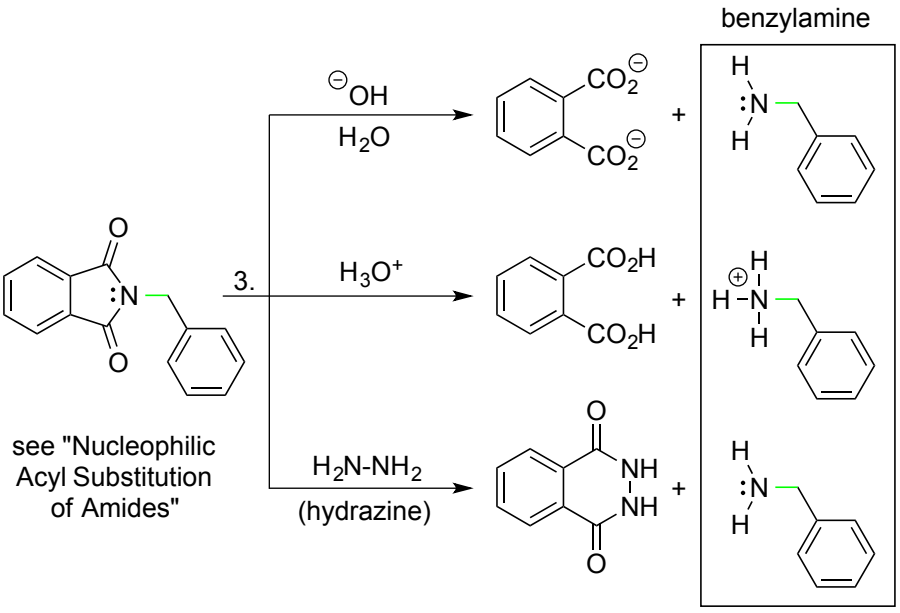
The deprotonation of phthalimide proceeds smoothly when hydroxide is used, giving the phthalimide anion.



The phthalimide anion can then be treated with benzyl bromide to achieve alkylation through S_N2 reaction.



Finally, basic hydrolysis, acidic hydrolysis, or treatment with hydrazine will liberate benzylamine. Depending upon the conditions chosen, either benzylamine or its conjugate acid (i.e., the protonated form) will be produced.



In summary, the Gabriel synthesis allows for the selective preparation of monosubstituted amines, without any danger of overalkylation. Phthalimide is always the reactant for a Gabriel synthesis. It is deprotonated to yield the phthalimide anion, which is then treated

with an unhindered alkyl halide bearing the R group desired in the ultimate amine product. After alkylation, the monosubstituted amine is liberated through double nucleophilic acyl substitution in acid, base, or using hydrazine.

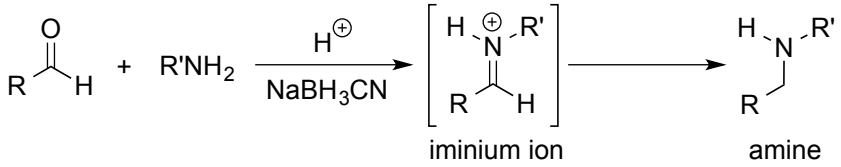
Problem 10. Prepare isobutylamine using the Gabriel synthesis.

Section 6: Reductive amination

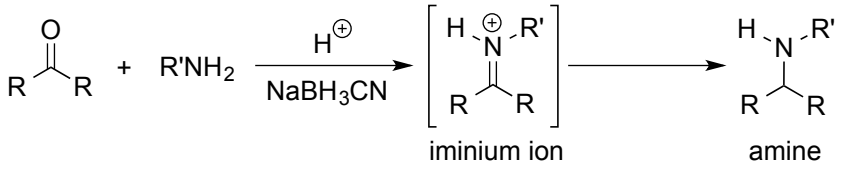
Reductive amination provides another selective method for amine synthesis. In Section 4, we saw the problems associated with the synthesis of amines through direct S_N2 alkylation. Reductive amination is another strategy for circumventing undesired overalkylation. Unlike the Gabriel synthesis, it can be employed in the synthesis of primary, secondary, or tertiary amines. Reductive amination relies upon a weak reducing agent, such as sodium cyanoborohydride ($NaBH_3CN$).

Sodium cyanoborohydride is a hydride donor, much like sodium borohydride. However, sodium cyanoborohydride will not reduce aldehydes or ketones. It is only capable of reducing the more electrophilic iminium ion, which is the final intermediate in the condensation of an amine with an aldehyde or a ketone.

In reductive amination, an aldehyde can be condensed with an amine to yield an iminium ion *in situ*. The iminium ion is then reduced to an amine by sodium cyanoborohydride.



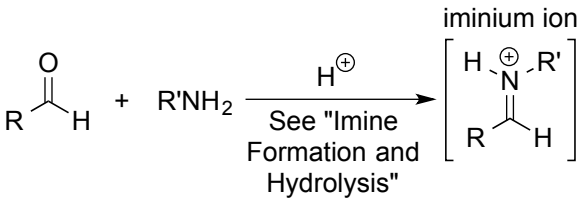
Alternatively, a ketone may undergo an analogous reductive amination.



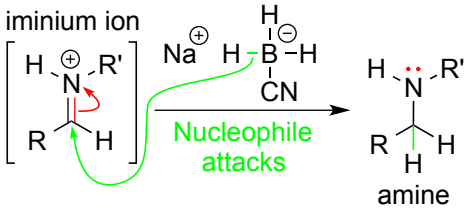
Ammonia (NH_3), primary amines ($R'NH_2$), or secondary amines (R'_2NH) can be used as reactants to prepare primary, secondary, or tertiary amine products, respectively.

Mechanistic considerations

• The mechanism for the condensation between an aldehyde and an amine is found in the section on imine formation and hydrolysis in Chapter 15. The last intermediate in this condensation is the iminium ion.

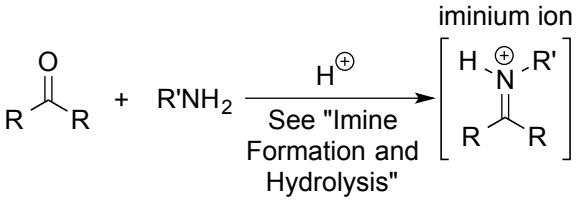


Once formed, the iminium ion is electrophilic enough (due to its positive charge) that it can be attacked by the very mild hydride donor sodium cyanoborohydride. This pushes the π electrons onto nitrogen as a lone pair.

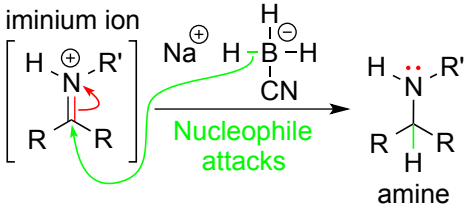


Since a primary amine ($R'NH_2$) was used as a reactant in this generic example, the product, which now contains one additional alkyl group, is a secondary amine.

• In Chapter 15, we also saw that ketones can condense with amines to afford iminium ions as the final intermediate prior to the formation of the imine itself.



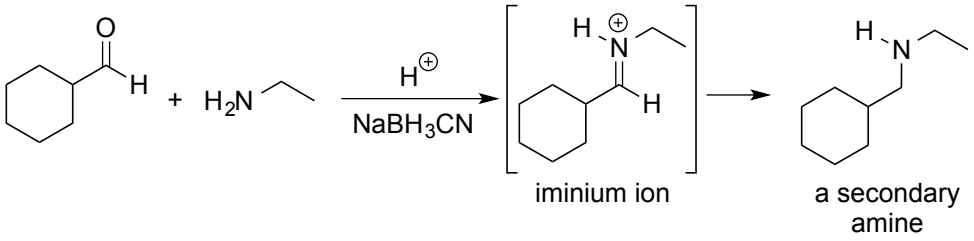
These iminium ions can be similarly reduced to amines through the attack of hydride donated from sodium cyanoborohydride.



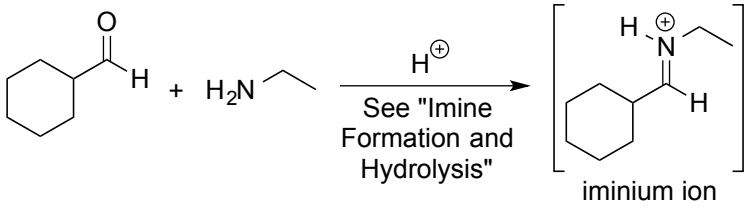
This generic example also produced a secondary amine because the reactant amine was primary. However, the new alkyl group in this product contains branching since a ketone was the coupling partner.

Specific examples of reductive amination

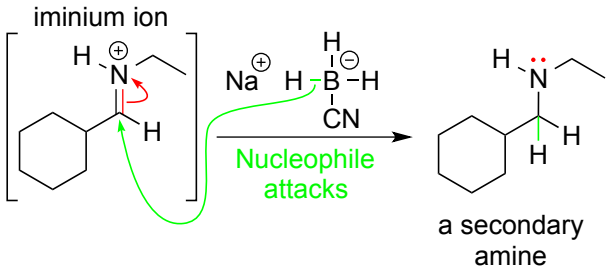
• In the following example, cyclohexanecarbaldehyde is condensed with ethylamine and reduced to afford a secondary amine product.



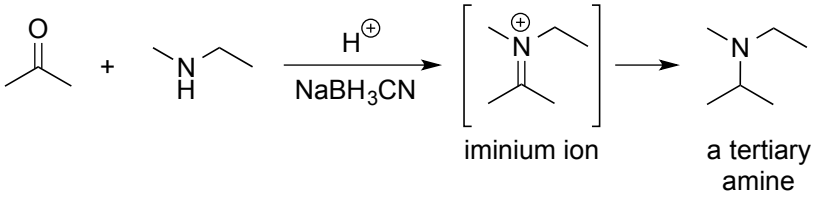
The first phase of the mechanism is the condensation of cyclohexanecarbaldehyde and ethylamine, in which the final intermediate prior to imine formation is the iminium ion.



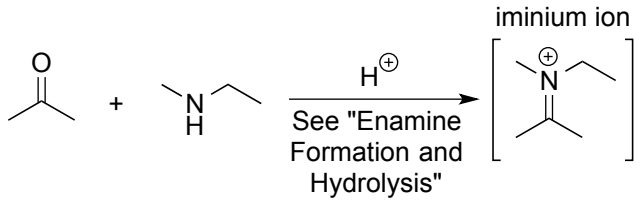
The electrophilic iminium ion is reduced by sodium cyanoborohydride to yield the final reductive amination product. Since a primary amine (ethylamine) was used as the reactant and one alkyl group was added during the reaction, the product is a secondary amine.



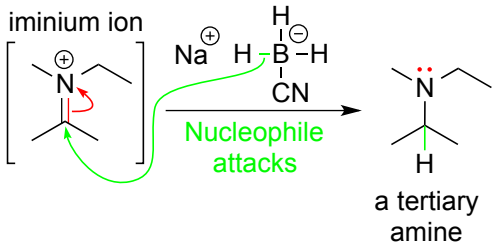
• In the next example, acetone and ethylmethylamine undergo reductive amination to generate ethylisopropylmethylamine.



The reaction begins with the condensation of acetone and ethylmethylamine. In the absence of the reducing agent, an enamine would result from this condensation because the nitrogen of the iminium ion has no proton to lose.



However, in the presence of sodium cyanoborohydride, a hydride is donated to the iminium ion. This reduction produces the final reaction product: ethylisopropylmethylamine. This product is a tertiary amine because the reactant amine was secondary and a single alkyl group was added through reductive amination.

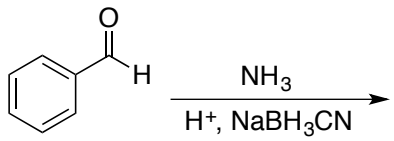


To recap, reductive amination enables us to selectively synthesize primary, secondary, or tertiary amines. The reaction consists of two mechanistic phases. First, an aldehyde or ketone condenses with an amine to afford an iminium ion. The iminium ion is then reduced by hydride donated from sodium cyanoborohydride to yield the final product.

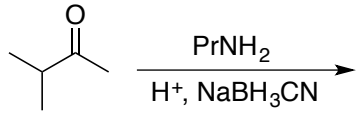
The choice of the starting amine impacts the level of substitution in the final product. Since one alkyl group is added during reductive amination, the use of ammonia (NH_3) as a reactant results in a primary amine product. A primary amine reactant generates a secondary amine product, and a secondary amine starting material results in a tertiary amine product.

Problem 11. Predict the products of the following reductive aminations.

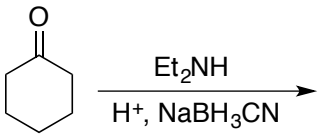
(a)



(b)

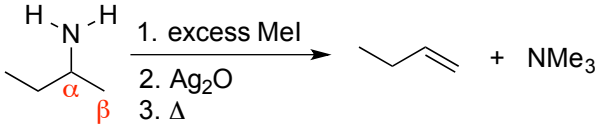


(c)



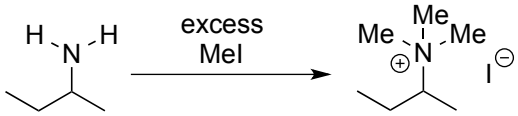
Section 7: Hofmann elimination

The Hofmann elimination is an E2 reaction of an amine, which can occur after it has been converted to a good leaving group by exhaustive methylation. The reaction has three steps. The amine is first treated with excess methyl iodide, thereby converting it into a quaternary ammonium cation. The counterion for this cation is initially iodide, but in the second step of the reaction, aqueous silver oxide is added. This results in the precipitation of silver iodide, and hydroxide then plays the role of the new counterion. Upon heating, hydroxide removes a proton from the less substituted β-carbon to afford the Hofmann elimination product, which is the less substituted alkene.

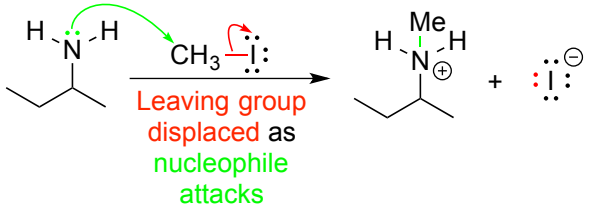


Mechanistic considerations

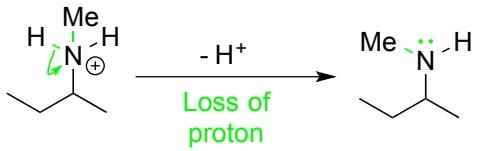
• In the first step of the reaction, the amine is exhaustively methylated through treatment with excess methyl iodide.



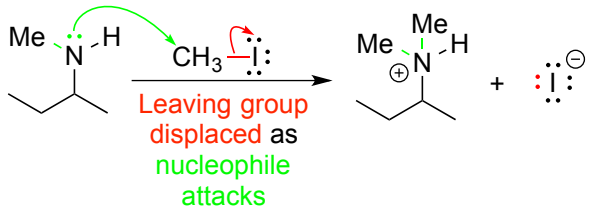
The reaction begins with the attack of nitrogen on methyl iodide. Iodide is concurrently displaced in this S_N2 reaction.



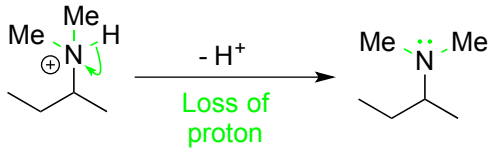
The ammonium ion thus formed can shed a proton to restore a lone pair to the amine.



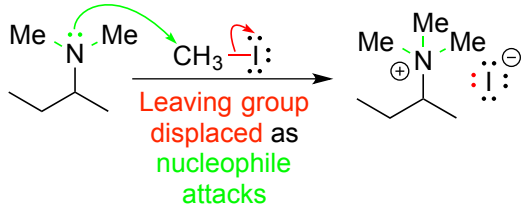
This new amine is nucleophilic again, so it engages in another S_N2 reaction with methyl iodide.



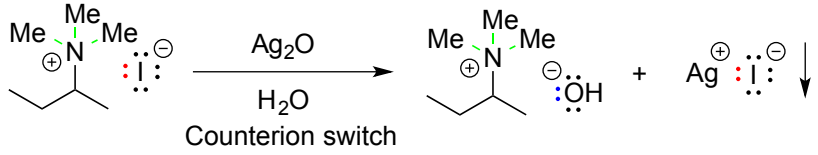
The last proton on nitrogen is lost, which yields a dimethylamino group on the substrate.



A final S_N2 reaction with methyl iodide installs a third methyl group and affords the quaternary ammonium cation, whose counterion is iodide.

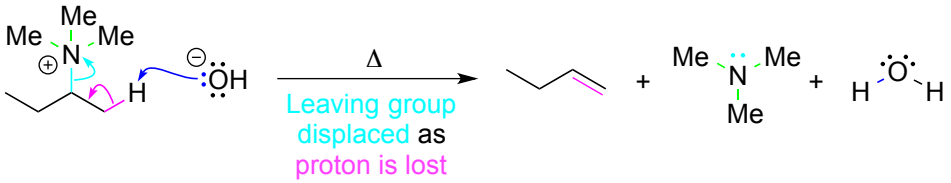


• In the second step of the reaction, aqueous silver oxide effects a counterion switch. Silver iodide is formed and precipitates from the reaction mixture (as denoted by the arrow pointing down). Hydroxide is the other byproduct formed from silver oxide in water, and it serves as the new counterion for the quaternary ammonium cation.



• Upon heating, an E2 reaction occurs. Hydroxide removes a proton from the less substituted β-carbon. A carbon-carbon π bond is then formed as trimethylamine (a good

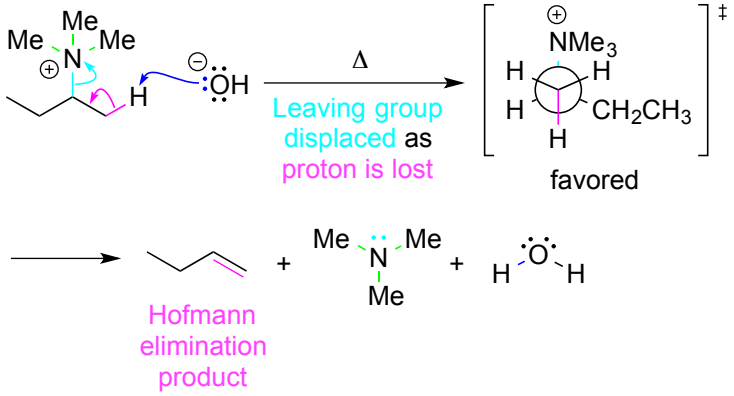
leaving group) simultaneously dissociates. The product is the less substituted alkene, which is known as the Hofmann product.



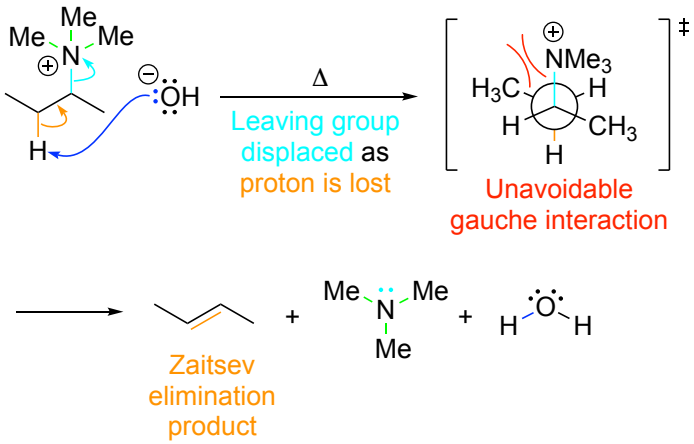
Regiochemical considerations

In our previous considerations of elimination reactions (see the sections on the E1 and E2 reactions in Chapter 7), we learned that there is typically a preference for the more substituted alkene product, which is known as the Zaitsev product. However, in this case, that preference is reversed.

The rationale for this reversal is found in the transition state for the elimination. Recall that E2 reactions require an anti-periplanar orientation of the proton and leaving group that are lost during the transformation. During formation of the Hofmann elimination product, the transition state with the necessary geometry contains no destabilizing steric interactions.

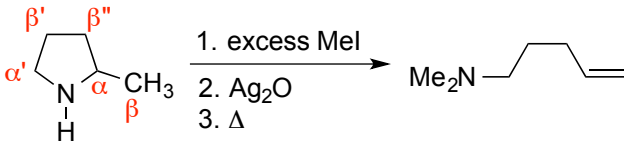


However, if a proton were to be removed from the more substituted β position to form the Zaitsev elimination product, there would be a gauche interaction between the bulky trimethylamino group and the methyl group on the more substituted β-carbon. That steric clash destabilizes this transition state, making the pathway leading to the Zaitsev product higher in energy (and therefore more difficult to access).

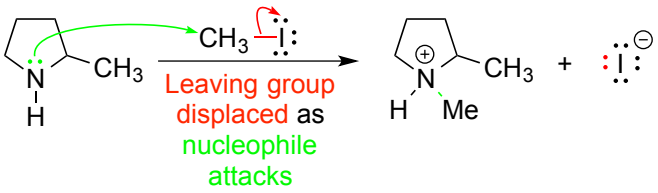


Another specific example of the Hofmann elimination

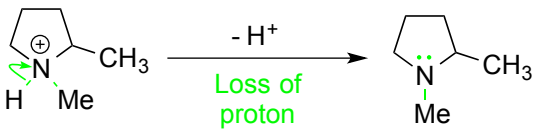
In the following example, a cyclic amine undergoes Hofmann elimination. In this instance, the dimethylamino leaving group remains tethered to the alkene in the product. As expected with Hofmann elimination, during the final E2 step a proton is removed from the least substituted β carbon, which is β (rather than β' or β").



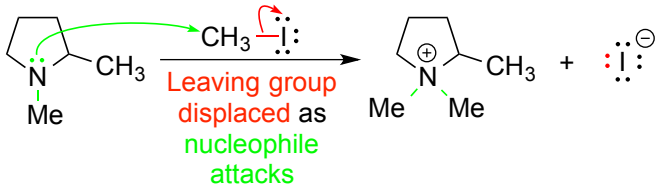
The reaction begins with exhaustive methylation of the amine. In this case, that requires only two rounds of alkylation. The first S_N2 reaction affords an ammonium salt.



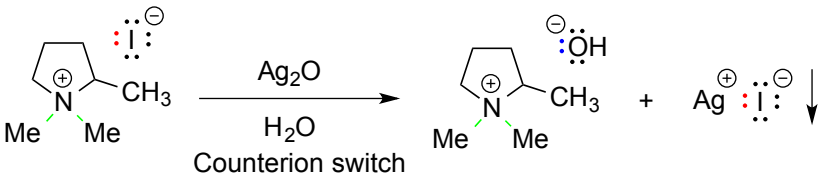
The ammonium salt sheds a proton to restore its nucleophilicity as the nitrogen re-acquires a lone pair.



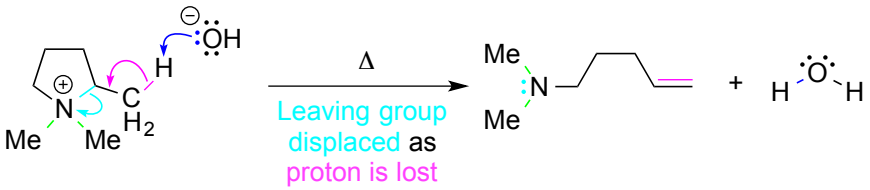
The next S_N2 reaction affords a quaternary ammonium cation that can be methylated no further.



During the second step of the reaction, the iodide counterion is swapped for hydroxide when silver oxide is added to the mixture.



Finally, upon heating, the E2 elimination occurs. Hydroxide removes a proton from the least substituted β position, and the π bond of an alkene is formed as the dimethylamino group dissociates.

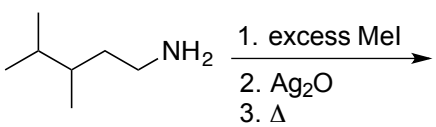


In conclusion, the Hofmann elimination entails E2 reaction of an amine that has been converted to a good leaving group through exhaustive methylation. There are three steps to the reaction. The first is treatment with excess methyl iodide to achieve the exhaustive methylation of the amino group. The second step is treatment with silver oxide, which causes the iodide counterion to be swapped for the more basic hydroxide counterion. Finally, when heated, the E2 reaction occurs.

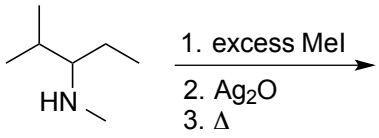
Since E2 elimination requires an anti-periplanar arrangement of the β-proton that is removed and the leaving group, the energy of the necessary transition state must be taken into account. Due to the steric bulk of the methylated amino group, the lowest-energy transition state is reached through removal of a proton from the least substituted β-carbon. This results in the Hofmann alkene (rather than the more substituted Zaitsev alkene).

Problem 12. Predict the product for each of the following Hofmann eliminations.

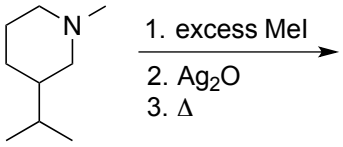
(a)



(b)

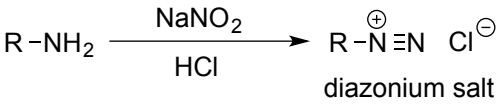


(c)



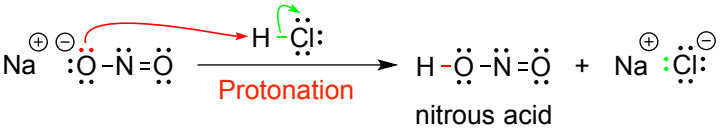
Section 8: Diazotization

The combination of sodium nitrite ($NaNO_2$) and hydrochloric acid produces nitrous acid (HONO). When a primary amine reacts with nitrous acid, a diazonium salt is formed. The diazonium ion may then be employed in subsequent transformations.

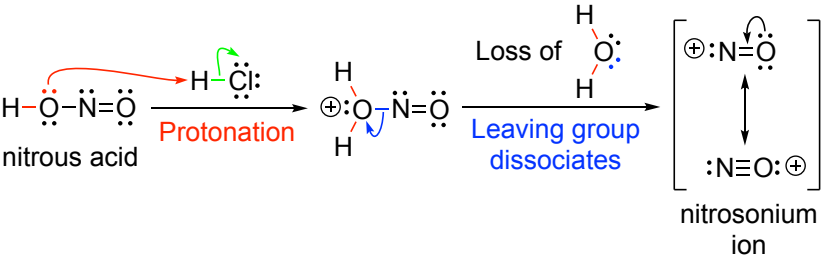


Mechanistic considerations

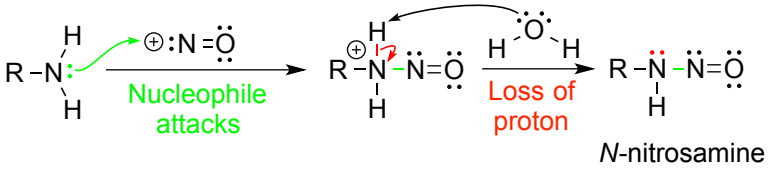
• The first phase of the mechanism is the formation of nitrous acid, and subsequently the nitrosonium ion, through the reaction between sodium nitrite and hydrochloric acid. This process begins with the protonation of nitrite. Nitrous acid results.



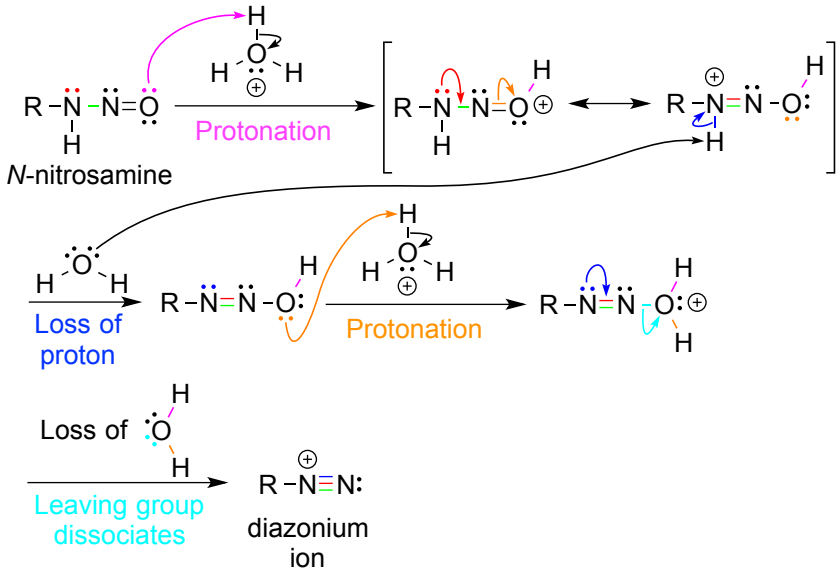
If a second protonation occurs on the hydroxyl group of nitrous acid, a good leaving group (water) is formed. The dissociation of water produces the nitrosonium ion.



• In the second phase of the mechanism, the electrophilic nitrosonium ion reacts with an amine. Nucleophilic attack of the amino group is the first step. The ammonium ion that results then loses a proton to water to afford an *N*-nitrosamine. When a secondary amine is used as the reactant, the reaction halts at this stage because the nitrogen bears a second R group and therefore has no protons left to lose.



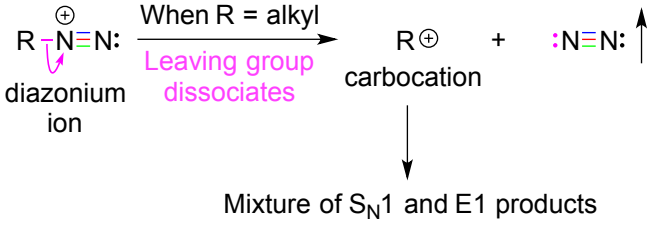
However, when a primary amine is the substrate, the reaction proceeds further through protonation of the nitrosamine oxygen. Loss of a proton from nitrogen then yields a neutral intermediate that is protonated again on the hydroxyl group. The loss of water follows to afford the diazonium ion.



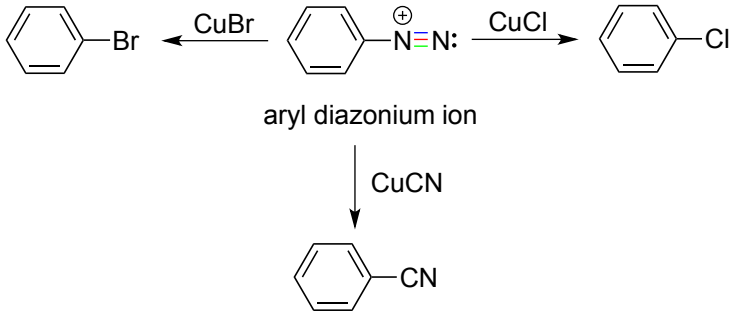
Reactions of diazonium ions

Diazonium ions can engage in a variety of reactions.

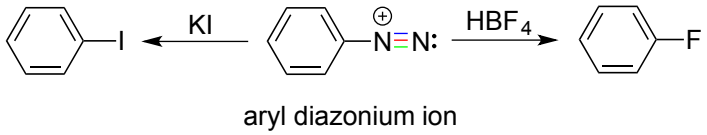
• Alkyl diazonium ions are *not* particularly useful because they are so unstable. They rapidly lose nitrogen (N_2), which is an excellent leaving group that bubbles out of the reaction mixture (as denoted by the arrow pointing up). The carbocation thus formed will yield a mixture of first-order substitution and elimination products (i.e., S_N1 and E1). Alternatively, second-order substitution and elimination pathways (i.e., S_N2 and E2) are also possible. The extreme reactivity of alkyl diazonium ions makes it difficult to use them in a productive fashion.



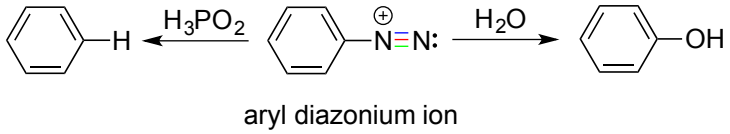
• Aryl diazonium ions, on the other hand, are much more useful because they are stable enough at low temperatures (0 °C) to be used in selective transformations, such as the Sandmeyer reactions. In the Sandmeyer reactions, an aryl diazonium ion is treated with a copper salt (CuBr, CuCl, or CuCN) to yield an aryl bromide, an aryl chloride, or an aryl nitrile. Mechanisms are not typically drawn for these reactions because they involve single-electron transfers.



There are also a series of related reactions that yield other substituted arenes (i.e., aromatic compounds). Treatment with potassium iodide (KI) produces an aryl iodide, while the use of fluoroboric acid (HBF_4) yields an aryl fluoride. The reaction with HBF_4 is sometimes called the Schiemann (or Balz-Schiemann) reaction.



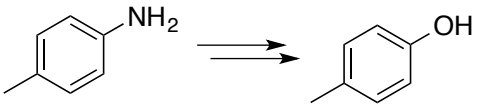
Hypophosphorous acid (H_3PO_2) will replace the diazonium ion with a hydrogen atom. Alternatively, treatment with water can be used to prepare a phenol.



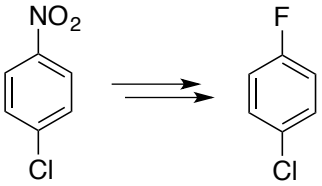
All of the aforementioned conversions can be described as substitution reactions of aryl diazonium salts because the diazonium ion is replaced by another group.

Problem 13. Perform the following conversions. Multiple steps may be required.

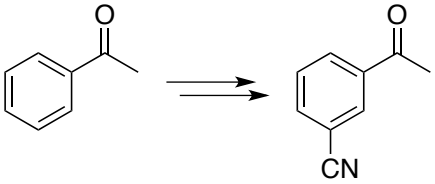
(a)



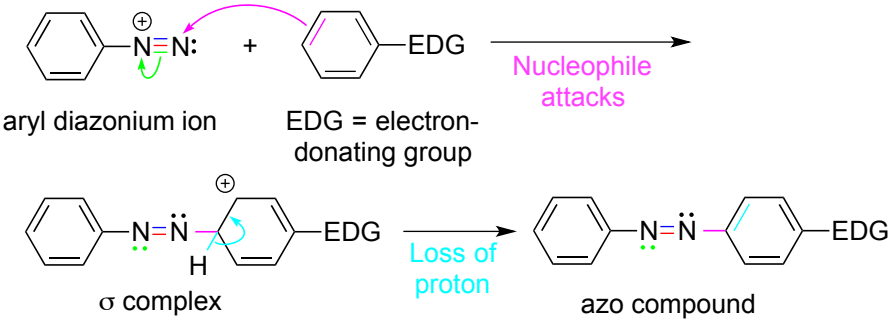
(b)



(c)



• Another type of reaction available to aryl diazonium salts is diazo coupling. In diazo coupling, the aryl diazonium salt is treated with an electron-rich substituted arene. An electrophilic aromatic substitution (EAS) reaction ensues, in which the diazonium ion serves as the electrophile. The electron-rich aromatic ring plays the role of the nucleophile. It attacks the diazonium ion to generate a σ complex. This σ complex possesses the resonance delocalization that we would expect based on our earlier examination of EAS reactions; however, these resonance forms are not shown below. As in any EAS reaction, the final mechanistic step is the loss of a proton from the sp^3 hybridized carbon, which restores aromaticity to the ring. The product of this reaction is known as an azo compound due to its –N=N– bridge. Azo compounds possess extended conjugation and are therefore colored compounds that are useful as organic dyes.



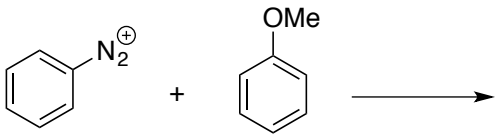
In summary, when a primary amine is treated with sodium nitrite and HCl, diazotization occurs. If the primary amine is specifically an arylamine (i.e., aniline or an aniline derivative), the diazonium ion is stable enough at 0 °C to be used in a variety of reactions. These reactions fall into two broad categories: substitution and diazo coupling.

There are a number of substitution reactions of diazonium ions. The Sandmeyer reactions involve treatment with a copper salt, namely CuBr, CuCl, or CuCN, to produce aryl bromides, chlorides, or nitriles. The Schiemann reaction utilizes HBF_4 to generate aryl fluorides. Diazonium ions may also be treated with KI to yield aryl iodides or with water to afford phenols. Finally, H_3PO_2 simply replaces the diazonium ion with a hydrogen atom.

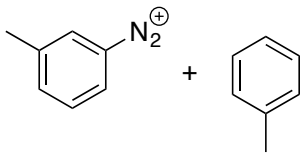
In diazo coupling, the diazonium ion acts as the electrophile in an EAS reaction. It is attacked on the terminal nitrogen by an electron-rich substituted arene, and the final product is an azo compound, which contains a –N=N– linkage between the two rings.

Problem 14. Provide the products of the following transformations.

(a)

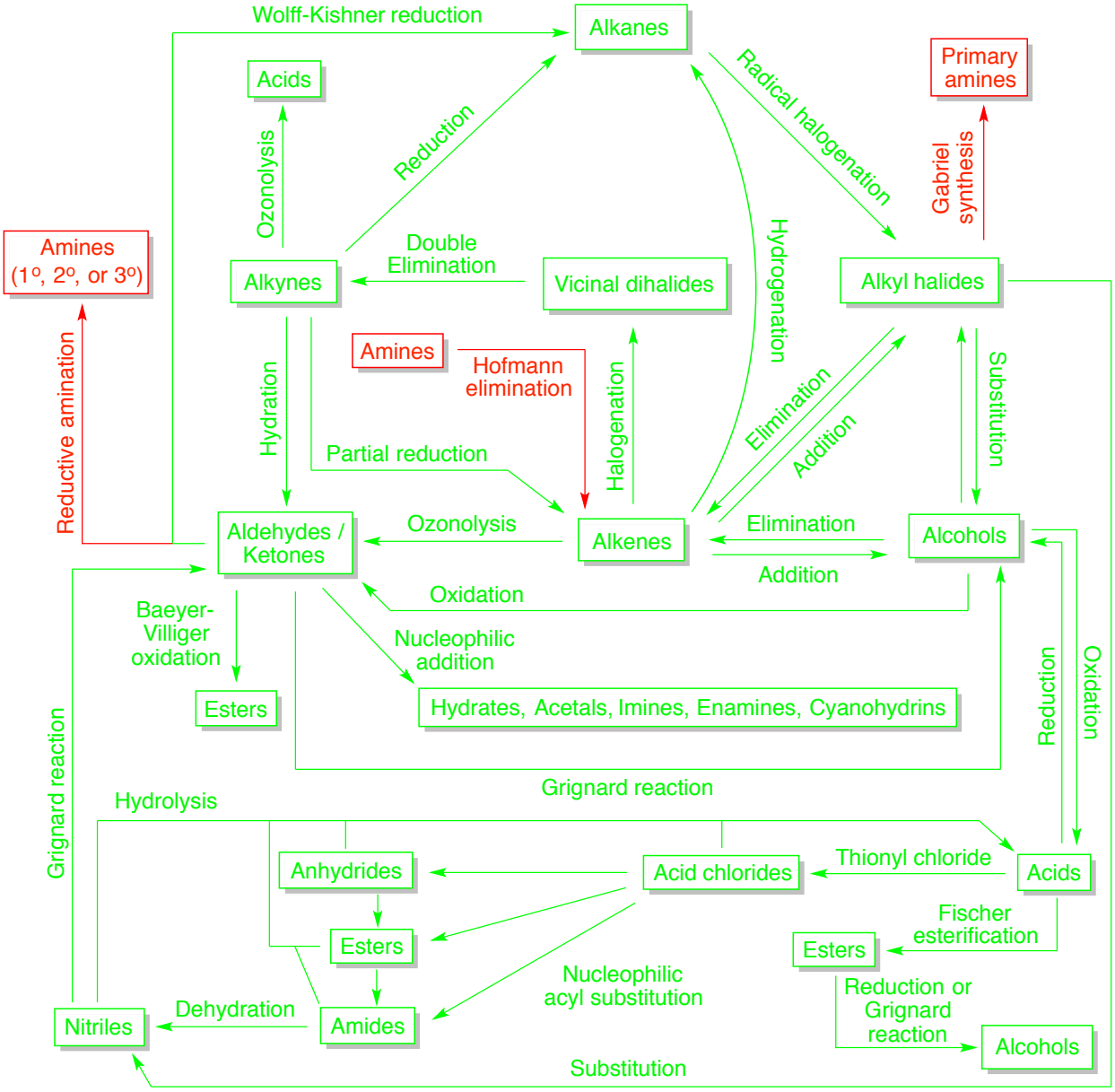


(b)

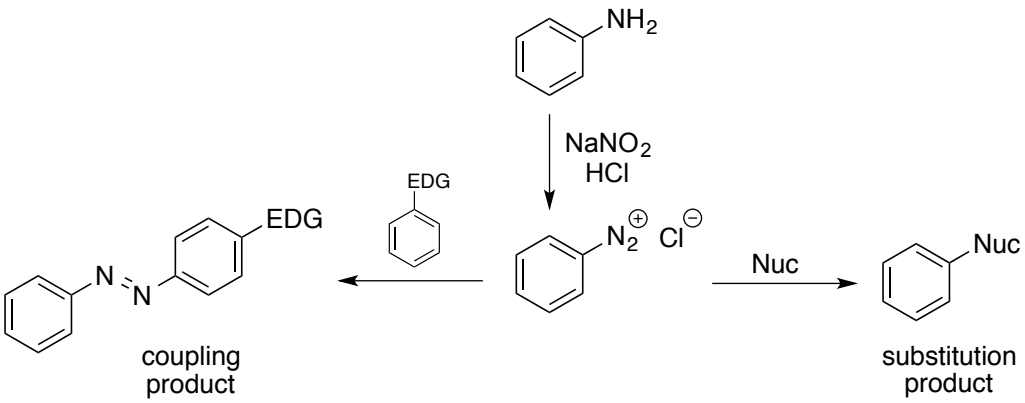


Section 9: Synthesis

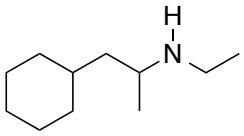
We've learned some new functional group interconversions in this chapter, which can be added to our web of connections between the various functionalities. All of the transformations in green have been encountered in previous chapters. The Gabriel synthesis enables the preparation of primary amines from alkyl halides. Reductive amination allows for the synthesis of a larger array of amines (primary, secondary, or tertiary) from ketones or aldehydes. Additionally, the Hofmann elimination converts amines into alkenes.



To this list, we can also add the very specific transformations of arylamines into substitution or coupling products via diazotization.



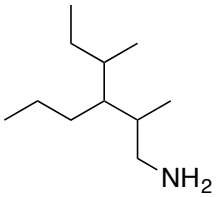
Problem 15. Devise a synthesis of the following amine, starting with phthalimide.



End-of-the-Chapter problems

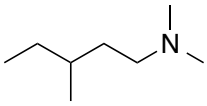
Problem 16. Identify the errors in each of the following names. Then, provide the correct names.

(a)



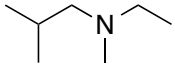
3-*sec*-butyl-2-methyl-1-hexanamine

(b)



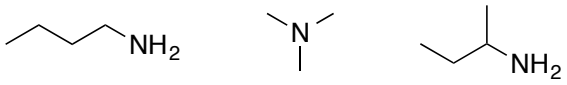
1,1,4-trimethylpentanamine

(c)

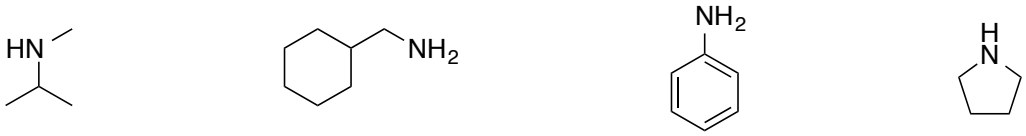


sec-butylethylmethylamine

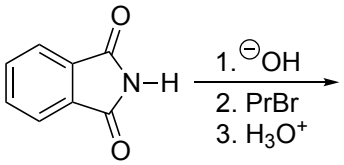
Problem 17. Rank the following amines in order of increasing boiling point.



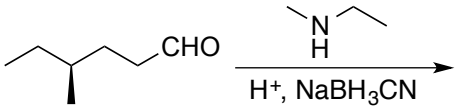
Problem 18. Which of the following amines could be prepared using a Gabriel synthesis and no additional transformations?



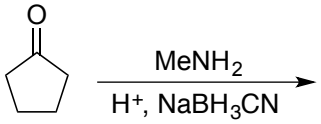
Problem 19. Provide the product of the following reaction, as well as a mechanism for steps 1 and 2 of the sequence.



Problem 20. A researcher conducted the following reaction and expected to obtain a mixture of diastereomeric products. However, at the end of the reaction, the investigator was unable to identify two compounds with different physical properties. Explain this outcome.

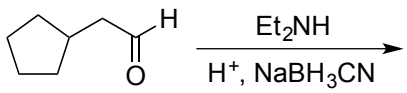


Problem 21. Predict the product of the following transformation, and provide a mechanism for its formation.

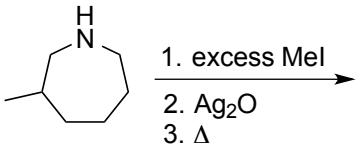


Problem 22. Predict the products of the following reactions.

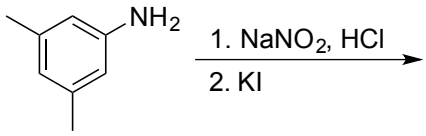
(a)



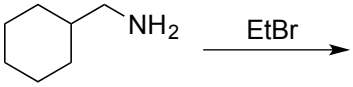
(b)


H
N
1. excess MeI
2. Ag_2O
3. Δ

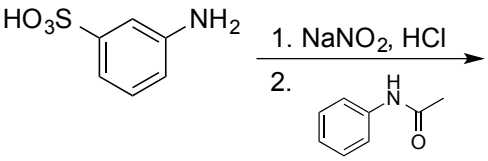
(c)


NH_2
1. $NaNO_2$, HCl
2. KI

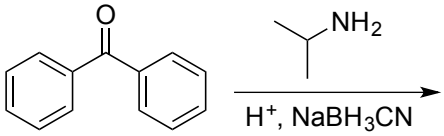
(d)


NH_2
EtBr

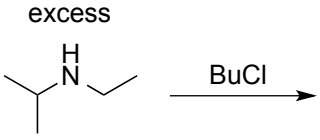
(e)


HO_3S
NH_2
1. $NaNO_2$, HCl
2.
H
N
O

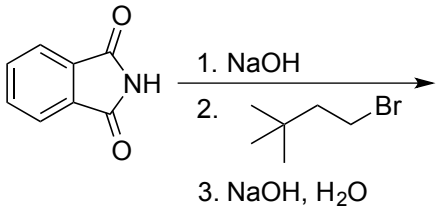
(f)


O
NH_2
H^+, $NaBH_3CN$

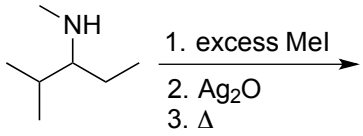
(g)


excess
H
N
BuCl

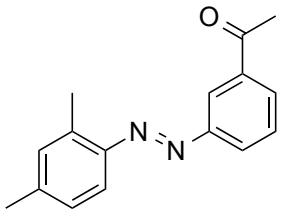
(h)



Problem 23. Provide a mechanism for the following transformation.

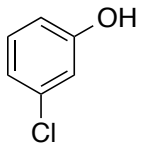


Problem 24. Devise a synthesis of the following azo compound from an arylamine. Pay special attention to the electronics of the coupling partners.

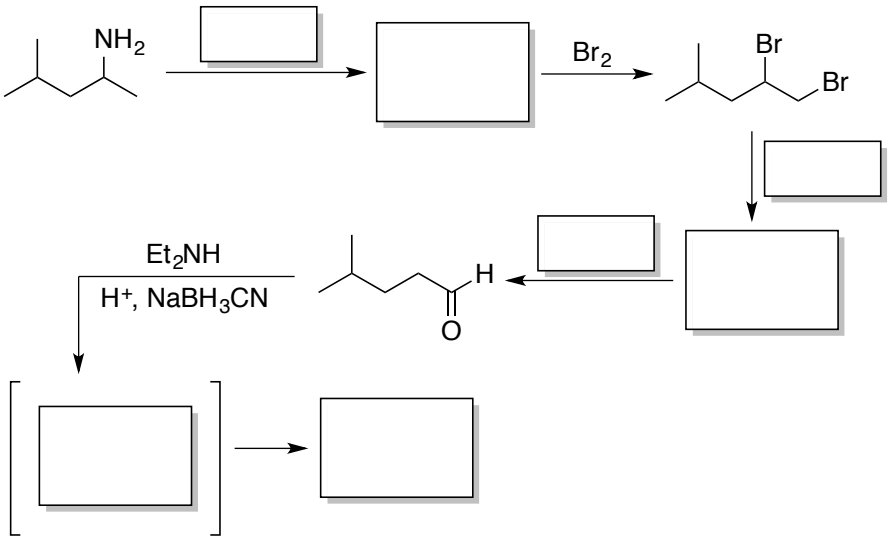


Problem 25. Provide a mechanism for the synthesis you proposed in Problem 24.

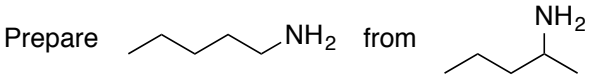
Problem 26. Devise a synthesis of *meta*-chlorophenol from benzene.



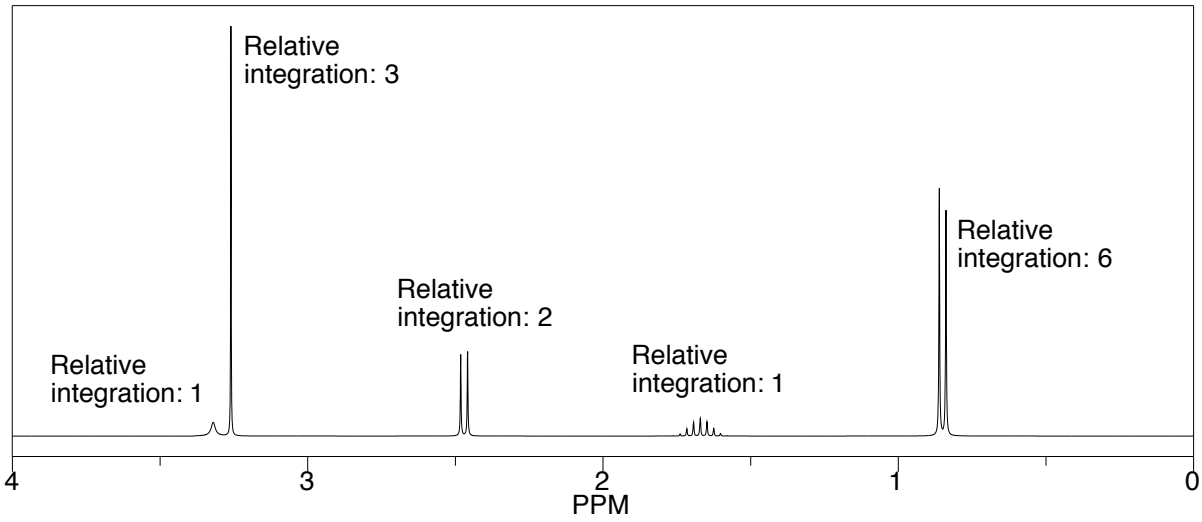
Problem 27. Fill in the missing compounds in the following scheme.



Problem 28. Devise a viable approach to the following synthesis problem.



Problem 29. Compound A is an alkene having the formula C_8H_{16}. It is subjected to ozonolysis and workup with dimethyl sulfide to afford Compound B. Compound B is then treated with methylamine, catalytic acid, and sodium cyanoborohydride to prepare Compound C, which exhibits the following NMR spectrum. Identify the structures of Compounds A, B, and C.



Problem 30. Devise a synthesis of 1,3,5-trichlorobenzene from benzene. Hint: You will need to use a *removable* directing group to orchestrate the placement of the chlorine atoms on the ring.

Credits

The following infrared spectra found in Chapter 5:

1-hexene
cyclohexane
m-toluic acid
isopropyl butyrate
4'-methoxyacetophenone
1-butanol
2-butanone
1-pentene
butyraldehyde
butyric acid
isobutyramide
acetophenone
phenylacetaldehyde
2,2,4-trimethylcyclopentanone
cyclohexanol
cyclohexyl amine
N-methyl cyclohexyl amine
N-methylbenzamide
isobutyric acid
pivalic acid
N-ethylacetanilide
phenylacetylene
butyronitrile
hexane
2-acetyl-N-tert-butyl-2-butenamide
1,4-dioxane
isobutyl isobutyrate
cis-3-hexene
trans-3-hexene
2,3-dimethyl-2-butene
2-methylbutanal
2-pentanol
ethylisopropylamine
3,3-dimethyl-2-butanone
1-pentyne
3,4-dihydro-2(1*H*)-naphthalenone

and the following infrared spectrum used in Chapter 7:

isopropenylbenzene

were obtained from the Spectral Database for Organic Compounds, SDBSWeb (http://sdbs.db.aist.go.jp/), National Institute of Advanced Industrial Science and Technology, 2014 – 2015.

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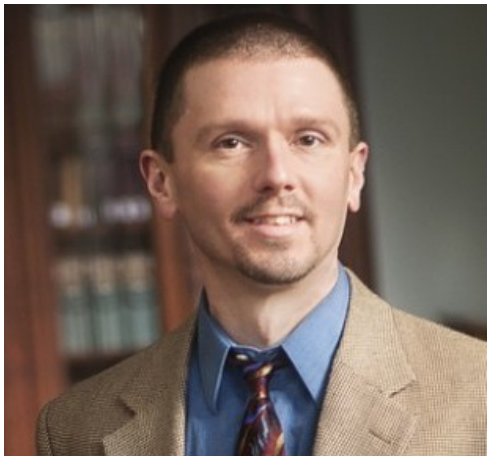
About The Author



Michael S. Leonard earned his B.A. in Chemistry from Goucher College in 1998 under the direction of Professor David E. Horn. He then transitioned to the University of Pennsylvania for his doctoral studies in the laboratory of Professor Madeleine M. Joullié. After obtaining his Ph.D. in 2003, he joined the faculty of Washington & Jefferson College, where he is currently Professor of Chemistry.