ORGANIC CHEMISTRY



Vollhardt and Schore
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Organic Chemistry

Vollhardt and Schore

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1: STRUCTURE AND BONDING IN ORGANIC MOLECULES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

1.1: The Scope of Organic Chemistry

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1.4: Electron-Dot Model of Bonding - Lewis Structures

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1.9: Structures and Formulas of Organic Molecules

1.E: Structure and Bonding in Organic Molecules (Exercises)

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1.1: The Scope of Organic Chemistry

Wöhler synthesis of Urea in 1828 heralded the birth of modern chemistry. The Art of synthesis is as old as Organic chemistry itself. Natural product chemistry is firmly rooted in the science of degrading a molecule to known smaller molecules using known chemical reactions and conforming the assigned structure by chemical synthesis from small, well known molecules using well established synthetic chemistry techniques. Once this art of synthesizing a molecule was mastered, chemists attempted to modify bioactive molecules in an attempt to develop new drugs and also to unravel the mystery of biomolecular interactions. Until the middle of the 20th Century, organic chemists approached the task of synthesis of molecules as independent tailor made projects, guided mainly by chemical intuition and a sound knowledge of chemical reactions. During this period, a strong foundation was laid for the development of mechanistic principles of organic reactions, new reactions and reagents. More than a century of such intensive studies on the chemistry of carbohydrates, alkaloids, terpenes and steroids laid the foundation for the development of logical approaches for the synthesis of molecules.

Organic chemistry encompasses a very large number of compounds (many millions), and our previous discussion and illustrations have focused on their structural characteristics. Now that we can recognize these actors (compounds), we turn to the roles they are inclined to play in the scientific drama staged by the multitude of chemical reactions that define organic chemistry.

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

First, we identify four broad classes of reactions based solely on the structural change occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are *additions*, *eliminations*, *substitutions*, and *rearrangements*.

The job of a synthetic chemist is akin to that of an architect (or civil engineer). While the architect could actually see the building he is constructing, a molecular architect called Chemist is handicapped by the fact that the molecule he is synthesizing is too small to be seen even through the most powerful microscope developed to date. With such a limitation, how does he ‘see’ the developing structure? For this purpose, a chemist makes use of spectroscopic tools. How does this chemist cut, tailor and glue the components on a molecule that cannot be seen with the naked eye? For this purpose chemists have developed molecular level tools called Reagents and Reactions. How does he clean the debris and produce pure molecules? This feat is achieved by crystallization, distillation and extensive use of chromatography techniques. A mastery over several such techniques enables the molecular architect (popularly known as organic chemist) to achieve the challenging task of synthesizing the mirade molecular structures encountered in Natural Products Chemistry, Drug Chemistry and modern Molecular Materials.

Contributors and Attributions

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1.2: Coulomb Forces - A Simplified View of Bonding

Coulomb Forces

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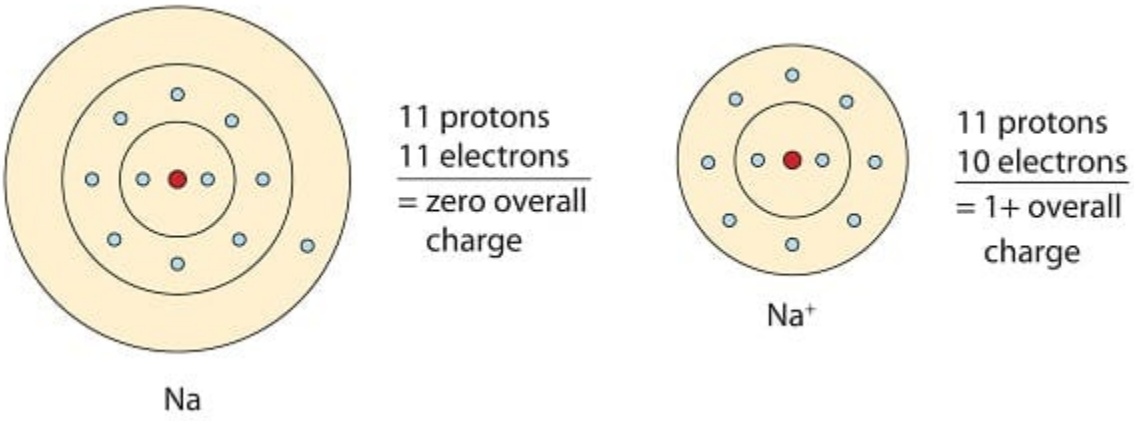
1.3: Ionic and Covalent Bonds - The Octet Rule

There are many types of chemical bonds and forces that bind molecules together. The two most basic types of bonds are characterized as either ionic or covalent. In ionic bonding, atoms transfer electrons to each other. Ionic bonds require at least one electron donor and one electron acceptor. In contrast, atoms with the same electronegativity share electrons in covalent bonds, because neither atom preferentially attracts or repels the shared electrons.

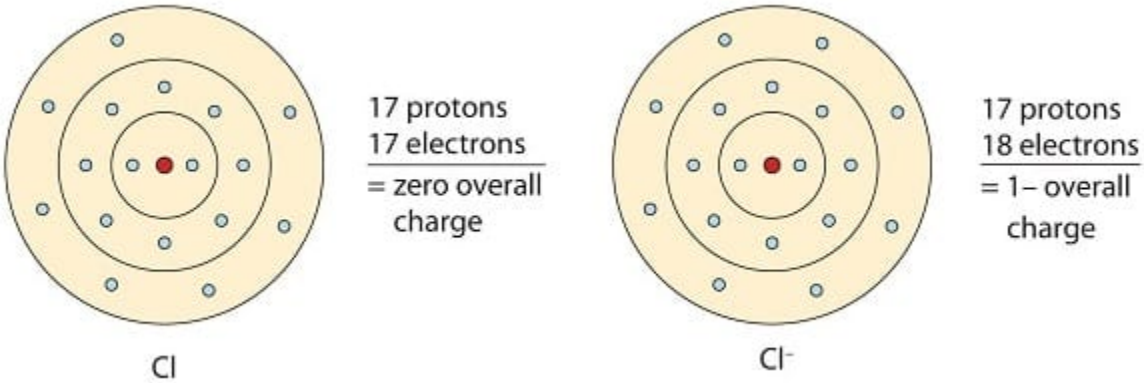
Introduction

Ionic bonding is the complete transfer of valence electron(s) between atoms. It is a type of chemical bond that generates two oppositely charged ions. In ionic bonds, the metal loses electrons to become a positively charged cation, whereas the nonmetal accepts those electrons to become a negatively charged anion. Ionic bonds require an electron donor, often a metal, and an electron acceptor, a nonmetal.

Ionic bonding is observed because metals have few electrons in their outer-most orbitals. By losing those electrons, these metals can achieve noble gas configuration and satisfy the octet rule. Similarly, nonmetals that have close to 8 electrons in their valence shells tend to readily accept electrons to achieve noble gas configuration. In ionic bonding, more than 1 electron can be donated or received to satisfy the octet rule. The charges on the anion and cation correspond to the number of electrons donated or received. In ionic bonds, the net charge of the compound must be zero.



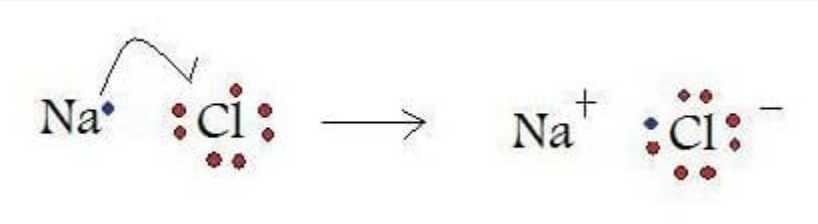
This sodium molecule donates the lone electron in its valence orbital in order to achieve octet configuration. This creates a positively charged cation due to the loss of electron.



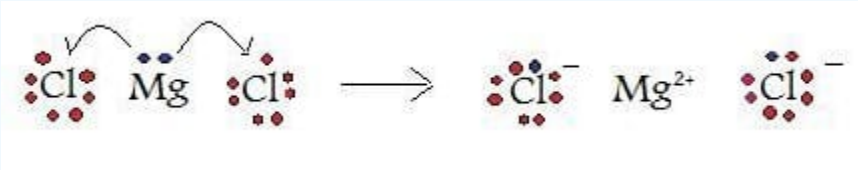
This chlorine atom receives one electron to achieve its octet configuration, which creates a negatively charged anion.

The predicted overall energy of the ionic bonding process, which includes the ionization energy of the metal and electron affinity of the nonmetal, is usually positive, indicating that the reaction is endothermic and unfavorable. However, this reaction is highly favorable because of the electrostatic attraction between the particles. At the ideal interatomic distance, attraction between these particles releases enough energy to facilitate the reaction. Most ionic compounds tend to dissociate in polar solvents because they are often polar. This phenomenon is due to the opposite charges on each ion.

Example 1.3.1: Chloride Salts



In this example, the sodium atom is donating its 1 valence electron to the chlorine atom. This creates a sodium cation and a chlorine anion. Notice that the net charge of the resulting compound is 0.



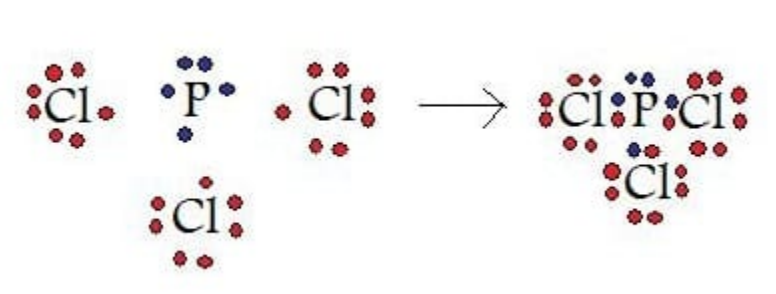
In this example, the magnesium atom is donating both of its valence electrons to chlorine atoms. Each chlorine atom can only accept 1 electron before it can achieve its noble gas configuration; therefore, 2 atoms of chlorine are required to accept the 2 electrons donated by the magnesium. Notice that the net charge of the compound is 0.

Covalent Bonding

Covalent bonding is the sharing of electrons between atoms. This type of bonding occurs between two atoms of the same element or of elements close to each other in the periodic table. This bonding occurs primarily between nonmetals; however, it can also be observed between nonmetals and metals.

If atoms have similar electronegativities (the same affinity for electrons), covalent bonds are most likely to occur. Because both atoms have the same affinity for electrons and neither has a tendency to donate them, they share electrons in order to achieve octet configuration and become more stable. In addition, the ionization energy of the atom is too large and the electron affinity of the atom is too small for ionic bonding to occur. For example: carbon does not form ionic bonds because it has 4 valence electrons, half of an octet. To form ionic bonds, Carbon molecules must either gain or lose 4 electrons. This is highly unfavorable; therefore, carbon molecules share their 4 valence electrons through single, double, and triple bonds so that each atom can achieve noble gas configurations. Covalent bonds include interactions of the sigma and pi orbitals; therefore, covalent bonds lead to formation of single, double, triple, and quadruple bonds.

Example 1.3.2: PCl_3



In this example, a phosphorous atom is sharing its three unpaired electrons with three chlorine atoms. In the end product, all four of these molecules have 8 valence electrons and satisfy the octet rule.

Bonding in Organic Chemistry

Ionic and covalent bonds are the two extremes of bonding. Polar covalent is the intermediate type of bonding between the two extremes. Some ionic bonds contain covalent characteristics and some covalent bonds are partially ionic. For example, most carbon-based compounds are covalently bonded but can also be partially ionic. Polarity is a measure of the separation of charge in a compound. A compound's polarity is dependent on the symmetry of the compound and on differences in electronegativity between atoms. Polarity occurs when the electron pushing elements, found on the left side of the periodic table, exchanges electrons with the electron pulling elements, on the right side of the table. This creates a spectrum of polarity, with ionic (polar) at one extreme, covalent (nonpolar) at another, and polar covalent in the middle.

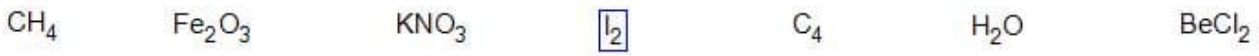
Both of these bonds are important in organic chemistry. Ionic bonds are important because they allow the synthesis of specific organic compounds. Scientists can manipulate ionic properties and these interactions in order to form desired products. Covalent bonds are especially important since most carbon molecules interact primarily through covalent bonding. Covalent bonding allows molecules to share electrons with other molecules, creating long chains of compounds and allowing more complexity in life.

References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry Structure and Function. New York: W. H. Freeman, 2007.
2. Petrucci, Ralph H. General Chemistry: Principles and Modern Applications. Upper Saddle River, NJ: Pearson Education, 2007.
3. Brown, Theodore L., Eugene H. Lemay, and Bruce E. Bursten. Chemistry: The Central Science. 6th ed. Englewood Cliffs, NJ: Prentice Hall, 1994.

Problems

1. Are these compounds ionic or covalent?



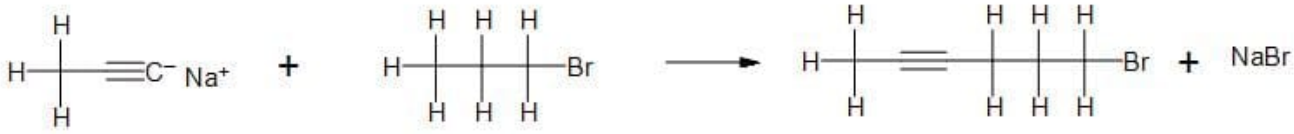
2. In the following reactions, indicate whether the reactants and products are ionic or covalently bonded.

a)

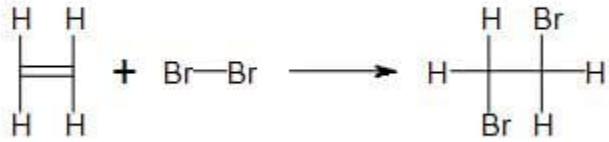


b) Clarification: What is the nature of the bond between sodium and amide? What kind of bond forms between the anion carbon chain and sodium?





c)



Solutions

- 1) From left to right: Covalent, Ionic, Ionic, Covalent, Covalent, Covalent, Ionic.
- 2a) All products and reactants are ionic.
- 2b) From left to right: Covalent, Ionic, Ionic, Covalent, Ionic, Covalent, Covalent, Ionic.
- 2c) All products and reactants are covalent.

Further Reading

Michigan State Virtual Textbook of Organic Chemistry

Chemical Bonding and Valence

MasterOrganicChemistry

Chemical Bonding

Understanding Periodic Trends

Carey 4th Edition On-Line Activity

Bond Types

Khan Academy

Leah4Sci

Intro to Organic Chemistry 3

Lewis Dots and the Octet Rule

Cliffs Notes

Covalent Bonding and Electronegativity

Slide Presentations

Web Pages

Counting Valence Electrons

The Octet Rule Rules!

*Exceptions to the Octet Rule

Videos

Video on Octet rule and Valance charges

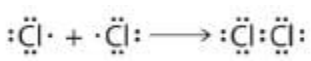
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1.4: Electron-Dot Model of Bonding - Lewis Structures

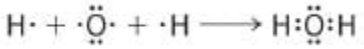
Using Lewis Dot Symbols to Describe Covalent Bonding

This sharing of electrons allowing atoms to "stick" together is the basis of covalent bonding. There is some intermediate distant, generally a bit longer than 0.1 nm, or if you prefer 100 pm, at which the attractive forces significantly outweigh the repulsive forces and a bond will be formed if both atoms can achieve a completen s^2np^6 configuration. It is this behavior that Lewis captured in his octet rule. The valence electron configurations of the constituent atoms of a covalent compound are important factors in determining its structure, stoichiometry, and properties. For example, chlorine, with seven valence electrons, is one electron short of an octet. If two chlorine atoms share their unpaired electrons by making a covalent bond and forming Cl_2, they can each complete their valence shell:

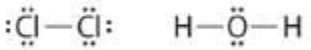


Each chlorine atom now has an octet. The electron pair being shared by the atoms is called a bonding pair ; the other three pairs of electrons on each chlorine atom are called lone pairs. Lone pairs are not involved in covalent bonding. If both electrons in a covalent bond come from the same atom, the bond is called a coordinate covalent bond.

We can illustrate the formation of a water molecule from two hydrogen atoms and an oxygen atom using Lewis dot symbols:



The structure on the right is the *Lewis electron structure*, or *Lewis structure*, for H_2O. With two bonding pairs and two lone pairs, the oxygen atom has now completed its octet. Moreover, by sharing a bonding pair with oxygen, each hydrogen atom now has a full valence shell of two electrons. Chemists usually indicate a bonding pair by a single line, as shown here for our two examples:



The following procedure can be used to construct Lewis electron structures for more complex molecules and ions:

1. **Arrange the atoms to show specific connections.** When there is a central atom, it is usually the least electronegative element in the compound. Chemists usually list this central atom first in the chemical formula (as in CCl_4 and CO_3^{2-}, which both have C as the central atom), which is another clue to the compound's structure. Hydrogen and the halogens are almost always connected to only one other atom, so they are usually *terminal* rather than central.

> Note
>
> The central atom is usually the least electronegative element in the molecule or ion; hydrogen and the halogens are usually terminal.

1. **Determine the total number of valence electrons in the molecule or ion**. Add together the valence electrons from each atom. (Recall from Chapter 2 that the number of valence electrons is indicated by the position of the element in the periodic table.) If the species is a polyatomic ion, remember to add or subtract the number of electrons necessary to give the total charge on the ion. For CO32–, for example, we add two electrons to the total because of the –2 charge.
2. **Place a bonding pair of electrons between each pair of adjacent atoms to give a single bond**. In H_2O, for example, there is a bonding pair of electrons between oxygen and each hydrogen.
3. **Beginning with the terminal atoms, add enough electrons to each atom to give each atom an octet (two for hydrogen)**. These electrons will usually be lone pairs.
4. **If any electrons are left over, place them on the central atom**. Some atoms are able to accommodate more than eight electrons.
5. **If the central atom has fewer electrons than an octet, use lone pairs from terminal atoms to form multiple (double or triple) bonds to the central atom to achieve an octet**. This will not change the number of electrons on the terminal atoms.

Now let's apply this procedure to some particular compounds, beginning with one we have already discussed.

YouTube Video

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H_2O

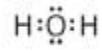
1. Because H atoms are almost always terminal, the arrangement within the molecule must be HOH.

2. Each H atom (group 1) has 1 valence electron, and the O atom (group 16) has 6 valence electrons, for a total of 8 valence electrons.

3. Placing one bonding pair of electrons between the O atom and each H atom gives H:O:H, with 4 electrons left over.

4. Each H atom has a full valence shell of 2 electrons.

5. Adding the remaining 4 electrons to the oxygen (as two lone pairs) gives the following structure:



This is the Lewis structure we drew earlier. Because it gives oxygen an octet and each hydrogen two electrons, we do not need to use step 6.

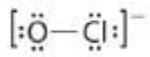
OCl^-

1. With only two atoms in the molecule, there is no central atom.

2. Oxygen (group 16) has 6 valence electrons, and chlorine (group 17) has 7 valence electrons; we must add one more for the negative charge on the ion, giving a total of 14 valence electrons.

3. Placing a bonding pair of electrons between O and Cl gives O:Cl, with 12 electrons left over.

4. If we place six electrons (as three lone pairs) on each atom, we obtain the following structure:



Each atom now has an octet of electrons, so steps 5 and 6 are not needed. The Lewis electron structure is drawn within brackets as is customary for an ion, with the overall charge indicated outside the brackets, and the bonding pair of electrons is indicated by a solid line. OCl^- is the hypochlorite ion, the active ingredient in chlorine laundry bleach and swimming pool disinfectant.

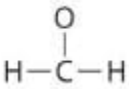
CH_2O

1. Because carbon is less electronegative than oxygen and hydrogen is normally terminal, C must be the central atom. One possible arrangement is as follows:



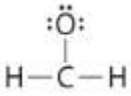
2. Each hydrogen atom (group 1) has one valence electron, carbon (group 14) has 4 valence electrons, and oxygen (group 16) has 6 valence electrons, for a total of [(2)(1) + 4 + 6] = 12 valence electrons.

3. Placing a bonding pair of electrons between each pair of bonded atoms gives the following:



Six electrons are used, and 6 are left over.

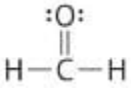
4. Adding all 6 remaining electrons to oxygen (as three lone pairs) gives the following:



Although oxygen now has an octet and each hydrogen has 2 electrons, carbon has only 6 electrons.

5. There are no electrons left to place on the central atom.

6. To give carbon an octet of electrons, we use one of the lone pairs of electrons on oxygen to form a carbon–oxygen double bond:



Both the oxygen and the carbon now have an octet of electrons, so this is an acceptable Lewis electron structure. The O has two bonding pairs and two lone pairs, and C has four bonding pairs. This is the structure of formaldehyde, which is used in embalming fluid.

An alternative structure can be drawn with one H bonded to O. *Formal charges*, discussed later in this section, suggest that such a structure is less stable than that shown previously.

Example

Write the Lewis electron structure for each species.

1. NCl_3
2. S_2^{2-}
3. NOCl

Given: chemical species

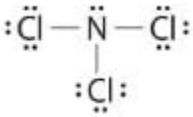
Asked for: Lewis electron structures

Strategy:

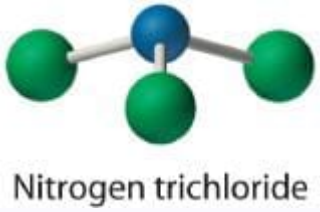
Use the six-step procedure to write the Lewis electron structure for each species.

Solution:

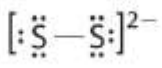
Nitrogen is less electronegative than chlorine, and halogen atoms are usually terminal, so nitrogen is the central atom. The nitrogen atom (group 15) has 5 valence electrons and each chlorine atom (group 17) has 7 valence electrons, for a total of 26 valence electrons. Using 2 electrons for each N–Cl bond and adding three lone pairs to each Cl account for (3 × 2) + (3 × 2 × 3) = 24 electrons. Rule 5 leads us to place the remaining 2 electrons on the central N:



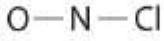
Nitrogen trichloride is an unstable oily liquid once used to bleach flour; this use is now prohibited in the United States.

1. 

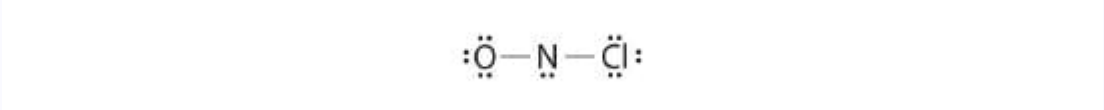
2. In a diatomic molecule or ion, we do not need to worry about a central atom. Each sulfur atom (group 16) contains 6 valence electrons, and we need to add 2 electrons for the –2 charge, giving a total of 14 valence electrons. Using 2 electrons for the S–S bond, we arrange the remaining 12 electrons as three lone pairs on each sulfur, giving each S atom an octet of electrons:



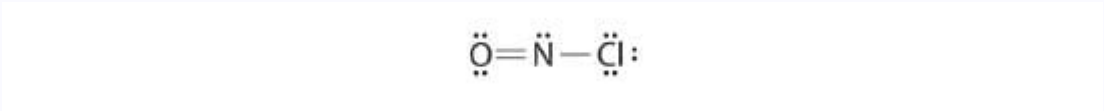
3. Because nitrogen is less electronegative than oxygen or chlorine, it is the central atom. The N atom (group 15) has 5 valence electrons, the O atom (group 16) has 6 valence electrons, and the Cl atom (group 17) has 7 valence electrons, giving a total of 18 valence electrons. Placing one bonding pair of electrons between each pair of bonded atoms uses 4 electrons and gives the following:



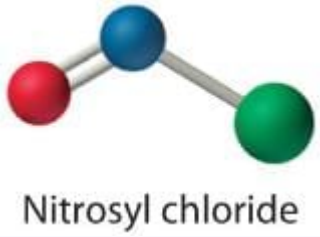
Adding three lone pairs each to oxygen and to chlorine uses 12 more electrons, leaving 2 electrons to place as a lone pair on nitrogen:



4. Because this Lewis structure has only 6 electrons around the central nitrogen, a lone pair of electrons on a terminal atom must be used to form a bonding pair. We could use a lone pair on either O or Cl. Because we have seen many structures in which O forms a double bond but none with a double bond to Cl, it is reasonable to select a lone pair from O to give the following:



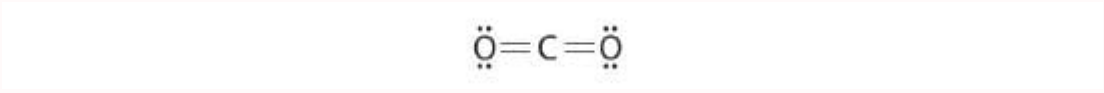
All atoms now have octet configurations. This is the Lewis electron structure of nitrosyl chloride, a highly corrosive, reddish-orange gas.



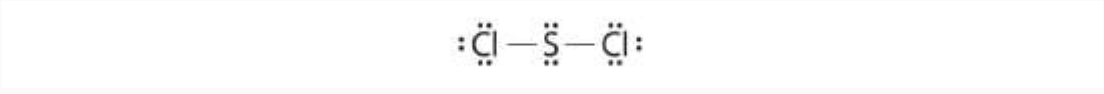
Exercise

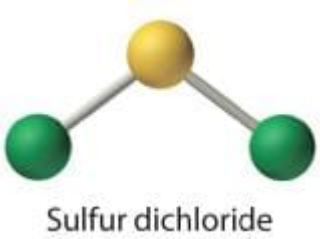
Write Lewis electron structures for CO_2 and SCl_2, a vile-smelling, unstable red liquid that is used in the manufacture of rubber.

Answer:

1. 



2. 



Formal Charges

It is sometimes possible to write more than one Lewis structure for a substance that does not violate the octet rule, as we saw for CH_2O, but not every Lewis structure may be equally reasonable. In these situations, we can choose the most stable Lewis structure by considering the formal charge on the atoms, which is the difference between the number of valence electrons in the free atom and the number assigned to it in the Lewis electron structure. The formal charge is a way of computing the charge distribution within a Lewis structure; the sum of the formal charges on the atoms within a molecule or an ion must equal the overall charge on the molecule or ion. A formal charge does *not* represent a true charge on an atom in a covalent bond but is simply used to predict the most likely structure when a compound has more than one valid Lewis structure.

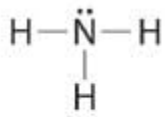
To calculate formal charges, we assign electrons in the molecule to individual atoms according to these rules:

- Nonbonding electrons are assigned to the atom on which they are located.
- Bonding electrons are divided equally between the bonded atoms.

For each atom, we then compute a formal charge:

$$\underset{(\textit{free atom})}{\textit{formal charge} = \textit{valence } e^-} - \underset{(\textit{atom in Lewis structure})}{\left(\textit{non} - \textit{bonding } e^- + \frac{\textit{bonding } e^-}{2}\right)} \tag{5.3.1}$$

To illustrate this method, let's calculate the formal charge on the atoms in ammonia (NH_3) whose Lewis electron structure is as follows:



Ammonia

A neutral nitrogen atom has five valence electrons (it is in group 15). From its Lewis electron structure, the nitrogen atom in ammonia has one lone pair and shares three bonding pairs with hydrogen atoms, so nitrogen itself is assigned a total of five electrons [2 nonbonding e^- + (6 bonding e^-/2)]. Substituting into Equation 5.3.1, we obtain

$$\textit{formal charge}\,(N) = 5\ \textit{valence } e^- - \left(2\ \textit{non} - \textit{bonding } e^- + \frac{6\ \textit{bonding } e^-}{2}\right) = 0 \tag{4.4.2}$$

A neutral hydrogen atom has one valence electron. Each hydrogen atom in the molecule shares one pair of bonding electrons and is therefore assigned one electron [0 nonbonding e^- + (2 bonding e^-/2)]. Using Equation 4.4.1 to calculate the formal charge on hydrogen, we obtain

$$\textit{formal charge}\,(H) = 1\ \textit{valence } e^- - \left(0\ \textit{non} - \textit{bonding } e^- + \frac{2\ \textit{bonding } e^-}{2}\right) = 0 \tag{4.4.3}$$

The hydrogen atoms in ammonia have the same number of electrons as neutral hydrogen atoms, and so their formal charge is also zero. Adding together the formal charges should give us the overall charge on the molecule or ion. In this example, the nitrogen and each hydrogen has a formal charge of zero. When summed the overall charge is zero, which is consistent with the overall charge on the NH_3 molecule.

Typically, the structure with the most charges on the atoms closest to zero is the more stable Lewis structure. In cases where there are positive or negative formal charges on various atoms, stable structures generally have negative formal charges on the more electronegative atoms and positive formal charges on the less electronegative atoms. The next example further demonstrates

how to calculate formal charges.

Example

Calculate the formal charges on each atom in the NH_4^+ ion.

Given: chemical species

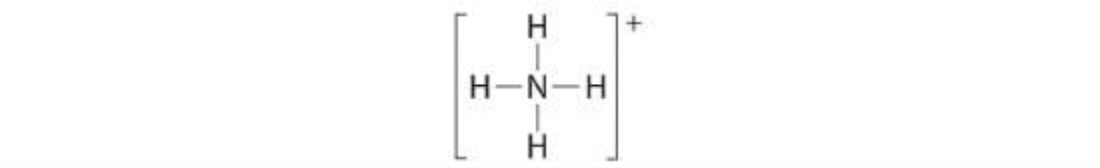
Asked for: formal charges

Strategy:

Identify the number of valence electrons in each atom in the NH_4^+ ion. Use the Lewis electron structure of NH_4^+ to identify the number of bonding and nonbonding electrons associated with each atom and then use Equation 4.4.1 to calculate the formal charge on each atom.

Solution:

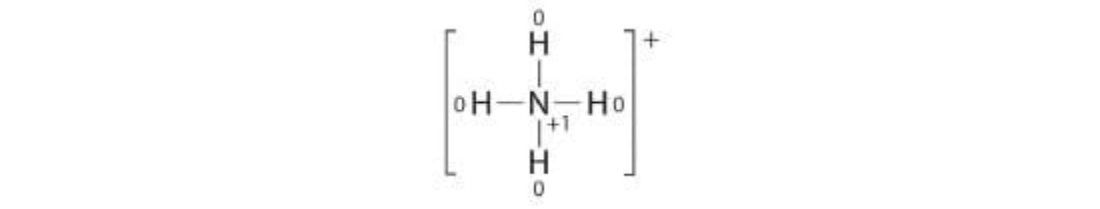
The Lewis electron structure for the NH_4^+ ion is as follows:



The nitrogen atom shares four bonding pairs of electrons, and a neutral nitrogen atom has five valence electrons. Using Equation 4.4.1, the formal charge on the nitrogen atom is therefore

Each hydrogen atom in has one bonding pair. The formal charge on each hydrogen atom is therefore

The formal charges on the atoms in the NH_4^+ ion are thus

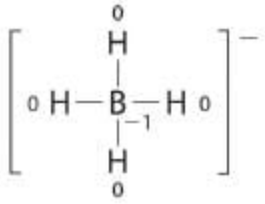


Adding together the formal charges on the atoms should give us the total charge on the molecule or ion. In this case, the sum of the formal charges is 0 + 1 + 0 + 0 + 0 = +1.

Exercise

Write the formal charges on all atoms in BH_4^-.

Answer:



If an atom in a molecule or ion has the number of bonds that is typical for that atom (e.g., four bonds for carbon), its formal charge is zero.

Using Formal Charges to Distinguish between Lewis Structures

As an example of how formal charges can be used to determine the most stable Lewis structure for a substance, we can compare two possible structures for CO_2. Both structures conform to the rules for Lewis electron structures.

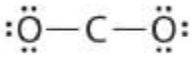
CO_2

1. C is less electronegative than O, so it is the central atom.

2. C has 4 valence electrons and each O has 6 valence electrons, for a total of 16 valence electrons.

3. Placing one electron pair between the C and each O gives O–C–O, with 12 electrons left over.

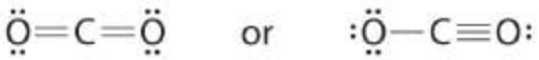
4. Dividing the remaining electrons between the O atoms gives three lone pairs on each atom:



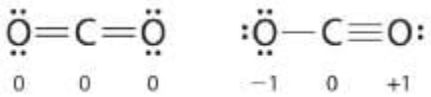
This structure has an octet of electrons around each O atom but only 4 electrons around the C atom.

5. No electrons are left for the central atom.

6. To give the carbon atom an octet of electrons, we can convert two of the lone pairs on the oxygen atoms to bonding electron pairs. There are, however, two ways to do this. We can either take one electron pair from each oxygen to form a symmetrical structure or take both electron pairs from a single oxygen atom to give an asymmetrical structure:



Both Lewis electron structures give all three atoms an octet. How do we decide between these two possibilities? The formal charges for the two Lewis electron structures of CO_2 are as follows:



Both Lewis structures have a net formal charge of zero, but the structure on the right has a +1 charge on the more electronegative atom (O). Thus the symmetrical Lewis structure on the left is predicted to be more stable, and it is, in fact, the structure observed experimentally. Remember, though, that formal charges do *not* represent the actual charges on atoms in a molecule or ion. They are used simply as a bookkeeping method for predicting the most stable Lewis structure for a compound.

Note

The Lewis structure with the set of formal charges **closest to zero** is usually the most stable.

Example

The thiocyanate ion (SCN^-), which is used in printing and as a corrosion inhibitor against acidic gases, has at least two possible Lewis electron structures. Draw two possible structures, assign formal charges on all atoms in both, and decide which is the preferred arrangement of electrons.

Given: chemical species

Asked for: Lewis electron structures, formal charges, and preferred arrangement

Strategy:

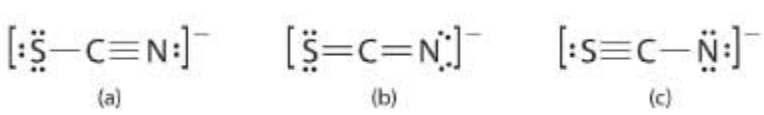
A Use the step-by-step procedure to write two plausible Lewis electron structures for SCN^-.

B Calculate the formal charge on each atom using Equation 4.4.1.

C Predict which structure is preferred based on the formal charge on each atom and its electronegativity relative to the other atoms present.

Solution:

A Possible Lewis structures for the SCN^- ion are as follows:



B We must calculate the formal charges on each atom to identify the more stable structure. If we begin with carbon, we notice that the carbon atom in each of these structures shares four bonding pairs, the number of bonds typical for carbon, so it has a formal charge of zero. Continuing with sulfur, we observe that in (a) the sulfur atom shares one bonding pair and has three lone pairs and has a total of six valence electrons. The formal charge on the sulfur atom is therefore

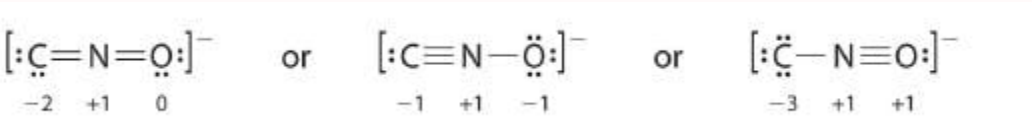
In (c), nitrogen has a formal charge of –2.

C Which structure is preferred? Structure (b) is preferred because the negative charge is on the more electronegative atom (N), and it has lower formal charges on each atom as compared to structure (c): 0, –1 versus +1, –2.

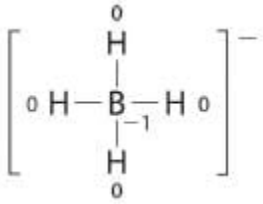
Exercise

Salts containing the fulminate ion (CNO^-) are used in explosive detonators. Draw three Lewis electron structures for CNO^- and use formal charges to predict which is more stable. (Note: N is the central atom.)

Answer:



The second structure is predicted to be more stable.



Drawing isomers of Lewis Structures

YouTube Video

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View this YouTube Video online

Contributors

- Anonymous

Layne Morsch (University of Illinois Springfield)

Three cases can be constructed that do not follow the octet rule, and as such, they are known as the exceptions to the octet rule. Following the Octet Rule for Lewis Dot Structures leads to the most accurate depictions of stable molecular and atomic structures and because of this we always want to use the octet rule when drawing Lewis Dot Structures. However, it is hard to imagine that one rule could be followed by all molecules. There is always an exception, and in this case, three exceptions. The octet rule is violated in these three scenarios:

1. When there are an odd number of valence electrons
2. When there are too few valence electrons
3. When there are too many valence electrons

Exception 1: Species with Odd Numbers of Electrons

The first exception to the Octet Rule is when there are an odd number of valence electrons. An example of this would be Nitrogen (II) Oxide (NO ,refer to figure one). Nitrogen has 5 valence electrons while Oxygen has 6. The total would be 11 valence electrons to be used. The Octet Rule for this molecule is fulfilled in the above example, however that is with 10 valence electrons. The last one does not know where to go. The lone electron is called an unpaired electron. But where should the unpaired electron go? The unpaired electron is usually placed in the Lewis Dot Structure so that each element in the structure will have the *lowest* formal charge possible. The formal charge is *the perceived charge on an individual atom in a molecule when atoms do not contribute equal numbers of electrons to the bonds they participate in*. The formula to find a formal charge is:

Formal Charge= [# of valence e^- the atom would have on its own] - [# of lone pair electrons on that atom]

- [# of bonds that atom participates in]

No formal charge at all is the most ideal situation. An example of a stable molecule with an odd number of valence electrons would be nitrogen monoxide. Nitrogen monoxide has 11 valence electrons. If you need more information about formal charges, see Lewis Structures. If we were to imagine nitrogen monoxide had ten valence electrons we would come up with the Lewis Structure (Figure 8.7.1):

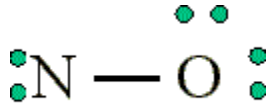


Figure 8.7.1. This is if Nitrogen monoxide has only *ten* valence electrons, which it does not.

Let's look at the formal charges of Figure 8.7.2 based on this Lewis structure. Nitrogen normally has five valence electrons. In Figure 8.7.1, it has two lone pair electrons and it participates in two bonds (a double bond) with oxygen. This results in nitrogen having a formal charge of +1. Oxygen normally has six valence electrons. In Figure 8.7.1, oxygen has four lone pair electrons and it participates in two bonds with nitrogen. Oxygen therefore has a formal charge of 0. The overall molecule here has a formal charge of +1 (+1 for nitrogen, 0 for oxygen. +1 + 0 = +1). However, if we add the eleventh electron to nitrogen (because we want the molecule to have the *lowest* total formal charge), it will bring both the nitrogen and the molecule's overall charges to zero, the most ideal formal charge situation. That is exactly what is done to get the correct Lewis structure for nitrogen monoxide (Figure 8.7.2):

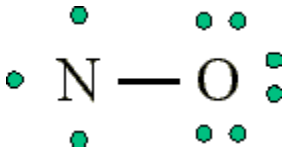


Figure 8.7.2. The proper Lewis structure for NO molecule

Free Radicals

There are actually very few stable molecules with odd numbers of electrons that exist, since that unpaired electron is willing to react with other unpaired electrons. Most odd electron species are highly reactive, which we call Free Radicals. Because of their instability, free radicals bond to atoms in which they can take an electron from in order to become stable, making them very chemically reactive. Radicals are found as both reactants and products, but generally react to form more stable molecules as soon as they can. In order to emphasize the existence of the unpaired electron, radicals are denoted with a dot in front of their chemical symbol as with , the hydroxyl radical. An example of a radical you may by familiar with already is the gaseous chlorine atom, denoted . Interestingly, odd Number of Valence Electrons will result in the molecule being paramagnetic.

Exception 2: Incomplete Octets

The second exception to the Octet Rule is when there are too few valence electrons that results in an incomplete Octet. There are even more occasions where the octet rule does not give the most correct depiction of a molecule or ion. This is also the case with incomplete octets. Species with incomplete octets are pretty rare and generally are only found in some beryllium, aluminum, and boron compounds including the boron hydrides. Let's take a look at one such hydride, BH_3 (Borane).

If one was to make a Lewis structure for BH_3 following the basic strategies for drawing Lewis structures, one would probably come up with this structure (Figure 8.7.3):

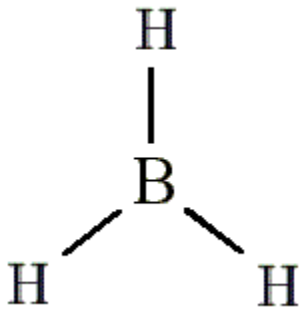


Figure 8.7.3

The problem with this structure is that boron has an incomplete octet; it only has six electrons around it. Hydrogen atoms can naturally only have only 2 electrons in their outermost shell (their version of an octet), and as such there are no spare electrons to form a double bond with boron. One might surmise that the failure of this structure to form complete octets must mean that this bond should be ionic instead of covalent. However, boron has an electronegativity that is very similar to hydrogen, meaning there is likely very little ionic character in the hydrogen to boron bonds, and as such this Lewis structure, though it does not fulfill the octet rule, is likely the best structure possible for depicting BH_3 with Lewis theory. One of the things that may account for BH_3's incomplete octet is that it is commonly a transitory species, formed temporarily in reactions that involve multiple steps.

Let's take a look at another incomplete octet situation dealing with boron, BF_3 (Boron trifluorine). Like with BH_3, the initial drawing of a Lewis structure of BF_3 will form a structure where boron has only six electrons around it (Figure 8.7.4).

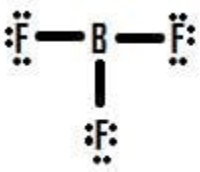


Figure 8.7.4

If you look Figure 8.7.4, you can see that the fluorine atoms possess extra lone pairs that they can use to make additional bonds with boron, and you might think that all you have to do is make one lone pair into a bond and the structure will be correct. If we add one double bond between boron and one of the fluorines we get the following Lewis Structure (Figure 8.7.5):

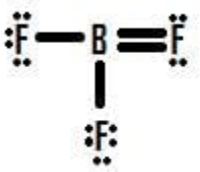


Figure 8.7.5

Each fluorine has eight electrons, and the boron atom has eight as well! Each atom has a perfect octet, right? Not so fast. We must examine the formal charges of this structure. The fluorine that shares a double bond with boron has six electrons around it (four from its two lone pairs of electrons and one each from its two bonds with boron). This is one less electron than the number of valence electrons it would have naturally (Group Seven elements have seven valence electrons), so it has a formal charge of +1. The two flourines that share single bonds with boron have seven electrons around them (six from their three lone pairs and one from their single bonds with boron). This is the same amount as the number of valence electrons they would have on their own, so they both have a formal charge of zero. Finally, boron has four electrons around it (one from each of its four bonds shared with fluorine). This is one more electron than the number of valence electrons that boron would have on its own, and as such boron has a formal charge of -1.

This structure is supported by the fact that the experimentally determined bond length of the boron to fluorine bonds in BF_3 is less than what would be typical for a single bond (see Bond Order and Lengths). However, this structure contradicts one of the major rules of formal charges: Negative formal charges are supposed to be found on the more electronegative atom(s) in a bond, but in the structure depicted in Figure 8.7.5, a *positive* formal charge is found on fluorine, which not only is the most electronegative element in the structure, but the most electronegative element in the entire periodic table ( ). Boron on the other hand, with the much lower electronegativity of 2.0, has the negative formal charge in this structure. This formal charge-electronegativity disagreement makes this double-bonded structure impossible.

However the large electronegativity difference here, as opposed to in BH_3, signifies significant polar bonds between boron and fluorine, which means there is a high ionic character to this molecule. This suggests the possibility of a semi-ionic structure such as seen in Figure 8.7.6:

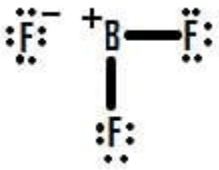


Figure 8.7.6

None of these three structures is the "correct" structure in this instance. The most "correct" structure is most likely a resonance of all three structures: the one with the incomplete octet (Figure 8.7.4), the one with the double bond (Figure 8.7.5), and the one with the ionic bond (Figure 8.7.6). The most contributing structure is probably the incomplete octet structure (due to Figure 8.7.5 being basically impossible and Figure 8.7.6 not matching up with the behavior and properties of BF_3). As you can see even when other possibilities exist, incomplete octets may best portray a molecular structure.

As a side note, it is important to note that BF_3 frequently bonds with a F^- ion in order to form BF_4^- rather than staying as BF_3. This structure completes boron's octet and it is more common in nature. This exemplifies the fact that incomplete octets are rare, and other configurations are typically more favorable, including bonding with additional ions as in the case of BF_3 .

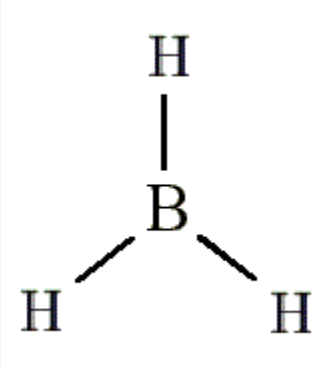
Example 8.7.1:

Draw the Lewis structure for boron trifluoride (BF_3).

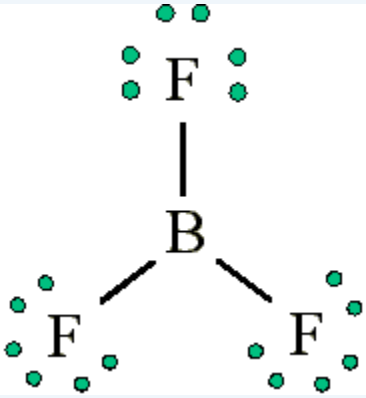
SOLUTION

1. Add electrons (3*7) + 3 = **24**

2. Draw connectivities:



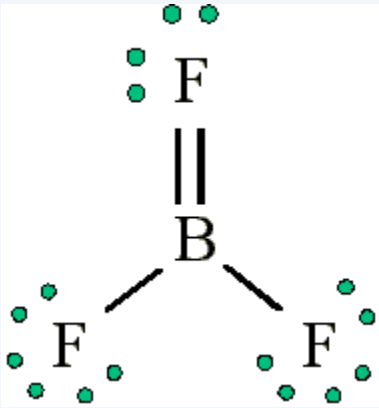
3. Add octets to outer atoms:



4. Add extra electrons (24-24=0) to central atom:

5. Does central electron have octet?

- NO. It has 6 electrons
- Add a multiple bond (double bond) to see if central atom can achieve an octet:

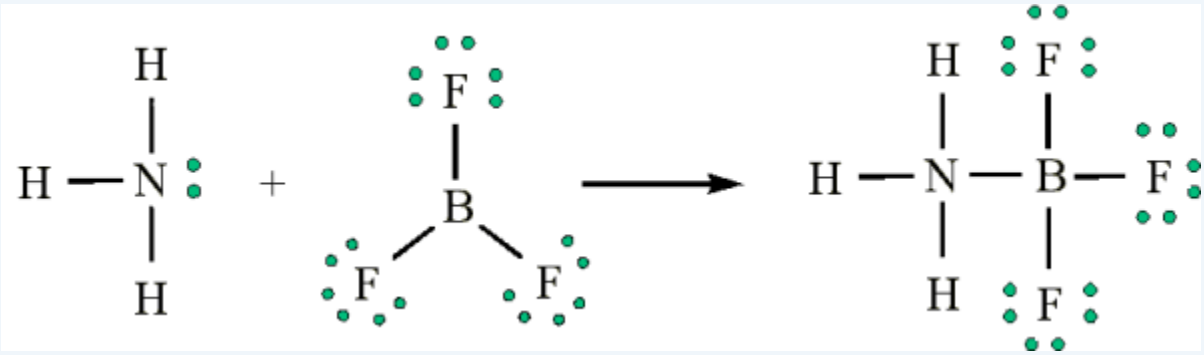


6. The central Boron now has an octet (there would be three resonance Lewis structures)

However...

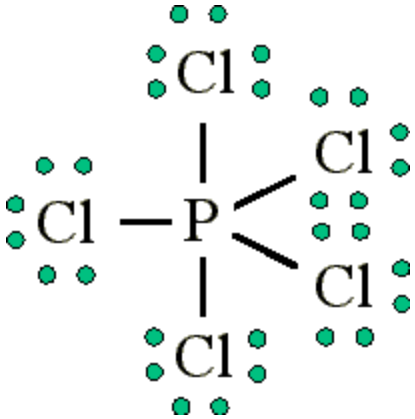
- In this structure with a double bond the fluorine atom is sharing extra electrons with the boron.
- The fluorine would have a '+' partial charge, and the boron a '-' partial charge, this is inconsistent with the electronegativities of fluorine and boron.
- Thus, ***the structure of BF_3, with single bonds, and 6 valence electrons around the central boron is the most likely structure***

BF_3 reacts strongly with compounds which have an unshared pair of electrons which can be used to form a bond with the boron:



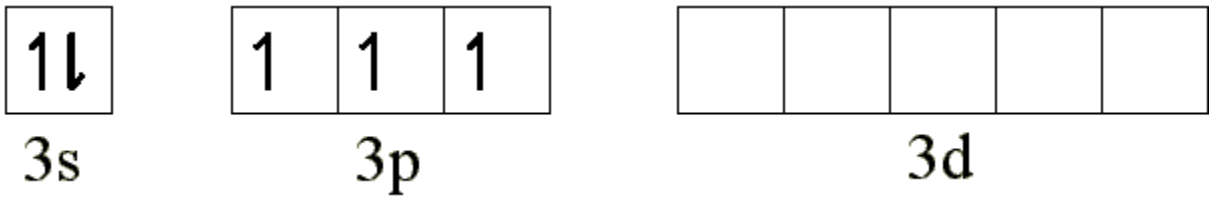
Exception 3: Expanded Valence Shells

More common than incomplete octets are expanded octets where the central atom in a Lewis structure has more than eight electrons in its valence shell. In expanded octets, the central atom can have ten electrons, or even twelve. *Molecules with expanded octets involve highly electronegative terminal atoms, and a nonmetal central atom found in the third period or below*, which those terminal atoms bond to. For example, is a legitimate compound (whereas) is not:



Note
Expanded valence shells are observed **only** for elements in period 3 (i.e. n=3) and beyond

The 'octet' rule is based upon available ns and n*p* orbitals for valence electrons (2 electrons in the *s* orbitals, and 6 in the *p* orbitals). Beginning with the n=3 principle quantum number, the d orbitals become available (*l*=2). The orbital diagram for the valence shell of phosphorous is:



Hence, the third period elements occasionally exceed the octet rule by using their empty d orbitals to accommodate additional electrons. Size is also an important consideration:

- The larger the central atom, the larger the number of electrons which can surround it
- Expanded valence shells occur most often when the central atom is bonded to small electronegative atoms, such as F, Cl and O.

There is currently much scientific exploration and inquiry into the reason why expanded valence shells are found. The top area of interest is figuring out where the extra pair(s) of electrons are found. Many chemists think that there is not a very large energy difference between the 3p and 3d orbitals, and as such it is plausible for extra electrons to easily fill the 3d orbital when an expanded octet is more favorable than having a complete octet. This matter is still under hot debate, however and there is even debate as to what makes an expanded octet more favorable than a configuration that follows the octet rule.

One of the situations where expanded octet structures are treated as more favorable than Lewis structures that follow the octet rule is when the formal charges in the expanded octet structure are smaller than in a structure that adheres to the octet rule, or when there are less formal charges in the expanded octet than in the structure a structure that adheres to the octet rule.

Example 8.7.2: The ion

Such is the case for the sulfate ion, SO_4^{-2}. A strict adherence to the octet rule forms the following Lewis structure:

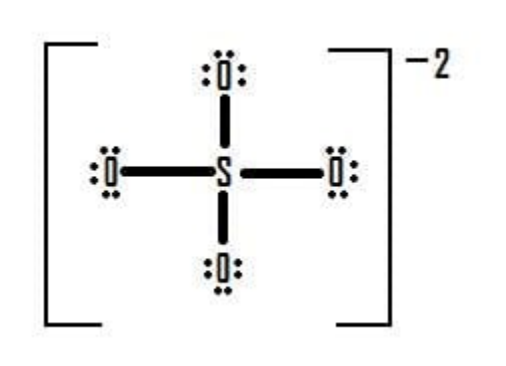


Figure 8.7.12

If we look at the formal charges on this molecule, we can see that all of the oxygen atoms have seven electrons around them (six from the three lone pairs and one from the bond with sulfur). This is one more electron than the number of valence electrons then they would have normally, and as such each of the oxygens in this structure has a formal charge of -1. Sulfur has four electrons around it in this structure (one from each of its four bonds) which is two electrons more than the number of valence electrons it would have normally, and as such it carries a formal charge of +2.

If instead we made a structure for the sulfate ion with an expanded octet, it would look like this:

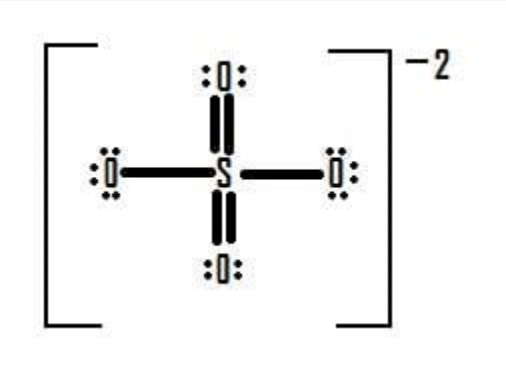


Figure 8.7.13

Looking at the formal charges for this structure, the sulfur ion has six electrons around it (one from each of its bonds). This is the same amount as the number of valence electrons it would have naturally. This leaves sulfur with a formal charge of zero. The two oxygens that have double bonds to sulfur have six electrons each around them (four from the two lone pairs and one each from the two bonds with sulfur). This is the same amount of electrons as the number of valence electrons that oxygen atoms have on their own, and as such both of these oxygen atoms have a formal charge of zero. The two oxygens with the single bonds to sulfur have seven electrons around them in this structure (six from the three lone pairs and one from the bond to sulfur). That is one electron more than the number of valence electrons that oxygen would have on its own, and as such those two oxygens carry a formal charge of -1. Remember that with formal charges, the goal is to keep the formal charges (or the difference between the formal charges of each atom) as small as possible. The number of and values of the formal charges on this structure (-1 and 0 (difference of 1) in Figure 8.7.12, as opposed to +2 and -1 (difference of 3) in Figure 8.7.12) is significantly lower than on the structure that follows the octet rule, and as such an expanded octet is plausible, and even preferred to a normal octet, in this case.

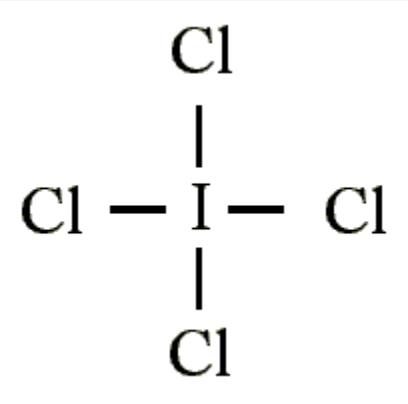
Example 8.7.3: The Ion

Draw the Lewis structure for ion.

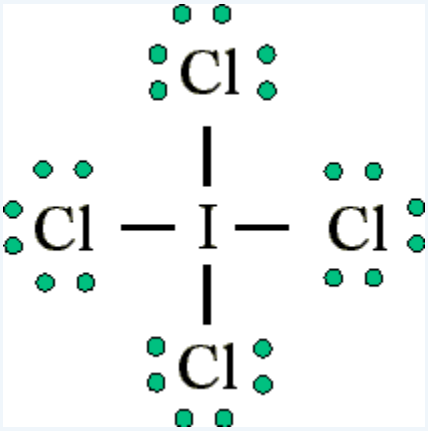
SOLUTION

1. Count up the valence electrons: 7+(4*7)+1 = **36** electrons

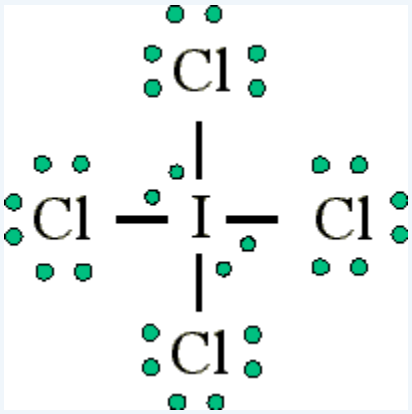
2. Draw the connectivities:



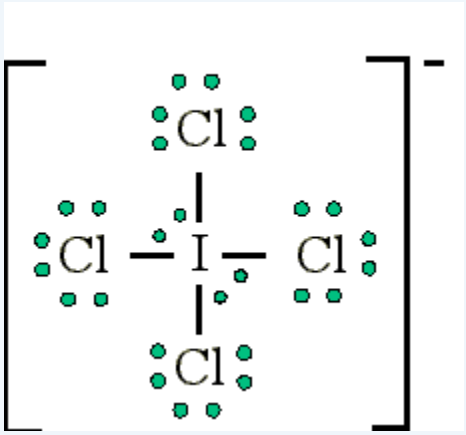
3. Add octet of electrons to outer atoms:



4. Add extra electrons (36-32=**4**) to central atom:



5. The ICl_4^- ion thus has 12 valence electrons around the central Iodine (in the 5*d* orbitals)



Expanded Lewis structures are also plausible depictions of molecules when experimentally determined bond lengths suggest partial double bond characters even when single bonds would already fully fill the octet of the central atom. Despite the cases for expanded octets, as mentioned for incomplete octets, it is important to keep in mind that, in general, the octet rule applies.

Contributors

- Mike Blaber (Florida State University)

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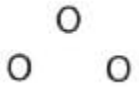
1.5: Resonance Forms

Resonance Structures

Sometimes, even when formal charges are considered, the bonding in some molecules or ions cannot be described by a single Lewis structure. Such is the case for ozone (O_3), an allotrope of oxygen with a V-shaped structure and an O–O–O angle of 117.5°.

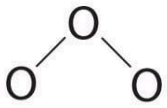
O_3

1. We know that ozone has a V-shaped structure, so one O atom is central:



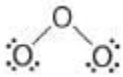
2. Each O atom has 6 valence electrons, for a total of 18 valence electrons.

3. Assigning one bonding pair of electrons to each oxygen–oxygen bond gives



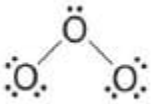
with 14 electrons left over.

4. If we place three lone pairs of electrons on each terminal oxygen, we obtain

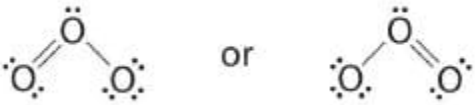


and have 2 electrons left over.

5. At this point, both terminal oxygen atoms have octets of electrons. We therefore place the last 2 electrons on the central atom:



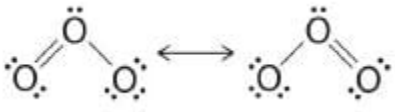
6. The central oxygen has only 6 electrons. We must convert one lone pair on a terminal oxygen atom to a bonding pair of electrons—but which one? Depending on which one we choose, we obtain either



Which is correct? In fact, neither is correct. Both predict one O–O single bond and one O=O double bond. As you will learn in

Section 4.8, if the bonds were of different types (one single and one double, for example), they would have different lengths. It turns out, however, that both O–O bond distances are identical, 127.2 pm, which is shorter than a typical O–O single bond (148 pm) and longer than the O=O double bond in O_2 (120.7 pm).

Equivalent Lewis dot structures, such as those of ozone, are called resonance structures . The position of the *atoms* is the same in the various resonance structures of a compound, but the position of the *electrons* is different. Double-headed arrows link the different resonance structures of a compound:



Before the development of quantum chemistry it was thought that the double-headed arrow indicates that the actual electronic structure is an *average* of those shown, or that the molecule oscillates between the two structures. Today we know that the electrons involved in the double bonds occupy an orbital that extends over all three oxygen molecules, combining *p* orbitals on all three.

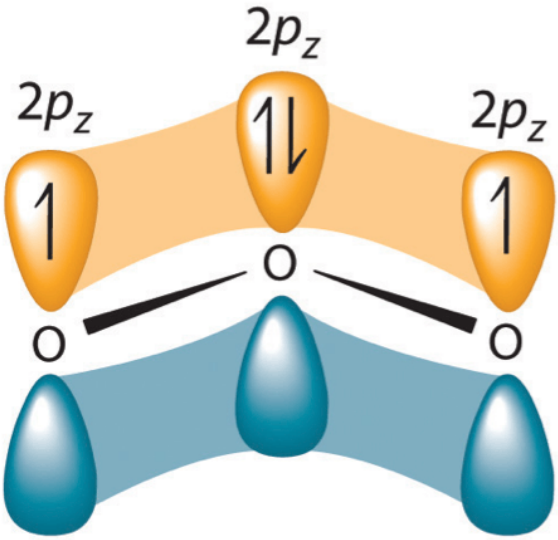


Figure 5.3.4 *The resonance structure of ozone involves a molecular orbital extending all three oxygen atoms. In ozone, a molecular orbital extending over all three oxygen atoms is formed from three atom centered p_z orbitals. Similar molecular orbitals are found in every resonance structure.*

We will discuss the formation of these molecular orbitals in the next chapter but it is important to understand that resonance structures are based on molecular orbitals not averages of different bonds between atoms. We describe the electrons in such molecular orbitals as being delocalized, that is they cannot be assigned to a bond between two atoms.

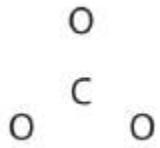
Note the Pattern

When it is possible to write more than one equivalent resonance structure for a molecule or ion, the actual structure involves a molecular orbital which is a linear combination of atomic orbitals from each of the atoms.

CO_3^{2-}

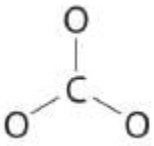
Like ozone, the electronic structure of the carbonate ion cannot be described by a single Lewis electron structure. Unlike O_3, though, the Lewis structures describing CO_3^{2-} has *three* equivalent representations.

1. Because carbon is the least electronegative element, we place it in the central position:

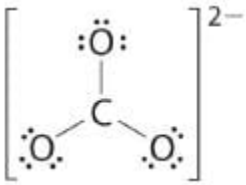


2. Carbon has 4 valence electrons, each oxygen has 6 valence electrons, and there are 2 more for the –2 charge. This gives 4 + (3 × 6) + 2 = 24 valence electrons.

3. Six electrons are used to form three bonding pairs between the oxygen atoms and the carbon:

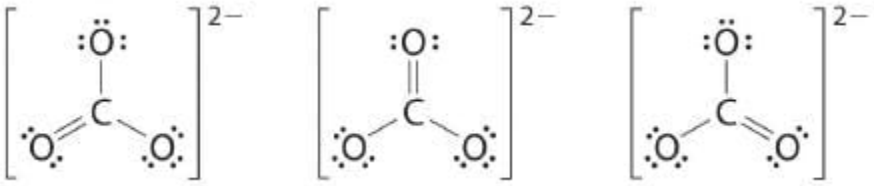


4. We divide the remaining 18 electrons equally among the three oxygen atoms by placing three lone pairs on each and indicating the –2 charge:

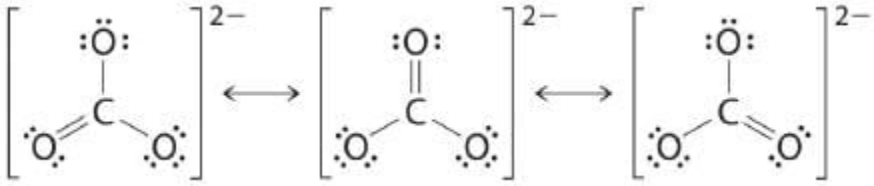


5. No electrons are left for the central atom.

6. At this point, the carbon atom has only 6 valence electrons, so we must take one lone pair from an oxygen and use it to form a carbon–oxygen double bond. In this case, however, there are *three* possible choices:



As with ozone, none of these structures describes the bonding exactly. Each predicts one carbon–oxygen double bond and two carbon–oxygen single bonds, but experimentally all C–O bond lengths are identical. We can write resonance structures (in this case, three of them) for the carbonate ion:



As the case for ozone, the actual structure involves the formation of a molecular orbital from p_z orbitals centered on each atom

and sitting above and below the plane of the CO_3^{2-} ion.

Example

Benzene is a common organic solvent that was previously used in gasoline; it is no longer used for this purpose, however, because it is now known to be a carcinogen. The benzene molecule (C_6H_6) consists of a regular hexagon of carbon atoms, each of which is also bonded to a hydrogen atom. Use resonance structures to describe the bonding in benzene.

Given: molecular formula and molecular geometry

Asked for: resonance structures

Strategy:

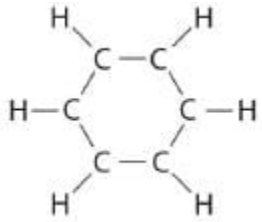
A Draw a structure for benzene illustrating the bonded atoms. Then calculate the number of valence electrons used in this drawing.

B Subtract this number from the total number of valence electrons in benzene and then locate the remaining electrons such that each atom in the structure reaches an octet.

C Draw the resonance structures for benzene.

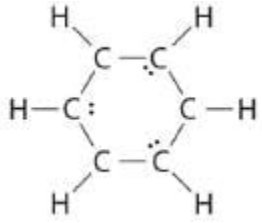
Solution:

A Each hydrogen atom contributes 1 valence electron, and each carbon atom contributes 4 valence electrons, for a total of (6 × 1) + (6 × 4) = 30 valence electrons. If we place a single bonding electron pair between each pair of carbon atoms and between each carbon and a hydrogen atom, we obtain the following:



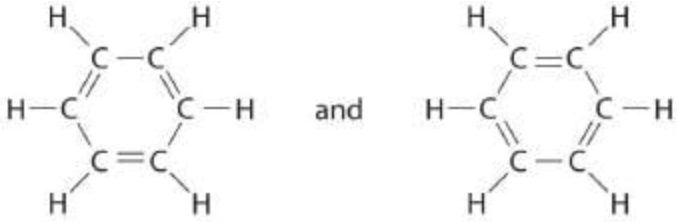
Each carbon atom in this structure has only 6 electrons and has a formal charge of +1, but we have used only 24 of the 30 valence electrons.

B If the 6 remaining electrons are uniformly distributed pairwise on alternate carbon atoms, we obtain the following:

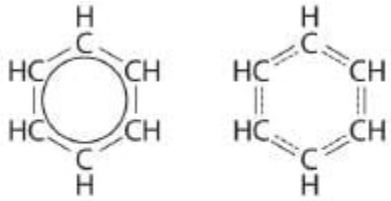


Three carbon atoms now have an octet configuration and a formal charge of −1, while three carbon atoms have only 6 electrons and a formal charge of +1. We can convert each lone pair to a bonding electron pair, which gives each atom an octet of electrons and a formal charge of 0, by making three C=C double bonds.

C There are, however, two ways to do this:



Each structure has alternating double and single bonds, but experimentation shows that each carbon–carbon bond in benzene is identical, with bond lengths (139.9 pm) intermediate between those typically found for a C–C single bond (154 pm) and a C=C double bond (134 pm). We can describe the bonding in benzene using the two resonance structures, but the actual electronic structure is an average of the two. The existence of multiple resonance structures for aromatic hydrocarbons like benzene is often indicated by drawing either a circle or dashed lines inside the hexagon:



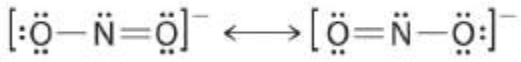
Benzene

This combination of *p* orbitals for benzene can be visualized as a ring with a node in the plane of the carbon atoms.

Exercise

The sodium salt of nitrite is used to relieve muscle spasms. Draw two resonance structures for the nitrite ion (NO_2^-).

Answer:



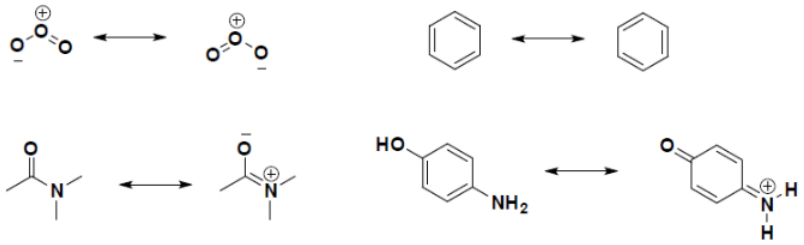
Resonance structures are particularly common in oxoanions of the *p*-block elements, such as sulfate and phosphate, and in aromatic hydrocarbons, such as benzene and naphthalene.

Rules for estimating stability of resonance structures

1. The **greater the number of covalent bonds**, the greater the stability since more atoms will have complete octets
2. The structure with the **least number of formal charges** is more stable
3. The structure with the **least separation of formal charge** is more stable
4. A structure with a **negative charge on the more electronegative atom** will be more stable
5. **Positive charges on the least electronegative atom** (most electropositive) is more stable
6. **Resonance forms that are equivalent have no difference in stability and contribute equally.** (eg. benzene)

Examples of Resonance

single Resonance configuration



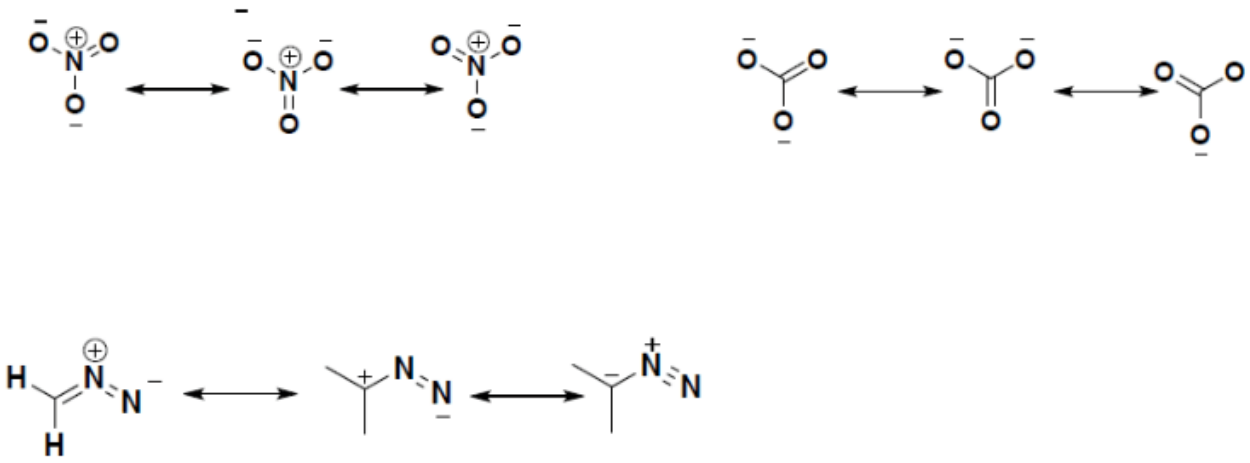
The above resonance structures show that the electrons are delocalized within the molecule and through this process the molecule gains extra stability. Ozone with both of its opposite charges creates a neutral molecule and through resonance it is a stable molecule. The extra electron that created the negative charge on either terminal oxygen can be delocalized by resonance through the terminal oxygens.

Benzene is an extremely stable molecule and it is accounted for its geometry and molecular orbital interaction, but most importantly it's due to its resonance structures. The delocalized electrons in the benzene ring make the molecule very stable and with its characteristics of a nucleophile, it will react with a strong electrophile only and after the first reactivity, the substituted benzene will depend on its resonance to direct the next position for the reaction to add a second substituent.

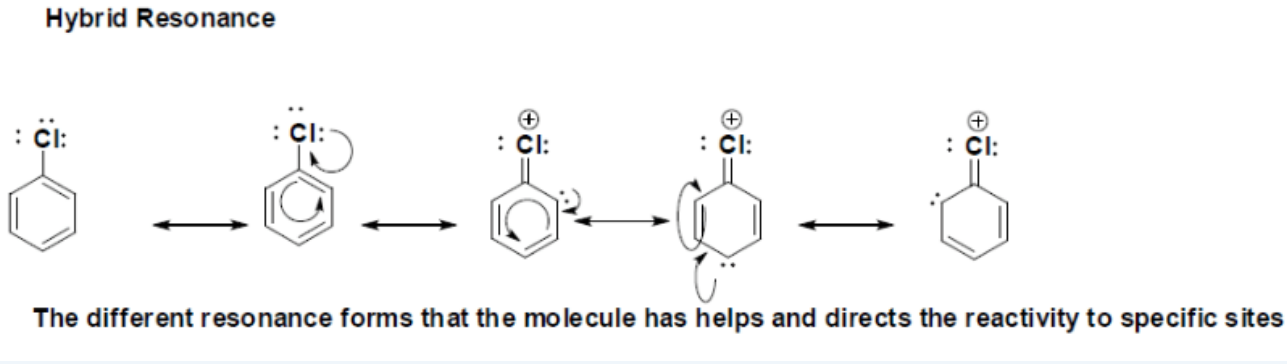
The next molecule, the Amide, is a very stable molecule that is present in most biological systems, mainly in proteins. By studies of NMR spectroscopy and X-Ray crystallography it is confirmed that the stability of the amide is due to resonance which through molecular orbital interaction creates almost a double bond between the Nitrogen and the carbon.

Example: Multiple Resonance of other Molecules

Molecules with more than one resonance form



Some structural resonance conformations are the major contributor or the dominant forms that the molecule exists. For example, if we look at the above rules for estimating the stability of a molecule, we see that for the third molecule the first and second forms are the major contributors for the overall stability of the molecule. The nitrogen is more electronegative than carbon so, it can handle the negative charge more than carbon. A carbon with a negative charge is the least favorable conformation for the molecule to exist, so the last resonance form contributes very little for the stability of the Ion.



The Hybrid Resonance forms show the different Lewis structures with the electron been delocalized. This is very important for the reactivity of chloro-benzene because in the presence of an electrophile it will react and the formation of another bond will be directed and determine by resonance. The long pair of electrons delocalized in the aromatic substituted ring is where it can potentially form a new bond with an electrophile, as it is shown there are three possible places that reactivity can take place, the first to react will take place at the *para* position with respect to the chloro substituent and then to either *ortho* position.

Contributors

- Sharon Wei (UCD), Liza Chu (UCD)

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1.6: Atomic Orbitals: A Quantum Mechanical Description of Electrons Around the Nucleus

After completing this section, you should be able to

1. describe the physical significance of an orbital.
2. list the atomic orbitals from 1s to 3*d* in order of increasing energy.
3. sketch the shapes of s and *p* orbitals.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- nodal plane
- node
- orbital
- quantum mechanics
- wave function

Atomic Orbitals

An orbital is the quantum mechanical refinement of Bohr's orbit. In contrast to his concept of a simple circular orbit with a fixed radius, orbitals are mathematically derived regions of space with different *probabilities* of having an electron.

One way of representing electron probability distributions was illustrated in Figure 6.5.2 for the 1s orbital of hydrogen. Because Ψ^2 gives the probability of finding an electron in a given volume of space (such as a cubic picometer), a plot of Ψ^2 versus distance from the nucleus (r) is a plot of the *probability density*. The 1s orbital is spherically symmetrical, so the probability of finding a 1s electron at any given point depends *only* on its distance from the nucleus. The probability density is greatest at $r = 0$ (at the nucleus) and decreases steadily with increasing distance. At very large values of r, the electron probability density is very small but *not* zero.

In contrast, we can calculate the *radial probability* (the probability of finding a 1s electron at a distance r from the nucleus) by adding together the probabilities of an electron being at all points on a series of x spherical shells of radius r_1, r_2, r_3,..., r_{x-1}, r_x. In effect, we are dividing the atom into very thin concentric shells, much like the layers of an onion (part (a) in Figure 1.2.1), and calculating the probability of finding an electron on each spherical shell. Recall that the electron probability density is greatest at $r = 0$ (part (b) in Figure 1.2.1), so the density of dots is greatest for the smallest spherical shells in part (a) in Figure 1.2.1. In contrast, the surface area of each spherical shell is equal to $4\pi r^2$, which increases very rapidly with increasing r (part (c) in Figure 1.2.1). Because the surface area of the spherical shells increases more rapidly with increasing r than the electron probability density decreases, the plot of radial probability has a maximum at a particular distance (part (d) in Figure 1.2.1). Most important, when r is very small, the surface area of a spherical shell is so small that the *total* probability of finding an electron close to the nucleus is very low; at the nucleus, the electron probability vanishes (part (d) in Figure 1.2.1).

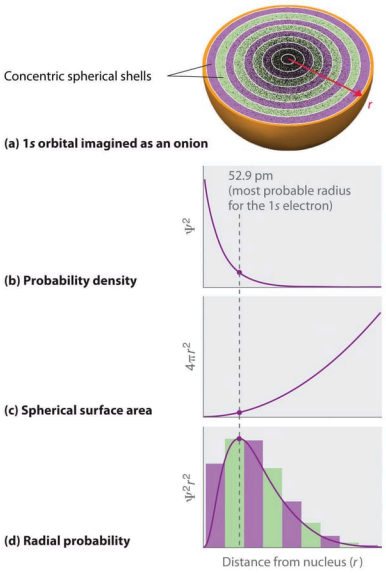


Figure 1.2.1 *Most Probable Radius for the Electron in the Ground State of the Hydrogen Atom. (a) Imagine dividing the atom's total volume into very thin concentric shells as shown in the onion drawing. (b) A plot of electron probability density Ψ^2 versus r shows that the electron probability density is greatest at r = 0 and falls off smoothly with increasing r. The density of the dots is therefore greatest in the innermost shells of the onion. (c) The surface area of each shell, given by $4\pi r^2$, increases rapidly with increasing r. (d) If we count the number of dots in each spherical shell, we obtain the total probability of finding the electron at a given value of r. Because the surface area of each shell increases more rapidly with increasing r than the electron probability density decreases, a plot of electron probability versus r (the radial probability) shows a peak. This peak corresponds to the most probable radius for the electron, 52.9 pm, which is exactly the radius predicted by Bohr's model of the hydrogen atom.*

For the hydrogen atom, the peak in the radial probability plot occurs at $r = 0.529$ Å (52.9 pm), which is exactly the radius calculated by Bohr for the $n = 1$ orbit. Thus the *most probable radius* obtained from quantum mechanics is identical to the radius calculated by classical mechanics. In Bohr's model, however, the electron was assumed to be at this distance 100% of the time, whereas in the Schrödinger model, it is at this distance only some of the time. The difference between the two models is attributable to the wavelike behavior of the electron and the Heisenberg uncertainty principle.

Figure 1.2.2 compares the electron probability densities for the hydrogen 1s, 2s, and 3s orbitals. Note that all three are spherically symmetrical. For the 2s and 3s orbitals, however (and for all other s orbitals as well), the electron probability density does not fall off smoothly with increasing *r*. Instead, a series of minima and maxima are observed in the radial probability plots (part (c) in Figure 1.2.2). The minima correspond to spherical nodes (regions of zero electron probability), which alternate with spherical regions of nonzero electron probability.

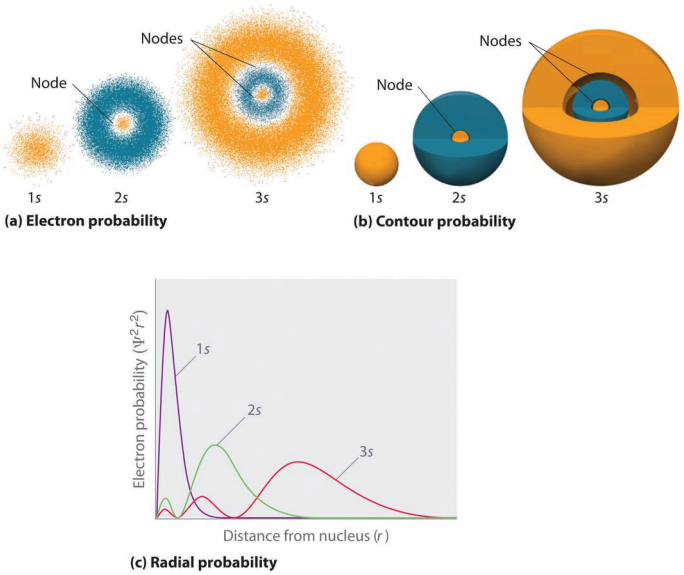


Figure 1.2.2: *Probability Densities for the 1s, 2s, and 3s Orbitals of the Hydrogen Atom. (a) The electron probability density in any plane that contains the nucleus is shown. Note the presence of circular regions, or nodes, where the probability density is zero. (b) Contour surfaces enclose 90% of the electron probability, which illustrates the different sizes of the 1s, 2s, and 3s orbitals. The cutaway drawings give partial views of the internal spherical nodes. The orange color corresponds to regions of space where the phase of the wave function is positive, and the blue color corresponds to regions of space where the phase of the wave function is negative. (c) In these plots of electron probability as a function of distance from the nucleus (r) in all directions (radial probability), the most probable radius increases as n increases, but the 2s and 3s orbitals have regions of significant electron probability at small values of r.*

s Orbitals

Three things happen to s orbitals as *n* increases (Figure 1.2.2):Edit section

1. They become larger, extending farther from the nucleus.
2. They contain more nodes. This is similar to a standing wave that has regions of significant amplitude separated by nodes, points with zero amplitude.
3. For a given atom, the s orbitals also become higher in energy as *n* increases because of their increased distance from the nucleus.

Orbitals are generally drawn as three-dimensional surfaces that enclose 90% of the electron density, as was shown for the hydrogen 1s, 2s, and 3s orbitals in part (b) in Figure 1.2.2. Although such drawings show the relative sizes of the orbitals, they do not normally show the spherical nodes in the 2s and 3s orbitals because the spherical nodes lie inside the 90% surface. Fortunately, the positions of the spherical nodes are not important for chemical bonding.

p OrbitalsEdit section

Only s orbitals are spherically symmetrical. As the value of l increases, the number of orbitals in a given subshell increases, and the shapes of the orbitals become more complex. Because the 2*p* subshell has $l = 1$, with three values of m_l (–1, 0, and +1), there are three 2*p* orbitals.

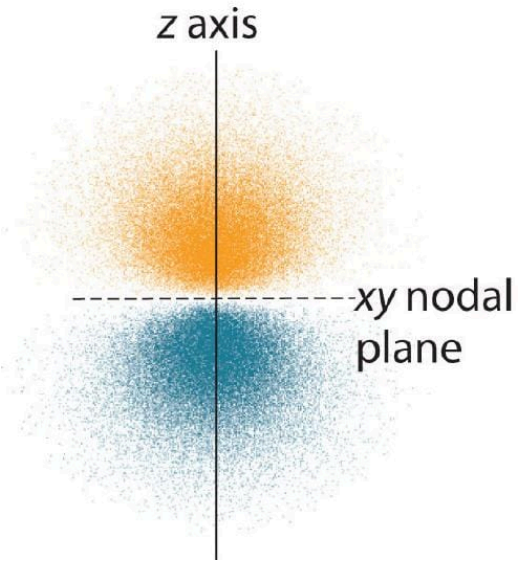


Figure 1.2.3: *Electron Probability Distribution for a Hydrogen 2p Orbital. The nodal plane of zero electron density separates the two lobes of the 2p orbital. As in Figure 1.2.2, the colors correspond to regions of space where the phase of the wave function is positive (orange) and negative (blue).*

The electron probability distribution for one of the hydrogen 2*p* orbitals is shown in Figure 1.2.3. Because this orbital has two lobes of electron density arranged along the *z* axis, with an electron density of zero in the *xy* plane (i.e., the *xy* plane is a nodal plane), it is a $2p_z$ orbital. As shown in Figure 1.2.4, the other two 2*p* orbitals have identical shapes, but they lie along the *x* axis ($2p_x$) and *y* axis ($2p_y$), respectively. Note that each *p* orbital has just one nodal plane. In each case, the phase of the wave function for each of the 2*p* orbitals is positive for the lobe that points along the positive axis and negative for the lobe that points along the negative axis. It is important to emphasize that these signs correspond to the *phase* of the wave that describes the electron motion, *not* to positive or negative charges.

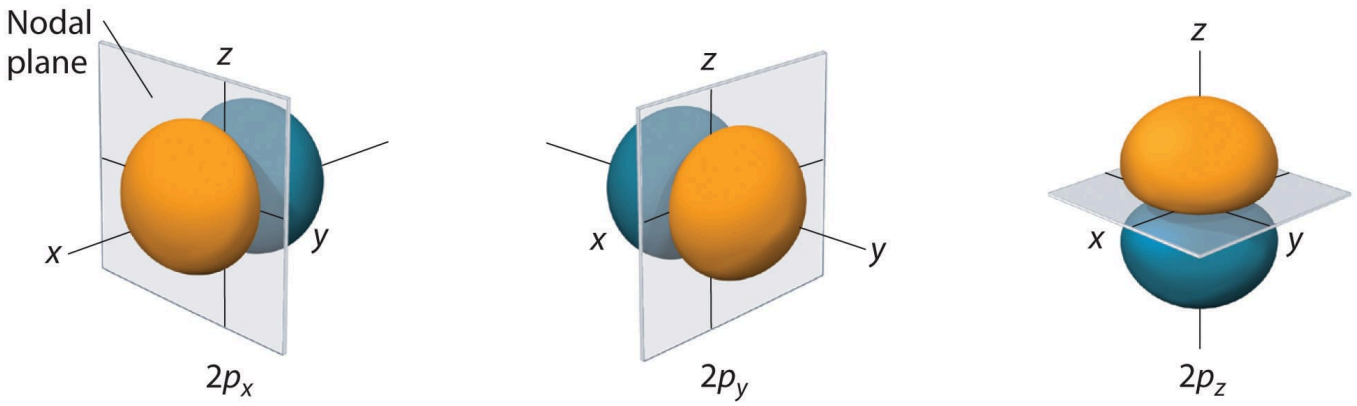


Figure 1.2.4 The Three Equivalent 2*p* Orbitals of the Hydrogen Atom

The surfaces shown enclose 90% of the total electron probability for the $2p_x$, $2p_y$, and $2p_z$ orbitals. Each orbital is oriented along the axis indicated by the subscript and a nodal plane that is perpendicular to that axis bisects each 2*p* orbital. The phase of the wave function is positive (orange) in the region of space where *x*, *y*, or *z* is positive and negative (blue) where *x*, *y*, or *z* is negative.

Just as with the s orbitals, the size and complexity of the *p* orbitals for any atom increase as the principal quantum number *n* increases. The shapes of the 90% probability surfaces of the 3*p*, 4*p*, and higher-energy *p* orbitals are, however, essentially the same as those shown in Figure 1.2.4.

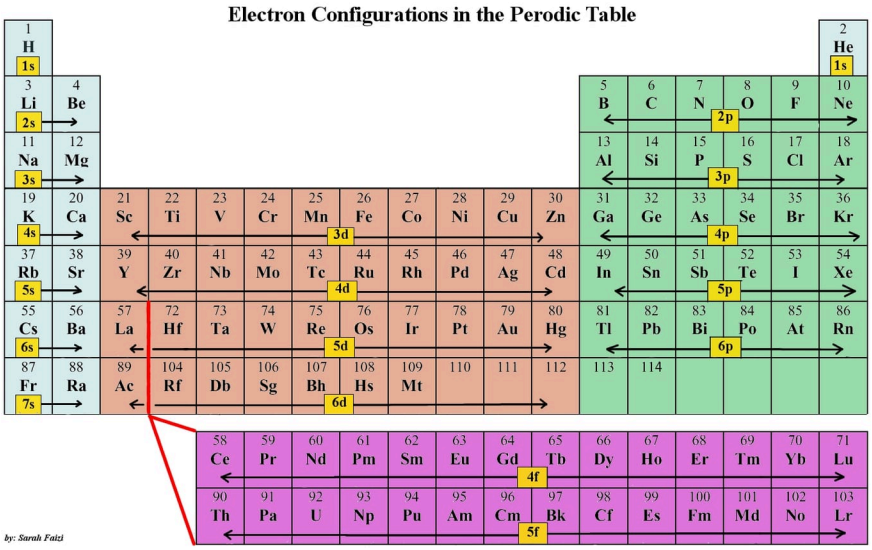
he electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells

and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

Electron ConfigurationsEdit section

Before assigning the electrons of an atom into orbitals, one must become familiar with the basic concepts of electron configurations. Every element on the periodic table consists of atoms, which are composed of protons, neutrons, and electrons. Electrons exhibit a negative charge and are found around the nucleus of the atom in electron orbitals, defined as the volume of space in which the electron can be found within 95% probability. The four different types of orbitals (s,p,d, and f) have different shapes, and one orbital can hold a maximum of two electrons. The p, d, and f orbitals have different sublevels, thus can hold more electrons.

As stated, the electron configuration of each element is unique to its position on the periodic table. The energy level is determined by the period and the number of electrons is given by the atomic number of the element. Orbitals on different energy levels are similar to each other, but they occupy different areas in space. The 1s orbital and 2s orbital both have the characteristics of an s orbital (radial nodes, spherical volume probabilities, can only hold two electrons, etc.) but, as they are found in different energy levels, they occupy different spaces around the nucleus. Each orbital can be represented by specific blocks on the periodic table. The s-block is the region of the alkali metals including helium (Groups 1 & 2), the d-block are the transition metals (Groups 3 to 12), the p-block are the main group elements from Groups 13 to 18, and the f-block are the lanthanides and actinides series.



Using the periodic table to determine the electron configurations of atoms is key, but also keep in mind that there are certain rules to follow when assigning electrons to different orbitals. The periodic table is an incredibly helpful tool in writing electron configurations. For more information on how electron configurations and the periodic table are linked, visit the Connecting Electrons to the Periodic Table module.

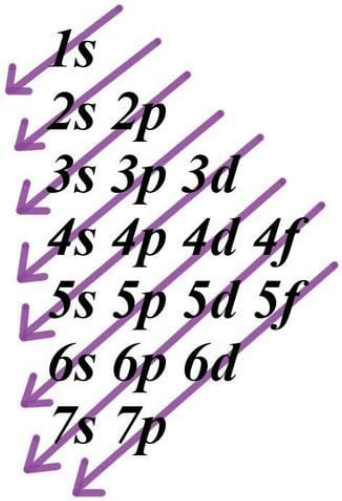
Rules for Assigning Electron OrbitalsEdit section

Occupation of OrbitalsEdit section

Electrons fill orbitals in a way to minimize the energy of the atom. Therefore, the electrons in an atom fill the principal energy levels in order of increasing energy (the electrons are getting farther from the nucleus). The order of levels filled looks like this:

1s, 2s, 2p, 3s, 3p, 4s, 3d, 4p, 5s, 4d, 5p, 6s, 4f, 5d, 6p, 7s, 5f, 6d, and 7p

One way to remember this pattern, probably the easiest, is to refer to the periodic table and remember where each orbital block falls to logically deduce this pattern. Another way is to make a table like the one below and use vertical lines to determine which subshells correspond with each other.



The number of valence electrons

The number of valence electrons of an element can be determined by the periodic table group (vertical column) in which the element is categorized. With the exception of groups 3–12 (the transition metals), the units digit of the group number identifies how many valence electrons are associated with a neutral atom of an element listed under that particular column.

The periodic table of the chemical elements

Periodic table group	Valence electrons
Group 1: alkali metals	1
Group 2: alkaline earth metals	2
Groups 3-12: transition metals	2* (The 4s shell is complete and cannot hold any more electrons)
Group 13: boron group	3
Group 14: carbon group	4
Group 15: pnictogens	5
Group 16: chalcogens	6
Group 17: halogens	7
Group 18: noble gases	8**

** The general method for counting valence electrons is generally not useful for transition metals. Instead the modified **d electron count method** is used.*

*** Except for helium, which has only two valence electrons.*

Exercises

Questions

Q1.2.1

Label the following orbitals:

1-2-1qu.gif

Solutions

S1.2.1

1 = 3s ; 2 = $2p_z$

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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1.7: Molecular Orbitals and Covalent Bonding

Learning Objectives

- To use molecular orbital theory to predict bond order

None of the approaches we have described so far can adequately explain why some compounds are colored and others are not, why some substances with unpaired electrons are stable, and why others are effective semiconductors. These approaches also cannot describe the nature of resonance. Such limitations led to the development of a new approach to bonding in which electrons are *not* viewed as being localized between the nuclei of bonded atoms but are instead delocalized throughout the entire molecule. Just as with the valence bond theory, the approach we are about to discuss is based on a quantum mechanical model.

Previously, we described the electrons in isolated atoms as having certain spatial distributions, called *orbitals*, each with a particular *orbital energy*. Just as the positions and energies of electrons in *atoms* can be described in terms of *atomic orbitals* (AOs), the positions and energies of electrons in *molecules* can be described in terms of molecular orbitals (MOs) A particular spatial distribution of electrons in a molecule that is associated with a particular orbital energy.—a spatial distribution of electrons *in a molecule* that is associated with a particular orbital energy. As the name suggests, molecular orbitals are not localized on a single atom but extend over the entire molecule. Consequently, the molecular orbital approach, called molecular orbital theory is a *delocalized* approach to bonding.

Molecular Orbital Theory: A Delocalized Bonding Approach

Although the molecular orbital theory is computationally demanding, the principles on which it is based are similar to those we used to determine electron configurations for atoms. The key difference is that in molecular orbitals, the electrons are allowed to interact with more than one atomic nucleus at a time. Just as with atomic orbitals, we create an energy-level diagram by listing the molecular orbitals in order of increasing energy. We then fill the orbitals with the required number of valence electrons according to the Pauli principle. This means that each molecular orbital can accommodate a maximum of two electrons with opposite spins.

Molecular Orbitals Involving Only *ns* Atomic Orbitals

We begin our discussion of molecular orbitals with the simplest molecule, H_2, formed from two isolated hydrogen atoms, each with a $1s^1$ electron configuration. As we explained in Chapter 9, electrons can behave like waves. In the molecular orbital approach, the overlapping atomic orbitals are described by mathematical equations called *wave functions*. The 1s atomic orbitals on the two hydrogen atoms interact to form two new molecular orbitals, one produced by taking the *sum* of the two H 1s wave functions, and the other produced by taking their *difference*:

$$\begin{aligned} MO(1) = &\quad AO(atom\ A) &+ &\quad AO(atom B) \\ MO(1) = &\quad AO(atom\ A) &- &\quad AO(atom B) \end{aligned} \tag{1.7.1}$$

The molecular orbitals created from Equation 1.7.1 are called linear combinations of atomic orbitals (LCAOs) Molecular orbitals created from the sum and the difference of two wave functions (atomic orbitals). A molecule must have as many molecular orbitals as there are atomic orbitals.

> A molecule must have as many molecular orbitals as there are atomic orbitals.

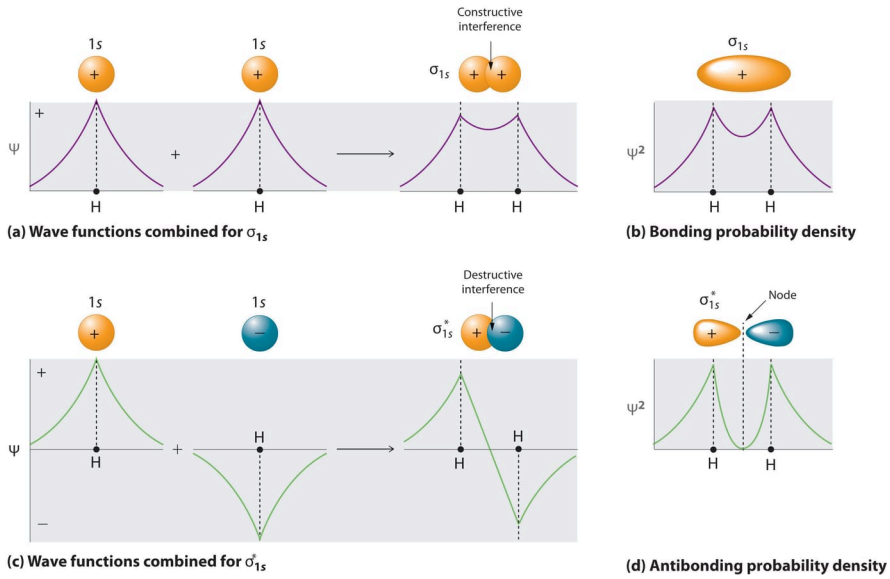


Figure 1.7.1: Molecular Orbitals for the H_2 Molecule. (a) This diagram shows the formation of a bonding σ_{1s} molecular orbital for H_2 as the sum of the wave functions (Ψ) of two H 1s atomic orbitals. (b) This plot of the square of the wave function (Ψ^2) for the bonding σ_{1s} molecular orbital illustrates the increased electron probability density between the two hydrogen nuclei. (Recall that the probability density is proportional to the *square* of the wave function.) (c) This diagram shows the formation of an antibonding σ^*_{1s} molecular orbital for H_2 as the difference of the wave functions (Ψ) of two H 1s atomic orbitals. (d) This plot of the square of the wave function (Ψ^2) for the σ^*_{1s} antibonding molecular orbital illustrates the node corresponding to zero electron probability density between the two hydrogen nuclei.

Adding two atomic orbitals corresponds to *constructive* interference between two waves, thus reinforcing their intensity; the internuclear electron probability density is *increased*. The molecular orbital corresponding to the sum of the two H 1s orbitals is called a σ_{1s} combination (pronounced "sigma one ess") (part (a) and part (b) in Figure 1.7.1). In a sigma (σ) orbital, (i.e., a bonding molecular orbital in which the electron density along the internuclear axis and between the nuclei has cylindrical symmetry), the electron density along the internuclear axis and between the nuclei has cylindrical symmetry; that is, all cross-sections perpendicular to the internuclear axis are circles. The subscript 1s denotes the atomic orbitals from which the molecular orbital was derived: The ≈ sign is used rather than an = sign because we are ignoring certain constants that are not important to our argument.

$$\sigma_{1s} \approx 1s\,(A) + 1s\,(B) \tag{1.7.2}$$

Conversely, subtracting one atomic orbital from another corresponds to *destructive* interference between two waves, which reduces their intensity and causes a *decrease* in the internuclear electron probability density (part (c) and part (d) in Figure 1.7.1). The resulting pattern contains a *node* where the electron density is zero. The molecular orbital corresponding to the difference is called σ^*_{1s} ("sigma one ess star"). In a sigma star (σ^*) orbital An antibonding molecular orbital in which there is a region of zero electron probability (a nodal plane) perpendicular to the internuclear axis., there is a region of zero electron probability, a nodal plane, perpendicular to the internuclear axis:

$$\sigma^\star_{1s} \approx 1s\,(A) - 1s\,(B) \tag{1.7.3}$$

The electron density in the σ_{1s} molecular orbital is greatest between the two positively charged nuclei, and the resulting electron–nucleus electrostatic attractions reduce repulsions between the nuclei. Thus the σ_{1s} orbital represents a bonding molecular orbital. A molecular orbital that forms when atomic orbitals or orbital lobes with the same sign interact to give increased electron probability between the nuclei due to constructive reinforcement of the wave functions. In contrast, electrons in the $\sigma^\star_{1s}$ orbital are generally found in the space outside the internuclear region. Because this allows the positively charged nuclei to repel one another, the $\sigma^\star_{1s}$ orbital is an antibonding molecular orbital (a molecular orbital that forms when atomic orbitals or orbital lobes of opposite sign interact to give decreased electron probability between the nuclei due to destructive reinforcement of the wave functions).

Antibonding orbitals contain a node perpendicular to the internuclear axis; bonding orbitals do not.

Energy-Level Diagrams

Because electrons in the σ_{1s} orbital interact simultaneously with both nuclei, they have a lower energy than electrons that interact with only one nucleus. This means that the σ_{1s} molecular orbital has a *lower* energy than either of the hydrogen 1s atomic orbitals. Conversely, electrons in the $\sigma^{\star}_{1s}$ orbital interact with only one hydrogen nucleus at a time. In addition, they are farther away from the nucleus than they were in the parent hydrogen 1s atomic orbitals. Consequently, the $\sigma^{\star}_{1s}$ molecular orbital has a *higher* energy than either of the hydrogen 1s atomic orbitals. The σ_{1s} (bonding) molecular orbital is *stabilized* relative to the 1s atomic orbitals, and the $\sigma^{\star}_{1s}$ (antibonding) molecular orbital is *destabilized*. The relative energy levels of these orbitals are shown in the energy-level diagram (a schematic drawing that compares the energies of the molecular orbitals (bonding, antibonding, and nonbonding) with the energies of the parent atomic orbitals) in Figure 1.7.2

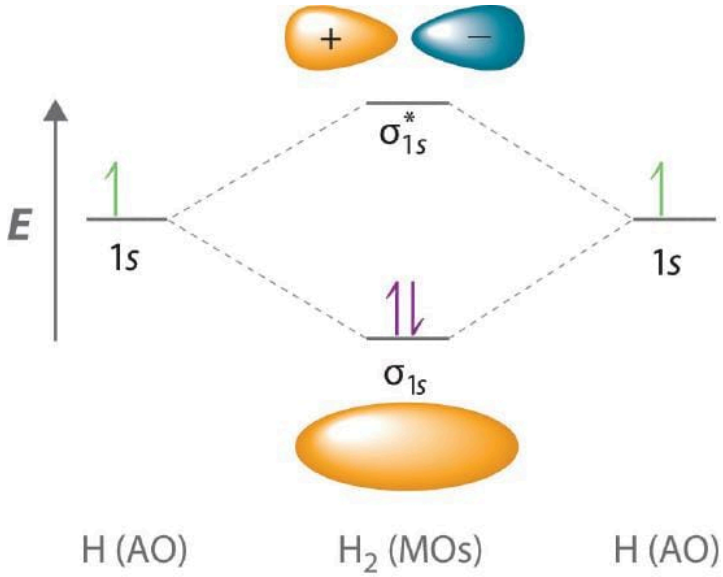


Figure 1.7.2: Molecular Orbital Energy-Level Diagram for H_2. The two available electrons (one from each H atom) in this diagram fill the bonding σ_{1s} molecular orbital. Because the energy of the σ_{1s} molecular orbital is lower than that of the two H 1s atomic orbitals, the H_2 molecule is more stable (at a lower energy) than the two isolated H atoms.

> A bonding molecular orbital is *always* lower in energy (more stable) than the component atomic orbitals, whereas an antibonding molecular orbital is *always* higher in energy (less stable).

To describe the bonding in a homonuclear diatomic molecule (a molecule that consists of two atoms of the same element) such as H_2, we use molecular orbitals; that is, for a molecule in which two identical atoms interact, we insert the total number of valence electrons into the energy-level diagram (Figure 1.7.2). We fill the orbitals according to the Pauli principle and Hund's rule: each orbital can accommodate a maximum of two electrons with opposite spins, and the orbitals are filled in order of increasing energy. Because each H atom contributes one valence electron, the resulting two electrons are exactly enough to fill the σ_{1s} bonding molecular orbital. The two electrons enter an orbital whose energy is lower than that of the parent atomic orbitals, so the H_2 molecule is more stable than the two isolated hydrogen atoms. Thus molecular orbital theory correctly predicts that H_2 is a stable molecule. Because bonds form when electrons are concentrated in the space between nuclei, this approach is also consistent with our earlier discussion of electron-pair bonds.

Bond Order in Molecular Orbital Theory

In the Lewis electron structures, the number of electron pairs holding two atoms together was called the *bond order*. In the molecular orbital approach, bond order One-half the net number of bonding electrons in a molecule. is defined as one-half the *net* number of bonding electrons:

$$bond\ order = \frac{number\ of\ bonding\ electrons - number\ of\ antibonding\ electrons}{2} \tag{1.7.4}$$

To calculate the bond order of H_2, we see from Figure 1.7.2 that the σ_{1s} (bonding) molecular orbital contains two electrons, while the $\sigma^{\star}_{1s}$ (antibonding) molecular orbital is empty. The bond order of H_2 is therefore

$$\frac{2-0}{2}=1 \tag{1.7.5}$$

This result corresponds to the single covalent bond predicted by Lewis dot symbols. Thus molecular orbital theory and the Lewis electron-pair approach agree that a single bond containing two electrons has a bond order of 1. Double and triple bonds contain four or six electrons, respectively, and correspond to bond orders of 2 and 3. We can use energy-level diagrams such as the one in Figure 1.7.2 to describe the bonding in other pairs of atoms and ions where n = 1, such as the H_2^+ ion, the He_2^+ ion, and the He_2 molecule. Again, we fill the lowest-energy molecular orbitals first while being sure not to violate the Pauli principle or Hund's rule.

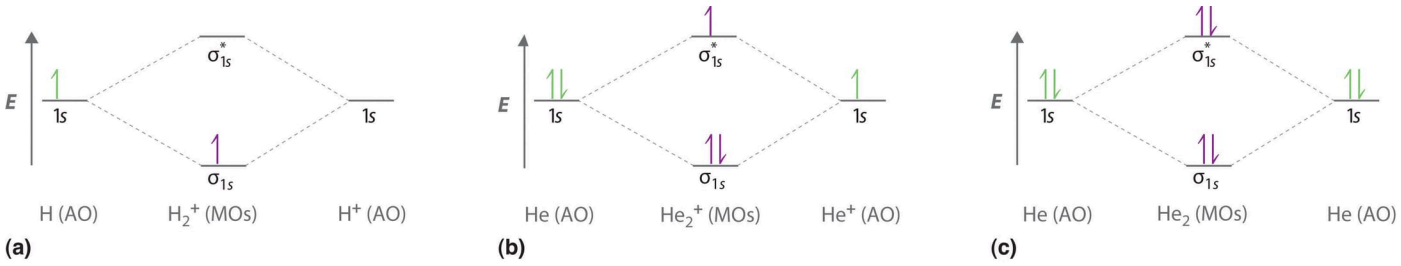


Figure 1.7.3: Molecular Orbital Energy-Level Diagrams for Diatomic Molecules with Only 1s Atomic Orbitals. (a) The H_2^+ ion, (b) the He_2^+ ion, and (c) the He_2 molecule are shown here.

for the H2+ ion the H has one unpaired electron in the 1s orbital so the H2+ has one unpaired electron in the sigmas 1 s orbital. for He2+ ion, He has a full 1 s orbital and He+ has one upaired electron in the 1 s orbital. This means that the sigmal 1s orbital is full and the sigmal*1s orbital has one upaired electron. For the He2 molecule, each He has a full 1 s orbital. This means that sigma 1s and sigma * 1s orbital are full.

Figure 1.7.3a shows the energy-level diagram for the H_2^+ ion, which contains two protons and only one electron. The single electron occupies the σ_{1s} bonding molecular orbital, giving a $(\sigma_{1s})^1$ electron configuration. The number of electrons in an orbital is indicated by a superscript. In this case, the bond order is

$$\frac{1-0}{2}=1/2$$

Because the bond order is greater than zero, the H_2^+ ion should be more stable than an isolated H atom and a proton. We can therefore use a molecular orbital energy-level diagram and the calculated bond order to predict the relative stability of species such as H_2^+. With a bond order of only 1/2 the bond in H_2^+ should be weaker than in the H_2 molecule, and the H–H bond should be longer. As shown in Table 1.7.1, these predictions agree with the experimental data.

Figure 1.7.3b is the molecular orbital energy-level diagram for He_2^+. This ion has a total of three valence electrons. Because the first two electrons completely fill the σ_{1s} molecular orbital, the Pauli principle states that the third electron must be in the $\sigma_{1s}^{\star}$ antibonding orbital, giving a $(\sigma_{1s})^2(\sigma_{1s}^{\star})^1$ electron configuration. This electron configuration gives a bond order of

$$\frac{2-1}{2}=1/2$$

As with H_2^+, the He_2^+ ion should be stable, but the He–He bond should be weaker and longer than in H_2. In fact, the He_2^+ ion can be prepared, and its properties are consistent with our predictions (Table 1.7.1).

Table 1.7.1: Molecular Orbital Electron Configurations, Bond Orders, Bond Lengths, and Bond Energies for some Simple Homonuclear Diatomic Molecules and Ions

Molecule or Ion	Electron Configuration	Bond Order	Bond Length (pm)	Bond Energy (kJ/mol)
H_2^+	$(\sigma_{1s})^1$	1/2	106	269
H_2	$(\sigma_{1s})^2$	1	74	436
He_2^+	$(\sigma_{1s})^2(\sigma_{1s}^{\star})^1$	1/2	108	251
He_2	$(\sigma_{1s})^2(\sigma_{1s}^{\star})^2$	0	not observed	not observed

Finally, we examine the He_2 molecule, formed from two He atoms with $1s^2$ electron configurations. Figure 1.7.3*c* is the molecular orbital energy-level diagram for He_2. With a total of four valence electrons, both the σ_{1s} bonding and σ^*_{1s} antibonding orbitals must contain two electrons. This gives a $(\sigma_{1s})^2 (\sigma^*_{1s})^2$ electron configuration, with a predicted bond order of (2 – 2) ÷ 2 = 0, which indicates that the He_2 molecule has no net bond and is not a stable species. Experiments show that the He_2 molecule is actually *less* stable than two isolated He atoms due to unfavorable electron–electron and nucleus–nucleus interactions.

In molecular orbital theory, *electrons in antibonding orbitals effectively cancel the stabilization resulting from electrons in bonding orbitals*. Consequently, any system that has equal numbers of bonding and antibonding electrons will have a bond order of 0, and it is predicted to be unstable and therefore not to exist in nature. In contrast to Lewis electron structures and the valence bond approach, molecular orbital theory is able to accommodate systems with an odd number of electrons, such as the H_2^+ ion.

> In contrast to Lewis electron structures and the valence bond approach, molecular orbital theory can accommodate systems with an odd number of electrons.

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Example 1.7.1

Use a molecular orbital energy-level diagram, such as those in Figure 1.7.2, to predict the bond order in the He_2^{2+} ion. Is this a stable species?

Given: chemical species

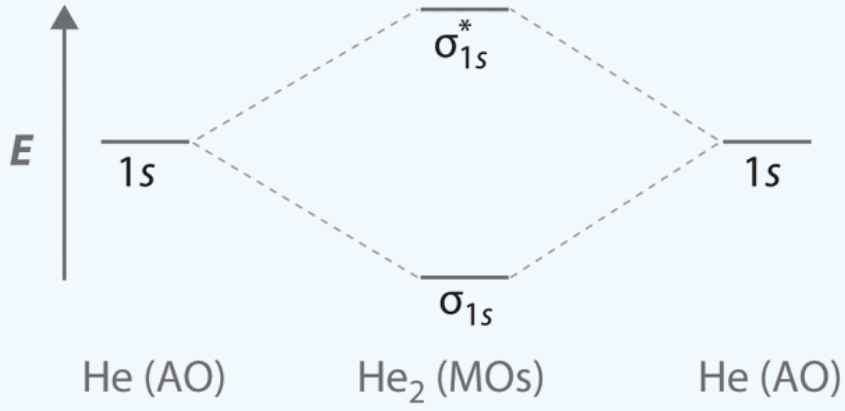
Asked for: molecular orbital energy-level diagram, bond order, and stability

Strategy:

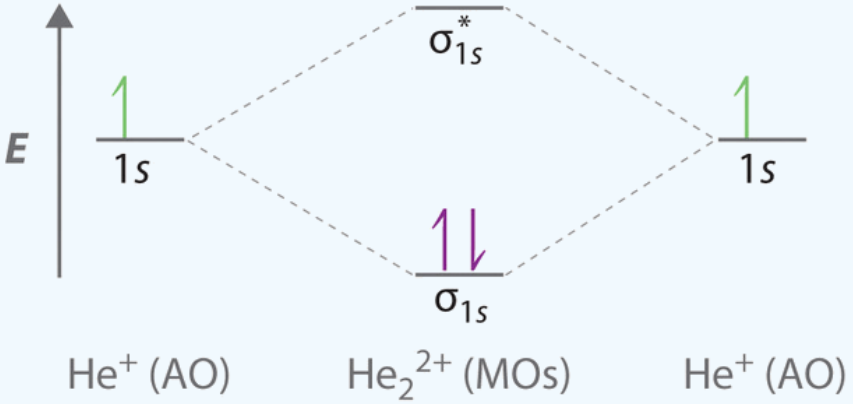
A. Combine the two He valence atomic orbitals to produce bonding and antibonding molecular orbital
B. s. Draw the molecular orbital energy-level diagram for the system.
C. Determine the total number of valence electrons in the He_2^{2+} ion. Fill the molecular orbitals in the energy-level diagram beginning with the orbital with the lowest energy. Be sure to obey the Pauli principle and Hund's rule while doing so.
D. Calculate the bond order and predict whether the species is stable.

Solution:

A Two He 1s atomic orbitals combine to give two molecular orbitals: a σ_{1s} bonding orbital at lower energy than the atomic orbitals and a σ^*_{1s} antibonding orbital at higher energy. The bonding in any diatomic molecule with two He atoms can be described using the following molecular orbital diagram:



B The He_2^{2+} ion has only two valence electrons (two from each He atom minus two for the +2 charge). We can also view He_2^{2+} as being formed from two He^+ ions, each of which has a single valence electron in the 1s atomic orbital. We can now fill the molecular orbital diagram:



Each He+ has one unpaired electron in the 1 s orbital. This means that He2 2+ has a full sigma 1 s orbital.

The two electrons occupy the lowest-energy molecular orbital, which is the bonding (σ_{1s}) orbital, giving a $(\sigma_{1s})^2$ electron configuration. To avoid violating the Pauli principle, the electron spins must be paired. **C** So the bond order is

$$\frac{2-0}{2}=1$$

He_2^{2+} is therefore predicted to contain a single He–He bond. Thus it should be a stable species.

Exercise 1.7.1

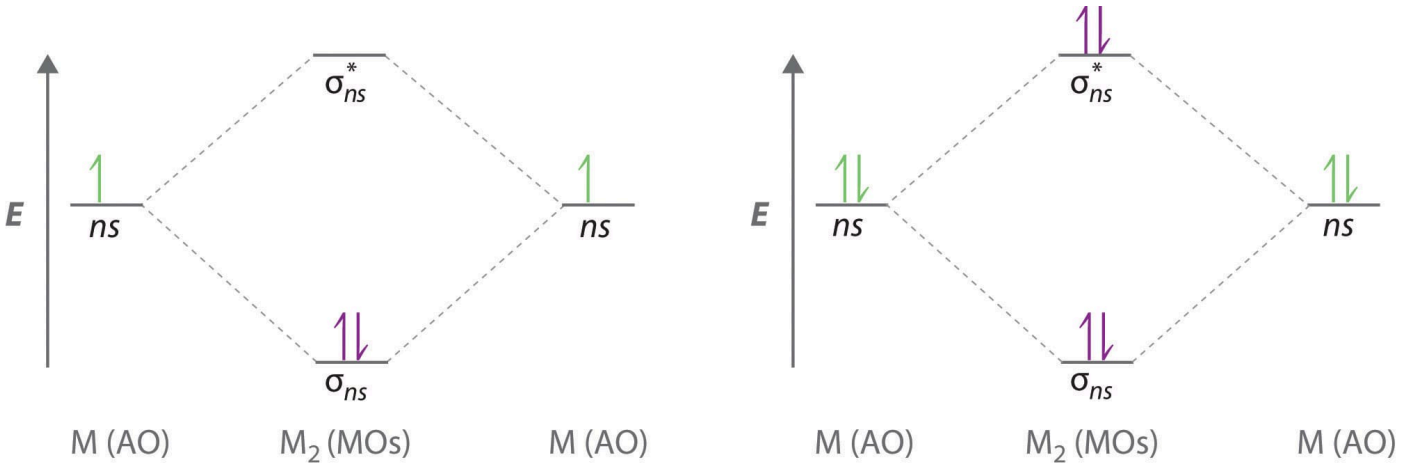
Use a molecular orbital energy-level diagram to predict the valence-electron configuration and bond order of the H_2^{2-} ion. Is this a stable species?

Answer available at the end of this section.

So far, our discussion of molecular orbitals has been confined to the interaction of valence orbitals, which tend to lie farthest from the nucleus. When two atoms are close enough for their valence orbitals to overlap significantly, the filled inner electron shells are largely unperturbed; hence they do not need to be considered in a molecular orbital scheme. Also, when the inner orbitals are completely filled, they contain exactly enough electrons to completely fill both the bonding and antibonding molecular orbitals that arise from their interaction. Thus the interaction of filled shells always gives a bond order of 0, so filled shells are not a factor when predicting the stability of a species. This means that we can focus our attention on the molecular orbitals derived from

valence atomic orbitals.

A molecular orbital diagram that can be applied to any **homonuclear diatomic molecule** with two identical alkali metal atoms (Li_2 and Cs_2, for example) is shown in part (a) in Figure 1.7.4, where M represents the metal atom. Only two energy levels are important for describing the valence electron molecular orbitals of these species: a σ_{ns} bonding molecular orbital and a σ^*_{ns} antibonding molecular orbital. Because each alkali metal (M) has an ns^1 valence electron configuration, the M_2 molecule has two valence electrons that fill the σ_{ns} bonding orbital. As a result, a bond order of 1 is predicted for all homonuclear diatomic species formed from the alkali metals (Li_2, Na_2, K_2, Rb_2, and Cs_2). The general features of these M_2 diagrams are identical to the diagram for the H_2 molecule in Figure 1.7.4. Experimentally, all are found to be stable in the gas phase, and some are even stable in solution.



(a) Alkali metals **(b) Alkaline earth metals**

Figure 1.7.4 : Molecular Orbital Energy-Level Diagrams for Alkali Metal and Alkaline Earth Metal Diatomic (M_2) Molecules. (a) For alkali metal diatomic molecules, the two valence electrons are enough to fill the σ_{ns} (bonding) level, giving a bond order of 1. (b) For alkaline earth metal diatomic molecules, the four valence electrons fill both the σ_{ns} (bonding) and the σ_{ns}* (nonbonding) levels, leading to a predicted bond order of 0.

Similarly, the molecular orbital diagrams for homonuclear diatomic compounds of the alkaline earth metals (such as Be_2), in which each metal atom has an ns^2 valence electron configuration, resemble the diagram for the He_2 molecule in part (c) in Figure 1.7.2 . As shown in part (b) in Figure 1.7.4, this is indeed the case. All the homonuclear alkaline earth diatomic molecules have four valence electrons, which fill both the σ_{ns} bonding orbital and the σ_{ns}* antibonding orbital and give a bond order of 0. Thus Be_2, Mg_2, Ca_2, Sr_2, and Ba_2 are all expected to be unstable, in agreement with experimental data.In the solid state, however, all the alkali metals and the alkaline earth metals exist as extended lattices held together by metallic bonding. At low temperatures, Be_2 is stable.

Example 1.7.2

Use a qualitative molecular orbital energy-level diagram to predict the valence electron configuration, bond order, and likely existence of the Na_2^- ion.

Given: chemical species

Asked for: molecular orbital energy-level diagram, valence electron configuration, bond order, and stability

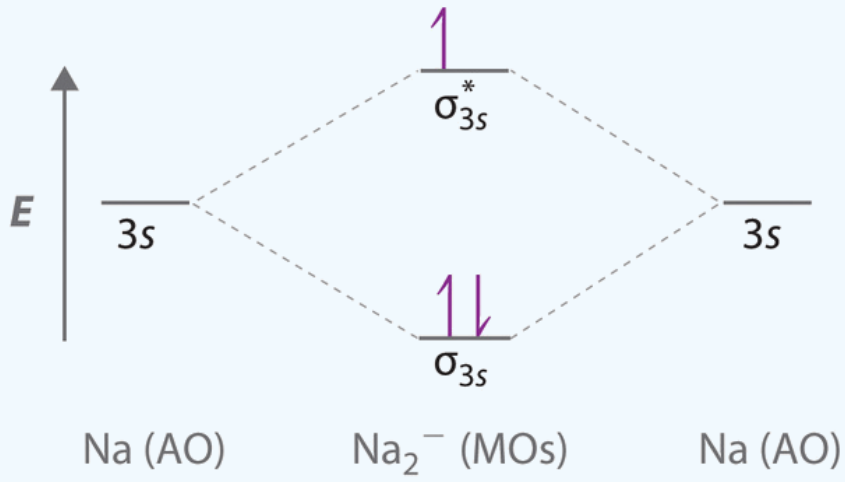
Strategy:

A. Combine the two sodium valence atomic orbitals to produce bonding and antibonding molecular orbitals. Draw the molecular orbital energy-level diagram for this system.

B. Determine the total number of valence electrons in the Na_2^- ion. Fill the molecular orbitals in the energy-level diagram beginning with the orbital with the lowest energy. Be sure to obey the Pauli principle and Hund's rule while doing so.
C. Calculate the bond order and predict whether the species is stable.

Solution:

A Because sodium has a [Ne]$3s^1$ electron configuration, the molecular orbital energy-level diagram is qualitatively identical to the diagram for the interaction of two 1s atomic orbitals. **B** The Na_2^- ion has a total of three valence electrons (one from each Na atom and one for the negative charge), resulting in a filled σ_{3s} molecular orbital, a half-filled σ_{3s^*} and a $(\sigma_{3s})^2 (\sigma^*_{3s})^1$ electron configuration.



C The bond order is (2-1)÷2=1/2 With a fractional bond order, we predict that the Na_2^- ion exists but is highly reactive.

Exercise 1.7.2

Use a qualitative molecular orbital energy-level diagram to predict the valence electron configuration, bond order, and likely existence of the Ca_2^+ ion.

Answer available at the end of this section.

Molecular Orbitals Formed from *ns* and *np* Atomic Orbitals

Atomic orbitals other than *ns* orbitals can also interact to form molecular orbitals. Because individual *p*, *d*, and *f* orbitals are not spherically symmetrical, however, we need to define a coordinate system so we know which lobes are interacting in three-dimensional space. Recall that for each *np* subshell, for example, there are np_x, np_y, and np_z orbitals. All have the same energy and are therefore degenerate, but they have different spatial orientations.

$$\sigma_{np_z} = np_z(A) - np_z(B) \tag{1.7.6}$$

Just as with *ns* orbitals, we can form molecular orbitals from *np* orbitals by taking their mathematical sum and difference. When two positive lobes with the appropriate spatial orientation overlap, as illustrated for two np_z atomic orbitals in part (a) in Figure 1.7.5, it is the mathematical *difference* of their wave functions that results in *constructive* interference, which in turn increases the electron probability density between the two atoms. The difference therefore corresponds to a molecular orbital called a σ_{np_z} *bonding molecular orbital* because, just as with the σ orbitals discussed previously, it is symmetrical about the internuclear axis (in this case, the *z*-axis):

$$\sigma_{np_z} = np_z(A) - np_z(B) \tag{1.7.7}$$

The other possible combination of the two np_z orbitals is the mathematical sum:

$$\sigma_{np_z} = np_z\,(A) + np_z\,(B) \tag{1.7.8}$$

In this combination, shown in part (b) in Figure 1.7.5, the positive lobe of one np_z atomic orbital overlaps the negative lobe of the other, leading to *destructive* interference of the two waves and creating a node between the two atoms. Hence this is an antibonding molecular orbital. Because it, too, is symmetrical about the internuclear axis, this molecular orbital is called a $\sigma_{np_z} = np_z\,(A) - np_z\,(B)$ *antibonding molecular orbital*. Whenever orbitals combine, *the bonding combination is always lower in energy* (more stable) than the atomic orbitals from which it was derived, and *the antibonding combination is higher in energy* (less stable).

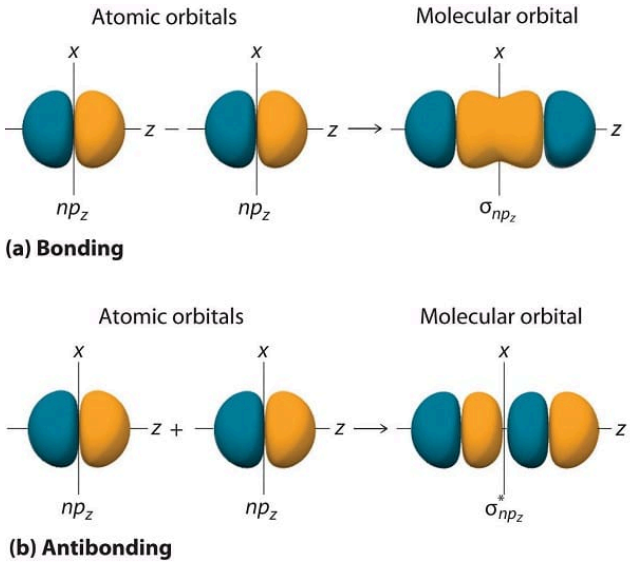


Figure 1.7.5 Formation of Molecular Orbitals from np_z Atomic Orbitals on Adjacent Atoms.(a) By convention, in a linear molecule or ion, the *z*-axis always corresponds to the internuclear axis, with +*z* to the right. As a result, the signs of the lobes of the np_z atomic orbitals on the two atoms alternate – + – +, from left to right. In this case, the σ (bonding) molecular orbital corresponds to the mathematical *difference*, in which the overlap of lobes with the same sign results in increased probability density between the nuclei. (b) In contrast, the σ* (antibonding) molecular orbital corresponds to the mathematical *sum*, in which the overlap of lobes with opposite signs results in a nodal plane of zero probability density perpendicular to the internuclear axis.

> Overlap of atomic orbital lobes with the *same sign* produces a bonding molecular orbital, regardless of whether it corresponds to the sum or the difference of the atomic orbitals.

The remaining *p* orbitals on each of the two atoms, np_x and np_y, do not point directly toward each other. Instead, they are perpendicular to the internuclear axis. If we arbitrarily label the axes as shown in Figure 1.7.6, we see that we have two pairs of *np* orbitals: the two np_x orbitals lying in the plane of the page, and two np_y orbitals perpendicular to the plane. Although these two pairs are equivalent in energy, the np_x orbital on one atom can interact with only the np_x orbital on the other, and the np_y orbital on one atom can interact with only the np_y on the other. These interactions are side-to-side rather than the head-to-head interactions characteristic of σ orbitals. Each pair of overlapping atomic orbitals again forms two molecular orbitals: one corresponds to the arithmetic sum of the two atomic orbitals and one to the difference. The sum of these side-to-side interactions increases the electron probability in the region above and below a line connecting the nuclei, so it is a bonding molecular orbital that is called a pi (π) orbital (a bonding molecular orbital formed from the side-to-side interactions of two or more parallel np atomic orbitals). The difference results in the overlap of orbital lobes with opposite signs, which produces a nodal plane perpendicular to the internuclear axis; hence it is an antibonding molecular orbital, called a pi star (π*) orbital An antibonding molecular orbital formed from the difference of the side-to-side interactions of two or more parallel *np* atomic orbitals, creating a nodal plane perpendicular to the internuclear axis..

$$\pi_{np_x} = np_x\,(A) + np_x\,(B) \tag{1.7.9}$$

$$\pi^{\star}_{np_x} = np_x\,(A) - np_x\,(B) \tag{1.7.10}$$

The two np_y orbitals can also combine using side-to-side interactions to produce a bonding π_{np_y} molecular orbital and an antibonding $\pi^{\star}_{np_y}$ molecular orbital. Because the np_x and np_y atomic orbitals interact in the same way (side-to-side) and have the same energy, the π_{np_x} and π_{np_y}molecular orbitals are a degenerate pair, as are the $\pi^{\star}_{np_x}$ and $\pi^{\star}_{np_y}$ molecular orbitals.

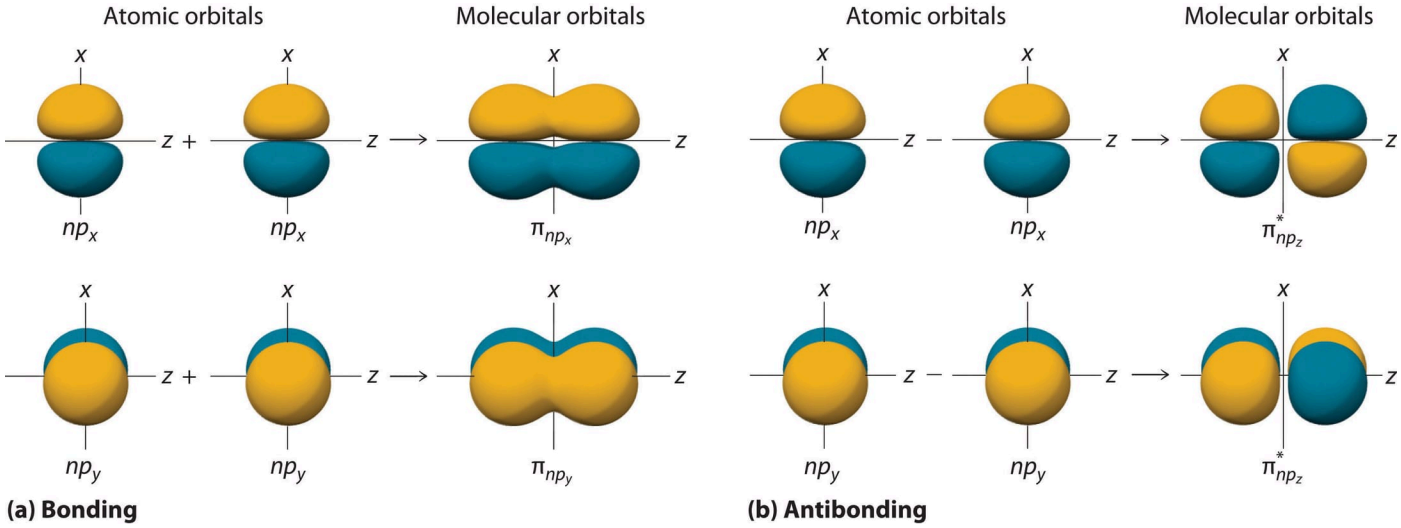


Figure 1.7.6: Formation of π Molecular Orbitals from np_x and np_y Atomic Orbitals on Adjacent Atoms.(a) Because the signs of the lobes of both the np_x and the np_y atomic orbitals on adjacent atoms are the same, in both cases the mathematical sum corresponds to a π (bonding) molecular orbital. (b) In contrast, in both cases, the mathematical difference corresponds to a π* (antibonding) molecular orbital, with a nodal plane of zero probability density perpendicular to the internuclear axis.

Figure 1.7.7 is an energy-level diagram that can be applied to two identical interacting atoms that have three *np* atomic orbitals each. There are six degenerate *p* atomic orbitals (three from each atom) that combine to form six molecular orbitals, three bonding and three antibonding. The bonding molecular orbitals are lower in energy than the atomic orbitals because of the increased stability associated with the formation of a bond. Conversely, the antibonding molecular orbitals are higher in energy, as shown. The energy difference between the σ and σ* molecular orbitals is significantly greater than the difference between the two π and π* sets. The reason for this is that the atomic orbital overlap and thus the strength of the interaction are greater for a σ bond than a π bond, which means that the σ molecular orbital is more stable (lower in energy) than the π molecular orbitals.

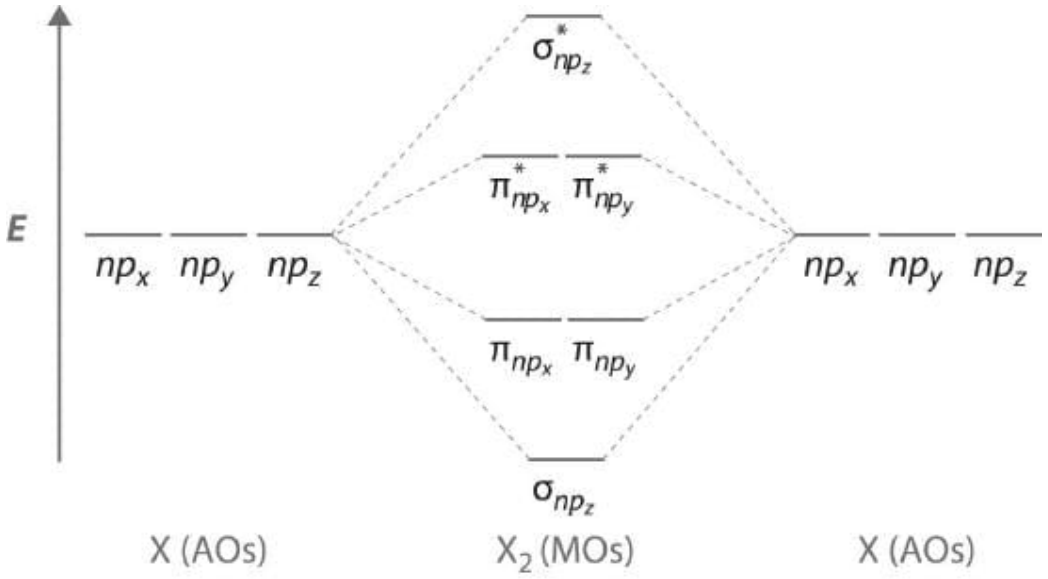


Figure 1.7.7 : The Relative Energies of the σ and π Molecular Orbitals Derived from np_x, np_y, and np_z Orbitals on Identical Adjacent Atoms. Because the two np_z orbitals point directly at each other, their orbital overlap is greater, so the difference in energy between the σ and σ* molecular orbitals is greater than the energy difference between the π and π* orbitals.

Although many combinations of atomic orbitals form molecular orbitals, we will discuss only one other interaction: an *ns* atomic

orbital on one atom with an np_z atomic orbital on another. As shown in Figure 1.7.8, the sum of the two atomic wave functions ($ns + np_z$) produces a σ bonding molecular orbital. Their difference ($ns - np_z$) produces a σ* antibonding molecular orbital, which has a nodal plane of zero probability density perpendicular to the internuclear axis.

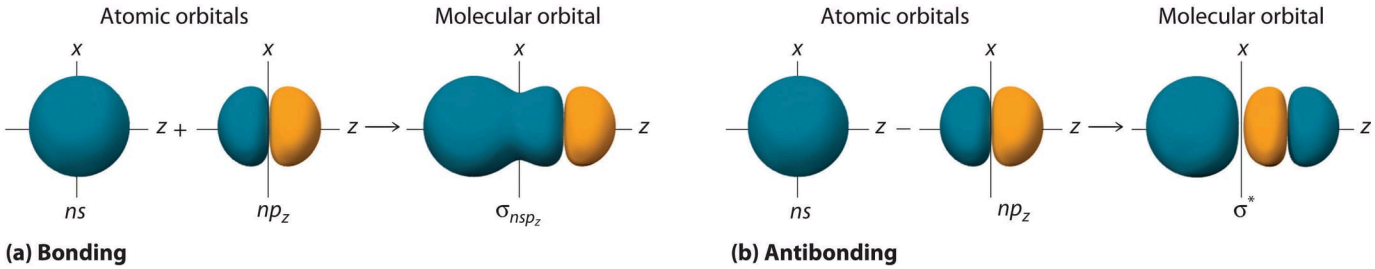


Figure 1.7.8 : Formation of Molecular Orbitals from an *ns* Atomic Orbital on One Atom and an np_z Atomic Orbital on an Adjacent Atom.(a) The mathematical sum results in a σ (bonding) molecular orbital, with increased probability density between the nuclei. (b) The mathematical difference results in a σ* (antibonding) molecular orbital, with a nodal plane of zero probability density perpendicular to the internuclear axis.

Summary

Molecular orbital theory, a delocalized approach to bonding, can often explain a compound's color, why a compound with unpaired electrons is stable, semiconductor behavior, and resonance, none of which can be explained using a localized approach. A **molecular orbital (MO)** is an allowed spatial distribution of electrons in a molecule that is associated with a particular orbital energy. Unlike an atomic orbital (AO), which is centered on a single atom, a molecular orbital extends over all the atoms in a molecule or ion. Hence the **molecular orbital theory** of bonding is a *delocalized* approach. Molecular orbitals are constructed using **linear combinations of atomic orbitals (LCAOs)**, which are usually the mathematical sums and differences of wave functions that describe overlapping atomic orbitals. Atomic orbitals interact to form three types of molecular orbitals.

A completely bonding molecular orbital contains no nodes (regions of zero electron probability) perpendicular to the internuclear axis, whereas a completely **antibonding molecular orbital** contains at least one node perpendicular to the internuclear axis. A **sigma (σ) orbital** (bonding) or a **sigma star (σ*) orbital** (antibonding) is symmetrical about the internuclear axis. Hence all cross-sections perpendicular to that axis are circular. Both a **pi (π) orbital** (bonding) and a **pi star (π*) orbital** (antibonding) possess a nodal plane that contains the nuclei, with electron density localized on both sides of the plane.

The energies of the molecular orbitals versus those of the parent atomic orbitals can be shown schematically in an **energy-level diagram**. The electron configuration of a molecule is shown by placing the correct number of electrons in the appropriate energy-level diagram, starting with the lowest-energy orbital and obeying the Pauli principle; that is, placing only two electrons with opposite spin in each orbital. From the completed energy-level diagram, we can calculate the **bond order**, defined as one-half the net number of bonding electrons. In bond orders, electrons in antibonding molecular orbitals cancel electrons in bonding molecular orbitals, while electrons in nonbonding orbitals have no effect and are not counted. Bond orders of 1, 2, and 3 correspond to single, double, and triple bonds, respectively. Molecules with predicted bond orders of 0 are generally less stable than the isolated atoms and do not normally exist.

Contributors and Attributions

Modified by Joshua Halpern (Howard University)

1. Orbitals or orbital lobes with the same sign interact to give increased electron probability along the plane of the internuclear axis because of *constructive* reinforcement of the wave functions. Consequently, electrons in such molecular orbitals help to hold the positively charged nuclei together. Such orbitals are **bonding molecular orbitals**, and they are always lower in energy than the parent atomic orbitals.
2. Orbitals or orbital lobes with opposite signs interact to give decreased electron probability density between the nuclei because of *destructive* interference of the wave functions. Consequently, electrons in such molecular orbitals are primarily located outside the internuclear region, leading to increased repulsions between the positively charged nuclei. These orbitals are called **antibonding molecular orbitals**, and they are always higher in energy than the parent atomic orbitals.
3. Some atomic orbitals interact only very weakly, and the resulting molecular orbitals give essentially no change in the electron probability density between the nuclei. Hence electrons in such orbitals have no effect on the bonding in a molecule or ion. These orbitals are **nonbonding molecular orbitals**, and they have approximately the same energy as the parent atomic

orbitals.

Answers

Exercise 1.7.1

H_2^{2-} has a valence electron configuration of $(\sigma_{1s})^2 (\sigma^\star_{1s})^2$ with a bond order of 0. It is therefore predicted to be unstable.

Exercise 1.7.2

Ca_2^+ has a $(\sigma_{4s})^2 (\sigma^\star_{4s})^1$ electron configurations and a bond order of 1/2 and should exist.

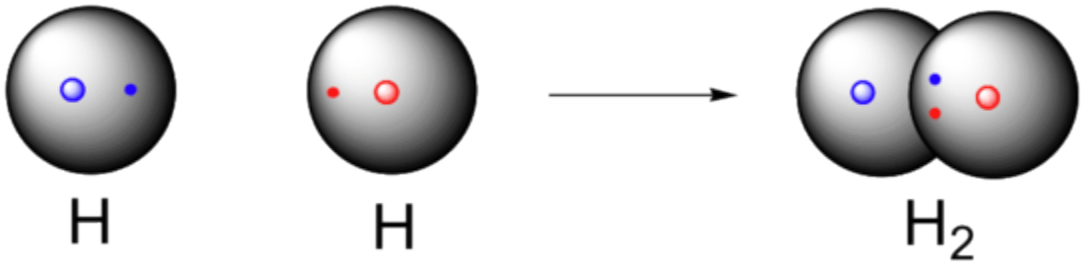
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1.8: Hybrid Orbitals: Bonding in Complex Molecules and Practice Problems

Formation of sigma bonds: the H_2 molecule

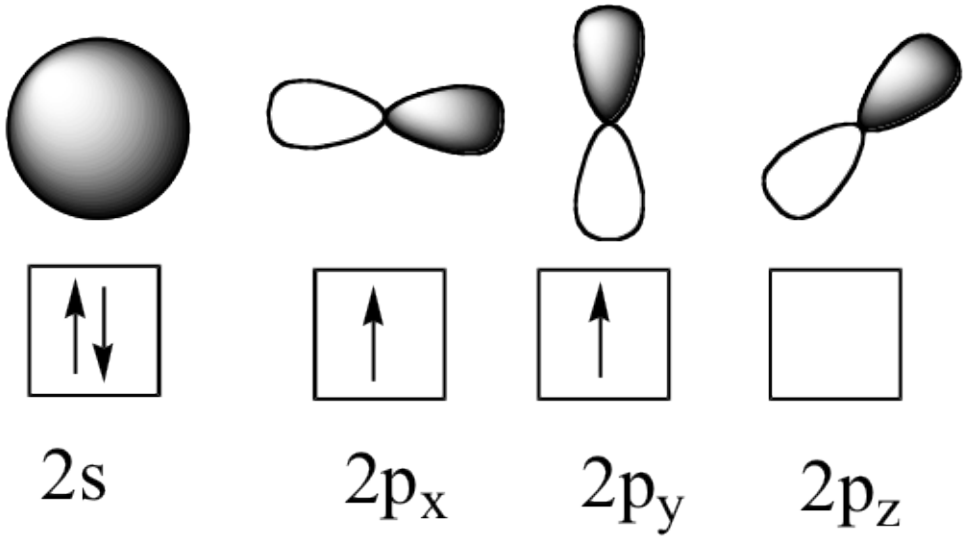
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two electrons from each of the hydrogen atoms are shared to form a covalent bond between the two atoms, what we mean in valence bond theory terms is that the two spherical 1s orbitals overlap, allowing the two electrons to form a pair within the two overlapping orbitals.



These two electrons are now attracted to the positive charge of *both* of the hydrogen nuclei, with the result that they serve as a sort of 'chemical glue' holding the two nuclei together.

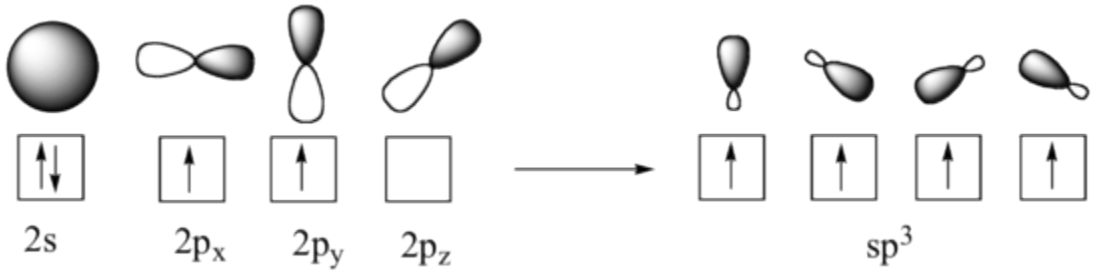
Bonding in Methane

Now let's turn to methane, the simplest organic molecule. Recall the valence electron configuration of the central carbon:

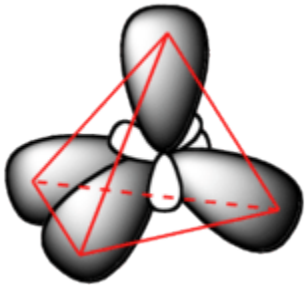


This picture, however, is problematic. How does the carbon form four bonds if it has only two half-filled *p* orbitals available for bonding? A hint comes from the experimental observation that the four C-H bonds in methane are arranged with tetrahedral geometry about the central carbon, and that each bond has the same length and strength. In order to explain this observation, valence bond theory relies on a concept called **orbital hybridization**. In this picture, the four valence orbitals of the carbon (one 2*s* and three 2*p* orbitals) combine mathematically (remember: orbitals are described by equations) to form four equivalent **hybrid**

orbitals, which are named **sp^3 orbitals** because they are formed from mixing one s and three p orbitals. In the new electron configuration, each of the four valence electrons on the carbon occupies a single sp^3 orbital.

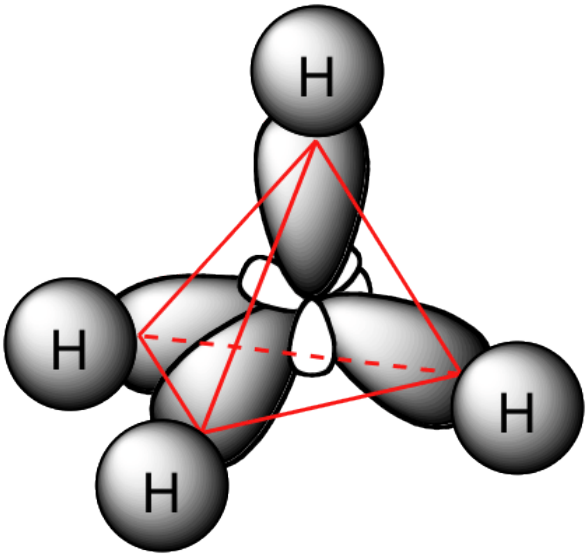


The sp^3 hybrid orbitals, like the *p* orbitals of which they are partially composed, are oblong in shape, and have two lobes of opposite sign. Unlike the *p* orbitals, however, the two lobes are of very different size. The larger lobes of the sp^3 hybrids are directed towards the four corners of a tetrahedron, meaning that the angle between any two orbitals is 109.5°.

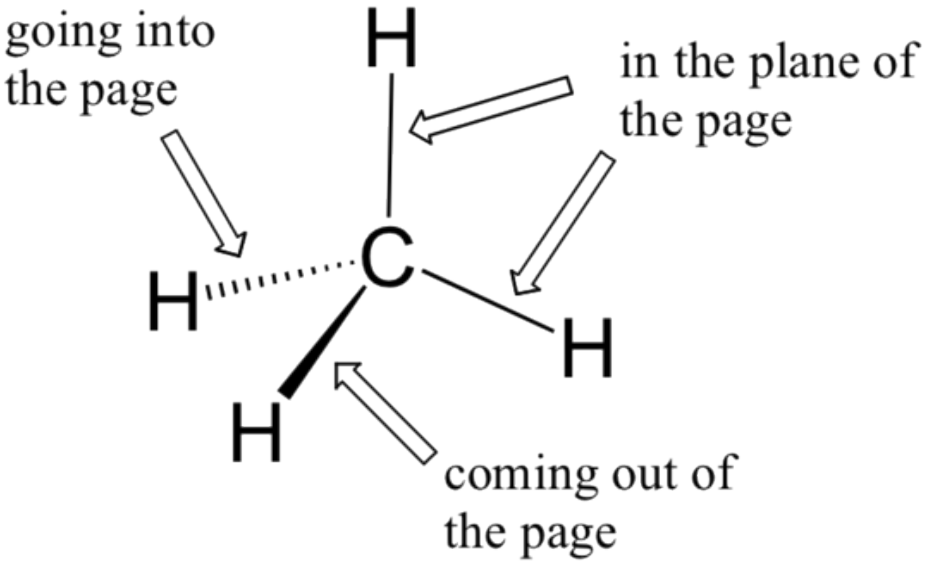


This geometric arrangement makes perfect sense if you consider that it is precisely this angle that allows the four orbitals (and the electrons in them) to be as far apart from each other as possible.This is simply a restatement of the Valence Shell Electron Pair Repulsion (VSEPR) theory that you learned in General Chemistry: electron pairs (in orbitals) will arrange themselves in such a way as to remain as far apart as possible, due to negative-negative electrostatic repulsion.

Each C-H bond in methane, then, can be described as an overlap between a half-filled 1s orbital in a hydrogen atom and the larger lobe of one of the four half-filled sp^3 hybrid orbitals in the central carbon. The length of the carbon-hydrogen bonds in methane is 1.09 Å (1.09×10^{-10} m).



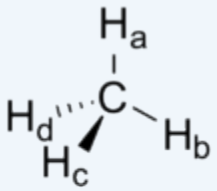
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: the solid / dashed wedge system. In this convention, a solid wedge simply represents a bond that is meant to be pictured emerging from the plane of the page. A dashed wedge represents a bond that is meant to be pictured pointing into, or behind, the plane of the page. Normal lines imply bonds that lie in the plane of the page.



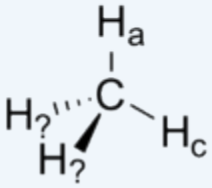
This system takes a little bit of getting used to, but with practice your eye will learn to immediately 'see' the third dimension being depicted.

Example

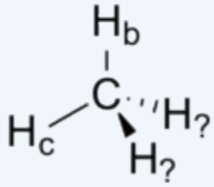
Imagine that you could distinguish between the four hydrogens in a methane molecule, and labeled them H_a through H_d. In the images below, the *exact same* methane molecule is rotated and flipped in various positions. Draw the missing hydrogen atom labels. (It will be much easier to do this if you make a model.)



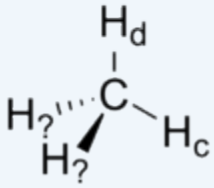
a)



b)



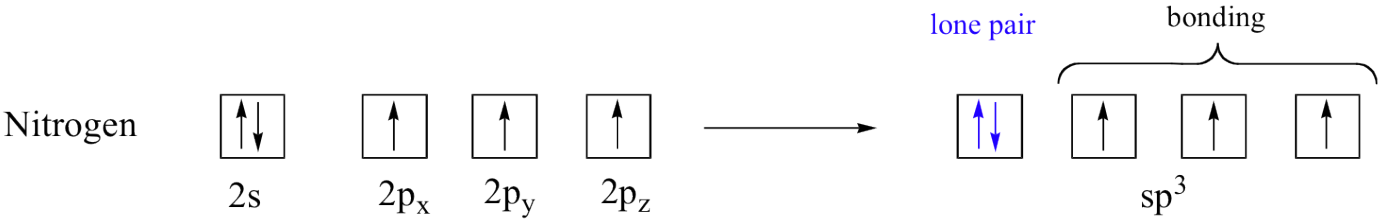
c)



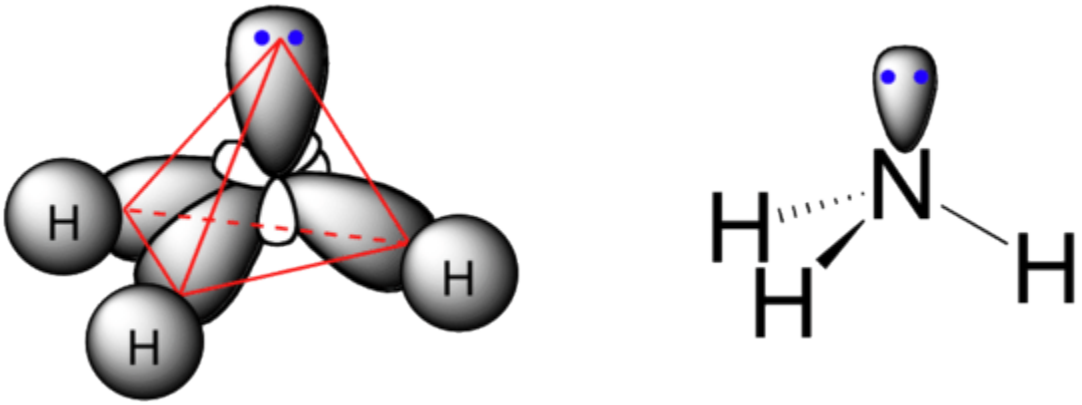
Example

Describe, with a picture and with words, the bonding in chloroform, $CHCl_3$.

Solutions

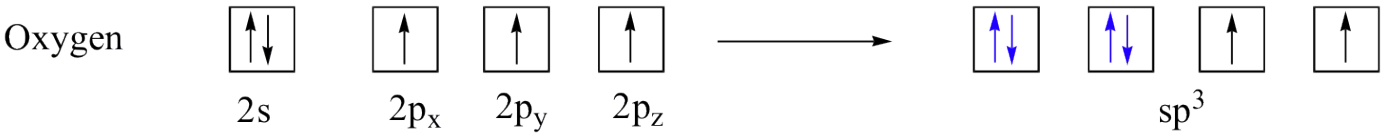


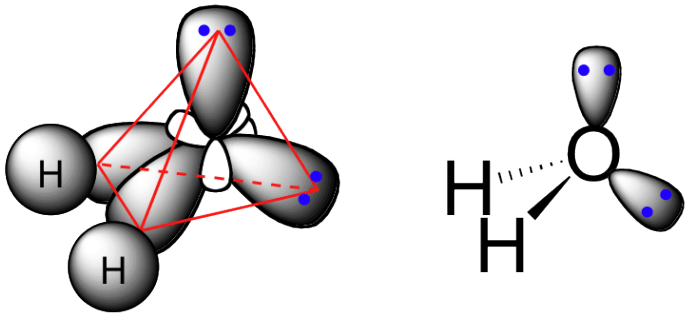
The bonding arrangement here is also tetrahedral: the three N-H bonds of ammonia can be pictured as forming the base of a trigonal pyramid, with the fourth orbital, containing the lone pair, forming the top of the pyramid.



Recall from your study of VSEPR theory in General Chemistry that the lone pair, with its slightly greater repulsive effect, 'pushes' the three N-H sbonds away from the top of the pyramid, meaning that the H-N-H bond angles are slightly less than tetrahedral, at 107.3˚ rather than 109.5˚.

VSEPR theory also predicts, accurately, that a water molecule is 'bent' at an angle of approximately 104.5˚. It would seem logical, then, to describe the bonding in water as occurring through the overlap of sp^3-hybrid orbitals on oxygen with 1sorbitals on the two hydrogen atoms. In this model, the two nonbonding lone pairs on oxygen would be located in sp^3 orbitals.





Some experimental evidence, however, suggests that the bonding orbitals on the oxygen are actually unhybridized 2*p* orbitals rather than sp^3 hybrids. Although this would seem to imply that the H-O-H bond angle should be 90° (remember that *p* orbitals are oriented perpendicular to one another), it appears that electrostatic repulsion has the effect of distorting this *p*-orbital angle to 104.5°. Both the hybrid orbital and the nonhybrid orbital models present reasonable explanations for the observed bonding arrangement in water, so we will not concern ourselves any further with the distinction.

Example

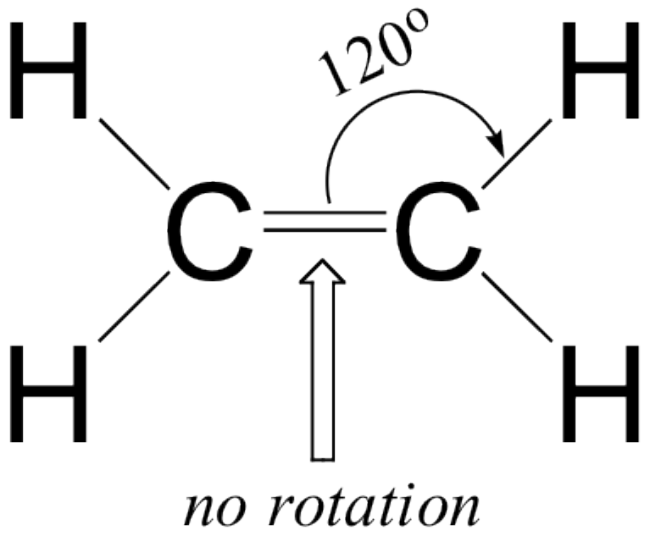
Draw, in the same style as the figures above, an orbital picture for the bonding in methylamine.

Solution

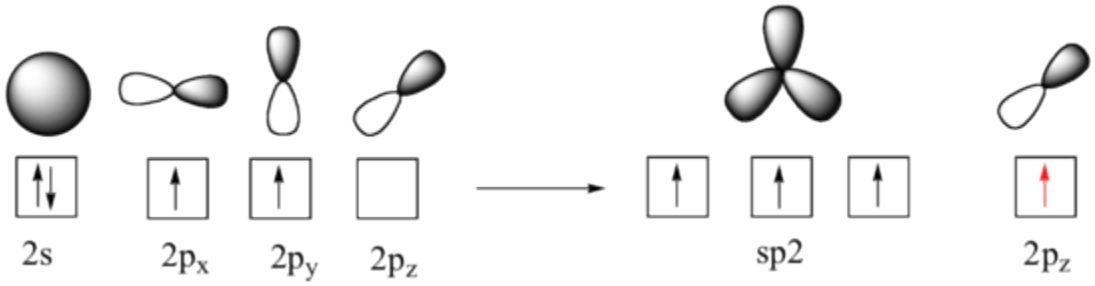
Formation of π bonds - sp^2 and sp hybridization

The valence bond theory, along with the hybrid orbital concept, does a very good job of describing double-bonded compounds such as ethene. Three experimentally observable characteristics of the ethene molecule need to be accounted for by a bonding model:

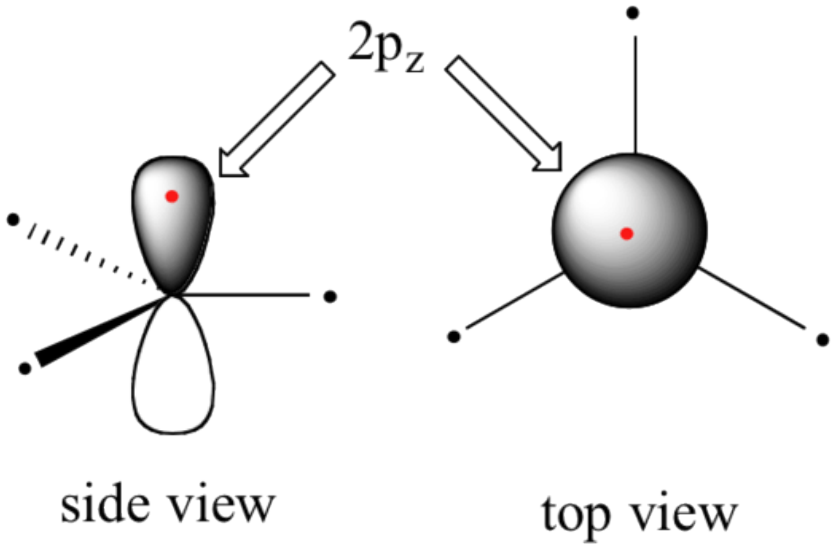
1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 1.34 Å, significantly shorter than the 1.54 Å single carbon-carbon bond in ethane.
3. There is a significant barrier to rotation about the carbon-carbon double bond.



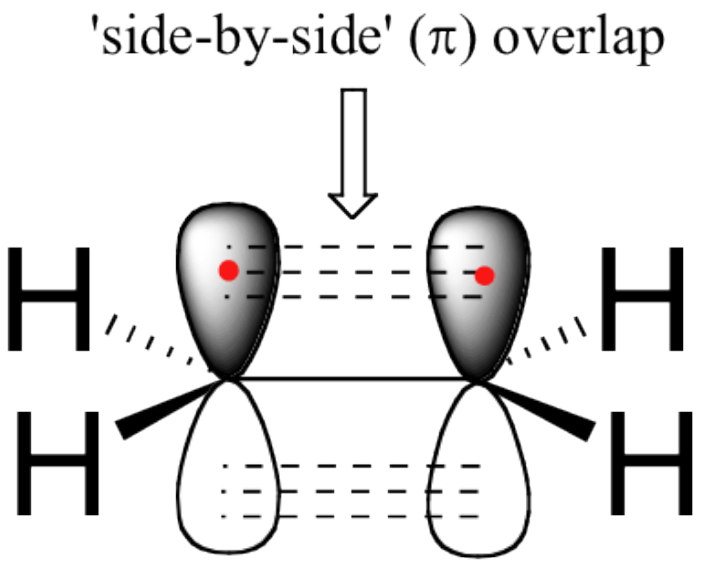
Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2s, $2p_x$ and $2p_y$ orbitals – combine to form three sp^2 hybrids, leaving the $2p_z$ orbital unhybridized.



The three sp^2 hybrids are arranged with trigonal planar geometry, pointing to the three corners of an equilateral triangle, with angles of 120°between them. The unhybridized $2p_z$ orbital is *perpendicular* to this plane (in the next several figures, sp^2 orbitals and the sigma bonds to which they contribute are represented by lines and wedges; only the $2p_z$ orbitals are shown in the 'space-filling' mode).

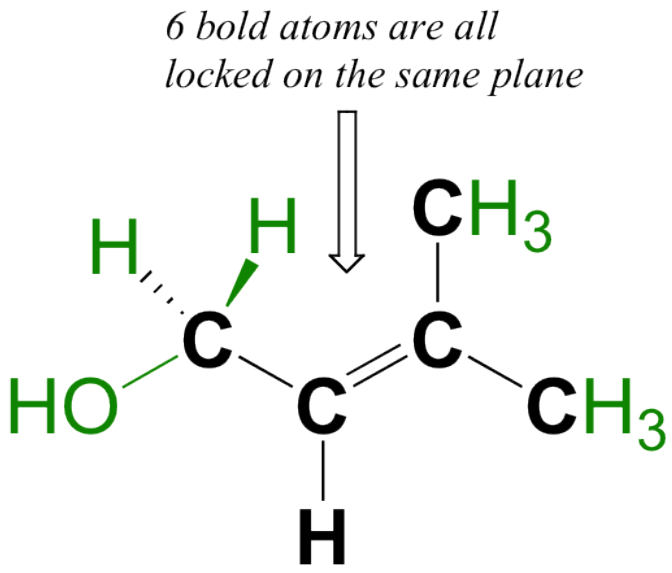


The carbon-carbon double bond in ethene consists of one sbond, formed by the overlap of two sp^2 orbitals, and a second bond, calleda **π (pi) bond**, which is formed by the *side-by-side* overlap of the two unhybridized $2p_z$ orbitals from each carbon.



spacefilling image of bonding in ethene

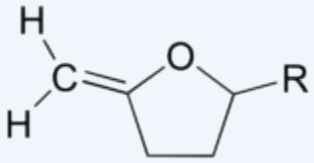
The pi bond does *not* have symmetrical symmetry. Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane. This argument extends to larger alkene groups: in each case, the six atoms of the group form a single plane.



Conversely, sbonds such as the carbon-carbon single bond in ethane (CH_3CH_3) exhibit free rotation, and can assume many different conformations, or shapes - this is one of the main subjects of Chapter 3.

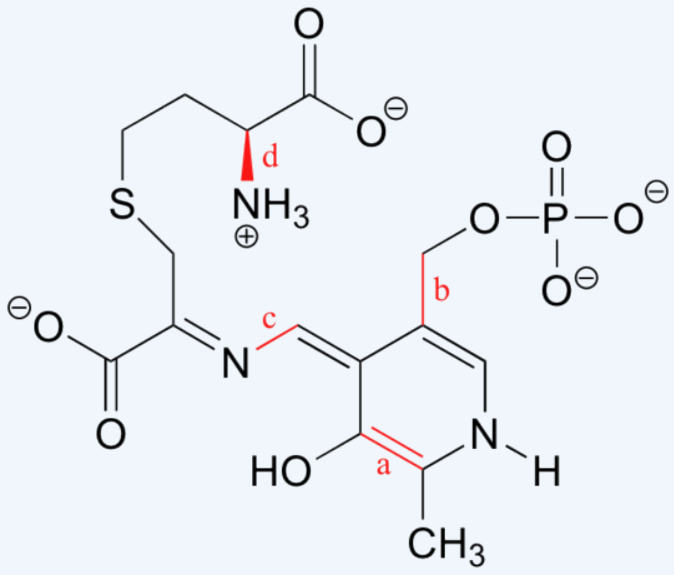
Example 1.20

Circle the six atoms in the molecule below that are 'locked' into the same plane.



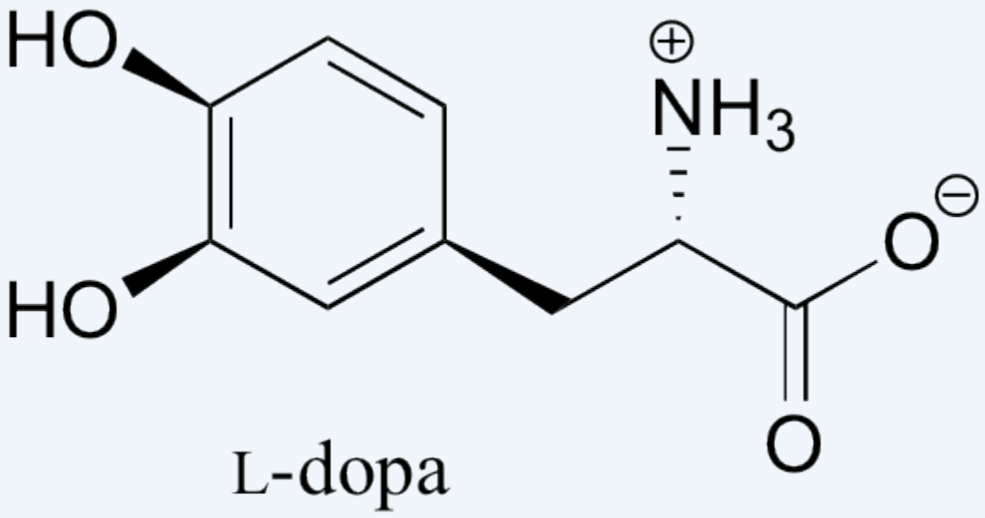
Example

What kinds of orbitals are overlapping in bonds a-d indicated below?



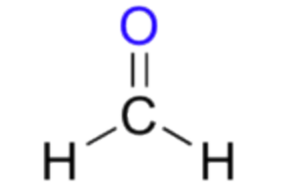
Example

What is wrong with the way the following structure is drawn?

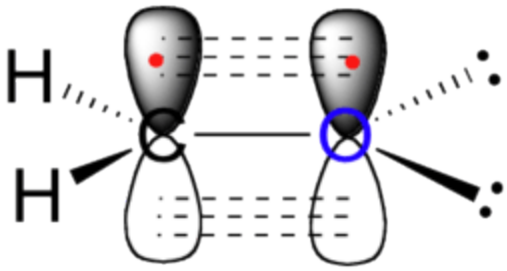


Solutions

A similar picture can be drawn for the bonding in carbonyl groups, such as formaldehyde. In this molecule, the carbon is sp^2-hybridized, and we will assume that the oxygen atom is also sp^2 hybridized. The carbon has three sigma bonds: two are formed by overlap between two of its sp^2 orbitals with the 1sorbital from each of the hydrogens, and the third sigma bond is formed by overlap between the remaining carbon sp^2 orbital and an sp^2 orbital on the oxygen. The two lone pairs on oxygen occupy its other two sp^2 orbitals.



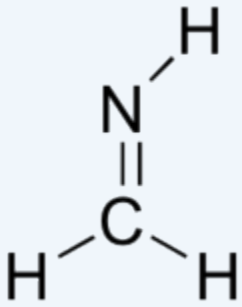
formaldehyde



The pi bond is formed by side-by-side overlap of the unhybridized $2p_z$ orbitals on the carbon and the oxygen. Just like in alkenes, the $2p_z$ orbitals that form the pi bond are perpendicular to the plane formed by the sigma bonds.

Example

Describe and draw the bonding picture for the imine group shown below. Use the drawing of formaldehyde above as your guide.



Solution

Contributors

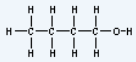
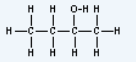
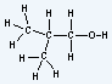
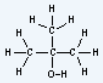
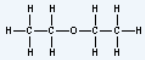
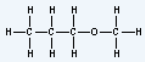
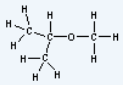
- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

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1.9: Structures and Formulas of Organic Molecules

It is necessary to draw structural formulas for organic compounds because in most cases a molecular formula does not uniquely represent a single compound. Different compounds having the same molecular formula are called **isomers**, and the prevalence of organic isomers reflects the extraordinary versatility of carbon in forming strong bonds to itself and to other elements. When the group of atoms that make up the molecules of different isomers are bonded together in fundamentally different ways, we refer to such compounds as **constitutional isomers**. There are seven constitutional isomers of $C_4H_{10}O$, and structural formulas for these are drawn in the following table. These formulas represent all known and possible $C_4H_{10}O$ compounds, and display a common structural feature. There are no double or triple bonds and no rings in any of these structures.

Structural Formulas for $C_4H_{10}O$ isomers

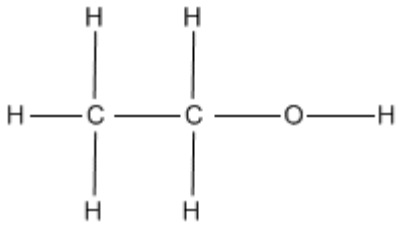
Kekulé Formula	Condensed Formula	Shorthand Formula
	$CH_3(CH_2)_3OH$	
	$C_2H_5CH(OH)CH_3$	
	$(CH_3)_2CHCH_2OH$	
	$(CH_3)_3COH$	
	$(C_2H_5)_2O$	
	$CH_3(CH_2)_2OCH_3$	
	$(CH_3)_2CHOCH_3$	

Simplification of structural formulas may be achieved without any loss of the information they convey. In **condensed structural formulas** the bonds to each carbon are omitted, but each distinct structural unit (group) is written with subscript numbers designating multiple substituents, including the hydrogens. **Shorthand (line) formulas** omit the symbols for carbon and hydrogen entirely. Each straight line segment represents a bond, the ends and intersections of the lines are carbon atoms, and the correct number of hydrogens is calculated from the tetravalency of carbon. Non-bonding valence shell electrons are omitted in these formulas.

Developing the ability to visualize a three-dimensional structure from two-dimensional formulas requires practice, and in most cases the aid of molecular models. As noted earlier, many kinds of model kits are available to students and professional chemists, and the beginning student is encouraged to obtain one.

Kekulé Formula

A structural formula displays the atoms of the molecule in the order they are bonded. It also depicts how the atoms are bonded to one another, for example single, double, and triple covalent bond. Covalent bonds are shown using lines. The number of dashes indicate whether the bond is a single, double, or triple covalent bond. Structural formulas are helpful because they explain the properties and structure of the compound which empirical and molecular formulas cannot always represent.

Ex. Kekulé Formula for Ethanol: 

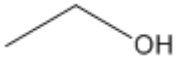
Condensed Formula

Condensed structural formulas show the order of atoms like a structural formula but are written in a single line to save space and make it more convenient and faster to write out. Condensed structural formulas are also helpful when showing that a group of atoms is connected to a single atom in a compound. When this happens, parenthesis are used around the group of atoms to show they are together.

Ex. Condensed Structural Formula for Ethanol: CH_3CH_2OH (Molecular Formula for Ethanol C_2H_6O).

Shorthand Formula

Because organic compounds can be complex at times, line-angle formulas are used to write carbon and hydrogen atoms more efficiently by replacing the letters with lines. A carbon atom is present wherever a line intersects another line. Hydrogen atoms are then assumed to complete each of carbon's four bonds. All other atoms that are connected to carbon atoms are written out. Line angle formulas help show structure and order of the atoms in a compound making the advantages and disadvantages similar to structural formulas.

Ex.Shorthand Formula for Ethanol: 

Contributors

- Jean Kim (UCD), Kristina Bonnett (UCD)

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1.E: Structure and Bonding in Organic Molecules (Exercises)

These are homework exercises to accompany Chapter 1 of Vollhardt and Schore's "Organic Chemistry" Textmap.

1.1: The Scope of Organic Chemistry: An Overview

1.2: Coulomb Forces: A Simplified View of Bonding

1.3: Ionic and Covalent Bonds: The Octet Rule

1.4: Electron-Dot Model of Bonding: Lewis Structures

1.5: Resonance Forms

1.6: Atomic Orbitals: A Quantum Mechanical Description of Electrons Around the Nucleus

1.7: Molecular Orbitals and Covalent Bonding

1.8: Hybrid Orbitals: Bonding in Complex Molecules and Practice Problems

Q25

Draw the Lewis Structures of the following molecules, and if necessary assign charges.

a. BrF
b. ClCN
c. $SOCl_2$
d. $CH_3CH_2NH_2$
e. $CH_3CH_2OCH_2CH_3$
f. $(CH_3)_2NNH_2$
g. CH_3NCNCH_3
h. CH_3COOH
i. N_2O_4

Q26

In problem 25 identify the polar covalent bonds with δ+ and δ- on the atoms according to their electronegativity.

Q27

Draw the Lewis Structures of the following species, and if necessary assign charges.

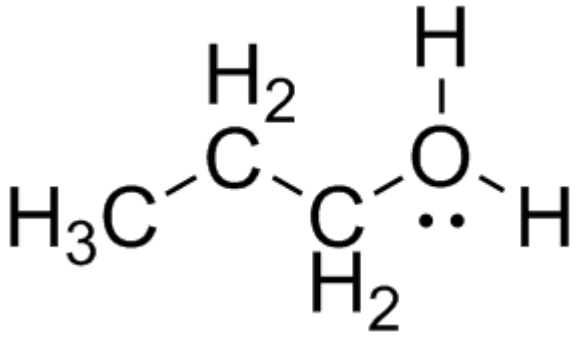
a. H_3O^+

b. NH_4^+
c. $CH_3CH_2^-$
d. $CH_3CH_2^+$
e. CH_3CH_2
f. CH_3CH
g. H^-
h. CH_3COO^-

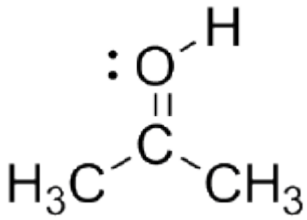
Q28

Add charges to the following Lewis Structures, if neutral do not add any charges.

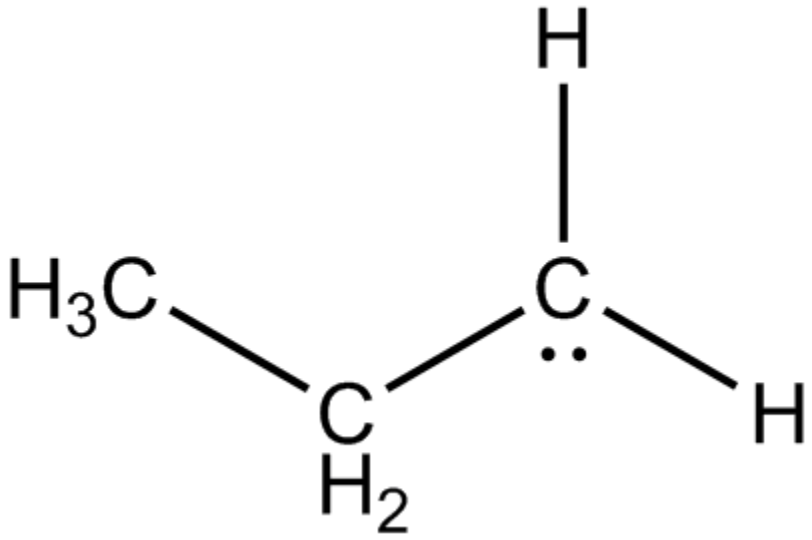
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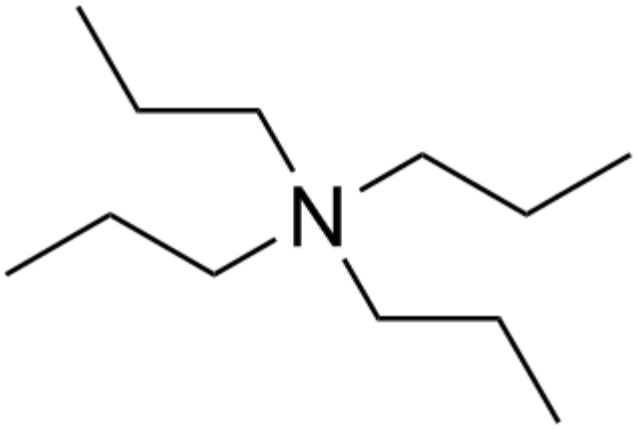
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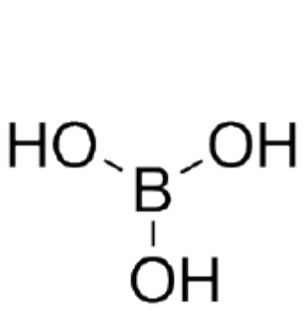
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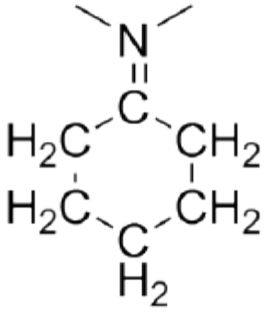
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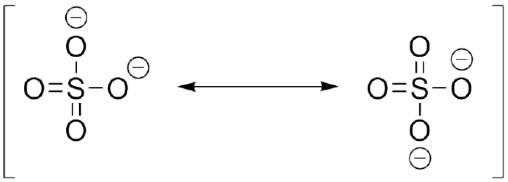


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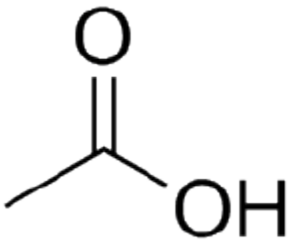


Q29

Sulfuric Acid is a known strong acid, it's deprotonated form SO_4^{2-}, has several resonance structures. Draw the remaining two using electron pushing arrows.



Acetic acid is a common household acid once deprotonated it forms an anion with resonance structures possible. Draw these with electron-pushing arrows.



Q30

In problem 25 several of the species have possible resonance structures. Draw the electron-pushing arrows and resulting resonance structures for 25.c, 25.h, 25.i. Identify the major contributor, and give reasons.

Q31

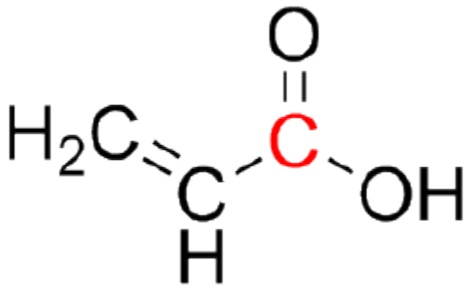
Draw all possible resonance structures of the following species.

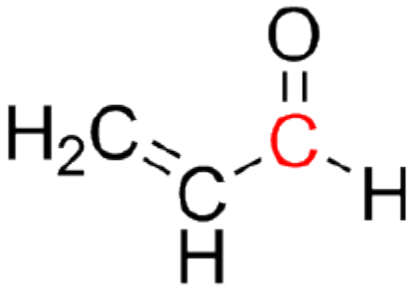
a. $CH_2COCH_3^-$
b. CH_2N_2
c. CO
d. $CH_2ON(CH_3)_2$
e. SCN^-
f. NO_3^{2-}

g. O_3

Q32

Draw all possible resonance structures of the following. Based on the resonance structures, which carbonyl carbon, marked in red, would be the most electron deficient?





Q33

Draw the Lewis structure for each compound.

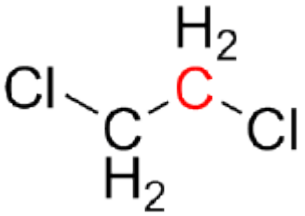
a. Fluorine and the Fluoride anion
b. GeH_4 and GeO
c. H_2O_2 (Hydrogen Peroxide)
d. Phosphine (PH_3) and Ammonia (NH_3)

Q34

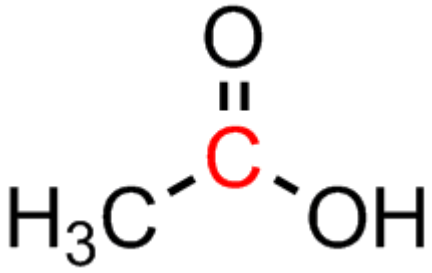
Draw the molecular orbital diagrams of H_2^+, He_2^{2+}, and He_2, and indicate the bond order. Compare and contrast the molecular orbital diagrams of He_2^+ and He_2, which is more favorable?

Q35

Predict the geometry for each red-highlighted atom and give the hybridization of that center.

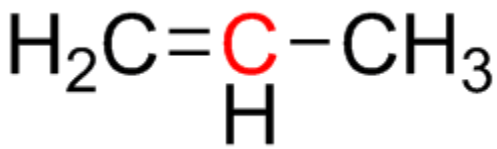


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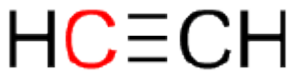


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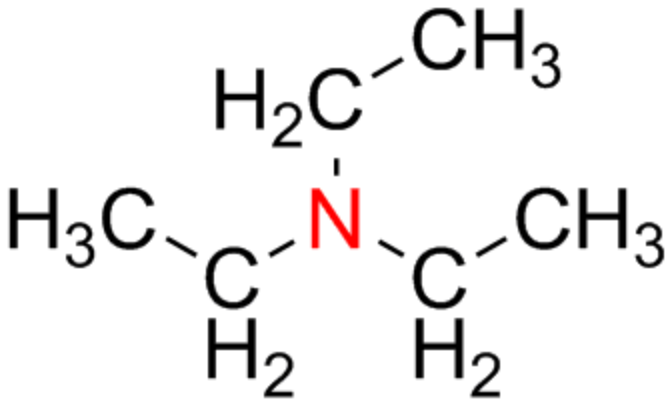
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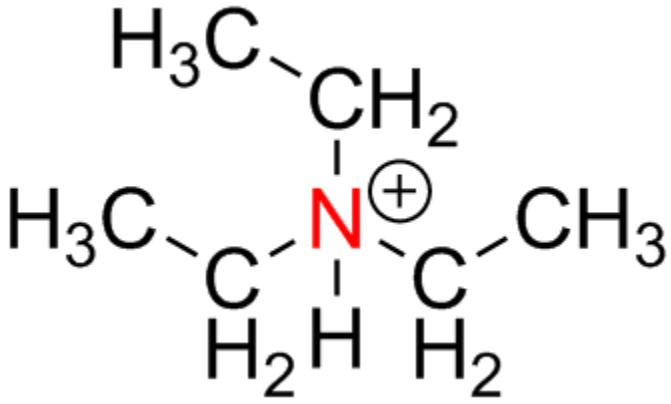
(d)



(e)



(f)



Q36

In problem 35 indicate the hybrid orbitals' interactions (sp^3, sp^2, sp) and the atomic orbitals used (s, p).

Q37

Draw the hybridized orbitals for each of the highlighted carbons in problem 35.

Q38

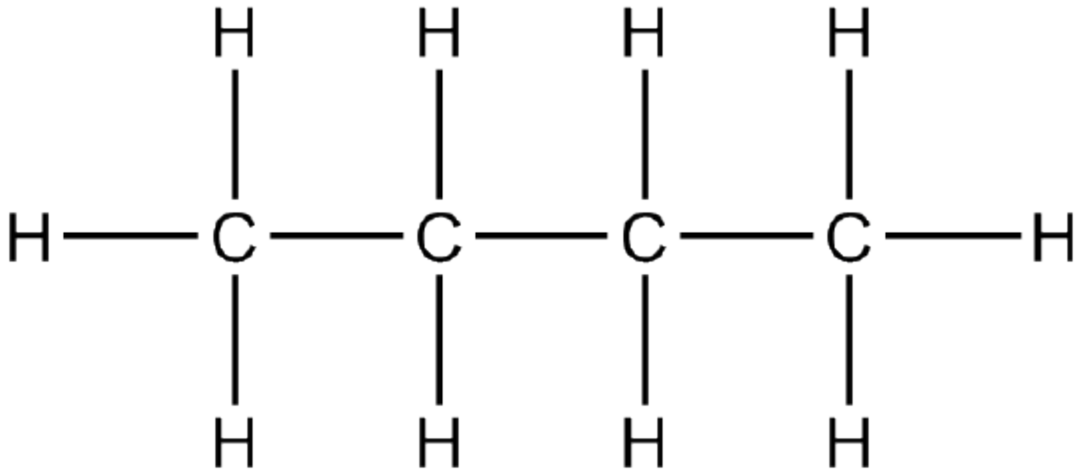
Determine the hybridization of each carbon based on the shape of each molecule.

(a) CH_3Br (b) CH_3CH_2OH (c) H_3CHCCH (d) CH_3^- (e) NH_4^+

Q39

Draw the Kekule structures for the following molecules, an example is given below.

Example. $CH_3CH_2CH_2CH_3$

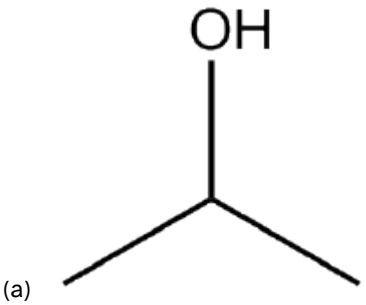


(a) CH_3CH_2OH (b) $(CH_3)_2CH_2OH$ (c) $(CH_3)_2NCHO$ (d) CH_2ClCH_2Cl (e) $HOOCCH_2COOH$

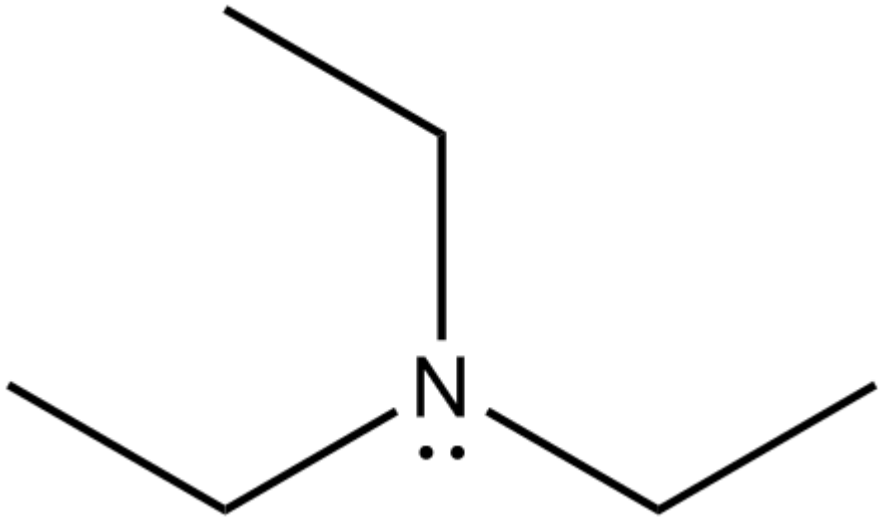
Q40

Draw the Kekule structures for the following molecules.

(a)

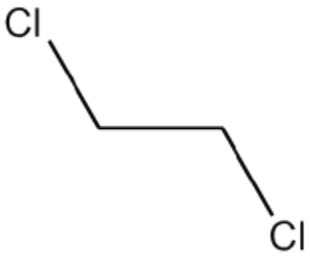


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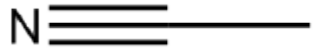


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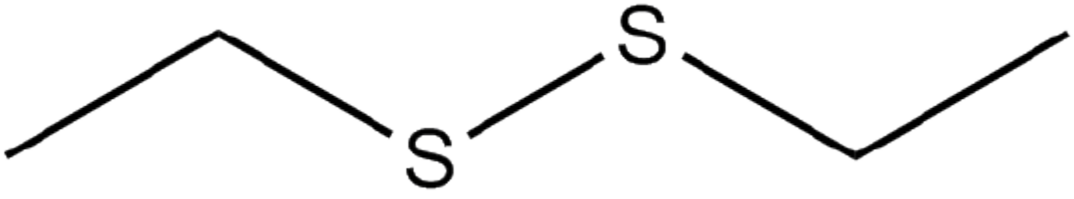
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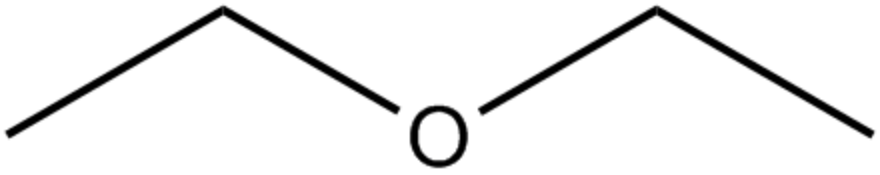


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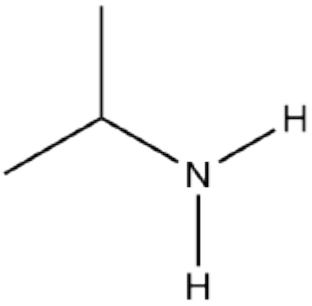
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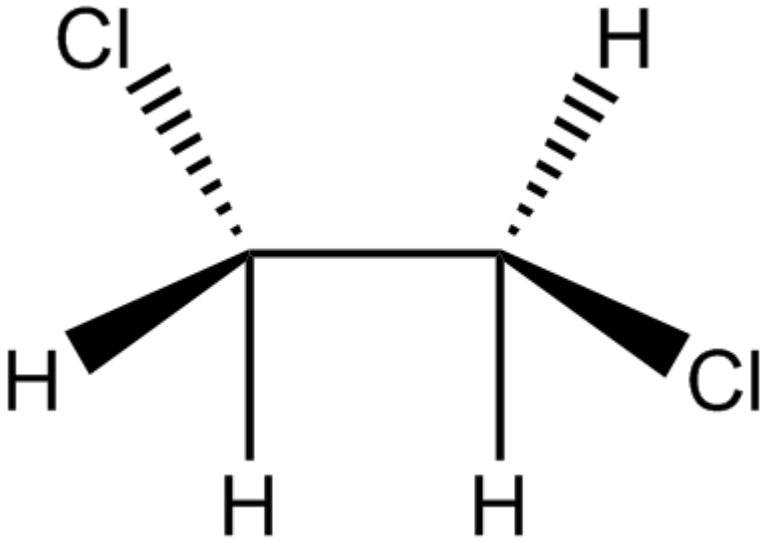


Q41

Convert the following structures into condensed formulas

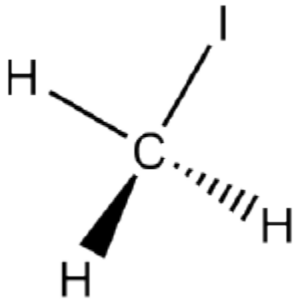


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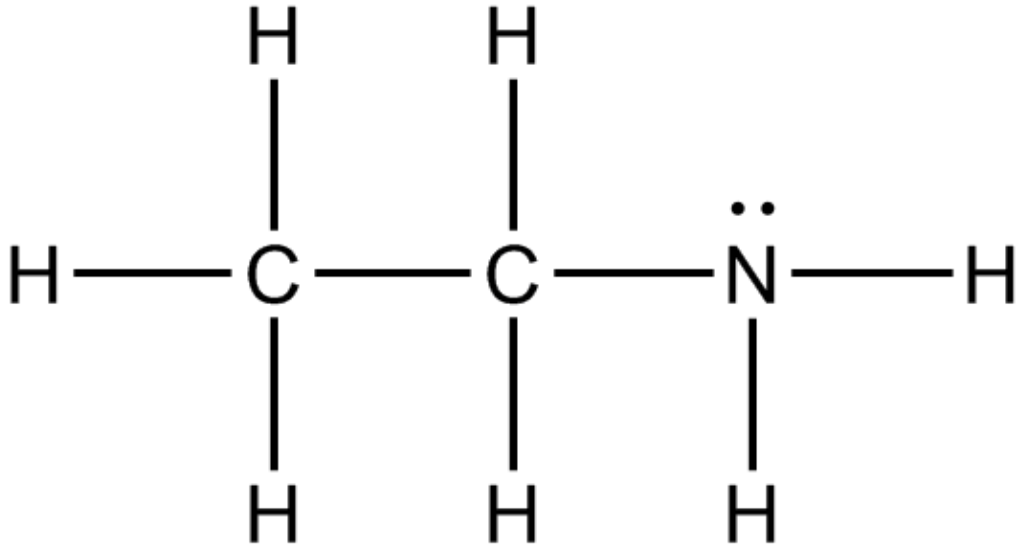
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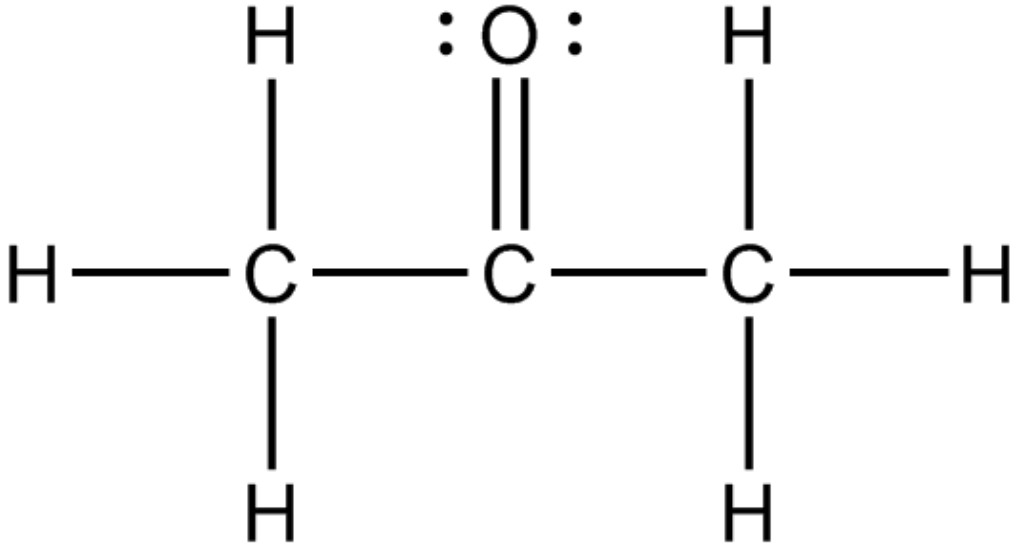
Q42

Give the condensed structures for the following Kekulé structures.

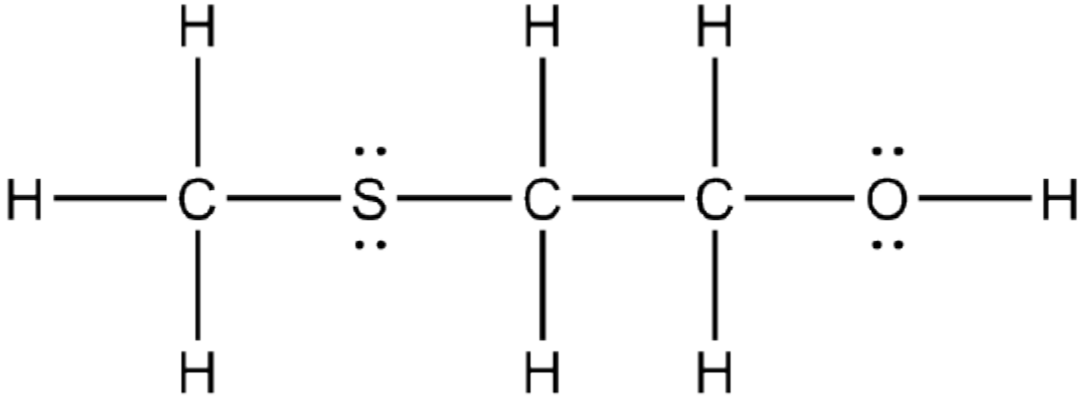


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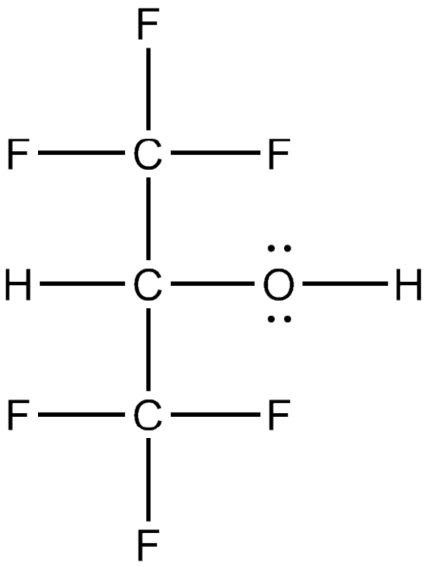
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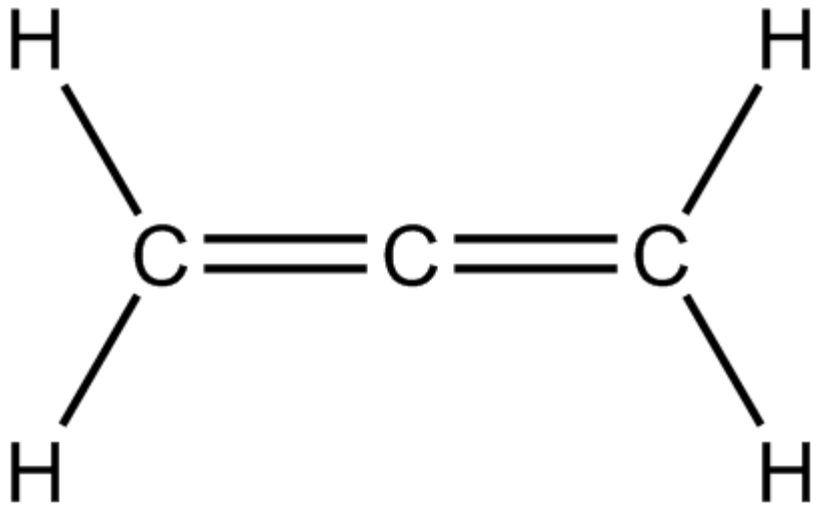
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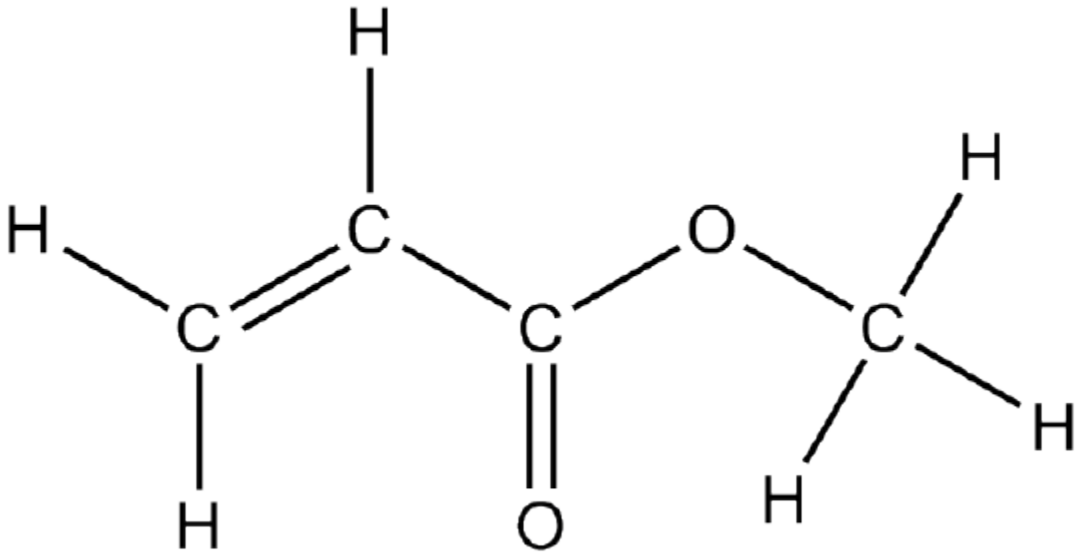
(d)



(e)



(f)



Q43

In the previous problem, 42, draw the Kekulé structures as bond line structures.

Q44

Draw the following condensed formulas as hashed-wedged line structures.

a. $CH_3CH_2OCH_2CN$
b. CH_2Cl_2
c. $(CH3CH_2)_3P$
d. $CH_2CHCH_2SiH_3$

Q45

Draw all possible constitutional isomers, in bond-line form, ofIthe following molecules.

(a) C_3H_8 (b) C_6H_{14} (c) C_4H_{10}

Q46

Draw line-bond structures of the following pairs of species and include all charges. Are any of the pairs resonance forms of the other species in the pair? If not explain the difference

(a) $H_3CCHCCH_2$ and $H_2CCCHCH_3$ (b) HCN and H_3CNH_2 (c) CH_3CH_2COH and CH_3CH_2CHOH

Q47

The following boron-halogen compounds have resonance structures possible. Draw them and in each compound indicate which structure is favored (hint: the octet rule takes precedent). Also, compare the relative energy levels of the three favored resonance structures, which is favored/lowest in energy?

(a) $(CH_3)_2BF$ (b) $(CH_3)_2BCl$ (c) $(CH_3)_2BBr$

Q48

Using the formula for the degrees of each angle, [(n-2)*180]/n, where n equals the number of sides, determine the angles in each of the following shapes. If the given shapes were considered bond-line structures, order them from highest to lowest favorability based on the angles (The best overlap in sp^3 hybridized carbon is at 104.5^o). Compare this answer to the following ring strain energies of each: cyclopropane (triangle)- 27.5 kcal/mol cyclobutane (square)- 26.3 kcal/mol cyclopentane (pentagon)- 6.2 kcal/mol cyclohexane (hexagon)-0.1 kcal/mol.

48.png

Q49

Give the hybridization orbital that the lone pair of each of the following species belongs in. Also, given that the 2p orbitals are higher in energy than the 2s orbitals, order the species from lowest to highest energy according to the s/p character. (sp^3= 1/4s and 3/4p) (sp^2= 1/3s and 2/3p) (sp= 1/2s and 1/2p).

(a) $CH_3CH_2CH_2^-$ (b) CH_3CHCH^- (c) CH_3CC^-

Based on their relative energy, which species would it be most favorable to undergo the following dissociation (HA represents the neutral hydrocarbon)?

49q.png

Q50

In each set which of the following positively polarized carbon bond atoms is the most electropositive?

(a) (i)$CHCl_3$ (ii) $CHCl_2$ (iii) CCl_4

(b) (i) $ClCH_2OCH_2Cl$ (ii) CH_3OCH_2Cl

(c) (i) $(CH_3)_3C^+$ (ii) $(CH_3CH_2)_3C^+$

Q51

The following molecule is a common insecticide, cyfluthrin. It is known to be very effective against invertibrates, but it is not nearly as toxic to mammals. In the following highlight one (a) highly polarized covalent single bond (b) one highly polarized double

bond (c) one sp^2 hybridized carbon atom (d) one sp hybridized carbon atom and (e) one conjugated system.

Q52

In the following reaction does the hybridization of the highlighted carbon atom change? Give the hybridization before and after.

52q.png

Q53

A combustion elemental analysis finds that a compound is made up of 84% carbon and 16% hydrogen (C=12.0, H=1.0, O=16.0). Which of the following could be the compound tested?

(a) CH_4O (b) $C_6H_{14}O_2$ (c) $C_{14}H_{22}$ (d) C_7H_{16}

Q54

As drawn, which of the following is a correct formal charge assignment?

54q.png

(a) +1 on F (b) -1 on N (c) +2 on N (d) -1 on B (e) +1 on B

Q55

The highlighted bond is formed by the interaction between what two orbitals?

55q.png

Q56

Which highlighted carbon center has the smallest bond angles?

(a) CO_2 (b) CH_2Cl_2 (c) HCCH (d) CO

Q57

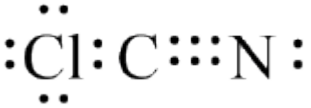
Which pair of structures are resonance hybrids?

(a) 57a.png (b) 57b.png (c) 57c.png (d) 57d.png

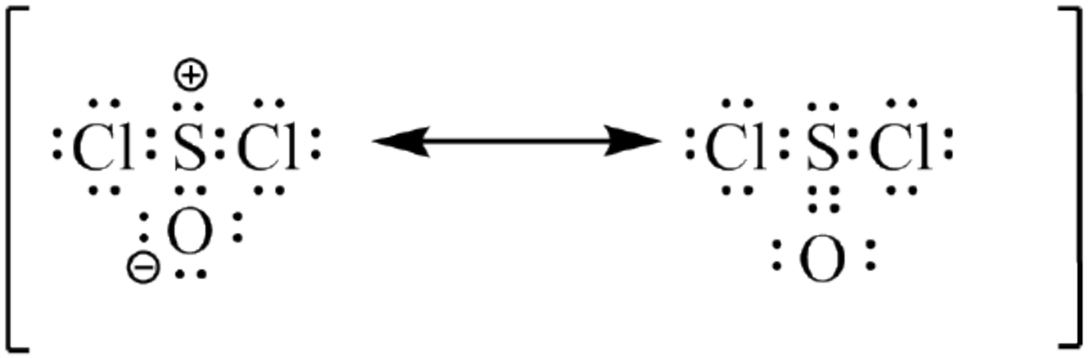
Solutions

S25.

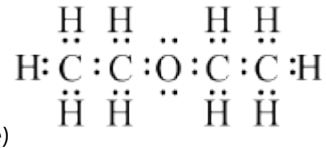
(a) 

(b) 

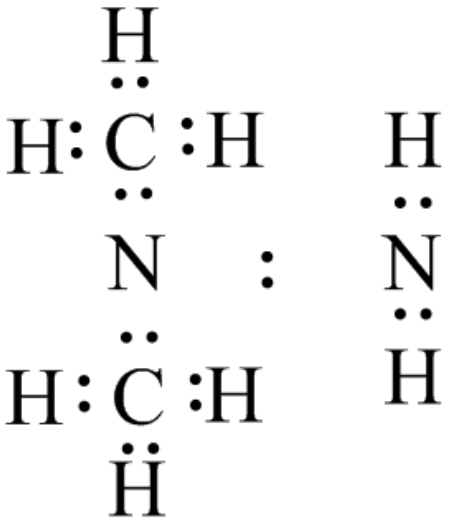
(c)



(d)



(e)



(f)

The lone pair is shared between the two N atoms.

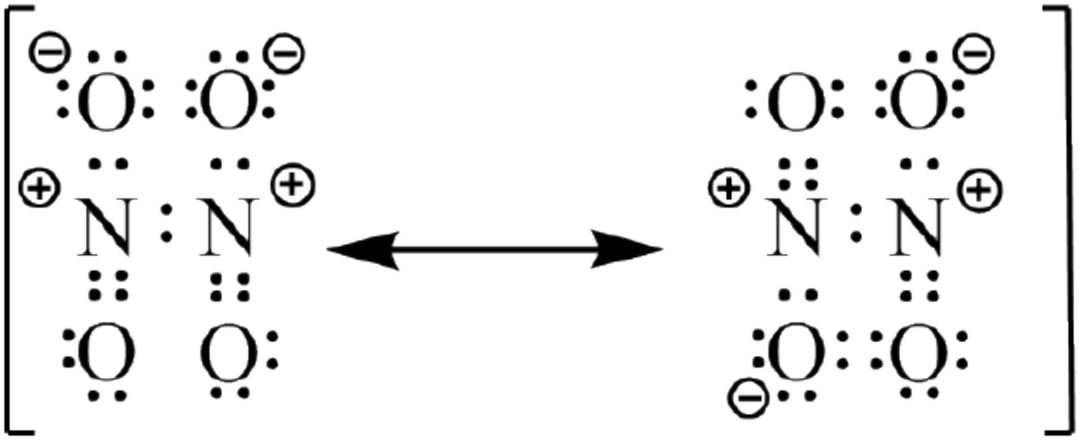


(g)

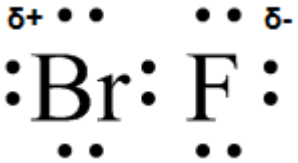
(h)

25hS.png

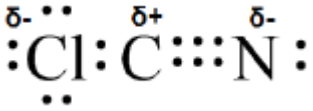
(i)



S26

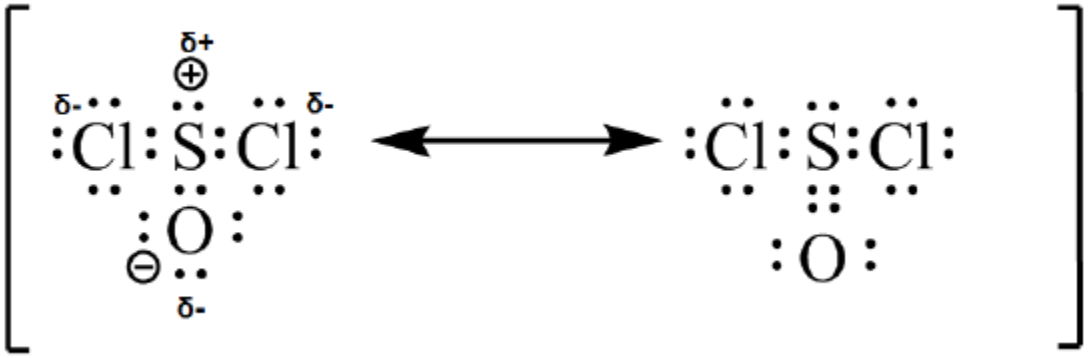


(a)

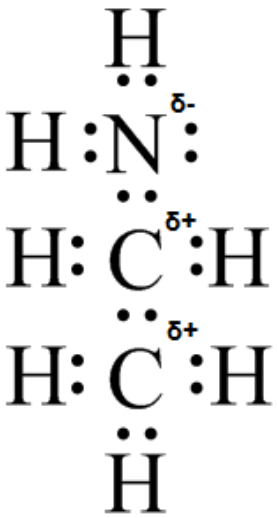


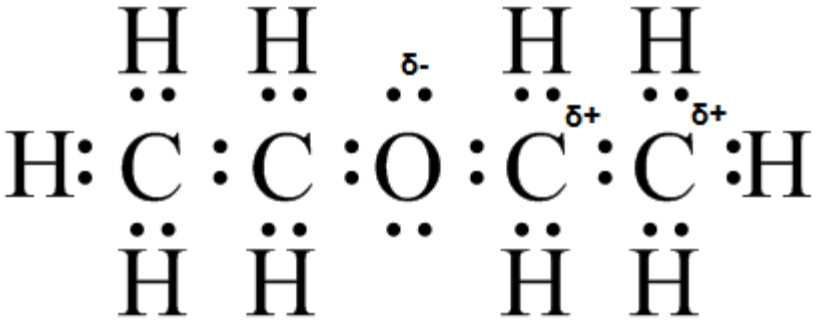
(b)

(c)

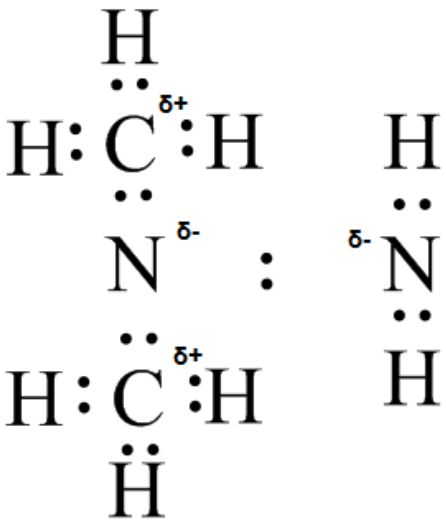


(d)

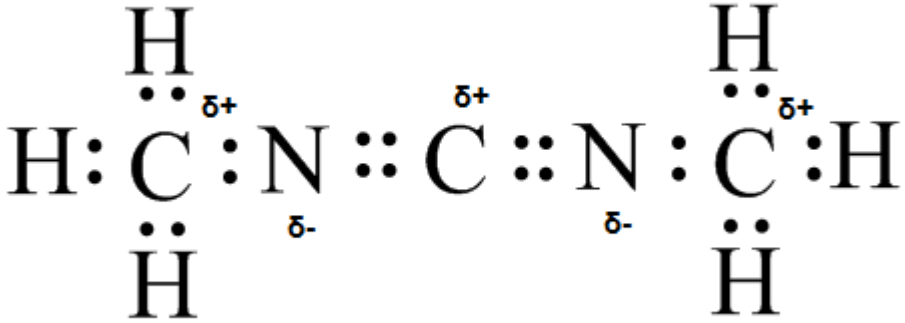




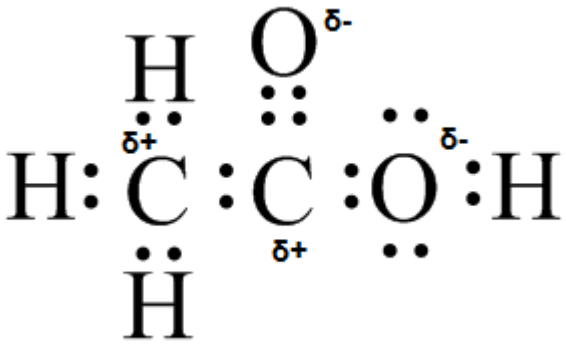
(e)



(f)



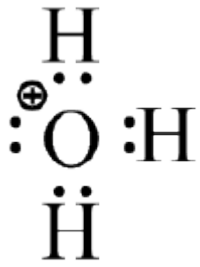
(g)



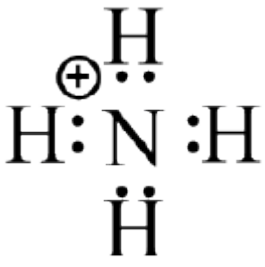
(h)

(i) 26N2O4.png

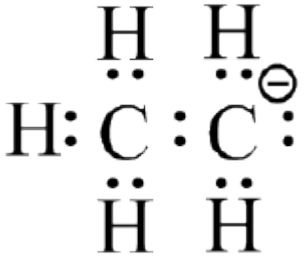
S27



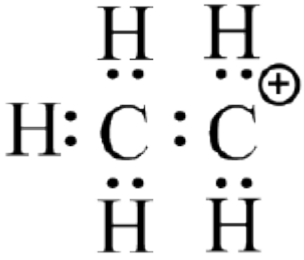
(a)



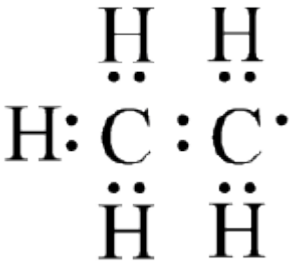
(b)



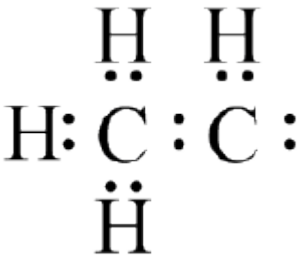
(c)



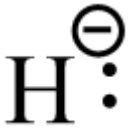
(d)



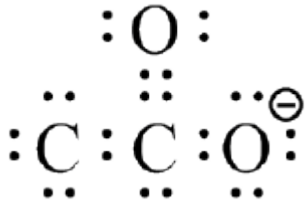
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(f)

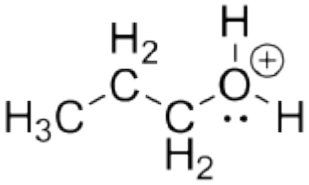


(g)

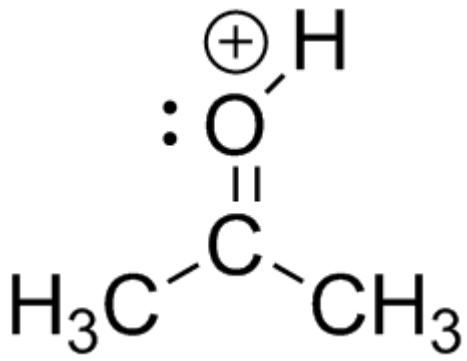


(h)

S28

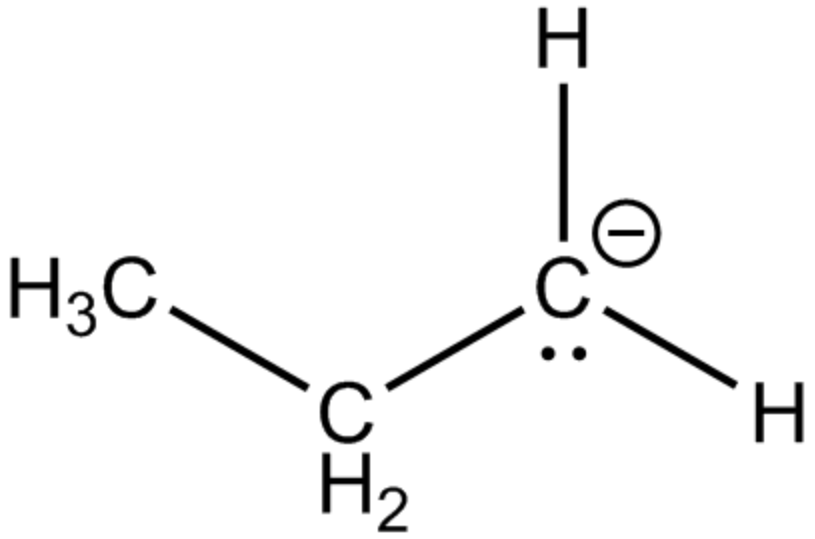


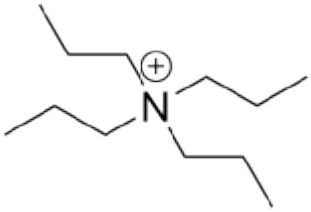
(a)



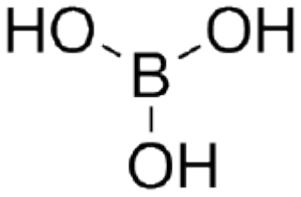
(b)

(c)



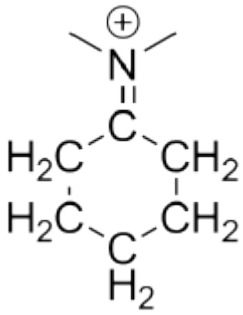


(d)



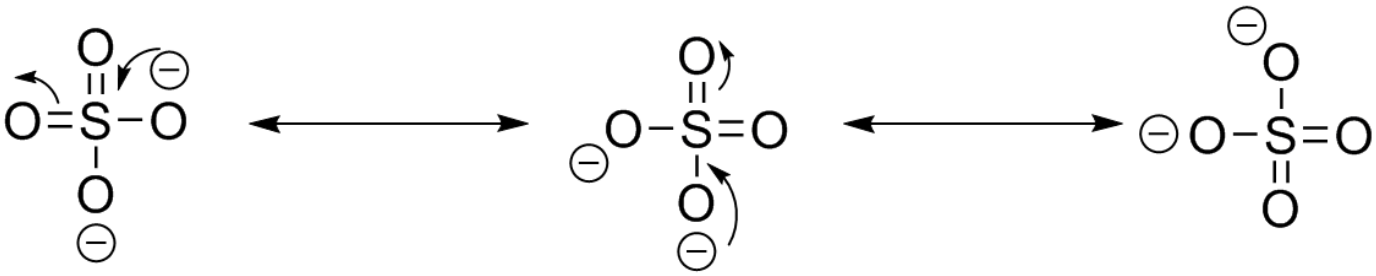
(e)

neutral (f)



S29

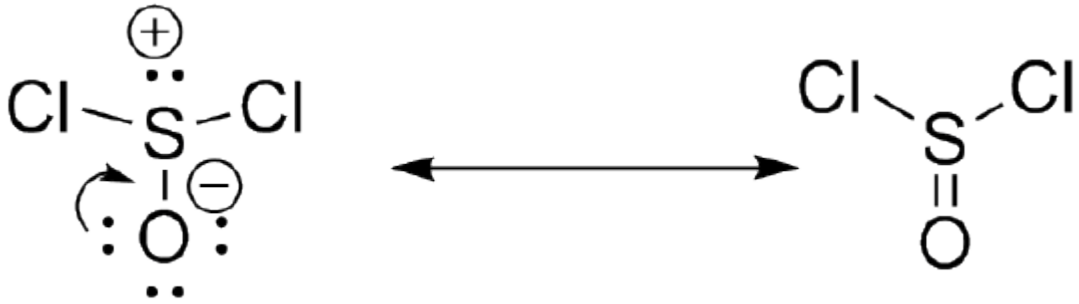
Sulfuric acid has two more possible resonance structures. Later, resonance/charge distribution will be mentioned; the resonance structures possible for the deprotonated sulfuric acid are one reason for why it is so strongly acidic.



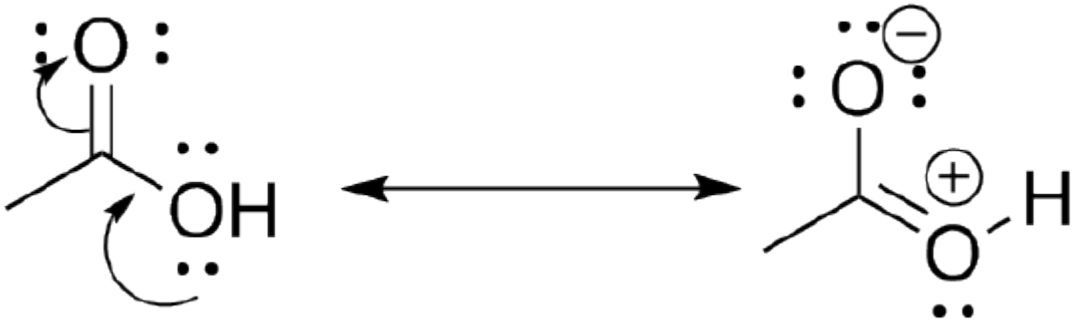
Acetic acid has one additional resonance structure possible, again a reason for its moderate acidity.



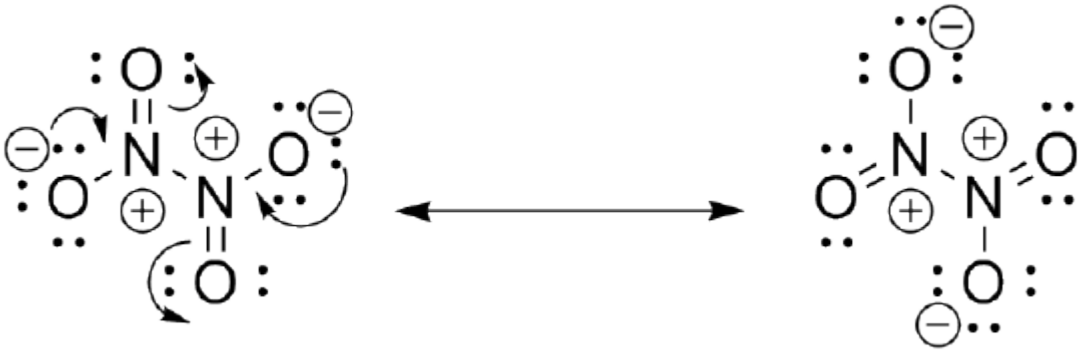
S30



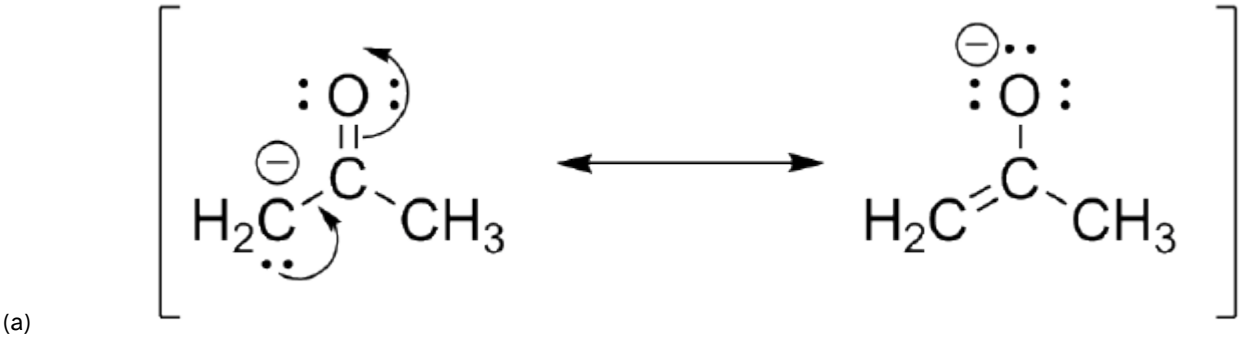
(c) The resonance structure with no charges is the major contributor.



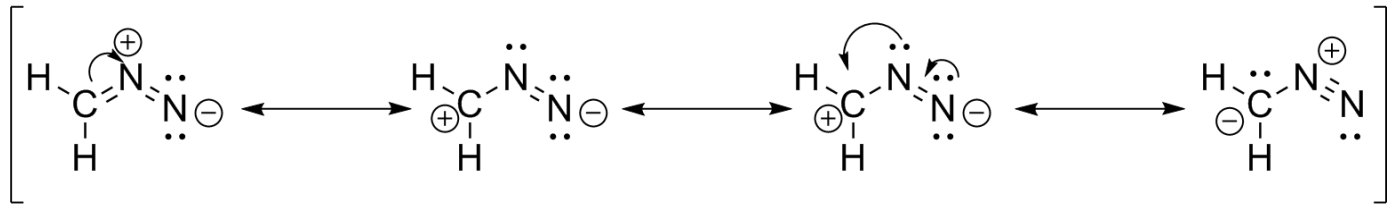
(h) Again, the resonance structure with no charges is the major contributor.



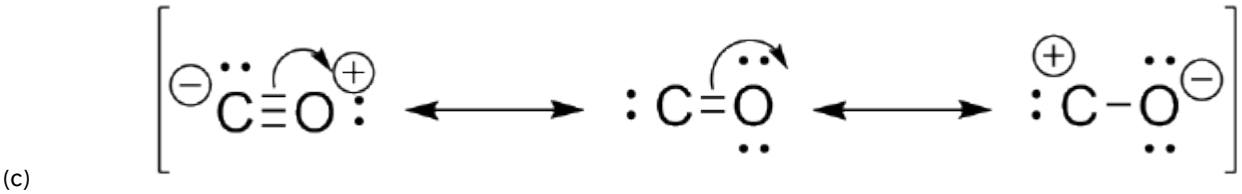
(i) Each resonance structure is equivalent, so there is no "major contributor".



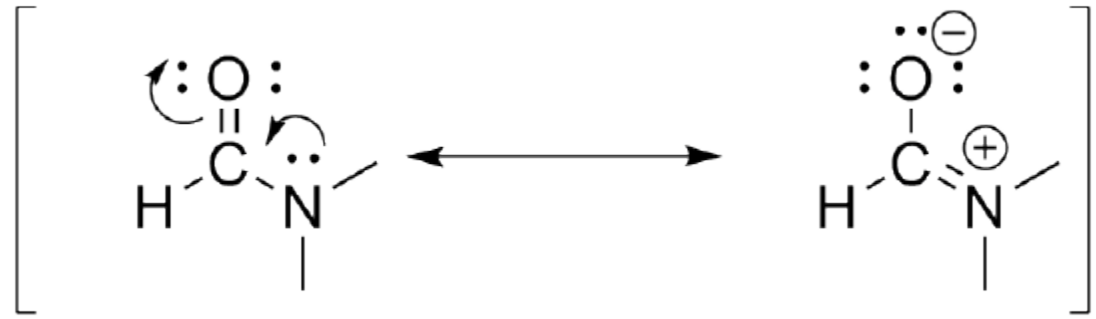
(a)



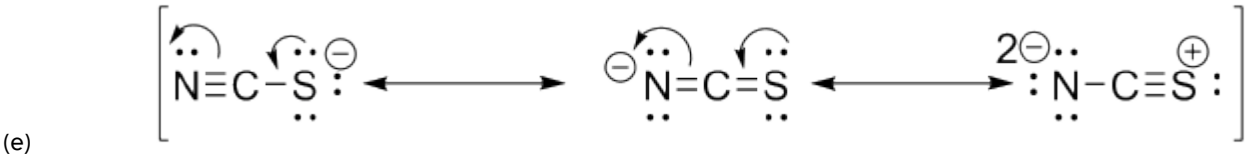
(b)



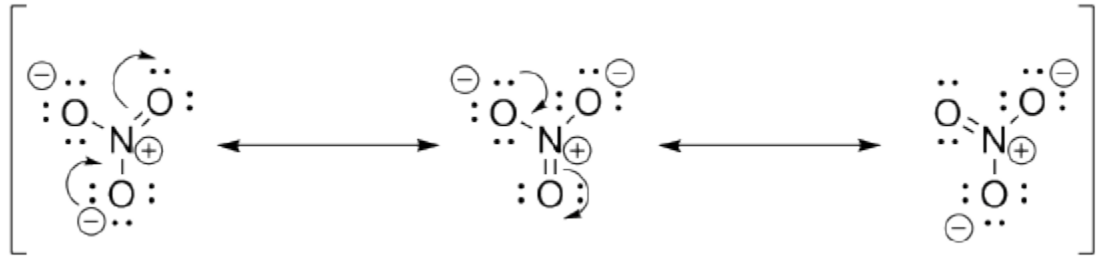
(c)



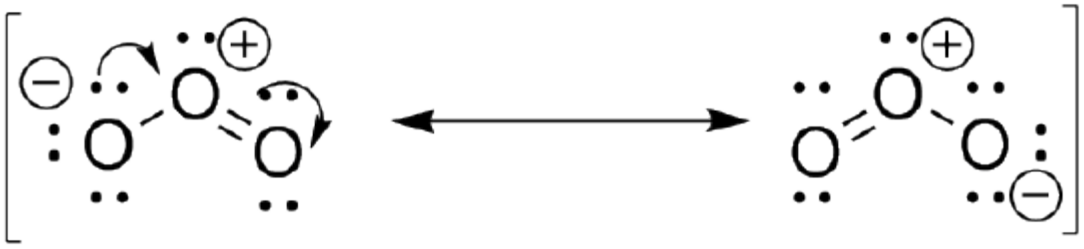
(d)



(e)

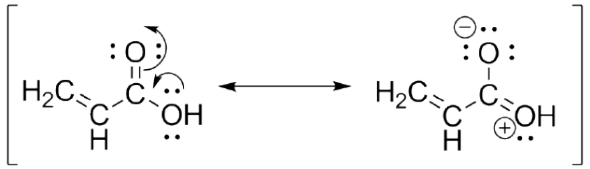


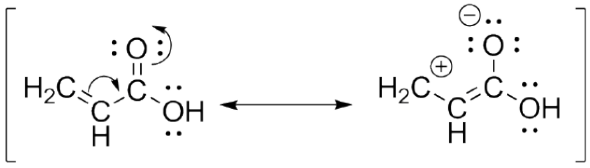
(f)

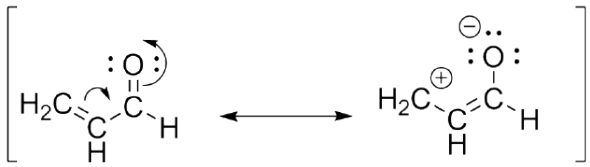


(g)

S32





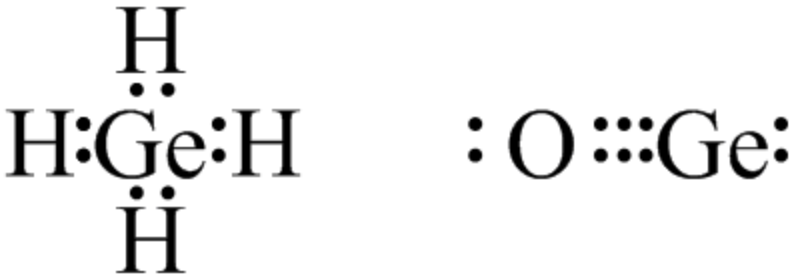


The first structure has two possible resonance structures, further distributing electrons more among the carbonyl carbon. However, the second structure only has one possible resonance structure. This distributes electrons to a lesser extent among the carbonyl carbon. Thus, in the second structure, the aldehyde, the carbon marked in red is more electron deficient than in the carboxylic acid.

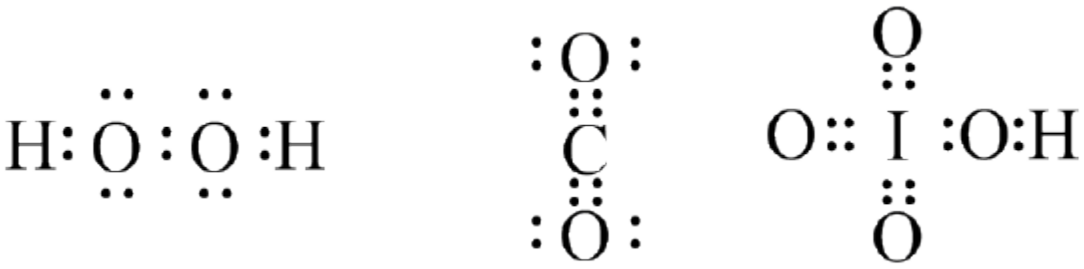
S33



(a) (b)



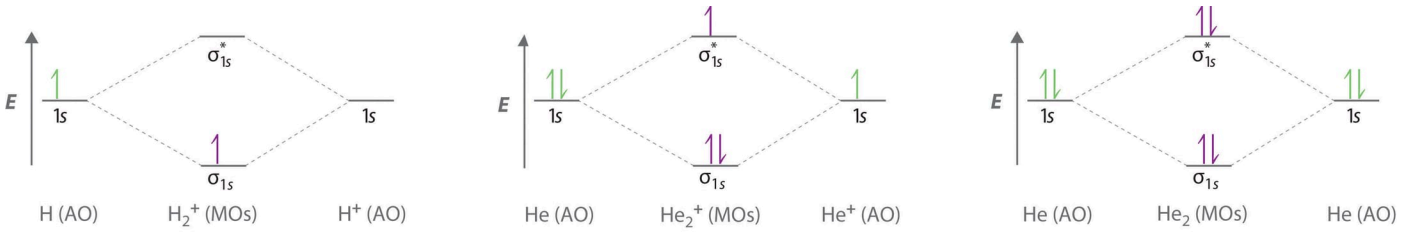
(c)



(d)



S34



H_2^+ has a bond order of 1/2, He_2^+ has a bond order of 1/2, and He_2 has a bond order of 0. The zero bond order indicates that He_2 is not favorable.

S35

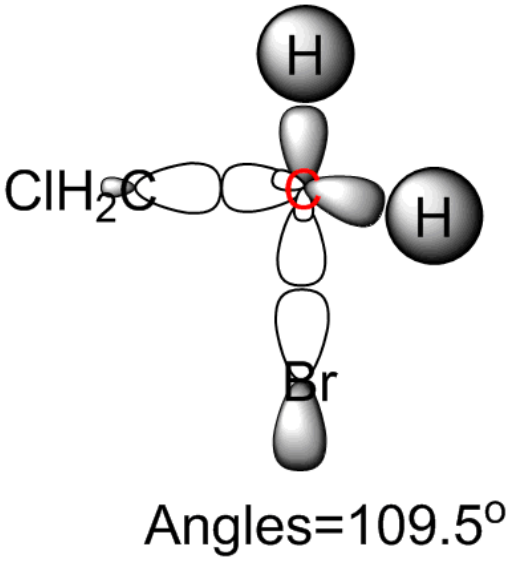
a. dichloroethane: The highlighted carbon center is tetrahedral with a hybridization of sp^3; it is bonded to four other groups.
b. acetic acid: The carbon center is trigonal planar with a hybridization of sp^2; it is bonded to three groups and has no lone pairs.
c. propene: The carbon center is trigonal planar with a hybridization sp^2; it is bonded to three groups and has no lone pairs.
d. acetylene: The carbon center is linear with a hybridization of sp; it is bonded to two groups with no lone pairs.
e. triethylamine: The nitrogen center is tetrahedral with a hybridization of sp^3; it is bonded to three groups with one lone pair.

f. triethylammonium ion: The nitrogen center is tetrahedral with a hybridization of sp^3; it is bonded to four groups with no lone pairs. All are sigma bonds.

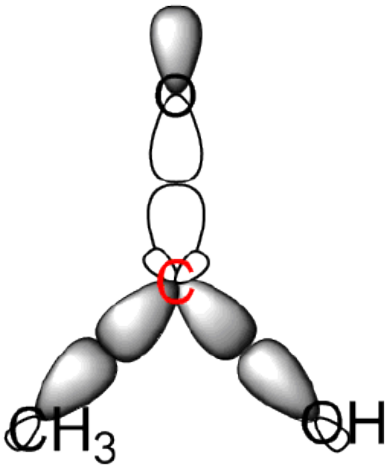
S36

a. The highlighted carbon forms bonds with one chlorine, two hydrogen atoms, and one other carbon. Each of these atoms connect to the central carbon forming sp^3-sp^3 hybridized orbitals. The carbon and hydrogen both use electrons from the s orbital, while the bonding electrons from the chlorine are from the p orbitals. All are sigma bonds.
b. The central carbon is sp^2 hybridized, and it is bonded to one carbon and two oxygen atoms. The bond to the carbon involves an sp^3-sp^2 overlap with the s orbital on the adjacent carbon involved in bonding, sigma bonding. The carbon oxygen double bond is slightly more complicated. The oxygen is less likely to undergo orbital hybridization. So, the C(sp^2)-O(p) sigma bond is formed along with the interaction of the second oxygen p orbital with the carbon p orbital to yield a pi bond. The carbon oxygen bond is similar forming a sigma bond through the C(sp^2)-O(p) interaction.
c. The central carbon is sp_2 hybridized and bonded to two other carbons and one hydrogen atom. The bond between the hydrogen atom involves the C(sp^2)-H(s) interaction yielding a sigma bond. The C=C double bond involves the C(sp^2)-C(sp^2) interaction creating a pi bond. The C-C single bond is a sigma bond involving the C(sp^2)-C(sp^3) hybrid orbitals.
d. The highlighted carbon is bonded to one hydrogen and one carbon atom. The C-H single bond is made up of the C(sp)-H(s) interaction yielding a sigma bond. The C-C triple bond is made up of the C(sp)-C(sp) hybrid orbitals yielding a sigma bond, s orbitals, and two pi bonds, using the two p orbitals.
e. The highlighted nitrogen is bonded to three identical carbon groups and has one lone pair. Each of the carbon atoms is sp^3 hybridized. So, a N(sp^3)-C(sp^3) yields a sigma bond.
f. The highlighted nitrogen is bonded to three identical carbon atoms and one hydrogen. There are no lone pairs on the nitrogen, and it is sp^3 hybridized. The N-C bonds are the same as in part (e), N(sp^3)-C(sp^3) yielding a sigma bond. The N-H bond is formed from the N(sp^3)-H(s) interaction, also a sigma bond.

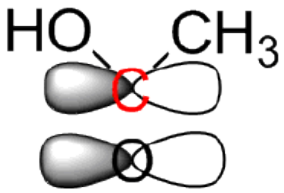
S37



(a) (b)

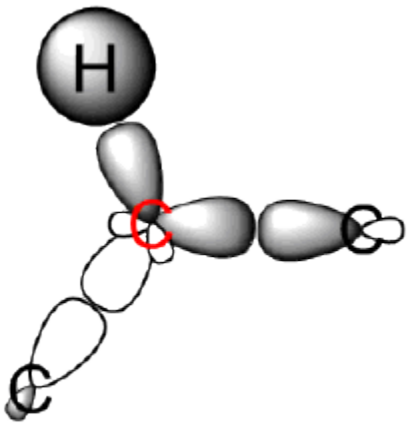


Sigma Bonding

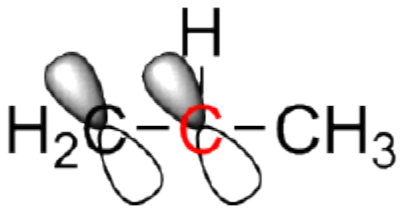


Pi Bonding

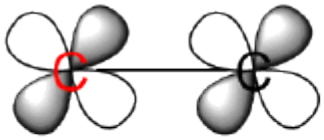
(c)



Sigma Bonding

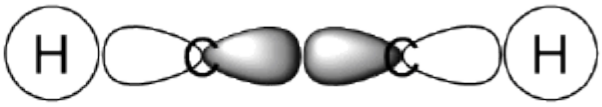


Pi Bonding



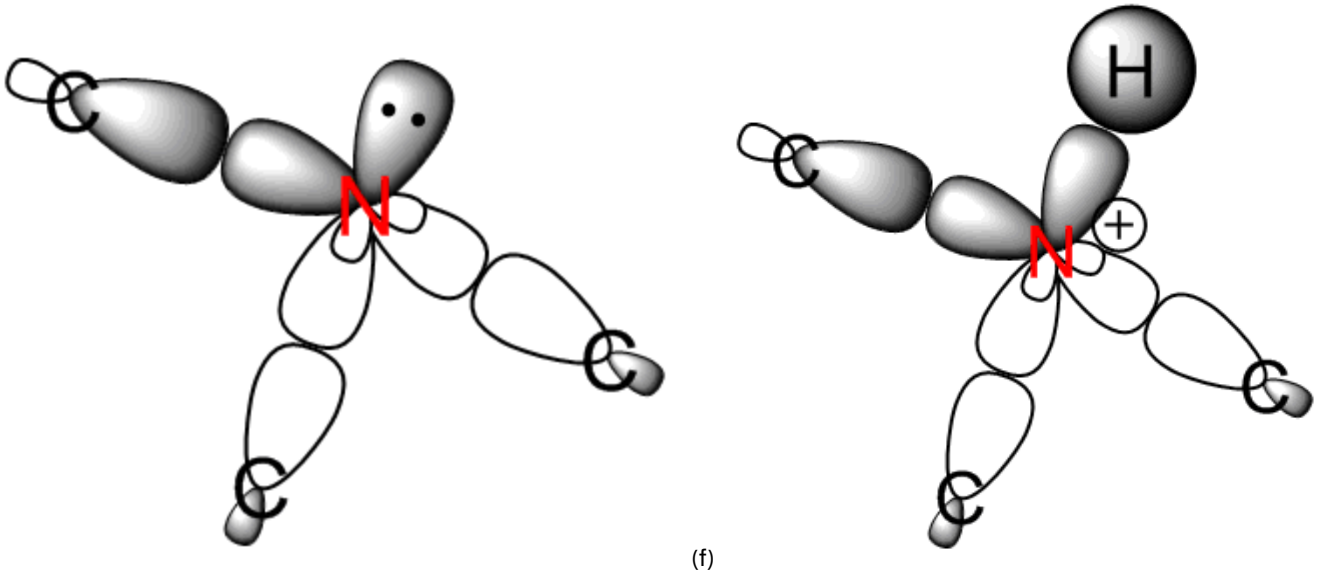
Two Pi Bonds
Stack on Top

(d)



Sigma Bonding

(e)



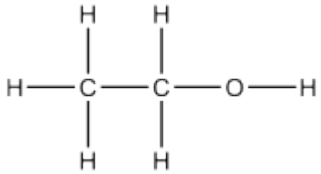
(f)

S38

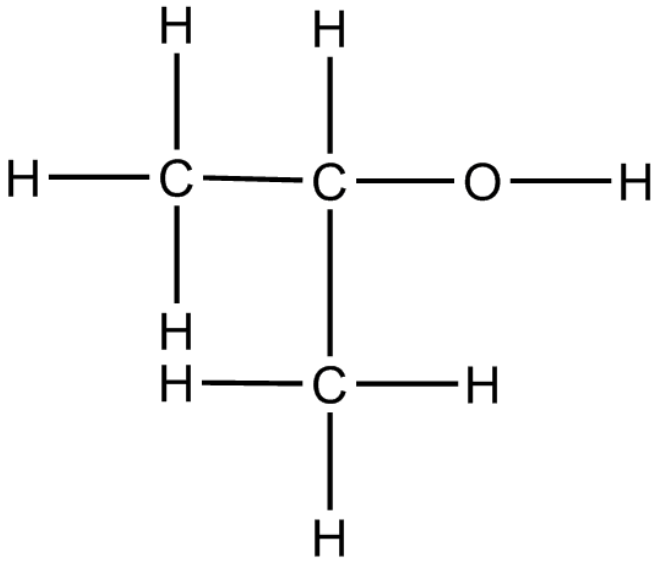
Each carbon's hybridization is listed from left to right in the chemical formula.

a. tetrahedral, sp^3
b. tetrahedral, sp^3 ; tetrahedral, sp^3
c. tetrahedral, sp^3 ; linear, sp ; linear, sp
d. tetrahedral, sp^3
e. tetrahedral, sp^3

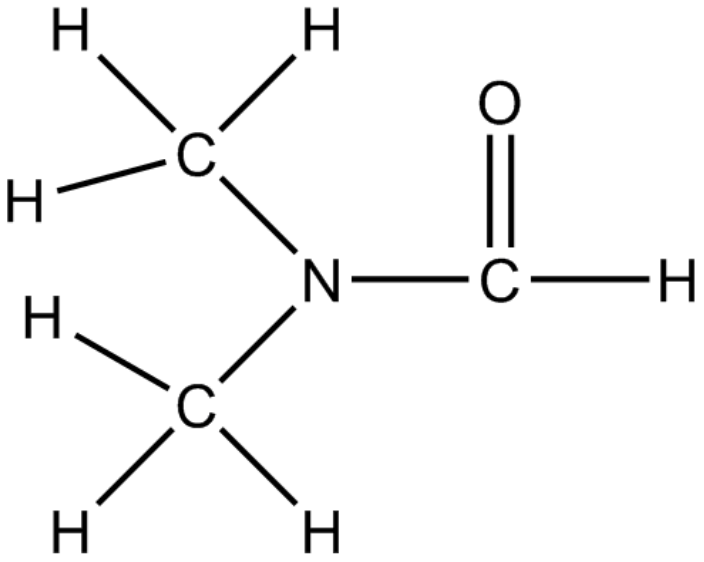
S39



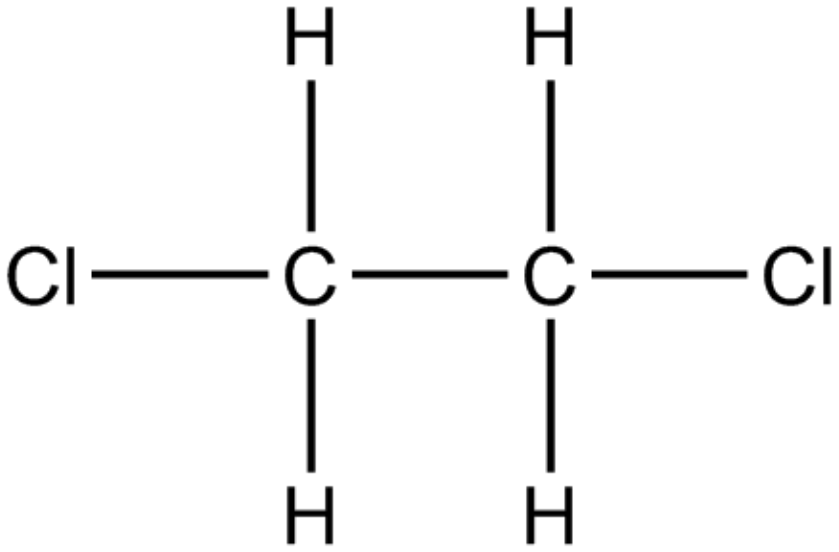
(a)



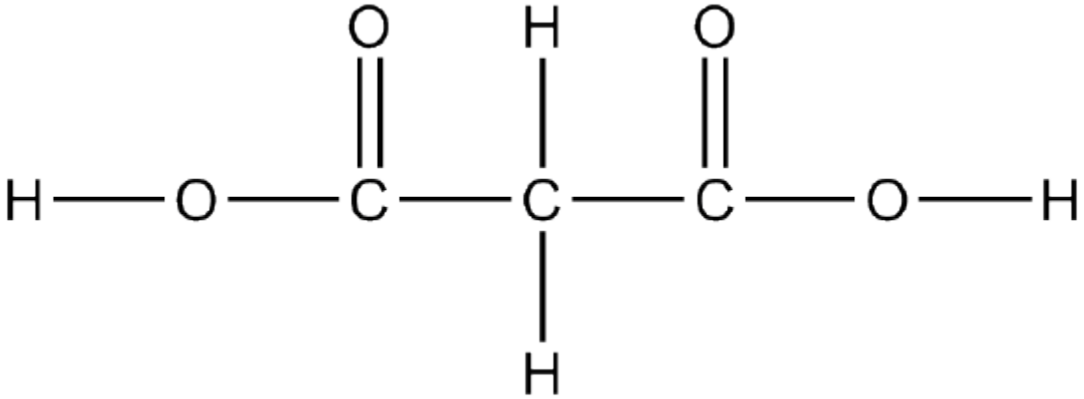
(b) (c)



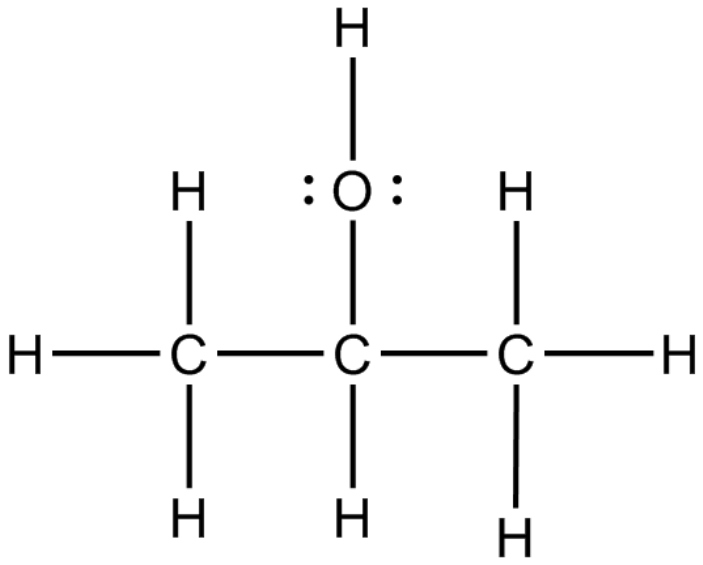
(d)



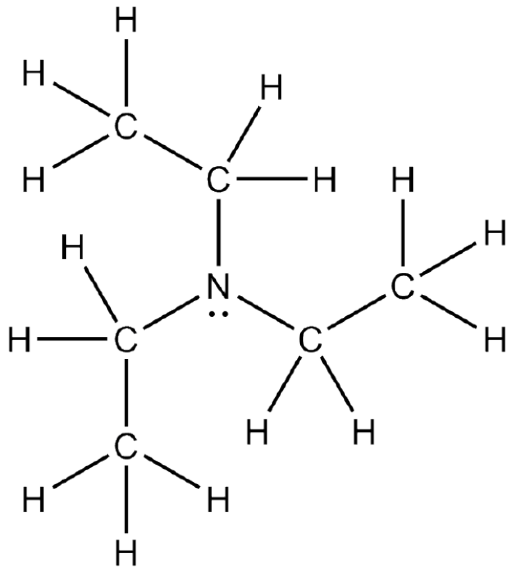
(e)



S40

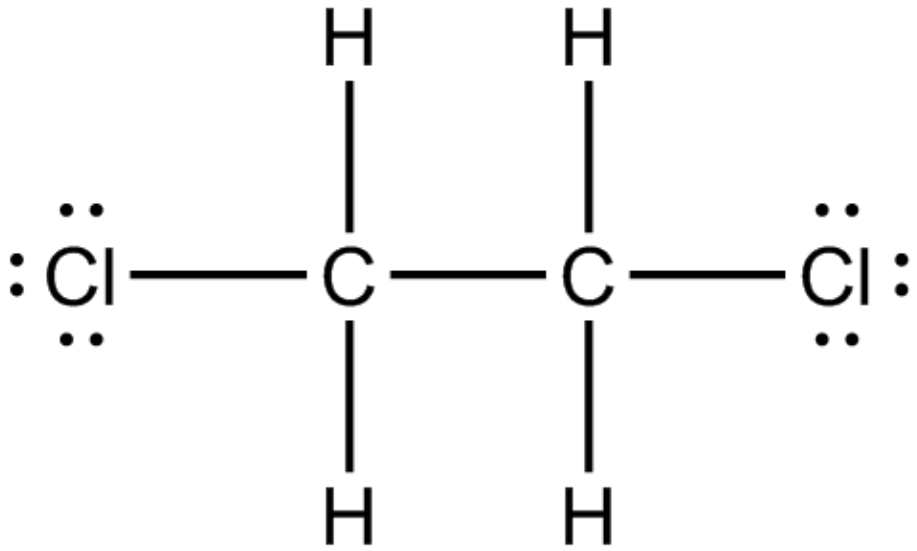


(a)

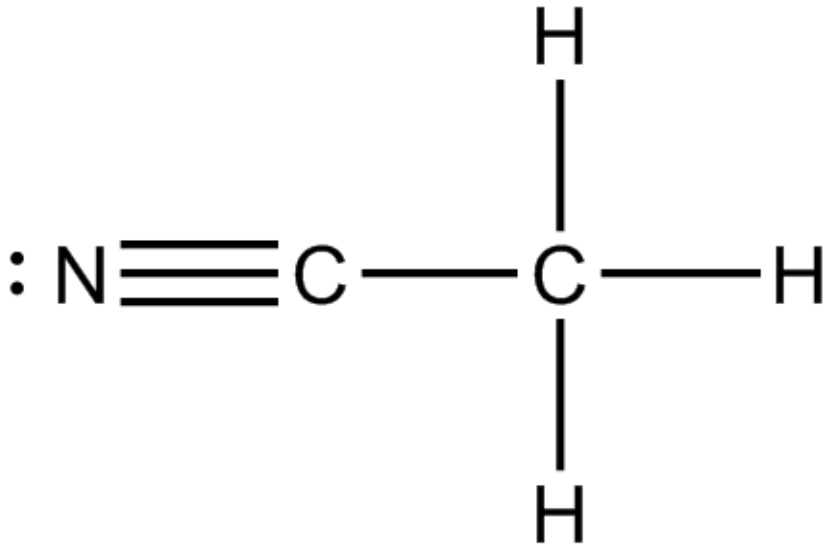


(b)

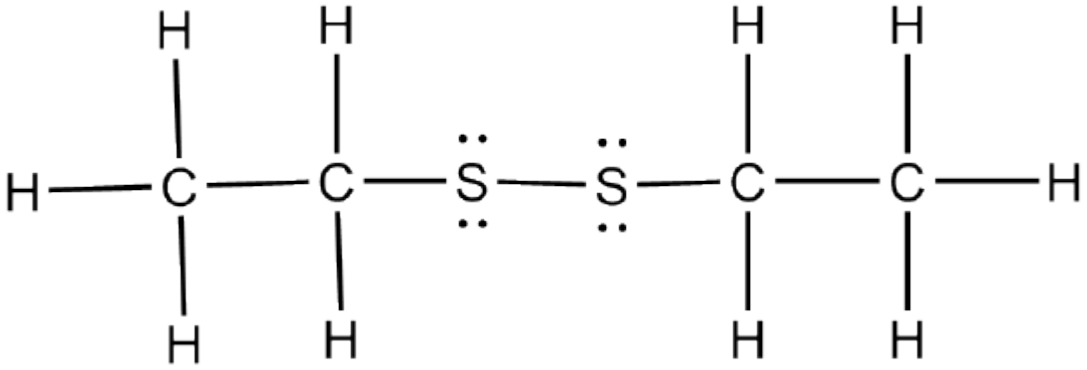
(c)



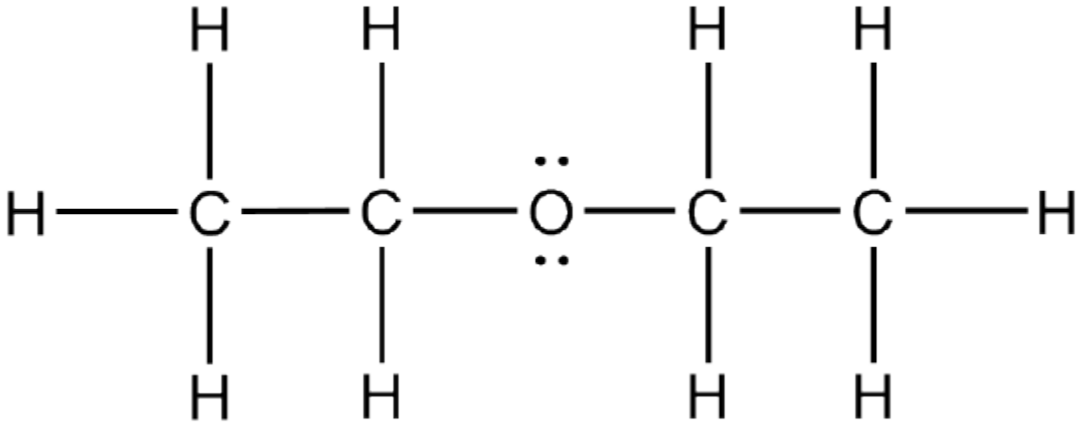
(d)



(e)



(f)



S41

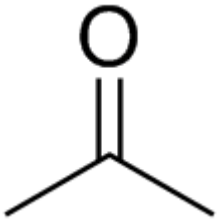
(a) $(CH_3)_2CHNH_2$ (b) $CClH_2CH_2Cl$ (c) CH_3I

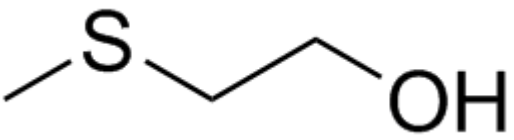
S42

(a) $CH_3CH_2NH_2$ (b) CH_3 C=O CH_3 (c) $CH_3SCH_2C_2OH$ (d) $CF_3CHOHCF_3$ (e) CH_2CCH_2 (f) CH_2CH C=O OCH_3

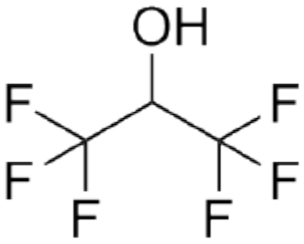
S43

(a)

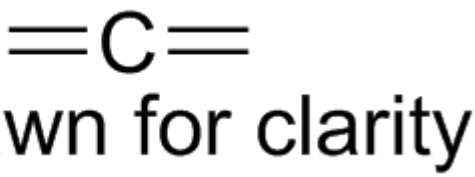
(b) 

(c) 

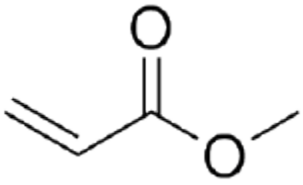
(d)



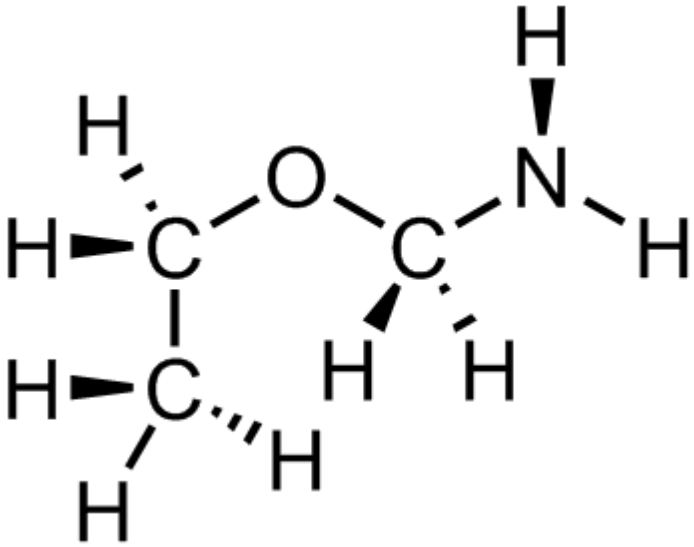
(e)

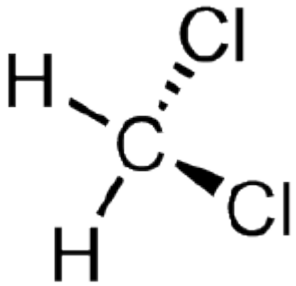


(f)

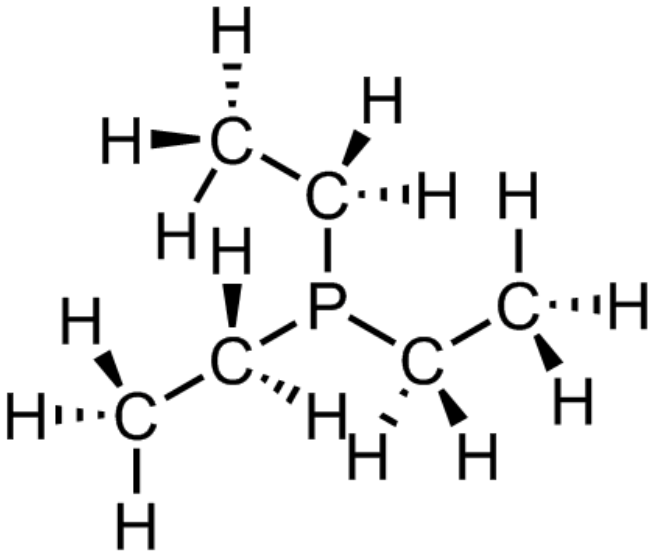


S44

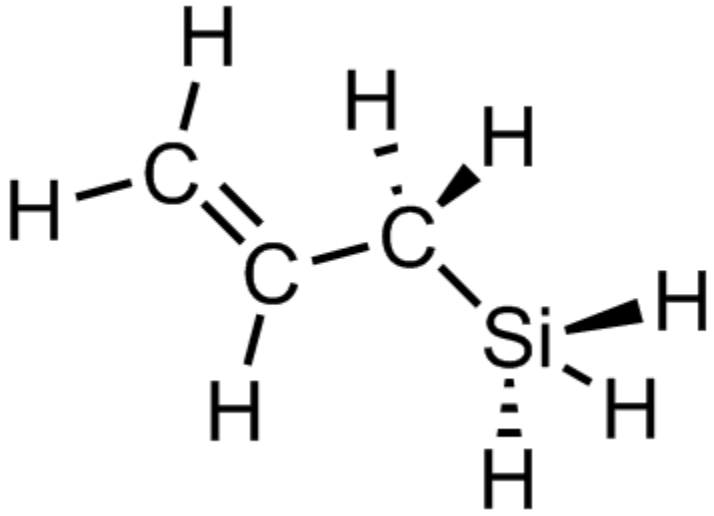
(a) 

(b) 

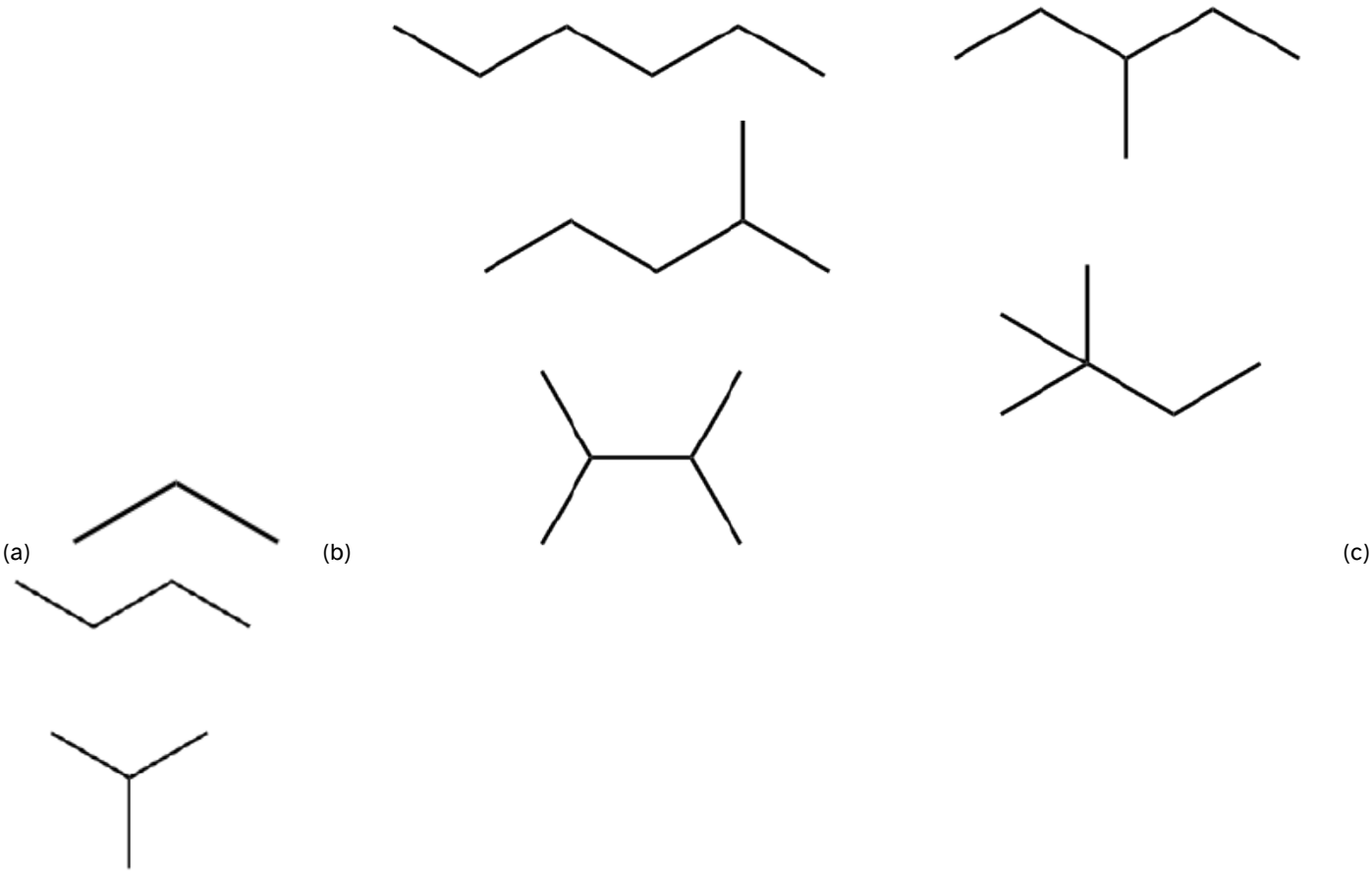
(c)



(d)



S45



S46

(a) 46as.png the two structures are identical (b) 46b.png These are not resonance structures; there additional H atoms. (c) 46c.png These are not resonance structures; there are three additional H atoms.

S47

47a.png In each case the double bonded resonance structure is preferred, due to the octet rule being fulfilled.

The lowest energy structure can be determined by thinking about the electronegativity of each halogen atom. The higher the electronegativity, the less favorable a positive charge is. The order of the electronegativity is as follows, F>Cl>Br, and so the reverse is the order of favorability. $(CH_3)_2BF$ (b) $(CH_3)_2BCl$ (c) $(CH_3)_2BBr$

S48

Triangle- 60^o Square- 90^o Pentagon- 108^o Hexagon- 120^o

This would lead to the expectation that the order of favorability is Pentagon>Square>Hexagon>Triangle. However, the order differs and is in fact Hexagon>Pentagon>Square>Triangle.

In reality this is due to different conformations of the shapes, so that the hexagon and pentagon are no longer flat/planar. This will be covered in more detail later on.

S49

$CH_3CH_2CH_2^-$ - sp^3 CH_3CHCH^- - sp^2 CH_3CC^- - sp

The order of energy is as follows, or increasing p character. $CH_3CC^-3CHCH^-3CH_2CH_2^-$

The reaction would be most favorable if the A^- is lowest in energy, so, the order of favorability is the reverse of above. $CH_3CH_2CH_2^-3CHCH^-3CC^-$

S50

(a) CCl_4

(b) $ClCH_2OCH_2Cl$

(c) $(CH_3)_3C^+$ The additional hydrocarbons on the ethyl group do marginally hyperconjugate and donate electrons to the center carbon, making it less electropositive.

S51

(a) 51a.png In this structure any sp^3 carbon connected to a heteroatom would be a polarized bond.

(b) 51b.png In this structure this is the only highly polarized double bond.

(c) 51c.png Any double bonded carbon could be considered sp^2 hybridized.

(d) 51d.png This is the only sp hybridized carbon.

(e)51e.png These two benzene rings are conjugated system.

S52

The hybridization changes from sp^2 to sp^3.

S53

(d) 84/12=7 Carbon and 14/1=14 Hydrogen

S54

(d) is correct, boron typically has 3 valence electrons. It currently is bonded to four different atoms; it has an octet. 8/2=4 electrons, and 3-4=-1 formal charge.

S55

The bond is formed by the interaction between the s orbital of the hydrogen and the sp^2 orbital of the carbon.

S56

(b) This is the only sp^3 hybridized highlighted carbon, characterized by bond angles of 104.5^o. Which is less than both sp^2 and sp, 120^o and 180^o respectively.

S57

(c) The number of electrons is the same and all atoms are in the same locations. Placement of charges is important to look at; in the pairs with no charges present then some atoms were moved around.

1.9: Structures and Formulas of Organic Molecules

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2: STRUCTURE AND REACTIVITY: ACIDS AND BASES, POLAR AND NONPOLAR MOLECULES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

2.1: Kinetics and Thermodynamics of Simple Chemical Processes

2.2: Keys to Success: Using Curved "Electron Pushing" Arrows to Describe Chemical Reactions

2.3: Acids and Bases; Electrophiles and Nucleophiles

2.4: Functional Groups: Centers of Reactivity

2.5: Straight-Chain and Branched Alkanes

2.6: Naming the Alkanes

2.7: Structural and Physical Properties of Alkanes

2.8: Rotation about Single Bonds: Conformations

2.9: Rotation in Substituted Ethanes

2.E: Structure and Reactivity: Acids and Bases, Polar and Nonpolar Molecules (Exercises)

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2.1: Kinetics and Thermodynamics of Simple Chemical Processes

Equilibrium Constant

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD \tag{6.5.1}$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b} \tag{6.5.2}$$

The notation [A] signifies the molar concentration of species A. An alternative expression for the equilibrium constant involves partial pressures:

$$K_P = \frac{P_C^c P_D^d}{P_A^a P_B^b} \tag{6.5.3}$$

Note that the expression for the equilibrium constant includes only solutes and gases; pure solids and liquids do not appear in the expression. For example, the equilibrium expression for the reaction

$$CaH_2(s) + 2H_2O(g) \rightleftharpoons Ca(OH)_2(s) + 2H_2(g) \tag{6.5.4}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2} \tag{6.5.5}$$

Observe that the gas-phase species H_2O and H_2 appear in the expression but the solids CaH_2 and $Ca(OH)_2$ do not appear.

The equilibrium constant is most readily determined by allowing a reaction to reach equilibrium, measuring the concentrations of the various solution-phase or gas-phase reactants and products, and substituting these values into the Law of Mass Action.

Gibbs Energy

The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called **Free Energy** (or Gibbs Free Energy), symbol **ΔG**, is defined as shown in the first equation below. Two things should be apparent from this equation. First, in cases where the entropy change is small, ΔG ≅ ΔH. Second, the importance of ΔS in determining ΔG increases with increasing temperature.

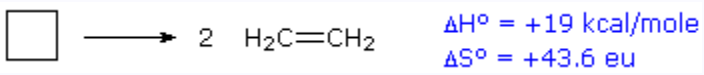
$$\Delta G^{o} = \Delta H^{o} – T\Delta S^{o} \tag{6.5.6}$$

where T is the absolute temperature measured in kelvin.

The free energy function provides improved insight into the thermodynamic driving forces that influence reactions. A negative ΔG° is characteristic of an **exergonic reaction**, one which is thermodynamically favorable and often spontaneous, as is the melting of ice at 1 °C. Likewise a positive ΔG° is characteristic of an **endergonic reaction**, one which requires an input of energy from the surroundings.

Example 6.5.1: Decomposition of Cyclobutane

For an example of the relationship of free energy to enthalpy consider the decomposition of cyclobutane to ethene, shown in the following equation. The standard state for all the compounds is gaseous.



This reaction is endothermic, but the increase in number of molecules from one (reactants) to two (products) results in a large positive ΔS°.

At 25 °C (298 °K), ΔG° = 19 kcal/mol – 298(43.6) cal/mole = 19 – 13 kcal/mole = +6 kcal/mole. Thus, the entropy change opposes the enthalpy change, but is not sufficient to change the sign of the resulting free energy change, which is endergonic. Indeed, cyclobutane is perfectly stable when kept at room temperature.

Because the entropy contribution increases with temperature, this energetically unfavorable transformation can be made favorable by raising the temperature. At 200 °C (473 °K), ΔG° = 19 kcal/mol – 473(43.6) cal/mole = 19 – 20.6 kcal/mole = –1.6 kcal/mole. This is now an exergonic reaction, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

$$\Delta G^o = -RT \ln K = -2.303 RT \log K \tag{2.1.1}$$

with

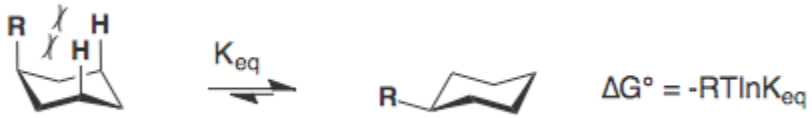
- R = 1.987 cal/ °K mole
- T = temperature in °K
- K = equilibrium constant

A second equation, shown above, is important because it demonstrates the fundamental relationship of ΔG° to the equilibrium constant, K. Because of the negative logarithmic relationship between these variables, a negative ΔG° generates a K>1, whereas a positive ΔG° generates a K<1. When ΔG° = 0, K = 1. Furthermore, small changes in ΔG° produce large changes in K. A change of 1.4 kcal/mole in ΔG° changes K by approximately a factor of 10. This interrelationship may be explored with the calculator on the right. Entering free energies outside the range -8 to 8 kcal/mole or equilibrium constants outside the range 10-6 to 900,000 will trigger an alert, indicating the large imbalance such numbers imply.

Substituted Cyclohexanes

A Values

Substituents on a cyclohexane prefer to be in the equatorial position. When a substituent is in the axial position, there are two gauche butane interactions more than when a substituent is in the equatorial position. We quantify the energy difference between the axial and equatorial conformations as the A-value, which is equivalent to the negative of the ΔG°, for the equilibrium shown below. Therefore the A-value, or -ΔG°, is the preference for the substituent to sit in the equatorial position.



Recall that the equilibrium constant is related to the change in Gibbs Energies for the reaction:

$$\Delta G^o = -RT \ln K_{eq} \tag{2.1.2}$$

The balance between reactants and products in a reaction will be determined by the free energy difference between the two sides

of the reaction. The greater the free energy difference, the more the reaction will favor one side or the other (Table 6.5.1).

***Table 6.5.1**: Below is a table of A-values for some common substituents.*

Substituent	ΔG° (kcal/mol)	A-value
-F	-0.28-0.24	0.24-0.28
-Cl	-0.53	0.53
-Br	-0.48	0.48
-I	-0.47	0.47
$-CH_3$ (-Me)	-1.8	1.8
$-CH_2CH_3$ (-Et)	-1.8	1.8
$-CH(CH_3)_2$ (-*i*-Pr)	-2.1	2.1
$-C(CH_3)_3$ (-*t*-Bu)	<-4.5	>4.5
$-CHCH_2$	-1.7	1.7
-CCH	-0.5	0.5
-CN	-0.25-0.15	0.15-0.25
$-C_6H_5$ (-Ph)	-2.9	2.9

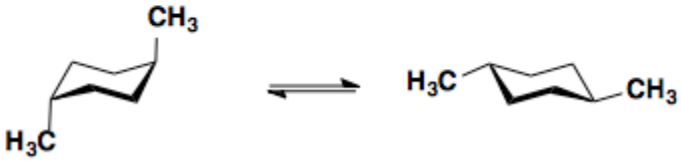
Polysubstituted Cyclohexanes

1,4-disubstitution

The A-values of the substituents are roughly additive in either the *cis*- or *trans*-diastereomers.



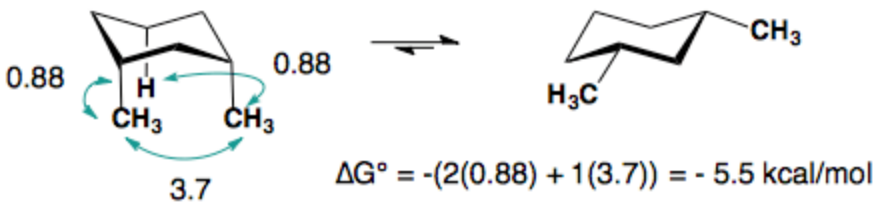
ΔG° = 0 kcal/mol



ΔG° = -2(1.74)= -3.48 kcal/mol

1,3-disubstitution

A-values are only additive in the *trans*-diastereomer:



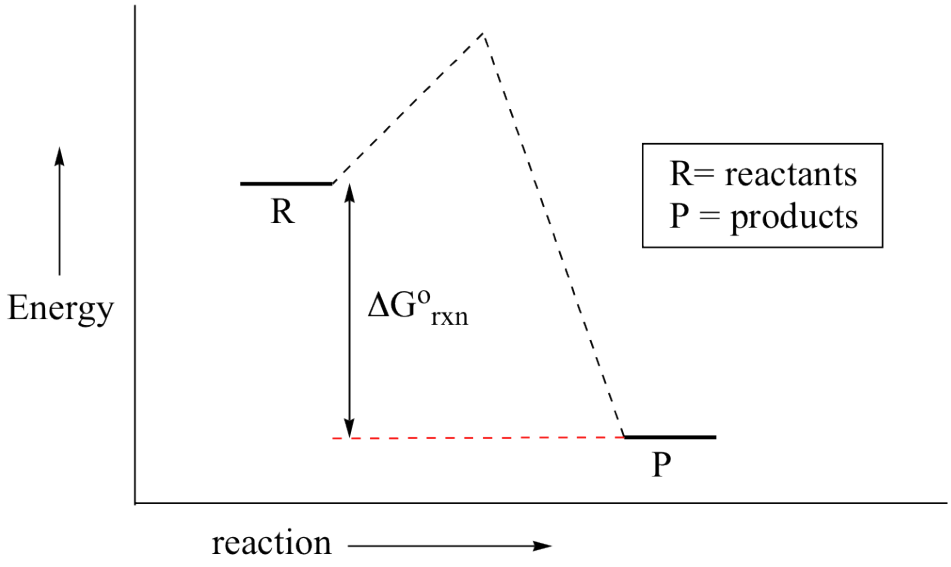
When there are *cis*-substituents on the chair, there is a new interaction in the di-axial conformation:

In the above example, each methyl group has one 1,3-diaxial interaction with a hydrogen. The methyl groups also interact with each other. This new diaxial interaction is extremely unfavorable based on their steric interaction (see: double-gauche pentane conformation).

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

You may recall from general chemistry that it is often convenient to describe chemical reactions with energy diagrams. In an energy diagram, the vertical axis represents the overall energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting compounds to final products. The energy diagram for a typical one-step reaction might look like this:



Despite its apparent simplicity, this energy diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the **thermodynamics** of a reaction, we are concerned with the difference in energy between reactants and products, and whether a reaction is 'downhill' (exergonic, energy releasing) or 'uphill (endergonic, energy absorbing). When we talk about **kinetics**, on the other hand, we are concerned with the *rate* of the reaction, regardless of whether it is uphill or downhill thermodynamically.

First, let's review what this energy diagram tells us about the thermodynamics of the reaction illustrated by the energy diagram

above. The energy level of the products is *lower* than that of the reactants. This tells us that the change in standard Gibbs Free Energy for the reaction (ΔG°_{rnx}) is negative. In other words, the reaction is exergonic, or 'downhill'. Recall that the ΔG°_{rnx} term encapsulates both ΔH°_{rnx}, the change in enthalpy (heat) and ΔS°_{rnx} , the change in entropy (disorder):

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{2.1.3}$$

where T is the absolute temperature in Kelvin. For chemical processes where the entropy change is small (~0), the enthalpy change is essentially the same as the change in Gibbs Free Energy. Energy diagrams for these processes will often plot the enthalpy (H) instead of Free Energy for simplicity.

The standard Gibbs Free Energy change for a reaction can be related to the reaction's equilibrium constant (\(K_{eq}_) by a simple equation:

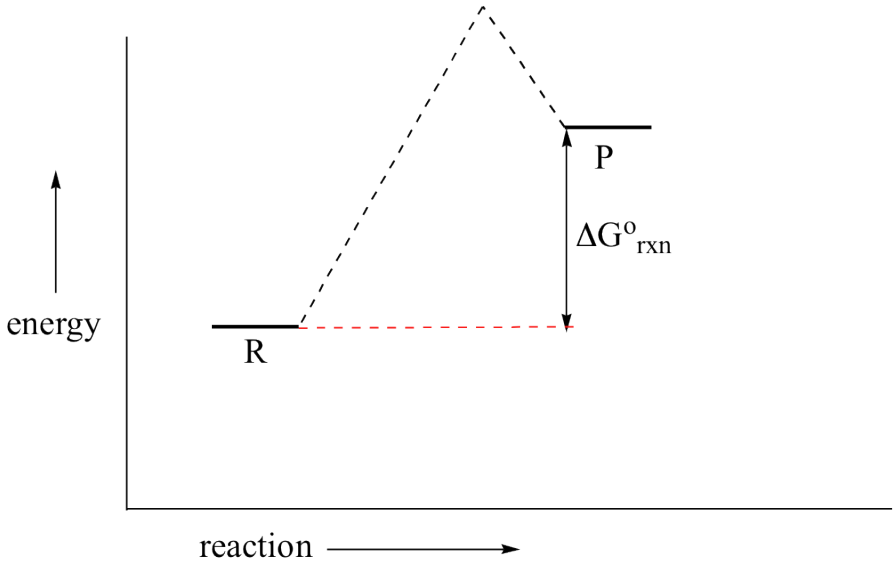
$$\Delta G^\circ = -RT \ln K_{eq} \tag{2.1.4}$$

where:

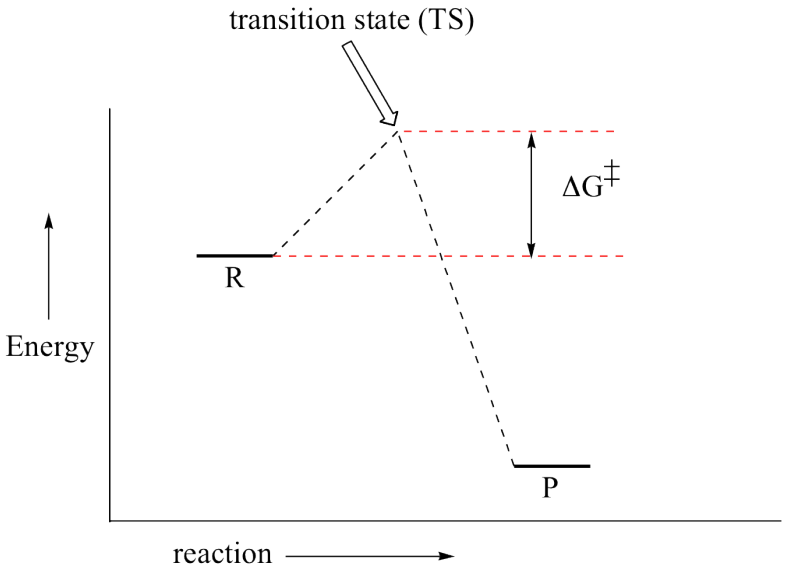
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 $J \times K^{-1} \times mol^{-1}$ *or* 1.987 $cal \times K^{-1} \times mol^{-1}$
- T = temperature in Kelvin (K)

If you do the math, you see that a negative value for ΔG°_{rnx} (an exergonic reaction) corresponds - as it should by intuition - to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

In a hypothetical endergonic (energy-absorbing) reaction the products would have a higher energy than reactants and thus ΔG°_{rnx} would be positive and K_{eq} would be less than 1, favoring reactants.

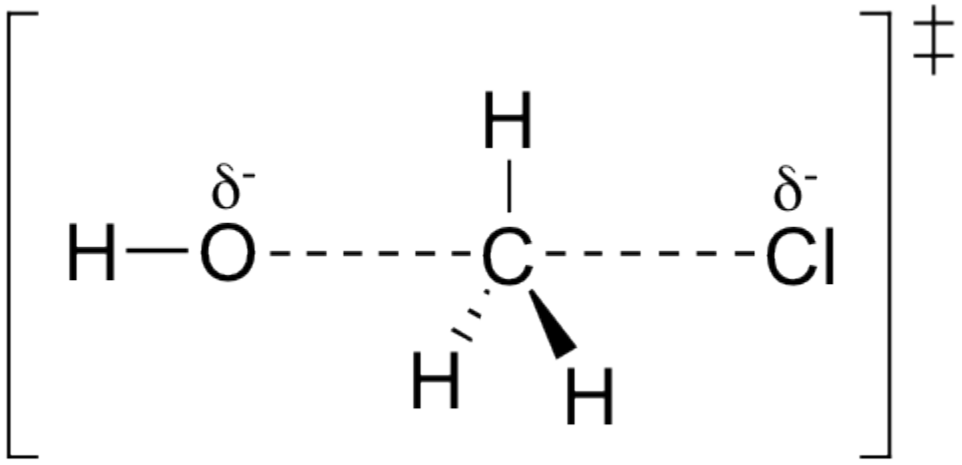


Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier, you may recall, is called the '**activation energy'** ($\Delta G^{\ddagger}$). The activation energy is what determines the kinetics of a reaction: the higher the energy hill, the slower the reaction. At the very top of the energy barrier, the reaction is at its **transition state** (TS), which is the point at which the bonds are in the process of breaking and forming. The transition state is an '**activated complex'**: a transient and dynamic state that, unlike more stable species, does not have any definable lifetime. It may help to imagine a transition state as being analogous to the exact moment that a baseball is struck by a bat. Transition states are drawn with dotted lines representing bonds that are in the process of breaking or forming, and the drawing is often enclosed by brackets. Here is a picture of a likely transition state for a substitution reaction between hydroxide and chloromethane:

$$CH_3Cl + HO^- \rightarrow CH_3OH + Cl^- \tag{2.1.5}$$



This reaction involves a collision between *two* molecules: for this reason, we say that it has **second order kinetics**. The **rate expression** for this type of reaction is:

rate = *k*[reactant 1][reactant 2]

. . . which tells us that the rate of the reaction depends on the **rate constant** *k* as well as on the concentration of *both* reactants. The rate constant can be determined experimentally by measuring the rate of the reaction with different starting reactant concentrations. The rate constant depends on the activation energy, of course, but also on temperature: a higher temperature means a higher *k* and a faster reaction, all else being equal. This should make intuitive sense: when there is more heat energy in the system, more of the reactant molecules are able to get over the energy barrier.

Here is one more interesting and useful expression. Consider a simple reaction where the reactants are A and B, and the product is AB (this is referred to as a **condensation reaction**, because two molecules are coming together, or condensing). If we know the rate constant *k* for the forward reaction and the rate constant $k_{reverse}$ for the reverse reaction (where AB splits apart into A and B), we can simply take the quotient to find our equilibrium constant K_{eq}:

$$A + B \rightleftharpoons AB \qquad K_{eq} = \frac{[AB]}{[A]\,[B]} = \frac{k_{forward}}{k_{reverse}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Further Reading

MasterOrganicChemistry

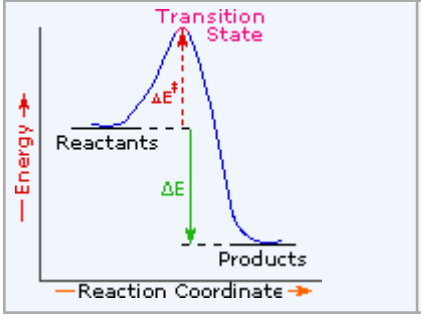
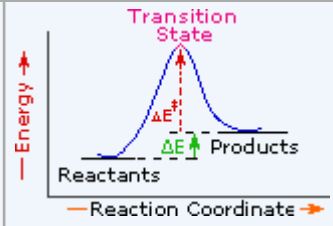
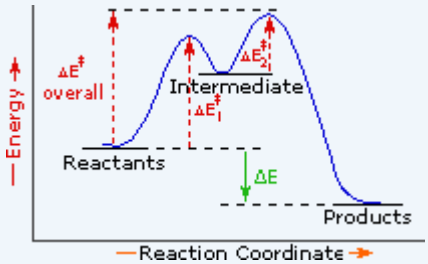
Equilibria

Websites

Reversible and irreversible reactions

Activation Energy

Since exothermic reactions are energetically (thermodynamically) favored, a careless thinker might conclude that all such reactions will proceed spontaneously to their products. Were this true, no life would exist on Earth, because the numerous carbon compounds that are present in and essential to all living organisms would spontaneously combust in the presence of oxygen to give carbon dioxide-a more stable carbon compound. The combustion of methane (eq.1), for example, does not occur spontaneously, but requires an initiating energy in the form of a spark or flame. The flaw in this careless reasoning is that we have focused only on the initial (reactant) and final (product) states of reactions. To understand why some reactions occur readily (almost spontaneously), whereas other reactions are slow, even to the point of being unobservable, we need to consider the intermediate stages of reactions.

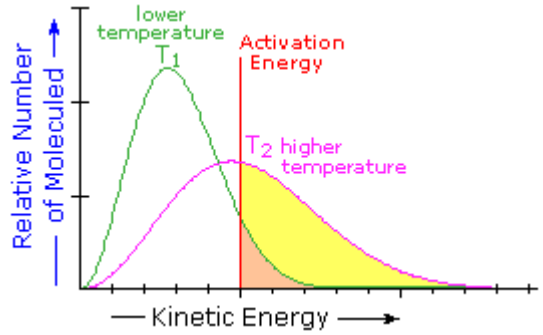
Exothermic **Single Step Reaction**	**Endothermic** **Single Step Reaction**	**Exothermic** **Two Step Reaction**
		

Every reaction in which bonds are broken will have a high energy **transition state** that must be reached before products can form. In order for the reactants to reach this transition state, energy must be supplied and reactant molecules must orient themselves

in a suitable fashion. The energy needed to raise the reactants to the transition state energy level is called the **activation energy, $\Delta E^{\ddagger}$**. An example of a single-step exothermic reaction profile is shown on the left above, and a similar single-step profile for an endothermic reaction is in the center. The activation energy is drawn in red in each case, and the overall energy change (ΔE) is in green.
The profile becomes more complex when a multi-step reaction path is described. An example of a two-step reaction proceeding by way of a high energy intermediate is shown on the right above. Here there are two transition states, each with its own activation energy. The overall activation energy is the difference in energy between the reactant state and the highest energy transition state. We see now why the rate of a reaction may not correlate with its overall energy change. In the exothermic diagram on the left, a significant activation energy must be provided to initiate the reaction. Since the reaction is strongly exothermic, it will probably generate enough heat to keep going as long as reactants remain. The endothermic reaction in the center has a similar activation energy, but this will have to be supplied continuously for the reaction to proceed to completion.

What is the source of the activation energy that enables a chemical reaction to occur? Often it is heat, as noted above in reference to the flame or spark that initiates methane combustion. At room temperature, indeed at any temperature above absolute zero, the molecules of a compound have a total energy that is a combination of translational (kinetic) energy, internal vibrational and rotational energies, as well as electronic and nuclear energies. The temperature of a system is a measure of the average kinetic energy of all the atoms and molecules present in the system. As shown in the following diagram, the average kinetic energy increases and the distribution of energies broadens as the temperature is raised from T_1 to T_2. Portions of this thermal or kinetic energy provide the activation energy for many reactions, the concentration of suitably activated reactant molecules increasing with temperature, e.g. orange area for T_1 and yellow plus orange for T_2. (Note that the area under a curve or a part of a curve is proportional to the number of molecules represented.)

Distribution of Molecular Kinetic Energy at Two Different Temperatures, T_1 & T_2



Reaction Rates and Kinetics

Chemical reactivity is the focus of chemistry, and the study of reaction rates provides essential information about this subject. Some reactions proceed so rapidly they seem to be instantaneous, whereas other reactions are so slow they are nearly unobservable. Most of the reactions described in this text take place in from 0.2 to 12 hours at 25 °C. Temperature is important, since fast reactions may be slowed or stopped by cooling, and slow reactions are accelerated by heating. When a reaction occurs between two reactant species, it proceeds faster at higher concentrations of the reactants. These facts lead to the following general analysis of reaction rates.

Reaction Rate =	**Number of Collisions between Reactant Molecules per Unit of Time**	•	**Fraction of Collisions with Sufficient Energy to pass the Transition State**	•	**an Orientational or Probability Factor**

Since reacting molecules must collide to interact, and the necessary activation energy must come from the kinetic energy of the colliding molecules, the first two factors are obvious. The third (probability) factor incorporates the orientational requirements of the reaction. For example, the addition of bromine to a double bond at the end of a six-carbon chain (1-hexene) could only occur if the colliding molecules came together in a way that allowed the bromine molecule to interact with the pi-electrons of the double bond.

The collision frequency of reactant molecules will be proportional to their concentration in the reaction system. This aspect of a reaction rate may be incorporated in a **rate equation**, which may take several forms depending on the number of reactants. Three general examples are presented in the following table.

Reaction Type	Rate Equation	Reaction Order
A ——> B	Reaction Rate = k•[A]	First Order Reaction (no collision needed)
A + B ——> C + D	Reaction Rate = k•[A]*[B]	Second Order Reaction
A + A ——> D	Reaction Rate = k•$[A]^2$	Second Order Reaction

These rate equations take the form **Reaction Rate = k[X] ^{n}[Y] ^{m}**, where the proportionality constant **k** reflects the unique characteristics of a specific reaction, and is called **the rate constant**. The concentrations of reactants X and Y are [X] and [Y] respectively, and **n** & **m** are exponential numbers used to fit the rate equation to the experimental data. The sum n + m is termed the **kinetic order** of a reaction. The first example is a simple first order process. The next two examples are second order reactions, since n + m = 2. The kinetic order of a reaction is usually used to determine its molecularity.

In writing a rate equation we have disconnected the collision frequency term from the activation energy and probability factors defined above, which are necessarily incorporated in the rate constant k. This is demonstrated by the following equation.

$$\text{Rate Constant (k)} = A\, e^{-\Delta E^{\ddagger}/RT}$$

The complex parameter A incorporates the probability factor. Because of the exponential relationship of k and the activation energy small changes in $\Delta E^{\ddagger}$ will cause relatively large changes in reaction rate. An increase in temperature clearly acts to increase k, but of greater importance is the increase in average molecular kinetic energy such an increase produces. This was illustrated in a previous diagram, increase in temperature from T_1 to T_2 producing a larger proportion of reactant molecules having energies equal or greater than the activation energy (designated by the red line.

Contributors

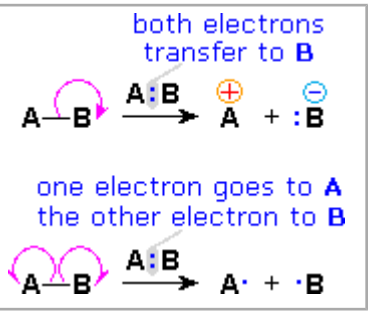
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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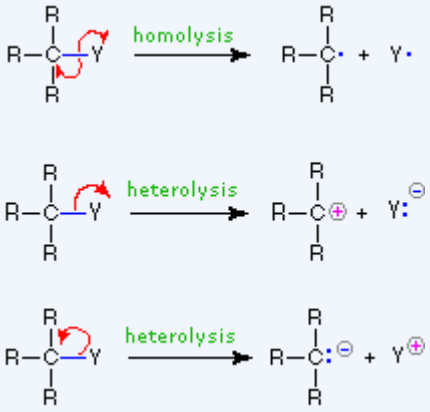
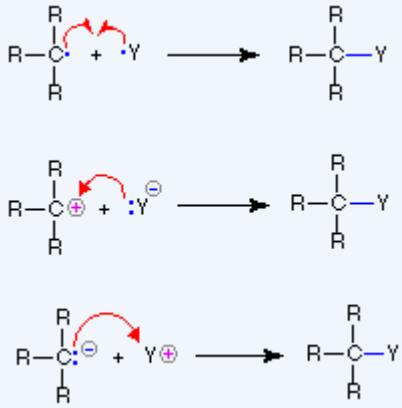
2.2: Keys to Success: Using Curved "Electron Pushing" Arrows to Describe Chemical Reactions

The Arrow Notation in Mechanisms

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

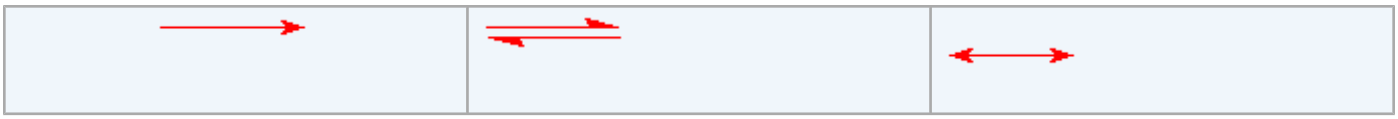
The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

Bond-Breaking	Bond-Making
	

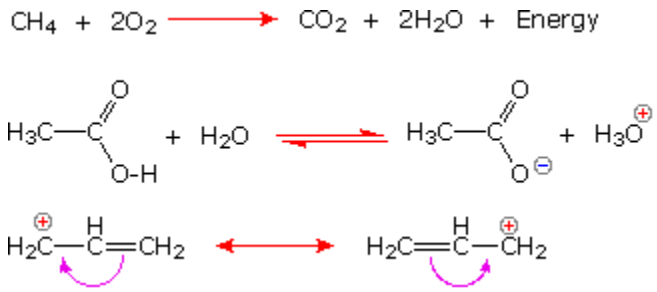
Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

The Reaction Arrow	**The Equilibrium Arrow**	**The Resonance Arrow**

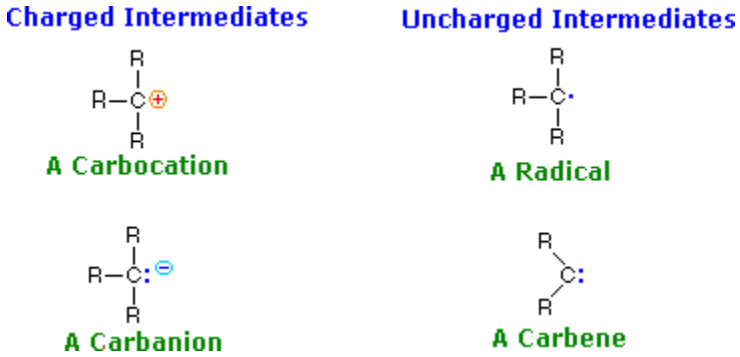


The following equations illustrate the proper use of these symbols:



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.



A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

> **Electrophile:** An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
> **Nucleophile:** An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined by Clicking Here

The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through

a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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2.3: Acids and Bases; Electrophiles and Nucleophiles

In 1923, chemists Johannes Brønsted and Martin Lowry independently developed definitions of acids and bases based on compounds abilities to either donate or accept protons (H^+ ions). Here, acids are defined as being able to donate protons in the form of hydrogen ions; whereas bases are defined as being able to accept protons. This took the Arrhenius definition one step further as water is no longer required to be present in the solution for acid and base reactions to occur.

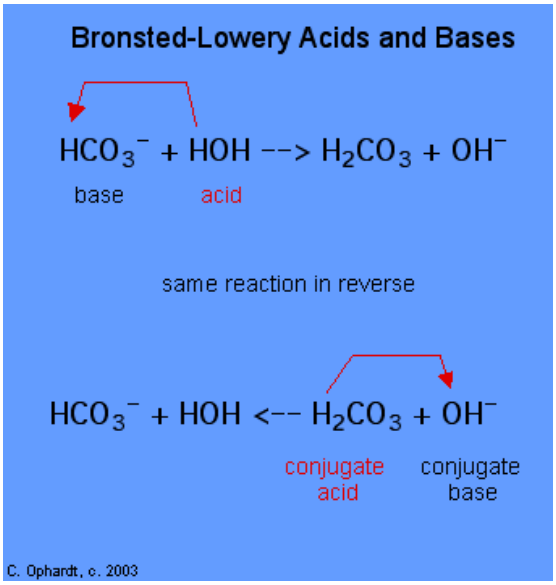
Brønsted-Lowery Definition

J.N. Brønsted and T.M. Lowry independently developed the theory of proton donors and proton acceptors in acid-base reactions, coincidentally in the same region and during the same year. The Arrhenius theory where acids and bases are defined by whether the molecule contains hydrogen and hydroxide ion is too limiting. The main effect of the Brønsted-Lowry definition is to identify the proton (H+) transfer occurring in the acid-base reaction. This is best illustrated in the following equation:

$$HA + Z \rightleftharpoons A^- + HZ^+ \tag{2.3.1}$$

Acid	Base	
Donates hydrogen ions	**Accepts hydrogen ions.**	
HCl^+	HOH →	$H_3O^+ + Cl^-$
HOH^+	NH_3 →	$NH_4^+ + OH^-$

The determination of a substance as a Brønsted-Lowery acid or base can only be done by observing the reaction. In the case of the HOH it is a base in the first case and an acid in the second case.



To determine whether a substance is an acid or a base, count the hydrogens on each substance before and after the reaction. If the number of hydrogens has decreased that substance is the acid (donates hydrogen ions). If the number of hydrogens has increased that substance is the base (accepts hydrogen ions). These definitions are normally applied to the reactants on the left. If the reaction is viewed in reverse a new acid and base can be identified. The substances on the right side of the equation are called conjugate acid and conjugate base compared to those on the left. Also note that the original acid turns in the conjugate base after the reaction is over.

Acids are Proton Donors and Bases are Proton Acceptors

For a reaction to be in equilibrium a transfer of electrons needs to occur. The acid will give an electron away and the base will receive the electron. Acids and Bases that work together in this fashion are called a *conjugate pair* made up of *conjugate acids* and *conjugate bases*.

$$HA + Z \rightleftharpoons A^- + HZ^+ \tag{2.3.2}$$

A stands for an Acidic compound and Z stands for a Basic compound

- A Donates H to form HZ^+.
- Z Accepts H from A which forms HZ^+
- A^- becomes conjugate base of HA and in the reverse reaction it accepts a H from HZ to recreate HA in order to remain in equilibrium
- HZ^+ becomes a conjugate acid of Z and in the reverse reaction it donates a H to A^- recreating Z in order to remain in equilibrium

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Questions

1. Why is HA an Acid?
2. Why is Z^- a Base?
3. How can A^- be a base when HA was and Acid?
4. How can HZ^+ be an acid when Z used to be a Base?

Now that we understand the concept, let's look at an an example with actual compounds!

$$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^- \tag{2.3.3}$$

- HCL is the acid because it is donating a proton to H_2O
- H_2O is the base because H_2O is accepting a proton from HCL
- H_3O^+ is the conjugate acid because it is donating an acid to CL turn into it's conjugate acid H_2O
- Cl^- is the conjugate base because it accepts an H from H_3O to return to it's conjugate acid HCl

How can H_2O be a base? I thought it was neutral?

Answers

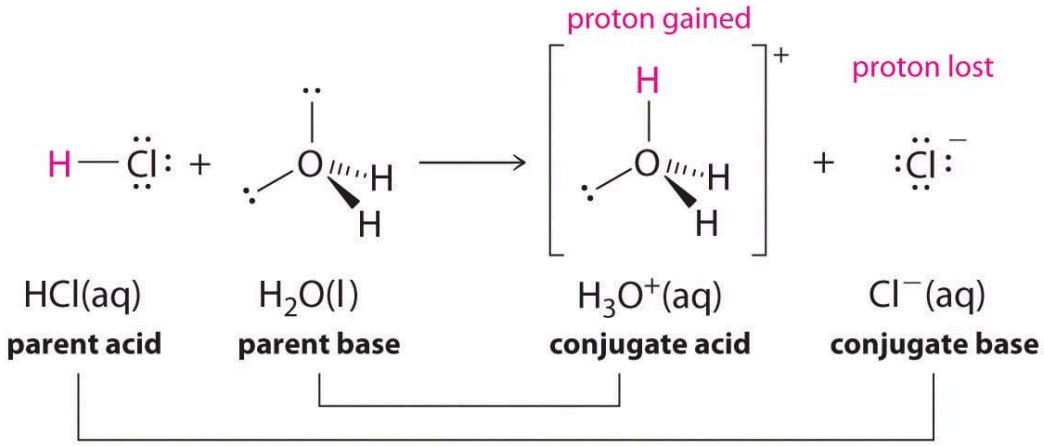
1. *It has a proton that can be transferred*
2. *It receives a proton from HA*
3. *A^- is a conjugate base because it is in need of a H in order to remain in equilibrium and return to HA*
4. *HZ^+ is a conjugate acid because it needs to donate or give away its proton in order to return to it's previous state of Z*
5. *In the* Brønsted-*Lowry Theory what makes a compound an element or a base is whether or not it donates or accepts protons. If the H_2O was in a different problem and was instead donating an H rather than accepting an H it would be an acid!*

Conjugate Acid–Base Pairs

In aqueous solutions, acids and bases can be defined in terms of the transfer of a proton from an acid to a base. Thus for every acidic species in an aqueous solution, there exists a species derived from the acid by the loss of a proton. These two species that differ by only a proton constitute a conjugate acid–base pair.

> All acid–base reactions contain two conjugate acid–base pairs.

For example, in the reaction of HCl with water, HCl, the parent acid, donates a proton to a water molecule, the parent base, thereby forming Cl^-. Thus HCl and Cl^- constitute a conjugate acid–base pair. By convention, we always write a conjugate acid–base pair as the acid followed by its conjugate base. In the reverse reaction, the Cl^- ion in solution acts as a base to accept a proton from H_2O and HCl. Thus H_3O^+ and H_2O constitute a second conjugate acid–base pair. In general, any acid–base reaction must contain two conjugate acid–base pairs, which in this case are HCl/Cl- and H_3O^+/H_2O.



Similarly, in the reaction of acetic acid with water, acetic acid donates a proton to water, which acts as the base. In the reverse reaction, H_3O^+ is the acid that donates a proton to the acetate ion, which acts as the base. Once again, we have two conjugate acid–base pairs: the parent acid and its conjugate base ($CH_3CO_2H/CH_3CO_2^-$) and the parent base and its conjugate acid (H_3O^+/H_2O).

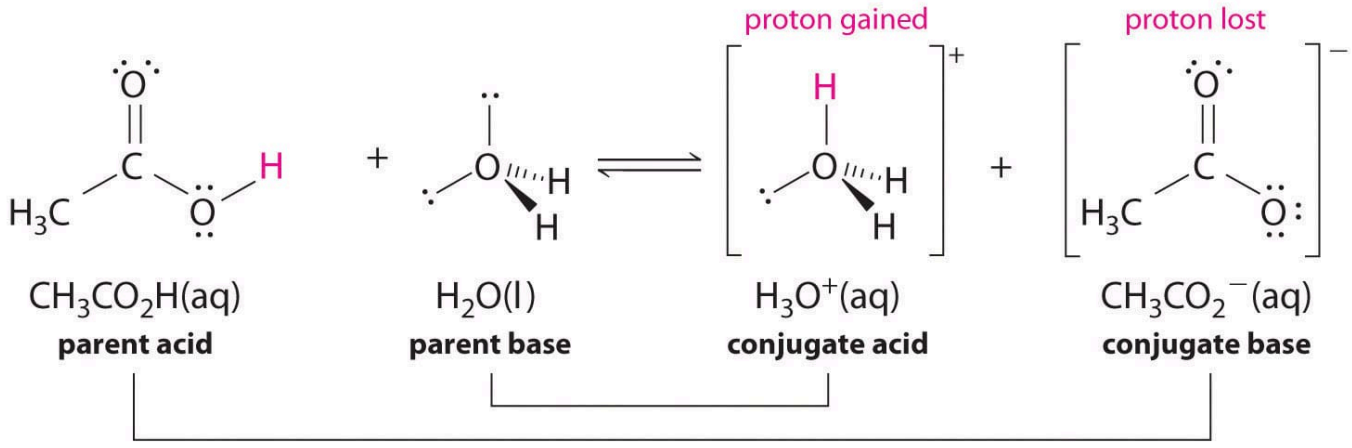


Figure 2.3.2

In the reaction of ammonia with water to give ammonium ions and hydroxide ions (Figure 16.3), ammonia acts as a base by accepting a proton from a water molecule, which in this case means that water is acting as an acid. In the reverse reaction, an ammonium ion acts as an acid by donating a proton to a hydroxide ion, and the hydroxide ion acts as a base. The conjugate acid–base pairs for this reaction are NH_4^+/NH_3 and H_2O/OH^-.

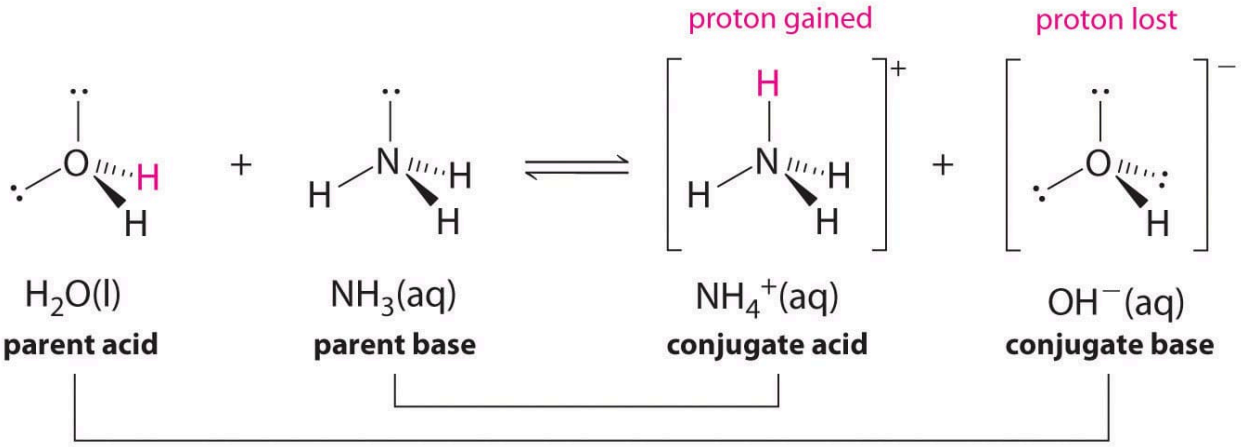


Figure 2.3.3: The Relative Strengths of Some Common Conjugate Acid–Base Pairs

Some common conjugate acid–base pairs are shown in Figure 2.3.4.

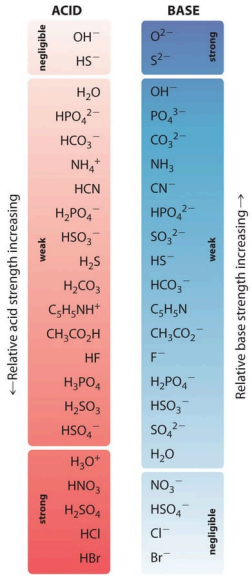


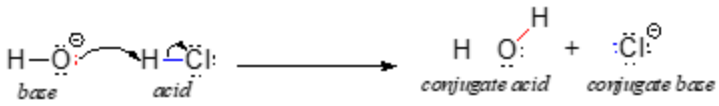
Figure 2.3.4: The strongest acids are at the bottom left, and the strongest bases are at the top right. The conjugate base of a strong acid is a very weak base, and, conversely, the conjugate acid of a strong base is a very weak acid.

Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Layne A. Morsch (University of Illinois Springfield)

The Brønsted-Lowry definition of acidity

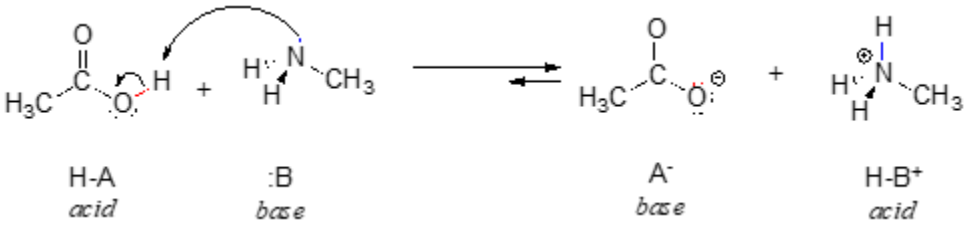
We'll begin our discussion of acid-base chemistry with a couple of essential definitions. The first of these definitions was proposed in 1923 by the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry, and has come to be known as the Brønsted-Lowry definition of acids and bases. An acid, by the Brønsted-Lowry definition, is a species which is able to donate a proton (H^+), while a base is a proton acceptor. We have already discussed in the previous chapter one of the most familiar examples of a Brønsted-Lowry acid-base reaction, between hydrochloric acid and hydroxide ion:



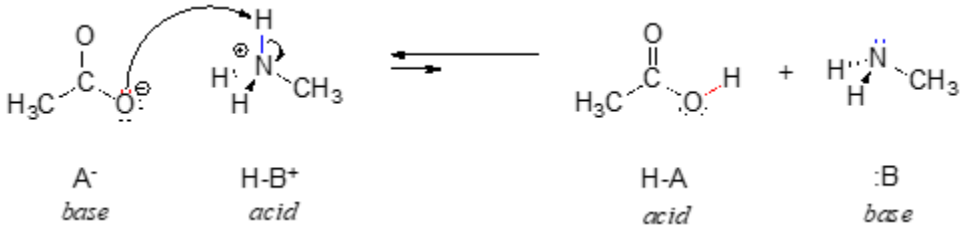
In this reaction, a proton is transferred from HCl (the acid, or proton *donor*) to hydroxide (the base, or proton *acceptor*). As we learned in the previous chapter, curved arrows depict the movement of electrons in this bond-breaking and bond-forming process.

After a Brønsted-Lowry acid donates a proton, what remains – in this case, a chloride ion – is called the **conjugate base**. Chloride is thus the conjugate base of hydrochloric acid. Conversely, when a Brønsted-Lowry base accepts a proton it is converted into its **conjugate acid** form: water is thus the conjugate acid of hydroxide.

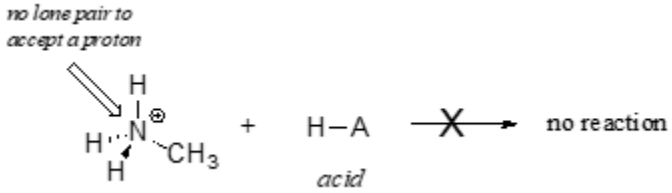
We can also talk about conjugate acid/base pairs: the two acid/base pairs involved in our first reaction are hydrochloric acid/chloride and hydroxide/water. In this next acid-base reaction, the two pairs involved are acetate/acetic acid and methyl ammonium/methylamine:



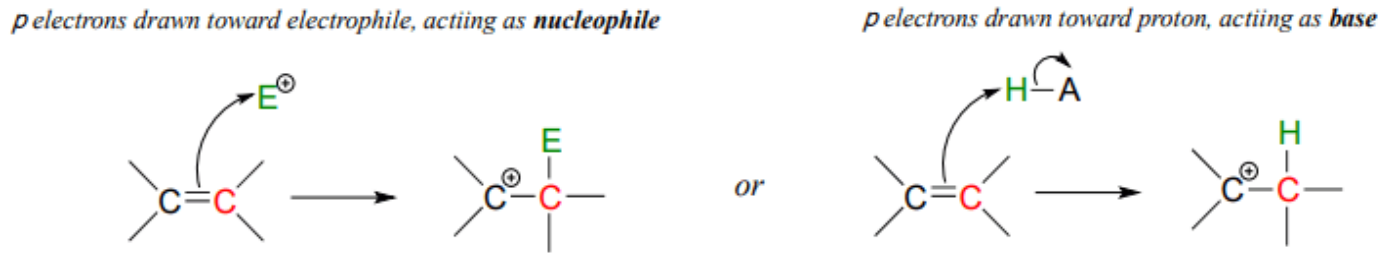
Throughout this text, we will often use the abbreviations HA and :B in order to refer in a general way to acidic and basic reactants:



In order to act as a proton acceptor, a base must have a reactive pair of electrons. In all of the examples we shall see in this chapter, this pair of electrons is a non-bonding lone pair, usually (but not always) on an oxygen, nitrogen, sulfur, or halogen atom. When acetate acts as a base in the reaction shown above, for example, one of its oxygen lone pairs is used to form a new bond to a proton. The same can be said for an amine acting as a base. Clearly, methyl ammonium ion cannot act as a base – it does not have a reactive pair of electrons with which to accept a new bond to a proton.



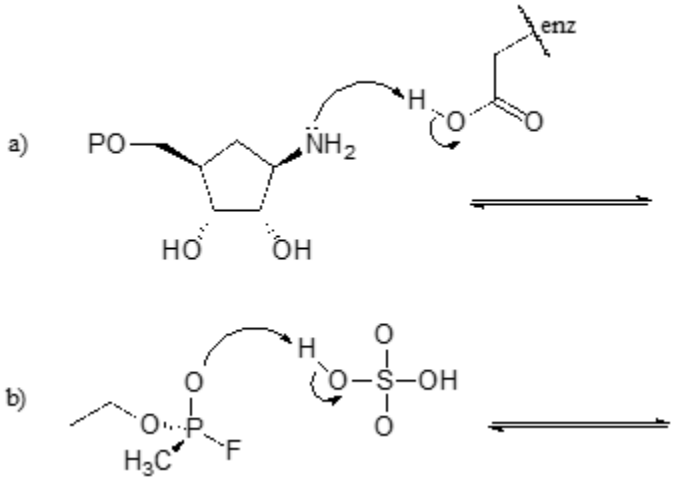
Later, in chapter 15, we will see several examples where the (relatively) reactive pair of electrons in a π bond act in a basic fashion.



In this chapter, we will concentrate on those bases with non-bonding (lone pair) electrons.

Example	

Exercise 7.1: Draw structures for the missing conjugate acids or conjugate bases in the reactions below.

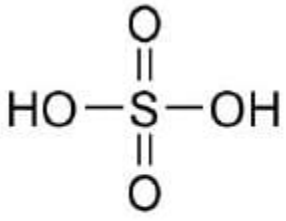


Solution

Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

You are no doubt aware that some acids are stronger than others. Sulfuric acid is strong enough to be used as a drain cleaner, as it will rapidly dissolve clogs of hair and other organic material.



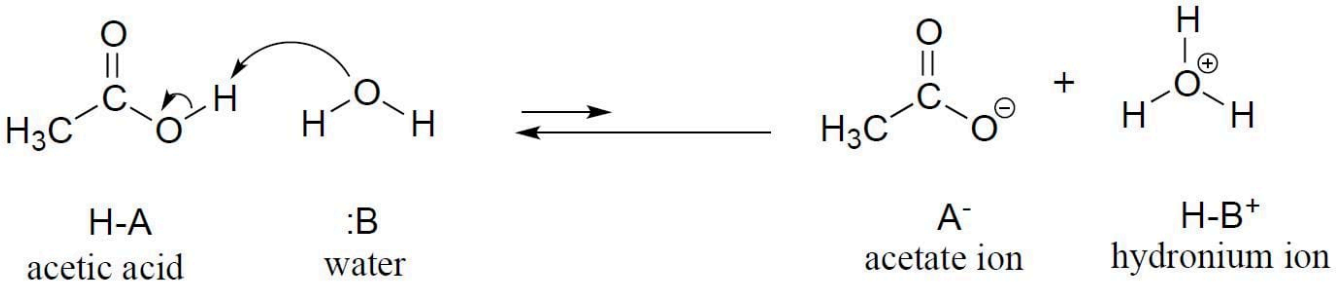
sulfuric acid

Not surprisingly, concentrated sulfuric acid will also cause painful burns if it touches your skin, and permanent damage if it gets

in your eyes (there's a good reason for those safety goggles you wear in chemistry lab!). Acetic acid (vinegar), will also burn your skin and eyes, but is not nearly strong enough to make an effective drain cleaner. Water, which we know can act as a proton donor, is obviously not a very strong acid. Even hydroxide ion could *theoretically* act as an acid – it has, after all, a proton to donate – but this is not a reaction that we would normally consider to be relevant in anything but the most extreme conditions.

The relative acidity of different compounds or functional groups – in other words, their relative capacity to donate a proton to a common base under identical conditions – is quantified by a number called the **dissociation constant**, abbreviated $\mathbf{K_a}$. The common base chosen for comparison is water.

We will consider acetic acid as our first example. When a small amount of acetic acid is added to water, a proton-transfer event (acid-base reaction) occurs to some extent.



Notice the phrase 'to some extent' – this reaction does *not* run to completion, with all of the acetic acid converted to acetate, its conjugate base. Rather, a *dynamic equilibrium* is reached, with proton transfer going in both directions (thus the two-way arrows) and finite concentrations of all four species in play. The nature of this equilibrium situation, as you recall from General Chemistry, is expressed by an equilibrium constant, K_{eq}. The equilibrium constant is actually a ratio of activities (represented by the symbol a), but activities are rarely used in courses other than analytical or physical chemistry. To simplify the discussion for general chemistry and organic chemistry courses, the activities of all of the solutes are replaced with molarities, and the activity of the solvent (usually water) is defined as having the value of 1.

In our example, we added a small amount of acetic acid to a large amount of water: water is the *solvent* for this reaction. Therefore, in the course of the reaction, the concentration of water changes very little, and the water can be treated as a pure solvent, which is always assigned an activity of 1. The acetic acid, acetate ion and hydronium ion are all *solutes,* and so their activities are approximated with molarities. The acid dissociation constant, or K_a, for acetic acid is therefore defined as:

$$K_{eq} = \frac{a_{CH_3COO^-} \cdot a_{H_3O^+}}{a_{CH_3COOH} \cdot a_{H_2O}} \approx \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][1]} \tag{2.3.4}$$

Because dividing by 1 does not change the value of the constant, the "1" is usually not written, and K_a is written as:

$$K_{eq} = K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.75 \times 10^{-5} \tag{2.3.5}$$

In more general terms, the dissociation constant for a given acid is expressed as:

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{2.3.6}$$

or

$$K_a = \frac{[A][H_3O^+]}{[HA^+]} \tag{2.3.7}$$

The first expression applies to a neutral acid such as like HCl or acetic acid, while the second applies to a cationic acid like ammonium (NH_4^+).

The value of K_a = 1.75 x 10^{-5} for acetic acid is very small - this means that very little dissociation actually takes place, and there

is much more acetic acid in solution at equilibrium than there is acetate ion. Acetic acid is a relatively weak acid, at least when compared to sulfuric acid ($K_a = 10^9$) or hydrochloric acid ($K_a = 10^7$), both of which undergo essentially complete dissociation in water.

A number like 1.75×10^{-5} is not very easy either to say or to remember. Chemists have therefore come up with a more convenient term to express relative acidity: the **pK_a** value.

$$pK_a = -\log K_a$$

Doing the math, we find that the pK_a of acetic acid is 4.8. The use of pK_a values allows us to express the acidity of common compounds and functional groups on a numerical scale of about –10 (very strong acid) to 50 (not acidic at all). Table 7 at the end of the text lists exact or approximate pK_a values for different types of protons that you are likely to encounter in your study of organic and biological chemistry. Looking at Table 7, you see that the pK_a of carboxylic acids are in the 4-5 range, the pK_a of sulfuric acid is –10, and the pK_a of water is 14. Alkenes and alkanes, which are not acidic at all, have pK_a values above 30. *The lower the pK_a value, the stronger the acid.*

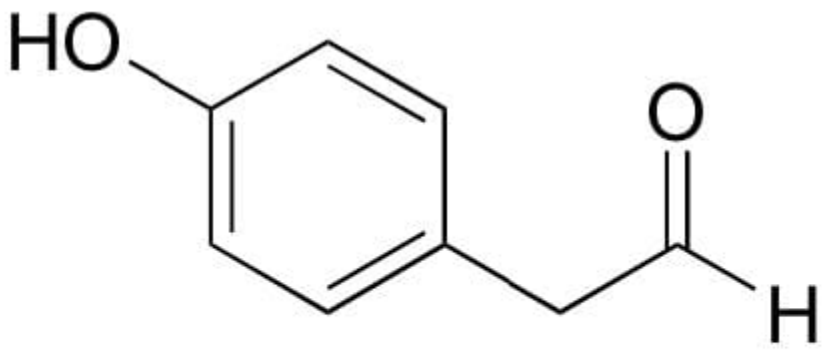
It is important to realize that pK_a is not at all the same thing as pH: the former is an inherent property of a compound or functional group, while the latter is the measure of the hydronium ion concentration in a particular aqueous solution:

$$pH = -\log [H_3O^+]$$

Any particular acid will always have the same pK_a (assuming that we are talking about an aqueous solution at room temperature) but different aqueous solutions of the acid could have different pH values, depending on how much acid is added to how much water.

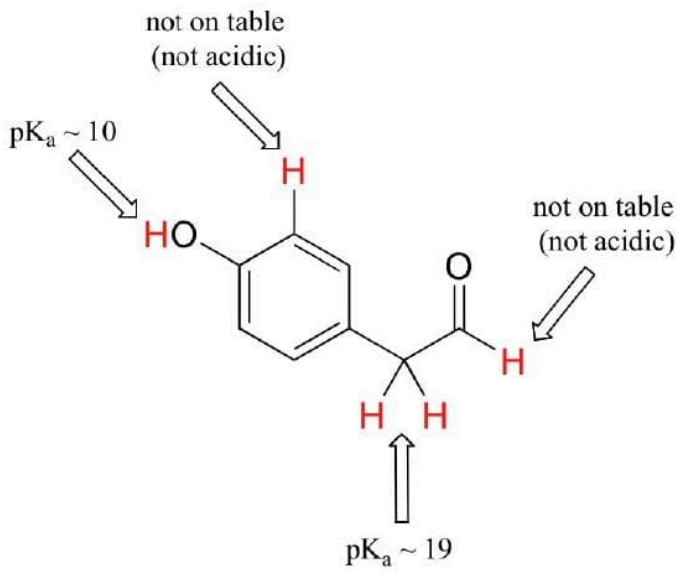
Our table of pK_a values will also allow us to compare the strengths of different bases by comparing the pK_avalues of their conjugate acids. The key idea to remember is this: *the stronger the conjugate acid, the weaker the conjugate base*. Sulfuric acid is the strongest acid on our list with a pK_a value of –10, so HSO_4^- is the weakest conjugate base. You can see that hydroxide ion is a stronger base than ammonia (NH_3), because ammonium (NH_4^+, $pK_a = 9.2$) is a stronger acid than water ($pK_a = 14.0$).

While Table 7 provides the pK_a values of only a limited number of compounds, it can be very useful as a starting point for estimating the acidity or basicity of just about any organic molecule. Here is where your familiarity with organic functional groups will come in very handy. What, for example, is the $pK_a$of cyclohexanol? It is not on the table, but as it is an alcohol it is probably somewhere near that of ethanol ($pK_a = 16$). Likewise, we can use Table 7 to predict that para-hydroxyphenyl acetaldehyde, an intermediate compound in the biosynthesis of morphine, has a pK_a in the neighborhood of 10, close to that of our reference compound, phenol.



p=hydroxyphenyl acetaldehyde

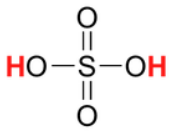
Notice in this example that we need to evaluate the potential acidity at *four* different locations on the molecule.



Aldehyde and aromatic protons are not at all acidic (pK_avalues are above 40 – not on our table). The two protons on the carbon next to the carbonyl are slightly acidic, with pK_a values around 19-20 according to the table. The most acidic proton is on the phenol group, so if the compound were to be subjected to a single molar equivalent of strong base, this is the proton that would be donated.

As you continue your study of organic chemistry, it will be a very good idea to commit to memory the approximate pK_a ranges of some important functional groups, including water, alcohols, phenols, ammonium, thiols, phosphates, carboxylic acids and carbons next to carbonyl groups (so-called a-carbons). These are the groups that you are most likely to see acting as acids or bases in biological organic reactions.

A word of caution: when using the pK_a table, be absolutely sure that you are considering the correct conjugate acid/base pair. If you are asked to say something about the basicity of ammonia (NH_3) compared to that of ethoxide ion ($CH_3CH_2O^-$), for example, the relevant pK_a values to consider are 9.2 (the pK_a of ammonium ion) and 16 (the pK_a of ethanol). From these numbers, you know that ethoxide is the stronger base. Do not make the mistake of using the pK_a value of 38: this is the pK_a of ammonia *acting as an acid*, and tells you how basic the NH_2^- ion is (very basic!)



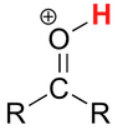
sulfuric acid
pK_a -10, 2.0



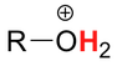
hydrochloric acid
pK_a -7



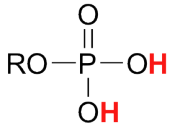
hydronium
pK_a 0.00



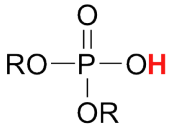
protonated ketone
pK_a ~ -7



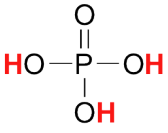
protonated alcohol
pK_a ~ -3



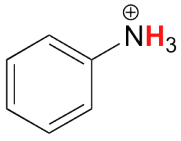
phosphate monoester [1]
pK_a ~ 1, 6.5



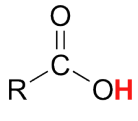
phosphate diester [1]
pK_a ~ 1.5



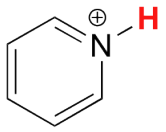
phosphoric acid
pK_a = 2.2, 7.2, 12.3



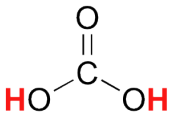
aniline
pK_a = 4.6



carboxylic acid
pK_a ~ 4-5



pyridinium
pK_a 5.3



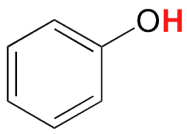
carbonic acid
pK_a 6.4, 10.3



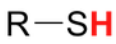
hydrogen cyanide
pK_a 9.2



ammonium
pK_a 9.2



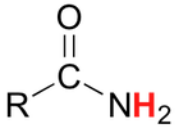
phenol
pK_a 9.9



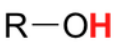
thiol
pK_a ~ 10-11



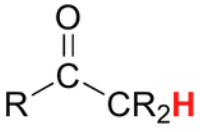
water
pK_a **14.0**



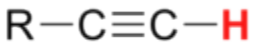
amide
pK_a ~ 17



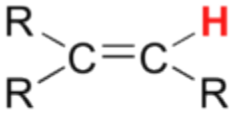
alcohol
pK_a ~ 16-18



α-proton
pK_a ~18-20



terminal alkyne
pK_a ~ 25



terminal alkene
pK_a ~ 35

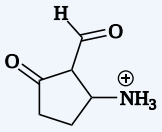


ammonia
pK_a ~ 35

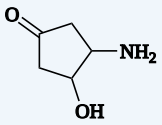
Example

Exercise 7.2: Using the pK_a table, estimate pK_a values for the most acidic group on the compounds below, and draw the structure of the conjugate base that results when this group donates a proton.

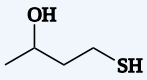
a)



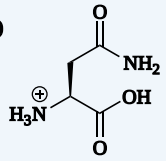
b)



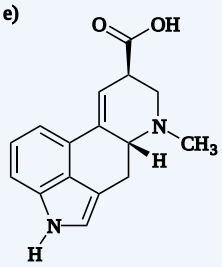
c)



d)



e)



Solution

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2.4: Functional Groups: Centers of Reactivity

Objectives

After completing this section, you should be able to

1. explain why the properties of a given organic compound are largely dependent on the functional group or groups present in the compound.
2. identify the functional groups present in each of the following compound types: alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, (carboxylic) acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.
3. identify the functional groups present in an organic compound, given its structure.
4. Given the structure of an organic compound containing a single functional group, identify which of the compound types listed under Objective 2, above, it belongs to.
5. draw the structure of a simple example of each of the compound types listed in Objective 2.

Key Terms

Make certain that you can define, and use in context, the key term below.

- functional group

Study Notes

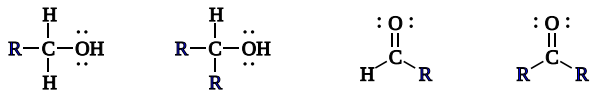
The concept of functional groups is a very important one. We expect that you will need to refer back to tables at the end of Section 3.1 quite frequently at first, as it is not really feasible to learn the names and structures of all the functional groups and compound types at one sitting. Gradually they will become familiar, and eventually you will recognize them automatically.

Functional groups are small groups of atoms that exhibit a characteristic reactivity. A particular functional group will almost always display its distinctive chemical behavior when it is present in a compound. Because of their importance in understanding organic chemistry, functional groups have specific names that often carry over in the naming of individual compounds incorporating the groups.

As we progress in our study of organic chemistry, it will become extremely important to be able to quickly recognize the most common functional groups, because they are the key structural elements that define how organic molecules react. For now, we will only worry about drawing and recognizing each functional group, as depicted by Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups tend to behave in organic reactions.

Drawing abbreviated organic structures

Often when drawing organic structures, chemists find it convenient to use the letter 'R' to designate part of a molecule outside of the region of interest. If we just want to refer in general to a functional group without drawing a specific molecule, for example, we can use 'R groups' to focus attention on the group of interest:



The 'R' group is a convenient way to abbreviate the structures of large biological molecules, especially when we are interested in something that is occurring specifically at one location on the molecule.

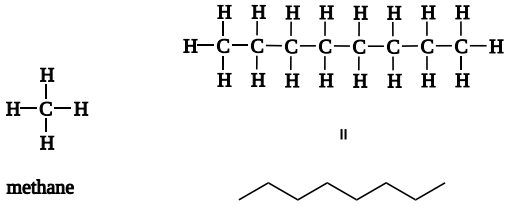
Common Functional Groups

In the following sections, many of the common functional groups found in organic chemistry will be described. Tables of these functional groups can be found at the bottom of the page.

Hydrocarbons

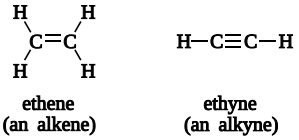
The simplest functional group in organic chemistry (which is often ignored when listing functional groups) is called an **alkane**, characterized by single bonds between two carbons and between carbon and hydrogen. Some examples of alkanes include methane, CH_4, is the natural gas you may burn in your furnace or on a stove. Octane, C_8H_{18}, is a component of gasoline.

Alkanes

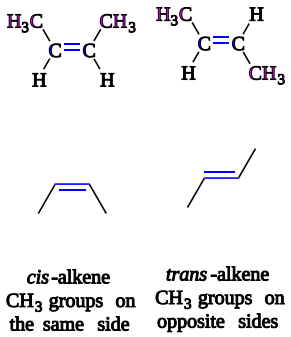


Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along with an apple - the apple emits ethene gas, setting off the ripening process in the bananas). Ethyne, commonly called acetylene, is used as a fuel in welding blow torches.

Alkenes and alkynes



Alkenes have trigonal planar electron geometry (due to sp^2 hybrid orbitals at the alkene carbons) while alkynes have linear geometry (due to sp hybrid orbitals at the alkyne carbons). Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans*** *(or Z and E which will be explained in detail in Chapter 7)*. The *cis* and *trans* forms of a given alkene are different molecules with different physical properties there is a very high energy barrier to rotation about a double bond. In the example below, the difference between *cis* and *trans* alkenes is readily apparent.

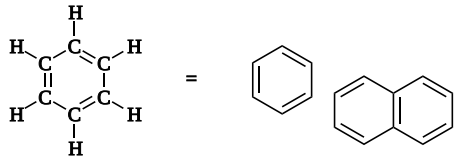


Alkanes, alkenes, and alkynes are all classified as **hydrocarbons**, because they are composed solely of carbon and hydrogen

atoms. Alkanes are said to be **saturated hydrocarbons**, because the carbons are bonded to the maximum possible number of hydrogens - in other words, they are *saturated* with hydrogen atoms. The double and triple-bonded carbons in alkenes and alkynes have fewer hydrogen atoms bonded to them - they are thus referred to as **unsaturated hydrocarbons**. As we will see in Chapter 7, hydrogen can be added to double and triple bonds, in a type of reaction called 'hydrogenation'.

The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We will learn more about the structure and reactions of aromatic groups in Chapter 15.

Aromatics

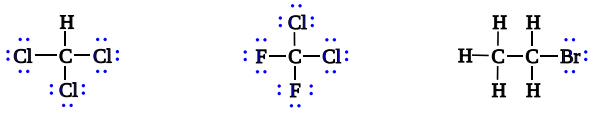


benzene naphthalene

Functional Groups with Carbon Single Bonds to other Atoms

Halides

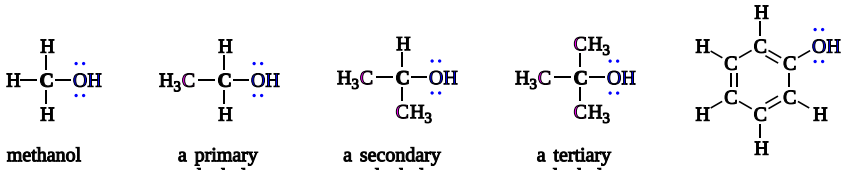
When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. The presence of a halogen atom (F, Cl, Br, or I), is often represented by X due to the similar chemistry of halogens. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol sprays until the late twentieth century, but its use was discontinued after it was found to have harmful effects on the ozone layer. Bromoethane is a simple alkyl halide often used in organic synthesis. Alkyl halides groups are quite rare in biomolecules.



trichloromethane (chloroform) dichlorodifluoromethane (Freon-12) bromoethane

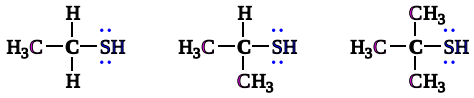
Alcohols and Thiols

In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded to only one other carbon. In a **secondary alcohol** and **tertiary alcohol,** the carbon is bonded to two or three other carbons, respectively. When the hydroxyl group is *directly* attached to an aromatic ring, the resulting group is called a **phenol**.



methanol a primary alcohol a secondary alcohol a tertiary alcohol a phenol

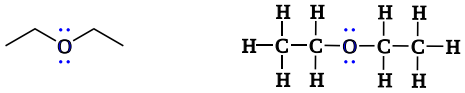
The sulfur analog of an alcohol is called a **thiol** (the prefix *thio*, derived from the Greek, refers to sulfur).



a primary thiol | a secondary thiol | a tertiary thiol

Ethers and sulfides

In an **ether** functional group, a central oxygen is bonded to two carbons. Below are the line and Lewis structures of diethyl ether, a common laboratory solvent and also one of the first medical anaesthesia agents.

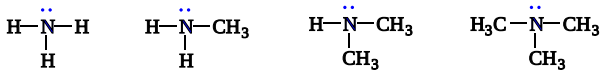


In **sulfides**, the oxygen atom of an ether has been replaced by a sulfur atom.



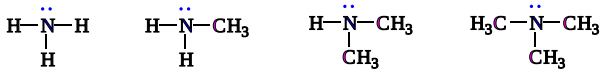
Amines

Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

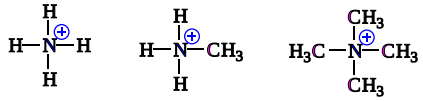


ammonia | a primary amine | a secondary amine | a tertiary amine

One of the most important properties of amines is that they are basic, and are readily protonated to form **ammonium** cations. In the case where a nitrogen has four bonds to carbon (which is somewhat unusual in biomolecules), it is called a quaternary ammonium ion.



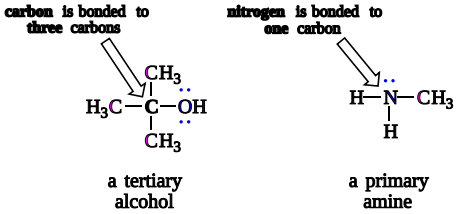
ammonia | a primary amine | a secondary amine | a tertiary amine



ammonium ion | a primary ammonium ion | a quaternary ammonium ion

Caution

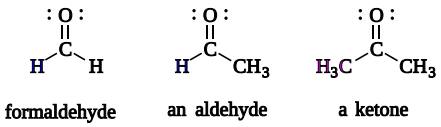
Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols and amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.



Carbonyl Containing Functional Groups

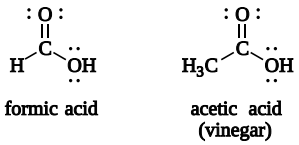
Aldehydes and Ketones

There are a number of functional groups that contain a carbon-oxygen double bond, which is commonly referred to as a **carbonyl**. **Ketones** and **aldehydes** are two closely related carbonyl-based functional groups that react in very similar ways. In a ketone, the carbon atom of a carbonyl is bonded to two other carbons. In an aldehyde, the carbonyl carbon is bonded on one side to a hydrogen, and on the other side to a carbon. The exception to this definition is formaldehyde, in which the carbonyl carbon has bonds to two hydrogens.

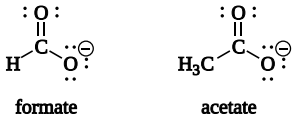


Carboxylic acids and acid derivatives

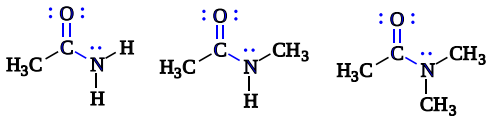
If a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to a **heteroatom** (in organic chemistry, this term generally refers to oxygen, nitrogen, sulfur, or one of the halogens), the functional group is considered to be one of the '**carboxylic acid derivatives'**, a designation that describes a grouping of several functional groups. The eponymous member of this grouping is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl (OH) group.



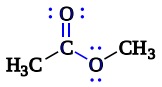
As the name implies, carboxylic acids are acidic, meaning that they are readily deprotonated to form the conjugate base form, called a **carboxylate** (much more about carboxylic acids in Chapter 20).

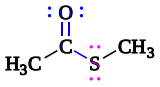


In **amides**, the carbonyl carbon is bonded to a nitrogen. The nitrogen in an amide can be bonded either to hydrogens, to carbons, or to both. Another way of thinking of an amide is that it is a carbonyl bonded to an amine.

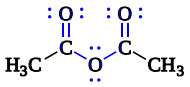


In **esters**, the carbonyl carbon is bonded to an oxygen which is itself bonded to another carbon. Another way of thinking of an ester is that it is a carbonyl bonded to an alcohol. **Thioesters** are similar to esters, except a sulfur is in place of the oxygen.

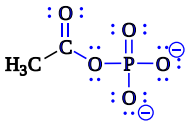

an ester

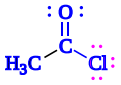

a thioester

In an **acid anhydride**, there are two carbonyl carbons with an oxygen in between. An acid anhydride is formed from combination of two carboxylic acids with the loss of water (anhydride).


an anhydride

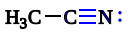
In an **acyl phosphate**, the carbonyl carbon is bonded to the oxygen of a phosphate, and in an **acid chloride**, the carbonyl carbon is bonded to a chlorine.


an acyl phosphate


an acid chloride

Nitriles and Imines

In a **nitrile** group, a carbon is triple-bonded to a nitrogen. Nitriles are also often referred to as **cyano** groups.

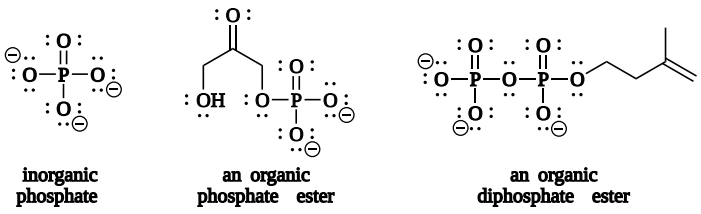

a nitrile

Molecules with carbon-nitrogen double bonds are called **imines**, or **Schiff bases**.


imines

Phosphates

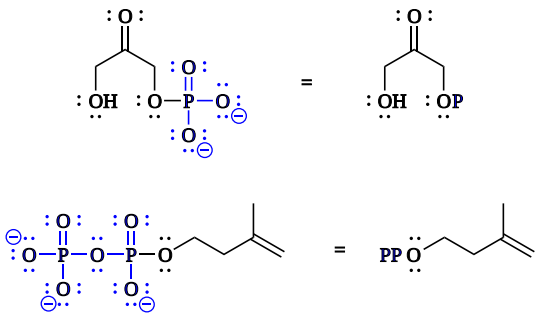
Phosphorus is a very important element in biological organic chemistry, and is found as the central atom in the **phosphate** group. Many biological organic molecules contain phosphate, diphosphate, and triphosphate groups, which are linked to a carbon atom by the **phosphate ester** functionality.


inorganic phosphate

an organic phosphate ester

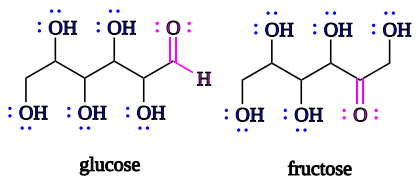
an organic diphosphate ester

Because phosphates are so abundant in biological organic chemistry, it is convenient to depict them with the abbreviation 'P'. Notice that this 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.

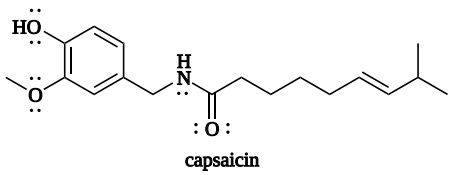


Molecules with Multiple Functional Groups

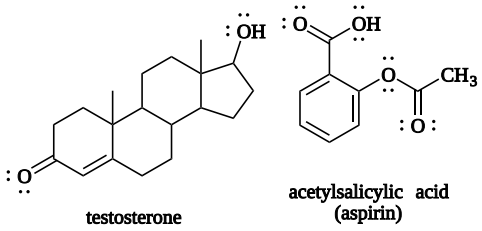
A single compound may contain several different functional groups. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').



Capsaicin, the compound responsible for the heat in hot peppers, contains phenol, ether, amide, and alkene functional groups.



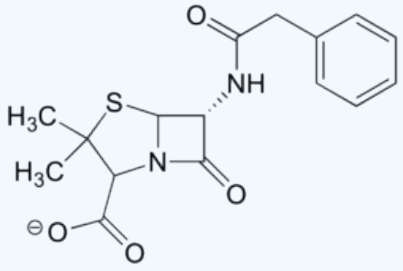
The male sex hormone testosterone contains ketone, alkene, and secondary alcohol groups, while acetylsalicylic acid (aspirin) contains aromatic, carboxylic acid, and ester groups.



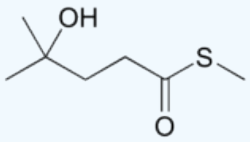
While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological and laboratory organic chemistry. The table found below provides a summary of all of the groups listed in this section, plus a few more that will be introduced later in the text.

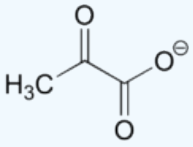
Exercise 2.4.1

Identify the functional groups in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.

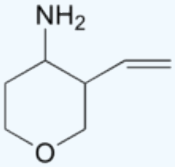
a) 

penicillin

b) 

c) 

pyruvate

d) 

Answer available at the end of this section.

2: Draw one example each (there are many possible correct answers) of compounds fitting the descriptions below, using line structures. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule).

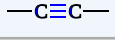
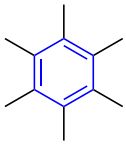
a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

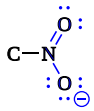
Functional Group Tables

Exclusively Carbon Functional Groups

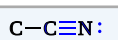
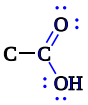
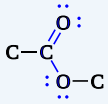
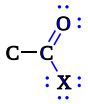
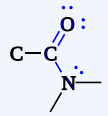
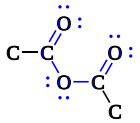
Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	alkene	$H_2C{=}CH_2$	ethene	ethylene
	alkyne	HC≡CH	ethyne	acetylene
	arene	C_6H_6	benzene	benzene

Functional Groups with Single Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	halide	H_3C-I	iodomethane	methyl iodide

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	alcohol	CH_3CH_2OH	ethanol	ethyl alcohol
	ether	$CH_3CH_2OCH_2CH_3$	diethyl ether	ether
	amine	$H_3C\text{-}NH_2$	aminomethane	methylamine
	nitro compound	$H_3C\text{-}NO_2$	nitromethane	
	thiol	$H_3C\text{-}SH$	methanethiol	methyl mercaptan
	sulfide	$H_3C\text{-}S\text{-}CH_3$	dimethyl sulfide	

Functional Groups with Multiple Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	nitrile	$H_3C\text{-}CN$	ethanenitrile	acetonitrile
	aldehyde	H_3CCHO	ethanal	acetaldehyde
	ketone	H_3CCOCH_3	propanone	acetone
	carboxylic acid	H_3CCO_2H	ethanoic Acid	acetic acid
	ester	$H_3CCO_2CH_2CH_3$	ethyl ethanoate	ethyl acetate
	acid halide	H_3CCOCl	ethanoyl chloride	acetyl chloride
	amide	$H_3CCON(CH_3)_2$	N,N-dimethylethanamide	N,N-dimethylacetamide
	acid Anhydride	$(H_3CCO)_2O$	ethanoic anhydride	acetic anhydride

Exercises

Questions

Q3.1.1

The following is the molecule for ATP, or the molecule responsible for energy in human cells. Identify the functional groups for ATP.

3-1qu.png

Solutions

S3.1.1

3.1.png

Answers

Exercise 2.4.1

a) carboxylate, sulfide, aromatic, two amide groups (one of which is cyclic)
b) tertiary alcohol, thioester
c) carboxylate, ketone
d) ether, primary amine, alkene

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2.5: Straight-Chain and Branched Alkanes

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes have the general formula C_nH_{2n+2} and can be subdivided into the following three groups: the **linear straight-chain alkanes**, **branched alkanes**, and **cycloalkanes**. Alkanes are also *saturated hydrocarbons*.

Cycloalkanes are cyclic hydrocarbons, meaning that the carbons of the molecule are arranged in the form of a ring. Cycloalkanes are also saturated, meaning that all of the carbons atoms that make up the ring are single bonded to other atoms (no double or triple bonds). There are also polycyclic alkanes, which are molecules that contain two or more cycloalkanes that are joined, forming multiple rings.

Molecular Formulas

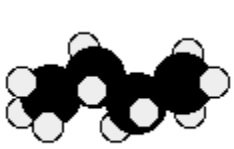
Alkanes are the simplest family of hydrocarbons - compounds containing carbon and hydrogen only. Alkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The first six alkanes are as follows:

methane	CH_4
ethane	C_2H_6
propane	C_3H_8
butane	C_4H_{10}
pentane	C_5H_{12}
hexane	C_6H_{14}

You can work out the formula of any of the alkanes using the general formula C_nH_{2n+2}

Isomerism

Isomers are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. That excludes any different arrangements which are simply due to the molecule rotating as a whole, or rotating about particular bonds. For example, both of the following are the same molecule. They are not isomers. Both are butane.

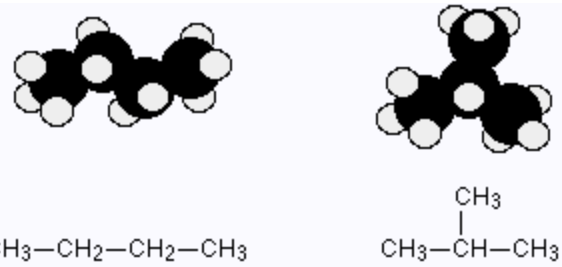




All of the alkanes containing four or more carbon atoms show structural isomerism, meaning that there are two or more different structural formulae that you can draw for each molecular formula.

Example 1: Butane or MethylPropane

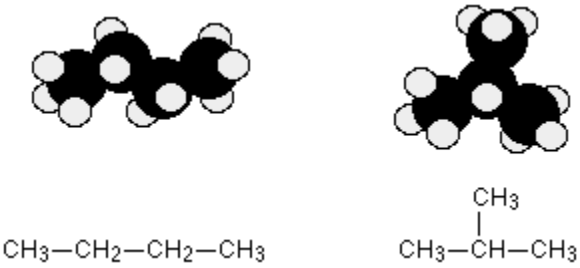
C_4H_{10} could be either of these two different molecules:



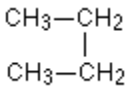
These are different molecules named butane (left) and 2-methylpropane (right).

There are also endless other possible ways that this molecule could twist itself. There is completely free rotation around all the carbon-carbon single bonds. If you had a model of a molecule in front of you, you would have to take it to pieces and rebuild it if you wanted to make an isomer of that molecule. If you can make an apparently different molecule just by rotating single bonds, it's not different - it's still the same molecule. In structural isomerism, the atoms are arranged in a completely different order. This is easier to see with specific examples. What follows looks at some of the ways that structural isomers can arise.

Constitutional isomers arise because of the possibility of branching in carbon chains. For example, there are two isomers of butane, C_4H_{10}. In one of them, the carbon atoms lie in a "straight chain" whereas in the other the chain is branched.



Be careful not to draw "false" isomers which are just twisted versions of the original molecule. For example, this structure is just the straight chain version of butane rotated about the central carbon-carbon bond.

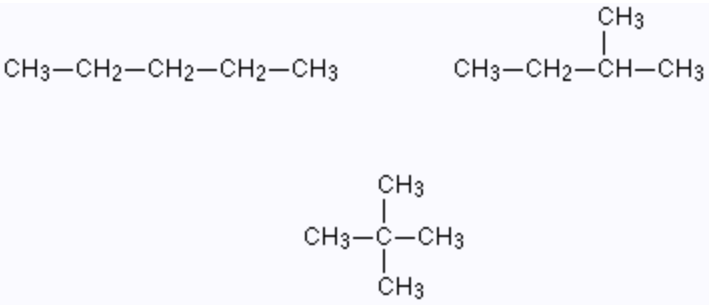


You could easily see this with a model. This is the example we've already used at the top of this page.



Example 2: Constitutional Isomers in Pentane

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

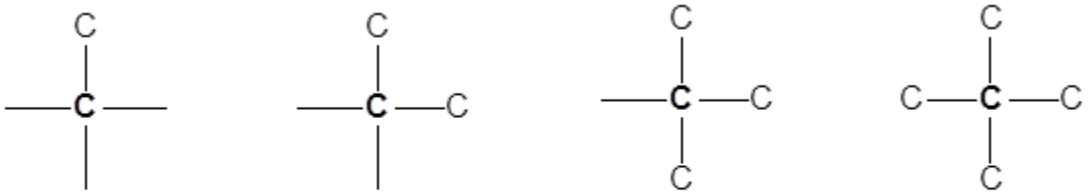


Examples of Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers		Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1		hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1		hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1		oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2		non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3		dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

Classification of Carbon and Hydrogen Atoms

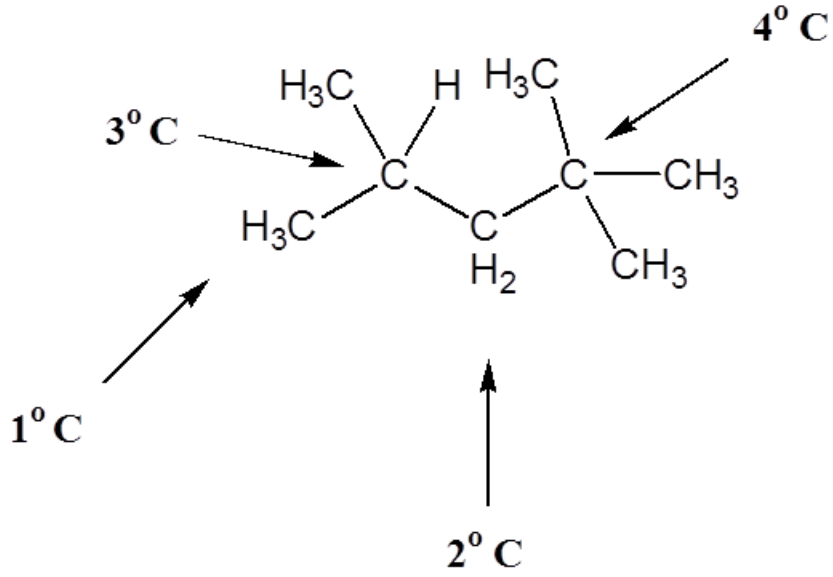
Carbons have a special terminology to describe how many other carbons they are attached to.



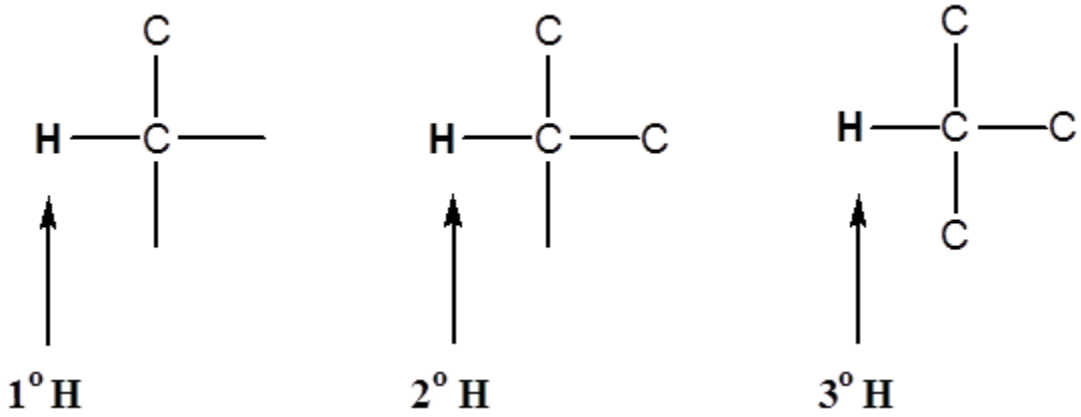
1^o 2^o 3^o 4^o

- Primary carbons (1^o) attached to one other C atom
- Secondary carbons (2^o) are attached to two other C's
- Tertiary carbons (3^o) are attached to theree other C's
- Quaternary carbons (4^o) are attached to four C's

For example, each of the three types of carbons are found in the 2,2 -dimethyl, 4-methylpentane molecule

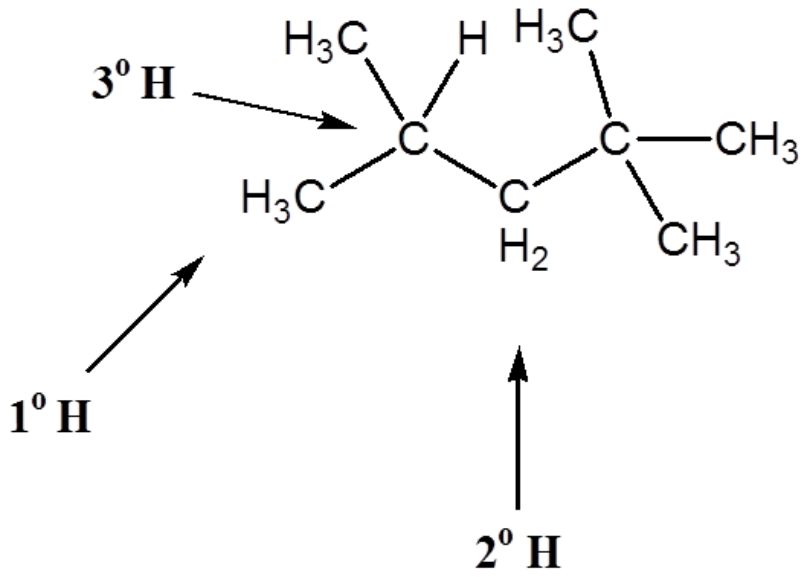


Hydrogen atoms are also classified in this manner. A hydrogen atom attached to a primary carbon atom is called a primary hydrogen; thus, isobutane, has nine primary hydrogens and one tertiary hydrogen.



- Primary hydrogens (1^{o}) are attached to carbons bonded to one other C atom
- Secondary hydrogens (2^{o}) are attached to carbons bonded to two other C's
- Tertiary hydrogens (3^{o}) are attached to carbons bonded to theree other C's

Each of the three types of carbons are found in the 2,2 -dimethyl, 4-methylpentane molecule



Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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2.6: Naming the Alkanes

Objectives

After completing this section, you should be able to

1. provide the correct IUPAC name for any given alkane structure (Kekulé, condensed or shorthand).
2. draw the Kekulé, condensed or shorthand structure of an alkane, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key term below.

- IUPAC system

Study Notes

The IUPAC system of nomenclature aims to ensure

1. that every organic compound has a unique, unambiguous name.
2. that the IUPAC name of any compound conveys the structure of that compound to a person familiar with the system.

One way of checking whether the name you have given to an alkane is reasonable is to count the number of carbon atoms implied by the chosen name. For example, if you named a compound 3-ethyl-4-methylheptane, you have indicated that the compound contains a total of 10 carbon atoms—seven carbon atoms in the main chain, two carbon atoms in an ethyl group, and one carbon atom in a methyl group. If you were to check the given structure and find 11 carbon atoms, you would know that you had made a mistake. Perhaps the name you should have written was 3-ethyl-4,4-dimethylheptane!

When naming alkanes, a common error of beginning students is a failure to pick out the longest carbon chain. For example, the correct name for the compound shown below is 3-methylheptane, not 2-ethylhexane.

Remember that every substituent must have a number, and do not forget the prefixes: di, tri, tetra, etc.

You must use commas to separate numbers, and hyphens to separate numbers and substituents. Notice that 3-methylhexane is one word.

Hydrocarbons having no double or triple bond functional groups are classified as **alkanes** or **cycloalkanes**, depending on whether the carbon atoms of the molecule are arranged only in chains or also in rings. Although these hydrocarbons have no functional groups, they constitute the framework on which functional groups are located in other classes of compounds, and provide an ideal starting point for studying and naming organic compounds. The alkanes and cycloalkanes are also members of a larger class of compounds referred to as **aliphatic**. Simply put, aliphatic compounds are compounds that do not incorporate any aromatic rings in their molecular structure.

The following table lists the IUPAC names assigned to simple continuous-chain alkanes from C-1 to C-10. A common **"ane"** suffix identifies these compounds as alkanes. Longer chain alkanes are well known, and their names may be found in many reference and text books. The names **methane** through **decane** should be memorized, since they constitute the root of many IUPAC names. Fortunately, common numerical prefixes are used in naming chains of five or more carbon atoms.

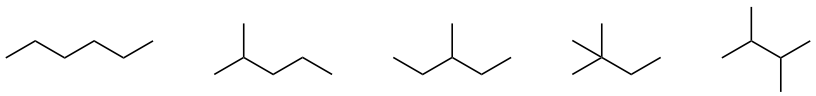
Table 3.4.1 : Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers		Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1		hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1		hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1		oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2		non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3		dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

Some important behavior trends and terminologies

1. The formulas and structures of these alkanes increase uniformly by a CH_2 increment.
2. A uniform variation of this kind in a series of compounds is called **homologous**.
3. These formulas all fit the $\mathbf{C_nH_{2n+2}}$ rule. This is also the highest possible H/C ratio for a stable hydrocarbon.
4. Since the H/C ratio in these compounds is at a maximum, we call them **saturated** (with hydrogen).

Beginning with butane (C_4H_{10}), and becoming more numerous with larger alkanes, we note the existence of alkane isomers. For example, there are five C_6H_{14} isomers, shown below as abbreviated line formulas (**A** through **E**):



A **B** **C** **D** **E**

Although these distinct compounds all have the same molecular formula, only one (**A**) can be called hexane. How then are we to name the others?

The **IUPAC** system requires first that we have names for simple unbranched chains, as noted above, and second that we have names for simple alkyl groups that may be attached to the chains. Examples of some common **alkyl groups** are given in the following table. Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

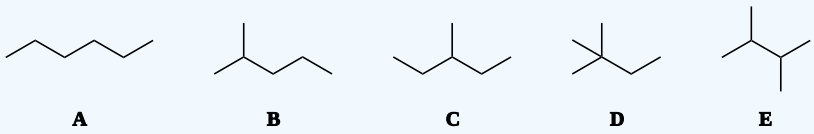
Table 3.4.2 : Alkyl Groups Names

Group	CH_3–	C_2H_5–	$CH_3CH_2CH_2$–	$(CH_3)_2CH$–	$CH_3CH_2CH_2CH_2$–	$(CH_3)_2CHCH_2$–	$CH_3CH_2CH(CH_3)$–	$(CH_3)_3C$–	R–
Name	Methyl	Ethyl	Propyl	Isopropyl	Butyl	Isobutyl	sec-Butyl	tert-Butyl	Alkyl

IUPAC Rules for Alkane Nomenclature

1. Find and name the longest continuous carbon chain.
2. Identify and name groups attached to this chain.
3. Number the chain consecutively, starting at the end nearest a substituent group.
4. Designate the location of each substituent group by an appropriate number and name.
5. Assemble the name, listing groups in alphabetical order.
6. The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

Example 3.4.1 : Alkanes



The IUPAC names of the isomers of hexane are: **A** hexane **B** 2-methylpentane **C** 3-methylpentane **D** 2,2-dimethylbutane **E** 2,3-dimethylbutane

Halogen Groups

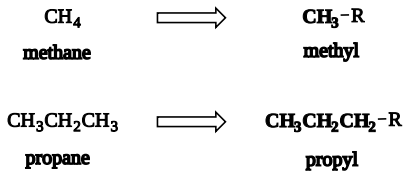
Halogen substituents are easily accommodated, using the names: fluoro (F-), chloro (Cl-), bromo (Br-) and iodo (I-).

Example 3.4.2 : Halogen Substitution

For example, $(CH_3)_2CHCH_2CH_2Br$ would be named 1-bromo-3-methylbutane. If the halogen is bonded to a simple alkyl group an alternative "alkyl halide" name may be used. Thus, C_2H_5Cl may be named chloroethane (no locator number is needed for a two carbon chain) or ethyl chloride.

Alkyl Groups

Alkanes can be described by the general formula C_nH_{2n+2}. An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.



The same concept can be applied to any of the straight chain alkane names provided in the table below.

Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$

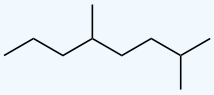
Name	Molecular Formula	Condensed Structural Formula
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Three Rules for Naming Alkanes

1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substituents and/or functional groups are written in alphabetical order.

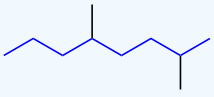
Example 3.4.3

What is the name of the follow molecule?

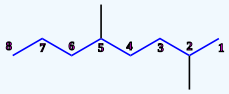


Solution

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in blue and consists of eight carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.

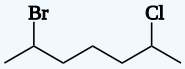


Rule 3: In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the following examples.

The name of this molecule is **2,5-dimethyloctane**

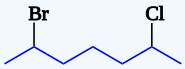
Example 3.4.4

What is the name of the follow molecule?



Solution

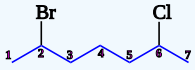
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number. In this example, numbering the chain from either the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.



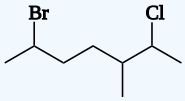
Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



The name of this molecule is: **2-bromo-6-chloroheptane**

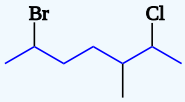
Example 3.4.5

What is the name of the follow molecule?

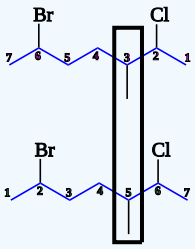


Solution

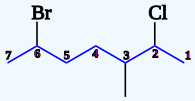
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

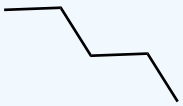
Parent chain: heptane Substitutents: 2-chloro 3-methyl 6-bromo

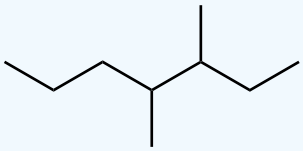
The name of this molecule is: **6-bromo-2-chloro-3-methylheptane**

Exercises

Exercise 3.4.1

Give the proper IUPAC names of the following compounds.

a) 

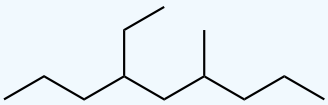
b) 

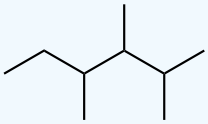
c) 

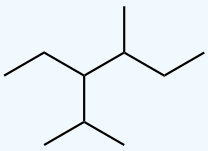
Answer available at the end of this section.

Exercise 3.4.2

Give the proper IUPAC names of the following compounds.

a) 

b) 

c) 

Answer available at the end of this section.

Exercise 3.4.3

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

a. 1,3-dimethylbutane
b. 4-ethylpentane
c. 2-ethyl-3-methylpentane

Answer available at the end of this section.

Exercise 3.4.4

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

a. 2,2-diethylheptane
b. 2-propylpentane
c. 4,4-diethylbutane

Answer available at the end of this section.

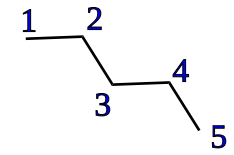
Answers

a) Since this structure is an unbranched alkane (all single bonds) with a 5 carbon chain length, its name would be **pentane**.

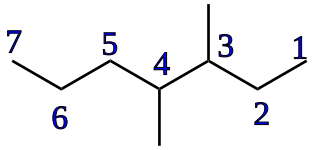
b) This alkane has a 7 carbon longest continuous chain length that we number from right to left to get the first methyl substituent we encounter to have the lowest possible number (3 versus being 4 if numbering from left to right). This causes it to have 2 methyl substituents at positions 3 & 4 so we would name it indicating those numbers and the prefix dimethyl which gives a proper IUPAC name of **3,4-dimethylheptane**.

c) This alkane has a 5 carbon longest continuous chain length (which could be numbered from left to right or right to left due to the symmetry at C-3). It has two methyl substituents off of C-3 so the proper IUPAC name is **3,3-dimethylpentane.**

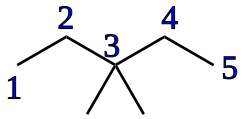
a)



b)



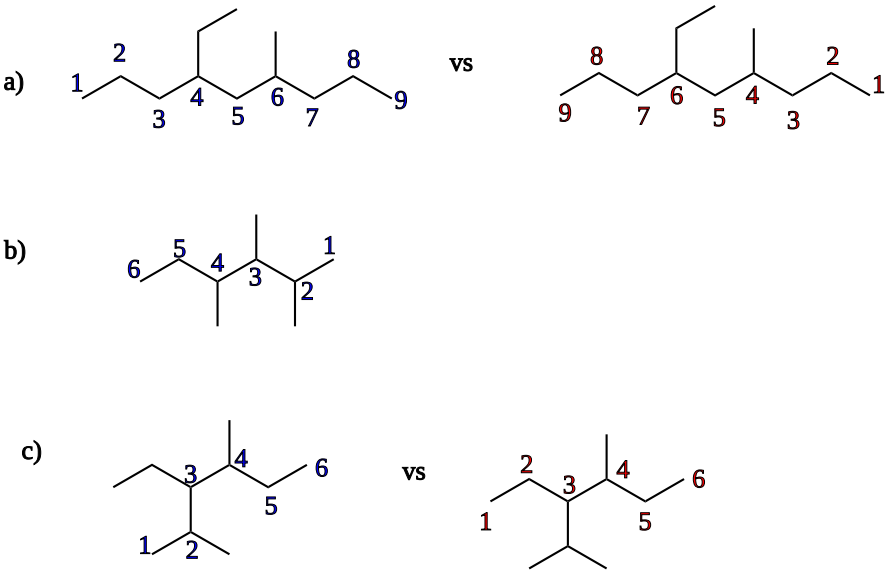
c)



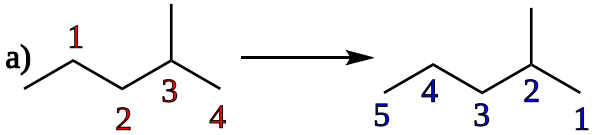
a) This alkane has a 9 carbon longest continuous chain length that we number from left to right (structure on left numbered in blue) to make the ethyl substituent be number 4. For the structure on the right (numbered in red) going from right to left, the methyl substituent is number 4. Since ethyl is higher in the alphabetical order, you want to make it have the lower number so the structure on the left (blue numbering) takes priority and the name is **4-ethyl-6-methylnonane**.

b) This alkane has a 6 carbon longest continuous chain length that we number from right to left to make the first methyl be C-2 (versus the opposite direction which would make the first methyl C-3). Since there are 3 methyl substituents at positions 2,3, & 4, this compound would have the name **2,3,4-trimethylhexane**.

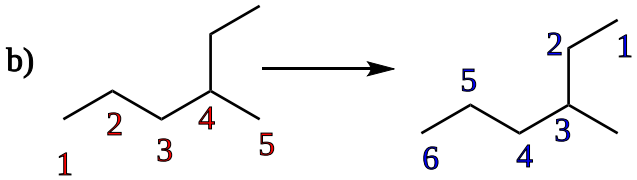
c) This 6 carbon alkane can be numbered along different chains (see below) as well as in the opposite directions. This shows the two different chains that can be drawn (making the first substituent in that chain the lowest number). The structure on the left (numbered in blue) is the correct choice since it causes more substituents to be on the longest continuous chain (3 vs 2 in the structure on the right). This would make the IUPAC name of the structure **3-ethyl-2,4-dimethylhexane**. (Notice how ethyl takes priority over methyl and the di- is not considered for alphabetizing.)



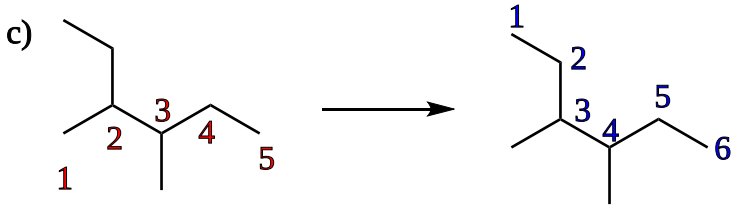
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), the correct name should be **2-methylpentane**.



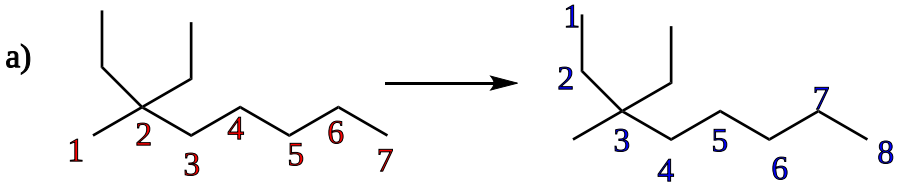
b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and we start the numbering on the end to the right to make the methyl substituent come off at C-3 (instead of beong at C-4 if we numbered it the opposite direction) the correct name should be **3-methyl hexane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and since this molecule is symmetrical (between carbon 3 & 4), you can start the numbers from either end. In this case, we have methyl substituents coming off of carbons 3 & 4 so the proper name is **3,4-dimethyl hexane**.

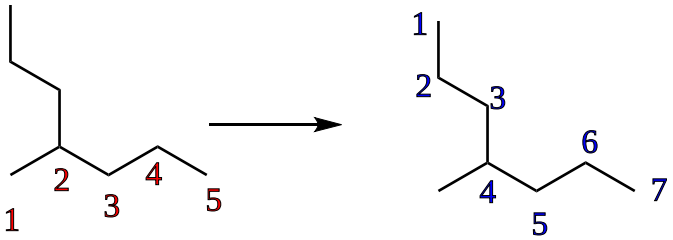


a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 8 C's and you have an ethyl substituent at C-3 and a methyl substituent also at C-3 so the proper name is **3- ethyl-3-methyloctane**.



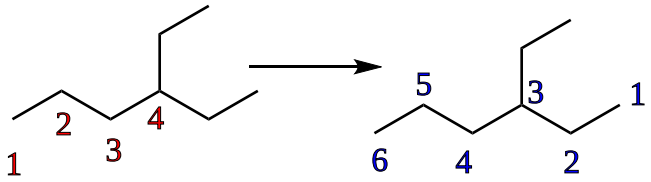
b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 7 C's and since this molecule is symmetrical (at carbon 4), you can start the numbers from either end. There is a methyl substituent at C-4 so the proper name is **4-methylheptane**.

b)



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right) going from right to left (to make the ethyl substituent have the lowest number possible), the correct name is **3-ethylhexane**

c)



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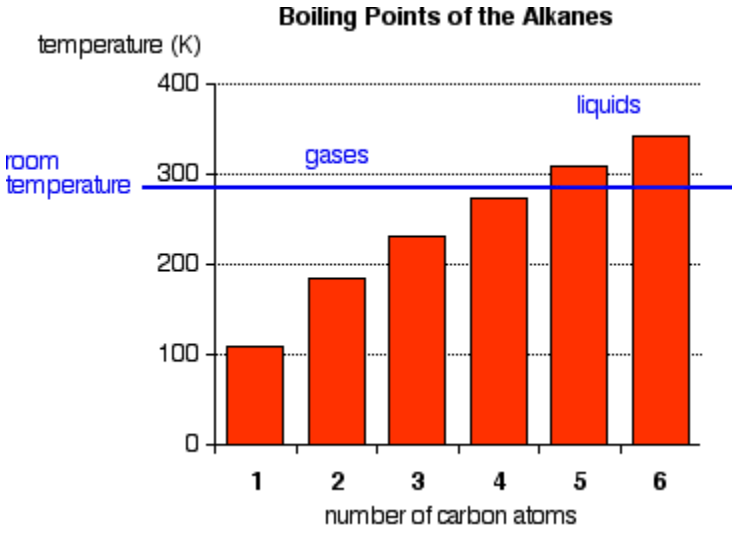
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2.7: Structural and Physical Properties of Alkanes

Alkanes are not very reactive and have little biological activity; all alkanes are colorless and odorless.

Boiling Points

The boiling points shown are for the "straight chain" isomers of which there is more than one. The first four alkanes are gases at room temperature, and solids do not begin to appear until about $C_{17}H_{36}$, but this is imprecise because different isomers typically have different melting and boiling points. By the time you get 17 carbons into an alkane, there are unbelievable numbers of isomers!



Cycloalkanes have boiling points that are approximately 20 K higher than the corresponding straight chain alkane.

There is not a significant electronegativity difference between carbon and hydrogen, thus, there is not any significant bond polarity. The molecules themselves also have very little polarity. A totally symmetrical molecule like methane is completely non-polar, meaning that the only attractions between one molecule and its neighbors will be Van der Waals dispersion forces. These forces will be very small for a molecule like methane but will increase as the molecules get bigger. Therefore, the boiling points of the alkanes increase with molecular size.

Where you have isomers, the more branched the chain, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules and only operate over very short distances between one molecule and its neighbors. It is more difficult for short, fat molecules (with lots of branching) to lie as close together as long, thin molecules.

Example

For example, the boiling points of the three isomers of C_5H_{12} are:

- pentane: 309.2 K
- 2-methylbutane: 301.0 K
- 2,2-dimethylpropane: 282.6 K

The slightly higher boiling points for the cycloalkanes are presumably because the molecules can get closer together because the ring structure makes them tidier and less "wriggly"!

Solubility

Alkanes (both alkanes and cycloalkanes) are virtually insoluble in water, but dissolve in organic solvents. However, liquid alkanes are good solvents for many other non-ionic organic compounds.

Solubility in Water

When a molecular substance dissolves in water, the following must occur:

- break the intermolecular forces within the substance. In the case of the alkanes, these are the Van der Waals dispersion forces.
- break the intermolecular forces in the water so that the substance can fit between the water molecules. In water, the primary intermolecular attractions are hydrogen bonds.

Breaking either of these attractions requires energy, although the amount of energy to break the Van der Waals dispersion forces in something like methane is relatively negligible; this is not true of the hydrogen bonds in water.

As something of a simplification, a substance will dissolve if there is enough energy released when new bonds are made between the substance and the water to compensate for what is used in breaking the original attractions. The only new attractions between the alkane and the water molecules are Van der Waals forces. These forces do not release a sufficient amount of energy to compensate for the energy required to break the hydrogen bonds in water. The alkane does not dissolve.

Note: This is a simplification because entropic effects are important when things dissolve.

Solubility in organic solvents

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals - either dispersion forces or dipole-dipole attractions. Therefore, when an alkane dissolves in an organic solvent, the Van der Waals forces are broken and are replaced by new Van der Waals forces. The two processes more or less cancel each other out energetically; thus, there is no barrier to solubility.

Contributors

Jim Clark (Chemguide.co.uk)

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2.8: Rotation about Single Bonds: Conformations

Objectives

After completing this section, you should be able to

1. explain the concept of free rotation about a carbon-carbon single bond.
2. explain the difference between conformational isomerism and structural isomerism.
3. draw the conformers of ethane using both sawhorse representation and Newman projection.
4. sketch a graph of energy versus bond rotation for ethane, and discuss the graph in terms of torsional strain.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- conformation (conformer, conformational isomer)
- dihedral angle
- eclipsed conformation
- Newman projection
- staggered conformation
- strain energy
- torsional strain (eclipsing strain)

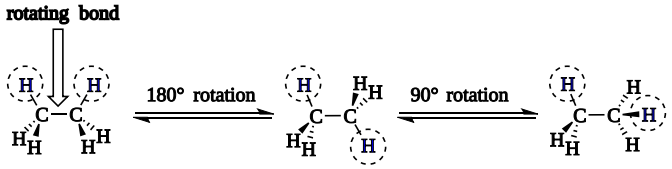
Study Notes

You should be prepared to sketch various conformers using both sawhorse representations and Newman projections. Each method has its own advantages, depending upon the circumstances. Notice that when drawing the Newman projection of the eclipsed conformation of ethane, you cannot clearly draw the rear hydrogens exactly behind the front ones. This is an inherent limitation associated with representing a 3-D structure in two dimensions.

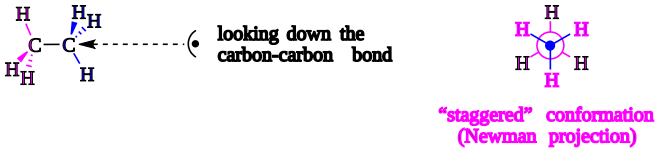
Conformational isomerism involves rotation about sigma bonds, and does not involve any differences in the connectivity of the atoms or geometry of bonding. Two or more structures that are categorized as conformational isomers, or **conformers**, are really just two of the exact same molecule that differ only in rotation of one or more sigma bonds.

Ethane Conformations

Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds does not result in any change in the shape of the molecule because the hydrogen atoms are essentially spherical. Rotation about the carbon-carbon bond, however, results in many different possible molecular conformations.



In order to better visualize these different conformations, it is convenient to use a drawing convention called the **Newman projection**. In a Newman projection, we look lengthwise down a specific bond of interest – in this case, the carbon-carbon bond in ethane. We depict the 'front' atom as a dot, and the 'back' atom as a larger circle.



The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons at 120°angles, which is what the actual tetrahedral geometry looks like when viewed from this perspective and flattened into two dimensions.

Interactive Element

Figure 3.6.1: A 3D Model of Staggered Ethane.

The lowest energy conformation of ethane, shown in the figure above, is called the 'staggered' conformation. In the staggered conformation, all of the C-H bonds on the front carbon are positioned at an angle of 60° relative to the C-H bonds on the back carbon. This angle between a sigma bond on the front carbon compared to a sigma bond on the back carbon is called the dihedral angle. In this conformation, the distance between the bonds (and the electrons in them) is maximized. Maximizing the distance between the electrons decreases the electrostatic repulsion between the electrons and results in a more stable structure.

If we now rotate the front CH_3 group 60° clockwise, the molecule is in the highest energy 'eclipsed' conformation, and the hydrogens on the front carbon are as close as possible to the hydrogens on the back carbon.



This is the highest energy conformation because of unfavorable electrostatic repulsion between the electrons in the front and back C-H bonds. The energy of the eclipsed conformation is approximately 3 kcal/mol (12 kJ/mol) higher than that of the staggered conformation. **Torsional strain** (or eclipsing strain) is the name give to the energy difference caused by the increased electrostatic repulsion of eclipsing bonds.

Another 60° rotation returns the molecule to a second staggared conformation. This process can be continued all around the 360° circle, with three possible eclipsed conformations and three staggered conformations, in addition to an infinite number of variations in between. We will focus on the staggered and eclipsed conformers since they are, respectively, the lowest and highest energy conformers.

Unhindered (Free) Rotations Do Not Exist in Ethane

The carbon-carbon bond is not *completely* free to rotate – the 3 kcal/mol torsional strain in ethane creates a barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not large enough to prevent rotation except at extremely cold temperatures. So at normal temperatures, the carbon-carbon bond is constantly rotating. However, at any given moment the molecule is more likely to be in a staggered conformation - one of the rotational 'energy valleys' - than in any other conformer. The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown in Figure 3.6.2.

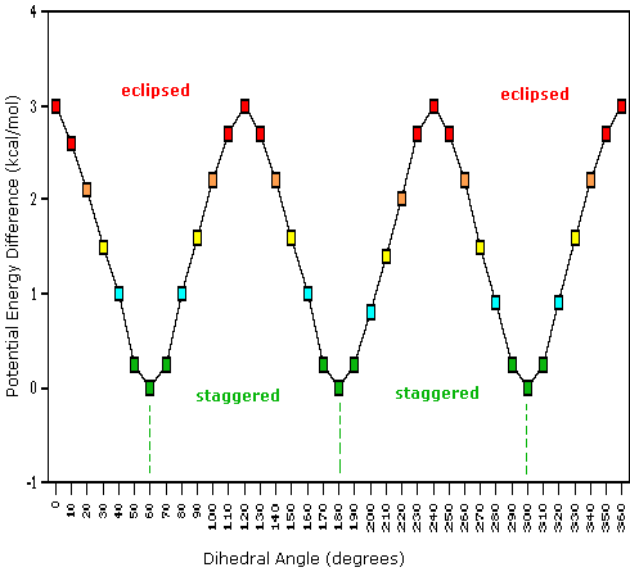


Figure 3.6.2: The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds. Valleys in the graph represent the low energy staggered conformers, while peaks represent the higher energy eclipsed conformers.

Although the conformers of ethane are in rapid equilibrium with each other, the 3 kcal/mol energy difference leads to a substantial preponderance of staggered conformers (> 99.9%) at any given time. The animation below illustrates the relationship between ethane's potential energy and its dihedral angle

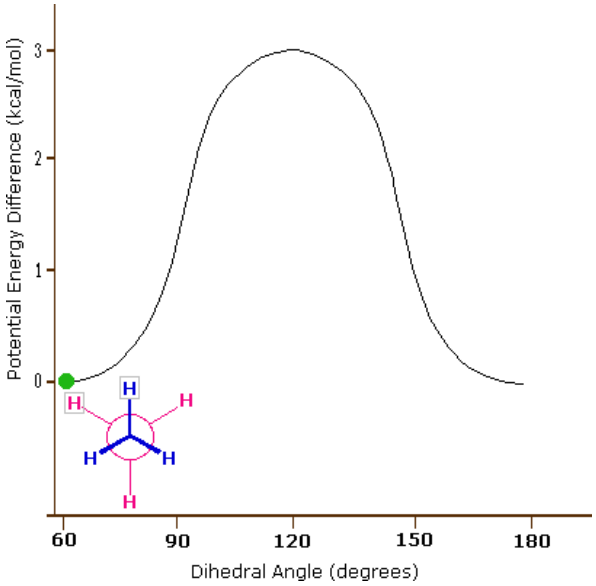


Figure 3.6.2: Animation of potential energy vs. dihedral angle in ethane

Exercises

1) What is the most stable rotational conformation of ethane and explain why it is preferred over the other conformation?

Solutions

1) Staggered, as there is less repulsion between the hydrogen atoms.

Questions

Q3.6.1

What is the most stable rotational conformation of ethane and explain why it is preferred over the other conformation?

Solutions

S3.6.1

Staggered, as there is less repulsion between the hydrogen atoms.

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2.9: Rotation in Substituted Ethanes

Objectives

After completing this section, you should be able to

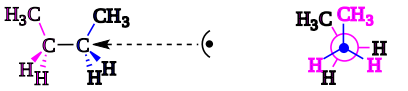
1. depict the staggered and eclipsed conformers of propane (or a similar compound) using sawhorse representations and Newman projections.
2. sketch a graph of energy versus bond rotation for propane (or a similar compound) and discuss the graph in terms of torsional strain.
3. depict the anti, gauche, eclipsed and fully eclipsed conformers of butane (or a similar compound), using sawhorse representations and Newman projections.
4. sketch a graph of energy versus C_2-C_3 bond rotation for butane (or a similar compound), and discuss it in terms of torsional and steric repulsion.
5. assess which of two (or more) conformers of a given compound is likely to predominate at room temperature from a semi-quantitative knowledge of the energy costs of the interactions involved.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- anti conformation
- gauche conformation
- eclipsed conformation
- steric repulsion (strain)

In butane, there are three rotating carbon-carbon sigma bonds to consider, but we will focus on the middle bond between C_2 and C_3. Below are two representations of butane in a conformation which puts the two CH_3 groups (C_1 and C_4) in the eclipsed position.

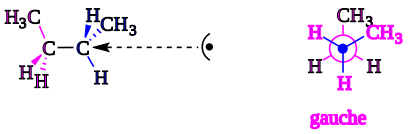


"eclipsed" (A)

Eclipsed interaction	Energy (kcal/mol)	Energy (kJ/mol)
H-H	1.0	4.0
H-CH_3	1.4	6.0
CH_3-CH_3	2.6	11.0

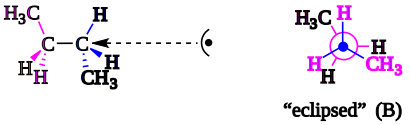
The CH_3-CH_3 groups create the significantly larger eclipsed interaction of 11.0 kJ/mol. There are also two H-H eclipsed interactions at 4.0 kJ/mol each to create a total of 2(4.0 kJ/mol) + 11.0 kJ/mol = 19.0 kJ/mol of strain. This is the highest energy conformation for butane, due to torsional strain caused by the electrostatic repulsion of electrons in the eclipsed bonds, but also because of another type of strain called '**steric repulsion**', between the two rather bulky methyl groups. Steric strain comes about when two large groups, such as two methyl groups, try to occupy the same space. What results is a repulsive non-covalent interaction caused by their respective electron densities.

If we rotate the front, (blue) carbon by 60°clockwise, the butane molecule is now in a staggered conformation.

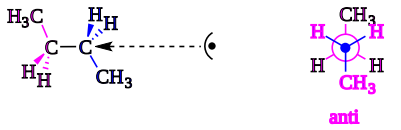


This is more specifically referred to as the **'gauche'** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be. There is still significant steric repulsion between the two bulky groups.

A further rotation of 60° gives us a second eclipsed conformation (B) in which both methyl groups are lined up with hydrogen atoms.



Due to steric repulsion between methyl and hydrogen substituents, this eclipsed conformation B is higher in energy than the gauche conformation. However, because there is no methyl-to-methyl eclipsing, it is lower in energy than eclipsed conformation A. One more 60° rotation produces the **'anti'** conformation, where the two methyl groups are positioned opposite each other and steric repulsion is minimized.



The anti conformation is the lowest energy conformation for butane. The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.

Interactive Element

Figure 2.9.1*:* A 3D Structure of the Anti Butane Conformer.

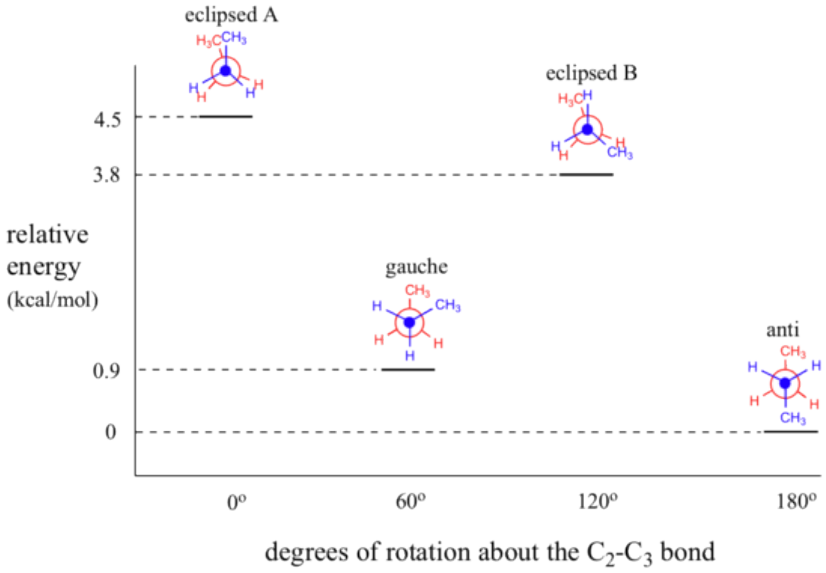


Figure 2.9.2: Potential curve vs dihedral angle of the C_2-C_3 bond of butane.

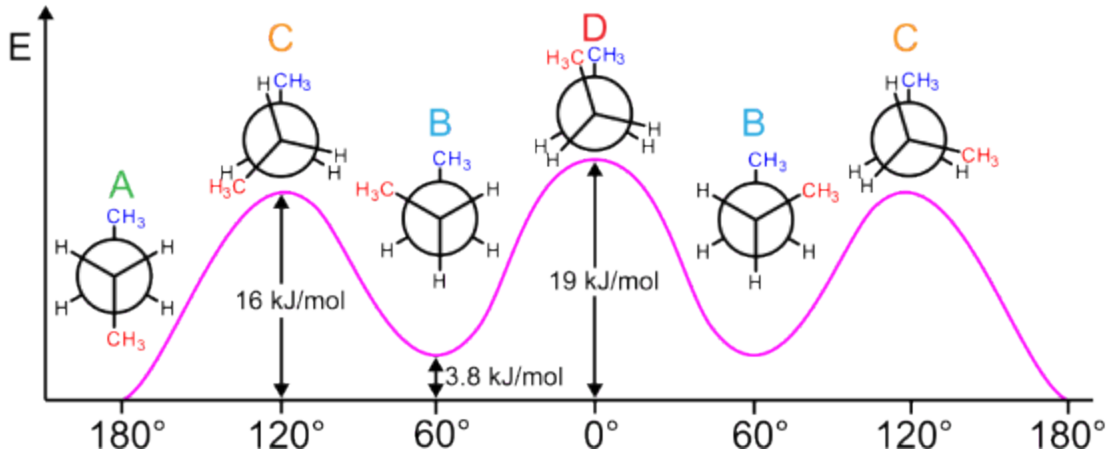
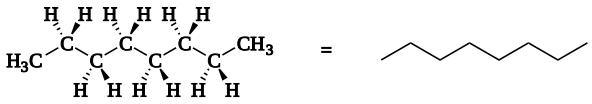


Figure 2.9.2: Newman projections of butane conformations & their relative energy differences (not total energies). Conformations form when butane rotates about one of its single covalent bond. Torsional/dihedral angle is shown on x-axis. Torsional/dihedral angle is shown on x-axis. Conformation names (according to IUPAC): **A**: anti-periplanar, anti or trans **B**: synclinal or gauche **C**: anticlinal or eclipsed **D**: syn-periplanar or cis. Source for conformation names & conformer classification: Pure & Appl. Chem., Vol. 68, No. 12, pp. 2193-2222, 1996. (Public Domain; Keministi).

At room temperature, butane is most likely to be in the lowest-energy anti conformation at any given moment in time, although the energy barrier between the anti and eclipsed conformations is not high enough to prevent constant rotation except at very low temperatures. For this reason (and also simply for ease of drawing), it is conventional to draw straight-chain alkanes in a zigzag form, which implies the anti conformation at all carbon-carbon bonds. For example octane is commonly drawn as:



octane

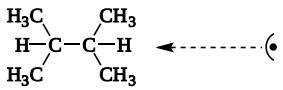
Drawing Newman Projections

Newman projections are a valuable method for viewing the relative positions of groups within molecule. Being able to draw the Newman projection for a given molecule is a valuable skill and will be used repeatedly throughout organic chemistry. Because organic molecules often contain multiple carbon-carbon bonds it is important to precisely know which bond and which direction is being sighted for the Newman projection. The details of the Newman projection change given the molecule but for typical alkanes a full conformational analysis involves a full 360^{o} rotation in 60^{o} increments. This will produce three staggered conformers and three eclipsed conformers. Typically, the staggered conformers are more stable and the eclipsed conformers are less stable. The least stable conformer will have the largest groups eclipsed while the most stable conformer will have the largest groups anti (180^{o}) to each other.

Example

Draw the Newman projection of 2,3 dimethylbutane along the C_2-C_3 bond. Then determine the least stable conformation.

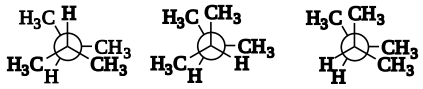
First draw the molecule and locate the indicated bond:



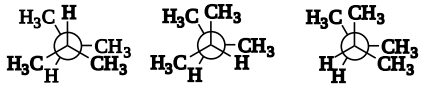
Because the question asks for the least stable conformation, focus on the three possible eclipsed Newman projections. Draw out three eclipsed Newman projections as a template. Because it is difficult to draw a true staggered Newman projection, it is common to show the bonds slightly askew.



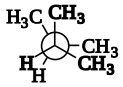
Place the substituents attached to the second carbon (C_3) on the back bonds of all three Newman projections. In this example they are 2 CH_3s and an H. Place the substituents in the same position on all three Newman projections.



Then place the substituents attached to the first carbon (C_2) on the front bonds of the Newman projection. In this example, the substituents are also 2 CH_3s and an H. Move the substituents through two 60° rotations to create the remaining two eclipsed Newman projections. Leave the substituents on the back carbon in place. Attempting to rotate the front and back carbons simultaneously is a common mistake and often leads to incorrect Newman projections.



Compare the Newman projections by looking the eclipsed interactions. Remember that the order of torsional strain interactions are CH_3-CH_3 > CH_3-H > H-H. The third structure has two CH_3-CH_3 torsional interactions which will make it the least stable conformer of 2,3 dimethyl butane.



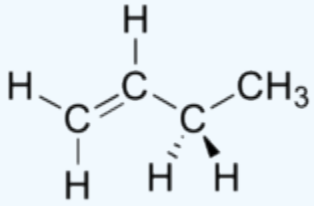
Example 2.9.1

Draw Newman projections of the eclipsed and staggered conformations of propane, as if viewed down the C_1-C_2 bond.

Answer available at the end of this section.

Example 2.9.2

Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below.



Answer available at the end of this section.

Exercises

Questions

Q3.7.1

Draw the energy diagram for the rotation of the bond highlighted in pentane.

3-7qu.png

Solutions

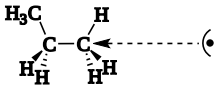
S3.7.1

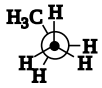
3.7.jpg

3-7sol.png

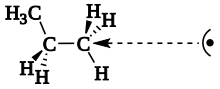
Answers

Example 2.9.1





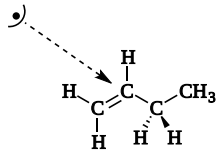
highest energy
(eclipsed)

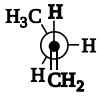




lowest energy
(staggered)

Example 2.9.2





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- 3.7: Conformations of Other Alkanes by Dietmar Kennepohl, Jim Clark, Krista Cunningham, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

2.E: Structure and Reactivity: Acids and Bases, Polar and Nonpolar Molecules (Exercises)

These are homework exercises to accompany Chapter 2 of Vollhardt and Schore's "Organic Chemistry" Textmap.

2.1: Kinetics and Thermodynamics of Simple Chemical Processes

2.2: Keys to Success: Using Curved "Electron Pushing" Arrows to Describe Chemical Reactions

2.3: Acids and Bases; Electrophiles and Nucleophiles

2.4: Functional Groups: Centers of Reactivity

2.5: Straight-Chain and Branched Alkanes

2.6: Naming the Alkanes

2.7: Structural and Physical Properties of Alkanes

2.8: Rotation about Single Bonds: Conformations

2.9: Rotation in Substituted Ethanes

Problems

Q26

A tray of ice cubes is left out on the counter in a room, and the ice cubes melt. If the room is a closed system, what is the total enthalpy of the system (room + ice)? The entropy of the system? What about the free energy? Is this process thermodynamically favorable? How would the temperature of the ice, now water, and the room compare?

Q27

(a) Using the following bond strengths, calculate the ΔH^o for each of the reactions.

Bond	Average Strength (kcal mol^{-1})
C-C	83
C=C	146
C-H	99
Cl-Cl	57

Bond	Average Strength (kcal mol^{-1})
H-Cl	102
C-Cl	78

(i) CH_3-CH=CH_2 + Cl_2 → CH_3-CHCl-CH_2Cl

(ii) CH_3-CH=CH_2 + Cl_2 → CH_2Cl-CH=CH_2 + HCl

(b) One of these reactions as a ΔS^o <0 (-35 cal mol^{-1}) and the other has a ΔS^o=0. Assign the two to the equations, and give your reasoning.

(c) Based on both ΔS^o and ΔH^o calculate ΔG^o for each reaction at 30°C and 800°C. Are the reactions favorable at these temperatures?

Q28

I. In each of the following equations label the Brønsted acid and base, on both sides.
II. Also, determine which way the equilibrium lies, left or right.
II. From the given pK_a of each acid calculate the equilibrium constant, K_{eq}. (pK_a H_3O^+ = -1.7)

a. $H_2O + HF \rightleftharpoons H_3O^+ + F^-$

pKa= 14 3.45

b. $H_2O + HCN \rightleftharpoons H_3O^+ + CN^-$

pKa= 14 9.2

c. $CH_3COOH + F^- \rightleftharpoons CH_3COO^- + HF$

pKa= 4.7 3.45

d. $H_3BO_3 + NH_3 \rightleftharpoons H_2BO_3^- + NH_4^+$

pKa= 9.3 9.3

Q29

In problem 28 use electron pushing arrows to show what is occurring, looking from left to right.

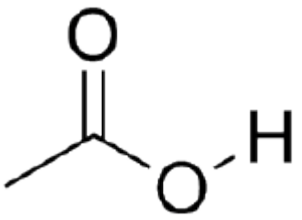
Q30

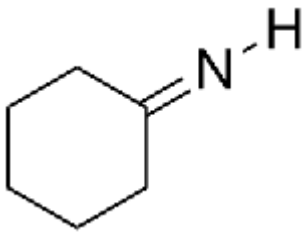
Determine whether each of the following species is a Lewis acid or Lewis base. Demonstrate this ability with an electron arrow pushing mechanism.

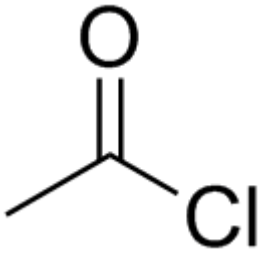
(a) $AlCl_3$ (b) H_2O (c) $ZnCl_2$ (d) $ScCl_3$ (e) N_3^- (f) $CH_3CH_2O^-$

Q31

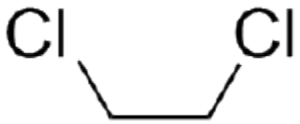
For each of the following molecules denote the bond polarities, δ^+ or δ^-.

(a) 

(b) 

(c) 

(d)



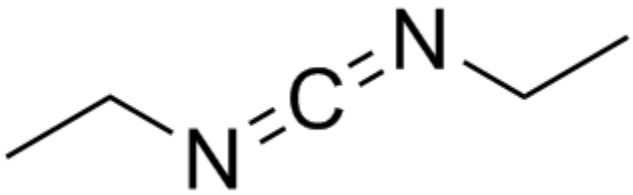


(e)

Q32

Identify whether each species is nucleophilic or electrophilic

(a) Fluoride anion, F^- (b) Hydride anion, H^- (c) acid chloride, CH_3COCl (d) $ScCl_3$ (e) N,N'-diethylcarbodiimide



Q33

Identify the functional groups present in each molecule below.

(a) 33aq.png (b) 33bq.png (c) 33cq.png (d) 33dq.png (e) 33eq.png (f) 33fq.png

Q34

Determine, based on Coulombic interaction, if the following are likely to react. No reaction is a possibility.

(a) ammonia (NH_3) and cyclohexanone (b) H^+ and ethanol (c) azide (N_3^-) and bromoethane (d) nitrogen (N_2) and propane (e) triethylamine and H^+

Q35

Draw the electron arrow pushing mechanism of the potential interaction in problem 34

Q36

Name each of the following compounds according to IUPAC.

(a) 2.36aq.png (b) 2.36bq.png (c) 2.36cq.png (d) 2.36dq.png (e) 2.36eq.png

(f) 2.36fq.png

Q37

Draw the following structures from the name

a. 2,3,4-trimethylpentane
b. 4-ethyl-3,4,5,5-tetramethylnonane
c. neopentane
d. 2,2,4,4-tetramethylpentane
e. 7-pentyltridecane
f. 2,3,4,5,6-pentamethylheptane

Q38

Draw the structures that correspond to the following names, correct any names that are not in accord with the rules of systematic nomenclature.

a. 3-methyl-2-fluoropentane
b. 1-chloro-3-bromo-2,2-dimethylbutane
c. 2-ethyl-2-chloro-4,5-methylhexane
d. 3-methylpentane

Q39

Draw all possible isomers of C_6H_{14}

Q40

In each of the following compounds identify each carbon as either primary (1^o), secondary (2^o), tertiary (3^o), or quaternary (4^o).

(a) cyclopentane (b) 3,3,5,5-tetraethylheptane (c) methylcyclopentane (d) 2,3,4-trimethylpentane

Q41

Identify each of the following alkyl groups as primary, secondary, tertiary, or quaternary. This is based off of the 1 position in the alkyl group, connected to the dashed bond. Also, give its IUPAC name.

(a) 2.41a.png (b) 2.41b.png (c) 2.41c.png (d) 2.41d.png

Q42

Does the molecule in (a) contain a tertiary carbon? Does the molecule in (b)? Explain why.

(a) 2.42a.png (b) 2.42b.png

Q43

Based on the following structures, think about the London dispersion forces and how that would affect the boiling point. Rank the following compounds in order from lowest to highest boiling point.

(a) 2,3,4-trimethylhexane (b) nonane (c) 2,3-dimethylpentane (d) 3-methylheptane

Q44

Draw the lowest energy Newman projection of the following:

a. 2,3-dimethylbutane C2-C3
b. 2,2-dimethylbutane C2-C3
c. 2-methylpentane C2-C3
d. 2-methylpropane

Q45

Draw the energy diagram, Energy vs. Torsional angle of the C2-C3 bond of butane, rotating increments of 60^{o} starting at the lowest energy conformation. Also draw the Newman projection of each.

Q46

Given that 85% of all molecules are anti- and 15% of all molecules are eclipsed conformation along a certain C-C bond, take for example C2-C3 of butane, draw the two Newman projections. Calculate the ΔG^{o} value using ΔG^{o}=-RTln(K), at 25^{o}C where R=1.986 cal deg^{-1} mol^{-1}. Does the given information make sense? If not, in what ways?

Q47

Identify the functional groups in each compound.

(a) 2.47a.png (aspirin) (b) 2.47b.png (dopamine) (c) 2.47c.png (erythritol- sweetener)

(d) 2.47d.png (limonene- in oranges and lemons, subtle differences in stereochemistry make a difference in the smell)

Q48

Name the alkyl group as if the dashed line were where it was connect to the rest of the molecule, state whether it is primary, secondary, or tertiary.

(a) 2.48a.png (b) 2.48b.png (c) 2.48c.png (d) 2.48d.png

Q49

Calculate the new value of k, relative to the initial value, using the Arrhenius equation with increases of 10, 25, and 60^{o}C. Assume the initial temperature is 300^{o}C.

Where E_a is the following

(a) 10 kcal mol^{-1} (b) 25 kcal mol^{-1} (c) 50 kcal mol^{-1}

Q50

An alternate form of the Arrhenius equation involves taking the natural logarithm of the equation giving the following.

$\ln k = \ln A - (E_a/RT)$

What plot involving both *k* and T would yield a straight line? Give some characteristics of the line, slope and intercept.

Q51

For question 35 draw the product that would result from the arrow pushing mechanism. Make sure not to draw a pentavalent carbon in (a) (use the oxygen atom) and (b) (substitute the bromine and have it leave).

Q52

Given that the Gibbs free energy is given by the following equation $\Delta G = \Delta H - T\Delta S$, fill in the table that yield a spontaneous process ($\Delta G < 0$)

ΔH	ΔS
Less than Zero	???
???	Greater than Zero

Q53

Under certain conditions the two following reactions are second order, proportional to both reactants concentrations. Write the rate law for each reaction, and similar to in problem 35 draw the structures with any electrostatic interactions.

(a) 2.53aq.png

(b) 2.53bq.png

Q54

Which of the following is true about 2,3-dimethylbutane?

a. There are 10 primary H's
b. There are 6 times as many primary H's as there are tertiary H's
c. There are 3 tertiary C's
d. There are no primary C's

Q55

Using $\Delta G = \Delta H - T\Delta S$, where $\Delta H = -1000$ cal/mol and $\Delta S = -2$cal/mol at T=200K, which of the following is true.

a. The reaction is endothermic
b. The reaction is not spontaneous
c. The reaction is exergonic
d. It is likely that the reaction involves one reactant and yields two products.

Q56

In 2-methylbutane what bond angles exist?

a. 90^{o}
b. 120^{o}
c. 180^{o}
d. 109.5^{o}

Q57

Which conformation describes the following Newman projection? Which one would be the lowest in energy?

2.57q.png

a. *anti* eclipsed
b. *anti* gauche
c. *gauche* staggered
d. *anti* staggered

Q58

The following molecule, isatin, has all of the following functional groups except for:

2.58q.png

a. aromatic ring
b. ketone
c. aldehyde
d. amide

Solutions

S26

The enthalpy of the system is zero, since the change is cancelled out by the ice gaining heat and the room losing heat. However, the entropy does increase and so the free energy decreases. This process is thermodynamically favorable as the free energy decreases. The end temperature of the ice and water would be equal.

S27

(a) ΔH^{o}= Bonds Broken - Bonds Formed

(i) ΔH^{o}= (C=C + Cl-Cl) - (2 C-Cl + C-C)

= (146 + 57) - (2(78) + 83) = -36 kcal mol^{-1}

(ii) ΔH^{o}= (C-H + Cl-Cl) - (C-Cl + H-Cl)

=(99 + 57) - (78 + 102) = -24 kcal mol^{-1}

(b) Reaction (i) involves the combination of two molecules into one. Fewer numbers of products concentrates the energy, and therefor leads to a negative ΔS^{o} value. Reaction (ii) starts with two molecules and results in two molecules. There is no change in

the entropy, and so $\Delta S^o = 0$.

(c) The two above values can be used to find the change in the Gibbs Free Energy using the following equation.

$\Delta G^o = \Delta H^o - T\Delta S^o$

(i) at 30^oC, or $(30 + 273.15) = 303.15$ K

$\Delta G^o = -36 - 303.15(-35 \times 10^{-3}) = -25$ kcal mol^{-1} Favorable

at 800^oC, or 973.15 K

$\Delta G^o = -36 - 1073.15(-35 \times 10^{-3}) = +1$ kcal mol^{-1} Not Favorable

(ii) at 30^oC

$\Delta G^o = -24 - 303.15(0) = -24$ kcal mol^{-1} Favorable

at 700^oC

$\Delta G^o = -24 - 1073.15(0) = -24$ kcal mol^{-1} Favorable

S28

(a) (i) H_2O=Weaker Base HF= Weaker Acid; H_3O^+= Stronger Acid F^-=Stronger Base

(ii) From above, the equilibrium would lie to the left

(iii) Using the pKa we can find the Ka for each acid, $Ka = 10^{-pKa}$ HF $K_a = 10^{-3.45}$ and H_3O^+ $K_a = 10^{1.7}$

$K_{a\ HF} = [F^-][H^+]/[HF]$ and $K_{a\ H3O^+} = [H^+][H_2O]/[H_3O^+]$ and $K_{eq} = [H_3O^+][F^-]/[H_2O][HF]$, from this we can see that $K_{eq} = K_{a\ HF}/K_{a\ H3O^+}$ or $10^{-3.45}/10^{1.7} = 7.08 \times 10^{-6}$. This makes sense because the favors the left, so calculating the equilibrium to the right would mean a very small equilibrium constant.

(b) (i) H_2O=Weaker Base HCN=Weaker Acid; H_3O^+=Stronger Acid CN^-=Stronger Base

(ii) From part (i), the equilibrium would lie to the left.

(iii) $K_{a\ H3O^+} = [H^+][H_2O]/[H_3O^+] = 10^{1.7}$ and $K_{a\ HCN} = [CN^-][H^+]/[HCN] = 10^{-9.2}$ and the $K_{eq} = K_{a\ HCN}/K_{a\ H3O^+} = 10^{-9.2}/10^{1.7} = 1.26 \times 10^{-11}$, the case is the same as the previous problem. The equilbrium constant for the reaction as drawn, left to right, is very small.

(c) (i) CH_3COOH=Weaker Acid F^-=Weaker Base; CH_3COO^-=Stronger Base HF=Stronger Acid

(ii) Due to part (i), the equilibrium would lie to the left.

(iii) $K_{a\ CH3COOH} = [H^+][CH_3COO^-]/[CH_3COOH] = 10^{-4.7}$ $K_{HF} = [H^+][F^-]/[HF] = 10^{-3.45}$ This results in $K_{eq} = K_{a\ CH3COOH}/K_{HF} = 10^{-4.7}/10^{-3.45} = 5.62 \times 10^{-2}$

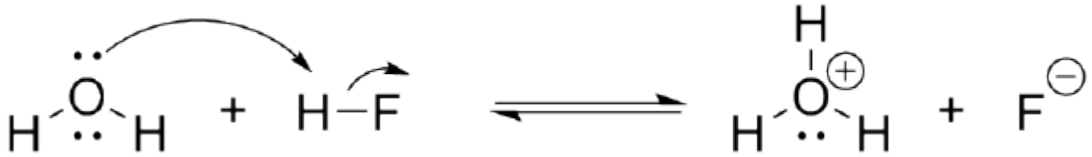
(d) (i) H_3BO_3= Equally Acid NH_3=Equally Basic; $H_2BO_3^-$=Equally Basic NH_4^+=Equally Acidic

(ii) The reaction equilibrium does not lie to either side. H_3BO_3 and NH_4^+ are equally acidic according to their pKa

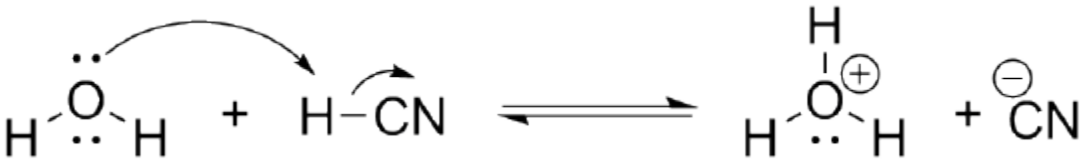
(iii) If the K_{eq} were calculated it be equal to 1. $10^{-9.3}/10^{-9.3}=1$.

S29

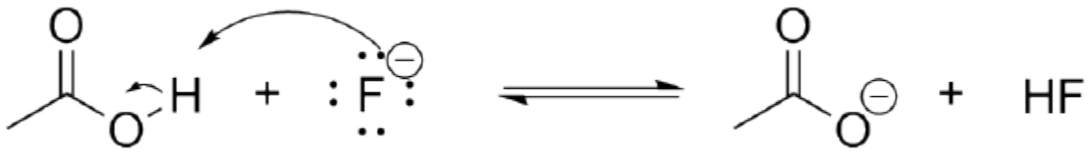
(a)



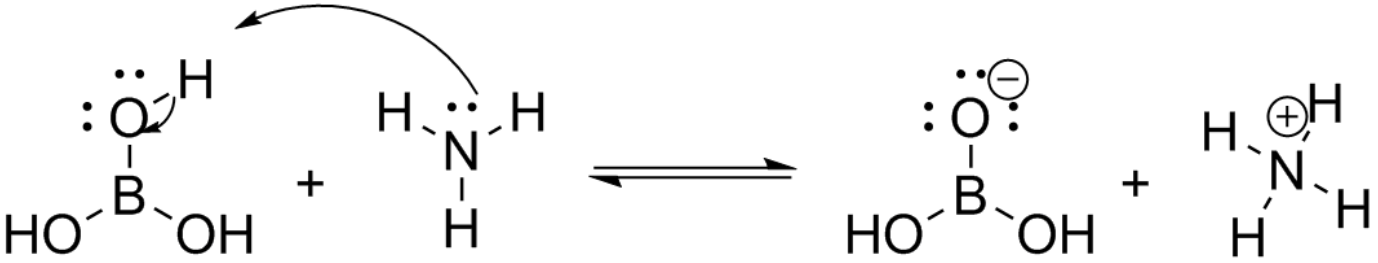
(b)



(c)

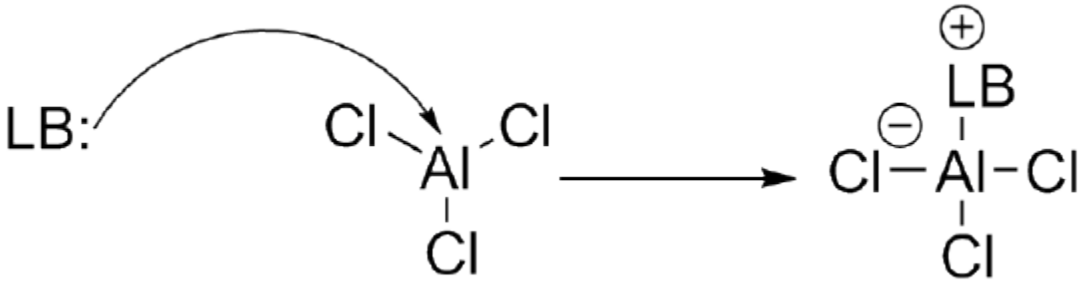


(c)



S30

(a) $AlCl_3$ is a Lewis acid. Aluminum is electron deficient, and with three electronegative halogens attached, the Aluminum center is an electron acceptor.



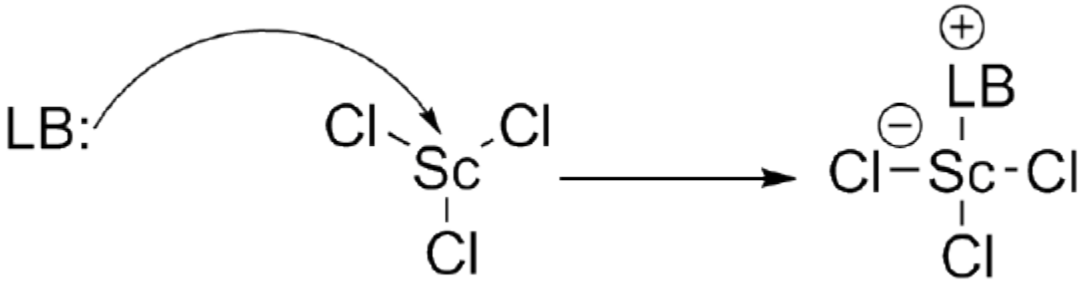
(b) H_2O is a Lewis base. The oxygen has two lone pairs of electrons, and is thus an electron donor.



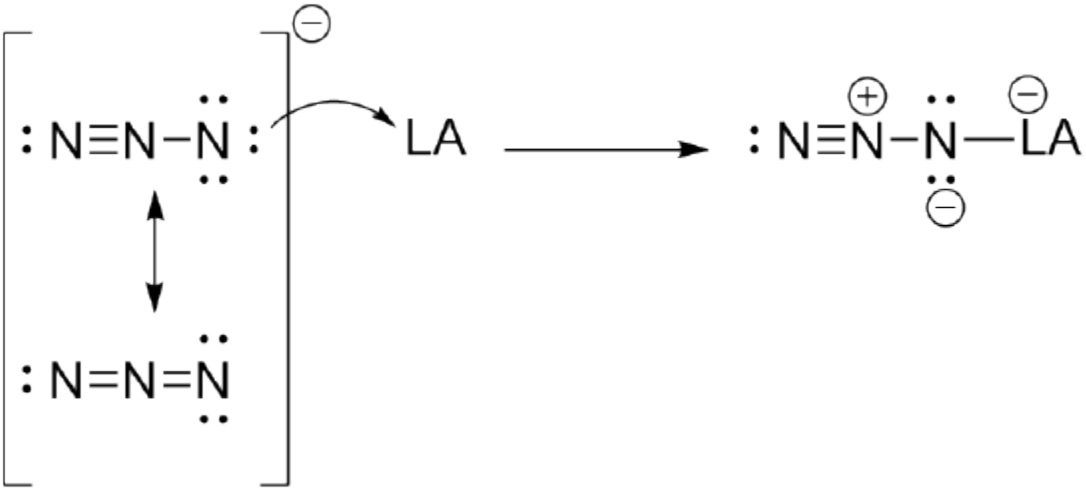
(c) $ZnCl_2$ is a Lewis acid. The zinc center is Zn^{2+}, losing two electrons from the 4s orbitals leaving it with a full 3d orbital. It is in a positive oxidation state and has two electronegative halogens attached, and so the zinc center is an electron acceptor.



(d) $ScCl_3$ is a Lewis acid. The scandium center is Sc^{3+}, lacking two electrons in the 4s orbitals and one from the 3d orbital, leaving it with a full 3p orbital. It is in a positive oxidation state hand has three electronegative halogens attached, and so the scandium center is an electron acceptor.



(e) N_3^- is a Lewis base. There are two possible resonance structures for this species, and in both there are lone pair electrons on the front nitrogen. It is an electron donor.

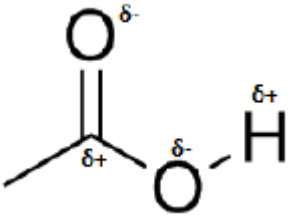


for simplicity, only one resonance structure was shown as the Lewis acid/base adduct.

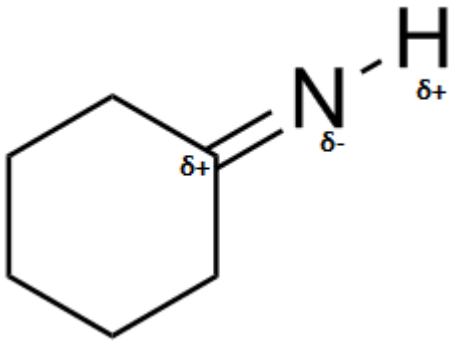
(f) $CH_3CH_2O^-$ is a Lewis base. The oxygen has three lone pairs of electrons, it is an electron donor. Even if it was not negatively charged it would still be a Lewis base, with two lone pairs.



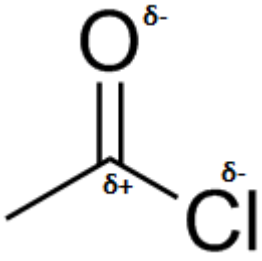
S31



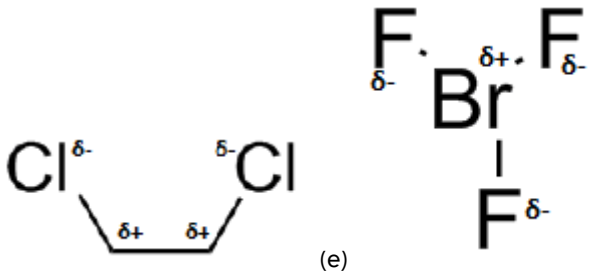
(a)



(b)



(c) (d)



(e)

S32

(a) The fluoride anion is negatively charged, and it is nucleophilic. (b) The hydride anion is negatively charged, and it is nucleophilic. (c) Acid chlorides are similar to esters and ketones in that there is an electrophilic carbon double bonded to the oxygen, but acid chlorides are typically much more reactive. (d) $ScCl_3$ was seen earlier to be Lewis acidic, and it is electrophilic. (e) The central carbon in N,N'-diethylcarbodiimide is electrophilic due to the bond polarizations between the two nitrogen atoms.

S33

(a) An aromatic ring and a carboxylic acid are present. (b) Alcohol (c) ester (d) haloalkane (e) anhydride, this is similar to an ester, but the difference is the oxygen atom placement. (f) amide

S34

a. The ketone provides an electrophilic carbon.
b. The alcohol has two lone pairs of electrons, and with a positive charge there is a Coulombic attraction.
c. The important thing here is the polarization of the C-Br bond, making the carbon electrophilic. The azide has an overall negative charge, and a Coulombic attraction is present.
d. There is no large polarization in bonds present. Both of these gases are not known for being nucleophilic or electrophilic.
e. This is a standard acid base reaction, but it can be explained by the Coulombic attraction between the positively charged hydrogen ion and the lone pair on the nitrogen.

S35

(a)2.34aa.png (b) 2.34ba.png (c) 2.34ca1.png (d) No reaction (e) 2.34ea.png

S36

(a) 2.36aa.png (b) 2.36ba.png (c) 2.36ca.png

(d) 2.36da.png (e) 2.36ea.png (f) 2.36fa.png

S37

(a) 2.37a.png (b) 2.37b.png (c) 2.37c.png (d) 2.37d.png

(e) 2.37e.png (f) 2.37f.png

S38

(a) 2.38a.png (b) 2.38b.png (c) 2.38c.png (d)2.38d.png or 2-methylpentane

S39

2.39a.png

S40

(a) 2.40a.png (b) 2.40b.png (c) 2.40c.png (d) 2.40d.png

S41

(a) primary, 2,2-dimethylbutyl (b) tertiary, 1-ethyl-1-methylbutyl (c) secondary, 1,3-dimethylbutyl (d) tertiary, 1,1,2,2-tetramethylethyl

S42

Molecule (a) does not contain a tertiary carbon, it is only bonded to two other carbon atoms. An oxygen atom does not affect this. Compound (b) does contain a tertiary carbon, as it is bonded to three other carbon atoms.

S43

2,3,4-trimethylpentane<2,3-dimethylhexane<3-methylheptane

This is a combination of both molecular weight and how branched the molecule is (affect the strength of the London dispersion forces). The higher the molecular weight the higher the boiling point, but also the more branched a molecule is the lower the boiling point.

S44

(a) 2.44a.png (b) 2.44b.png (c) 2.44c.png (d) 2.44d.png

S45

graph.png

2.45.png

S46

2.46.png

ΔG^{o}=-(1.986)(273+25)ln(85/15)= -1027 cal or -1.027 kcal

The given information makes sense in that a larger percentage of the molecules are present in the Anti conformation due to its lower energy. However, other conformations are not included, some lower in energy than the eclipsed form such as staggered. These are likely to also make a contribution.

S47

(a) 2.47aa.png (b) 2.47b.a.png (c) 2.47c.a.png (d) 2.47da.png

S48

(a) 1,6,6-trimethylhexyl, secondary (b) 1,1,2,2-tetramethylbutyl, tertiary (c) 2,2-dimethylbutyl, primary (d) 2-methylethyl or isopropyl, primary

S49

The Arrhenius equation is k=A$e^{-(E_a/RT)}$ where A is a constant. To calculate the new k value use the following k_2/k_1=A$e^{-(E_a/RT2)}$/A$e^{-(E_a/RT_1)}$ and the constant, A, cancels.

k_2=[$e^{-(E_a/RT2)}$/$e^{-(E_a/RT_1)}$]k_1 also remember to convert the E_a from kcal to cal.

(a) 10^{o}C - k_2=[$e^{-(10,000/(1.986)(310))}$/$e^{-(10,000/(1.986)(300))}$]$k_1$= 1.71$k_1$

25^{o}C - k_2= 3.64k_1

60^{o}C - k_2=16.4k_1

(b) 10^{o}C - k_2=3.87k_1

25^{o}C - k_2=25.2k_1

60^{o}C - k_2=1090k_1

(c) 10^{o}C- k_2=15.0k_1

25^{o}C- k_2=636k_1

60^{o}C- k_2=1.19x10^{6}k_1

Note the increase in affect of the temperature the larger the activation energy.

S50

ln$k$=lnA-(E_a/RT)

A plot of ln*k* vs. 1/T would yield a straight line. The slope of this line would be -(E_a/R) with an x-intercept of E_a/(R(lnA)) and a y-intercept of lnA.

S51

(a) 2.51a.png (b) 2.51b.png (c) 2.51c.png This is an example of a substitution reaction, which you'll learn about later.

(d) No Reaction (e) 2.51d.png

S52

ΔG=ΔH-TΔS

ΔH	ΔS
Less than Zero	ΔS can either be any positive value, or a negative value such that |TΔS|<|ΔH|
ΔH can either be any negative value, or a positive value such that |ΔH|<|TΔS|	Greater than Zero

S53

(a) Rate=*k*[$CH_3CH_2O^-$][alkyl bromide]

2.53aa.png

(b) Rate=*k*[CHC^-][alkyl bromide]

2.53ba.png

S54

2.54a.png (b) is correct, there are 12 primary H's and 2 tertiary H's.

(a) There are 10 primary H's - incorrect, there are 12 primary H's

(c) There are 3 tertiary C's - incorrect, there are 2 tertiary C's

(d) There are no primary C's - There are 4 primary C's

S55

ΔG=ΔH-TΔS=-1000-(200)(-2)=-600 cal/mol, so (c) is true. exergonic means that ΔG<0.

(a) The reaction is endothermic - incorrect, ΔH<0

(b) The reaction is not spontaneous - incorrect, ΔG<0

(d) It is likely that the reaction involves one reactant and yields two products. - incorrect, with a negative change in entropy, it is more likely that two reactants yielded one product.

S56

This molecule is entirely sp^3 hybridized, so all angles are 109.5^o, (d).

S57

(c) - *gauche* staggered is the conformation. The two CH_3 groups are separated by 60^o and no group is eclipsed. The lowest energy conformation would be (d) *anti* staggered, where the larger CH_3 groups are anti and there is no eclipsed group.

S58

(c), aldehyde is not in the molecule. There is a ketone, but no aldehyde.

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3: REACTIONS OF ALKANES: BOND-DISSOCIATION ENERGIES, RADICAL HALOGENATION, AND RELATIVE REACTIVITY

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

3.1: Strength of Alkane Bonds: Radicals

3.2: Structure of Alkyl Radicals: Hyperconjugation

3.3: Conversion of Petroleum: Pyrolysis

3.4: Chlorination of Methane: The Radical Chain Mechanism

3.5: Other Radical Halogenations of Methane

3.6: Keys to Success: Using the "Known" Mechanism as a model for the "Unknown"

3.7: Chlorination of Higher Alkanes: Relative Reactivity and Selectivity

3.8: Selectivity in Radical Halogenation with Fluorine and Bromine

3.9: Synthetic Radical Halogenation

3.10: Synthetic Chlorine Compounds and the Stratospheric Ozone Layer

3.11: Combustion and the Relative Stabilities of Alkanes

3.E: Reactions of Alkanes (Exercises)

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3.1: Strength of Alkane Bonds: Radicals

In chemistry, a **radical** (more precisely, a **free radical**) is an atom, molecule, or ion that has unpaired valence electrons or an open electron shell, and therefore may be seen as having one or more "dangling" covalent bonds.

With some exceptions, these "dangling" bonds make free radicals highly chemically reactive towards other substances, or even towards themselves: their molecules will often spontaneously dimerize or polymerize if they come in contact with each other. Most radicals are reasonably stable only at very low concentrations in inert media or in a vacuum.

Free radicals may be created in a number of ways, including synthesis with very dilute or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. The latter can be affected by any process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Indeed, radicals are intermediate stages in many chemical reactions.

History

The first organic free radical identified was triphenylmethyl radical. This species was discovered by Moses Gomberg in 1900 at the University of Michigan USA. Historically, the term *radical* in radical theory was also used for bound parts of the molecule, especially when they remain unchanged in reactions. These are now called functional groups. For example, methyl alcohol was described as consisting of a methyl "radical" and a hydroxyl "radical". Neither are radicals in the modern chemical sense, as they are permanently bound to each other, and have no unpaired, reactive electrons; however, they can be observed as radicals in mass spectrometry when broken apart by irradiation with energetic electrons.

Depiction in chemical reactions

In this chapter, we will learn about some reactions in which the key steps involve the movement of *single* electrons. You may recall from way back in section 6.1A that single electron movement is depicted by a single-barbed**'fish-hook'** arrow (as opposed to the familiar double-barbed arrows that we have been using throughout the book to show two-electron movement).

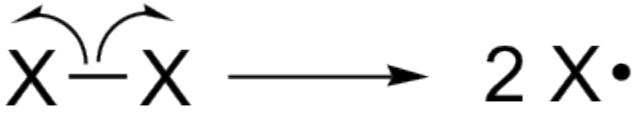


curved, two-barbed arrow:
two electron movement



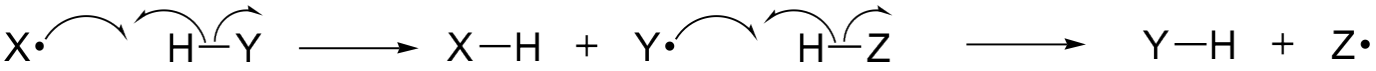
curved, single-barbed ('fish-hook') arrow:
single electron movement

Single-electron mechanisms involve the formation and subsequent reaction of free radical species, highly unstable intermediates that contain an unpaired electron. We will learn in this chapter how free radicals are often formed from **homolytic cleavage**, an event where the two electrons in a breaking covalent bond move in opposite directions.



(In contrast, essentially all of the reactions we have studied up to now involve bond-breaking events in which both electrons move in the same direction: this is called **heterolytic cleavage**).

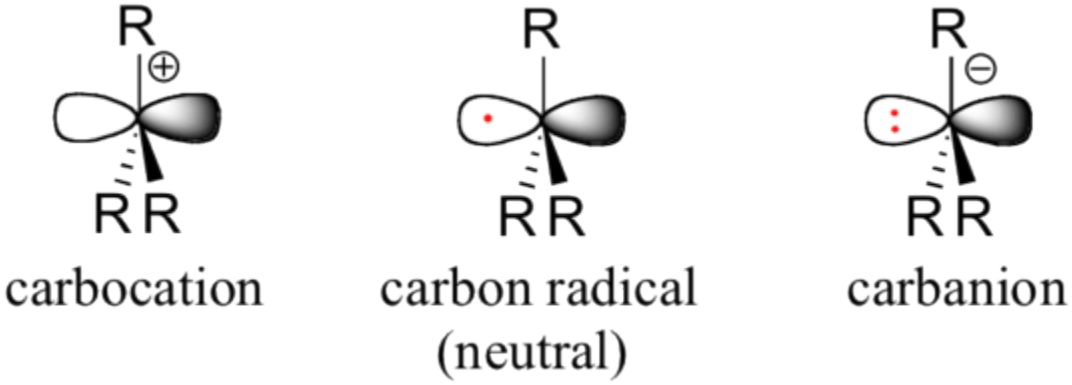
We will also learn that many single-electron mechanisms take the form of a radical chain reaction, in which one radical causes the formation of a second radical, which in turn causes the formation of a third radical, and so on.



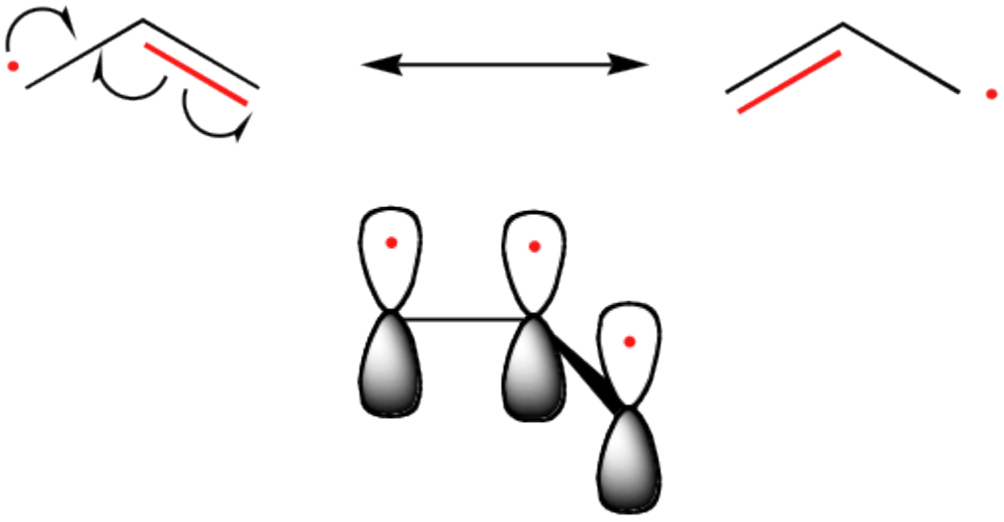
The high reactivity of free radical species and their ability to initiate chain reactions is often beneficial - we will learn in this chapter about radical polymerization reactions that form useful materials such as plexiglass and polyproylene fabric. We will also learn about radical reactions that are harmful, such as the degradation of atmospheric ozone by freon, and the oxidative damage done to lipids and DNA in our bodies by free radicals species. Finally, we will see how some enzymes use bound metals to catalyze high e

The geometry and relative stability of carbon radicals

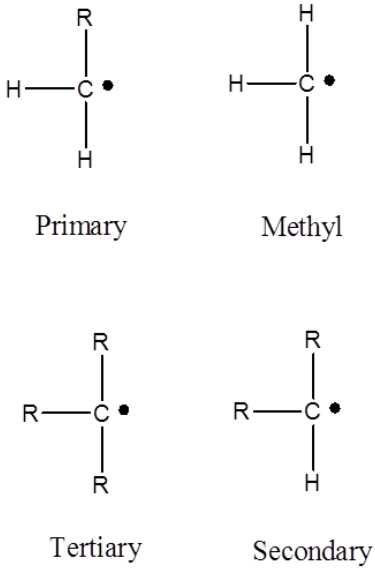
As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp^2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$orbital. Contrast this picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.



The trend in the stability of carbon radicals parallels that of carbocations (section 8.4B): tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, can be considered to be electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups. Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons.

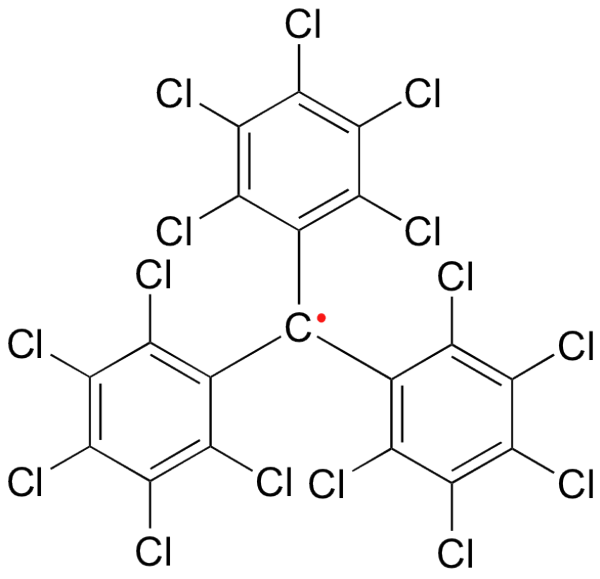


Trends in radical stability



Allyic & Benzlic > 3^{o} > 2^{o} > 1^{o} > Methyl

Template:ExampleStart
Exercise 17.1: Draw the structure of a benzylic radical compound, and then draw a resonance form showing how the radical is stabilized.
Template:ExampleEnd
With enough resonance stabilization, radicals can be made that are quite unreactive. One example of an inert organic radical structure is shown below.



In this molecule, the already extensive resonance stabilization is further enhanced by the ability of the chlorine atoms to shield the radical center from external reagents. The radical is, in some sense, inside a protective 'cage'.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

The Relationship between Bond Order and Bond Energy

Triple bonds between like atoms are shorter than double bonds, and because more energy is required to completely break all three bonds than to completely break two, a triple bond is also stronger than a double bond. Similarly, double bonds between like atoms are stronger and shorter than single bonds. Bonds of the same order between *different* atoms show a wide range of bond energies, however. Table 8.6 lists the average values for some commonly encountered bonds. Although the values shown vary widely, we can observe four trends:

Table 8.6 Average Bond Energies (kJ/mol) for Commonly Encountered Bonds at 273 K

Single Bonds									Multiple Bonds	
H–H	432	C–C	346	N–N	≈167	O–O	≈142	F–F	155	C=C	602
H–C	411	C–Si	318	N–O	201	O–F	190	F–Cl	249	C≡C	835
H–Si	318	C–N	305	N–F	283	O–Cl	218	F–Br	249	C=N	615
H–N	386	C–O	358	N–Cl	313	O–Br	201	F–I	278	C≡N	887
H–P	≈322	C–S	272	N–Br	243	O–I	201	Cl–Cl	240	C=O	749
H–O	459	C–F	485	P–P	201	S–S	226	Cl–Br	216	C≡O	1072
H–S	363	C–Cl	327			S–F	284	Cl–I	208	N=N	418
H–F	565	C–Br	285			S–Cl	255	Br–Br	190	N≡N	942
H–Cl	428	C–I	213			S–Br	218	Br–I	175	N=O	607
H–Br	362	Si–Si	222					I–I	149	O=O	494
H–I	295	Si–O	452							S=O	532

Source: Data from J. E. Huheey, E. A. Keiter, and R. L. Keiter, *Inorganic Chemistry*, 4th ed. (1993).

1. Bonds between hydrogen and atoms in the same column of the periodic table decrease in strength as we go down the column. Thus an H–F bond is stronger than an H–I bond, H–C is stronger than H–Si, H–N is stronger than H–P, H–O is stronger than H–S, and so forth. The reason for this is that the region of space in which electrons are shared between two atoms becomes proportionally smaller as one of the atoms becomes larger (part (a) in Figure 8.11).
2. Bonds between like atoms usually become *weaker* as we go down a column (important exceptions are noted later). For example, the C–C single bond is stronger than the Si–Si single bond, which is stronger than the Ge–Ge bond, and so forth. As two bonded atoms become larger, the region between them occupied by bonding electrons becomes *proportionally* smaller, as illustrated in part (b) in Figure 8.11. Noteworthy exceptions are single bonds between the period 2 atoms of groups 15, 16, and 17 (i.e., N, O, F), which are unusually weak compared with single bonds between their larger congeners. It is likely that the N–N, O–O, and F–F single bonds are weaker than might be expected due to strong repulsive interactions between lone pairs of electrons on *adjacent* atoms. The trend in bond energies for the halogens is therefore

$$\text{Cl–Cl} > \text{Br–Br} > \text{F–F} > \text{I–I}$$

Similar effects are also seen for the O–O versus S–S and for N–N versus P–P single bonds.

Note

Bonds between hydrogen and atoms in a given column in the periodic table are weaker down the column; bonds between like atoms usually become weaker down a column.

3. Because elements in periods 3 and 4 rarely form multiple bonds with themselves, their multiple bond energies are not accurately known. Nonetheless, they are presumed to be significantly weaker than multiple bonds between lighter atoms of the same families. Compounds containing an Si=Si double bond, for example, have only recently been prepared, whereas compounds containing C=C double bonds are one of the best-studied and most important classes of organic compounds.

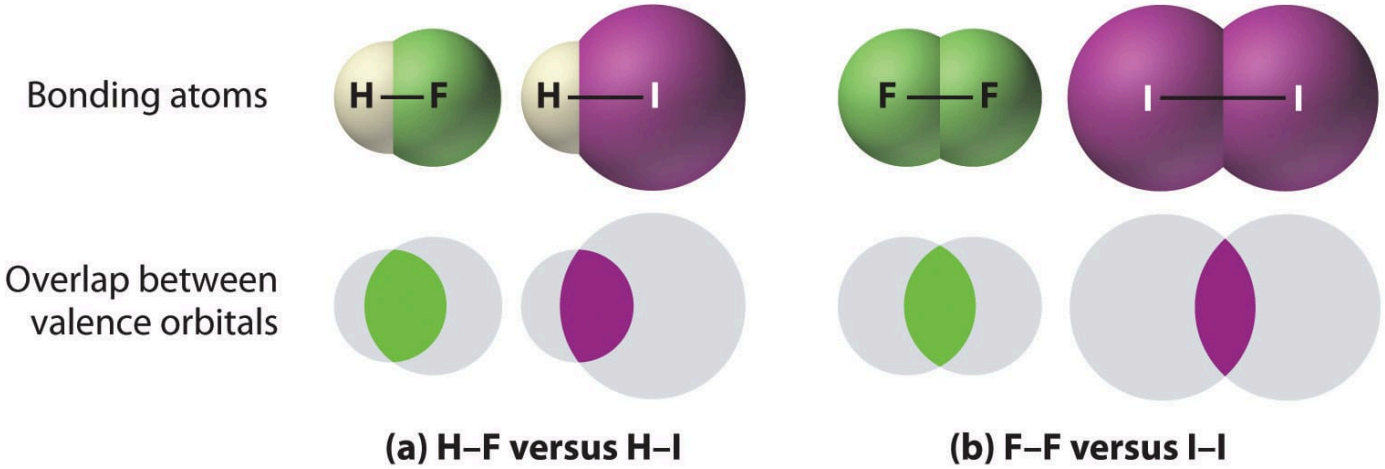


Figure 8.11 *The Strength of Covalent Bonds Depends on the Overlap between the Valence Orbitals of the Bonded Atoms. The relative sizes of the region of space in which electrons are shared between (a) a hydrogen atom and lighter (smaller) vs. heavier (larger) atoms in the same periodic group; and (b) two lighter versus two heavier atoms in the same group. Although the absolute amount of shared space increases in both cases on going from a light to a heavy atom, the amount of space relative to the size of the bonded atom decreases; that is, the percentage of total orbital volume decreases with increasing size. Hence the strength of the bond decreases.*

4. Multiple bonds between carbon, oxygen, or nitrogen and a period 3 element such as phosphorus or sulfur tend to be unusually strong. In fact, multiple bonds of this type dominate the chemistry of the period 3 elements of groups 15 and 16. Multiple bonds to phosphorus or sulfur occur as a result of *d*-orbital interactions, as we discussed for the SO_4^{2-} ion in Section 8.6. In contrast, silicon in group 14 has little tendency to form discrete silicon–oxygen double bonds. Consequently, SiO_2 has a three-dimensional network structure in which each silicon atom forms four Si–O single bonds, which makes the physical and chemical properties of SiO_2 very different from those of CO_2.

Note
Bond strengths increase as bond order **increases**, while bond distances **decrease**.

Table: Average bond energies:

Bond	**(kJ/mol)**
C-F	485

C-Cl	328
C-Br	276
C-I	240
C-C	348
C-N	293
C-O	358
C-F	485
C-C	348
C=C	614
C≡C	839

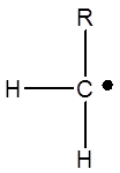
Contributors

- Kim Song (UCD), Donald Le (UCD)

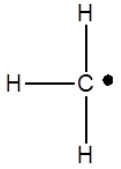
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3.2: Structure of Alkyl Radicals: Hyperconjugation

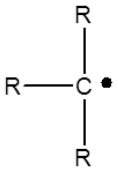
Trend in Radical Stability



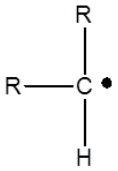
Primary



Methyl



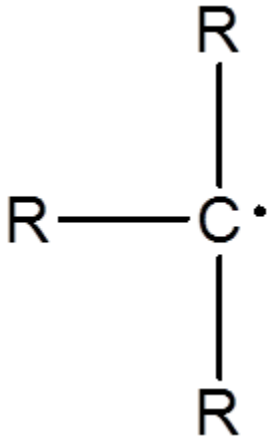
Tertiary



Secondary

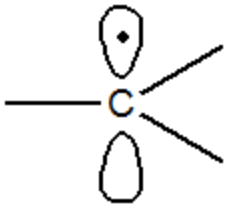
$3^o > 2^o > 1^o >$ Methyl

In order to understand the reason for this ordering in radical stability we must first look at the structure of a alkyl radical.

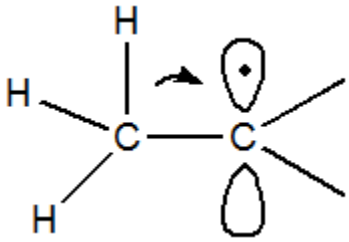


Experimental data have shown that radicals have a trigonal planar geometry associated with sp^2 hybridization.

The unpaired electron is contained in a p orbital which is perpendicular to the molecular plane.



This trigonal planar geometry allows for sigma on adjacent carbons to align and overlap with the p orbital. The alignment allows for the electrons in the sigma bond to donate electrons into the electron deficient p orbital. This process is called hyperconjugation.



The more alkyl substituents, and therefore more sigma bonds, the electron density is donated into the p orbitals. This is why the general trend in radical stability is true $3^{o} > 2^{o} > 1^{o}$ > Methyl.

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3.3: Conversion of Petroleum: Pyrolysis

Objectives

After completing this section, you should be able to

1. describe the general nature of petroleum deposits, and recognize why petroleum is such an important source of organic compounds.
2. explain, in general terms, the processes involved in the refining of petroleum.
3. define the octane number of a fuel, and relate octane number to chemical structure.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- catalytic cracking
- catalytic reforming
- fractional distillation
- octane number (octane rating)

Study Notes

The refining of petroleum into usable fractions is a very important industrial process. In the laboratory component of this course, you will have the opportunity to compare this industrial process to the distillation procedure as it is performed in the student laboratory.

Petroleum

The petroleum that is pumped out of the ground is a complex mixture of several thousand organic compounds, including straight-chain alkanes, cycloalkanes, alkenes, and aromatic hydrocarbons with four to several hundred carbon atoms. The identities and relative abundance of the components vary depending on the source - Texas crude oil is somewhat different from Saudi Arabian crude oil. In fact, the analysis of petroleum from different deposits can produce a “fingerprint” of each, which is useful in tracking down the sources of spilled crude oil. For example, Texas crude oil is “sweet,” meaning that it contains a small amount of sulfur-containing molecules, whereas Saudi Arabian crude oil is “sour,” meaning that it contains a relatively large amount of sulfur-containing molecules.

Gasoline

Petroleum is converted to useful products such as gasoline in three steps: distillation, cracking, and reforming. Recall from Chapter 1 that distillation separates compounds on the basis of their relative volatility, which is usually inversely proportional to their boiling points. Part (a) in Figure 3.8.1 shows a cutaway drawing of a column used in the petroleum industry for separating the components of crude oil. The petroleum is heated to approximately 400°C (750°F) and becomes a mixture of liquid and vapor. This mixture, called the feedstock, is introduced into the refining tower. The most volatile components (those with the lowest boiling points) condense at the top of the column where it is cooler, while the less volatile components condense nearer the bottom. Some materials are so nonvolatile that they collect at the bottom without evaporating at all. Thus the composition of the liquid condensing at each level is different. These different fractions, each of which usually consists of a mixture of compounds with similar numbers of carbon atoms, are drawn off separately. Part (b) in Figure 3.8.1 shows the typical fractions collected at refineries, the number of carbon atoms they contain, their boiling points, and their ultimate uses. These products range from gases used in natural and bottled gas to liquids used in fuels and lubricants to gummy solids used as tar on roads and roofs.

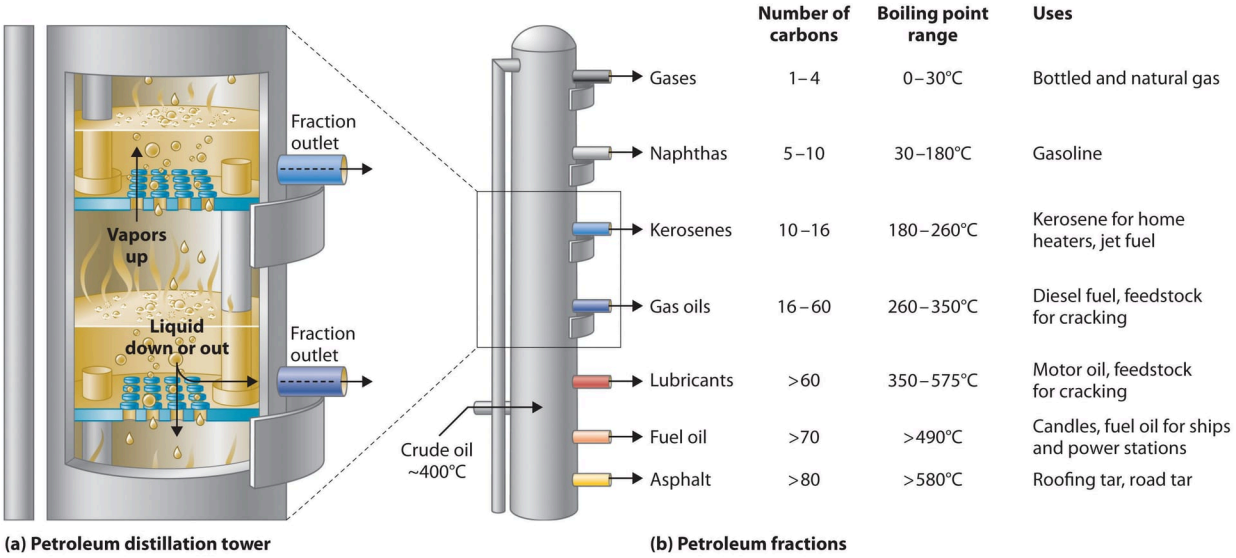


Figure 3.8.1: The Distillation of Petroleum. (a) This is a diagram of a distillation column used for separating petroleum fractions. (b) Petroleum fractions condense at different temperatures, depending on the number of carbon atoms in the molecules, and are drawn off from the column. The most volatile components (those with the lowest boiling points) condense at the top of the column, and the least volatile (those with the highest boiling points) condense at the bottom. (CC BY-NC-SA; anonymous)

The economics of petroleum refining are complex. For example, the market demand for kerosene and lubricants is much lower than the demand for gasoline, yet all three fractions are obtained from the distillation column in comparable amounts. Furthermore, most gasolines and jet fuels are blends with very carefully controlled compositions that cannot vary as their original feedstocks did. To make petroleum refining more profitable, the less volatile, lower-value fractions are converted to more volatile, higher-value mixtures that have carefully controlled formulas. The first process used to accomplish this transformation is cracking, in which the larger and heavier hydrocarbons in the kerosene and higher-boiling-point fractions are heated to temperatures as high as 900°C. High-temperature reactions cause the carbon–carbon bonds to break, which converts the compounds to lighter molecules similar to those in the gasoline fraction. Thus in cracking, a straight-chain alkane with a number of carbon atoms corresponding to the kerosene fraction is converted to a mixture of hydrocarbons with a number of carbon atoms corresponding to the lighter gasoline fraction. The second process used to increase the amount of valuable products is called reforming; it is the chemical conversion of straight-chain alkanes to either branched-chain alkanes or mixtures of aromatic hydrocarbons. Using metals such as platinum brings about the necessary chemical reactions. The mixtures of products obtained from cracking and reforming are separated by fractional distillation.

Octane Ratings

The quality of a fuel is indicated by its octane rating, which is a measure of its ability to burn in a combustion engine without knocking or pinging. Knocking and pinging signal premature combustion (Figure 3.8.2), which can be caused either by an engine malfunction or by a fuel that burns too fast. In either case, the gasoline-air mixture detonates at the wrong point in the engine cycle, which reduces the power output and can damage valves, pistons, bearings, and other engine components. The various gasoline formulations are designed to provide the mix of hydrocarbons least likely to cause knocking or pinging in a given type of engine performing at a particular level.

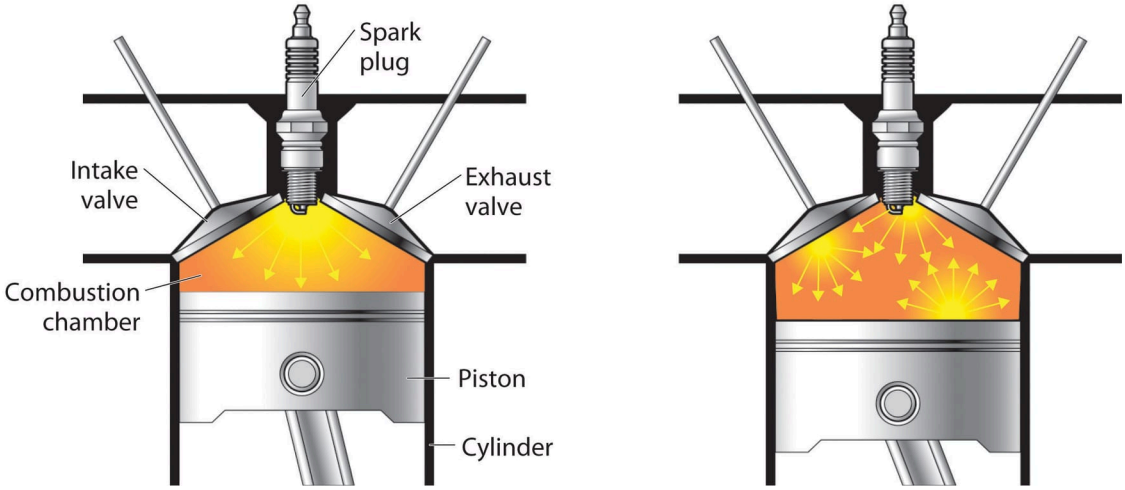


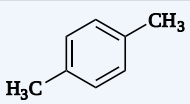
Figure 3.8.2: The Burning of Gasoline in an Internal Combustion Engine. (a) Normally, fuel is ignited by the spark plug, and combustion spreads uniformly outward. (b) Gasoline with an octane rating that is too low for the engine can ignite prematurely, resulting in uneven burning that causes knocking and pinging. (CC BY-NC-SA; anonymous)

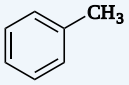
The octane scale was established in 1927 using a standard test engine and two pure compounds: n-heptane and isooctane (2,2,4-trimethylpentane). n-Heptane, which causes a great deal of knocking on combustion, was assigned an octane rating of 0, whereas isooctane, a very smooth-burning fuel, was assigned an octane rating of 100. Chemists assign octane ratings to different blends of gasoline by burning a sample of each in a test engine and comparing the observed knocking with the amount of knocking caused by specific mixtures of n-heptane and isooctane. For example, the octane rating of a blend of 89% isooctane and 11% n-heptane is simply the average of the octane ratings of the components weighted by the relative amounts of each in the blend. Converting percentages to decimals, we obtain the octane rating of the mixture:

$$0.89(100) + 0.11(0) = 89 \tag{3.3.1}$$

As shown in Table 3.3.1, many compounds that are now available have octane ratings greater than 100, which means they are better fuels than pure isooctane. In addition, anti-knock agents, also called octane enhancers, have been developed. One of the most widely used for many years was **tetraethyl lead** [$(C_2H_5)_4Pb$], which at approximately 3 g/gal gives a 10–15-point increase in octane rating. Since 1975, however, lead compounds have been phased out as gasoline additives because they are highly toxic. Other enhancers, such as methyl t-butyl ether (MTBE), have been developed to take their place. They combine a high octane rating with minimal corrosion to engine and fuel system parts. Unfortunately, when gasoline containing MTBE leaks from underground storage tanks, the result has been contamination of the groundwater in some locations, resulting in limitations or outright bans on the use of MTBE in certain areas. As a result, the use of alternative octane enhancers such as ethanol, which can be obtained from renewable resources such as corn, sugar cane, and, eventually, corn stalks and grasses, is increasing.

Table 3.3.1: The Octane Ratings of Some Hydrocarbons and Common Additives

Name	Condensed Structural Formula	Octane Rating	Name	Condensed Structural Formula	Octane Rating
n-heptane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	0	*o*-xylene	skeletal structure of o-xylene.cdxml	107
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	25	ethanol	CH_3CH_2OH	108
n-pentane	$CH_3CH_2CH_2CH_2CH_3$	62	*t*-butyl alcohol	$(CH_3)_3COH$	113
isooctane	$(CH_3)_3CCH_2CH(CH_3)_2$	100	*p*-xylene		116

Name	Condensed Structural Formula	Octane Rating	Name	Condensed Structural Formula	Octane Rating
benzene		106	methyl *t*-butyl ether	$H_3COC(CH_3)_3$	116
methanol	CH_3OH	107	toluene		118

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3.4: Chlorination of Methane: The Radical Chain Mechanism

Objectives

After completing this section, you should be able to

1. explain why the radical halogenation of alkanes is not usually a particularly good method of preparing pure samples of alkyl halides.
2. use C — H bond energies to account for the fact that in radical chlorinations, the reactivity of hydrogen atoms decreases in the order

$$\text{tertiary} > \text{secondary} > \text{primary}.$$

3. predict the approximate ratio of the expected products from the monochlorination of a given alkane.

Study Notes

The following terms are synonymous:

1. methyl hydrogens, primary hydrogens, and 1° hydrogens.
2. methylene hydrogens, secondary hydrogens, and 2° hydrogens.
3. methine hydrogens, tertiary hydrogens, and 3° hydrogens.

Note that in radical chlorination reactions, the reactivity of methine, methylene and methyl hydrogens decreases in the ratio of approximately 5 : 3.5 : 1. This will aid in the prediction of expected products from the monochlorination of a given alkane.

Radical Halogenation

Alkanes (the simplest of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen (Cl_2 or Br_2) to form a haloalkane. This reaction is very important in organic chemistry because it functionalizes alkanes which opens a gateway to further chemical reactions.

General Reaction

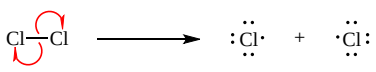
$$CH_4 + Cl_2 + energy \rightarrow CH_3Cl + HCl$$

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism which is characterized by three steps: **initiation**, **propagation,** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining.

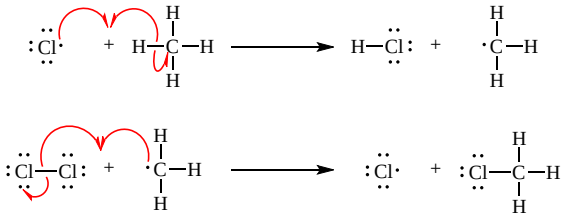
Step 1: Initiation

During the initiation step free radicals are created when ultraviolet light or heat causes the X-X halogen bond to undergo homolytic to create two halogen free radicals. It is important to note that this step is not energetically favorable and cannot occur without some external energy input. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy.



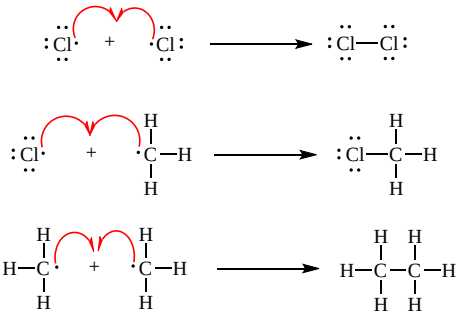
Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical abstracts hydrogen atom from methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step, the methyl radical reacts with more of the chlorine starting material (Cl_2). One of the chlorine atoms becomes a radical and the other combines with the methyl radical to form the alkyl halide product.

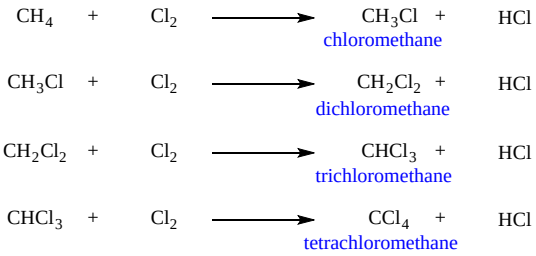


Step 3: Termination

In the three termination steps of this mechanism, radicals produced in the mechanism an undergo radical coupling to form a sigma bond. These are called termination steps because a free radical is not produced as a product, which prevents the reaction from continuing. Combining the two types of radicals produced can be combined to from three possible products. Two chlorine radicals and couple to form more halogen reactant (Cl_2). A chlorine radical and a methyl radical can couple to form more product (CH_3Cl). An finally, two methyl radicals can couple to form a side product of ethane (CH_3CH_3).



This reaction is a poor synthetic method due to the formation of polyhalogenated side products. The desired product occurs when one of the hydrogen atoms in the methane has been replaced by a chlorine atom. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms to produce a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.



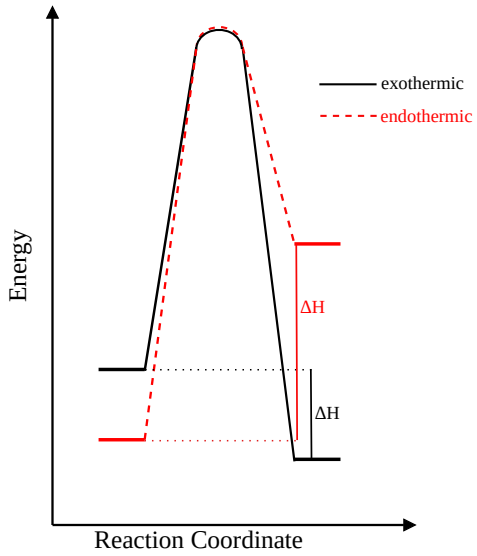
Energetics

Why do these reactions occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy ΔH that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically

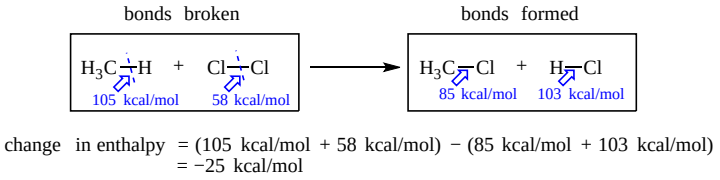
favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



$$\text{change in enthalpy} = (105 \text{ kcal/mol} + 58 \text{ kcal/mol}) - (85 \text{ kcal/mol} + 103 \text{ kcal/mol})$$
$$= -25 \text{ kcal/mol}$$

Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

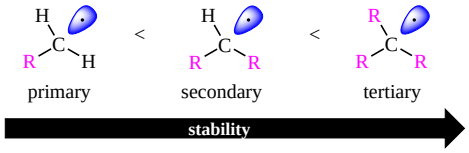
Chlorination of Other Alkanes

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 °C gives 45% 1-chloropropane and 55% 2-chloropropane.

$$CH_3\text{-}CH_2\text{-}CH_3 + Cl_2 \rightarrow 45\%\ CH_3\text{-}CH_2\text{-}CH_2Cl + 55\%\ CH_3\text{-}CHCl\text{-}CH_3$$

These results suggest strongly that 2°-hydrogens are inherently more reactive than 1°-hydrogens, by a factor of about 3.5:1. Further experiments showed that 3°-hydrogens are about 5 times more toward halogen atoms 1°-hydrogens. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3°-hydrogen, despite the presence of nine 1°-hydrogens in the molecule.

$$(CH_3)_3CH + Cl_2 \rightarrow 65\%\ (CH_3)_3CCl + 35\%\ (CH_3)_2CHCH_2Cl$$



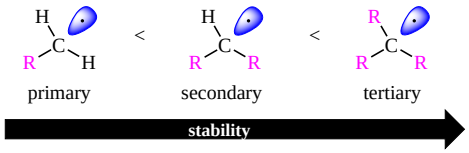
The Relative Reactivity of Hydrogens to

Radical Chlorination

This difference in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured. These values are given in the following table.

R (in R–H)	methyl	ethyl	i-propyl	t-butyl
Bond Dissociation Energy (kcal/mole)	103	98	95	93

This data shows that a tertiary C-H bond (93 kcal/mole) is easier to break than a secondary (95 kcal/mole) and primary (98 kcal/mole) C-H bond. These bond dissociation energies can be used to estimate the relative stability of the radicals formed after homolytic cleavage. Because a tertiary C-H bond requires less energy to undergo homolytic cleavage than a secondary or primary C-H bond, it can be inferred that a tertiary radical is more stable than secondary or primary.



Relative Stability of Free Radicals

Exercise 3.4.1

Write out the complete mechanism for the chlorination of methane.

Answer available at the end of this section.

Exercise 3.4.2

Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.

Answer available at the end of this section.

Exercise 3.4.3

Which step of the radical chain mechanism requires outside energy? What can be used as this energy?

Answer available at the end of this section.

Exercise 3.4.4

Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Answer available at the end of this section.

Exercise 3.4.5

1) Predict the mono-substituted halogenated product(s) of chlorine gas reacting with 2-methylbutane.

2) Predict the relative amount of each mono-brominated product when 3-methylpentane is reacted with Br_2. Consider 1°, 2°, 3° hydrogen.

3) For the following compounds, give all possible monochlorinated derivatives.

a) 

b) 

c) 

d) 

e) 

f) 

Answer available at the end of this section.

Answers

Exercise 3.4.1

The answer to this problem is actually above in the initiation, propagation and termination descriptions.

Exercise 3.4.2

Since the second step in propagation is energetically favorable and fast, it drives the equilibrium toward products, even though the first step is not favorable.

Exercise 3.4.3

Initiation step requires energy which can be in the form of light or het.

Exercise 3.4.4

To calculate the enthalpy of reaction, you subtract the BDE of the bonds formed from the BDE of the bonds broken.

Bonds broken are C-H and Br-Br.

Bonds formed are H-Br adn C-Br.

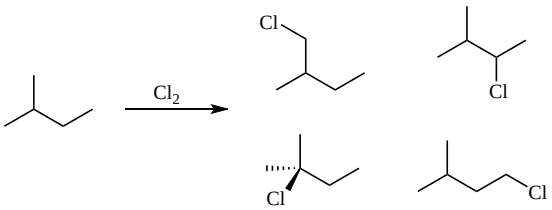
Bonds broken - bonds formed = change in enthalpy

(101 kcal/mol + 46 kcal/mol) - (87 kcal/mol + 70 kcal/mol) = change in enthalpy

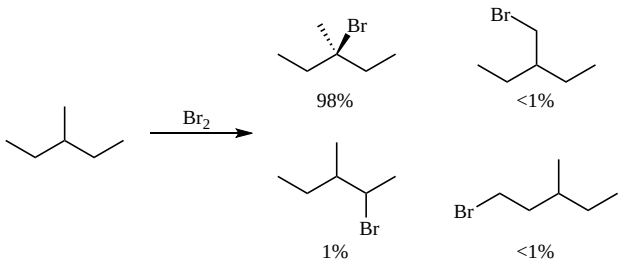
-10 kcal/mol = change in enthalpy for bromination of ethane.

Exercise 3.4.5

1)

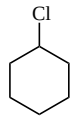


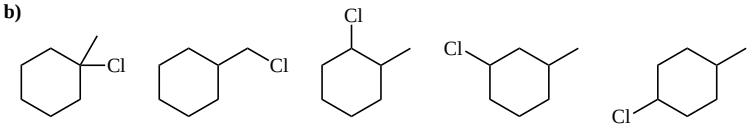
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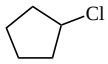


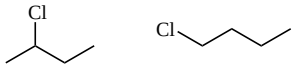
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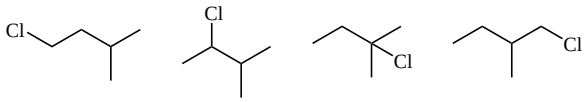
3)

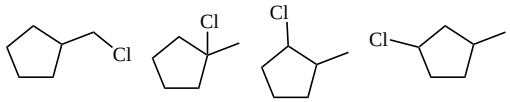
a) 

b) 

c) 

d) 

e) 

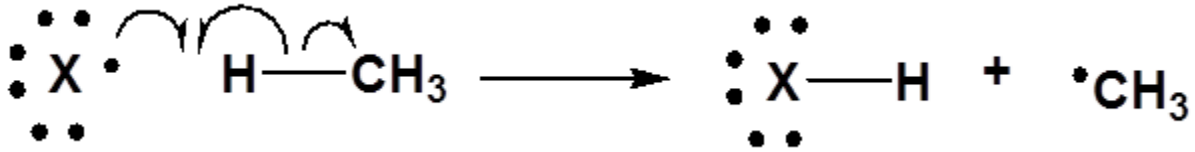
f) 

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3.5: Other Radical Halogenations of Methane

For the radical halogenation of methane, fluorine is the most reactive and iodine is the least reactive. The reason for this can be seen in the enthalpy for the first propagation step in the different halognations of methane. For fluorine the step is exothermic, however, for chlorine, bromine, and iodine the step is endothermic. This trend comes from the relative bond strengths of the H-X bond which is formed. The H-F bond is strong which causes the high reactivity of fluorine in these reactions. Correspondingly, reactions with fluorine have a relatively small activation energy and Iodine have relatively large activation energy. In the case of Iodine the energy of activation is so high that Iodination of methane does not occur.



Enthalpy of the Propagation Steps for the Halogenation of Methane

F: -130 Kj/mol

Cl: +8 Kj/mol

Br: +75 Kj/mol

I: +142 Kj/mol

Relative reactivity of X• in Hydrogen Abstraction reactions

F• > C• > Br• > I•

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3.6: Keys to Success: Using the "Known" Mechanism as a model for the "Unknown"

Alkanes (the most basic of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen to form a haloalkane. This reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

Introduction

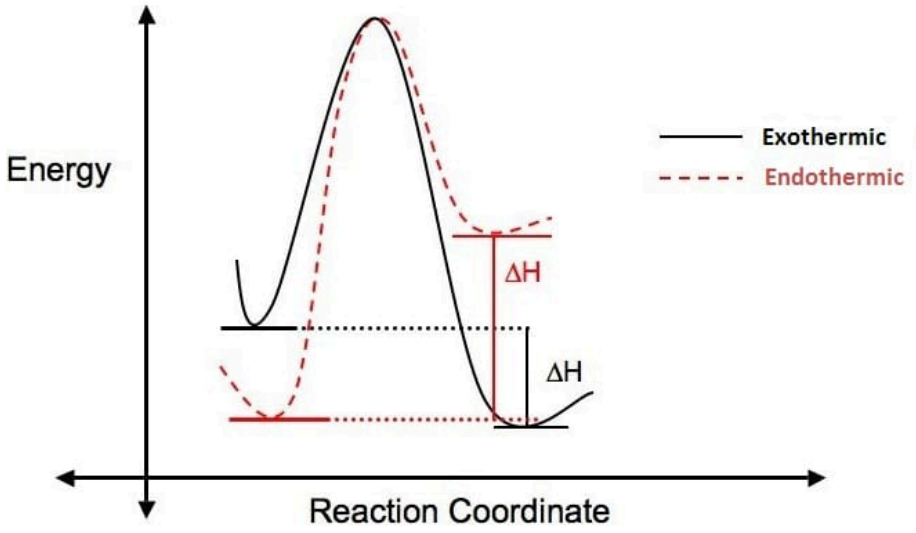
While the reactions possible with alkanes are few, there are many reactions that involve haloalkanes. In order to better understand the mechanism (a detailed look at the step by step process through which a reaction occurs), we will closely examine the chlorination of methane. When methane (CH_4) and chlorine (Cl_2) are mixed together in the absence of light at room temperature nothing happens. However, if the conditions are changed, so that either the reaction is taking place at high temperatures (denoted by Δ) or there is ultra violet irradiation, a product is formed, chloromethane (CH_3Cl).

Energetics

Why does this reaction occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy (ΔH) that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

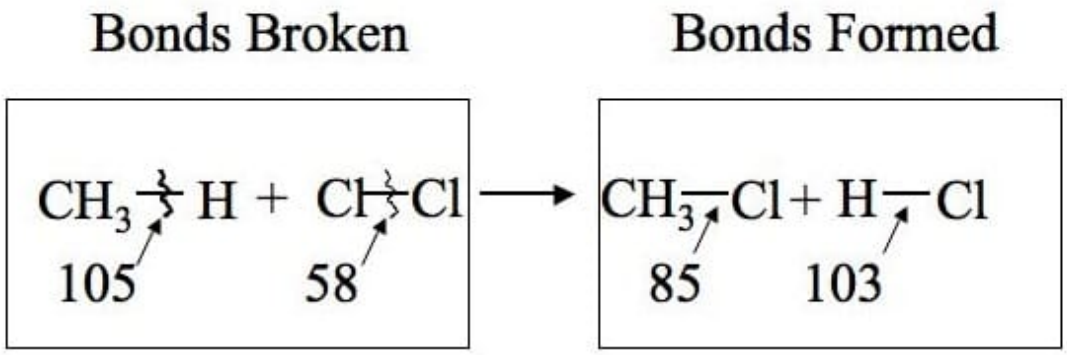
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies ($\Delta H°$):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed} \tag{3.6.1}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



$$\text{Change in enthalpy} = (105 + 58) - (85 + 103)$$
$$= -25\text{kcal/mol}$$

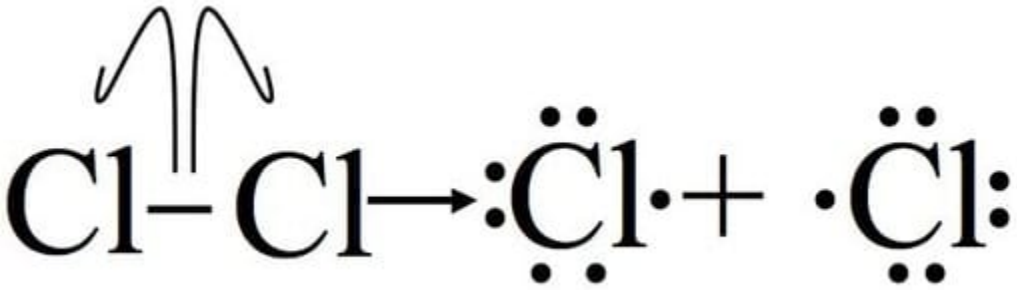
Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism. The radical chain mechanism is characterized by three steps: **initiation**, **propagation** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining. The first propagation step uses up one of the products from initiation, and the second propagation step makes another one, thus the cycle can continue until indefinitely.

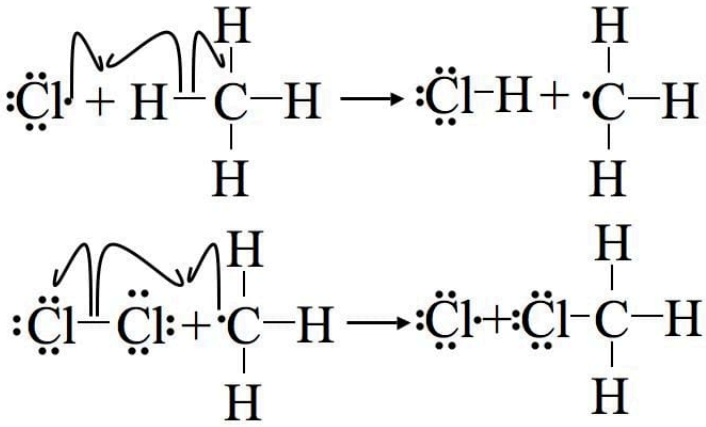
Step 1: Initiation

Initiation breaks the bond between the chlorine molecule (Cl_2). For this step to occur energy must be put in, this step is not energetically favorable. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy. It is important to note that this part of the mechanism cannot occur without some external energy input, through light or heat.

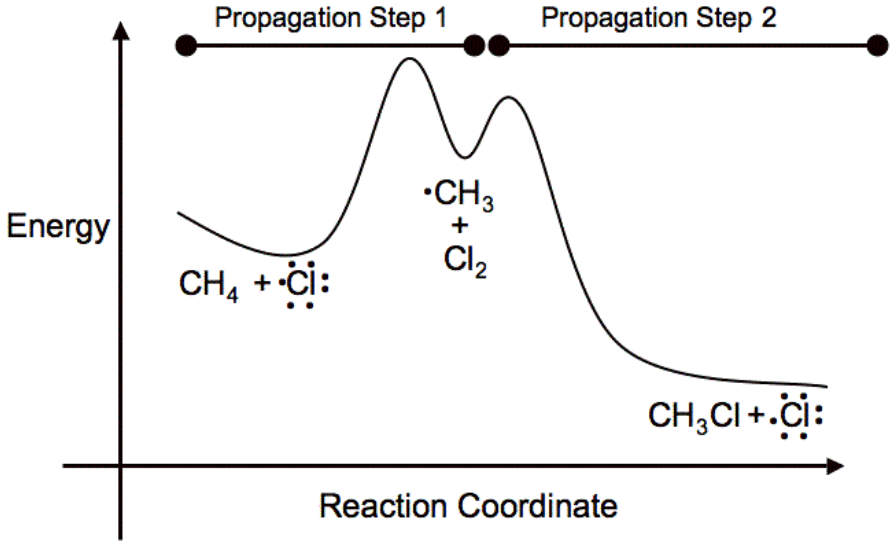


Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical combines with a hydrogen on the methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step more of the chlorine starting material (Cl_2) is used, one of the chlorine atoms becomes a radical and the other combines with the methyl radical.

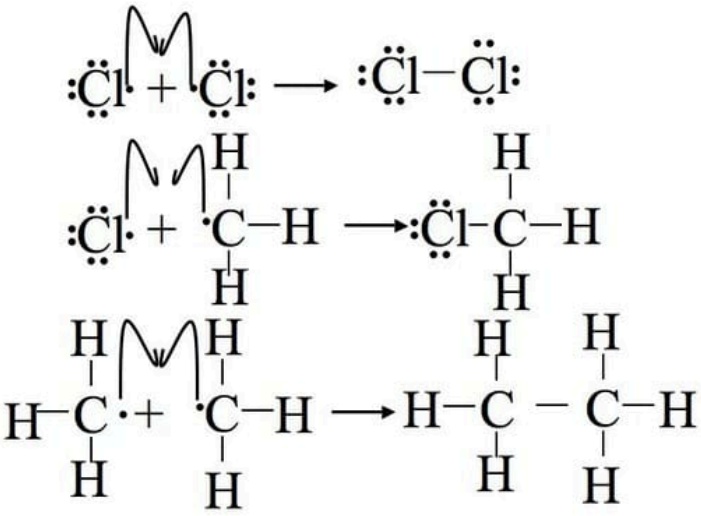


The first propagation step is endothermic, meaning it takes in heat (requires 2 kcal/mol) and is not energetically favorable. In contrast the second propagation step is exothermic, releasing 27 kcal/mol. Since the second propagation step is so exothermic, it occurs very quickly. The second propagation step uses up a product from the first propagation step (the methyl radical) and following Le Chatelier's principle, when the product of the first step is removed the equilibrium is shifted towards it's products. This principle is what governs the unfavorable first propagation step's occurance.



Step 3: Termination

In the termination steps, all the remaining radicals combine (in all possible manners) to form more product (CH_3Cl), more reactant (Cl_2) and even combinations of the two methyl radicals to form a side product of ethane (CH_3CH_3).



Problems with the Chlorination of Methane

The chlorination of methane does not necessarily stop after one chlorination. It may actually be very hard to get a monosubstituted chloromethane. Instead di-, tri- and even tetra-chloromethanes are formed. One way to avoid this problem is to use a much higher concentration of methane in comparison to chloride. This reduces the chance of a chlorine radical running into a chloromethane and starting the mechanism over again to form a dichloromethane. Through this method of controlling product ratios one is able to have a relative amount of control over the product.

References

1. Matyjaszewski, Krzysztof, Wojciech Jakubowski, Ke Min, Wei Tang, Jinyu Huang, Wade A. Braunecker, and Nicolay V. Tsarevsky. "Diminishing Catalyst Concentration in Atom Transfer Radical Polymerization with Reducing Agents." Proceedings of the National Academy of Sciences of the United States of America 103 (2006): 15309-5314.
2. Morgan, G. T. "A State Experiment in Chemical Research." Science 72 (1930): 379-90.
3. Phillips, Francis C. "# Researches upon the Chemical Properties of Gases." Researches upon the Chemical Properties of Gases 17 (1893): 149-236.

Outside Links

- Video of Mechanism: http://www.jbpub.com/organic-online/...s/chlormet.htm
- Wikipedia of Radical Chain Mechanism: http://en.Wikipedia.org/wiki/Free_ra...l_halogenation
- Wikipedia of Le Chatelier's Principle: http://en.Wikipedia.org/wiki/Le_Chat...#Concentration

Problems

Answers to these questions are in an attached slide

1. Write out the complete mechanism for the chlorination of methane.
2. Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.
3. Compounds other than chlorine and methane go through halogenation with the radical chain mechanism. Write out a generalized equation for the halogenation of RH with X_2including all the different steps of the mechanism.
4. Which step of the radical chain mechanism requires outside energy? What can be used as this energy?
5. Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Contributors

- Kristen Kelley and Britt Farquharson

Further Reading

Wikipedia

Free radical halogenation

Khan Academy

Free radical reactions

Carey 5th Ed Online

Radical substitution reactions

Chemtube3D

Radical Chlorination of alkanes

MasterOrganicChemistry

Free radical halogenation

Selectivity in free radical reactions

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3.7: Chlorination of Higher Alkanes: Relative Reactivity and Selectivity

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3.8: Selectivity in Radical Halogenation with Fluorine and Bromine

Objectives

After completing this section, you should be able to

1. explain why the radical halogenation of alkanes is not usually a particularly good method of preparing pure samples of alkyl halides.
2. use C – H bond energies to account for the fact that in radical chlorinations, the reactivity of hydrogen atoms decreases in the order

$$\text{tertiary} > \text{secondary} > \text{primary}.$$

3. predict the approximate ratio of the expected products from the monochlorination of a given alkane.

Study Notes

The following terms are synonymous:

1. methyl hydrogens, primary hydrogens, and 1° hydrogens.
2. methylene hydrogens, secondary hydrogens, and 2° hydrogens.
3. methine hydrogens, tertiary hydrogens, and 3° hydrogens.

Note that in radical chlorination reactions, the reactivity of methine, methylene and methyl hydrogens decreases in the ratio of approximately 5 : 3.5 : 1. This will aid in the prediction of expected products from the monochlorination of a given alkane.

Radical Halogenation

Alkanes (the simplest of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen (Cl_2 or Br_2) to form a haloalkane. This reaction is very important in organic chemistry because it functionalizes alkanes which opens a gateway to further chemical reactions.

General Reaction

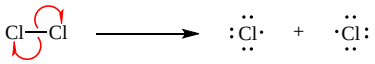
$$CH_4 + Cl_2 + energy \rightarrow CH_3Cl + HCl$$

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism which is characterized by three steps: **initiation**, **propagation,** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining.

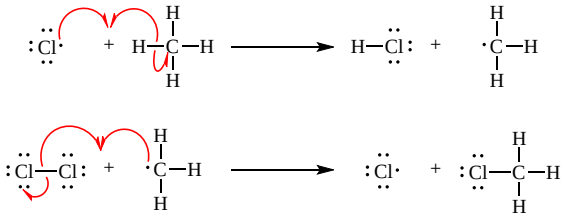
Step 1: Initiation

During the initiation step free radicals are created when ultraviolet light or heat causes the X-X halogen bond to undergo homolytic to create two halogen free radicals. It is important to note that this step is not energetically favorable and cannot occur without some external energy input. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy.



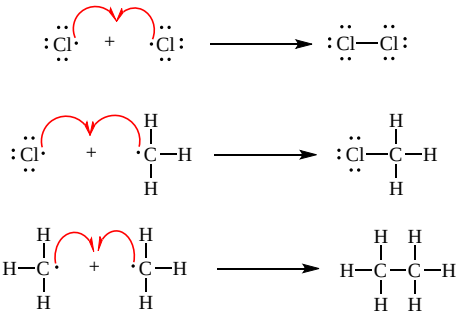
Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical abstracts hydrogen atom from methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step, the methyl radical reacts with more of the chlorine starting material (Cl_2). One of the chlorine atoms becomes a radical and the other combines with the methyl radical to form the alkyl halide product.

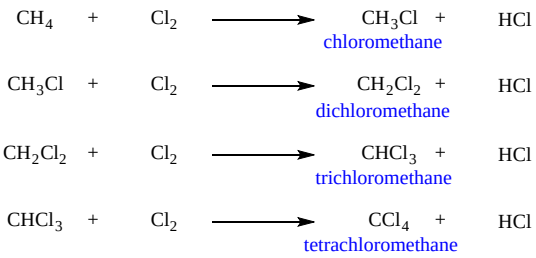


Step 3: Termination

In the three termination steps of this mechanism, radicals produced in the mechanism an undergo radical coupling to form a sigma bond. These are called termination steps because a free radical is not produced as a product, which prevents the reaction from continuing. Combining the two types of radicals produced can be combined to from three possible products. Two chlorine radicals and couple to form more halogen reactant (Cl_2). A chlorine radical and a methyl radical can couple to form more product (CH_3Cl). An finally, two methyl radicals can couple to form a side product of ethane (CH_3CH_3).



This reaction is a poor synthetic method due to the formation of polyhalogenated side products. The desired product occurs when one of the hydrogen atoms in the methane has been replaced by a chlorine atom. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms to produce a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.



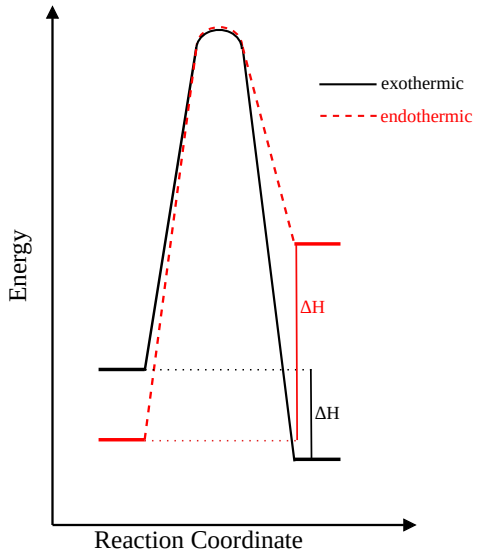
Energetics

Why do these reactions occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy ΔH that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically

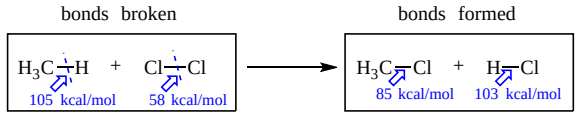
favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



change in enthalpy = (105 kcal/mol + 58 kcal/mol) − (85 kcal/mol + 103 kcal/mol)
= −25 kcal/mol

Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

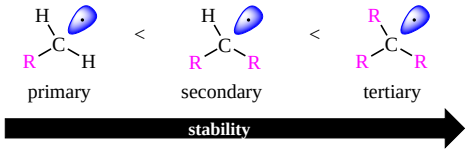
Chlorination of Other Alkanes

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 °C gives 45% 1-chloropropane and 55% 2-chloropropane.

$$CH_3\text{-}CH_2\text{-}CH_3 + Cl_2 \rightarrow 45\%\ CH_3\text{-}CH_2\text{-}CH_2Cl + 55\%\ CH_3\text{-}CHCl\text{-}CH_3$$

These results suggest strongly that 2°-hydrogens are inherently more reactive than 1°-hydrogens, by a factor of about 3.5:1. Further experiments showed that 3°-hydrogens are about 5 times more toward halogen atoms 1°-hydrogens. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3°-hydrogen, despite the presence of nine 1°-hydrogens in the molecule.

$$(CH_3)_3CH + Cl_2 \rightarrow 65\%\ (CH_3)_3CCl + 35\%\ (CH_3)_2CHCH_2Cl$$



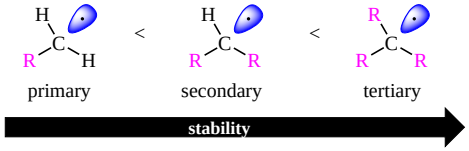
The Relative Reactivity of Hydrogens to

Radical Chlorination

This difference in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured. These values are given in the following table.

R (in R–H)	methyl	ethyl	i-propyl	t-butyl
Bond Dissociation Energy (kcal/mole)	103	98	95	93

This data shows that a tertiary C-H bond (93 kcal/mole) is easier to break than a secondary (95 kcal/mole) and primary (98 kcal/mole) C-H bond. These bond dissociation energies can be used to estimate the relative stability of the radicals formed after homolytic cleavage. Because a tertiary C-H bond requires less energy to undergo homolytic cleavage than a secondary or primary C-H bond, it can be inferred that a tertiary radical is more stable than secondary or primary.



Relative Stability of Free Radicals

Exercise 3.8.1

Write out the complete mechanism for the chlorination of methane.

Answer available at the end of this section.

Exercise 3.8.2

Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.

Answer available at the end of this section.

Exercise 3.8.3

Which step of the radical chain mechanism requires outside energy? What can be used as this energy?

Answer available at the end of this section.

Exercise 3.8.4

Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Answer available at the end of this section.

Exercise 3.8.5

1) Predict the mono-substituted halogenated product(s) of chlorine gas reacting with 2-methylbutane.

2) Predict the relative amount of each mono-brominated product when 3-methylpentane is reacted with Br_2. Consider 1°, 2°, 3° hydrogen.

3) For the following compounds, give all possible monochlorinated derivatives.

a) 

b) 

c) 

d) 

e) 

f) 

Answer available at the end of this section.

Answers

Exercise 3.8.1

The answer to this problem is actually above in the initiation, propagation and termination descriptions.

Exercise 3.8.2

Since the second step in propagation is energetically favorable and fast, it drives the equilibrium toward products, even though the first step is not favorable.

Exercise 3.8.3

Initiation step requires energy which can be in the form of light or het.

Exercise 3.8.4

To calculate the enthalpy of reaction, you subtract the BDE of the bonds formed from the BDE of the bonds broken.

Bonds broken are C-H and Br-Br.

Bonds formed are H-Br adn C-Br.

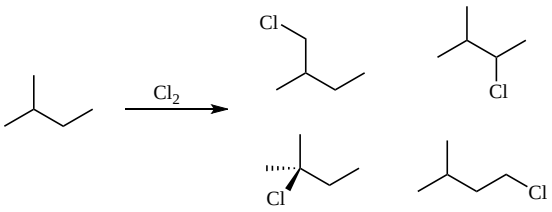
Bonds broken - bonds formed = change in enthalpy

(101 kcal/mol + 46 kcal/mol) - (87 kcal/mol + 70 kcal/mol) = change in enthalpy

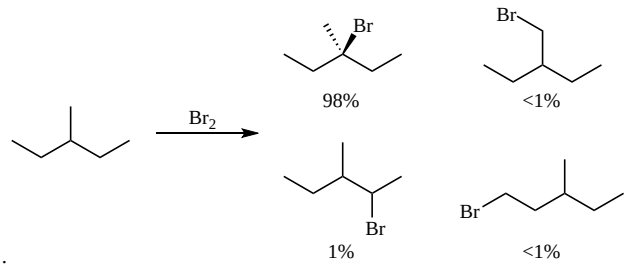
-10 kcal/mol = change in enthalpy for bromination of ethane.

Exercise 3.8.5

1)

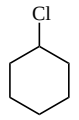


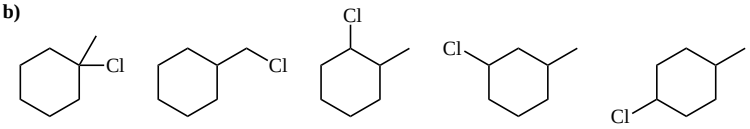
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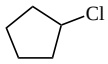


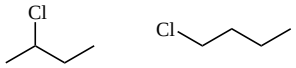
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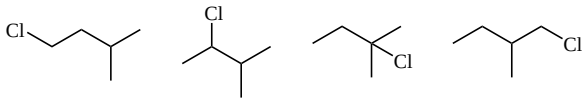
3)

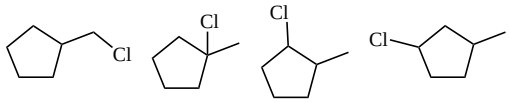
a) 

b) 

c) 

d) 

e) 

f) 

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- 10.2: Preparing Alkyl Halides from Alkanes - Radical Halogenation by Britt Farquharson, Dietmar Kennepohl, Jim Clark, Kristen Kelley, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

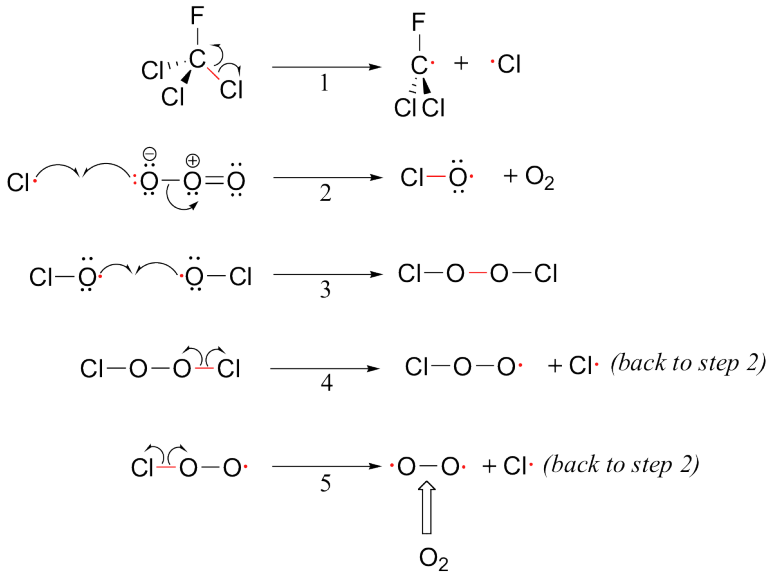
3.9: Synthetic Radical Halogenation

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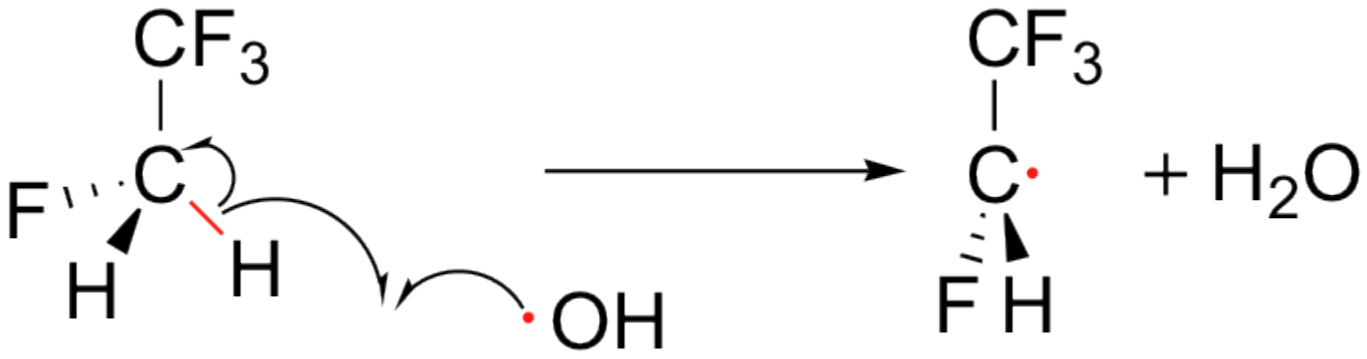
3.10: Synthetic Chlorine Compounds and the Stratospheric Ozone Layer

The high reactivity of free radicals and the multiplicative nature of radical chain reactions can be useful in the synthesis of materials such as polyethylene plastic - but these same factors can also result in dangerous consequences. You are probably aware of the danger posed to the earth's protective stratospheric ozone layer by the use of chlorofluorocarbons (CFCs) as refrigerants and propellants in aerosol spray cans. Freon-11, or $CFCl_3$, is a typical CFC that was widely used until fairly recently. It can take months or years for a CFC molecule to drift up into the stratosphere from the surface of the earth, and of course the concentration of CFCs at this altitude is very low. Ozone, on the other hand, is continually being formed in the stratosphere. Why all the concern, then, about destruction of the ozone layer - how could such a small amount of CFCs possibly do significant damage? The problem lies in the fact that the process by which ozone is destroyed is a chain reaction, so that a single CFC molecule can initiate the destruction of many ozone molecules before a chain termination event occurs.

Although there are several different processes by which the ozone destruction process might occur, the most important is believed to be the chain reaction shown below.



To address the problem of ozone destruction, scientists are developing new organohalogen refrigerant compounds that are less stable than the older CFCs like Freon-11, in the hope that the new compounds will break down in the lower atmosphere before they reach an altitude where they can harm the ozone layer. Most of the new compounds contain carbon-hydrogen bonds, which are subject to homolytic cleavage initiated by hydroxide radicals present in the lower atmosphere.



This degradation occurs *before* the refrigerant molecules have a chance to drift up to the stratosphere where the ozone plays its important protective role. The degradation products are quite unstable and quickly degrade further, by a variety of mechanisms, into relatively harmless by-products. The hydroxide radical is sometimes referred to as an atmospheric 'detergent' due to its ability to degrade refrigerants and other volatile organic pollutants which have escaped into the atmosphere.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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3.11: Combustion and the Relative Stabilities of Alkanes

Alkane Heats of Combustion

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3.E: Reactions of Alkanes (Exercises)

These are homework exercises to accompany Chapter 3 of Vollhardt and Schore's "Organic Chemistry" Textmap.

3.1: Strength of Alkane Bonds: Radicals

3.2: Structure of Alkyl Radicals: Hyperconjugation

3.3: Conversion of Petroleum: Pyrolysis

3.4: Chlorination of Methane: The Radical Chain Mechanism

3.5: Other Radical Halogenations of Methane

3.6: Keys to Success: Using the "Known" Mechanism as a model for the "Unknown"

3.7: Chlorination of Higher Alkanes: Relative Reactivity and Selectivity

3.8: Selectivity in Radical Halogenation with Fluorine and Bromine

3.9: Synthetic Radical Halogenation

3.10: Synthetic Chlorine Compounds and the Stratospheric Ozone Layer

3.11: Combustion and the Relative Stabilities of Alkanes

Problems

Q15

Indicate whether each Hydrogen present is primary, secondary, or tertiary. Why is quaternary not an option?

(a) ethane (b) 2,2-dimethylpropane (c) 1-methylcyclobutane

Q16

In each pair of radicals, determine whether the radical is primary, secondary, or tertiary and also decide which radical is more favorable. Give the general reason why for all of the cases.

(a) 3.16a.png (b) 3.16b.png (c) 3.16c.png

Q17

Draw the electron pushing arrow mechanism for all possible pyrolysis radicals that can form from butane, assuming only C-C bonds are broken. What type of bond cleavage is this, heterolytic or homolytic?

Q18

Draw all the possible pyrolysis radical products for 2-methylbutane, and determine which bond is most likely to be broken.

Q19

Calculate the ΔH^{o} (kJ/mol) of the following reactions using the given bond dissociation energies.

Bond Dissociation Energies (Homolytic)	ΔH^{o} (kJ/mol)
CH_3-H (methane)	439
C_2H_5-H (ethane)	423
$(CH_3)_3C$-H	404
H-H	435
H-Cl	431
H-Br	364
CH_3-Cl	356
CH_3-Br	293
C_2H_5-Cl	352
C_2H_5-Br	293
$(CH_3)_3C$-Cl	356
$(CH_3)_3C$-Br	297
Cl-Cl	242
Br-Br	192

(a) $CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$ (b) $CH_4 + Br_2 \rightarrow CH_3Br + HBr$

(c) $C_2H_6 + Cl_2 \rightarrow C_2H_5Cl + HCl$ (d) $C_2H_6 + Br_2 \rightarrow C_2H_5Br + HBr$

(e) $(CH_3)_3CH + Cl_2 \rightarrow (CH_3)_3CCl + HCl$ (f) $(CH_3)_3CH + Br_2 \rightarrow (CH_3)_3CBr + HBr$

(g) $H_2 + Cl_2 \rightarrow 2HCl$

Q20

Predict all possible constitutional isomers possible if monohalogenation were performed on the molecules in problem 15 with Br_2. Give the name of the haloalkane.

Q21

Given the following alkanes, draw the most likely product to form upon monohalogenation with Br_2 (keep in mind that this may not be the only product to form though). If the reaction was performed with Cl_2 would there be more or less selectivity in the desired

product formation? Why?

(a) 3.21aq.png (b) 3.21bq.png (c) 3.21cq.png

Q22

Draw out the full mechanism of the monochlorination of ethane with electron-pushing arrows. Label the three overall steps of the mechanism.

Q23

Calculate the statistical probablity of monobromination of propane on each unique carbon, and discuss why this is not likely. Given that the experimental monobromination produces two products, 97% one and 3% the other, assign these percentages to the corresponding product.

Q24

Draw the mechanism of the bromination of propene using Br_2, on the carbon adjacent to the double bond. Can you draw any resonance structures for the intermediates in the propagation steps? Would you expect this to make the radical more or less stable?

Q25

Based on the previous question, how do you think the ΔH^o to form the propene radical would compare to that of a propane radical?

Q26

Similar to problem 21, describe the resemblence to products and reactants of an early and a late transition state. In a monohalogenation, what step is early what step is late (propagation and termination)?

Q27

Draw the line-bond structure of the major product for the following reaction, if a reaction occurs, assume monohalogenation.

(a) 3.25aq.png (b) 3.25bq.png (c) 3.25cq.png

(d)3.25dq.png (e) 3.25eq.png

Q28

For problem 27.c, calculate the product ratios using the following information (hint use the number of hydrogens in each category present to calculate the ratios).

Chlorination: 1^o Reactivity=1 2^o Reactivity=4 3^o Reactivity=5

Q29

Halo alkanes are synthetically useful compounds as you'll learn later. However, the radical halogenation is not always selective as seen in problem 27. If any of the products of the reactions were to be used as subsequent reagents, which would be more useful, 27.c or 27.d?

Q30

What are potential problems of trying to brominate the second carbon in hexane? If however, this does form draw the Newman Projection of the most favorable staggered conformation looking down the C2-C3 axis.

Q31

Calculate the ΔH^{o} value for the bromination and iodination of propene, on the secondary carbon, assume monohalogenation. The bond dissociation values are as follows. What is the major difference between the two values? (Note this problem uses kcal mol^{-1})

Bond	Bond Dissociation Energy (kcal mol^{-1})
Br-Br	46
I-I	36
$(CH_3)_2CH$-H	98.5
H-Br	87
H-I	71
Secondary C-I	56
Secondary C-Br	71

Q32

Draw the bond polarity present of chloroethane, explain how this affects the electronics of the carbon attached to the chloro group.

Q33

Write a balanced combustion reaction for the following hydrocarbons, sugars, and alchols. Assume complete combustion, what is one typical product of incomplete combustion?

(a) butane (b) octane (c) glucose (C_6H12O_6) (d) methanol

Q34

At 25^{o}C the heat of combustion of 2-butanone, $CH_3CHOCH_2CH_3$, is 2444.1 kJ mol^{-1} and the heat of combustion of butanal, $CHOCH_2CH_2CH_3$, is 2470.3 kJ mol^{-1}. Which combustion is more endothermic? What does this tell us about the relative stability of the two compounds?

Q35

Often times NBS, N-bromosuccinimide, is substituted for Br_2 in radical halogenation reactions to keep the concentration of Br_2 low. This low concentration favors the radical halogenation and not other alkene reactions, that you will learn later on. Using NBS, drawn below, draw the radical bromination of propene.

NBS.png N-bromosuccinimide

Q36

Peroxides are also good initiators for radical reactions. Given the peroxide, RO-OR, draw the initiation step of the general peroxide and the propagation of that radical to create bromine radicals with HBr.

Q37

One radical inhibitor BHT, butylated hydroxytoluene, is often added to diethylether, $CH_3CH_2OCH_2CH_3$, to prevent explosive peroxides from forming. Given BHT's structure below, draw the radical formation on the oxygen of BHT with a general radical, $R^{\bullet}$. The phenoxy radical is stabilized/made unreactive by steric hindrance of the tertbutyl groups and also resonance.

BHT.png

Q38

Draw the two radical halogenation products of 2-methylpropane, also known as isobutane, with Cl_2. Given the percentages of the two products are 37% and 63%, calculate the reactivity of each hydrogen and the ratio between the two.

Q39

Given the following reactions and the relative ΔH^o, what is most likely the rate limiting step of the radical halogenation mechanism?

1) X-X $\rightarrow$ $2X^{\bullet}$ $\Delta H_1^o > 0$

2) R-CH_3 + $X^{\bullet}$ $\rightarrow$ R-$CH_2^{\bullet}$ + HX $\Delta H_2^o > \Delta H_1^o$

3) R-$CH_2^{\bullet}$ + $X^{\bullet}$ $\rightarrow$ R-CH_2X $\Delta H_3^o < 0$

Q40

Explain or use a mechanism to show how BHT, or other radical inhibitors, could cause a radical halogenation to come to a stop?

Q41

Given the following heats of combustion; propane ΔH= -2202 kJ/mol, gasoline ΔH=-44,000 kJ/kg, diesel ΔH=-45,000 kJ/kg; what fuel could potentially provide the most miles per weight of fuel?

Q42

Write out the reactions for the complete combustion of propane and gasoline, assuming gasoline is completely C_8H_{18} (gasoline is actually a mixture of smaller and larger hydrocarbons).

Q43

Draw the transition states of the reaction of $Cl^{\bullet}$ and $Br^{\bullet}$ with a secondary carbon, compare the radical character of that carbon between the two transition states.

Q44

CFC's, chlorofluorocarbons (CF_2Cl_2), saw widespread use as refrigerants and as aerosols. However, due to their low boiling point, when sprayed into the air they rise up to the atmosphere and are exposed to large amounts of uv radiation. This light, often seen as $h\nu$ in chemical equations, provides the energy needed to break the CFC's into radicals. Chlorine radicals are formed and this degrades the protective layer of ozone into oxygen, O_2. Draw the formation of the chlorine radical from a CFC.

Q45

N-bromosuccinimide, NBS, is a reagent with what purpose?

(a) a strong base (b) a strong acid (c) radical initiator (d) radical inhibitor

Q46

Name the following compound.

3.46q.png

Q47

A polymer scientist is trying to perform a halogenation on the following polymer to perform a subsequent reaction (the structure repeats itself to form a length of n units). She/he has been using Cl_2 to perform the radical halogenation, but cannot obtain a uniformly halogenated product. What suggestion would you give her/him to try and achieve a more uniformly halogenated product?

3.47q.png

Q48

Given that a radical halogenation with chlorine yields an early transition state, as defined in Hammond's Postulate, is the halogenation likely to be endothermic or exothermic?

Solutions

S15

(a) 3.15a.png (b) 3.15b.png (c) 3.15c.png

There can be no quaternary Hydrogen because a Carbon can only have four covalent bonds. In (b) the central carbon has no attached Hydrogen, but it is a quaternary carbon.

S16

(a) left- tertiary right-secondary; the left is more favorable (b) left-primary right-tertiary; the right is more favorable (c) left- primary right- secondary; the right is more favorable

For all of theses cases the more favorable radical is as follows $3^{o}>2^{o}>1^{o}$. Since the radical is electron deficient, the more carbon substituents the more hyperconjugation that can occur. This stabilizes the radical, this "rule" is also true for carbocations as you will see later.

S17

3.17a.png Make sure to draw single electron arrows. Also, this is homolytic bond cleavage because one electron goes to each atom involved in bonding.

S18

3.18a.png The stability of radicals is as follows: $3^{o}>2^{o}>1^{o}>CH_3$, and so the second pair of radicals is most likely to form. A secondary and a primary radical are formed, compared to the other products that contain a methyl radical.

S19

ΔH^o=(ΔH^o Bonds Broken)-(ΔH^o Bonds Formed)

(a) $CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$ ΔH^o=(CH_3-H + Cl-Cl)-(CH_3-Cl + H-Cl)=(439+242)-(356+431)=-106 kJ mol^{-1}

(b) $CH_4 + Br_2 \rightarrow CH_3Br + HBr$ ΔH^o=(CH_3-H + Br-Br)-(CH_3-Br + H-Br)=(439+192)-(293+364)=-26 kJ mol^{-1}

(c) $C_2H_6 + Cl_2 \rightarrow C_2H_5Cl + HCl$ ΔH^o=(C_2H_5-H + Cl-Cl)-(C_2H_5-Cl + H-Cl)=(423+242)-(352+431)=-118 kJ mol^{-1}

(d) $C_2H_6 + Br_2 \rightarrow C_2H_5Br + HBr$ ΔH^o=(C_2H_5-H + Br-Br)-(C_2H_5-Br + H-Br)=(423+192)-(293+364)=-42 kJ mol^{-1}

(e) $(CH_3)_3CH + Cl_2 \rightarrow (CH_3)_3CCl + HCl$ ΔH^o=((CH_3)$_3$C-H + Cl-Cl)-((CH_3)$_3$C-Cl + H-Cl)=(404+242)-(356+431)=-141 kJ mol^{-1}

(f) $(CH_3)_3CH + Br_2 \rightarrow (CH_3)_3CBr + HBr$ ΔH^o=((CH_3)$_3$C-H + Br-Br)-((CH_3)$_3$C-Br + H-Br)=(404+192)-(297+364)=-65 kJ mol^{-1}

(g) $H_2 + Cl_2 \rightarrow 2HCl$ ΔH^o=(H-H + Cl-Cl)-2(H-Cl)=(435+242)-2(431)=-185 kJ mol^{-1}

S20

(a) ethane; bromethane (b) 2,2-dimethylpropane; 1-bromo-2,2-dimethylpropane (c) 1-methylcyclobutane; (bromomethyl)cyclobutane, 1-bromo-1-methylcyclobutane, 1-bromo-2-methylcyclobutane, 1-bromo-3-methylcyclobutane

S21

a. 3.21aa.png
b. 3.21ba.png
c. 3.21ca.png

If the reaction were performed with Cl_2 the product formation would not likely be as selective. This is due to the fact that the radical formation with chlorine is exothermic and the radical formation with bromine is endothermic. Hammond's postulate explains that the transition state of exothermic reaction will be more similar to the reactants, less like a radical, leading to a less selective radical formation. Whereas the transition state of an endothermic reaction will be more similar to the products, more radical like, leading to a selective radical formation.

S22

2.22.png

S23

3.png The statistical distribution is calculated from the following: Total Carbons=3, Two external carbons are not unique, so probability=2/3 x 100% The center carbon probability is 1/3 x 100%. However, this is not likely, because the secondary carbon forms a much more stable radical than a primary radical.

S24

3.24a.png As you'll learn, this is not the only reaction that can occur. Alkene chemistry will be discussed later on.

S25

Since the propene radical is more favorable than the propane radical, the ΔH^o would be lower than that of propane.

S26

An early transition state resembles the reactants, and a late transition state resembles the products (Hammond's postulate). The formation of the alkyl radical, propagation, is an early transition state (if you draw the reaction coordinate diagram for this step it should be endothermic), and the formation of the alkyl halide, termination, is a late transition state (if you draw the reaction coordinate diagram for this step it should be exothermic).

S27

(a) 3.25aa.png (b) 3.25ba.png

(c) 3.25ca.png (d) 3.25da.png Notice how the chlorination is not as selective as the bromination.

(e) 3.25ea.png

S28

Assuming there is no primary chlorination, which in reality is likely not the case, only 2^{o} and 3^{o} hydrogen atoms are taken into account.

2^{o}=2 Multiply by reactivity=Relative Yield => 8 Ratio= 8/(5+8) x 100%=62% 2^{o}

3^{o}=1 Multiply by reactivity=Relative Yield => 5 Ratio=5/(5+8) x 100%=38% 3^{o}

S29

27.d produces a much more pure mixture of products, and thus is more likely to be useful. Whereas, the chlorination, 27.c, of the same alkane potentially yields a mixture of products. This mixture would require a difficult separation, and is much less likely to be synthetically useful.

However, if a different haloalkane were desired, then this could be useful after purification. As you see later on, though, there are other methods of creating haloalkanes that are more selective.

S30

The problem with this is that there are several secondary carbons, all about as equally likely to form a radical. There are three groups of unique hydrogens on the molecule, the two primary, the adjacent secondary, and the most interior secondary. Statistically speaking the inner two and second most outer two are equally likely to be brominated, there are equal number of hydrogens. If however, the second carbon is brominated, the following is the most favorable conformation.

Since the methyl group is much larger than the bromine, the rest of the carbon chain is adjacent to the bromine to reduce the steric interaction. It is also anti to the methyl group to further reduce steric interaction.

3.30a.png

S31

This problem could be broken up into the individual steps of the mechanism, and the ΔH^{o} values for each step could be summed together to get the same value.

Bromination:

ΔH^{o}=Bonds Broken - Bonds Made = (Br-Br + Secondary C-H) - (Secondary C-Br + H-Br) = (46 + 98.5) - (71 + 87)= -13.5 kcal mol^{-1}

Iodination:

ΔH^{o}=Bonds Broken - Bonds Made = (I-I + Secondary C-H) - (Secondary C-I + H-I) = (36 + 98.5) - (56 + 71)= +7.5 kcal mol^{-1}

The main difference between the two is that the bromination is exothermic, whereas the iodination is endothermic. This explains why no reaction occurs in 27.b

S32

3.32a.png The connectivity to a chlorine atom produces a highly polarized bond. This chlorination has further reactivity as you will see later on, taking advantage of the electron deficient carbon.

S33

With any complete combustion reaction the only products are CO_2 and H_2O.

(a) butane $2C_4H_{10} + 13O_2 \rightarrow 8CO_2 + 10H_2O$

(b) octane $2C_8H_{18} + 17O_2 \rightarrow 16CO_2 + 18H_2O$

(c) glucose $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$

(d) methanol $4CH_3 + 7O_2 \rightarrow 4CO_2 + 6H_2O$

If any incomplete combustion occurred, carbon monoxide, CO, would be produced.

S34

Butanal's combustion is more exothermic than that of 2-butanone. The heats of combustion tell us that 2-butanone is more stable, as it has a lower heat of combustion an thus less potential combustion energy in the compound.

S35

3.35a.png

S36

3.36a.png

S37

3.37a.png

S38

3.38a.png Total number of abstractable Hydrogens=(3x3)+1=10

Relative Reactivity=[(Percentage)/(Number of Hydrogens)]

Tertiary Reactivity = 63/1=63

Primary Reactivity =37/9=4.1

The ratio between the two is 63/4.1=15

S39

The most endothermic step, most postive value of ΔH^o, is most likely to be the rate limiting step. So, (2) is the rate limiting step.

S40

The inihibitor stops interrupts the propagation step, effectively terminating the reaction. If a carbon or halogen radical does form, it will react with the BHT to form the radical in problem 37. The phenoxy radical in BHT is unreactive, and the reaction stops there.

3.40a.png

S41

First, convert the 2202 kJ/mol to kJ/kg.

(-2202 kJ/mol) x (1 mol/44.1 g) x (1000g / 1kg) = -49,931 kJ/mol ~ 50,000 kJ/kg

Since propane has the largest, most negative, heat of combustion it is likely to yield the best mileage. It, and natural gas, is commonly used as a fuel in buses.

S42

Propane: $C_3H_8 + 5O_2 \rightarrow 3CO_2 + 4H_2O$

"Gasoline": $2C_8H_{18} + 27O_2 \rightarrow 16CO_2 + 18H_2O$

S43

3.43a.png

The transition state with the chlorine radical is considered an early transition state and more similar to the reactants. The transition state with the bromine radical is considered a late transition state and more similar to the products.

S44

3.44a.png

S45

(c) NBS is a radical initiator.

S46

3.46a.png

S47

As you may have seen in previous problems, radical halogenation with chlorine is less selective than with bromine. A good suggestion would be to use Br_2, as it will almost exclusively be added to the tertiary carbon if used in a 1:1 stoichiometric ratio. Wheras, the chlorine will also be added to the secondary carbons, thus producing a non-uniform product.

S48

From Hammond's Postulate, an early transition state indicates an endothermic reaction.

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4: CYCLOALKANES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

Cycloalkanes are cyclic hydrocarbons with the carbons of the molecule arranged in the form of one or more rings. Cycloalkanes are saturated hydrocarbons, meaning that all of the carbons atoms that make up the ring are single bonded to other atoms (no double or triple bonds).



- Topic hierarchy

4.1: Names and Physical Properties of Cycloalkanes
4.2: Ring Strain and the Structure of Cycloalkanes
4.3: Cyclohexane: A Strain-Free Cycloalkane
4.4: Substituted Cyclohexanes
4.5: Larger Cycloalkanes
4.6: Polycyclic Alkanes
4.7: Carbocyclic Products in Nature
4.E: Cycloalkanes (Exercises)

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4.1: Names and Physical Properties of Cycloalkanes

Objectives

After completing this section, you should be able to:

- Name a substituted or unsubstituted cycloalkane, given its Kekulé structure, shorthand structure or condensed structure.
- Draw the Kekulé, shorthand or condensed structure for a substituted or unsubstituted cycloalkane, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

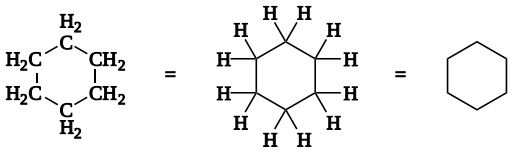
- cycloalkane

Study Notes

Provided that you have mastered the IUPAC system for naming alkanes, you should find that the nomenclature of cycloalkanes does not present any particular difficulties.

Many organic compounds found in nature contain rings of carbon atoms. These compounds are known as **cycloalkanes**. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The simplest examples of this class consist of a single, un-substituted carbon ring, and these form a homologous series similar to the unbranched alkanes.

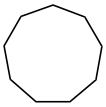
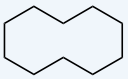
Like alkanes, cycloalkane molecules are often drawn as skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens. Cyclohexane, one of the most common cycloalkanes is shown below as an example.



Cyclic hydrocarbons have the prefix "cyclo-". The IUPAC names, molecular formulas, and skeleton structures of the cycloalkanes with 3 to 10 carbons are given in Table 4.1.1. Note that the general formula for a cycloalkane composed of n carbons is C_nH_{2n}, and not C_nH_{2n+2} as for alkanes. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so are still considered to be **saturated** with hydrogen.

Table 4.1.1: Examples of Simple Cycloalkanes

Cycloalkane	Molecular Formula	Skeleton Structure
Cyclopropane	C_3H_6	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	

Cycloalkane	Molecular Formula	Skeleton Structure
Cyclohexane	C_6H_{12}	
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

IUPAC Rules for Nomenclature

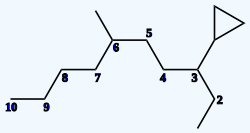
The naming of substituted cycloalkanes follows the same basic steps used in naming alkanes.

1. Determine the parent chain.
2. Number the substituents of the ring beginning at one substituent so that the nearest substituent is numbered the lowest possible. If there are multiple choices that are still the same, go to the next substituent and give it the lowest number possible.
3. Name the substituents and place them in alphabetical order.

More specific rules for naming substituted cycloalkanes with examples are given below.

1. Determine the cycloalkane to use as the parent. If there is an alkyl straight chain that has a greater number of carbons than the cycloalkane, then the alkyl chain must be used as the primary parent chain. Cycloalkanes substituents have an ending "-yl". If there are two cycloalkanes in the molecule, use the cycloalkane with the higher number of carbons as the parent.

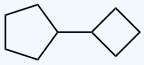
Example 4.1.1



The longest straight chain contains 10 carbons, compared with cyclopropane, which only contains 3 carbons. The parent chain in this molecule is decane and cyclopropane is a substituent. The name of this molecule is 3-cyclopropyl-6-methyldecane.

Example 4.1.2

Name the cycloalkane structure.

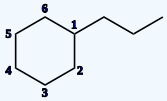


Solution

There are two different cycloalkanes in this molecule. Because it contains more carbons, the cyclopentane ring will be named as the parent chain. The smaller ring, cyclobutane, is named as a substituent on the parent chain. The name of this molecule is cyclobutylcyclopentane.

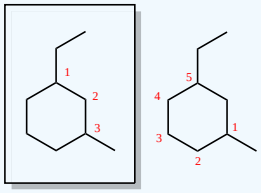
2. When there is only one substituent on the ring, the ring carbon attached to the substituent is automatically carbon #1. Indicating the number of the carbon with the substituent in the name is optional.

Example 4.1.3

	
1-chlorocyclobutane or cholorocyclobutane	1-propylcyclohexane or propylcyclohexane

3. If there are multiple substituents on the ring, number the carbons of the cycloalkane so that the carbons with substituents have the lowest possible number. A carbon with multiple substituents should have a lower number than a carbon with only one substituent or functional group. One way to make sure that the lowest number possible is assigned is to number the carbons so that when the numbers corresponding to the substituents are added, their sum is the lowest possible.
4. When naming the cycloalkane, the substituents must be placed in alphabetical order. Remember the prefixes di-, tri-, etc. , are not used for alphabetization.

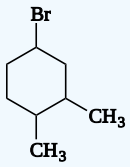
Example 4.1.4



In this example, the ethyl or the methyl subsistent could be attached to carbon one. The ethyl group attachment is assigned carbon 1 because ethyl comes before methyl alphabetically. After assigning carbon 1 the cyclohexane ring can be numbered going clockwise or counterclockwise. When looking at the numbers produced going clockwise produces lower first substituent numbers (1,3) than when numbered counterclockwise (1,5). So the correct name is 1-ethyl-3-methylcyclohexane.

Example 4.1.5

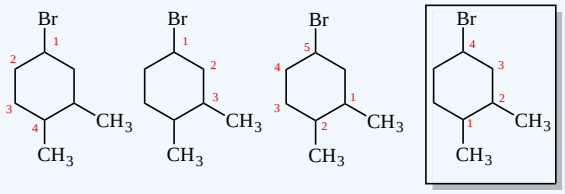
Name the following structure using IUPAC rules.



Solution

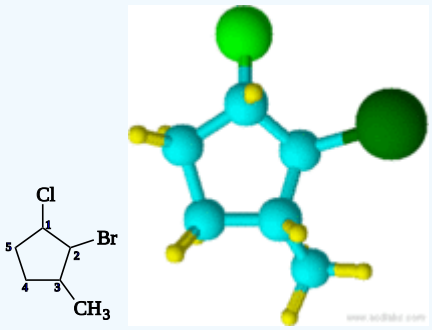
Remember when dealing with cycloalkanes with more than two substituents, finding the lowest possible 2nd substituent numbering takes precedence. Consider a numbering system with each substituent attachment point as being carbon one. Compare them and whichever produces the lowest first point of difference will be correct.

The first structure would have 1,4 for the relationship between the first two groups. The next structure would have 1,3. The final 2 structures both have 1,2 so those are preferable to the first two. Now we have to determine which is better between the final 2 structures. The 3rd substituent on structure 3 would be at the 5 position leading to 1,2,5 while in the final structure the 3rd methyl group is on carbon 4 leading to 1,2,4. This follows the rules of giving the lowest numbers at the first point of difference.



The correct name for the molecule is 4-Bromo-1,2-dimethylcyclohexane.

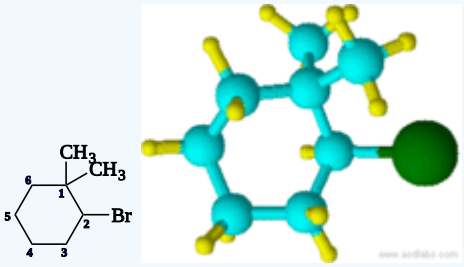
Example 4.1.6



2-bromo-1-chloro-3-methylcyclopentane

Notice that "b" of bromo alphabetically precedes the "m" of methyl. Also, notice that the chlorine attachment point is assigned carbon 1 because it comes first alphabetically and the overall sum of numbers would be the same if the methyl attachment carbon was assigned as 1 and the chlorine attachment as 3.

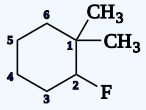
Example 4.1.7



(2-bromo-1,1-dimethylcyclohexane)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order.

Example 4.1.8



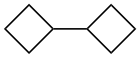
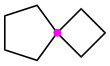
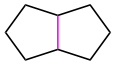
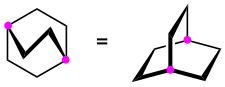
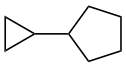
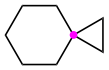
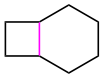
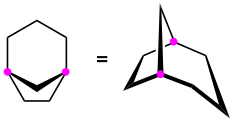
2-fluoro-1,1,-dimethylcyclohexane **NOT** 1,1-dimethyl-2-fluorocyclohexane also 2-fluoro-1,1,-dimethylcyclohexane **NOT** 1-fluoro-2,2-dimethylcyclohexane (as that would give a larger number to the first point of difference)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order of the substituents. Notice that the attachment point of the two methyl groups is assigned carbon 1 despite the fact that fluorine comes first alphabetically. This is because this assignment allows for a lower overall numbering of substituents, so assigning alphabetical priority is not necessary.

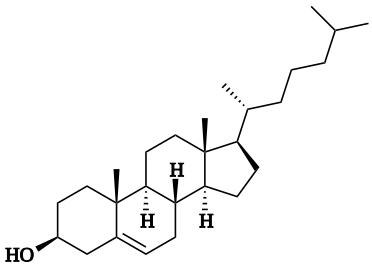
Polycyclic Compounds

Hydrocarbons having more than one ring are common, and are referred to as **bicyclic** (two rings), **tricyclic** (three rings) and in general, **polycyclic compounds**. The molecular formulas of such compounds have H/C ratios that decrease with the number of rings. In general, for a hydrocarbon composed of n carbon atoms associated with m rings the formula is: $\mathrm{C}_n\mathrm{H}_{2n+2-2m}$. The structural relationship of rings in a polycyclic compound can vary. They may be separate and independent, or they may share one or two common atoms. Some examples of these possible arrangements are shown in the following table.

Table 4.1.2: Examples of Isomeric $\mathrm{C}_8\mathrm{H}_{14}$ Bicycloalkanes

Isolated Rings	Spiro Rings	Fused Rings	Bridged Rings
No common atoms	One common atom	One common bond	Two common atoms
			
			

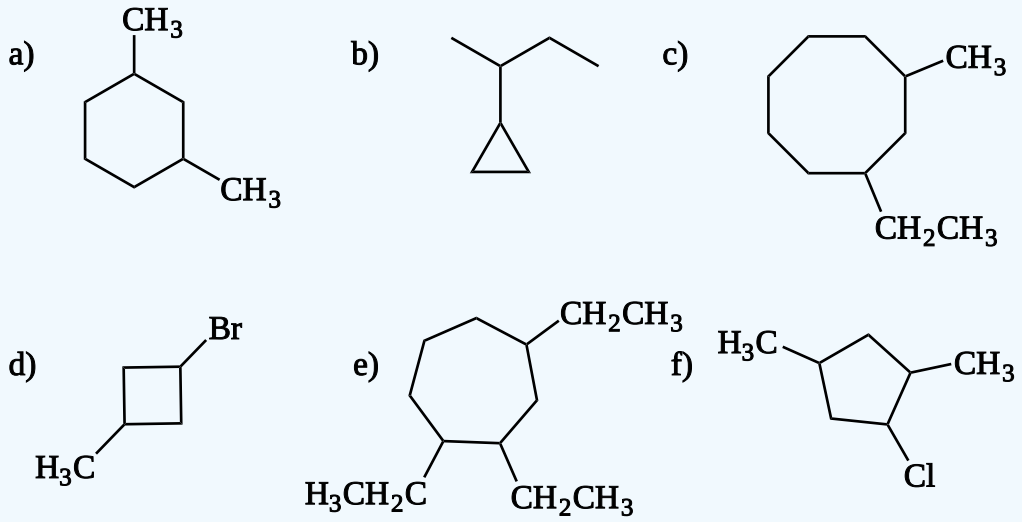
Polycyclic compounds, like cholesterol shown below, are biologically important and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules, and will not be covered here.



Cholesterol (polycyclic)

Exercise 4.1.1

Give the IUPAC names for the following cycloalkane structures.



Answer available at the end of this section.

Exercise 4.1.2

Draw the structures for the IUPAC names below.

a. 2,3-dicyclopropylpentane
b. 1,2,3-triethylcyclopentane
c. 3-cyclobutyl-2-methylhexane
d. 2-bromo-1-chloro-4-methylcyclohexane
e. 1-bromo-5-propylcyclododecane

Answer available at the end of this section.

Objectives

After completing this section, you should be able to

- draw structural formulas that distinguish between *cis* and *trans* disubstituted cycloalkanes.
- construct models of *cis* and *trans* disubstituted cycloalkanes using ball-and-stick molecular models.

Key Terms

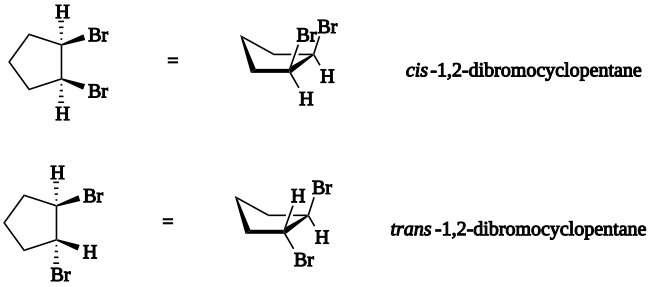
Make certain that you can define, and use in context, the key terms below.

- constitutional isomer
- stereoisomer
- *cis*-*trans* isomers

Previously, constitutional isomers have been defined as molecules that have the same molecular formula, but different atom connectivity. In this section, a new class of isomers, stereoisomers, will be introduced. **Stereoisomers** are molecules that have the same molecular formula, the same atom connectivity, but they differ in the relative spatial orientation of the atoms.

Cycloalkanes are similar to open-chain alkanes in many respects. They both tend to be nonpolar and relatively inert. One important difference, is that cycloalkanes have much less freedom of movement than open-chain alkanes. As discussed in Sections 3.6 and 3.7, open-chain alkanes are capable of rotation around their carbon-carbon sigma bonds. The ringed structures of cycloalkanes prevent such free rotation, causing them to be more rigid and somewhat planar.

Di-substituted cycloalkanes are one class of molecules that exhibit stereoisomerism. 1,2-dibromocyclopentane can exist as two different stereoisomers: *cis*-1,2-dibromocyclopentane and *trans*-1,2-dibromocyclopentane. The *cis*-1,2-dibromocyclopentane and *trans*-1,2-dibromocyclopentane stereoisomers of 1,2-dibromocyclopentane are shown below. Both molecules have the same molecular formula and the same atom connectivity. They differ only in the relative spatial orientation of the two bromines on the ring. In *cis*-1,2-dibromocyclopentane, both bromine atoms are on the same "face" of the cyclopentane ring, while in *trans*-1,2-dibromocyclopentane, the two bromines are on opposite faces of the ring. Stereoisomers require an additional nomenclature prefix be added to the IUPAC name in order to indicate their spatial orientation. Di-substituted cycloalkane stereoisomers are designated by the nomenclature prefixes ***cis*** (Latin, meaning on this side) and ***trans*** (Latin, meaning across).



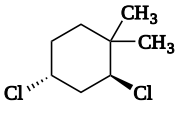
Representing 3D Structures

By convention, chemists use heavy, wedge-shaped bonds to indicate a substituent located above the plane of the ring (coming out of the page), a dashed line for bonds to atoms or groups located below the ring (going back into the page), and solid lines for bonds in the plane of the page.

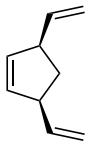


cis-1,3-dimethylcyclobutane

trans-5-bromo-1,4,6-trimethyl-1,3-cycloheptadiene

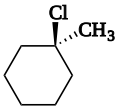


trans-2,4-dichloro-1,1-dimethylcyclohexane



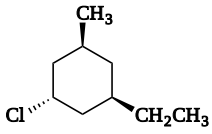
cis-3,5-divinylcyclopentene

In general, if any two sp^3 carbons in a ring have two different substituent groups (not counting other ring atoms) cis/trans stereoisomerism is possible. However, the cis/trans designations are not used if both groups are on the same carbon. For example, the chlorine and the methyl group are on the same carbon in 1-chloro-1-methylcyclohexane and the *trans* prefix should not be used.



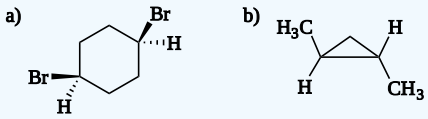
1-chloro-1-methylcyclohexane

If more than two ring carbons have substituents, the stereochemical notation distinguishing the various isomers becomes more complex and the prefixes *cis* and *trans cannot be used to formally name the molecule*. However, the relationship of any two substituents can be informally described using *cis* or *trans*. For example, in the tri-substituted cyclohexane below, the methyl group is *cis* to the ethyl group, and also *trans* to the chlorine. However, the entire molecule cannot be designated as either a *cis* or trans *isomer*. Later sections will describe how to name these more complex molecules (5.5: Sequence Rules for Specifying Configuration)



Example 4.1.1

Name the following cycloalkanes:



Solution

These two example represent the two main ways of showing spatial orientation in cycloalkanes.

a. In example "a" the cycloalkane is shown as being flat and in the plane of the page. The positioning of the substituents is shown by using dash-wedge bonds. Cis/trans positioning can be determined by looking at the type of bonds attached to the substituents. If the substituents are both on the same side of the ring (Cis) they would both have either dash bonds or wedge bonds. If the the substituents are on opposite side of the ring (Trans) one substituent would have a dash bond and the other a wedge bond. Because both bromo substituents have a wedge bond they are one the same side of the ring and are cis. The name of this molecule is cis-1,4-Dibromocyclohexane.
b. Example "b" shows the cycloalkane ring roughly perpendicular to the plane of the page. When this is done, the upper and lower face of the ring is defined and each carbon in the ring will have a bond one the upper face and a bond on the lower face. Cis substituents will either both be on the upper face or the lower face. Trans substituents will have one on the upper face and one one the lower face. In example "b", one of the methyl substituents is on the upper face of the ring and one is on the lower face which makes them trans to each other. The name of this molecule is *trans*-1,2-Dimethylcyclopropane.

Exercise 4.1.2

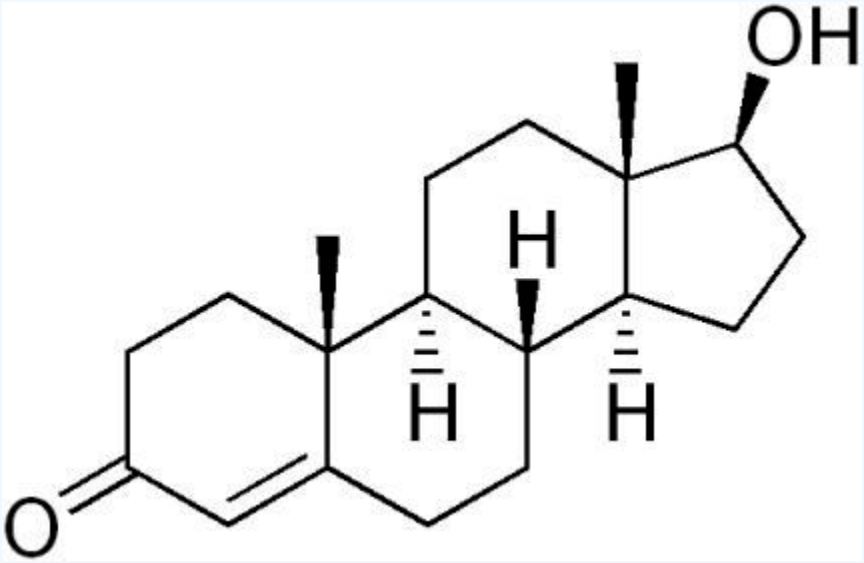
Draw the following molecules:

1. *trans*-1,3-dimethylcyclohexane
2. *trans*-1,2-dibromocyclopentane
3. *cis*-1,3-dichlorocyclobutane

Answer available at the end of this section.

Exercise 4.1.3

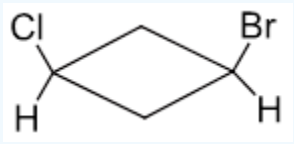
Cis/Trans nomenclature can be used to describe the relative positioning of substituents on molecules with more complex ring structures. The molecule below is tesosterone, the primary male sex hormone. Is the OH and the adjacent methyl group cis or trans to each other? What can you deduce about the relative positions of the indicated hydrogens?

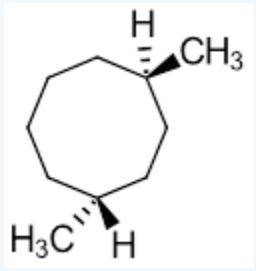


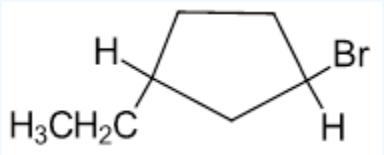
Answer available at the end of this section.

Exercise 4.1.4

Name the following compounds:







Answer available at the end of this section.

Exercise 4.1.5

Draw the following molecules:

a. *trans*-1,3-dimethylcyclohexane
b. *trans*-1,2-dibromocyclopentane
c. *cis*-1,3-dichlorocyclobutane

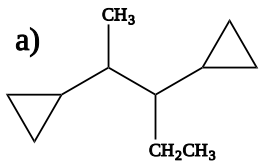
Answer available at the end of this section.

Answers

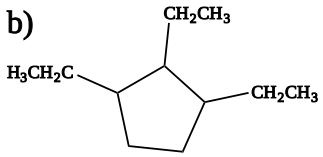
Exercise 4.1.1

a. 1,3-Dimethylcyclohexane
b. 2-Cyclopropylbutane
c. 1-Ethyl-3-methylcyclooctane
d. 1-Bromo-3-methylcyclobutane
e. 1,2,4-Triethylcycloheptane
f. 1-Chloro-2,4-dimethylcyclopentane

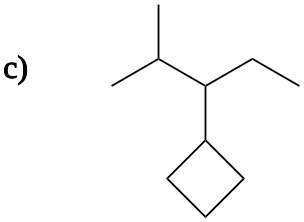
Exercise 4.1.2



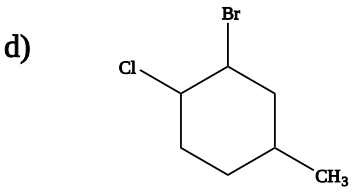
2,3-dicyclopropylpentane



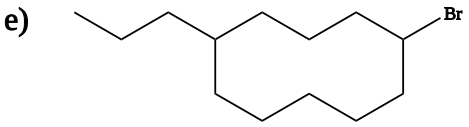
1,2,3-triethylcyclopentane



3-cyclobutyl-2-methylhexane

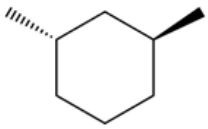


2-bromo-1-chloro-4-methylcyclohexane

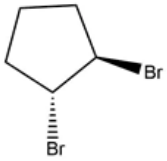


1-bromo-5-propylcyclodecane

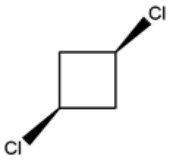
Exercise 4.1.2



1



2



3

Exercise 4.1.3

Both the OH and the methyl group have wedge bonds. This implies that they are both on the same side of the testosterone ring making them cis. Two of the hydrogens have wedge bonds while one has a wedge. This means two of the hydrogens are on one side of the testosterone ring while one is on the other side.

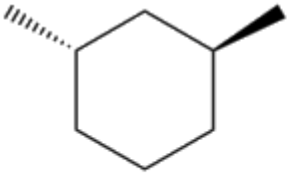
Exercise 4.1.4

Cis-1-Bromo-3-Chlorocyclobutane

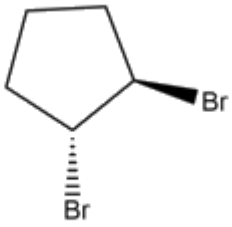
Trans-1,4-Dimethylcyclooctane

Trans-1-Bromo-3-ethylcyclopentane

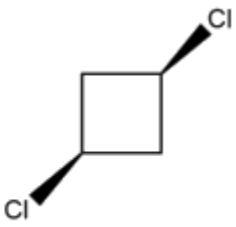
Exercise 4.1.5



1



2



3

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4.2: Ring Strain and the Structure of Cycloalkanes

Objectives

After completing this section, you should be able to:

- Describe the Baeyer strain theory.
- Describe how the measurement of heats of combustion provides information about the amount of strain present in a cycloalkane ring.
- Determine the relative stability of cyclic compounds, by assessing such factors as angle strain, torsional strain and steric strain.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- angle strain
- steric strain
- torsional strain
- ring strain
- heat of combustion

Heat of Combustion as a Measure of Bond Strength

The combustion of carbon compounds, especially hydrocarbons, has been the most important source of heat energy for human civilizations throughout recorded history. The practical importance of this reaction cannot be denied, but the massive and uncontrolled chemical changes that take place in combustion make it difficult to deduce mechanistic paths. Using the combustion of propane as an example, we see from the following equation that every covalent bond in the reactants has been broken and an entirely new set of covalent bonds have formed in the products. No other common reaction involves such a profound and pervasive change, and the mechanism of combustion is so complex that chemists are just beginning to explore and understand some of its elementary features.

$$\mathrm{CH_3CH_2CH_3 + 5\,O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + heat}$$

Since all the covalent bonds in the reactant molecules are broken, the quantity of heat evolved in this reaction, and any other combustion reaction, is related to the strength of these bonds (and, of course, the strength of the bonds formed in the products). Precise heat of combustion measurements can provide useful information about the structure of molecules and their relative stability.

For example, heat of combustion is useful in determining the relative stability of isomers. Pentane has a heat of combustion of -782 kcal/mol, while that of its isomer, 2,2-dimethylpropane (neopentane), is –777 kcal/mol. These values indicate that 2,3-dimethylpentane is 5 kcal/mol more stable than pentane, since it has a lower heat of combustion.

Ring Strain

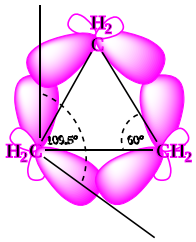
Table $4.2.1$ lists the heat of combustion data for some simple cycloalkanes. These cycloalkanes do not have the same molecular formula, so the heat of combustion per each CH_2 unit present in each molecule is calculated (the fourth column) to provide a useful comparison. From the data, cyclopropane and cyclobutane have significantly higher heats of combustion per CH_2, while cyclohexane has the lowest heat of combustion. This indicates that cyclohexane is more stable than cyclopropane and cyclobutane, and in fact, that cyclohexane has a same relative stability as long chain alkanes that are not cyclic. This difference in stability is seen in nature where six membered rings are by far the most common. What causes the difference in stability or the strain in small cycloalkanes?

Table 4.2.1: Heats of combustion of select hydrocarbons

Cycloalkane $(CH_2)_n$	CH_2 Units n	$\Delta H^{25°}$ kcal/mol	$\Delta H^{25°}$ per CH_2 Unit	Ring Strain kcal/mol
Cyclopropane	n = 3	468.7	156.2	27.6
Cyclobutane	n = 4	614.3	153.6	26.4
Cyclopentane	n = 5	741.5	148.3	6.5
Cyclohexane	n = 6	882.1	147.0	0.0
Cycloheptane	n = 7	1035.4	147.9	6.3
Cyclooctane	n = 8	1186.0	148.2	9.6
Cyclononane	n = 9	1335.0	148.3	11.7
Cyclodecane	n = 10	1481	148.1	11.0
$CH_3(CH_2)_mCH_3$	m = large	—	147.0	0.0

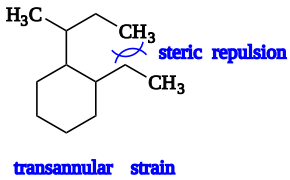
The Baeyer Theory on the Strain in Cycloalkane Rings

In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane are less stable than cyclohexane, because the the smaller rings are more "strained". There are many different types of strain that contribute to the overall ring strain in cycloalkanes, including angle strain, torsional strain, and steric strain. **Torsional strain** and **steric strain** were previously defined in the discussion of conformations of butane. **Angle Strain** occurs when the sp^3 hybridized carbons in cycloalkanes do not have the expected ideal bond angle of 109.5^o, causing an increase in the potential energy. An example of angle strain can be seen in the diagram of cyclopropane below in which the bond angle is 60^o between the carbons. The compressed bond angles causes poor overlap of the hybrid orbitals forming the carbon-carbon sigma bonds which in turn creates destabilization.



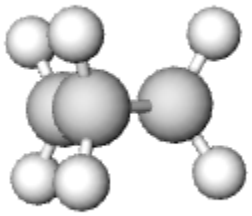
The C-C-C bond angles in cyclopropane (diagram above) (60^o) and cyclobutane (90^o) are much different than the ideal bond angle of 109.5^o. This bond angle causes cyclopropane and cyclobutane to be less stable than molecules such as cyclohexane and cyclopentane, which have a much lower ring strain because the bond angle between the carbons is much closer to 109.5^o. Changes in chemical reactivity as a consequence of angle strain are dramatic in the case of cyclopropane, and are also evident for cyclobutane.

In addition to angle strain, there is also steric (transannular) strain and torsional strain in many cycloalkanes. Transannular strain exists when there is steric repulsion between atoms.



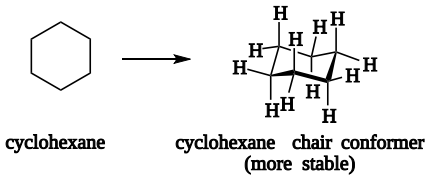
Because cycloalkane lack the ability to freely rotate, torsional (eclipsing) strain exists when a cycloalkane is unable to adopt a

staggered conformation around a C-C bond. Torsional strain is especially prevalent in small cycloalkanes, such as cyclopropane, whose structures are nearly planar.



The Eclipsed C-H Bonds in Cyclopropane

Larger rings like cyclohexane, deal with torsional strain by forming conformers in which the rings are not planar. A conformer is a stereoisomer in which molecules of the same connectivity and formula exist as different isomers, in this case, to reduce ring strain. The ring strain is reduced in conformers due to the rotations around the sigma bonds, which decreases the angle and torsional strain in the ring. The non-planar structures of cyclohexane are very stable compared to cyclopropane and cyclobutane, and will be discussed in more detail in the next section.



The Types of Strain Which Contribute to Ring Strain in Cycloalkanes

- Angle Strain - The strain caused by the increase or reduction of bond angles
- Torsional Strain - The strain caused by eclipsing bonds on adjacent atoms
- Steric Strain - The strain caused by the repulsive interactions of atoms trying to occupy the same space

Exercise 4.2.1

trans-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.

Answer available at the end of this section.

Exercise 4.2.2

Cyclobutane has more torsional stain than cyclopropane. Explain this observation.

Answer available at the end of this section.

Exercises

1. *Trans*-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.
2. The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however

have hydrogen-methyl interactions, but are not as high in energy than methyl-methyl interactions.

Objectives

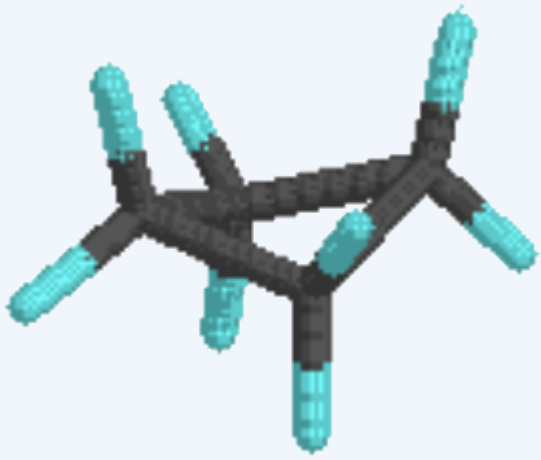
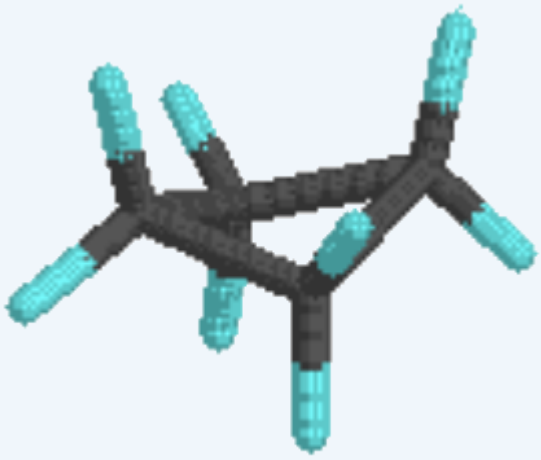
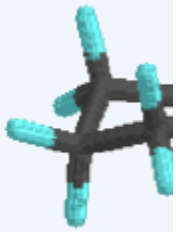
After completing this section, you should be able to

1. describe, and sketch the conformation of cyclopropane, cyclobutane, and cyclopentane.
2. describe the bonding in cyclopropane, and use this to account for the high reactivity of this compound.
3. analyze the stability of cyclobutane, cyclopentane and their substituted derivatives in terms of angular strain, torsional strain and steric interactions.

Study Notes

Notice that in both cyclobutane and cyclopentane, torsional strain is reduced at the cost of increasing angular (angle) strain.

Although the customary line drawings of simple cycloalkanes are geometrical polygons, the actual shape of these compounds in most cases is very different.

cyclopropane	cyclobutane	cyclopen
		

Cyclopropane is necessarily planar (flat), with the carbon atoms at the corners of an equilateral triangle. The 60° bond angles are much smaller than the optimum 109.5° angles of a normal tetrahedral carbon atom, and the resulting angle strain dramatically influences the chemical behavior of this cycloalkane. Cyclopropane also suffers substantial eclipsing strain, since all the carbon-carbon bonds are fully eclipsed. Cyclobutane reduces some bond-eclipsing strain by folding (the out-of-plane dihedral angle is about 25°), but the total eclipsing and angle strain remains high. Cyclopentane has very little angle strain (the angles of a pentagon are 108°), but its eclipsing strain would be large (about 40 kJ/mol) if it remained planar. Consequently, the five-membered ring adopts non-planar puckered conformations whenever possible.

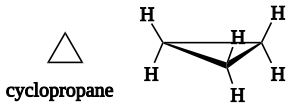
Rings larger than cyclopentane would have angle strain if they were planar. However, this strain, together with the eclipsing strain inherent in a planar structure, can be relieved by puckering the ring. Cyclohexane is a good example of a carbocyclic system that virtually eliminates eclipsing and angle strain by adopting non-planar conformations. Cycloheptane and cyclooctane have greater strain than cyclohexane, in large part due to transannular crowding (steric hindrance by groups on opposite sides of the ring).

Cyclic systems are a little different from open-chain systems. In an open chain, any bond can be rotated 360°, going through many different conformations. That complete rotation isn't possible in a cyclic system, because the parts that would be trying to twist away from each other would still be connected together. Thus cyclic systems have fewer "degrees of freedom" than aliphatic systems; they have "restricted rotation".

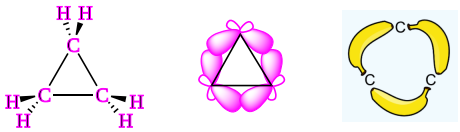
Because of the restricted rotation of cyclic systems, most of them have much more well-defined shapes than their aliphatic counterparts. Let's take a look at the basic shapes of some common rings. Many biologically important compounds are built around structures containing rings, so it's important that we become familiar with them. In nature, three- to six-membered rings are frequently encountered, so we'll focus on those.

Cyclopropane

A three membered ring has no rotational freedom whatsoever. A plane is defined by three points, so the three carbon atoms in cyclopropane are all constrained to lie in the same plane. This lack of flexibility does not allow cyclopropane to form more stable conformers which are non-planar.



The main source of ring strain in cyclopropane is angle strain. All of the carbon atoms in cyclopropane are tetrahedral and would prefer to have a bond angle of 109.5^{o} The angles in an equilateral triangle are actually 60^{o}, about half as large as the optimum angle. The large deviation from the optimal bond angle means that the C-C sigma bonds forming the cyclopropane ring are bent. Maximum bonding occurs when the overlapping orbitals are pointing directly toward each other. The severely strained bond angles in cyclopropane means that the orbitals forming the C-C bonds overlap at a slight angle making them weaker. This strain is partially overcome by using so-called “banana bonds”, where the overlap between orbitals is no longer directly in a line between the two nuclei, as shown here in three representations of the bonding in cyclopropane:



The constrained nature of cyclopropane causes neighboring C-H bonds to all be held in eclipsed conformations. Cyclopropane is always at maximum torsional strain. This strain can be illustrated in a Newman projections of cyclopropane as shown from the side.



Newman Projection of cyclopropane

Cyclopropane isn't large enough to introduce any steric strain. Steric strain does not become a factor until we reach six membered rings. Before that point, rings are not flexible enough to allow for two ring substituents to interact with each other.

The combination of torsional and angle strain creates a large amount of ring strain in cyclopropane which weakens the C-C ring bonds (255 kJ/mol) when compared to C-C bonds in open-chain propane (370 kJ/mol).

Cyclobutane

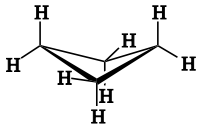
Cyclobutane is a four membered ring. The larger number of ring hydrogens would cause a substantial amount of torsional strain if cyclobutane were planar.



cyclobutane

In three dimensions, cyclobutane is flexible enough to buckle into a "puckered" shape which causes the C-H ring hydrogens to slightly deviate away from being completely eclipsed. This conformation relives some of the torsional strain but increases the angle strain because the ring bond angles decreases to 88^{o}.

In a line drawing, this butterfly shape is usually shown from the side, with the near edges drawn using darker lines.



The deviation of cyclobutane's ring C-H bonds away from being fully eclipsed can clearly be seen when viewing a Newman projections signed down one of the C-C bond.



Newman projection of cyclobutane

- With bond angles of 88^{o} rather than 109.5^{o} degrees, cyclobutane has significant amounts of angle strain, but less than in cyclopropane.
- Although torsional strain is still present, the neighboring C-H bonds are not exactly eclipsed in the cyclobutane's puckered conformation.
- Steric strain is very low. Cyclobutane is still not large enough that substituents can reach around to cause crowding.
- Overall the ring strain in cyclobutane (110 kJ/mol) is slightly less than cyclopropane (115 kJ/mol).

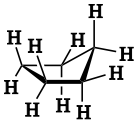
Cyclopentane

Cyclopentanes are even more stable than cyclobutanes, and they are the second-most common cycloalkane ring in nature, after cyclohexanes. Planar cyclopentane has virtually no angle strain but an immense amount of torsional strain. To reduce torsional strain, cyclopentane addops a non-planar conformation even though it slightly increases angle strain.



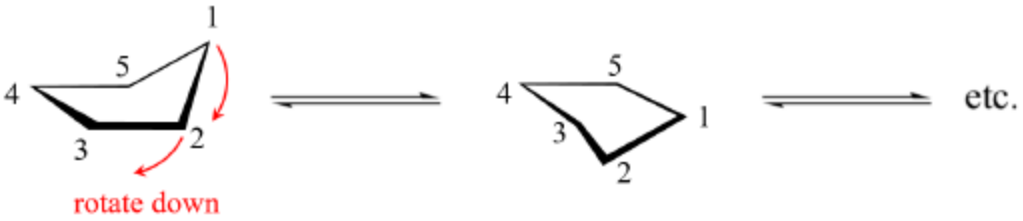
cyclopentane

The lowest energy conformation of cyclopentane is known as the ‘envelope’, with four of the ring atoms in the same plane and one out of plane (notice that this shape resembles an envelope with the flap open). The out-of-plane carbon is said to be in the ***endo*** position (‘*endo’* means ‘inside’). The envelope removes torsional strain along the sides and flap of the envelope. However, the neighboring carbons are eclipsed along the "bottom" of the envelope, away from the flap.

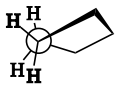


3D structure of cyclopentane (notice that the far top right carbon is the endo position).

At room temperature, cyclopentane undergoes a rapid bond **rotation** process in which each of the five carbons takes turns being in the *endo* position.



Cyclopentane distorts only very slightly into an "envelope" shape in which one corner of the pentagon is lifted up above the plane of the other four. The envelope removes torsional strain along the sides and flap of the envelope by allowing the bonds to be in an almost completely staggered position. However, the neighboring bonds are eclipsed along the "bottom" of the envelope, away from the flap. Viewing a Newman projections of cyclopentane signed down one of the C-C bond show the staggered C-H bonds.

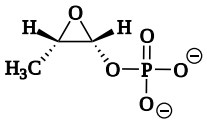


Newman projection of cyclopentane

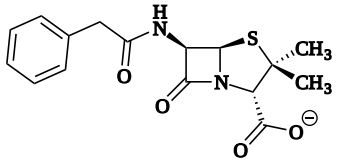
- The angle strain in the envelope conformation of cyclopentane is low. The ideal angle in a regular pentagon is about 107°, very close to the preferred 109.5° tetrahedral bond angle.
- There is some torsional strain in cyclopentane. The envelope conformation reduces torsional strain by placing some bonds in nearly staggered positions. However, other bonds are still almost fully eclipsed.
- Cyclopentane is not large enough to allow for steric strain to be created.
- Overall, cyclopentane has very little ring strain (26 kJ/mol) when compared to cyclopropane and cyclobutane.

C_3-C_5 Cycloalkanes in Nature

If one of the carbon-carbon bonds is broken in cyclopropane or cyclobutane, the ring will 'spring' open, releasing energy as the bonds reassume their preferred tetrahedral geometry. The effectiveness of two antibiotic drugs, fosfomycin and penicillin, is due in large part to the high reactivity of the three- and four-membered rings in their structures.

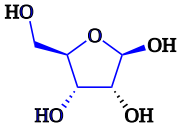


fosfomycin

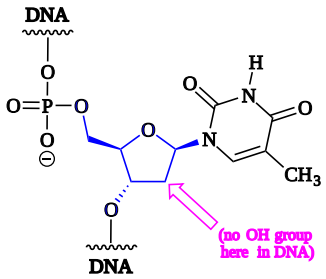


penicillin G

One of the most important five-membered rings in nature is a sugar called ribose – DNA and RNA are both constructed upon 'backbones' derived from ribose. Pictured below is one thymidine (T) deoxy-nucleotide from a stretch of DNA. Since the ribose has lost one of the OH groups (at carbon 2 of the ribose ring), this is part of a deoxyribonucleic acid (DNA). If the OH at carbon 2 of the ribose ring was present, this would be part of a ribonucleic acid (RNA).

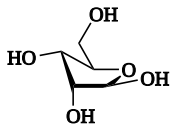


ribose



The lowest-energy conformations for ribose are envelope forms in which either C_3 or C_2 are *endo*, on the same side as the C_5

substituent.



Exercise 4.2.1

If cyclobutane were to be planar, how many H-H eclipsing interactions would there be? Assuming 4 kJ/mol per H-H eclipsing interaction what would the strain be on this “planar” molecule?

Answer available at the end of this section.

Exercise 4.2.1

In the two conformations of *trans*-1,2-Dimethylcyclopentane one is more stable than the other. Explain why this is.

Diagrams illustrating the resonance curves of a system, showing frequency response and amplitude relationships on a graph.

Answer available at the end of this section.

Exercise 4.2.3

In methylcyclopentane, which carbon would most likely be in the *endo* position?

Answer available at the end of this section.

Exercise 4.2.4

If cyclobutane were to be planar how many H-H eclipsing interactions would there be, and assuming 4 kJ/mol per H-H eclipsing interaction what is the strain on this “planar” molecule?

Answer available at the end of this section.

Exercise 4.2.5

In the two conformations of *trans*-cyclopentane one is more stable than the other. Explain why this is.

Diagrams illustrating the resonance curves of a system, showing frequency response and amplitude relationships on a graph.

Answer available at the end of this section.

Answers

Exercise 4.2.1

The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however have hydrogen-methyl eclipsing interactions which are not as high in energy as methyl-methyl interactions.

Exercise 4.2.2

Cyclobutane has 4 CH_2 groups while cyclopropane only has 3. More CH2 groups means cyclobutane has more eclipsing H-H interactions and therefore has more

torsional strain.

Exercise 4.2.1

There are eight eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

Exercise 4.2.1

The first conformation is more stable. Even though the methyl groups are *trans* in both models, they are anti to one another in the first structure (which is lower energy) while they are gauche in the second structure increasing strain within the molecule.

Exercise 4.2.3

The ring carbon attached to the methyl group would most likely be the endo carbon. The large methyl group would create the most torsional strain if eclipsed. Being in the *endo* position would place the bonds is a more staggered position which would reduce strain.

Exercise 4.2.4

There are eight eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

Exercise 4.2.5

The first conformation is more stable. Even though the methyl groups are *trans* in both models, in the second structure they are eclipsing one another, therefore increasing the strain within the molecule compared to the first structure where the larger methyl groups are anti to one another.

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4.3: Cyclohexane: A Strain-Free Cycloalkane

Objectives

After completing this section, you should be able to

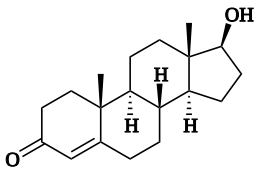
1. explain why cyclohexane rings are free of angular strain.
2. draw the structure of a cyclohexane ring in the chair conformation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

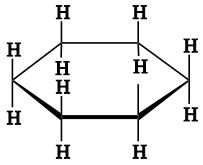
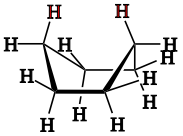
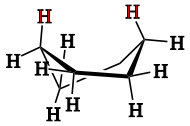
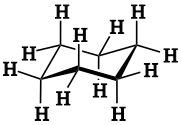
- chair conformation
- twist-boat conformation

We will find that cyclohexanes tend to have the least angle strain and consequently are the most common cycloalkanes found in nature. A wide variety of compounds including, hormones, pharmaceuticals, and flavoring agents have substituted cyclohexane rings.



testosterone, which contains three cyclohexane rings and one cyclopentane ring

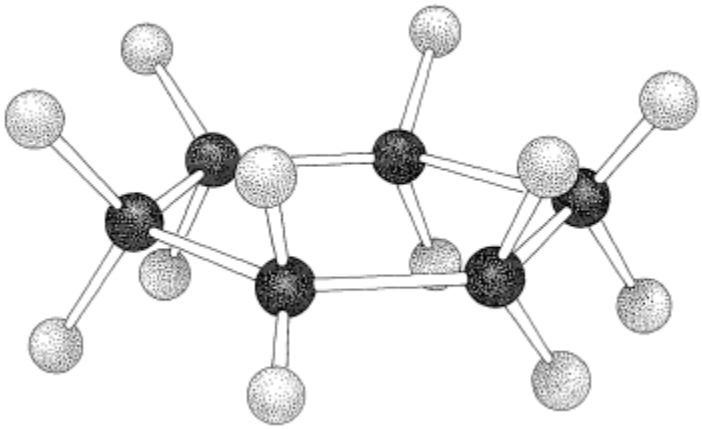
Rings larger than cyclopentane would have angle strain if they were planar. However, this strain, together with the eclipsing strain inherent in a planar structure, can be relieved by puckering the ring. Cyclohexane is a good example of a carbocyclic system that virtually eliminates eclipsing and angle strain by adopting non-planar conformations. Cycloheptane and cyclooctane have greater strain than cyclohexane, in large part due to transannular crowding (steric hindrance by groups on opposite sides of the ring). Cyclohexane has the possibility of forming multiple conformations each of which have structural differences which lead to different amounts of ring strain.

 **planar structure** severe angle strain (120°) severe eclipsing strain (all bonds) small steric strain	 **boat conformation** slight angle strain eclipsing strain at two bonds steric crowding of two hydrogens	 **twist boat conformation** slight angle strain small eclipsing strain small steric strain	 **chair conformation** no angle strain no eclipsing strain small steric strain

Conformations of Cyclohexane

A planar structure for cyclohexane is clearly improbable. The bond angles would necessarily be 120°, 10.5° larger than the ideal tetrahedral angle. Also, every carbon-hydrogen bond in such a structure would be eclipsed. The resulting angle and eclipsing

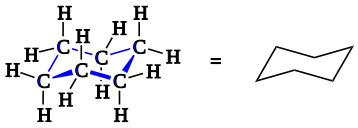
strains would severely destabilize this structure. The ring strain of planar cyclohexane is in excess of 84 kJ/mol so it rarely discussed other than in theory.



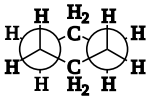
Cyclohexane in the strained planar configuration showing how the hydrogens become eclipsed.

Chair Conformation of Cyclohexane

The flexibility of cyclohexane allows for a conformation which is almost free of ring strain. If two carbon atoms on opposite sides of the six-membered ring are bent out of the plane of the ring, a shape is formed that resembles a reclining beach chair. This **chair conformation** is the lowest energy conformation for cyclohexane with an overall ring strain of 0 kJ/mol. In this conformation, the carbon-carbon ring bonds are able to assume bonding angles of ~111^{o} which is very near the optimal tetrahedral 109.5^{o} so angle strain has been eliminated.



Also, the C-H ring bonds are staggered so torsional strain has also been eliminated. This is clearly seen when looking at a Newman projection of chair cyclohexane sighted down the two central C-C bonds.

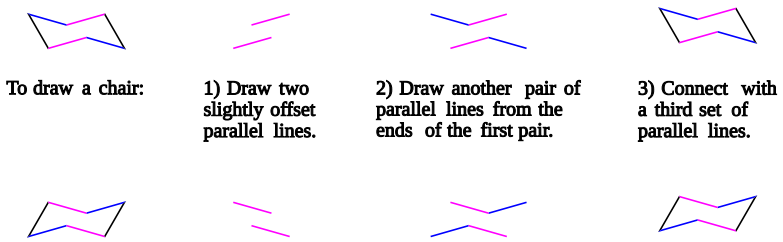


Newman projection of cyclohexane

Interactive Element

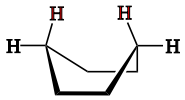
The 3D Structure of Chair Cyclohexane

How to Draw the Chair Conformation



Boat Conformation of Cyclohexane

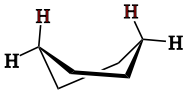
The **Boat Conformation** of cyclohexane is created when two carbon atoms on opposite sides of the six-membered ring are both lifted up out of the plane of the ring creating a shape which slightly resembles a boat. The boat conformation is less stable than the chair form for two major reasons. The boat conformation has unfavorable steric interactions between a pair of 1,4 hydrogens (the so-called "flagpole" hydrogens) that are forced to be very close together (1.83Å). This steric hindrance creates a repulsion energy of about 12 kJ/mol. An additional cause of the higher energy of the boat conformation is that adjacent hydrogen atoms on the 'bottom of the boat' are forced into eclipsed positions. For these reasons, the boat conformation about 30 kJ/mol less stable than the chair conformation.



A boat structure of cyclohexane (the interfering "flagpole" hydrogens are shown in red)

Twist-Boat Conformation of Cyclohexane

The boat form is quite flexible and by twisting it at the bottom created the **twist-boat conformer**. This conformation reduces the strain which characterized the boat conformer. The flagpole hydrogens move farther apart (the carbons they are attached to are shifted in opposite directions, one forward and one back) and the eight hydrogens along the sides become largely but not completely staggered. Though more stable than the boat conformation, the twist-boat (sometimes skew-boat) conformation is roughly 23 kJ/mol less stable than the chair conformation.



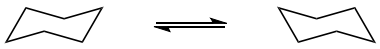
A twist-boat structure of cyclohexane

Half Chair Conformation of Cyclohexane

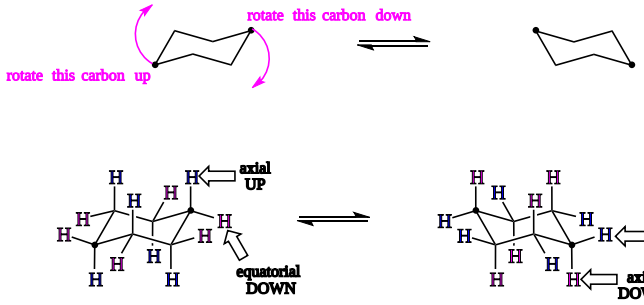
Cyclohexane can obtain a partially plane conformation called "half chair" but with only with excessive amounts of ring strain. The half chair conformation is formed by taking planar cyclohexane and lifting one carbon out of the plane of the ring. The half chair conformation has much of the same strain effects predicted by the fully planar cyclohexane. In the planar portion of half chair cyclohexane the C-C bond angles are forced to 120^{o} which creates significant amounts of angle strain. Also, the corresponding C-H bonds are fully eclipsed which create torsional strain. The out-of-plane carbon allows for some of the ring's bond angles to reach 109.5^{o} and for some of C-H bonds to not be fully eclipsed. Overall, the half chair conformation is roughly 45 kJ/mol less stable than the chair conformation.

Conformation Changes in Cyclohexane - "Ring Flips"

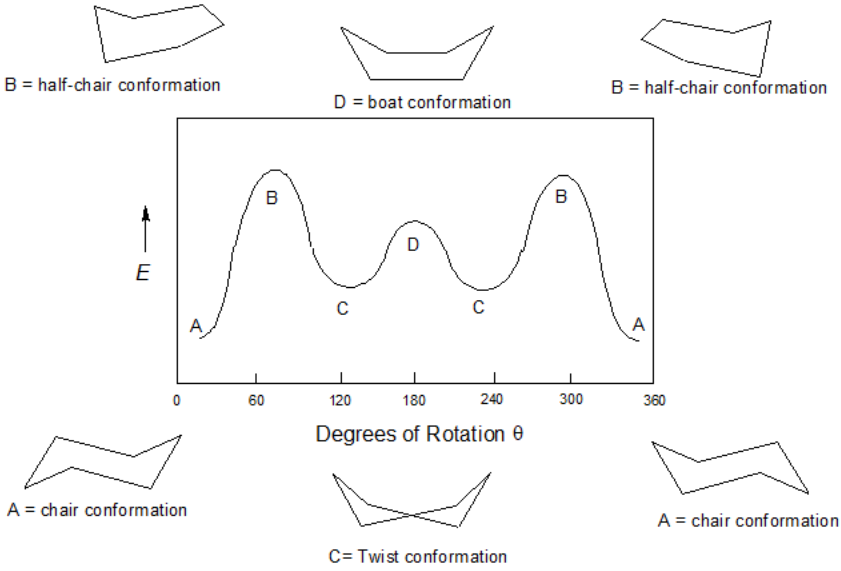
Cyclohexane is rapidly rotating between the two most stable conformations known as the chair conformations in what is called the "ring flip" shown below. The importance of the ring flip will be discussed in the next section.



"Ring flip" describes the rapid equilibrium of cyclohexane rings between the two chair conformations



It is important to note that one chair does not immediately become the other chair, rather the ring must travel through the higher energy conformations as transitions. At room temperature the energy barrier created by the half chair conformation is easily overcome allowing for equilibration between the two chair conformation on the order of 80,000 times per second. Although cyclohexane is continually converting between these different conformations, the stability of the chair conformation causes it to comprises more than 99.9% of the equilibrium mixture at room temperature.



1" id="MathJax-Element-12-Frame" role="presentation" style="position:relative;" tabindex="0">Image of energy diagram of cyclohexane conformations

1" role="presentation" style="position:relative;" tabindex="0">

Exercises

1) Consider the conformations of cyclohexane: half chair, chair, boat, twist boat. Order them in increasing ring strain in the molecule.

Solutions

1) Chair < Twist Boat < Boat < half chair (most ring strain)

Questions

Q4.5.1

Consider the conformations of cyclohexane, chair, boat, twist boat. Order them in increasing strain in the molecule.

Solutions

S4.5.1

Chair < Twist Boat < Boat (most strain)

Objectives

After completing this section, you should be able to

1. Draw the chair conformation of cyclohexane, with axial and equatorial hydrogen atoms clearly shown and identified.
2. identify the axial and equatorial hydrogens in a given sketch of the cyclohexane molecule.
3. explain how chair conformations of cyclohexane and its derivatives can interconvert through the process of ring flip.

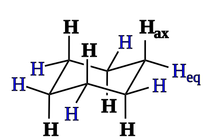
Key Terms

Make certain that you can define, and use in context, the key terms below.

- axial position
- equatorial position
- ring flip

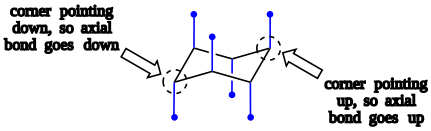
Axial and Equatorial Positions in Cyclohexane

Careful examination of the chair conformation of cyclohexane, shows that the twelve hydrogens are not structurally equivalent. Six of them are located about the periphery of the carbon ring, and are termed **equatorial**. The other six are oriented above and below the approximate plane of the ring (three in each location), and are termed **axial** because they are aligned parallel to the symmetry axis of the ring.

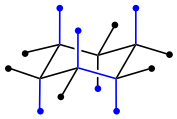


In the figure above, the equatorial hydrogens are colored blue, and the axial hydrogens are black. Since there are two equivalent chair conformations of cyclohexane in rapid equilibrium, all twelve hydrogens have 50% equatorial and 50% axial character.

How To Draw Axial and Equatorial Bonds

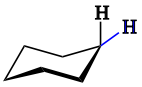


Draw axial bonds **straight up** or **straight down.**



Draw equatorial bonds **up and out** or **down and out.**

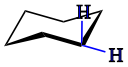
How **not** to draw the chair:



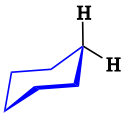
Incorrect. Equatorial bond should be **down** and **out**.



Incorrect. Axial bond should be **straight up**.



Incorrect. Axial bond should be **straight down,** equatorial bond should be **up** and **out**.



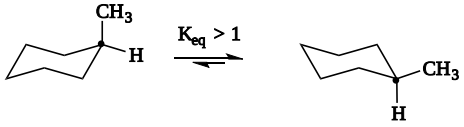
Incorrect. Ring should be tilted slightly.

Aside from drawing the basic chair, the key points are:

- Axial bonds alternate up and down, and are shown "vertical".
- Equatorial groups are approximately horizontal, but actually somewhat distorted from that (slightly up or slightly down), so that the angle from the axial group is a bit more than a right angle -- reflecting the common 109.5^{o} bond angle.
- Each carbon has an axial and an equatorial bond.
- Each face of the cyclohexane ring has three axial and three equatorial bonds.
- Each face alternates between axial and equatorial bonds. Then looking at the "up" bond on each carbon in the cyclohexane ring they will alternate axial-equatorial-axial ect.
- When looking down at a cyclohexane ring:
  - the equatorial bonds will form an "equator" around the ring.
  - The axial bonds will either face towards you or away. These will alternate with each axial bond. The first axial bond will be coming towards with the next going away. There will be three of each type.
- Note! The terms cis and trans in regards to the stereochemistry of a ring are not directly linked to the terms axial and equatorial. It is very common to confuse the two. It typically best not to try and directly inter convert the two naming systems.

Axial vs. Equatorial Substituents

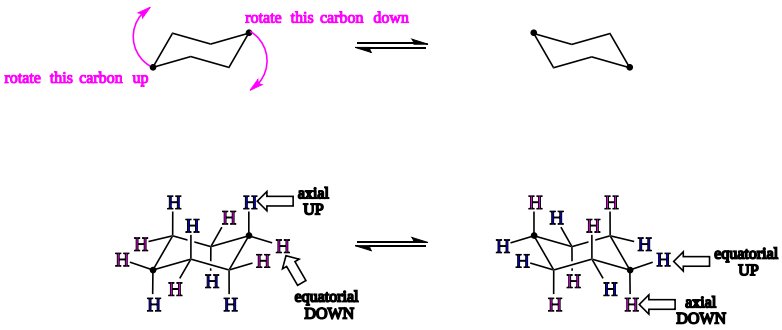
When a substituent is added to cyclohexane, the ring flip allows for two distinctly different conformations. One will have the substituent in the axial position while the other will have the substituent in the equatorial position. In the next section will discuss the energy differences between these two possible conformations. Below are the two possible chair conformations of methylcyclohexane created by a ring-flip. Although the conformation which places the methyl group in the equatorial position is more stable by 7 kJ/mol, the energy provided by ambient temperature allows the two conformations to rapidly interconvert.



methyl group axial

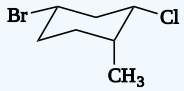
methyl group equatorial (more stable by **7 kJ/mol**)

The figure below illustrates how to convert a molecular model of cyclohexane between two different chair conformations - this is something that you should practice with models. Notice that a 'ring flip' causes equatorial groups to become axial, and vice-versa.



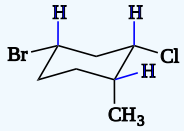
Example 4.3.1

For the following please indicate if the substituents are in the axial or equatorial positions.



Solution

Due to the large number of bonds in cyclohexane it is common to only draw in the relevant ones (leaving off the hydrogens unless they are involved in a reaction or are important for analysis). It is still possible to determine axial and equatorial positioning with some thought. With problems such as this it is important to remember that each carbon in a cyclohexane ring has one axial and one equatorial bond. Also, remember that axial bonds are perpendicular with the ring and appear to be going either straight up or straight down. Equatorial bonds will be roughly in the plane of the cyclohexane ring (only slightly up or down). Sometimes it is valuable to draw in the additional bonds on the carbons of interest.



With this it can be concluded that the bromine and chlorine substituents are attached in equatorial positions and the CH_3 substituent is attached in an axial position.

Exercises

1) Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

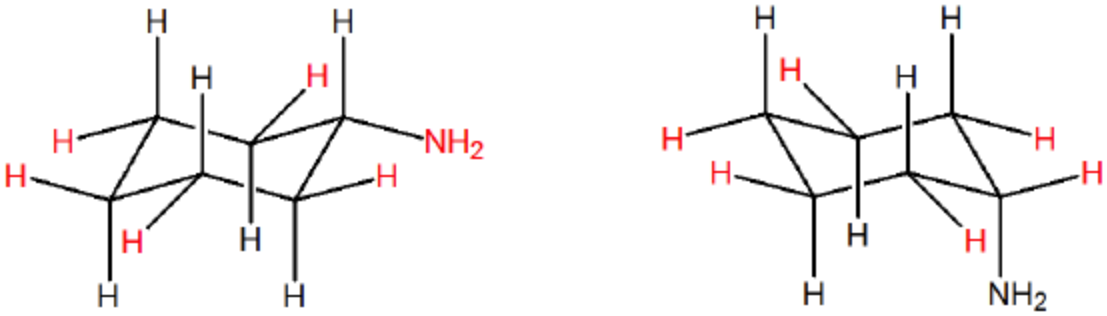
2) Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

3) In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).

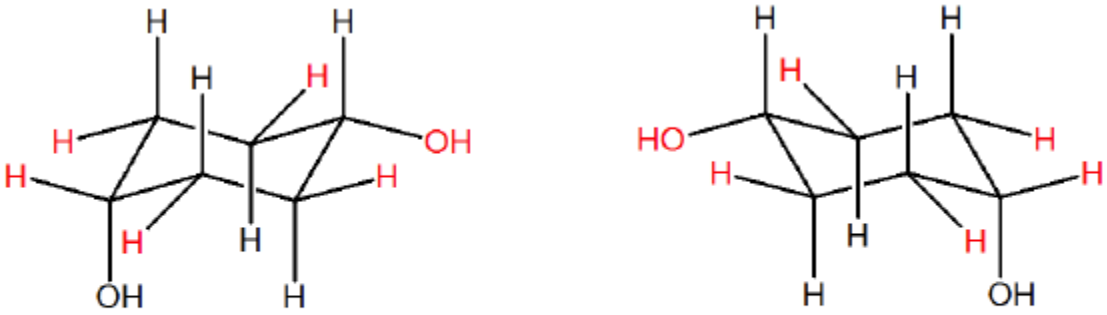
4-6-3qu.png

Solutions

1)

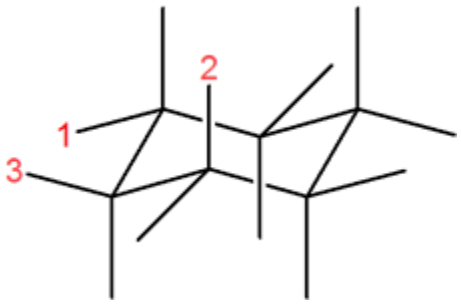


2)



3) Original conformation: 1 = axial, 2 = equatorial, 3 = axial

Flipped chair now looks like this.



Questions

Q4.6.1

Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

Q4.6.2

Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

Q4.6.3

In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).

4-6-3qu.png

Solutions

S4.6.1

4.6-1.png

S4.6.2

4.6-2.png

S4.6.3

Original conformation: 1 = axial, 2 = equatorial, 3 = axial

Flipped chair now looks like this.

4-6-3sol.png

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4.4: Substituted Cyclohexanes

Objectives

After completing this section, you should be able to

1. account for the greater stability of the equatorial conformers of monosubstituted cyclohexanes compared to their axial counterparts, using the concept of 1,3-diaxial interaction.
2. compare the gauche interactions in butane with the 1,3-diaxial interactions in the axial conformer of methylcyclohexane.
3. arrange a given list of substituents in increasing or decreasing order of 1,3-diaxial interactions.

Key Terms

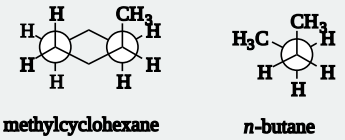
Make certain that you can define, and use in context, the key term below.

- 1,3-diaxial interaction

Study Notes

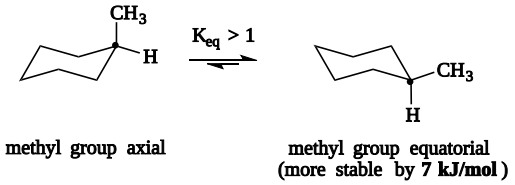
1,3-Diaxial interactions are steric interactions between an axial substituent located on carbon atom 1 of a cyclohexane ring and the hydrogen atoms (or other substituents) located on carbon atoms 3 and 5.

Be prepared to draw Newman-type projections for cyclohexane derivatives as the one shown for methylcyclohexane. Note that this is similar to the Newman projections from chapter 3 such as *n*-butane.

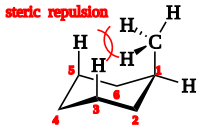


Newman projections of methylcyclohexane and *n*-butane

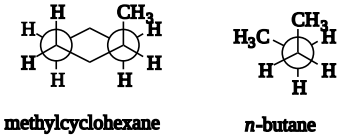
When a substituent is added to a cyclohexane ring, the two possible chair conformations created during a ring flip are not equally stable. In the example of methylcyclohexane the conformation where the methyl group is in the equatorial position is more stable than the axial conformation by 7.6 kJ/mol at 25^{o} C. The percentages of the two different conformations at equilibrium can be determined by solving the following equation for K (the equilibrium constant): $\Delta E = -RTlnK$. In this equation ΔE is the energy difference between the two conformations, R is the gas constant (8.314 J/mol•K), T is the temperature in Kelvin, and K is the equilibrium constant for the ring flip conversion. Using this equation, we can calculate a K value of 21 which means about 95% methylcyclohexane molecules have the methyl group in the equatorial position at 25^{o} C.



The energy difference between the two conformations comes from strain, called 1,3-diaxial interactions, created when the axial methyl group experiences steric crowding with the two axial hydrogens located on the same side of the cyclohexane ring. Because axial bonds are parallel to each other, substituents larger than hydrogen experience greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents are in the equatorial orientation***. When the methyl group is in the equatorial position this strain is not present which makes the equatorial conformer more stable and favored in the ring flip equilibrium.



Actually, 1,3-diaxial steric strain is directly related to the steric strain created in the gauche conformer of butane discussed in Section: 3-7. When butane is in the gauche conformation 3.8 kJ/mol of strain was created due the steric crowding of two methyl group with a 60° dihedral angle. When looking at the a Newman projection of axial methylcyclohexane the methyl group is at a 60° dihedral angle with the ring carbon in the rear. This creates roughly the same amount of steric strain as the gauche conformer of butante. Given that there is actually two such interactions in axial methylcyclohexane, it makes sense that there is 2(3.8 kJ/mol) = 7.6 kJ/mol of steric strain in this conformation. The Newman projection of equatorial methylcyclohexane shows no such interactions and is therefore more stable.



Newman projections of methyl cyclohexane and butane showing similarity of 1,3-diaxial and gauche interactions.

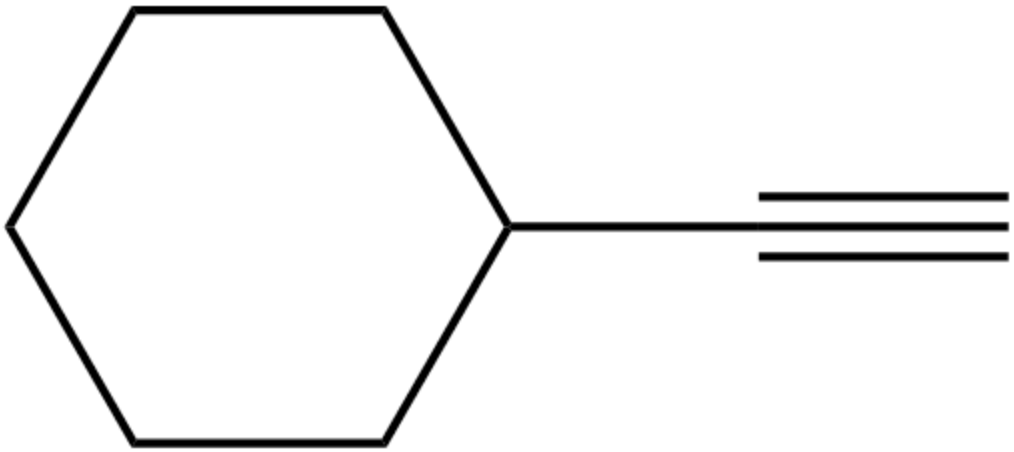
Strain values for other cyclohexane substituents can also be considered. The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane determined the amount of strain generated. The strain generated can be used to evaluate the relative tendency of substituents to exist in an equatorial or axial location. Looking at the energy values in this table, it is clear that as the size of the substituent increases, the 1,3-diaxial energy tends to increase, also. Note that it is the size and not the molecular weight of the group that is important. Table 4.7.1 summarizes some of these strain values values.

Table 4.7.1: A Selection of ΔG° Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes

Substituent	-ΔG° (kcal/mol)	Substituent	-ΔG° (kcal/mol)
CH_3-	1.7	O_2N-	1.1
CH_2H_5-	1.8	$N\equiv C-$	0.2
$(CH_3)_2CH-$	2.2	CH_3O-	0.5
$(CH_3)_3C-$	≥ 5.0	HO_2C-	0.7
$F-$	0.3	$H_2C=CH-$	1.3
$Cl-$	0.5	C_6H_5-	3.0
$Br-$	0.5		
$I-$	0.5		

Exercises

1) In the molecule, cyclohexyl ethyne there is little steric strain, why?



2) Calculate the energy difference between the axial and equatorial conformations of bromocyclohexane?

3) Using your answer from Question 2) estimate the percentages of axial and equatorial conformations of bromocyclohexane at 25^{o} C.



4) There very little in 1,3-diaxial strain when going from a methyl substituent (3.8 kJ/mol) to an ethyl substituent (4.0 kJ/mol), why? It may help to use molecular model to answer this question.

Solutions

1) The ethyne group is linear and therefore does not affect the hydrogens in the 1,3 positions to say to the extent as a bulkier or a bent group (e.g. ethene group) would. This leads to less of a strain on the molecule.

4.7.png

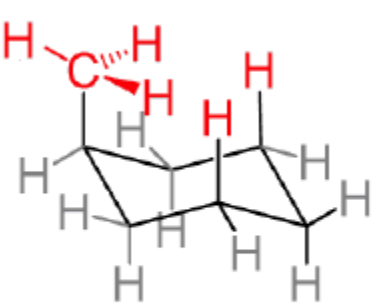
2) The equatorial conformation of bromocyclohexane will have two 1,3 diaxial interactions. The table above states that each interaction accounts for 1.2 kJ/mol of strain. The total strain in equatorial bromocyclohexane will be 2(1.2 kJ/mol) = 2.4 kJ/mol.

3) Remembering that the axial conformation is higher in energy, the energy difference between the two conformations is ΔE = (E equatorial - E axial) = (0 - 2.4 kJ/mol) = -2.4 kJ/mol. After converting ^{o}C to Kelvin and kJ/mol to J/mol we can use the equation $\Delta E = -RT \ln K$ to find that $-\Delta E/RT = \ln K$ or (2.4 x 10^{3} J/mol) / (8.313 kJ/mol K • 298 K) = lnK. From this we calculate that K = 2.6. Because the ring flip reaction is an equilibrium we can say that K = [Equatorial] / [Axial]. If assumption is made that [Equatorial] = X then [Axial] must be 1-X. Plugging these values into the equilibrium expression produces K = [X] / [1-X]. After plugging in the calculated value for K, X can be solved algebraically. 2.6 = [X] / [1-X] → 2.6 - 2.6X = X → 2.6 = 3.6X → 2.6/3.6 = X = 0.72. This means that bromocyclohexane is in the equatorial position 72% of the time and in the axial position 28% of the time.

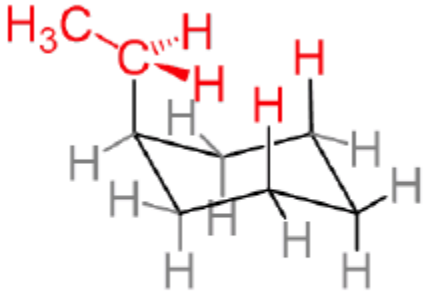


Bromo group axial **Bromo** group equitorial

4) The fact that C-C sigma bonds can freely rotate allows the ethyl subsistent to obtain a conformation which places the bulky CH_3 group away from the cyclohexane ring. This forces the ethyl substituent to have only have 1,3- diaxial interactions between hydrogens, which only provides a slight difference to a methyl group.



Methylcyclohexane



Ethylcyclohexane

Exercises

Questions

Q4.7.1

In the molecule, cyclohexyl ethyne there is little steric strain, why?

Solutions

S4.7.1

The ethyne group is linear and therefore does not affect the hydrogens in the 1,3 positions to say to the extent as a bulkier or a bent group (e.g. ethene group) would. This leads to less of a strain on the molecule.

4.7.png

Objective

After completing this section, you should be able to use conformational analysis to determine the most stable conformation of a given disubstituted cyclohexane.

Key Terms

Make certain that you can define, and use in context, the key term below.

- conformational analysis

Study Notes

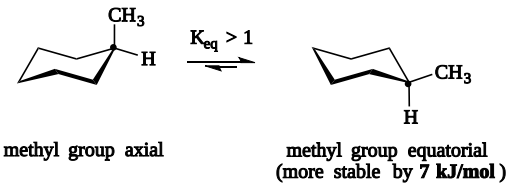
When faced with the problem of trying to decide which of two conformers of a given disubstituted cyclohexane is the more stable, you may find the following generalizations helpful.

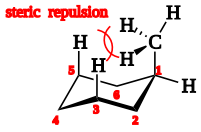
1. A conformation in which both substituents are equatorial will always be more stable than a conformation with both groups axial.
2. When one substituent is axial and the other is equatorial, the most stable conformation will be the one with the bulkiest substituent in the equatorial position. Steric bulk decreases in the order

   tert-butyl > isopropyl > ethyl > methyl > hydroxyl > halogens

Monosubstituted Cyclohexanes

In the previous section, it was stated that the chair conformation in which the methyl group is equatorial is more stable because it minimizes steric repulsion, and thus the equilibrium favors the more stable conformer. This is true for all monosubstituted cyclohexanes. The chair conformation which places the substituent in the equatorial position will be the most stable and be favored in the ring flip equilibrium.





Disubstituted Cyclohexanes

Determining the more stable chair conformation becomes more complex when there are two or more substituents attached to the cyclohexane ring. To determine the stable chair conformation, the steric effects of each substituent, along with any additional steric interactions, must be taken into account for both chair conformations.

In this section, the effect of conformations on the relative stability of disubstituted cyclohexanes is examined using the two principles:

i. Substituents prefer equatorial rather than axial positions in order to minimize the steric strain created of 1,3-diaxial

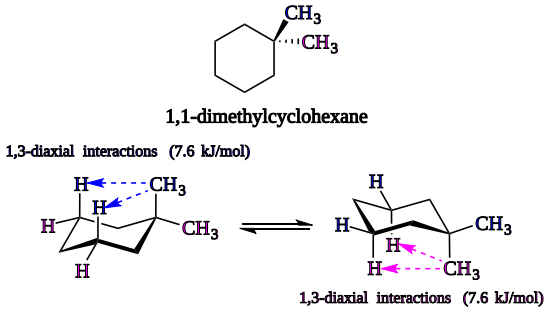
interactions.

ii. The more stable conformation will place the larger substituent in the equatorial position.

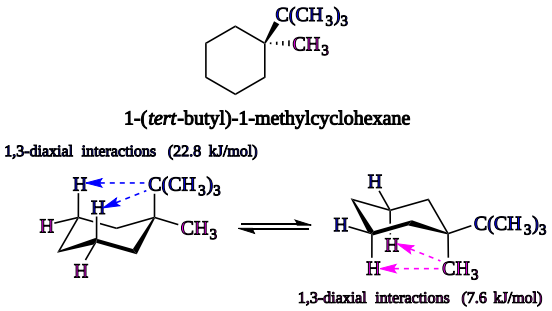
1,1-Disubstituted Cyclohexanes

The more stable chair conformation can often be determined empirically or by using the energy values of steric interactions previously discussed in this chapter. Note, in some cases there is no discernable energy difference between the two chair conformations which means they are equally stable.

1,1-dimethylcyclohexane does not have *cis* or *trans* isomers, because both methyl groups are on the same ring carbon. Both chair conformers have one methyl group in an axial position and one methyl group in an equatorial position giving both the same relative stability. The steric strain created by the 1,3-diaxial interactions of a methyl group in an axial position (versus equatorial) is 7.6 kJ/mol (from Table 4.7.1), so both conformers will have equal amounts of steric strain. Thus, the equilibrium between the two conformers does not favor one or the other. Note, that both methyl groups cannot be equatorial at the same time without breaking bonds and creating a different molecule.

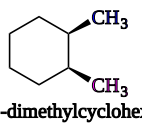


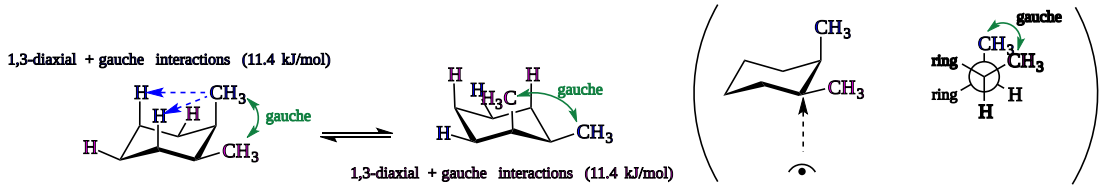
However, if the two groups are different, as in 1-*tert*-butyl-1-methylcyclohexane, then the equilibrium favors the conformer in which the larger group (*tert*-butyl in this case) is in the more stable equatorial position. The energy cost of having one tert-butyl group axial (versus equatorial) can be calculated from the values in table 4.7.1 and is approximately 22.8 kJ/mol. The conformer with the *tert*-butyl group axial is approximately 15.2 kJ/mol (22.8 kJ/mol - 7.6 kJ/mol) less stable then the conformer with the *tert*-butyl group equatorial. Solving for the equilibrium constant K shows that the equatorial is preferred about 460:1 over axial. This means that 1-*tert*-butyl-1-methylcyclohexane will spend the majority of its time in the more stable conformation, with the *tert*-butyl group in the equatorial position.



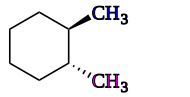
Cis and *trans* stereoisomers of 1,2-dimethylcyclohexane

In *cis*-1,2-dimethylcyclohexane, both chair conformations have one methyl group equatorial and one methyl group axial. As previously discussed, the axial methyl group creates 7.6 kJ/mol of steric strain due to 1,3-diaxial interactions. It is important to note, that both chair conformations also have an additional 3.8 kJ/mol of steric strain created by a gauche interaction between the two methyl groups. Overall, both chair conformations have 11.4 kJ/mol of steric strain and are of equal stability.

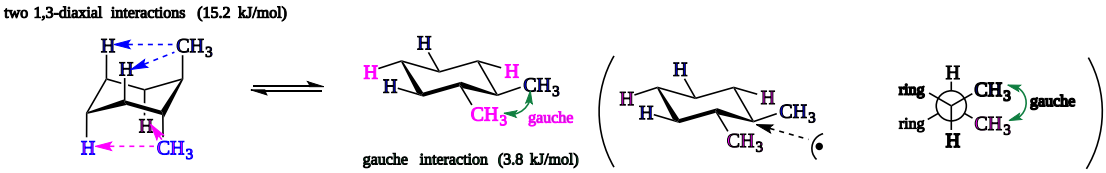




In *trans*-1,2-dimethylcyclohexane, one chair conformer has both methyl groups axial and the other conformer has both methyl groups equatorial. The conformer with both methyl groups equatorial has no 1,3-diaxial interactions however there is till 3.8 kJ/mol of strain created by a gauche interaction. The conformer with both methyl groups axial has four 1,3-Diaxial interactions which creates 2 x 7.6 kJ/mol (15.2 kJ/mol) of steric strain. This conformer is (15.2 kJ/mol -3.8 kJ/mol) 11.4 kJ/mol less stable than the other conformer. The equilibrium will therefore favor the conformer with both methyl groups in the equatorial position.

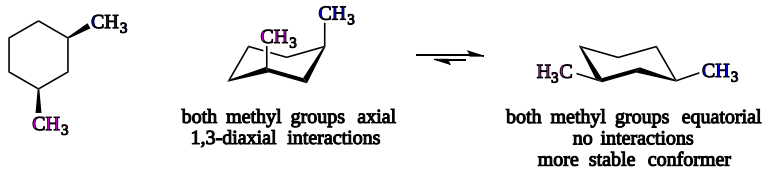


trans-1,2-dimethylcyclohexane

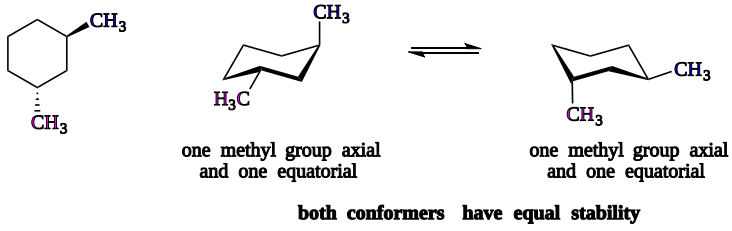


Cis and *trans* stereoisomers of 1,3-dimethylcyclohexane

A similar conformational analysis can be made for the *cis* and *trans* stereoisomers of 1,3-dimethylcyclohexane. For *cis*-1,3-dimethylcyclohexane one chair conformation has both methyl groups in axial positions creating 1,3-diaxial interactions. The other conformer has both methyl groups in equatorial positions thus creating no 1,3-diaxial interaction. Because the methyl groups are not on adjacent carbons in the cyclohexane rings gauche interactions are not possible. Even without energy calculations it is simple to determine that the conformer with both methyl groups in the equatorial position will be the more stable conformer.



For *trans*-1,3-dimethylcyclohexane both conformations have one methyl axial and one methyl group equatorial. Each conformer has one methyl group creating a 1,3-diaxial interaction so both are of equal stability.



Summary of Disubstitued Cyclohexane Chair Conformations

When considering the conformational analyses discussed above a pattern begins to form. There are only two possible relationships which can occur between ring-flip chair conformations:

1) AA/EE: One chair conformation places both substituents in axial positions creating 1,3-diaxial interactions. The other conformer places both substituents in equatorial positions creating no 1,3-diaxial interactions. This diequatorial conformer is the more stable regardless of the substituents.

2) AE/EA: Each chair conformation places one substituent in the axial position and one substituent in the equatorial position. If the substituents are the same, there will be equal 1,3-diaxial interactions in both conformers making them equal in stability. However, if the substituents are different then different 1,3-diaxial interactions will occur. The chair conformation which places the larger substituent in the equatorial position will be favored.

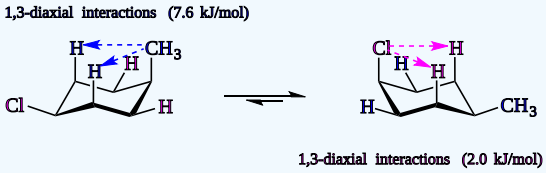
Substitution type	Chair Conformation Relationship
cs-1,2-disubstituted cyclohexanes	AE/EA
trans-1,2-disubstituted cyclohexanes	AA/EE
cis-1,3-disubstituted cyclohexanes	AA/EE
trans-1,3-disubstituted cyclohexanes	AE/EA
cis-1,4-disubstituted cyclohexanes	AE/EA
trans-1,4-disubstituted cyclohexanes	AA/EE

Example 4.4.1

For *cis*-1-chloro-4-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *cis*-1,4-disubstitued cyclohexanes should have two chair conformations each with one substituent axial and one equatorial. Based on this, we can surmise that the energy difference of the two chair conformations will be based on the difference in the 1,3-diaxial interactions created by the methyl and chloro substituents.



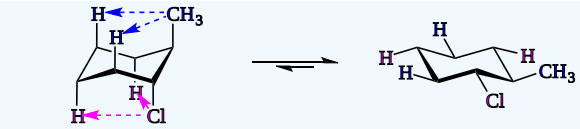
As predicted, each chair conformer places one of the substituents in the axial position. Because the methyl group is larger and has a greater 1,3-diaxial interaction than the chloro, the most stable conformer will place it the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol - 2.0 kJ/mol) 5.6 kJ/mol more stable than the other.

Example 4.4.2

For *trans*-1-chloro-2-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *trans*-1,2-disubstitued cyclohexanes should have one chair conformation with both substituents axial and one conformation with both substituents equatorial. Based on this, we can predict that the conformer which places both substituents equatorial will be the more stable conformer. The energy difference of the two chair conformations will be based on the 1,3-diaxial interactions created by both the methyl and chloro substituents.

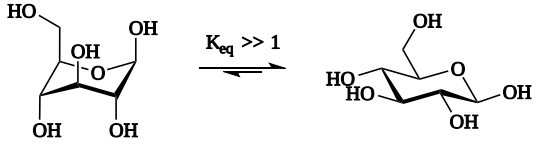


As predicted, one chair conformer places both substituents in the axial position and other places both substituents equatorial. The more stable conformer will place both substituents in the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol + 2.0 kJ/mol) 9.6 kJ/mol more stable than the other.

Conformational Analysis of Complex Six Membered Ring Structures

Cyclohexane can have more than two substituents. Also, there are multiple six membered rings which contain atoms other than carbon. All of these systems usually form chair conformations and follow the same steric constraints discussed in this section. Because the most commonly found rings in nature are six membered, conformational analysis can often help in understanding the usual shapes of some biologically important molecules. In complex six membered ring structures a direct calculation of 1,3-diaxial energy values may be difficult. In these cases a determination of the more stable chair conformer can be made by empirically applying the principles of steric interactions.

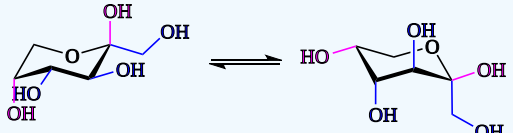
A later chapter will discuss how many sugars can exist in cyclic forms which are often six remembered rings. When in an aqueous solution the six carbon sugar, glucose, is usually a six membered ring adopting a chair conformation. When looking at the two possible ring-clip chair conformations, one has all of the substituents axial and the other has all the substutents equatorial. Even without a calculation, it is clear that the conformation with all equatorial substituents is the most stable and glucose will most commonly be found in this conformation.



glucose
(β-glucopyranose form)

Example 4.4.3

The six carbon sugar, fructose, in aqueous solution is also a six-membered ring in a chair conformation. Which of the two possible chair conformations would be expected to be the most stable?



fructose
(β-fructopyranose form)

Solution

The lower energy chair conformation is the one with three of the five substituents (including the bulky –CH_2OH group) in the equatorial position (pictured on the right). The left structure has 3 equatorial substituents while the structure on the right only has two equatorial substituents.

Exercises

1. Draw the two chair conformations for *cis*-1-ethyl-2-methylcyclohexane using bond-line structures and indicate the more energetically favored conformation.

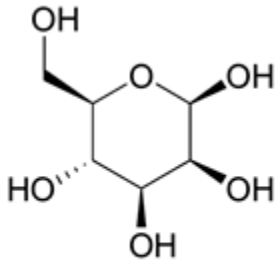
2. Draw the most stable conformation for *trans*-1-ethyl-3-methylcyclohexane using bond-line structures.

3. Draw the most stable conformation for trans-1-*t*-butyl-4-methylcyclohexane using bond-line structures.

4. Draw the most stable conformation fo *trans*-1-isopropyl-3-methylcyclohexane.

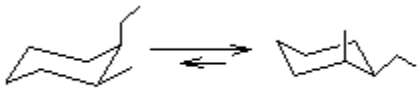
5. Can a 'ring flip' change a *cis*-disubstituted cyclohexane to *trans*? Explain.

6. Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

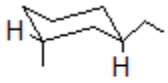


mannose

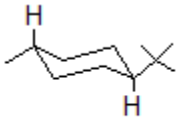
Solutions

1. 

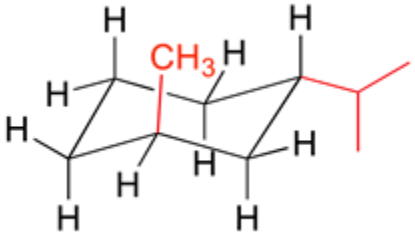
larger ethyl group in equatorial position is favored

2. 

larger ethyl group in equatorial position is favored

3. 

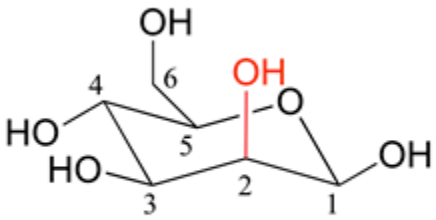
both alkyl groups in equatorial position

4. 

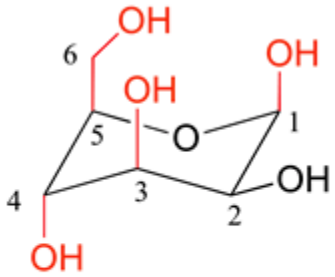
The bulkier isopropyl groups is in the equatorial position.

5. No. In order to change the relationship of two substituents on a ring from *cis* to *trans*, you would need to break and reform two covalent bonds. Ring flips involve only *rotation* of single bonds.

6.



major chair form of mannose
(only one substituent axial)



minor chair form of mannose
(four substituents axial)

Exercises

Questions

Q4.8.1

For the following molecules draw the most stable chair conformation and explain why you chose this as an answer

1 = *trans*-1,2-dimethylcyclohexane

2 = *cis*-1,3-dimethylcyclohexane

Solutions

S4.8.1

1 – The most stable conformation would be to have the methyl groups equatorial reducing steric interaction

2 – The most stable conformation would be to have the groups equatorial this would reduce the strain if they were axial

4.8.png

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4.5: Larger Cycloalkanes

The Baeyer strain theory suggested that the larger cycloalkanes ring are difficult to synthesize because of angle strain associated with planar rings, as calculated in Table 12-3. We now know that, except for cyclopropane, none of the cycloalkanes have planar carbon rings and that the higher cycloalkanes have normal or nearly normal bond angles. The reason that the higher cycloalkanes are generally difficult to synthesize from open-chain compounds is not so much angle strain, as Baeyer hypothesized, but the low probability of having reactive groups on the two fairly remote ends of a long hydrocarbon chain come together to effect cyclization. Usually, coupling of reactive groups on the ends of *different* molecules occurs in preference to cyclization, unless the reactions are carried out in very dilute solutions. This is called the **high-dilution** technique for achieving ring formation when the ring-forming reaction has to compete with rapid inter-molecular reactions.

With regard to conformations of the larger cycloalkanes, we first note that the chair form of cyclohexane is a "perfect" conformation for a cycloalkane. The $\mathrm{C{-}C{-}C}$ bond angles are close to their normal values, all the adjacent hydrogens are staggered with respect to one another, and the 1,3-axial hydrogens are not close enough together to experience nonbonded repulsions. About the only qualification one could put on the ideality of the chair form is that the trans conformation of butane is somewhat more stable than the gauche conformation (Section 5-2), and that all of the $\mathrm{C{-}C{-}C{-}C}$ segments of cyclohexane have the gauche arrangement. Arguing from this, J. Dale[6] has suggested that large cycloalkane rings would tend to have trans $\mathrm{C{-}C{-}C{-}C}$ segments to the degree possible and, indeed, cyclotetradecane seems to be most stable in a rectangular conformation with trans $\mathrm{C{-}C{-}C{-}C}$ bond segments (Figure 12-16). This conformation has a number of possible substituent positions, but because only single isomers of monosubstituted cyclotetradecanes have been isolated, rapid equilibration of the various conformational isomers must occur. Other evidence indicates that the barrier to interconversion of these conformations is about $7\ \mathrm{kcal\ mol^{-1}}$.

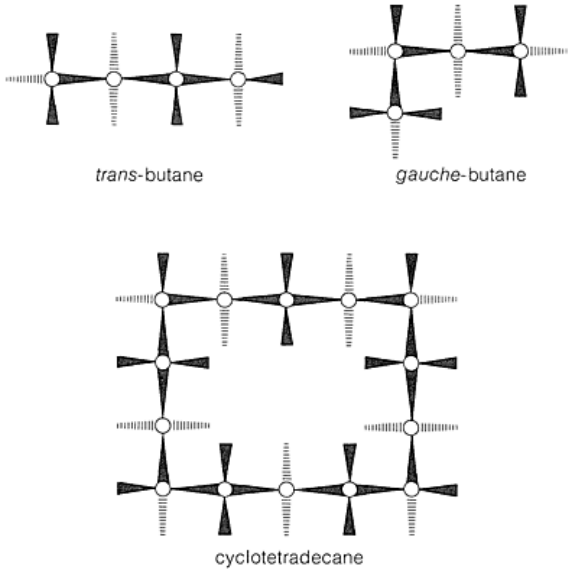
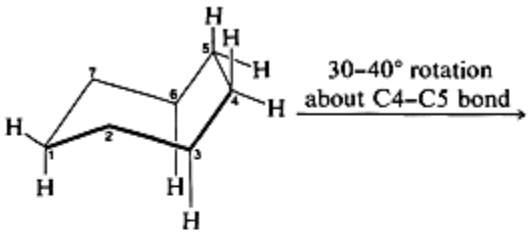


Figure 12-16 Favored conformation of cyclotetradecane as proposed by Dale. For comparison, the trans and gauche forms of butane are shown by the same convention. (The convention implies that the wedged lines are $\mathrm{C{-}C}$ or $\mathrm{C{-}H}$ bonds projecting out of the plane of the paper, with the wide end closest to you, and the broken lines are $\mathrm{C{-}H}$ bonds projecting behind the plane of the paper. The result is an "aerial" view of the molecule in the most stable staggered conformation.)

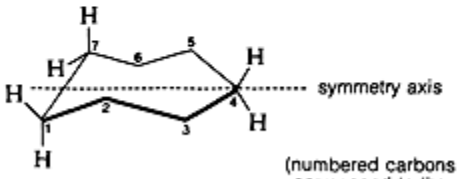
With the cycloalkanes having 7 to 10 carbons, there are problems in trying to make either trans or gauche $\mathrm{C{-}C{-}C{-}C}$ segments, because the sizes of these rings do not allow the proper bond angles or torsional angles, or else there are more or less serious nonbonded repulsions. Consequently each of these rings assumes a compromise conformation with some eclipsing, some nonbonded repulsions, and some angle distortions. Brief comments on some of these conformations follow. It will be useful to use molecular models to see the interactions involved.

Cycloheptane

Possible conformations for cycloheptane include the “comfortable” appearing chair form, 7. However, this form has eclipsed hydrogens at C_4 and C_5 as well as nonbonded interactions between the axial-like hydrogens on C_3 and C_6. The best compromise conformation is achieved by a 30°-40° rotation around the C_4—C_5 bond to relieve the eclipsing of the hydrogens. This spreads the interfering hydrogens at C_3 and C_6 and results in a somewhat less strained conformation called the *twist chair*. The twist chair, 8, is very flexible and probably only about $3\ \text{kcal mol}^{-1}$ of activation is required to interconvert the various possible monosubstituted cycloheptane conformations.



7

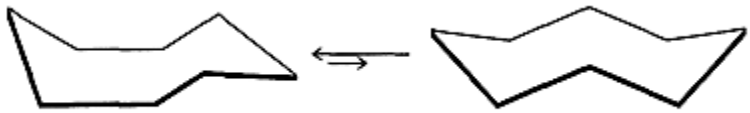


(numbered carbons correspond to the same ones in 7)

8

Cyclooctane

There are several more or less reasonable looking cyclooctane conformations. After much research it now is clear that the favored conformation is the *boat-chair*, 9, which is in equilibrium with a few tenths percent of the *crown* conformation, 10 :



9 10

The activation energy for interconversion of these two forms is about $10\ \text{kcal mol}^{-1}$. The boat-chair conformation 9 is quite flexible and movement of its CH_2 groups between the various possible positions occurs with an activation energy of only about $5\ \text{kcal mol}^{-1}$.

Cyclononane

Several more or less reasonable conformations of cyclononane also can be developed, but the most favorable one is called the *twist-boat-chair*, which has three-fold symmetry (Figure 12-17). The activation energy for inversion of the ring is about $6\ \text{kcal mol}^{-1}$.

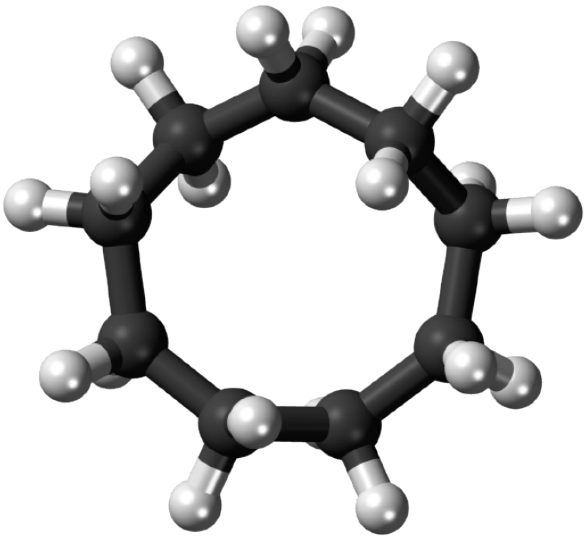
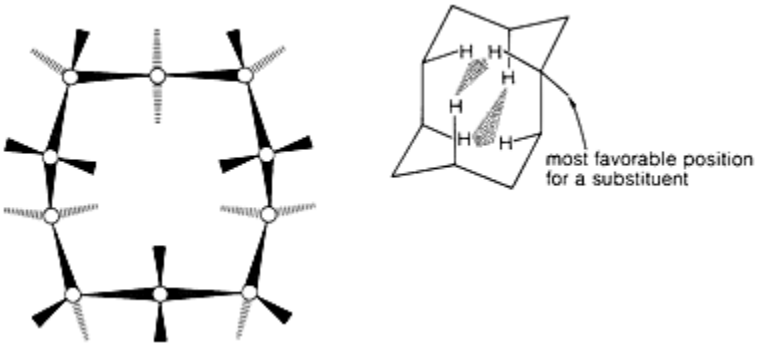


Figure 12-17: Twist boat-chair conformation of cyclononane (Public Domain; Jynto). I**Color code:** Carbon, C: black Hydrogen, H: white

Cyclodecane

The stable conformation of cyclodecane (Figure 12-18) is similar to that of cyclotetradecane (Figure 12-16). However, there are relatively short $\mathrm{H}\cdots\mathrm{H}$ distances and the $\mathrm{C}{-}\mathrm{C}{-}\mathrm{C}$ bond angles are somewhat distorted because of cross-ring hydrogen-hydrogen repulsions. The most stable position for a substituent on the cyclodecane ring is the one indicated in Figure 12-18. The least stable positions are those in which a substituent replaces any of the six hydrogens shown, because nonbonded interactions are particularly strong at these positions. The activation energy for interconversion of substituent positions is about $6\ \mathrm{kcal\ mol^{-1}}$.



Most stable conformation of cyclodecane; Dale and sawhorse representations. The shaded area in the sawhorse convention indicates substantial nonbonded $\mathrm{H}\cdots\mathrm{H}$ interactions.

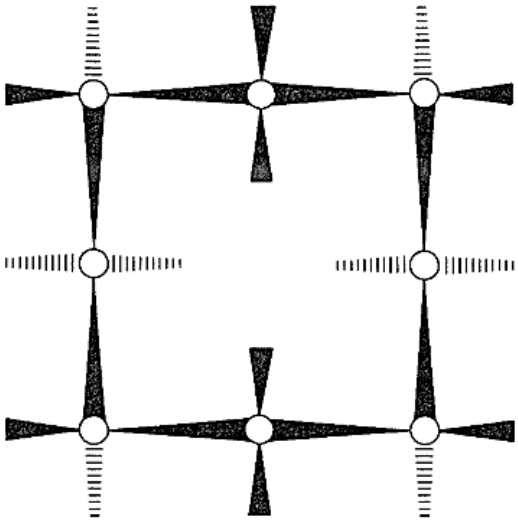


Figure 12-16).

[6]Pronounced Dalluh.

Contributors and Attributions

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4.6: Polycyclic Alkanes

Objective

After completing this section, you should be able to draw the structures and construct molecular models of simple polycyclic molecules.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- bridgehead carbon atom
- polycyclic molecule

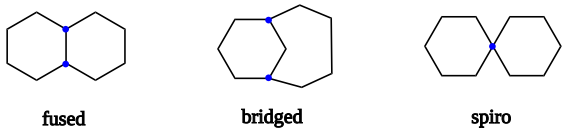
Study Notes

A *bridgehead carbon atom* is a carbon atom which is shared by at least two rings. The hydrogen atom which is attached to a bridgehead carbon may be referred to as a bridgehead hydrogen.

Note that bicyclo[2.2.1]heptane is the systematic name of norborane. You need not be concerned over the IUPAC name of norbornane. The nomenclature of compounds of this type is beyond the scope of this course.

Nomenclature of Bicyclic Ring Systems

There are many hydrocarbons and hydrocarbon derivatives with two rings having common carbon atoms. There are three main ways that the two rings can be connected. The first is called a **fused bicyclic** ring structure where the two rings share a covalent bond and a have two **bridgehead** carbons (marked in red on the structures below). A bridgehead is defined as a carbon that is part of two or more rings. Hydrogens attached to bridge head carbons are often referred to as bridge head hydrogens. The two rings can also be connected by a bridge containing one or more carbons to form a **bridged bicyclic** molecule. Lastly, the two rings can be joined with a singe bridge head carbon to form **spiro bicyclic** molecules.



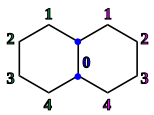
• = bridgehead carbons

Bicyclic Isomers of $C_{10}H_{18}$

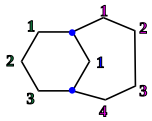
Naming Fused and Bridged Compounds

Fused and bridged bicyclic compounds are follow similar naming conventions:

1. Count the total number of carbons in both rings. This is the parent name. (eg. ten carbons in the system would be decane)
2. Count the number of carbons between the bridgeheads, then place the numbers in square brackets in descending order separated by periods. Fused and bridged bycyclic compounds should have three numbers such as [2.2.0]. For fused compounds one of the numbers should be zero.
3. Place the word **bicyclo** at the beginning of the name.

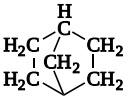


bicyclo[4.4.0]decane

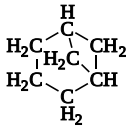


bicyclo[4.3.1]decane

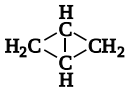
Examples with carbons and hydrogens explicitly shown:



bicyclo[2.2.1]heptane



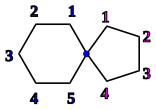
bicyclo[3.1.1]heptane



bicyclo[1.1.0]butane

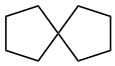
Naming Spiro Compounds

Spiro bicyclics are named using the same basic rules. Because there is only one bridgehead carbon only two numbers will be required in the brackets. Also, the word **spiro** is placed at the beginning.



spiro[5.4]decane

Examples



spiro[4.4]nonane

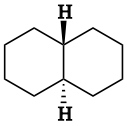


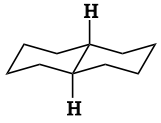
spiro[3.2]hexane

Conformations in Bicyclic Ring Systems

As expected, the connection of two rings has defined effects on the possible conformations. However, the ideas previously discussed in this chapter can be used for conformational analysis. Fused rings have the possibility of two isomers where the bridgehead hydrogens are either *cis* or *trans* along the shared bond. These two isomers have significant differences in flexibility and stability as seen in bicyclo[4,4,0]decane more commonly known as decalin. If the positioning of the bridgehead hydrogens are shown in a fused ring the prefix cis or trans should be included in the name.

The trans-isomer is the easiest to describe because the fusion of the two rings creates a rigid, roughly planar, structure made up of two chair conformations. Unlike cyclohexane, the two rings cannot flip from one chair form to another. Accordingly, the orientation of the any substituents is fixed in either an axial or equatorial position in *trans*-decalin. This means that the C-C bonds coming away from the fused edge are held in equatorial positions relative to each ring thus preventing the possibility of any 1,3-diaxial interactions occurring between ring atoms.





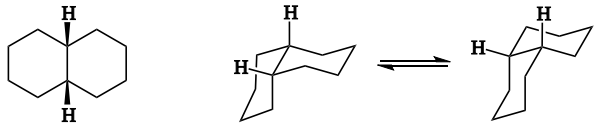
***trans* -decalin**
(rigid)

Interactive Element

The 3D Structure of *Trans*-Decalin

2kcal mol–1" id="MathJax-Element-1-Frame" role="presentation" style="position:relative;" tabindex="0">

The two rings in *cis*-decalin are also both held in a chair conformations. In comparison, the chair-chair forms of *cis*-decalin are relatively flexible, and inversion of both rings at once occurs fairly easily.

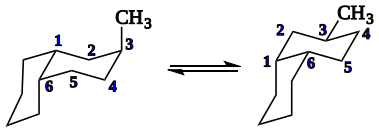


***cis* -decalin**
(more flexible)

Interactive Element

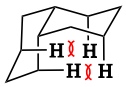
The 3D Structure of *Cis*-Decalin

The flexibility of *cis*-decalin allows for a substituent to interconvert between axial and equatorial conformations. In much the same fashion as cyclohexane, equatorial substituents tend to create less steric strain and create a more stable conformer.



(Note: atoms are mapped in blue for clarity.)

A major difference in *cis*-decalin is the fact that one of C-C bonds coming away from the fused edge is held an an axial position. This is true in both ring-flip conformations. This axial C-C bond causes 1,3-diaxial interactions to occur in *cis*-decalin making it roughly 8.4 kJ/mol less stable than *trans*-decalin. This amount of 1,3-diaxial steric strain is roughly equivalent to that of an ethyl substituent attached to a cyclohexane ring (8.0 kJ/mol)



= steric strain

Bicyclic compounds with a bridge typically have very little flexibility and are often held in a ridged conformation. The molecule norbornane represent a cyclohexane ring connected by a single carbon bridge.

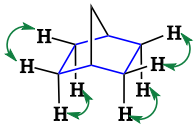


norbornane, or
bicyclo[2.2.1]heptane

Interactive Element

The 3D Structure of Norbornane

Norbornane is estimated to have 72 kJ/mol of ring strain which can be understood when viewing the contained rings. The carbon bridge in norbornane holds the cyclohexane ring at the bottom in a boat conformation creating torsional strain from eclipsing bonds along the edge.



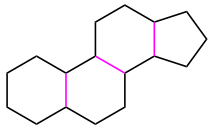
(green arrows used to illustrate eclipsing hydrogens)

Also, the carbon bridge forms a cyclopentane ring (shown in red below making up the right side of the structure) with increased angle strain throughout the whole molecule.

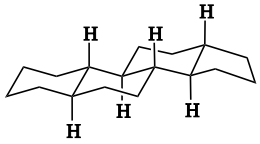


Polycyclic Systems in Nature

Fused ring systems like decalin are very common in natural products. In fact, similar ring systems are found in steroids, which are an important class of lipids. Steroids generally have structures that include three six-membered rings and a five-membered ring connected by three fused bonds. Most natural steroids have a *trans* configuration at all three fusion points. This tends to give steroids a rigid and semi-flat structure.

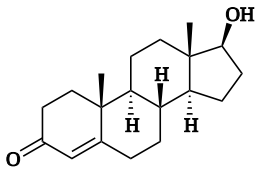


basic steroid ring confguration (fused bonds highlighted in purple)

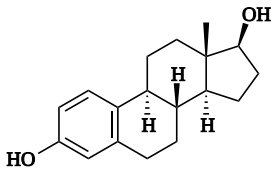


trans-trans-trans

Sex hormones are an example of steroids. The primary male hormone, testosterone, is responsible for the development of secondary sex characteristics. Two female sex hormones, progesterone and estrogen (or estradiol) control the ovulation cycle. Notice that the male and female hormones have only slight differences in structures, but yet have very different physiological effects. Testosterone promotes the normal development of male genital organs and is synthesized from cholesterol in the testes. It also promotes secondary male sexual characteristics such as deep voice, facial and body hair.



testosterone

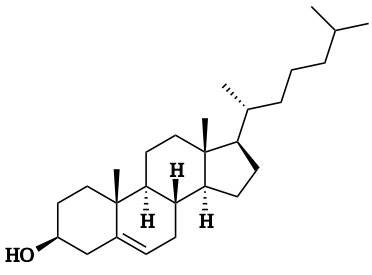


estradiol

Interactive Element

The 3D Structure of Estradiol

The best known and most abundant steroid in the body is cholesterol. Cholesterol is formed in brain tissue, nerve tissue, and the blood stream. It is the major compound found in gallstones and bile salts. Cholesterol also contributes to the formation of deposits on the inner walls of blood vessels. These deposits harden and obstruct the flow of blood. This condition, known as atherosclerosis, results in various heart diseases, strokes, and high blood pressure.



cholesterol

Exercises

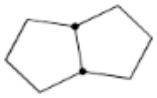
1)

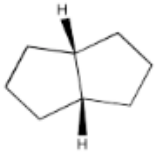
a) 

b) 

c) 

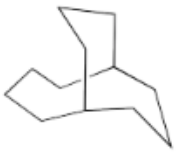
d) 

e) 

= 

f) 

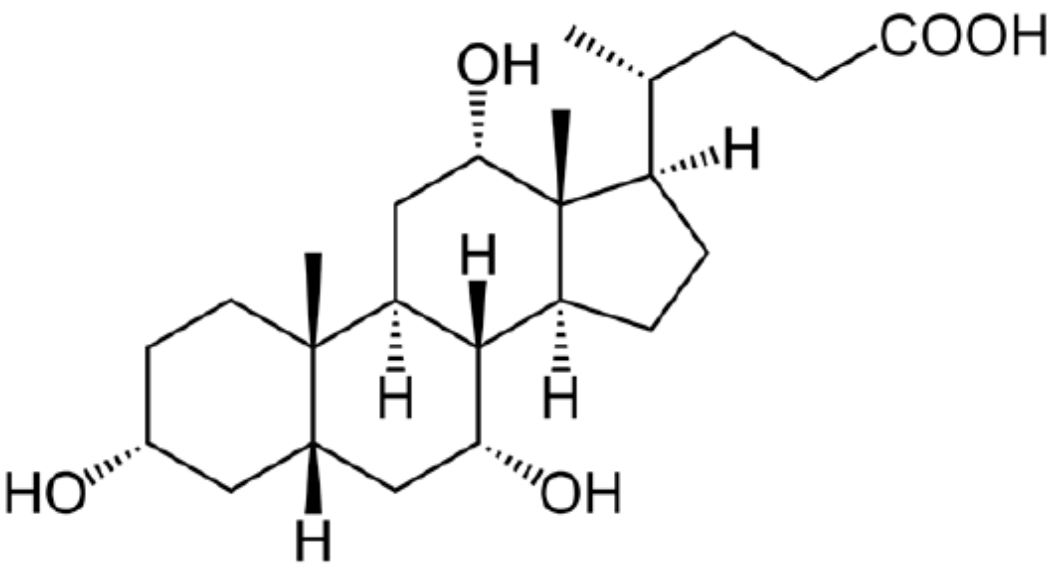
g) 

h) 

i) 

j) 

3) The following molecule is cholic acid. Determine if the three fused bonds have a *cis* or *trans* configuration.



Solutions

1)

a) Bicyclo[2.1.1]hexane

b) Bicyclo[3.2.1]octane

c) Bicyclo[2.1.0]pentane (more commonly called "housane")

d) Bicyclo[2.2.2]octane

e) cis-Bicyclo[3.3.0]octane

f) cis-Bicyclo[1.1.0]butane

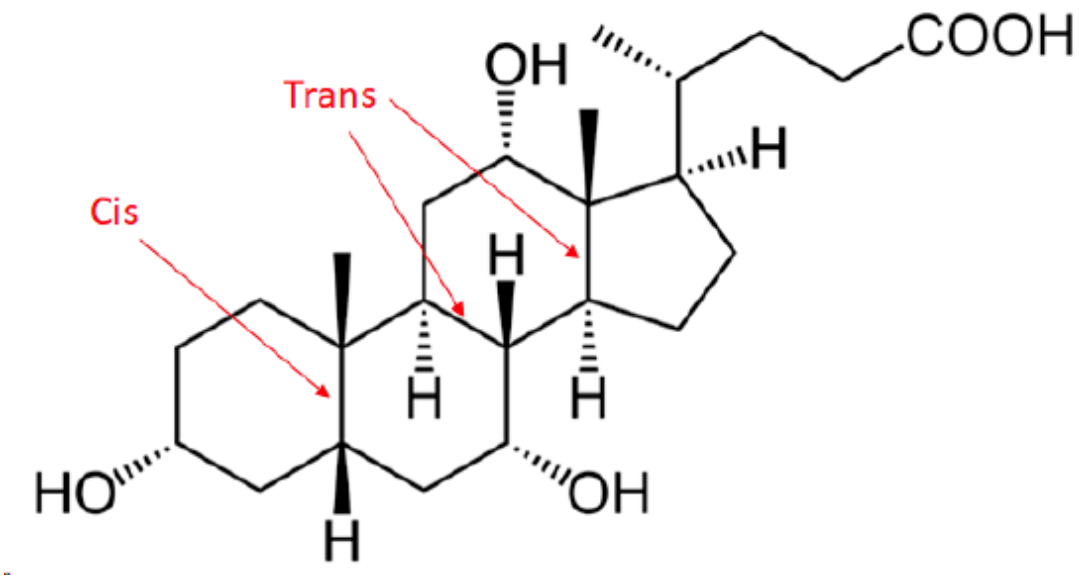
g) Bicyclo[1.1.1]pentane

h) Bicyclo[4.3.3]dodecane

i) Spiro[5.2]octane

j) Spiro[3.3]heptane

2)



Questions

Q4.9.1

Someone stated that *trans*-decalin is more stable than *cis*-decalin. Explain why this is incorrect.

Solutions

S4.9.1

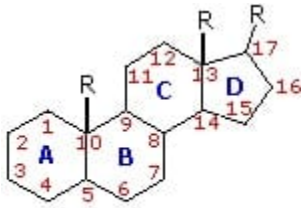
Cis-decalin has fewer steric interactions than *trans*-decalin.

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- 4.9: Conformations of Polycyclic Molecules by Chris Schaller, Dietmar Kennepohl, Gamini Gunawardena, Krista Cunningham, Layne Morsch, Marjorie C. Caserio, Steven Farmer is licensed CC BY-SA 4.0.

4.7: Carbocyclic Products in Nature

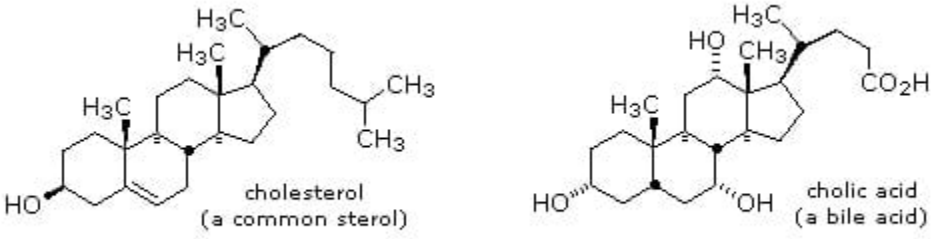
The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl if it is not a functional group. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.



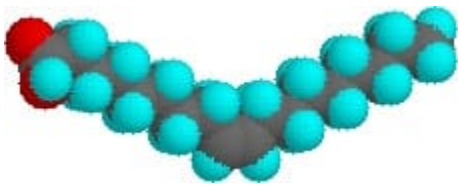
The Steroid
Carbon Skeleton

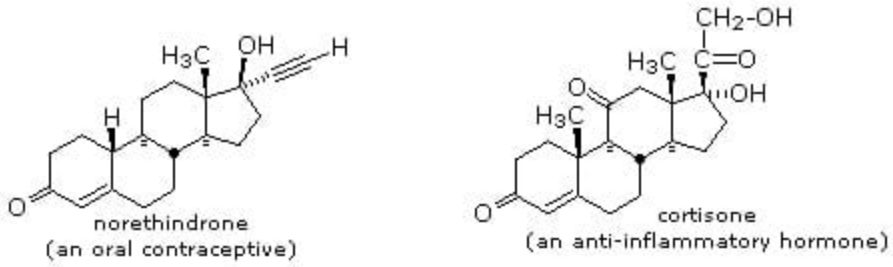
Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.

The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration. This is shown in the last of the toggled displays, along with the preferred conformations of the rings.

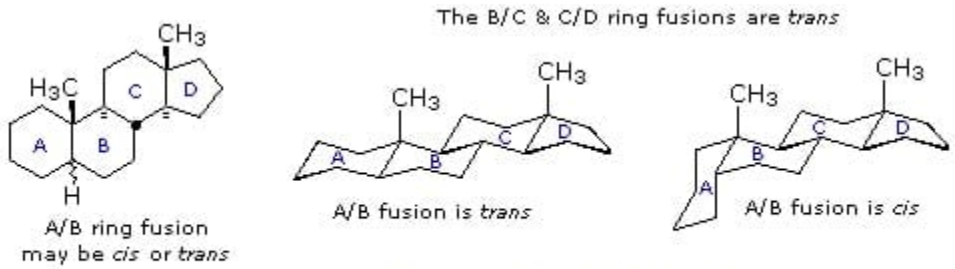


Typical Animal Steroids





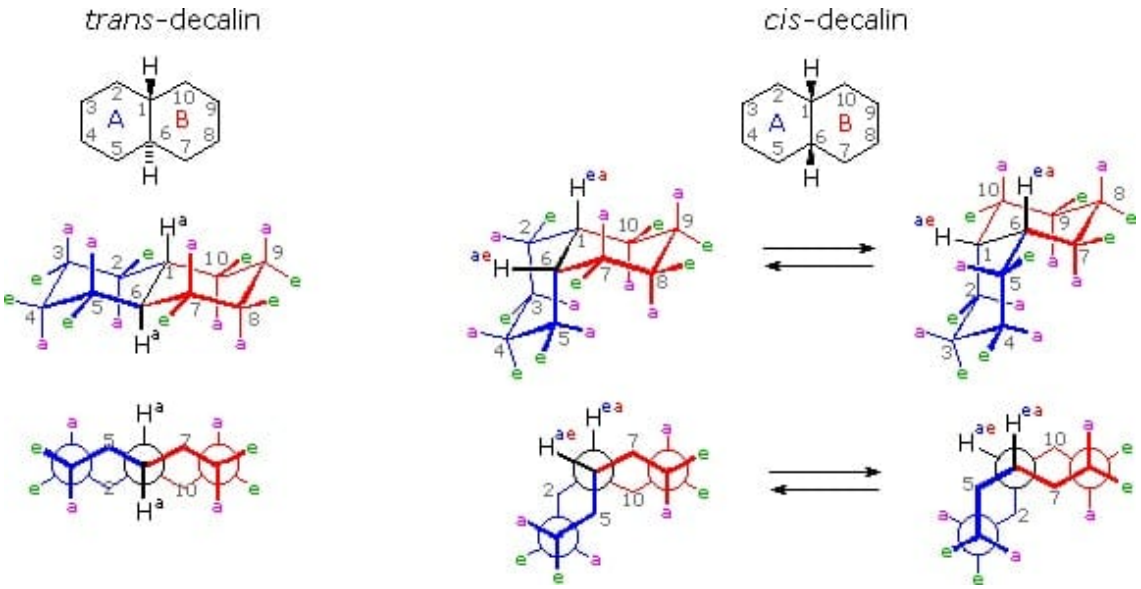
Medicinally Useful Steroids

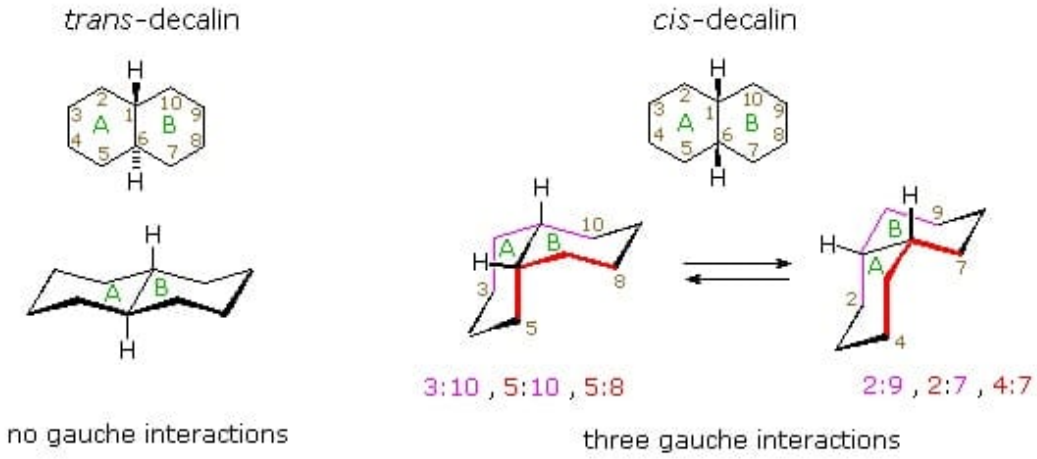


Common Steroid Conformations

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black.



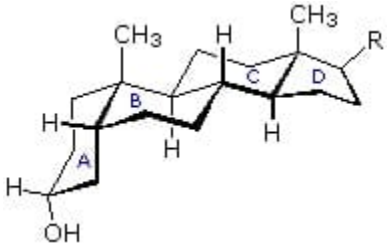


The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (H^a) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the sameconformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed 180° apart. This is too great a distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation. However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



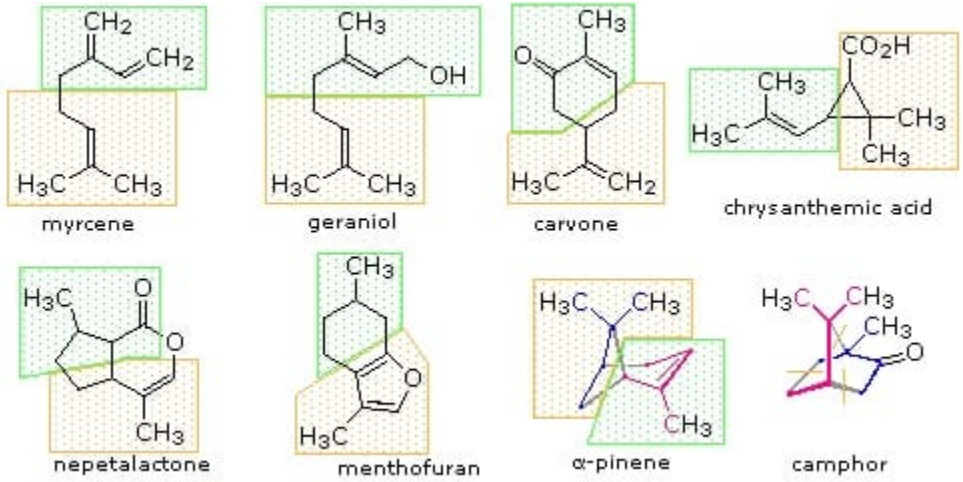
Contributors

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the **isoprene rule**. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes, representing the four most common classes are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.



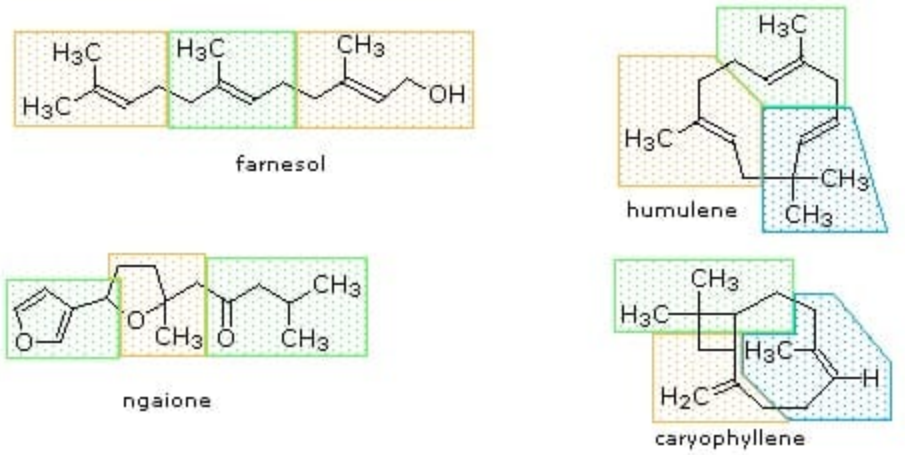


Figure: Monoterpenes and diterpenes

The isopentane units in most of these terpenes are easy to discern, and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in center of the molecule cannot be dissected in this manner. Evidence exists that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

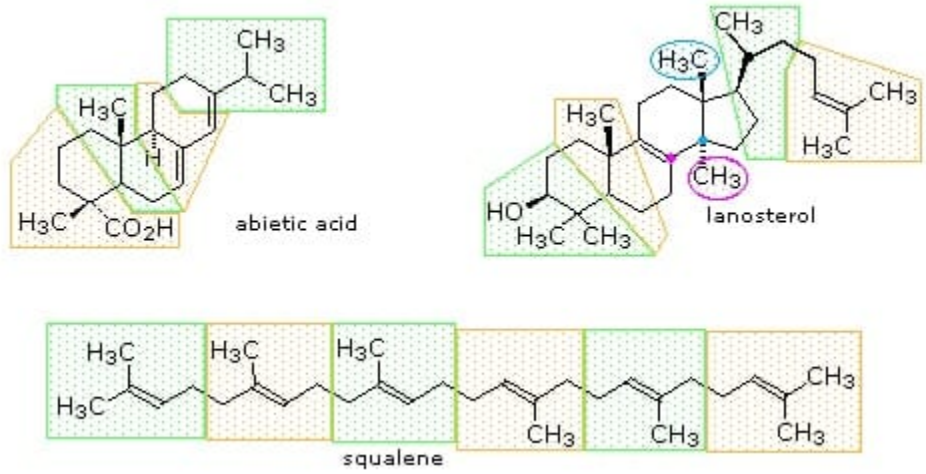
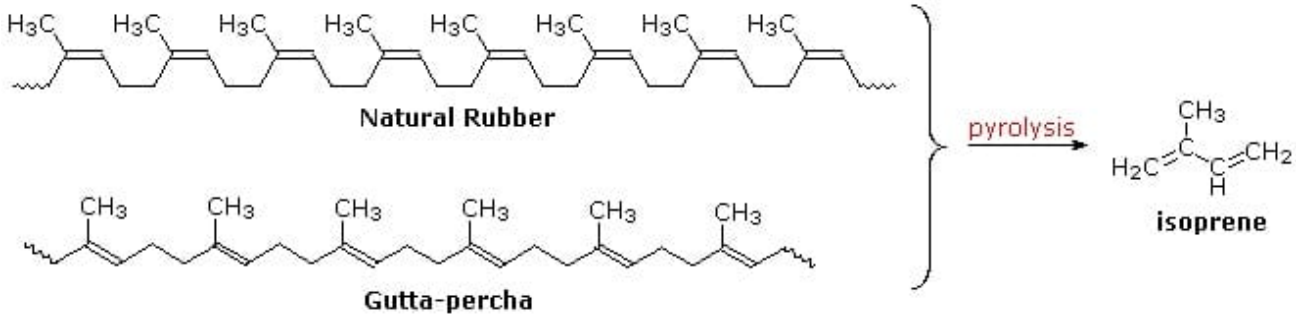


Figure: Triterpenes

Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.



The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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4.E: Cycloalkanes (Exercises)

These are homework exercises to accompany Chapter 4 of Vollhardt and Schore's "Organic Chemistry" Textmap.

4.1: Names and Physical Properties of Cycloalkanes

4.2: Ring Strain and the Structure of Cycloalkanes

4.3: Cyclohexane: A Strain-Free Cycloalkane

4.4: Substituted Cyclohexanes

4.5: Larger Cycloalkanes

4.6: Polycyclic Alkanes

4.7: Carbocyclic Products in Nature

Practice Problems

Q21

Draw all of the different structures with the formula C_6H_{12} with only one ring and name them.

Q22

Draw all of the different structures with the formula C_7H_{14} with only one ring and name them.

Q23

Name each of the following structures.

4.23q.png

Q24

Draw the following structures, and if the name is not in accordance with IUPAC naming, give the proper name.

(a) isopropylcyclohexane (b) 1,1-dimethylcyclobutane (c) cyclobutylcyclopentane (d) cyclopropylpropane (e) 1-iodo-4-chlorocyclohexane (f) 1-ethyl-2-cyclobutane

Q25

Draw the following structures, no indication of the ring conformation is necessary.

a. *trans*-1-bromo-2-methylcyclohexane

b. *cis*-1-bromo-2-methylcyclohexane
c. *trans*-1-bromo-2-iodocyclopropane
d. 1-bromo-2-iodocyclopropane
e. 1-fluoro-4-methylcycloheptane

Q26

Given that the ideal bond angle for an sp^3 hybrdized carbon is 109.5^o and that the ideal angle for an sp^2 hybridized carbon is 120^o, what radical is the most stable based on the angle strain? Is the radical more stable than the previous cycloalkane, again based on angle strain alone? (Hint, a transition from an sp^3 hybridized to an sp^2 hybridized carbon occurs).

(a) cyclobutane (angle=88^o) (b) cyclopropane (angle=60^o) (c) cyclohexane (angle ~ 109.5^o)

Solutions

S21

4.21a.png4.21b.png

S22

Notice how many more different structures that can be drawn for C_7H_{14} than C_6H_{12}. If more than one ring were an option, even more structures could be drawn.

4.22a..png

S23

4.23a.png

S24

4.24a.png

S25

4.25a.png

S26

Given that the ideal bond angle for an sp^3 hybrdized carbon is 109.5^o and that the ideal angle for an sp^2 hybridized carbon is 120^o, what radical is the most stable based on the angle strain? Is the radical more stable than the previous cycloalkane, again based on angle strain alone? (Hint, a transition from an sp^3 hybridized to an sp^2 hybridized carbon occurs).

(a) cyclobutane (angle=88^o)

- Before the radical forms: 109.5-88= 21.5^o
- After the radical forms: 120-88= 32^o

The radical creates more ring strain

(b) cyclopropane (angle=60^{o})

- Before the radical forms: 109.5-60=49.5^{o}
- After the radical forms: 120-60=60^{o}

The radical creates more ring strain

(c) cyclohexane (angle ~ 109.5^{o})

- Before the radical forms: 109.5-109.5=0
- After the radical forms: 120-109.5=10.5^{o} The radical creates more ring strain

The cyclohexane radical is the most stable based on angle strain alone

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5: STEREOISOMERS

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of their most interesting type of isomer is the mirror-image stereoisomers, a non-superimposable set of two molecules that are mirror image of one another. The existence of these molecules are determined by concept known as chirality.



- Topic hierarchy

5.1: Chiral Molecules
5.2: Optical Activity
5.3: Absolute Configuration: R-S Sequence Rules
5.4: Fischer Projections
5.5: Molecules Incorporating Several Stereocenters: Diastereomers
5.6: Meso Compounds
5.7: Stereochemistry in Chemical Reactions
5.8: Resolution: Separation of Enantiomers
5.E: Stereoisomers (Exercises)

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5.1: Chiral Molecules

Objectives

After completing this section, you should be able to

1. use molecular models to show that only a tetrahedral carbon atom satisfactorily accounts for the lack of isomerism in molecules of the type CH_2XY, and for the existence of optical isomerism in molecules of the type CHXYZ.
2. determine whether two differently oriented wedge-and-broken-line structures are identical or represent a pair of enantiomers.

Key Terms

Make certain that you can define, and use in context, the key term below.

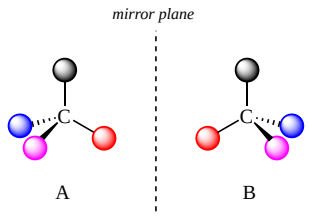
- enantiomer

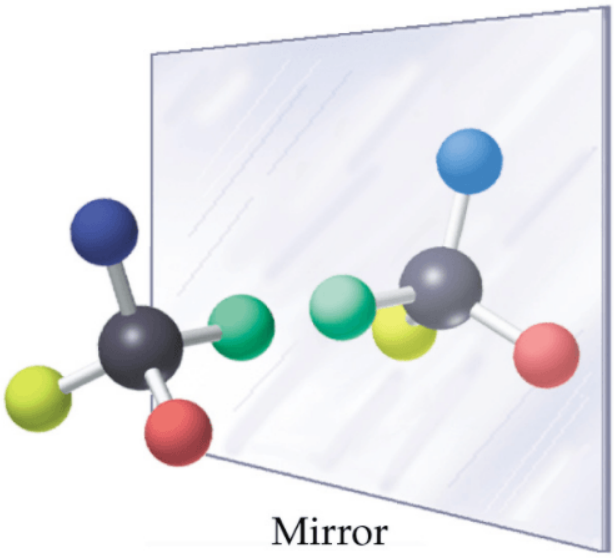
Study Notes

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of the most interesting types of isomer is the mirror-image stereoisomer, a non-superimposable set of two molecules that are mirror images of one another. The existence of these molecules are determined by a a concept known as **chirality**. The word “chiral” was derived from the Greek word for hand, because our hands are a good example of chirality since they are non-superimposable mirror images of each other.

Chiral Molecules

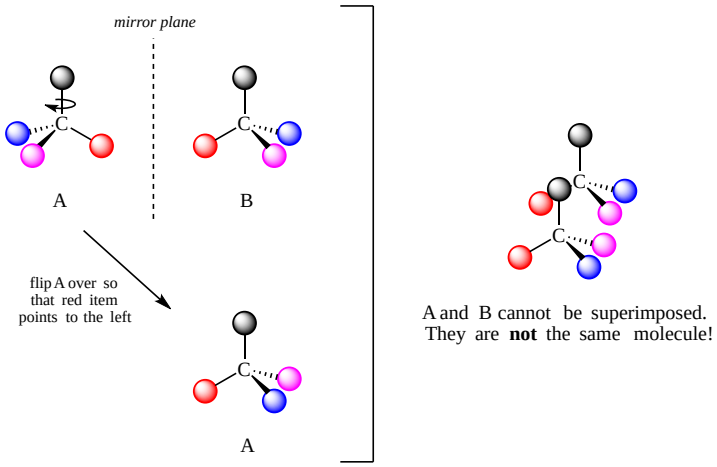
The term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Certain organic molecules are chiral meaning that they are not superimposable on their mirror image. Chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral (sp^3-hybridized) carbons with four different substituents. Consider the molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors.





The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.



A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule.

A and B are called **stereoisomers or optical isomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

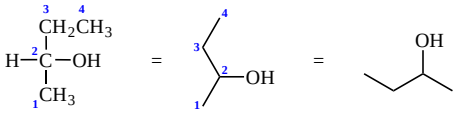
The Many Synonyms of the Chiral Carbon

Be aware - all of the following terms can be used to describe a chiral carbon.

> chiral carbon = asymmetric carbon = optically active carbon = stereo carbon = stereo center = chiral center

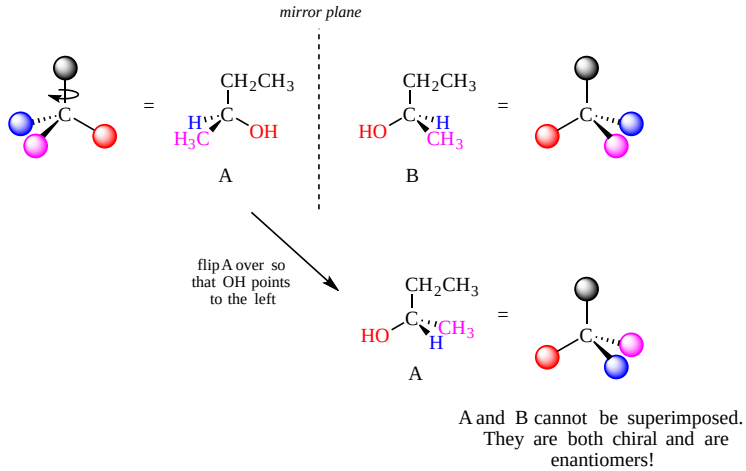
Let's apply our chirality discussion to real molecules.

Consider 2-butanol, drawn in two dimensions below.



2-butanol
(drawn in 2D)

Carbon #2 is a chiral center: it is sp^3-hybridized and tetrahedral (even though it is not drawn that way above), and the four substituents attached to is are different: a hydrogen (H) , a methyl (-CH_3) group, an ethyl (-CH_2CH_3) group, and a hydroxyl (OH) group. If the bonding at C_2 of 2-butanol is drawn in three dimensions and this structure called A. Then the mirror image of A can be drawn to form structure B.



A and B cannot be superimposed.
They are both chiral and are
enantiomers!

When we try to superimpose A onto B, we find that we cannot do it. Because structure A and B are not superimposable on their mirror image they are both chiral molecules. Because A and B are different due only to the arrangement of atoms in space they are stereoisomers. Because A and B are mirror images of each other they are also enantiomers. When looking at simplified line structures is clear that there are two distinct ways of drawing 2-butanol which only differ in their spatial arrangement around a chiral carbon.

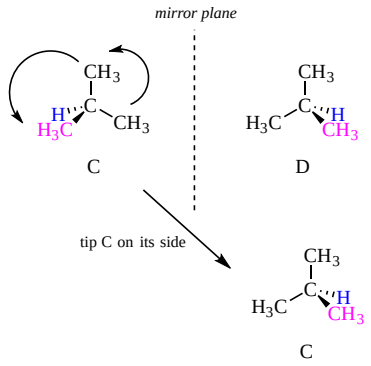


two enantiomers of 2-butanol

The 3D Structures of the Two Enantiomers of 2-Butanol

For comparison, 2-propanol, is an achiral molecule because is lacks a chiral carbon. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral carbon. Being achiral means that 2-propanol should be superimposable on its mirror image which is shown in the figure below. A more detailed explaination on why 2-propanol is achiral will be given in the next section.

2-propanol is achiral:



C and D can be superimposed.
They are the same molecule!

Stereoisomers

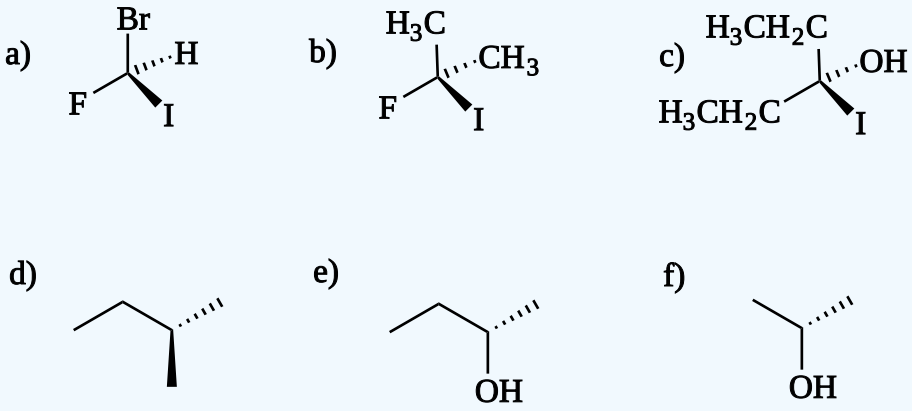
Stereoisomers have been defined as molecules with the same connectivity but different arrangements of the atoms in space. It is important to note that there are two types of stereoisomers: geometric and optical.

Optical isomers are molecules whose structures are mirror images but cannot be superimposed on one another in any orientation. Optical isomers have identical physical properties, although their chemical properties may differ in asymmetric environments. Molecules that are nonsuperimposable mirror images of each other are said to be chiral.

Geometric isomers differ in the relative position(s) of substituents in a rigid molecule. Simple rotation about a C–C σ bond in an alkene, for example, cannot occur because of the presence of the π bond. The substituents are therefore rigidly locked into a particular spatial arrangement. Thus a carbon–carbon multiple bond, or in some cases a ring, prevents one geometric isomer from being readily converted to the other. The members of an isomeric pair are identified as either cis or trans, and interconversion between the two forms requires breaking and reforming one or more bonds. Because their structural difference causes them to have different physical and chemical properties, cis and trans isomers are actually two distinct chemical compounds.mers have the same connectivity, but different arrangements of atoms in space. Geometric isomers will be discussed in more detain in **Sections 7.4 and 7.5**.

Exercise 5.1.1

Identify the following molecules as chiral or achiral.



Answer available at the end of this section.

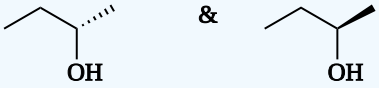
Exercise 5.1.2

Determine if the following sets of compounds in each group are enantiomers or the same compound.

a) 

b) 

c) 

d) 

Answer available at the end of this section.

Objectives

After completing this section, you should be able to

1. determine whether or not a compound is chiral, given its Kelulé, condensed or shorthand structure, with or without the aid of molecular models.
2. label the chiral centres (carbon atoms) in a given Kelulé, condensed or shorthand structure.

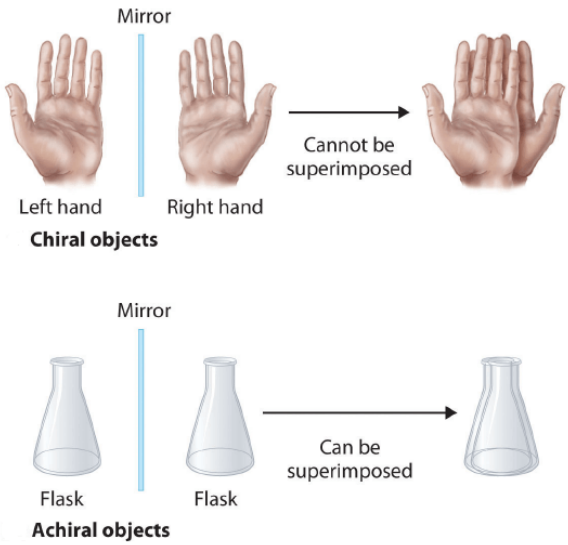
Key Terms

Make certain that you can define, and use in context, the key terms below.

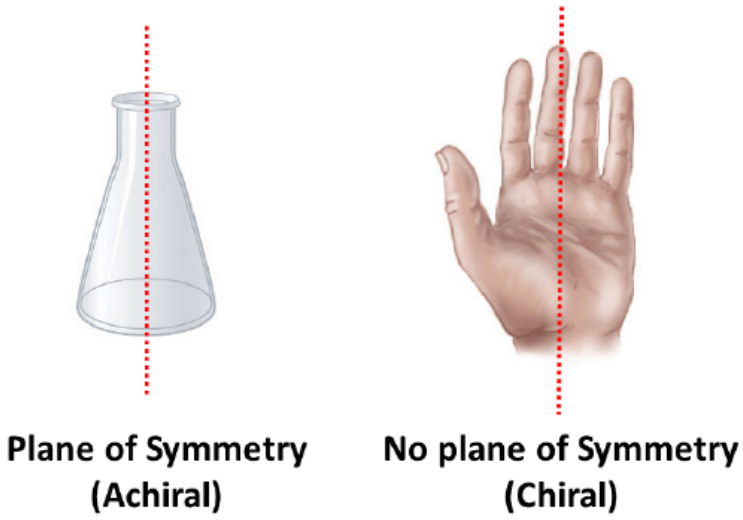
- achiral
- chiral
- chiral (stereogenic) centre
- plane of symmetry

Symmetry and Chirality

Molecules that are nonsuperimposable mirror images of each other are said to be chiral (pronounced “ky-ral,” from the Greek cheir, meaning “hand”). Examples of some familiar chiral objects are your hands. Your left and right hands are nonsuperimposable mirror images. (Try putting your right shoe on your left foot—it just doesn’t work.) An achiral object is one that can be superimposed on its mirror image, as shown by the superimposed flasks 25.7.1b in the figure below. .

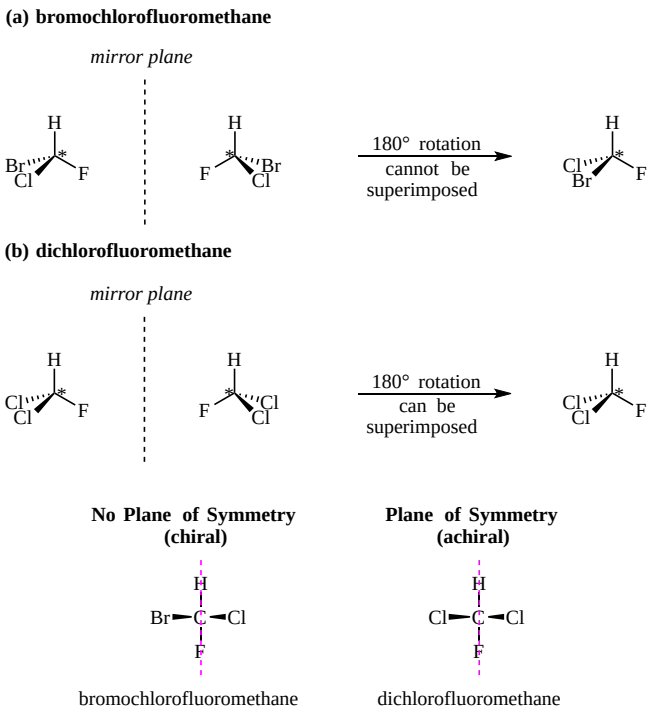


An an important questions is why is one chiral and the other not? The answer is that the flask has a plane of symmetry and your hand does not. A plane of symmetry is a plane or a line through an object which divides the object into two halves that are mirror images of each other. When looking at the flask, a line can be drawn down the middle which separates it into two mirror image halves. However, a similar line down the middle of a hand separates it into two non-mirror image halves. This idea can be used to predict chirality. If an object or molecule has a plane of symmetry it is achiral. If if lacks a plane of symmetry it is chiral.



Symmetry can be used to explain why a carbon bonded to four different substituents is chiral. When a carbon is bonded to fewer than four different substituents it will have a plane of symmetry making it achiral. A carbon atom that is bonded to four different substituents loses all symmetry, and is often referred to as an asymmetric carbon. The lack of a plane of symmetry makes the carbon chiral. The presence of a single chiral carbon atom sufficient to render the molecule chiral, and modern terminology refers to such groupings as chiral centers or stereo centers.

An example is shown in the bromochlorofluoromethane molecule shown in part (a) of the figure below. This carbon, is attached to four different substituents making it chiral. which is often designated by an asterisk in structural drawings. If the bromine atom is replaced by another chlorine to make dichlorofluoromethane, as shown in part (b) below, the molecule and its mirror image can now be superimposed by simple rotation. Thus the carbon is no longer a chiral center. Upon comparison, bromochlorofluoromethane lacks a plane of symmetry while dichlorofluoromethane has a plane of symmetry.

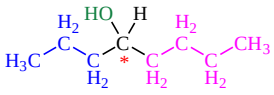


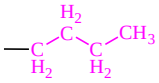
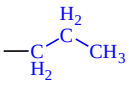
Identifying Chiral carbons

Identifying chiral carbons in a molecule is an important skill for organic chemists. The presence of a chiral carbon presents the possibility of a molecule having multiple stereoisomers. Most of the chiral centers we shall discuss in this chapter are asymmetric carbon atoms, but it should be recognized that other tetrahedral or pyramidal atoms may become chiral centers if appropriately substituted. Also, when more than one chiral center is present in a molecular structure, care must be taken to analyze their relationship before concluding that a specific molecular configuration is chiral or achiral. This aspect of stereoisomerism will be treated later. Because an carbon requires four different substituents to become asymmertric, it can be said, with few exceptions, that sp^2 and sp hybridized carbons involved in multiple bonds are achiral. Also, any carbon with more than one hydrogen, such as a $-CH_3$ or $-CH_2-$ group, are also achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions, the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral.

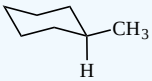
Determining if a carbon is bonded to four distinctly different substituents can often be difficult to ascertain. Remember even the slightest difference makes a substituent unique. Often these difference can be distant from the chiral carbon itself. Careful consideration and often the building of molecular models may be required. A good example is shown below. It may appear that the molecule is achiral, however, when looking at the groups directly attached to the possible chiral carbon, it is clear that they all different. The two alkyl groups are differ by a single $-CH_2-$ group which is enough to consider them different.



Substituent	
	butyl
	propyl
—OH	hydroxyl
—H	hydrogen

Example 5.1.1

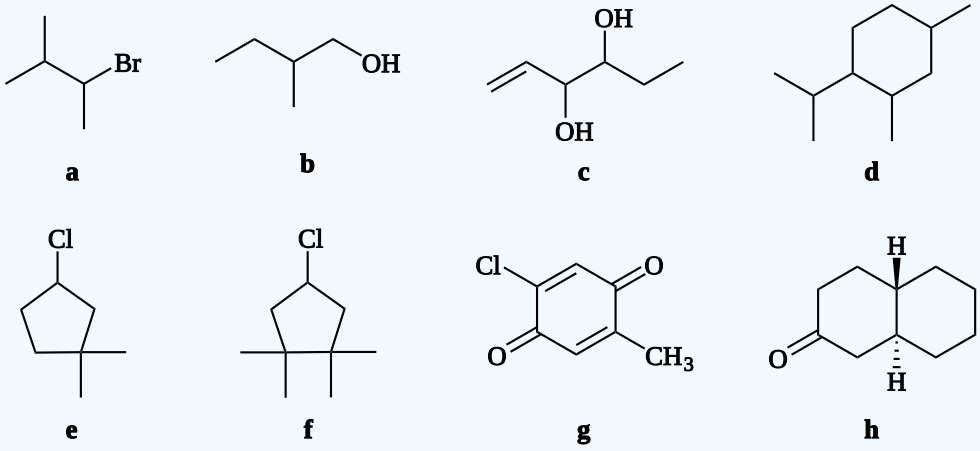
Predict if the following molecule would be chiral or achiral:



Answer available at the end of this section.

Exercise 5.2.1

Determine if each of the following molecules are chiral or achiral. For chiral molecules indicate any chiral carbons.



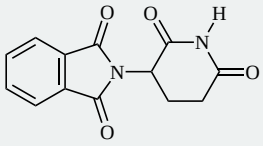
a **b** **c** **d**

e **f** **g** **h**

Answer available at the end of this section.

Note

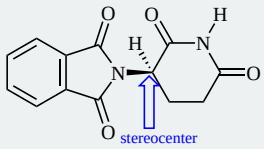
In the 1960's, a drug called thalidomide was widely prescribed in the Western Europe to alleviate morning sickness in pregnant women.



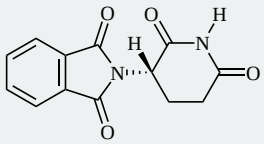
thalidomide

Thalidomide had previously been used in other countries as an antidepressant, and was believed to be safe and effective for both purposes. The drug was not approved for use in the U.S.A. It was not long, however, before doctors realized that something had gone horribly wrong: many babies born to women who had taken thalidomide during pregnancy suffered from severe birth defects.

Researchers later realized the problem lay in the fact that thalidomide was being provided as a mixture of two different isomeric forms.

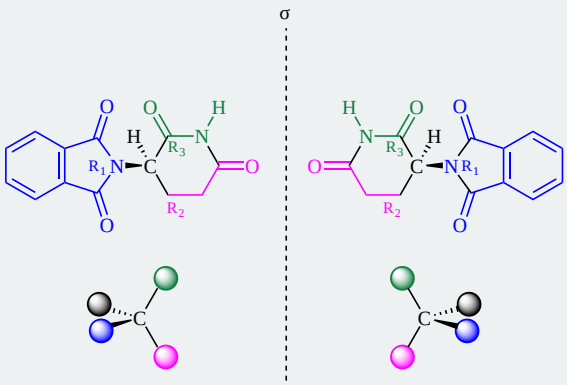


effective isomer



mutagenic isomer

One of the isomers is an effective medication, the other caused the side effects. Both isomeric forms have the same molecular formula and the same atom-to-atom connectivity, so they are not constitutional isomers. Where they differ is in the arrangement in three-dimensional space about one tetrahedral, sp^3-hybridized carbon. These two forms of thalidomide are **stereoisomers**. If you make models of the two stereoisomers of thalidomide, you will see that they too are mirror images, and cannot be superimposed.



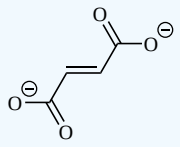
As a historical note, thalidomide was never approved for use in the United States. This was thanks in large part to the efforts of Dr. Frances Kelsey, a Food and Drug officer who, at peril to her career, blocked its approval due to her concerns about the lack of adequate safety studies, particularly with regard to the drug's ability to enter the bloodstream of a developing fetus. Unfortunately, though, at that time clinical trials for new drugs involved widespread and unregulated distribution to doctors and their patients across the country, so families in the U.S. were not spared from the damage caused.

Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

Example 5.2.2

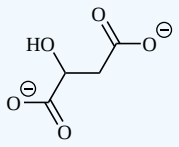
Label the molecules below as chiral or achiral, and locate all stereocenters.

a)



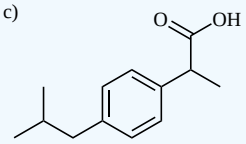
fumarate
(a citric acid cycle intermediate)

b)



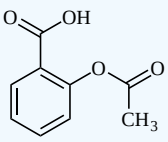
malate
(a citric acid cycle intermediate)

c)



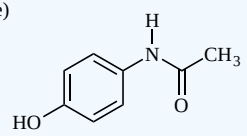
ibuprofen

d)



acetylsalicylic acid
(aspirin)

e)



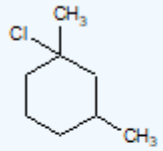
acetaminophen
(active ingredient in Tylenol)

Answer available at the end of this section.

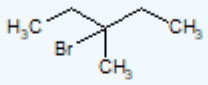
Exercise 5.2.2

1) For the following compounds, star (*) each chiral center, if any.

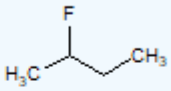
(a)



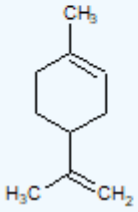
(b)



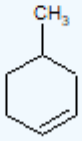
(c)



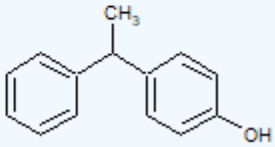
(d)



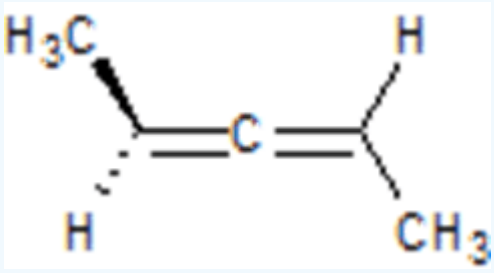
(e)



(f)



2) Explain why the following compound is chiral.



3) Determine which of the following objects is chiral.

a) A Glove.

b) A nail.

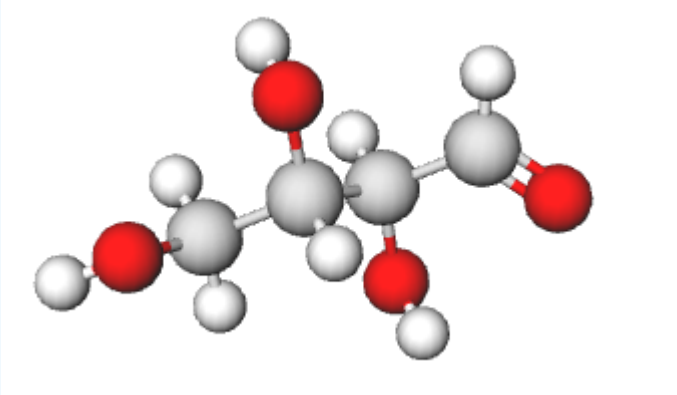
c) A pair of sunglasses.

d) The written word "Chiral".

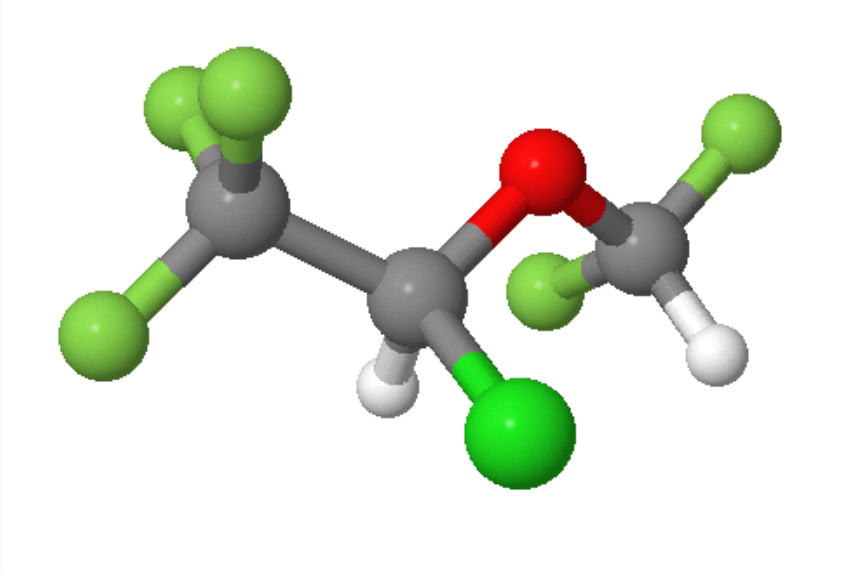
4) Place an "*" by all of the chrial carbons in the following molecules.

a)

Erythrose, a four carbon sugar.



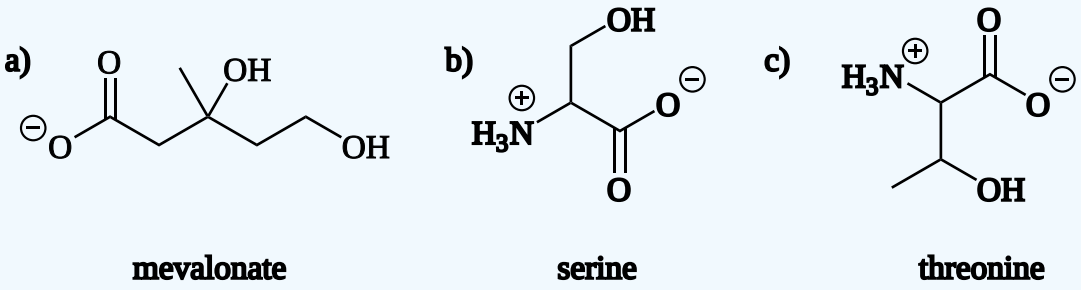
b) Isoflurane, an anestetic. Bright green = Chlorine, Pale green = Fluorine.



Answer available at the end of this section.

Exercise 5.2.3

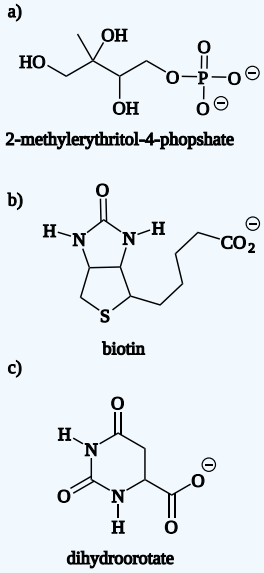
Circle all of the carbon stereocenters in the molecules below.



Answer available at the end of this section.

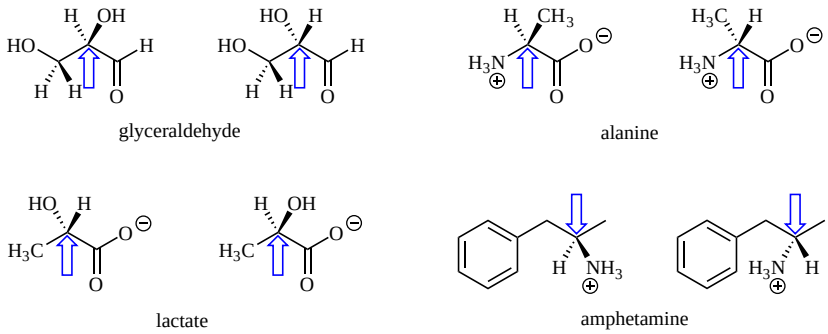
Exercise 5.2.4

Circle all of the carbon stereocenters in the molecules below.

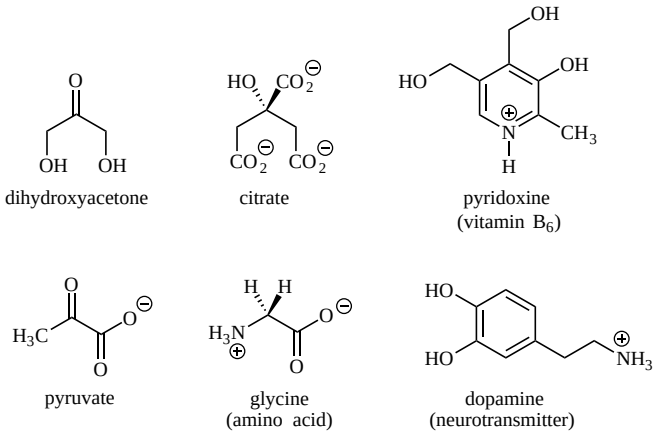


Answer available at the end of this section.

Here are some more examples of chiral molecules that exist as pairs of enantiomers. In each of these examples, there is a single stereocenter, indicated with an arrow. (Many molecules have more than one stereocenter, but we will get to that that a little later!)



Here are some examples of molecules that are **achiral** (*not* chiral). Notice that none of these molecules has a stereocenter.

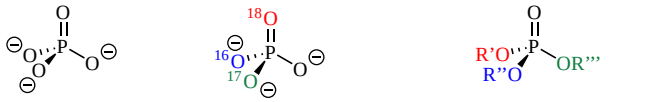


It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. Chirality is tied conceptually to the idea of asymmetry, and *any molecule that has a plane of symmetry cannot be chiral*. When looking for a plane of symmetry, however, we must consider all possible conformations that a molecule could adopt. Even a very simple molecule like ethane, for example, is asymmetric in many of its countless potential conformations – but it has obvious symmetry in both the eclipsed and staggered conformations, and for this reason it is achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions (see section 3.7B), the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral. Carbon stereocenters are also referred to quite frequently as **chiral carbons**.

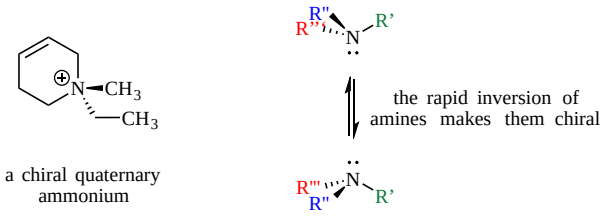
When evaluating a molecule for chirality, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are not stereocenters – look, for example, at the drawings of glycine and citrate in the figure above. Just because you see dashed and solid wedges in a structure, do not automatically assume that you are looking at a stereocenter.

Other elements in addition to carbon can be stereocenters. The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter.



We will see in chapter 10 how researchers, in order to investigate the stereochemistry of reactions at the phosphate center, incorporated sulfur and/or ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

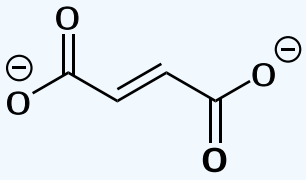
Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



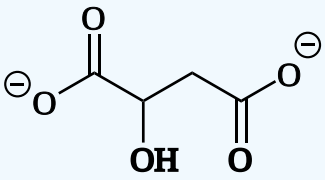
Exercise 5.2.5

Label the molecules below as chiral or achiral, and circle all stereocenters.

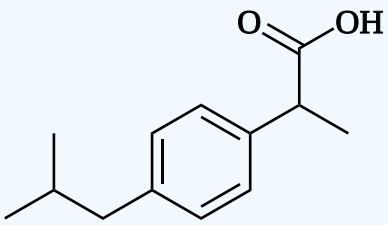
a) fumarate (a citric acid cycle intermediate)



b) malate (a citric acid cycle intermediate)



b) malate (a citric acid cycle intermediate)

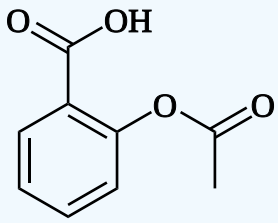


Answer available at the end of this section.

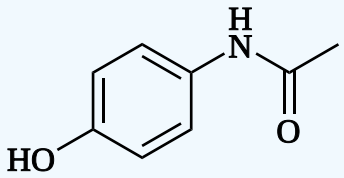
Exercise 5.2.6

Label the molecules below as chiral or achiral, and circle all stereocenters.

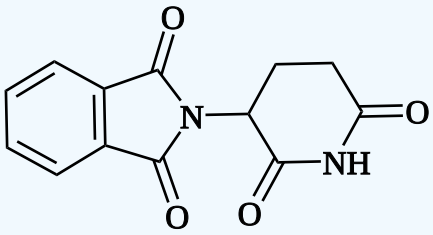
a) acetylsalicylic acid (aspirin)



b) acetaminophen (active ingredient in Tylenol)



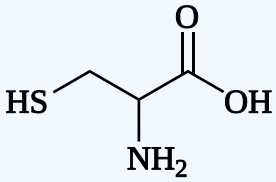
c) thalidomide (drug that caused birth defects in pregnant mothers in the 1960's)



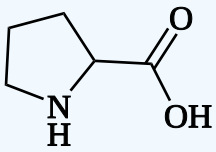
Answer available at the end of this section.

Exercise 5.2.7

Draw both enantiomers of the following chiral amino acids.



a) Cysteine



b) Proline

Answer available at the end of this section.

Exercise 5.2.8

Draw both enantiomers of the following compounds from the given names.

a) 2-bromobutane

b) 2,3-dimethyl-3-pentanol

Answer available at the end of this section.

Exercise 5.2.9

Which of the following body parts are chiral?

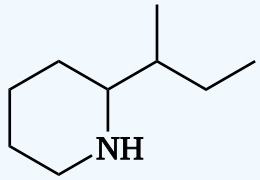
a) Hands b) Eyes c) Feet d) Ears

Answer available at the end of this section.

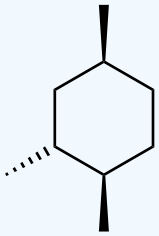
Exercise 5.2.10

Circle the chiral centers in the following compounds.

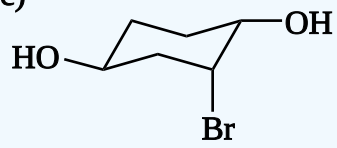
a)



b)



c)

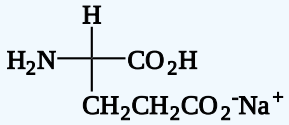


Answer available at the end of this section.

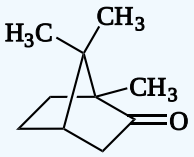
Exercise 5.2.11

Identify the chiral centers in the following compounds.

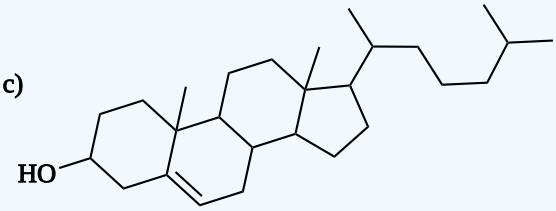
a)



b)



c)



Answer available at the end of this section.

Answers

Exercise 5.1.1

a. chiral (4 different groups off C)
b. achiral (2 identical -CH_3 substituents off central C)
c. achiral (2 identical -CH_2CH_3 substituents off central C)
d. achiral (2 identical CH_3 substituents off carbon 2)
e. chiral (4 different groups off carbon 2)
f. achiral (2 identical CH_3 substituents off central C)

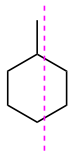
Exercise 5.1.2

a. enantiomers – non superimposable mirror images

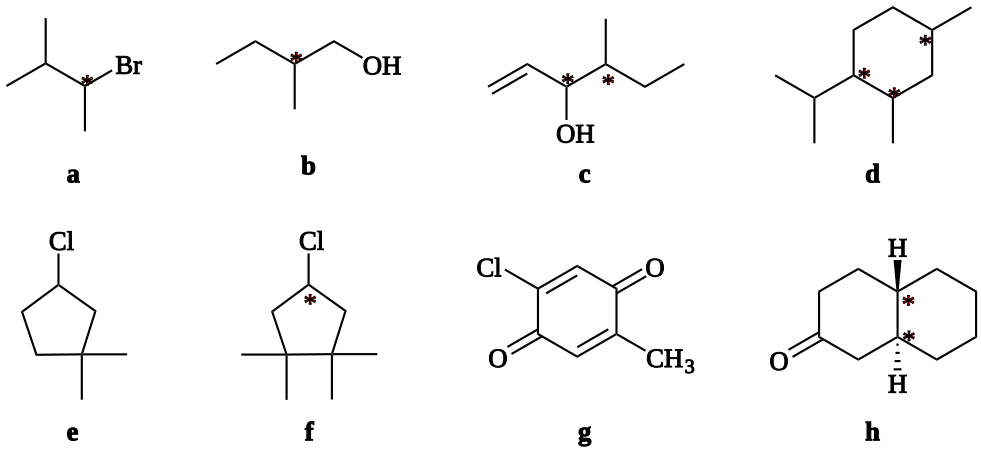
b. same compound – when you rotate the molecule on the right it is identical to the one on the left
c. enantiomers – non superimposable mirror images
d. enantiomers – non superimposable mirror images

Example 5.1.1

Achiral. When determining the chirality of a molecule, it best to start by locating any chiral carbons. An obvious candidate is the ring carbon attached to the methyl substituent. The question then becomes: does the ring as two different substituents making the substituted ring carbon chiral? With an uncertainty such as this, it is then helpful try to identify any planes of symmetry in the molecule. This molecule does have a plane of symmetry making the molecule achiral. The plane of symmetry would be easier see if the molecule were view from above. Typically, monosubstituted cycloalkanes have a similar plane of symmetry making them all achiral.



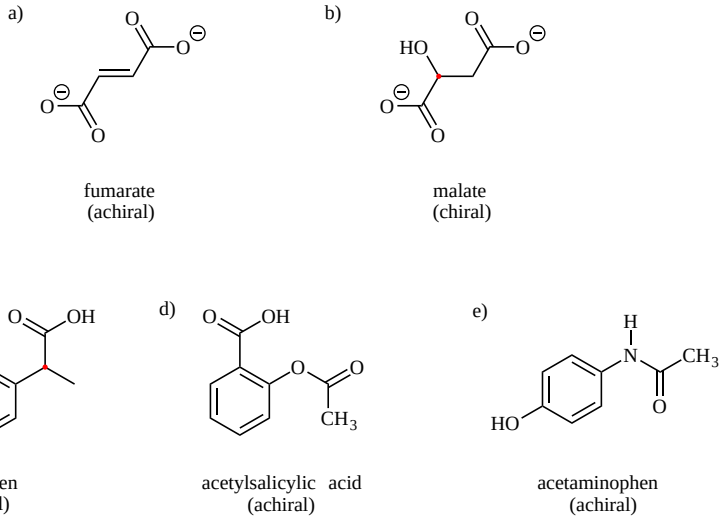
Exercise 5.2.1



Explanation

Structures F and G are achiral. The former has a plane of symmetry passing through the chlorine atom and bisecting the opposite carbon-carbon bond. The similar structure of compound E does not have such a symmetry plane, and the carbon bonded to the chlorine is a chiral center (the two ring segments connecting this carbon are not identical). Structure G is essentially flat. All the carbons except that of the methyl group are sp^2 hybridized, and therefore trigonal-planar in configuration. Compounds C, D & H have more than one chiral center, and are also chiral.

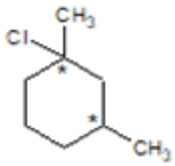
Example 5.2.2

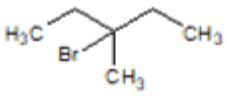


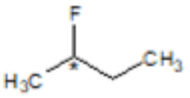
Exercise 5.2.2

1)

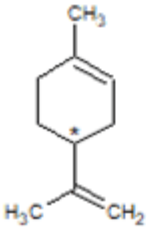
(a) (b) (c)

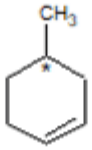


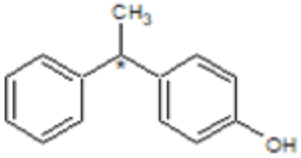




(d) (e) (f)







2) Though the molecule does not contain a chiral carbon, it is chiral as it is non-superimposable on its mirror image due to its twisted nature (the twist comes from the structure of the double bonds needing to be at 90° angles to each other, preventing the molecule from being planar).

3)

a) Just as hands are chiral a glove must also be chiral.

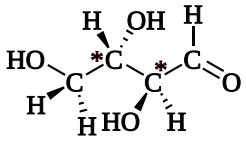
b) A nail has a plane of symmetry which goes down the middle making it a achiral.

c) A pair of sunglasses has a plane of symmetry which goes through the nose making it achiral.

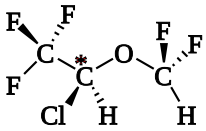
d) Most written words are chiral. Look one in a mirror to confirm this.

4

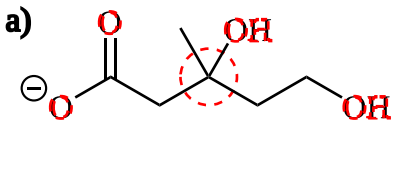
a)



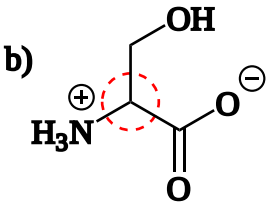
b)



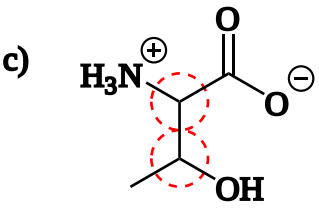
Exercise 5.2.3



mevalonate



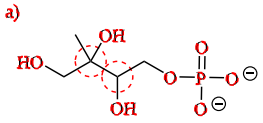
serine



threonine

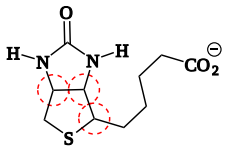
Exercise 5.2.4

a)



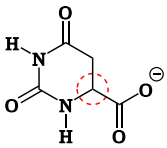
2-methylerythritol-4-phopshate

b)



biotin

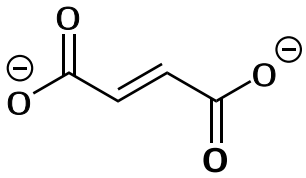
c)



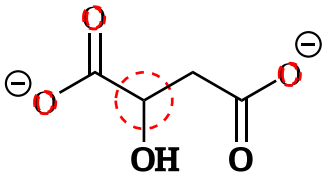
dihydroorotate

Exercise 5.2.5

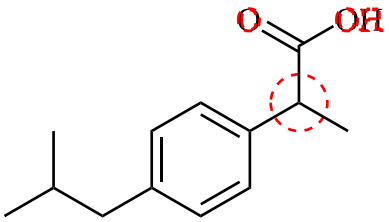
a) achiral (no stereocenters)



b) chiral

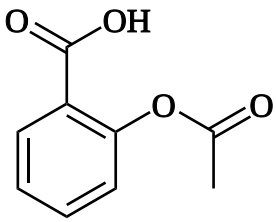


c) chiral

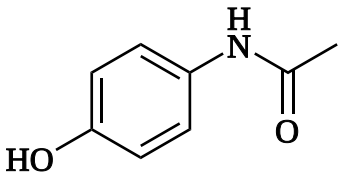


Exercise 5.2.6

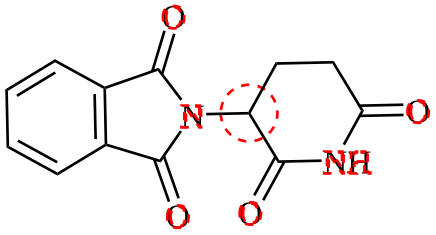
a) achiral (no stereocenters)



b) achiral (no stereocenters)

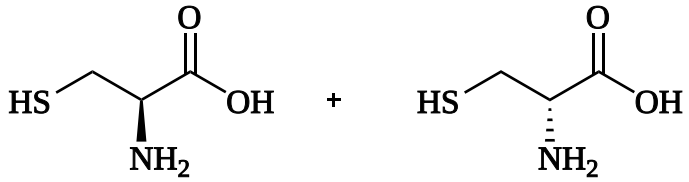


c) chiral

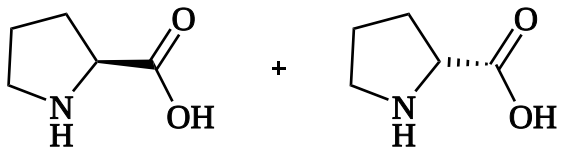


Exercise 5.2.7

a)



b)

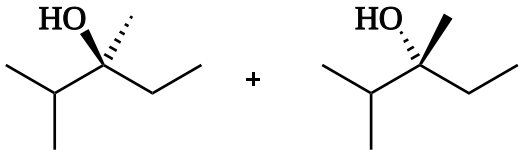


Exercise 5.2.8

a)



b)



Exercise 5.2.9

a) Hands- chiral since the mirror images cannot be superimposed (think of the example in the beginning of the section)

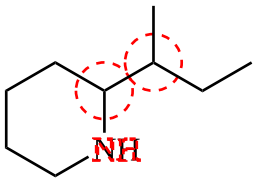
b) Eyes- achiral since mirror images that are superimposable

c) Feet- chiral since the mirror images cannot be superimposed (Does your right foot fit in your left shoe?)

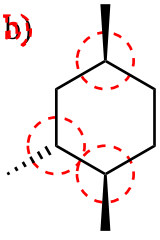
d) Ears- chiral since the mirror images cannot be superimposed

Exercise 5.2.10

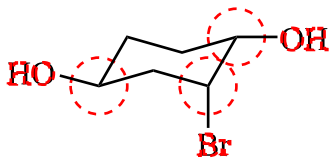
a)



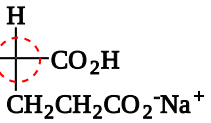
b)

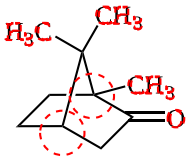


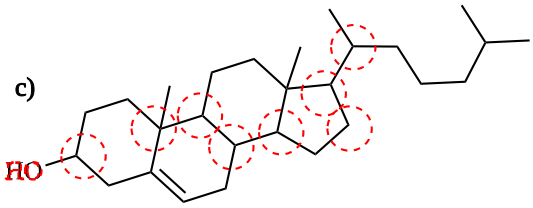
c)



Exercise 5.2.11

a) 

b) 

c) 

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5.2: Optical Activity

Objectives

After completing this section, you should be able to

1. describe the nature of plane-polarized light.
2. describe the features and operation of a simple polarimeter.
3. calculate the specific rotation of a compound, given the relevant experimental data.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- analyzer
- dextrorotatory
- levorotatory
- optically active
- plane-polarized light
- polarimeter
- polarizer
- specific rotation, $[\alpha]_D^{20}$

Study Notes

A *polarizer* is a device through which only light waves oscillating in a single plane may pass. A *polarimeter* is an instrument used to determine the angle through which plane-polarized light has been rotated by a given sample. You will have the opportunity to use a polarimeter in the laboratory component of the course. An *analyzer* is the component of a polarimeter that allows the angle of rotation of plane-polarized light to be determined.

Specific rotations are normally measured at 20°C, and this property may be indicated by the symbol $[\alpha]_D^{20}$. Sometimes the solvent is specified in parentheses behind the specific rotation value, for example,

$$[\alpha]_D^{20} = +12^o\,(\text{chloroform})$$

For liquids, the specific rotation may be obtained using the neat liquid rather than a solution; in such cases the formula is

$$[\alpha]_D^{\text{temp}}\,(\text{neat}) = \alpha \times l \times d$$

where α is the observed rotation, l is the path length of the cell (measured in decimetres, dm), and d is the density of the liquid.

Identifying and distinguishing enantiomers is inherently difficult, since their physical and chemical properties are largely identical. Fortunately, a nearly two hundred year old discovery by the French physicist Jean-Baptiste Biot has made this task much easier. This discovery disclosed that the right- and left-handed enantiomers of a chiral compound perturb plane-polarized light in opposite ways. This perturbation is unique to chiral molecules, and has been termed **optical activity**.

Polarimetry

Plane-polarized light is created by passing ordinary light through a polarizing device, which may be as simple as a lens taken from polarizing sun-glasses. Such devices transmit selectively only that component of a light beam having electrical and magnetic field vectors oscillating in a single plane. The plane of polarization can be determined by an instrument called a **polarimeter** (Figure

5.2.1).

Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer (α = 0°). If the analyzer is turned 90° to the plane of initial polarization, all the light will be blocked from reaching the detector.

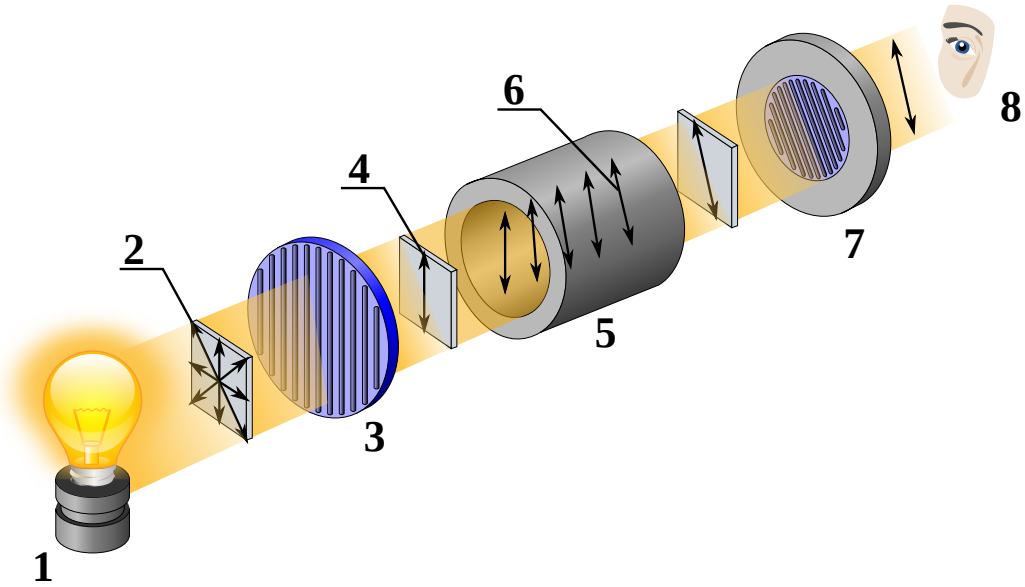


Figure 5.2.1: Operating principle of an optical polarimeter. 1. Light source 2. Unpolarized light 3. Linear polarizer 4. Linearly polarized light 5. Sample tube containing molecules under study 6. Optical rotation due to molecules 7. Rotatable linear analyzer 8. Detector. (CC BY-SA 3.0 Unported; Kaidor via Wikipedia)

Chemists use polarimeters to investigate the influence of compounds (in the sample cell) on plane polarized light. Samples composed only of achiral molecules (e.g. water or hexane), have no effect on the polarized light beam. However, if a single enantiomer is examined (all sample molecules being right-handed, or all being left-handed), the plane of polarization is rotated in either a clockwise (positive) or counter-clockwise (negative) direction, and the analyzer must be turned an appropriate matching angle, **α**, if full light intensity is to reach the detector. In the above illustration, the sample has rotated the polarization plane clockwise by +90°, and the analyzer has been turned this amount to permit maximum light transmission.

The observed rotations (α) of enantiomers are opposite in direction. One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** or (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** or (–). The prefixes dextro and levo come from the Latin *dexter*, meaning right, and *laevus*, for left, and are abbreviated *d* and *l* respectively. If equal quantities of each enantiomer are examined , using the same sample cell, then the magnitude of the rotations will be the same, with one being positive and the other negative. To be absolutely certain whether an observed rotation is positive or negative it is often necessary to make a second measurement using a different amount or concentration of the sample. In the above illustration, for example, α might be –90° or +270° rather than +90°. If the sample concentration is reduced by 10%, then the positive rotation would change to +81° (or +243°) while the negative rotation would change to –81°, and the correct α would be identified unambiguously.

Since it is not always possible to obtain or use samples of exactly the same size, the observed rotation is usually corrected to compensate for variations in sample quantity and cell length. Thus it is common practice to convert the observed rotation, α, to a **specific rotation**, by the following formula:

$$[\alpha]_D = \frac{\alpha}{lc} \tag{5.3.1}$$

where

- $[\alpha]_D$ is the specific rotation
- l is the cell length in dm
- c is the concentration in g/ml

- D designates that the light used is the 589 line from a sodium lamp

Compounds that rotate the plane of polarized light are termed **optically active**. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers. For example, the lactic acid enantiomers have the following specific rotations:

- Carvone from caraway: $[\alpha]_D^{20} = +62.5^o$ (this isomer may be referred to as (+)-carvone or d-carvone)
- Carvone from spearmint: $[\alpha]_D^{20} = -62.5^o$ (this isomer may be referred to as (–)-carvone or l-carvone)

and carvone enantiomers have the following specific rotations:

- Lactic acid from muscle tissue: $[\alpha]_D^{20} = +2.5^o$ (this isomer may be referred to as (+)-lactic acid or d-lactic acid)
- Lactic acid from sour milk: $[\alpha]_D^{20} = -2.5^o$ (this isomer may be referred to as (–)-lactic acid or l-lactic acid)

A 50:50 mixture of enantiomers has no observable optical activity. Such mixtures are called **racemates** or racemic modifications, and are designated (±). When chiral compounds are created from achiral compounds, the products are racemic unless a single enantiomer of a chiral co-reactant or catalyst is involved in the reaction. The addition of HBr to either cis- or trans-2-butene is an example of racemic product formation (the chiral center is colored red).

$$\mathrm{CH_3CH{=}CHCH_3 + HBr \longrightarrow (\pm)\ CH_3CH_2HBrCHC_3}$$

Chiral organic compounds isolated from living organisms are usually optically active, indicating that one of the enantiomers predominates (often it is the only isomer present). This is a result of the action of chiral catalysts we call enzymes, and reflects the inherently chiral nature of life itself. Chiral synthetic compounds, on the other hand, are commonly racemates, unless they have been prepared from enantiomerically pure starting materials.

There are two ways in which the condition of a chiral substance may be changed:

1. A racemate may be separated into its component enantiomers. This process is called **resolution**.
2. A pure enantiomer may be transformed into its racemate. This process is called **racemization**.

Enantiomeric Excess

The "optical purity" is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample of pure enantiomer. It is expressed as a percentage. If the sample only rotates plane-polarized light half as much as expected, the optical purity is 50%.

$$\%\ \text{optical purity} = \frac{\text{specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Because *R* and *S* enantiomers have equal but opposite optical activity, it naturally follows that a 50:50 racemic mixture of two enantiomers will have no observable optical activity. If we know the specific rotation for a chiral molecule, however, we can easily calculate the ratio of enantiomers present in a mixture of two enantiomers, based on its measured optical activity. When a mixture contains more of one enantiomer than the other, chemists often use the concept of **enantiomeric excess (ee)** to quantify the difference. Enantiomeric excess can be expressed as:

$$ee = \frac{(\%\ \text{more abundant enantiomer} - 50) \times 100\%}{50}$$

For example, a mixture containing 60% *R* enantiomer (and 40% S enantiomer) has a 20% enantiomeric excess of R: ((60-50) x 100) / 50 = 20 %.

Exercise 5.2.1

The specific rotation of (S)-carvone is (+)61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a neat sample of a mixture of *R* and *S* carvone is measured at (-)23°. Which enantiomer is in excess, and what is its ee? What are the percentages of (*R*)- and (*S*)-carvone in the sample?

Answer available at the end of this section.

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration.

Separation of Chiral Compounds

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used of this technique is known as chiral resolution.

Exercise 5.2.2

A 3.200 g sample of morphine ($[\alpha]_D$ = -132) was dissolved in 10.0 mL of acetic acid ($[\alpha]_D$ = 0). If it is put into a sample tube with a path length of 2.00 cm, what would be its observed rotation (α)?

Answer available at the end of this section.

Exercise 5.2.3

Is the morphine in the previous excercise dextrorotatory or levorotatory?

Answer available at the end of this section.

Exercise 5.2.4

Label the following compounds as dextrorotatory or levorotatory.

a. sucrose ($[\alpha]_D$ = + 66.7)
b. cholesterol ($[\alpha]_D$ = - 31.5)
c. cocaine ($[\alpha]_D$ = - 16)
d. chloroform ($[\alpha]_D$ = 0)

Answer available at the end of this section.

Exercise 5.2.5a

The specific rotation of (S)-carvone is (+) 61^o when measured neat (pure liquid sample with no solvent). The optical rotation of a neat sample of a mixture of R and S carvone is measured at (-) 23 ^{o}.

a) Which enantiomer is in excess?

Answer available at the end of this section.

Exercise 5.2.5b

b) What are the percentages of (S)- and (*R*)- carvone in the sample mixture?

Answer available at the end of this section.

Exercise 5.2.5c

c) What is the ee (enantiomeric excess)?

Answer available at the end of this section.

Exercise 5.2.6a

Determine the ee's of the following from the percentages

- 95 % (*R*)- tartaric acid and 5.0 % (*S*)- tartaric acid

Answer available at the end of this section.

Exercise 5.2.6b

Determine the ee's of the following from the percentages

- 75 % (S)- limonene and 25 % (*R*)- limonene

Answer available at the end of this section.

Exercise 5.2.6c

Determine the ee's of the following from the percentages

- 85 % (*R*) cysteine

Answer available at the end of this section.

Exercise 5.2.6d

Determine the ee's of the following from the percentages

- 50 % (S) alanine

Answer available at the end of this section.

Answers

Exercise 5.2.1

The observed rotation of the mixture is levorotary (negative, counter-clockwise), and the specific rotation of the pure *S* enantiomer is given as dextrorotary (positive, clockwise), meaning that the pure *R* enantiomer must be levorotary, and the mixture must contain more of the *R* enantiomer than of the *S* enantiomer.

Rotation (*R*/S Mix) = [Fraction(S) × Rotation (S)] + [Fraction(*R*) × Rotation (*R*)]

Let Fraction (S) = x, therefore Fraction (*R*) = 1 – x.

Rotation (*R*/S Mix) = x[Rotation (S)] + (1 – x)[Rotation (*R*)].

–23 = x(+61) + (1 – x)(–61)

Solve for x: x = 0.3114 and (1 – x) = 0.6885

Therefore the percentages of (*R*)- and (S)-carvone in the sample are 68.9% and 31.1%, respectively.

ee = [(% more abundant enantiomer – 50) × 100]/50. = [68.9 – 50) × 100]/50 = 37.8%.

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration

Exercise 5.2.2

The specific rotation, $[\alpha]_D$ = (observed rotation, α (degrees))/ [(pathlength, *l* (dm)) x (concentration, c (g/cm^3))] = α/(*l* x c)

Solving for α, α = $[\alpha]_D$ x *l* x c

($[\alpha]_D$ = -132) x (*l* = 2.00 cm = 0.200 dm) x (c = 3.20 g / 10.0 cm^3 = 0.320 g/cm^3)

α = -132 x 0.200 dm x 0.320 g/cm^3 = -8.45 °

Exercise 5.2.3

Since morphine has a (-) rotation, it indicates that it rotates light to the left (counterclockwise) and morphine is levorotatory.

Exercise 5.2.4

a. sucrose ($[\alpha]_D$ = + 66.7) dextrorotatory
b. cholesterol ($[\alpha]_D$ = - 31.5) levorotatory
c. cocaine ($[\alpha]_D$ = - 16) levorotatory
d. chloroform ($[\alpha]_D$ = 0) neither, not optically active

Exercise 5.2.5*a*

Since the pure S enantiomer ((+) 61°) is dextrorotatory (positive, clockwise), the *R* enantiomer must be levorotatory. The observed rotation of the mixture is levorotatory since its negative (counterclockwise). This means the mixture must contain more of the *R* enantiomer than the S enantiomer.

Exercise 5.2.5*b*

Optical rotation (α) of the (*R*/S mixture) = [fraction (S) x $[\alpha]_D$ (S)] + [fraction (*R*) x $[\alpha]_D$ (*R*)]

To determine the fraction of S and R, we make y = fraction (S) and 1 – y = fraction (*R*)

-23° = y x (61°) + (1 – y) x (-61°) solving for y: y = 0.3114 and (1-y) = 0.6885

Therefore the percentage of (S)-carvone is 31.1 % and (*R*)-carvone is 68.9 %

Exercise 5.2.5*c*

ee = [(% more abundant isomer – 50) x 100]/50 = [(68.9 – 50) x100]/50 = 37.8 % ee

Exercise 5.2.6*a*

[(95 – 50) x 100] / 50 = 90 % ee (*R*)-tartaric acid

Exercise 5.2.6*b*

[(75 – 50) x 100] / 50 = 50 % ee (S)- limonene

Exercise 5.2.6*c*

(85 – 50) x 100] / 50 = 70 % ee (*R*)-cysteine

Exercise 5.2.6*d*

(50 – 50) x 100] / 50 = 0 % ee, racemic mixture

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5.3: Absolute Configuration: R-S Sequence Rules

Objectives

After completing this section, you should be able to

1. assign Cahn-Ingold-Prelog priorities to a given set of substituents.
2. determine whether a given wedge-and-broken-line structure corresponds to an *R* or an *S* configuration, with or without the aid of molecular models.
3. draw the wedge-and-broken-line structure for a compound, given its IUPAC name, complete with *R* or *S* designation.
4. construct a stereochemically accurate model of a given enantiomer from either a wedge-and-broken-line structure or the IUPAC name of the compound, complete with *R* or *S* designation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- absolute configuration
- *R* configuration
- *S* configuration

Study Notes

When designating a structure as *R* or *S*, you must ensure that the atom or group with the lowest priority is pointing away from you, the observer. The easiest way to show this is to use the wedge-and-broken-line representation. You can then immediately determine whether you are observing an *R* configuration or an *S* configuration.

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The method for this is formally known as *R*/*S* nomenclature.

Introduction

The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, is also often called the Cahn-Ingold-Prelog rules. In addition to the Cahn-Ingold system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

1. X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
2. Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

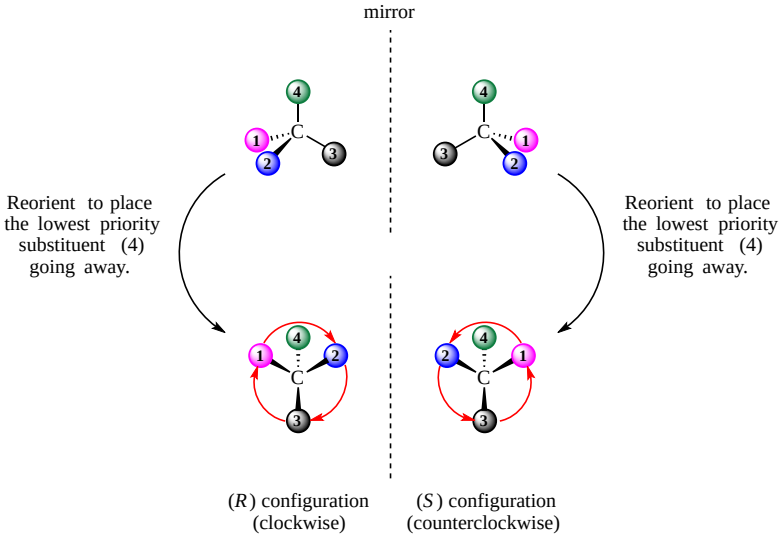
However, for non-laboratory purposes, it is beneficial to focus on the (*R*)/(*S*) system. The sign of optical rotation, although different for the two enantiomers of a chiral molecule,at the same temperature, **cannot** be used to establish the absolute configuration of an enantiomer; this is because the sign of optical rotation for a particular enantiomer may change when the temperature changes.

Stereocenters are labeled (*R*) or (*S*)

The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as (*R*) or (*S*).

The **Cahn-Ingold-Prelog** rules of assign priorities the groups directly bonded to the chiral carbon. Having ranked the four

groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) is given a dash bond to indicate it points directly away from us. We then look at the three remaining substituents, which now appear to radiate toward us which is shown by using wedge bonds. If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent is clockwise, we say that the chirality center has the (R) configuration (Latin rectus, meaning “right”). If an arrow from is counterclockwise, the chirality center has the (S) configuration (Latin sinister, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a Right (clockwise) turn. Note, the (R) or (S) configurations represent the two enantiomers of a chiral molecule. The (R) or (S) configuration is often added as a prefix, in parenthesis, to a chiral molecule's name to indicate which enantiomer is being discussed (e.g., (R)-2-bromobutane). If more than chiral carbon is present in a chiral molecule, each carbon's number is included before the (R) or (S) configuration. Ex: (2R,4S,6R)-2-bromo-6-chloro-4-methylheptane.



Sequence Rules to Assign Priorities to Substituents

Before applying the (*R*) and (*S*) nomenclature to a stereocenter, the substituents must be prioritized according to the following rules:

Rule 1

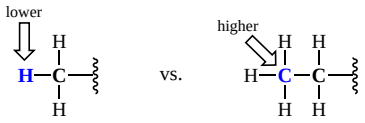
First, examine at the atoms directly attached to the stereocenter of the compound. A atom with a higher atomic number takes precedence over a atom with a lower atomic number. Hydrogen is the lowest possible priority atom, because it has the lowest atomic number.

1. The atom with higher atomic number has higher priority (I > Br > Cl > S > P > F > O > N > C > H).
2. When comparing isotopes, the atom with the higher mass number has higher priority [^{18}O > ^{16}O or ^{15}N > ^{14}N or ^{13}C > ^{12}C or T (^{3}H) > D (^{2}H) > H].

Rule 2

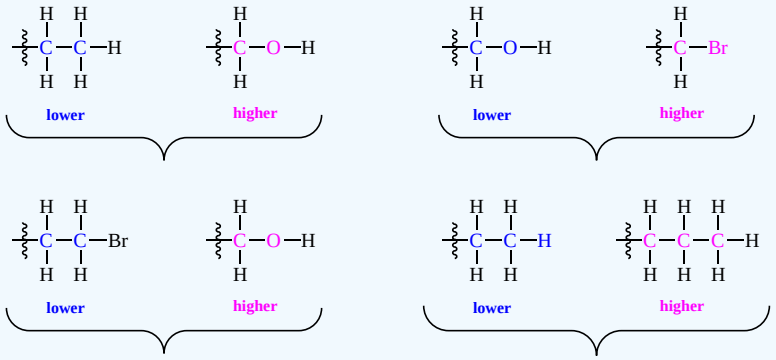
If there are two or more substituents which have the same element directly attached to chiral carbon, proceed along the substituent chains until a point of difference is found. Determine which of the chains has the first connection to an atom with the highest priority (the highest atomic number). That chain has the higher priority.

For example: an ethyl substituent takes priority over a methyl substituent. At the connectivity of the stereocenter, both have a carbon atom, which are equal in rank. Going down the chains, a methyl has only has hydrogen atoms attached to it, whereas the ethyl has two hydrogen atoms and a carbon atom. The carbon atom on the ethyl is the first point of difference and has a higher atomic number than hydrogen; therefore the ethyl takes priority over the methyl.



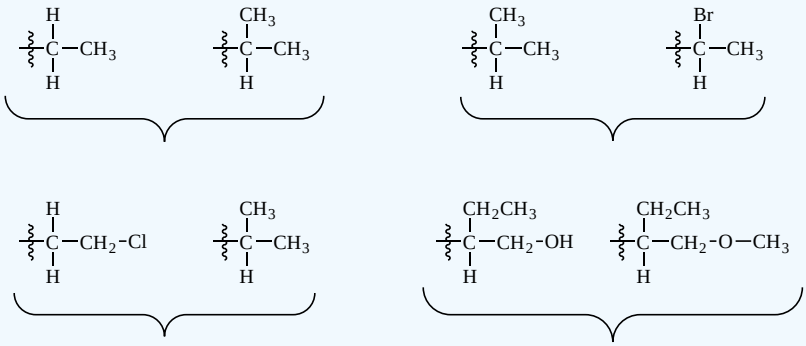
The "-H" (left) ranks lower than the "C-" (right) based on the relative molecular weights at the first point of difference.

Example 5.3.1



Worked Exercise 5.3.1

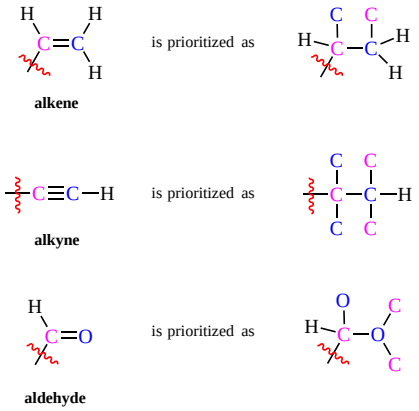
For the following pairs of substituents, determine which would have the higher and lower priority based on the **Cahn-Ingold-Prelog** rules. Explain your answer.



Answer available at the end of this section.

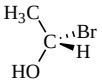
Rule 3

For assigning priority, multiple bonds are treated as if each bond of the multiple bond is bonded to a unique atom. For example, an alkene substituent (CH_2=CH-) has higher priority than an ethyl substituent (CH_3CH_2-). The alkene carbon priority is "two" bonds to carbon atoms and one bond to a hydrogen atom compared with the ethyl carbon that has only one bond to a carbon atom and two bonds to two hydrogen atoms. Similarly, alkyne substituent (HCC-) would have an even higher priority because the alkyne carbon is treated as if it is bonded to three carbons. This method remains the same with compounds containing a carbonyl (C=O) group. The carbon of an aldehyde substituent (O=CH-) is treated as if it is bonded to a hydrogen and two oxygen atoms.



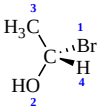
Determining (*R*) or (*S*) Configuration Using a Molecular Model

In order to demonstrate how to determine the (*R*)/(*S*) configuration of the chiral carbon in the following molecule using molecular models, first construct a model of the bromoethanol structure:

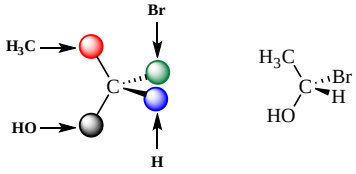


First make a molecular model of a tetrahedral carbon with four different substituents. In many cases, this will appear as a carbon with four bonds with a different colored ball attached to each bond.

For the molecule in question, determine the location of the chiral carbon and assign CIP priorities to the substituents. In this case, Br gets the highest priority because it has the highest atomic number. The O in the OH substituent gets priority 2 and the C in CH_3 gets priority 3. Lastly, H gets the lowest priority, 4, because it has the smallest atomic number.



Now take your molecular model and orientate it to match the molecule in question. Remember in the dash/wedge representation, two regular bonds are in the plane of the page. The wedge bond is coming toward you and the dashed bond is going away from you. If you were to hold a piece of paper directly in front of you, the substituents with the regular bond should both be touching the piece of paper. The dashed bond should be pointing behind the piece of paper and the wedge bond should be pointing in front.

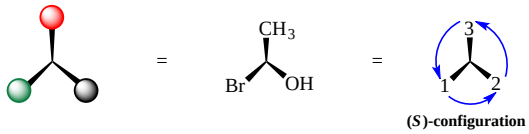


In this structure, the bromine is going away from you, the hydrogen is coming toward you and the hydroxide and methyl groups are in the plane of the page.

Then based on the position, assign each substituent on the chiral carbon a colored ball on your molecular model. In this case, bromine is going away so it is assigned the green ball. The hydrogen is coming toward you so it is assigned the blue ball. The last two substituents are in the plane of the page, however, the CH_3 is positioned higher so it is assigned the red ball which leaves OH being assigned the black ball.

Lastly, grab onto the ball for the lowest priority substitutent, in this case the blue one, and point the other three substituents towards you. The three bonds should be angled towards you as if they all have wedge bonds. Assign the original substituents and

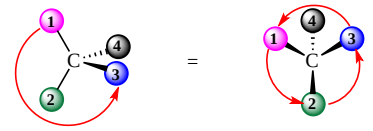
their corresponding CIP priorities to the three colored balls. The green ball was assigned to bromine which was given priority one. The OH was assigned to the black ball and given priority two. The CH_3 was assigned to the red ball and given priority three. In this case the priorities are going counter clockwise so the chiral carbon has an **(S)** configuration.



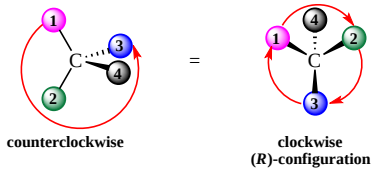
Determining (*R*) or (S) Configuration Without a Molecular Model

If a molecular model cannot be used there are a couple of simple methods which can be applied if the dash/wedge bond system is being used.

After assigning CIP priorities, if the lowest priority substituent (4) is on the dash bond the configuration of substituents 1-3 can be assigned directly. As shown in the figure below, the configuration of substituents 1-3 does not change when moving to sight down the bond of substituent 4. In both cases, substituents 1-3 are ordered in a counterclockwise fashion which gives the chiral carbon an (S) configuration.



The opposite is true if the lowest priority substituent (4) is on the wedge bond. As shown in the figure below, the configuration of substituents 1-3 is inverted when moving to sight down the bond of substituent 4. When the lowest priority substituent is on the wedge bond, the configuration of substituents 1-3 can be assigned directly only if the direction is inverted. i.e. clockwise = (S) and counterclockwise = (*R*).

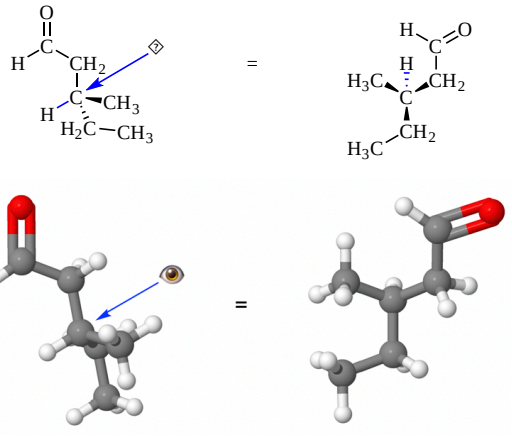


With the lowest priority group in front, drawing an arc from 1 to 2 to 3 gives the reverse of the configuration.

However, if the lowest priority substituent is on one of the regular bonds when the dash/wedge system is being used then configurations are best assigned by changing perspectives. This method can also be used if the three-dimensional configuration of the chiral carbon is represented. First, locate the chiral carbon and assign CIP priorities to its substituents. Then while perceiving the drawn molecule as a three-dimensional image, mentally change your perspective such that you are looking down the bond between the chiral carbon and the lowest CIP ranked substituent (#4). If done correctly, the bonds for substituents 1-3 should be coming towards you as wedge bonds. You can then follow the direction of the CIP priority numbers to determine the (*R*)/(S) configuration of the chiral carbon.

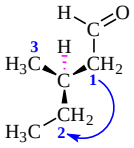


Locate the chiral carbon and assign CIP priorities to its substituents.



Mentally sight down the bond between the chiral carbon and the lowest CIP ranked substituent.

This bond is shown in magenta.



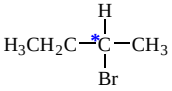
clockwise
(*R*)-configuration

Follow the direction of the CIP priority numbers to determine the (*R*)/(S) configuration.

Drawing the Structure of a Chiral Molecule from its Name

Draw the structure of (S)-2-Bromobutane:

1) Draw the basic structure of the molecule and determine the location of the chiral carbon.



2) Determine the chiral carbon's substituents and assign them a CIP priority.

-H (Priority 4)

-CH_3 (Priority 3)

-CH_2CH_3 (Priority 2)

-Br (Priority 1)

3) Draw the chiral carbon in a dash/wedge form and add the lowest priority substituent to the dash bond. In this case, the lowest priority substituent is -H.



4) Add the remaining substituents in a clockwise fashion for (*R*) and a counterclockwise fashion for (*S*).



clockwise
(*R*)-configuration

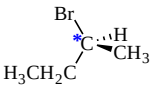


counterclockwise
(*S*)-configuration

The molecule posed in this question has an (S) configuration so the remaining substituents are added in a counterclockwise fashion.



counterclockwise
(*S*)-configuration



(*S*)-2-bromobutane

Exercise 5.3.1

1) Orient the following so that the least priority (4) atom is paced behind, then assign stereochemistry ((*R*) or (S)).

5.5qu.png

2) Draw (*R*)-2-bromobutan-2-ol.

3) Assign (*R*)/(S) to the following molecule.

5.5(3).png

4) Which in the following pairs would have a higher CIP priority?

a. -H or -Cl
b. -Br or -I
c. $-CH_2OH$ or $-OCH_3$
d. $-CH_2CH_3$ or $-CH{=}CH_2$
e. $-NH_2$ or -OH

5) Rank the following substituents in order of their CIP priority:

a. -H, $-OCH_3$, $-CH_2OH$, -OH
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. -CN, $-NH_2$, -CH=O, $-NHCH_3$
d. -SH, $-SCH_3$, -OH, $-OOCH_3$

6) Determine if the chiral carbon in the following molecules have an (*R*) or (S) configuration. Red = Oxygen & Blue = Nitrogen.

a)

b)

Answer available at the end of this section.

Exercise 5.3.2

Identify which substituent in the following sets has a higher ranking.

a. -H or $-CH_3$
b. $-CH_2CH_2CH_3$ or CH_2CH_3

c. $-CH_2Cl$ or CH_2OH

Answer available at the end of this section.

Exercise 5.3.3

Identify which substituent in the following sets has a higher ranking.

a. $-NH_2$ or $-N{=}NH$
b. $-CH_2CH_2OH$ or $-CH_2OH$
c. $-CH{=}CH_2$ or $-CH_2CH_3$

Answer available at the end of this section.

Exercise 5.3.4

Place the following sets of substituents in each group in order of lowest priority (1^{st}) to highest priority (4^{th})

a. $-NH_2$, -F, -Br, $-CH_3$
b. -SH, $-NH_2$, -F, -H

Answer available at the end of this section.

Exercise 5.3.5

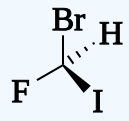
Place the following sets of substituents in each group in order of lowest priority (1^{st}) to highest priority (4^{th})

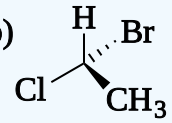
a. $-CH_2CH_3$, -CN, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$
b. $-CH_2NH_2$, $-CH_2SH$, $-C(CH_3)_3$, -CN

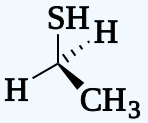
Answer available at the end of this section.

Exercise 5.3.6

Assign the following chiral centers as (*R*) or (*S*).

a) 

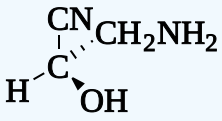
b) 

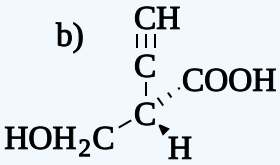
c) 

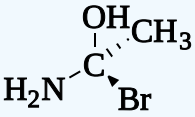
Answer available at the end of this section.

Exercise 5.3.7

Assign the following chiral centers as (*R*) or (*S*).

a) 

b) 

c) 

Answer available at the end of this section.

Exercise 5.3.8

Draw the structure of (*R*)-2-bromohexane.

Answer available at the end of this section.

Exercise 5.3.9

Draw the structure of (S)-2-methyl-3-pentanol.

Answer available at the end of this section.

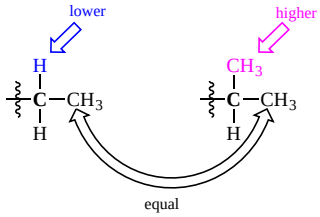
References

1. Schore and Vollhardt. *Organic Chemistry Structure and Function*. New York:W.H. Freeman and Company, 2007.
2. McMurry, John and Simanek, Eric. *Fundamentals of Organic Chemistry*. 6th Ed. Brooks Cole, 2006.

Answers

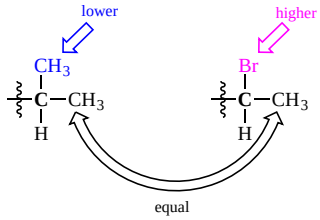
Worked Exercise 5.3.1

A 1-methylethyl substituent takes precedence over an ethyl substituent. Connected to the first carbon atom, ethyl only has one other carbon, whereas the 1-methylethyl has two carbon atoms attached to the first; this is the first point of difference. Therefore, 1-methylethyl ranks higher in priority than ethyl, as shown below:



The "C-" (right) ranks higher than the "H-" (left) based on the first point of difference and their relative atomic numbers.

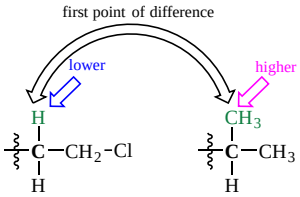
However:



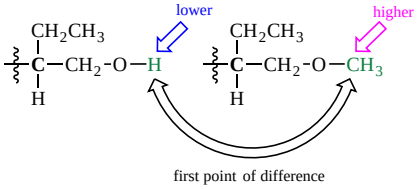
In this case, even though the bold carbon on the right structure has two connections to a non-hydrogen atom (C), it is the lower priority. This is because one of the atoms attached to the bold carbon on the left molecule ranks higher than any of the atoms attached to the bold carbon on the right structure, since Br has a higher atomic number than C.

Caution!!

Keep in mind that priority is determined by the **first** point of difference along the two similar substituent chains. After the first point of difference, the rest of the chain is irrelevant.



When looking for the first point of difference on similar substituent chains, one may encounter branching. If there is branching, choose the branch that is higher in priority. If the two substituents have similar branches, rank the elements within the branches until a point of difference.



Exercise 5.3.1

1) A is (S) and B is (*R*).

5.5sol.png

2)

5.5(2).png

3) The stereocenter is (*R*).

4)

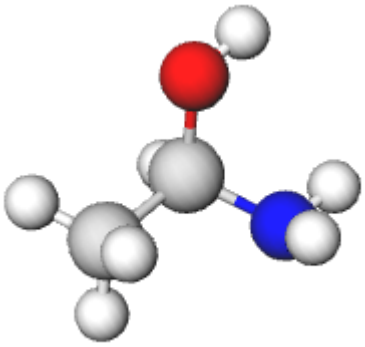
a. -Cl
b. -I
c. $-OCH_3$
d. $-CH=CH_2$
e. -OH

5) Rank the following substituents in order of their CIP priority:

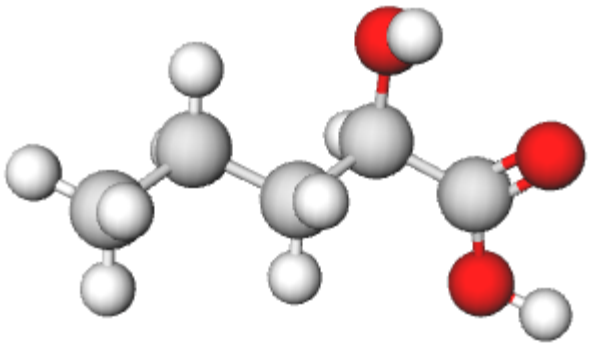
a. $-OCH_3$, -OH, $-CH_2OH$, -H,
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. $-NHCH_3$, $-NH_2$, -CH=O, -CN
d. $-SCH_3$, -SH, $-OOCH_3$, -OH

6)

a) The chiral carbon is (*R*). The four substituents of the chiral carbon are -OH (1), $-NH_2$ (2), $-CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a clockwise fashion so the chiral carbon is (*R*).



b) The chiral carbon is (S). The four substituents of the chiral carbon are $-CO_2H$ (1), -OH (2), $-CH_2CH_2CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a counterclockwise fashion so the chiral carbon is (S).



Exercise 5.3.2

a. **$-CH_3$**
b. **$-CH_2CH_2CH_3$**
c. **$-CH_2Cl$**

Exercise 5.3.3

a) **-N=NH**
b) **$-CH_2OH$**
c) **$-CH=CH_2$**

Exercise 5.3.4

a) $-CH_3 < -NH_2 < -F, < -Br$
b) $-H < -NH_2 < -F, < -SH$

Exercise 5.3.5

a) $-CH_2CH_3 < -CH_2CH_2OH < -CH_2CH_2CH_2OH, < -CN$
b) $-C(CH_3)_3 < -CH_2NH_2 < -CN < -CH_2SH$

Exercise 5.3.6

a) **(*S*)**: I > Br > F > H. The lowest priority substituent is going backwards so following the highest priority, it goes left (counterclockwise).

b) **(*R*)**: Br > Cl > CH_3 > H. Using a model kit, you need to rotate the H to the back position where the Br is. This causes the priority to go to the left (clockwise) when looking at it with the H in the back position. Alternatively, if you do not have a model kit, you can imagine the structure 3-dimensionally and since the lowest priority (H) is facing up (as drawn), if you look at it from below, starting with Br (1^{st} priority) and moving towards Cl (2^{nd} priority), you are moving right (clockwise) which represents (*R*) stereochemistry.

c) **Neither (*R*) or (*S*)**: Since there are two identical substituents (H's) the molecule is achiral and cannot be assigned (*R*) or (*S*).

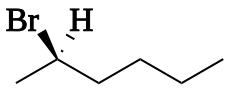
Exercise 5.3.7

a) **(*R*)**: OH > CN (C triple bonded to N) > CH_2NH_2 > H. The H needs to be moved to the back position which causes the priority to go to the right (clockwise) which indicates (*R*).

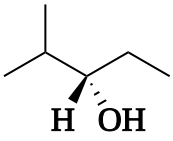
b) **(*S*)**: COOH > CH_2OH > CCH > H. Since the H is coming forward, you can assign the priority and it goes to the right (clockwise which would be (*R*)) but since the lowest priority is forward, you have to switch it to (S). Alternatively, you can rotate the molecule to put the lowest priority to the back and you'll see that it rotates left (or counterclockwise) for (*S*).

c) **(*S*)**: Br > OH > NH_2 > CH_3. Since the lowest priority is going back, you can follow the priority and see that it is going left (counterclockwise) and therefore (*S*).

Exercise 5.3.8



Exercise 5.3.9



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5.4: Fischer Projections

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
2. draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.

Key Terms

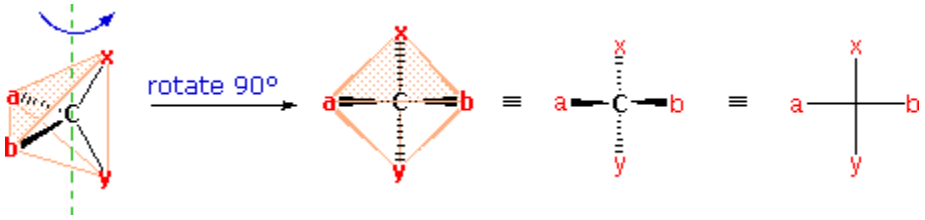
Make certain that you can define, and use in context, the key term below.

- Fischer projection

Study Notes

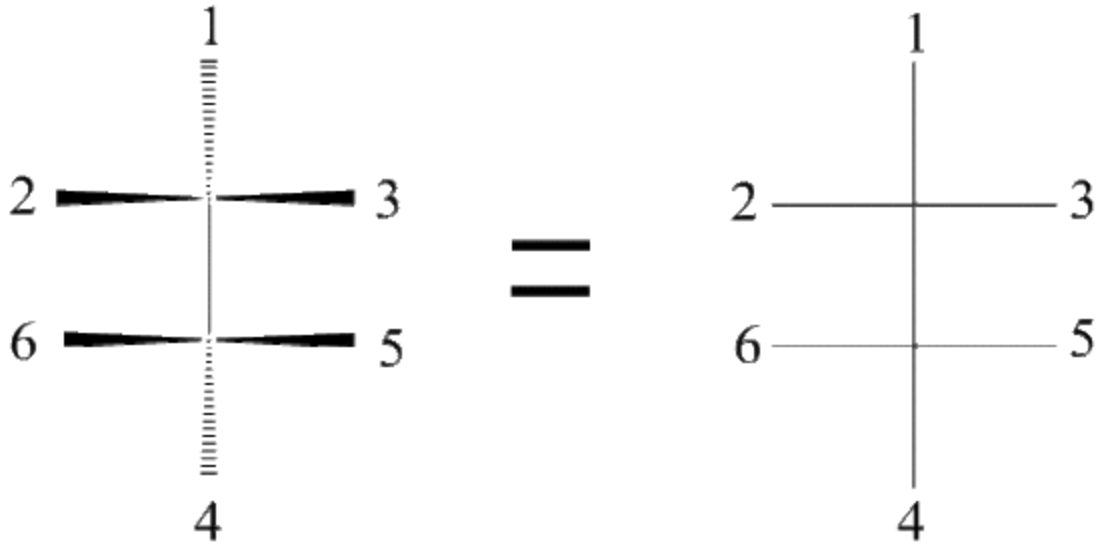
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and hatched line notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. In a Fischer projection drawing, the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines. The two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon). The two vertical bonds are directed behind the central carbon (away from the viewer). Since this is not the usual way in which we have viewed such structures, the following diagram shows how a stereogenic carbon positioned in the common two-bonds-in-a-plane orientation (x–C–y define the reference plane) is rotated into the Fischer projection orientation (the far right formula). When writing Fischer projection formulas it is important to remember these conventions. Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180° within the plane, thus maintaining this relationship. **The structure must not be flipped over or rotated by 90°**.

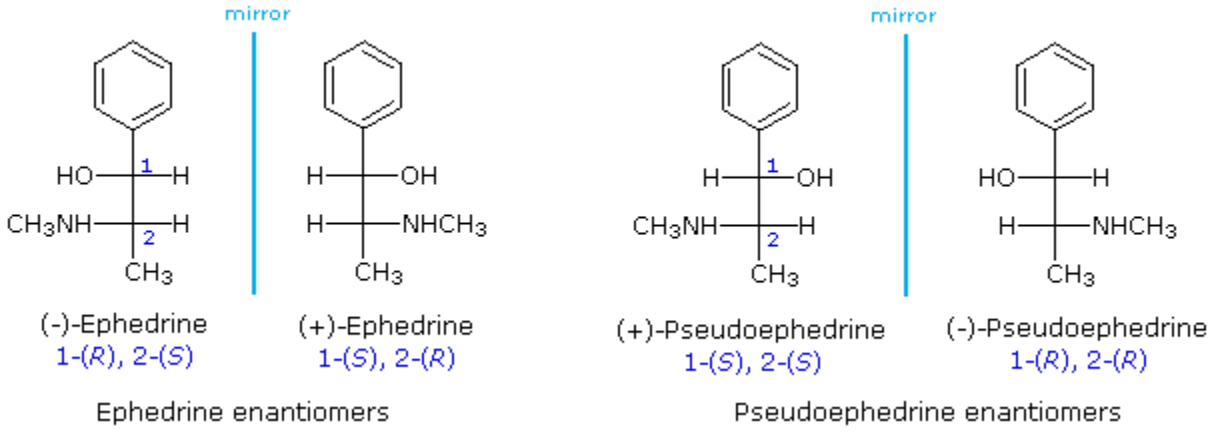


In the above diagram, if x = CO_2H, y = CH_3, a = H & b = OH, the resulting formula describes (*R*)-(−)-lactic acid. The mirror-image formula, where x = CO_2H, y = CH_3, a = OH & b = H, would, of course, represent (*S*)-(+)-lactic acid.

The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines represents the central carbon.

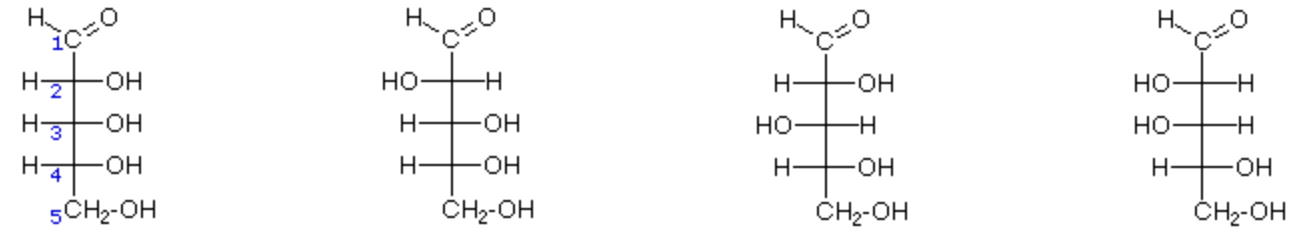


Using the Fischer projection notation, the stereoisomers of 2-methylamino-1-phenylpropanol are drawn in the following manner. Note that it is customary to set the longest carbon chain as the vertical bond assembly.



The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses. Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**. Fischer formulas for these isomers, which Fischer designated as the "D"-family, are shown in the diagram. Each of these compounds has an enantiomer, which is a member of the "L"-family so, as expected, there are eight stereoisomers in all. Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

How to make Fischer Projections

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

Example 25.2.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

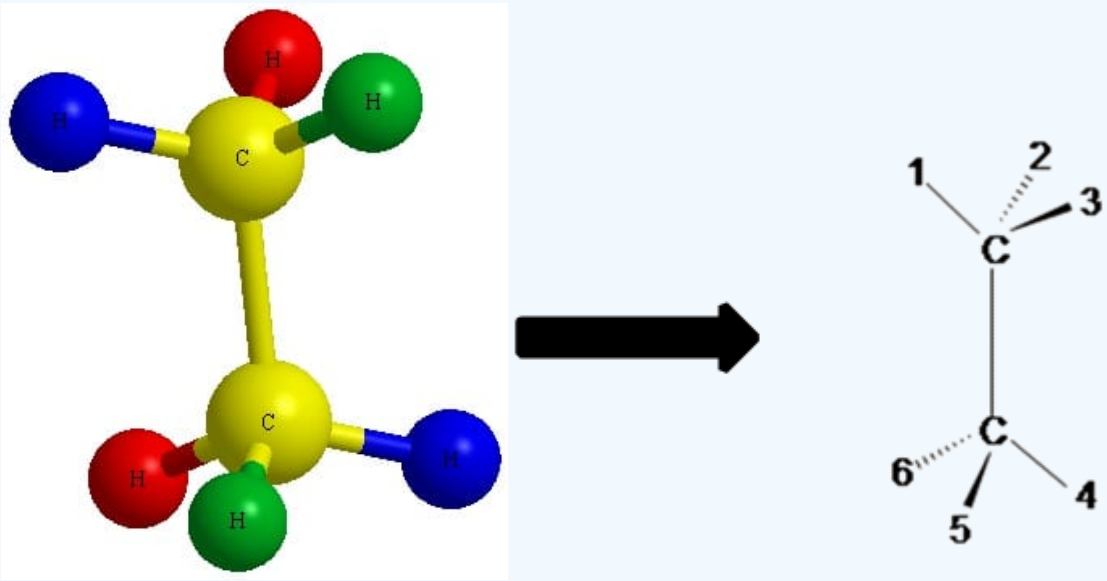


Figure A Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a "flat" Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

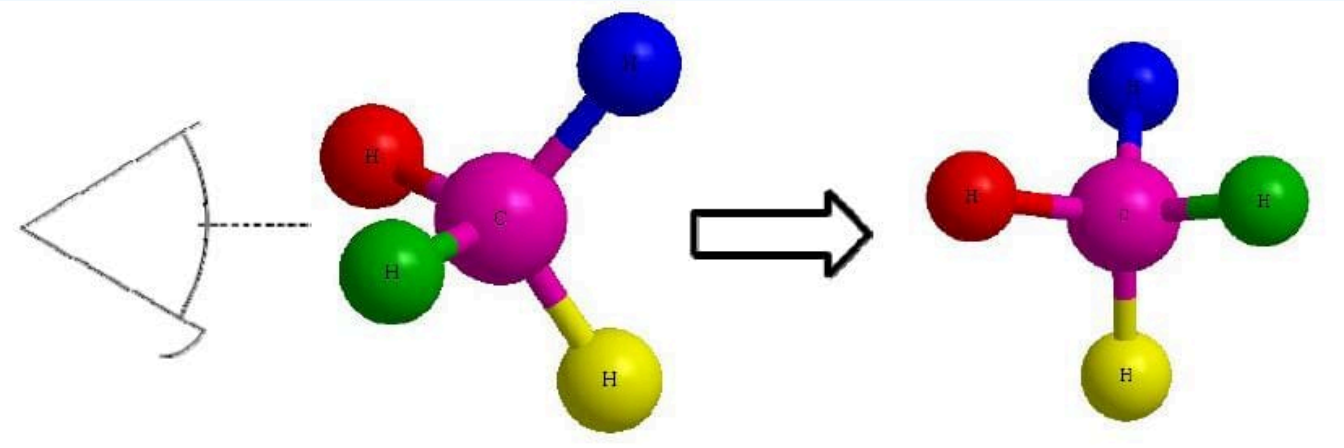
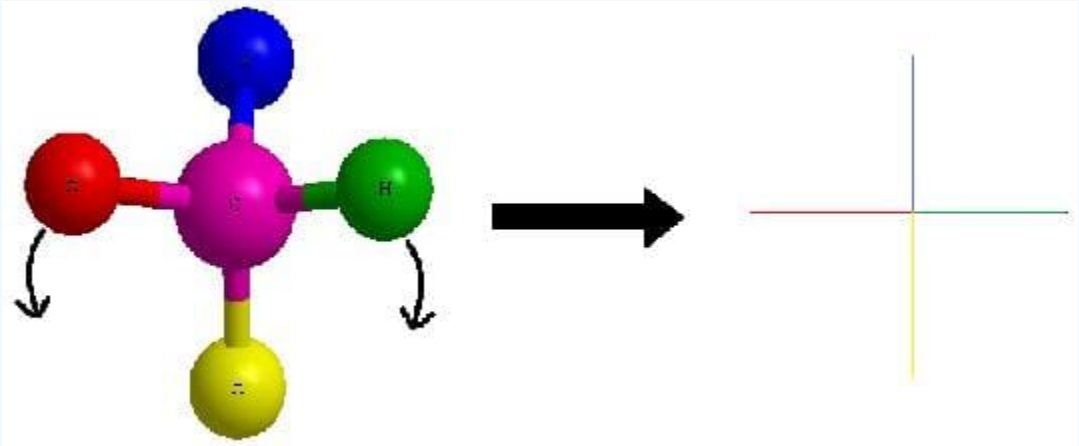


Figure C Figure D

Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.

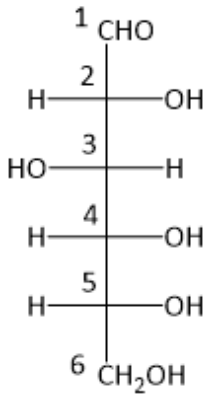


As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

Exercises

Exercise 25.2.1

Determine if carbon #2 in D-glucose is R or S.

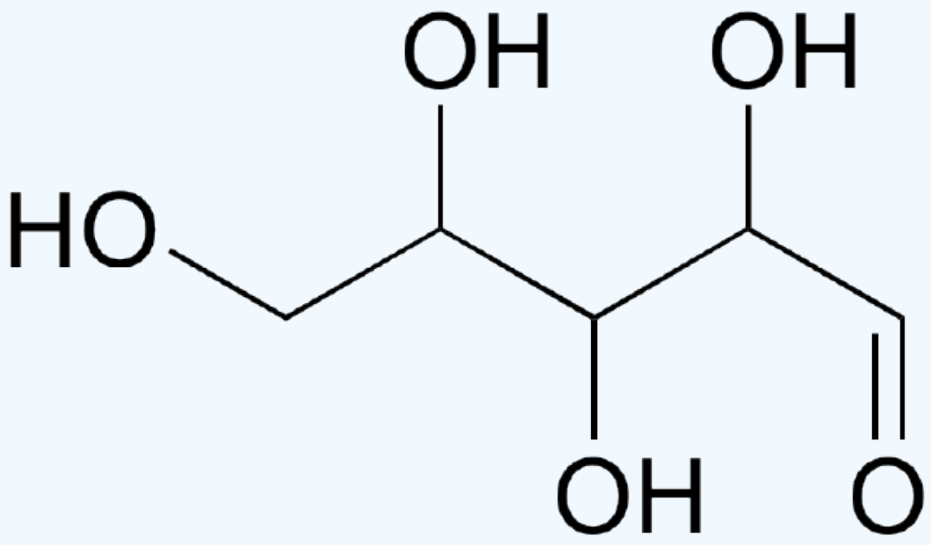


D-Glucose

Answer available at the end of this section.

Exercise 25.2.2

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer available at the end of this section.

Contributors and Attributions

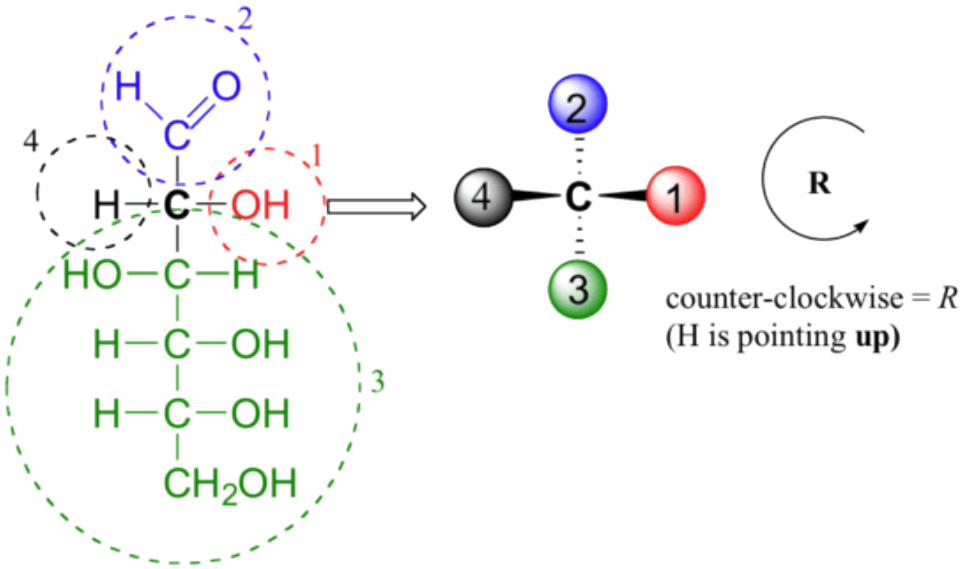
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

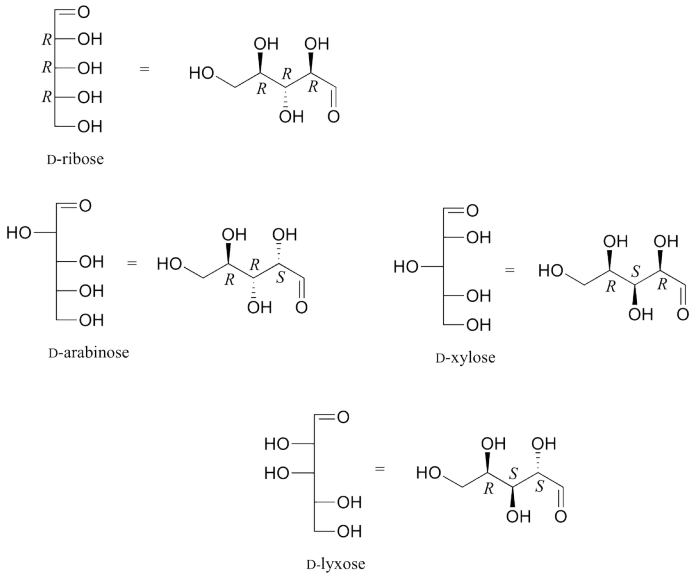
Answers

Exercise 25.2.1

When deciding whether a stereocenter in a Fischer projection is *R* or S, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means S. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



Exercise 25.2.2



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5.5: Molecules Incorporating Several Stereocenters: Diastereomers

Objectives

After completing this section, you should be able to

1. calculate the maximum number of stereoisomers possible for a compound containing a specified number of chiral carbon atoms.
2. draw wedge-and-broken-line structures for all possible stereoisomers of a compound containing two chiral carbon atoms, with or without the aid of molecular models.
3. assign (*R*)/(S) configurations to wedge-and-broken-line structures containing two chiral carbon atoms, with or without the aid of molecular models.
4. determine, with or without the aid of molecular models, whether two wedge-and-broken-line structures containing two chiral carbon atoms are identical, represent a pair of enantiomers, or represent a pair of diastereomers.
5. draw the wedge-and-broken-line structure of a specific stereoisomer of a compound containing two chiral carbon atoms, given its IUPAC name and (*R*)/(S) configuration.

Key Terms

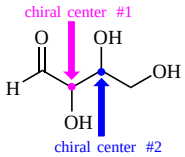
Make certain that you can define, and use in context, the key term below.

- diastereomer

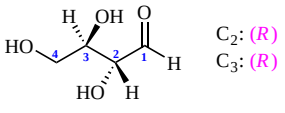
Diastereomers are two molecules which are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers. Unlike enantiomers which **are mirror images** of each other and **non-superimposable**, diastereomers are **not mirror images** of each other and **non-superimposable**. Diastereomers can have different physical properties and reactivity. They have different melting points and boiling points and different densities. In order for diastereomer stereoisomers to occur, a compound must have **two or more** stereocenters.

Introduction

So far, we have been analyzing compounds with a single chiral center. Next, we turn our attention to those which have multiple chiral centers. We'll start with some stereoisomeric four-carbon sugars with two chiral centers.



We will start with a common four-carbon sugar called D-erythrose.

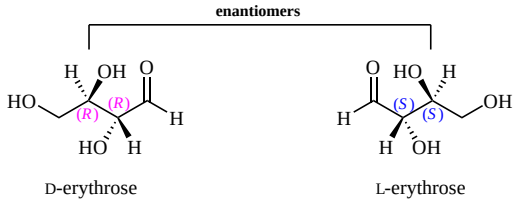


D-erythrose

A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry

class. We will use the *D/L* designations here to refer to different sugars, but we won't worry about learning the system.

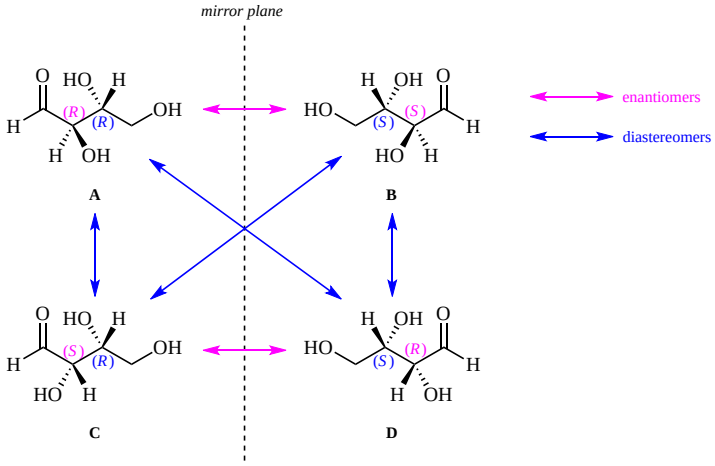
As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the (*R*) configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose have an enantiomer? Of course it does – if it is a chiral molecule, it must. The enantiomer of erythrose is its mirror image, and is named L-erythrose (once again, you should use models to convince yourself that these mirror images of erythrose are not superimposable).



Notice that both chiral centers in L-erythrose both have the (S) configuration. To avoid confusion, we will simply refer to the different stereoisomers by capital letters.

Now let's consider all the possible stereoisomers.

Look first at compound A below. Both chiral centers in have the (*R*) configuration (you should confirm this for yourself!). The mirror image of Compound A is compound B, which has the (S) configuration at both chiral centers. If we were to pick up compound A, flip it over and put it next to compound B, we would see that they are *not* superimposable (again, confirm this for yourself with your models!). A and B are nonsuperimposable mirror images: in other words, enantiomers.



Now, look at compound C, in which the configuration is (S) at chiral center 1 and (*R*) at chiral center 2. Compounds A and C are stereoisomers: they have the same molecular formula and the same bond connectivity, but a different arrangement of atoms in space (recall that this is the definition of the term 'stereoisomer). However, they are *not* mirror images of each other (confirm this with your models!), and so they are *not* enantiomers. By definition, they are **diastereomers** of each other.

Notice that compounds C and B also have a diastereomeric relationship, by the same definition.

So, compounds A and B are a pair of enantiomers, and compound C is a diastereomer of both of them. Does compound C have its own enantiomer? Compound D is the mirror image of compound C, and the two are not superimposable. Therefore, C and D are a pair of enantiomers. Compound D is also a diastereomer of compounds A and B.

This can also seem very confusing at first, but there some simple shortcuts to analyzing stereoisomers:

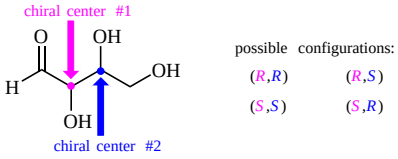
Stereoisomer Shortcuts

If ***all*** of the chiral centers are of opposite (*R*)/(S) configuration between two stereoisomers, they are enantiomers.

If ***at least one, but not all*** of the chiral centers are opposite between two stereoisomers, they are diastereomers.

> These shortcuts to not take into account the possibility of additional stereoisomers due to alkene groups: we will come to that later

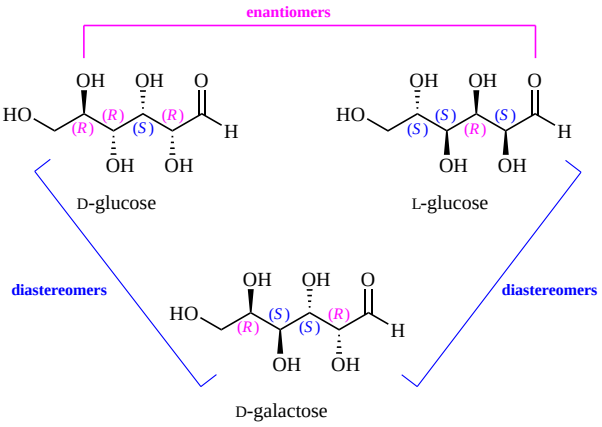
Here's another way of looking at the four stereoisomers, where one chiral center is associated with red and the other blue. Pairs of enantiomers are stacked together.



We know, using the shortcut above, that the enantiomer of (*R*,*R*) must be (*S*,*S*) - both chiral centers are different. We also know that (*R*,*S*) and (*S*,*R*) are diastereomers of (*R*,*R*), because in each case one - but not both - chiral centers are different.

Determining the Maximum Number of Stereoisomers for a Compound

In general, a structure with *n* stereocenters will have a maximum of 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can exist in either an open-chain or a cyclic form). There are two enantiomers of glucose, called D-glucose and L-glucose. The D-enantiomer is the common sugar that our bodies use for energy. It has $n = 4$ stereocenters, so therefore there are $2^n = 2^4 = 16$ possible stereoisomers (including D-glucose itself).



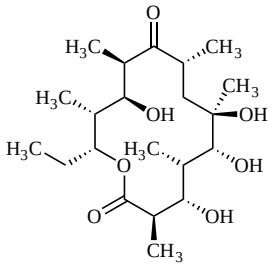
In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown above: in D-galactose, one of four stereocenters is inverted relative to D-glucose. Diastereomers which differ in only one stereocenter (out of two or more) are called **epimers**. D-glucose and D-galactose can therefore be refered to as epimers as well as diastereomers.

Example 5.5.1

- Draw the structure of L-galactose, the enantiomer of D-galactose.
- Draw the structure of two more diastereomers of D-glucose. One should be an epimer.

Answer available at the end of this section.

Erythronolide B, a precursor to the 'macrocyclic' antibiotic erythromycin, has 10 stereocenters. It's enantiomer is that molecule in which all 10 stereocenters are inverted.



erythronolide B

In total, there are 2^{10} = 1024 stereoisomers in the erythronolide B family: 1022 of these are diastereomers of the structure above, one is the enantiomer of the structure above, and the last ***is*** the structure above.

We know that enantiomers have identical physical properties and equal but opposite degrees of specific rotation. Diastereomers, in theory at least, have different physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that it is very difficult to separate them. In addition, the specific rotations of diastereomers are unrelated – they could be the same sign or opposite signs, and similar in magnitude or very dissimilar.

Exercise 5.5.1

Determine the number of stereoisomers a molecule can have with...

a. 3 chiral centers
b. 1 chiral center
c. 6 chiral centers

Answer available at the end of this section.

Exercise 5.5.2*a*

What is the relationship between enantiomers?

Answer available at the end of this section.

Exercise 5.5.2*b*

How does the stereochemistry in diastereomers differ from each other?

Answer available at the end of this section.

Exercise 5.5.2*c*

What are epimers?

Answer available at the end of this section.

Exercise 5.5.3a

Draw the structure of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

Exercise 5.5.3b

Draw both diastereomers of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

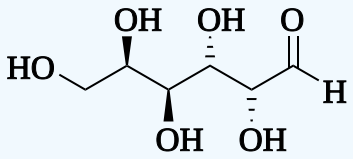
Exercise 5.5.3c

Draw the enantiomer of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

Exercise 5.5.4a

Draw the structure of L-galactose, the enantiomer of D-galactose.



S, R, R, S

D-galactose

Answer available at the end of this section.

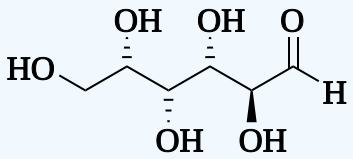
Exercise 5.5.4b

Draw a diastereomer of D-galactose that is an epimer.

Answer available at the end of this section.

Exercise 5.5.4c

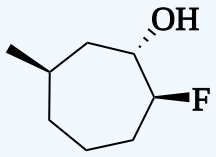
Identify if the following diastereomer of galactose is an epimer of D- galactose or L- galactose.



Answer available at the end of this section.

Exercise 5.5.5a

For the compound shown below, label each chiral center as R or S.



Answer available at the end of this section.

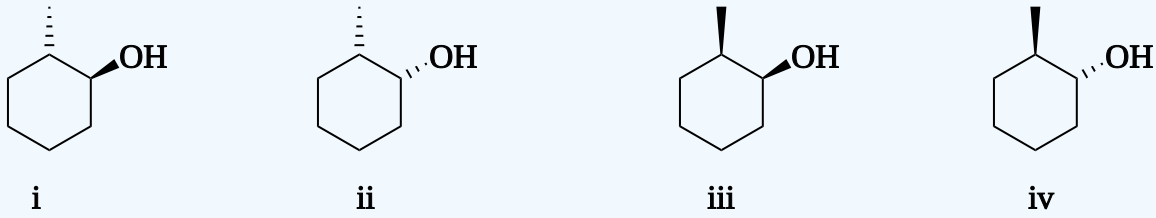
Exercise 5.5.5b

How many stereoisomers are possible for the compound in part a)?

Answer available at the end of this section.

Exercise 5.5.6

Consider the stereoisomers below.



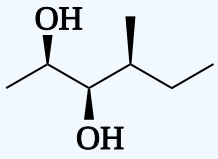
i ii iii iv

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of ii?
c. Which is/are an epimer of i?

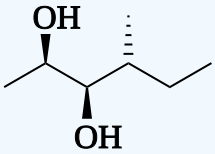
Answer available at the end of this section.

Exercise 5.5.7

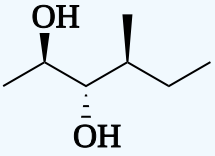
Consider the 8 stereoisomers below.



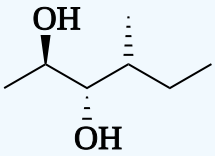
i



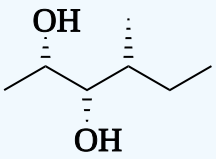
ii



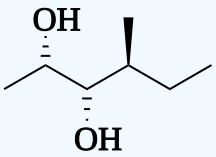
iii



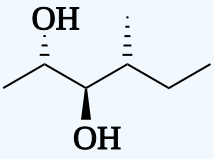
iv



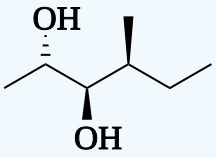
v



vi



vii



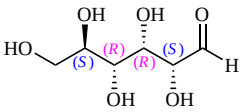
viii

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of i?
c. Which is/are an epimer of i?

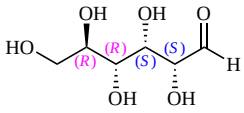
Answer available at the end of this section.

Answers

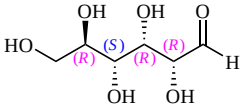
Example 5.5.1



L-galactose



L-mannose
(epimer of D-glucose)



L-gulose
(diasteromer of D-glucose)

Exercise 5.5.1

Since a molecule with n chiral centers can have 2^n stereoisomers...

a. 2^3 = 8 possible stereoisomers
b. 2^1 = 2 possible stereoisomers
c. 2^6 = 64 possible stereoisomers

Exercise 5.5.2*a*

They are mirror images of each other and when 2 or more chiral centers are present, every stereocenter is the opposite in its enantiomer.

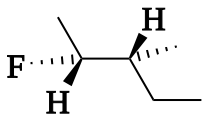
Exercise 5.5.2*b*

In diastereomers, one or more of the chiral centers is the opposite but they all can't be the opposite or else they'd be enantiomers.

Exercise 5.5.2*c*

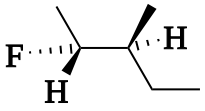
Epimers are when **only one** chiral center is the opposite (in molecules with 2 or more chiral centers) in its diastereomer.

Exercise 5.5.3*a*

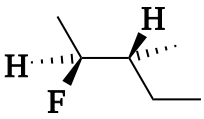


2R,3R

Exercise 5.5.3*b*

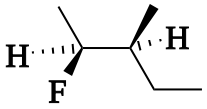


2R,3S



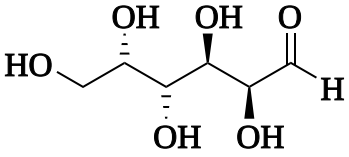
2S,3R

Exercise 5.5.3*c*



2S,3S

Exercise 5.5.4*a*

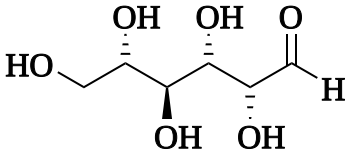


S, *R*, *R*, *S*

L-galactose

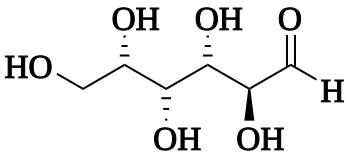
Exercise 5.5.4*b*

You can draw an epimer by drawing D-galactose with 1 (and only 1) of its chiral centers reversed. Here's an example when you switch only the first chiral center (in red). (There are 3 other epimers that could be drawn as long as you only swap a single chiral center in the diastereomer that you use.)



R, *R*, *R*, *S*

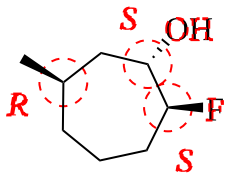
Exercise 5.5.4*c*



S, *R*, *S*, *S*

Since the diastereomer above only varies from L-galactose by 1 chiral center, the above is an epimer in relationship to L-galactose. Since it varies from D-galactose by 3 chiral centers, it is not an epimer but a diastereomer. Since not all of the chiral centers are swapped, it is not an enantiomer!

Exercise 5.5.5*a*



Exercise 5.5.5*b*

Since there are 3 chiral centers, 2^3 = 8 possible stereoisomers.

Exercise 5.5.6

a. iv is an enantiomer of i since both chiral centers are switched and they are non superimposable mirror images.
b. i & iv are diastereomers of ii since they are stereoisomers that are not mirror images.
c. ii and iii are epimers of i since they are diastereomers with only 1 chiral center switched and the other one the same.

Exercise 5.5.7

a. v is an enantiomer since all three chiral centers are switched and they are non superimposable mirror images.
b. ii, iii, iv, vi, vii & viii are diastereomers of i since they are stereoisomers that are not mirror images.
c. ii,iii & viii are epimers of i since they are diastereomers with only 1 chiral center switched and the other chiral centers the same.

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5.6: Meso Compounds

Objectives

After completing this section, you should be able to

1. determine whether or not a compound containing two chiral carbon atoms will have a meso form, given its Kekulé, condensed or shorthand structure, or its IUPAC name.
2. draw wedge-and-broken-line structures for the enantiomers and meso form of a compound such as tartaric acid, given its IUPAC name, or its Kekulé, condensed or shorthand structure.
3. make a general comparison of the physical properties of the enantiomers, meso form and racemic mixture of a compound such as tartaric acid.

Key Terms

Make certain that you can define, and use in context, the key term below.

- meso compound

Study Notes

You may be confused by the two sets of structures showing “rotations.” Of course in each case the two structures shown are identical, they represent the same molecule looked at from two different perspectives. In the first case, there is a 120° rotation around the single carbon-carbon bond. In the second, the whole molecule is rotated 180° top to bottom.

Introduction

A meso compound is an achiral compound that has chiral centers. A meso compound contains an internal plane of symmetry which makes it superimposable on its mirror image and is optically **inactive** although it contains two or more stereocenters. Remember, an internal plane of symmetry was shown to make a molecule achiral in **Section 5.2**.

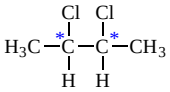
In general, a meso compound should contain two or more identical substituted stereocenters. Also, it has an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of reflected stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other, and therefore, resulting the molecule being **optically inactive**.

Identification

A meso compound must have:

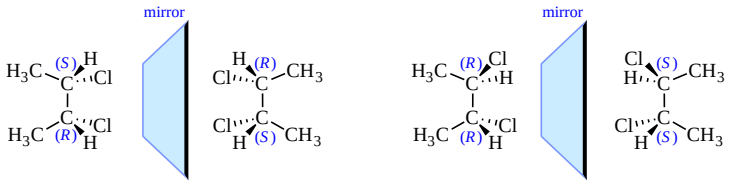
1. Two or more stereocenters.
2. An internal plane of symmetry, or internal mirror, that lies in the compound.
3. Stereochemistry that cancels out. This means reflected stereocenter should have the same substituents and be inverted. For instance, in a meso compound with two stereocenters one should be R and the other S.

The compounds 2,3-dichlorobutane contains two chiral carbons and therefore would be expected to provide 2^2 = 4 different stereoisomers. These stereoisomers should be made up of two pairs of enantiomers.



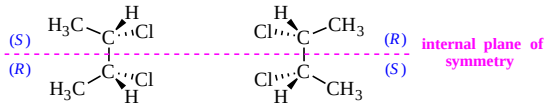
2,3-dichlorobutane

After drawing out all the possible stereoisomers of 2,3-dichlorobutane, the pair on the right in the figure below are mirror images. Also, they are non-superimposable because they have distinctly different conformation (R,R & S,S). This makes the pair enantiomers of each other. However, the pair on the left represent a meso compound, they both are identical despite being mirror images.



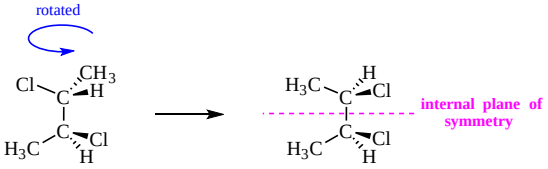
identical (meso) **enantiomers**

Upon further investigation, the meso compound has an internal plane of symmetry which is not present in the pair of enantiomers. The plane of symmetry in the meso compound comes about because there are two chiral carbons present, both chiral carbons are identically substituted (Cl, H, CH_3), and one chiral carbon is R and the other is S. Despite being represented as mirror images, both structures represent the same compound. This is best proven by making molecular models of both representations and then superimposing them. Overall, 2,3-dichlorobutane only has three possible stereosiomers, the pair of enantiomers and the meso compound.



identical (meso)

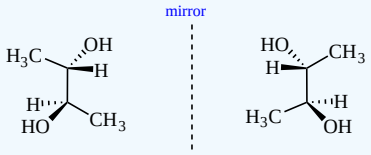
When looking for an internal plane of symmetry, it is important to remember that sigma bonds (single bonds) can rotate. Just because the immediate representation of a molecule does not have a plane of symmetry does not mean that one cannot be obtained through rotation. Often the substituents attached to a stereocenter need to be rotated to recognize the internal plane of symmetry. As the stereocenter is rotated, its configuration does not change. Building a molecular model when considering a possible meso compound is an invaluable tool because it allows for easy rotation of chiral carbons. An example of how rotation of a chiral carbon can reveal an internal plane of symmetry is shown below.



meso compound

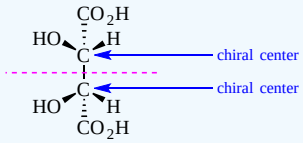
Example 5.6.1

Below are the two mirror images of (meso)-2,3-Butanediol. Because it is a meso compound, the two structures are identical. Show that both mirror images can be obtained by simply rotating the three-dimensional structure provided below.



(meso)-2,3-butanediol

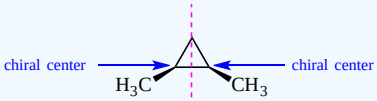
Example 5.6.2



1

1 has a plane of symmetry (the horizontal plane going through the red broken line) and, therefore, is achiral; 1 has chiral centers. Thus, 1 is a meso compound.

Example 5.6.3

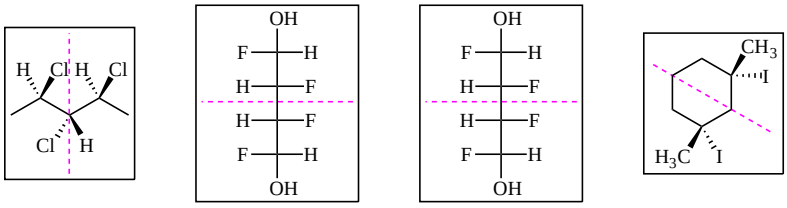


2

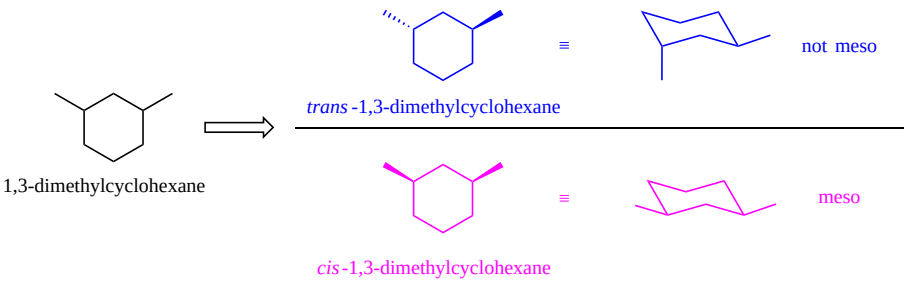
This molecules has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has has two chiral centers. Thus, its is a meso compound.

Other Examples of Meso Compounds

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cycloalkanes. Although two chiral carbons must be present, meso compounds can have many more. Notice that in every case a plane of symmetry is present.

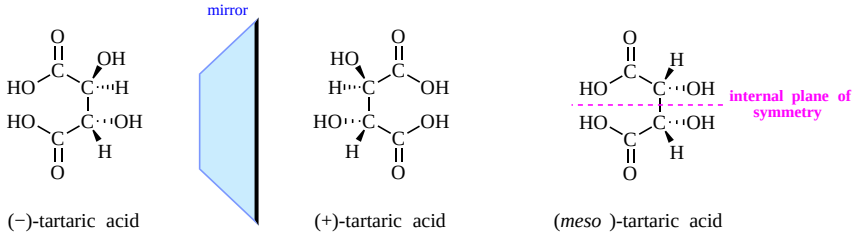


In general, a disubstituted cycloalkane is meso if the two substituents are the same and they are in a *cis* conformation. *Trans* disubstituted cycloalkanes are not meso regardless if the two substituents are the same.



Optical Activity Analysis of a Meso Compound

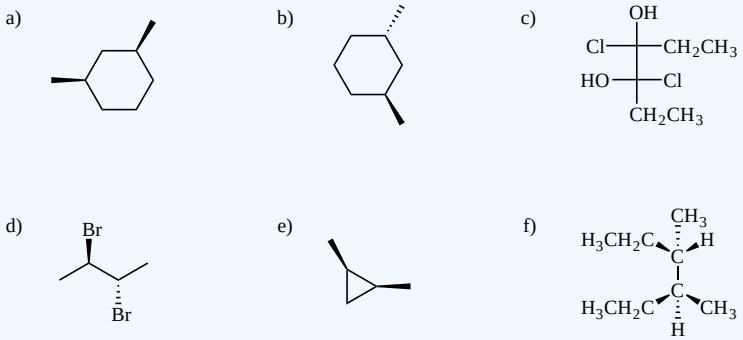
When the optical activity of a meso compound is attempted to be determined with a polarimeter, the indicator will not show (+) or (-). It simply means there is no certain direction of rotation of the polarized light, neither levorotatory (-) and dexorotatory (+) because a meso compound is achiral (optically inactive). Investigations of isomeric tartaric acid (2,3-dihydroxybutanedioic acid), carried out by Louis Pasteur in the mid 19th century, were instrumental in elucidating some of the subtleties of stereochemistry. Tartaric acid, has two chiral but only three stereoisomers. Two of these stereoisomers are enantiomers and the third is an achiral a **meso** compound. Some physical properties of these stereoisomers of tartaric acid are given in the table below. Notice that the enantiomers have the same amount of optical rotation but in different directons. Meso-tartaric acid produces no optical rotation because it is achiral and not optically active. Meso-tartaric acid is actually a diastereomer of both (-) and (+)-tartaric acid, which gives it a distinctly different melting point.



(+)-tartaric acid:	$[\alpha]_D$ = +13°	m.p. 172 °C
(–)-tartaric acid:	$[\alpha]_D$ = –13°	m.p. 172 °C
meso-tartaric acid:	$[\alpha]_D$ = 0°	m.p. 140 °C

Exercise 5.6.1

1) Determine which of the following molecules are meso.



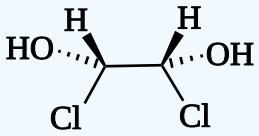
2) Explain why 2,3-dibromobutane has the possibility of being a meso compound while 2,3-dibromopentane does not.

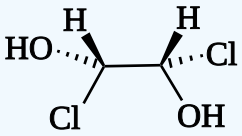
3) Observe the following compound and determine if it is a meso compound. If so indicate the plane of symmetry. Red = oxygen. Remember sigma bonds are able to rotate.

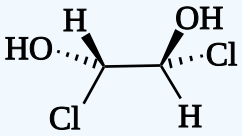
Answer available at the end of this section.

Exercise 5.6.1

Which of the following are meso compounds?

a) 

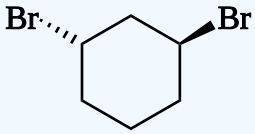
b) 

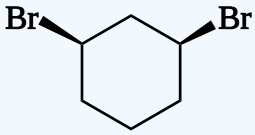
c) 

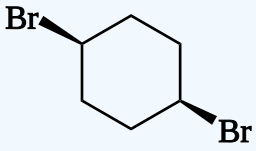
Answer available at the end of this section.

Exercise 5.6.2

Which of the following are meso compounds?

a) 

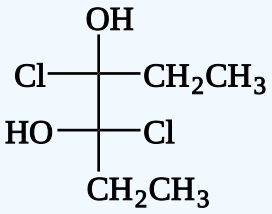
b) 

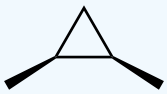
c) 

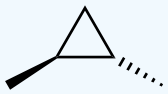
Answer available at the end of this section.

Exercise 5.6.3

Which of the following are meso compounds?

a) 

b) 

c) 

Answer available at the end of this section.

Exercise 5.6.4

Determine (and draw) if any of the forms of 3,4-dichlorohexane are a meso compound.

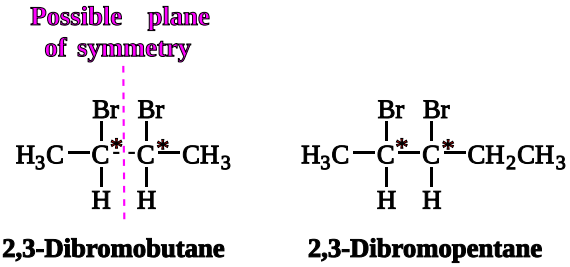
Answer available at the end of this section.

Answers

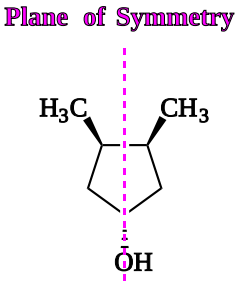
Exercise 5.6.1

1) A C, D, E are meso compounds.

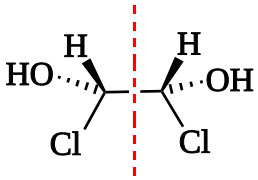
2) One of the requirements of a meso compound is that the reflected chiral carbons have the same substituents. The compound 2,3-dibromobutane, fulfills this requirement (Br, H, CH_3) and can possibly be a meso compound if the two chiral carbons have the appropriate configuration (R & S). The substituents of the two chiral carbons in 2,3-dibromopentane do not have the same substituents (Br, H, CH_3 vs. Br, H, CH_2CH_3). This 2,3-dibromopentane cannot form a meso compound regardless of the configurations of its chiral carbons.



3) The compound is meso.

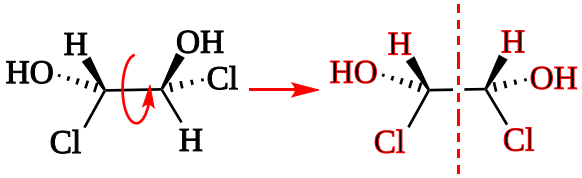


a) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) between the C's (and it has stereochemistry of S & *R*).



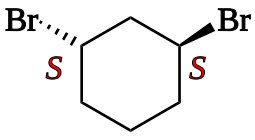
b) This is not a meso compound. No matter how you rotate the C-C bond, you do not see a plane of symmetry (and its stereochemistry is S & S)

c) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) that can be seen when you rotate the C-C bond (and it has stereochemistry of S & *R*).

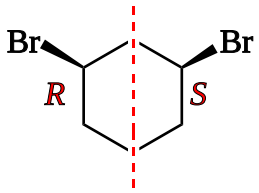


Exercise 5.6.2

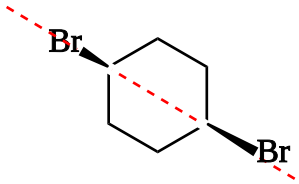
a) This is not a meso compound. There is no plane of symmetry and has stereochemistry of S & S.



b) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) and it has stereochemistry of *R* & S.

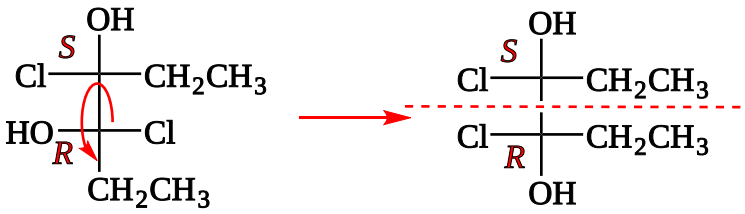


c) This is not a meso compound (even though it has planes of symmetry). The plane of symmetry shown in red makes it so that both chiral centers have symmetrical groups (the ring) and thus the compound is not chiral (so it can't be a meso compound).

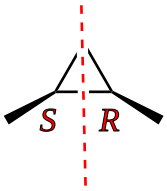


Exercise 5.6.3

a) This is a meso compound. If you rotate between the C-C bond, you can see that it has a mirror plane between the C's (shown in red on the structure to the right). Notice how rotating a C-C bond doesn't change the stereochemistry of the molecule (S & *R*).



b) This is a meso compound. You can see the plane of symmetry in red and the compound has stereochemistry of S & *R*.

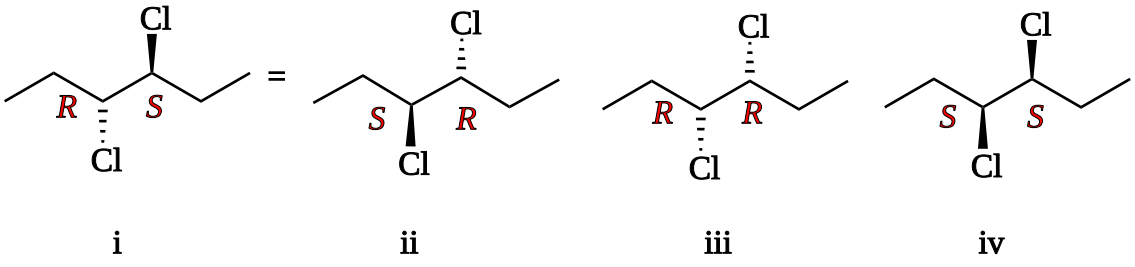


c) This is not a meso compound. There is no plane of symmetry and it has stereochemistry of S & S.



Exercise 5.6.4

Looking at the 4 different possibilities below, i & ii are equivalent structures (with R & S stereochemistry) so it is a meso compound. iii & iv are not meso compounds but are enantiomers to each other.



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5.7: Stereochemistry in Chemical Reactions

Objectives

After completing this section, you should be able to

1. identify a compound as being prochiral.
2. identify the *Re* and *Si* faces of prochiral sp^2 centre.
3. identify atoms (or groups of atoms) as *pro-R* or *pro-S* on a prochiral sp^3 centre.

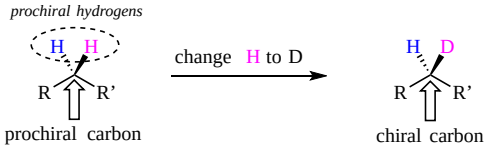
Key Terms

Make certain that you can define, and use in context, the key terms below.

- prochiral
- *pro-R*
- *pro-S*
- *Re*
- *Si*

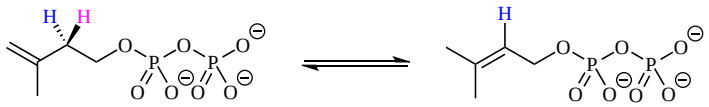
Prochiral Carbons

When a tetrahedral carbon can be converted to a chiral center by changing only one of the attached groups, it is referred to as a '**prochiral'** carbon. The two hydrogens on the prochiral carbon can be described as 'prochiral hydrogens'.

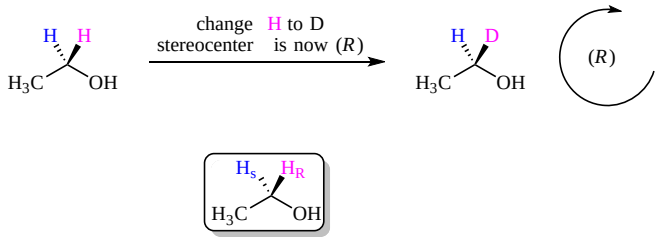


Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the ^{2}H isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

Prochirality is an important concept in biological chemistry, because enzymes can distinguish between the two 'identical' groups bound to a prochiral carbon center due to the fact that *they occupy different regions in three-dimensional space*. Consider the isomerization reaction below, which is part of the biosynthesis of isoprenoid compounds. We do not need to understand the reaction itself (it will be covered in chapter 14); all we need to recognize at this point is that the isomerase enzyme is able to distinguish between the prochiral 'red' and the 'blue' hydrogens on the isopentenyl diphosphate (IPP) substrate. In the course of the left to right reaction, IPP specifically loses the 'red' hydrogen and keeps the 'blue' one.

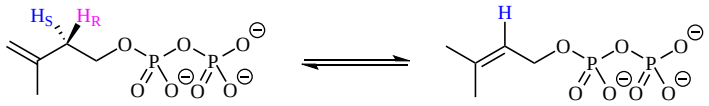


Prochiral hydrogens can be unambiguously designated using a variation on the *R/S* system for labeling chiral centers. For the sake of clarity, we'll look at a very simple molecule, ethanol, to explain this system. To name the 'red' and 'blue' prochiral hydrogens on ethanol, we need to engage in a thought experiment. If we, in our imagination, were to arbitrarily change red H to a deuterium, the molecule would now be chiral and the chiral carbon would have the *R* configuration (D has a higher priority than H).



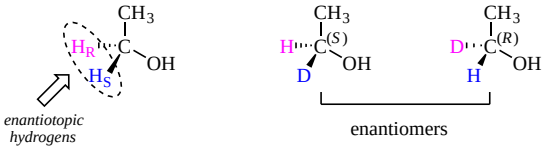
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it H_R. Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be S, so we can refer to blue H as the *pro*-S hydrogen of ethanol, and label it H_S.

Looking back at our isoprenoid biosynthesis example, we see that it is specifically the *pro-R* hydrogen that the isopentenyl diphosphate substrate loses in the reaction.



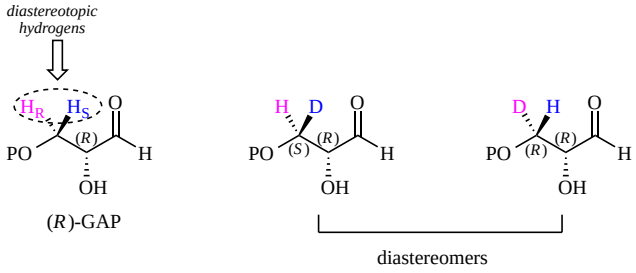
isopentenyl diphosphate dimethylallyl diphosphate

Prochiral hydrogens can be designated either enantiotopic or diastereotopic. If either H_R or H_S on ethanol were replaced by a deuterium, the two resulting isomers would be enantiomers (because there are no other stereocenters anywhere on the molecule).



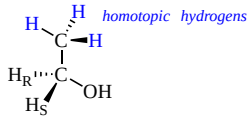
Thus, these two hydrogens are referred to as **enantiotopic**.

In (*R*)-glyceraldehyde-3-phosphate ((*R*)-GAP), however, we see something different:



R)-GAP already has one chiral center. If either of the prochiral hydrogens H_R or H_S is replaced by a deuterium, a second chiral center is created, and the two resulting molecules will be diastereomers (one is *S,R,* one is *R,R*). Thus, in this molecule, H_R and H_S are referred to as **diastereotopic** hydrogens.

Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl (CH_3) group of ethanol (and on *any* methyl group) are homotopic. An enzyme cannot distinguish among homotopic hydrogens.



Example 5.7.1

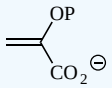
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as H_R or H_S.

a)



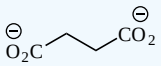
dihydroorotate
(a nucleotide biosynthesis intermediate)

b)



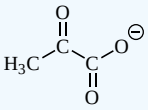
phosphoenolpyruvate
(a glycolysis intermediate)

c)



succinate
(a citric acid cycle intermediate)

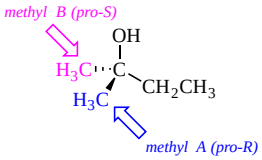
d)



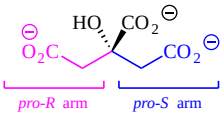
pyruvate
(endpoint of glycolysis)

Answer available at the end of this section.

Groups other than hydrogens can be considered prochiral. The alcohol below has two prochiral methyl groups - the red one is *pro-R*, the blue is *pro-S*. How do we make these designations? Simple - just arbitrarily assign the red methyl a higher priority than the blue, and the compound now has the *R* configuration - therefore red methyl is *pro-R*.

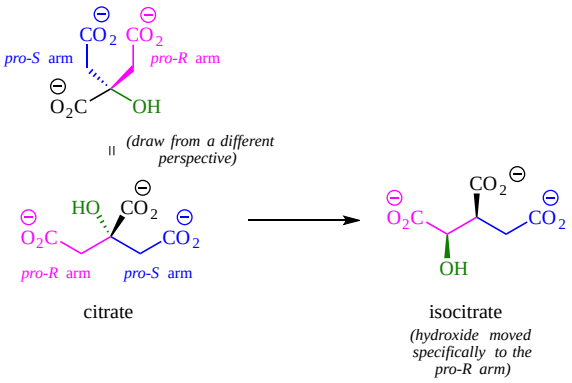


Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro-S*.



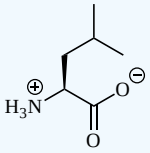
citrate

In an isomerization reaction of the citric acid (Krebs) cycle, a hydroxide is shifted specifically to the *pro-R* arm of citrate to form isocitrate: again, the enzyme catalyzing the reaction distinguishes between the two prochiral arms of the substrate (we will study this reaction in chapter 13).



Exercise 5.7.1

Assign *pro-R* and *pro-S* designations to all prochiral groups in the amino acid leucine. (*Hint*: there are two pairs of prochiral groups!). Are these prochiral groups diastereotopic or enantiotopic?

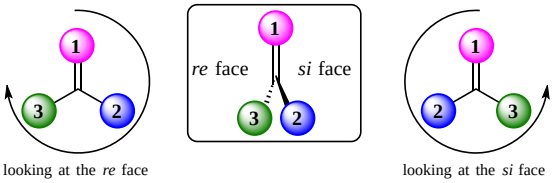


leucine

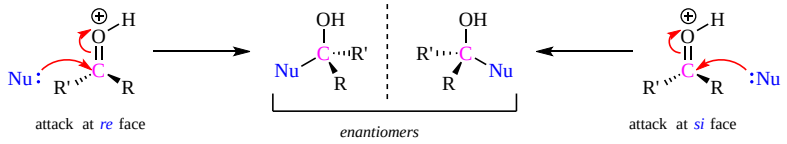
Answer available at the end of this section.

Prochiral Carbonyl and Imine Groups

Trigonal planar, sp^2-hybridized carbons are not, as we well know, chiral centers– but they can be prochiral centers if they are bonded to three different substitutuents. We (and the enzymes that catalyze reactions for which they are substrates) can distinguish between the two planar 'faces' of a prochiral sp^2 - hybridized group. These faces are designated by the terms ***re*** and ***si***. To determine which is the *re* and which is the *si* face of a planar organic group, we simply use the same priority rankings that we are familiar with from the R/S system, and trace a circle: *re* is clockwise and *si* is counterclockwise.

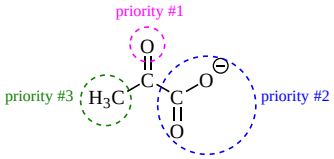


When the two groups adjacent to a carbonyl (C=O) are not the same, we can distinguish between the re and si 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Nucleophilic additions to carbonyls will be covered in greater detail in **Chapter 19**. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.

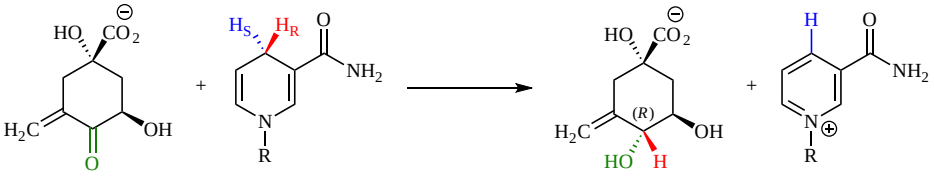


Note: R is higher priority than R'

Below, for example, we are looking down on the *re* face of the ketone group in pyruvate. If we flipped the molecule over, we would be looking at the *si* face of the ketone group. Note that the carboxylate group does not have *re* and *si* faces, because two of the three substituents on that carbon are identical (when the two resonance forms of carboxylate are taken into account).



As we will see in chapter 10, enzymes which catalyze reactions at carbonyl carbons act specifically from one side or the other.

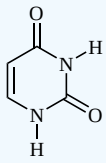


*looking at the **si** face of the ketone*

We need not worry about understanding the details of the reaction pictured above at this point, other than to notice the stereochemistry involved. The *pro-R* hydrogen (along with the two electrons in the C-H bond) is transferred to the *si* face of the ketone (in green), forming, in this particular example, an alcohol with the *R* configuration. If the transfer had taken place at the *re* face of the ketone, the result would have been an alcohol with the *S* configuration.

Exercise 5.7.2

For each of the carbonyl groups in uracil, state whether we are looking at the *re* or the *si* face in the structural drawing below.



uracil

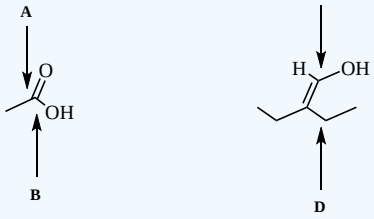
Answer available at the end of this section.

Exercise 5.7.3

a) State which of the following hydrogen atoms are *pro-R* or *pro-S*.



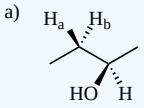
b) Identify which side is Re or Si.

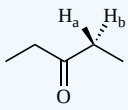


Answer available at the end of this section.

Exercise 5.7.4

State whether the H's indicated below are pro-*R* or pro-*S* for the following structures.

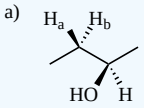
a) 

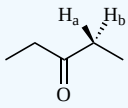
b) 

Answer available at the end of this section.

Exercise 5.7.5

In the structures below, determine if the H's are homotopic, enantiotopic, or diastereotopic.

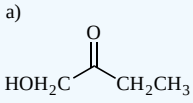
a) 

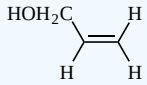
b) 

Answer available at the end of this section.

Exercise 5.7.6

State whether you are looking down at the molecule from the re face or si face.

a) 

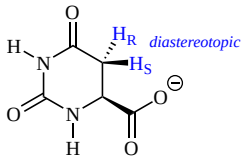
b) 

Answer available at the end of this section.

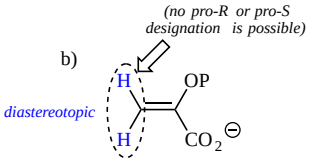
Answers

Example 5.7.1

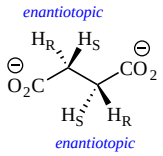
a)



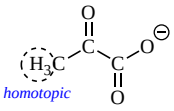
b)



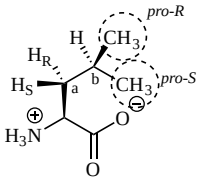
c)



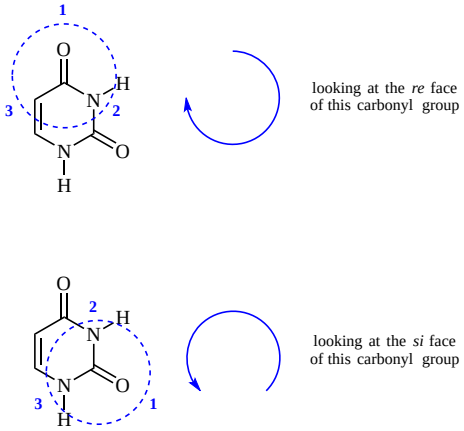
d)



Exercise 5.7.1



Exercise 5.7.2



Exercise 5.7.3

a) Left compound: H_a = *pro*-S and H_b = *pro*-*R*; Right compound: H_a = *pro*-*R* and H_b = *pro*-S

b) A – Re; B – Si; C – Re; D – Si\)

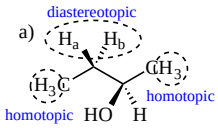
Exercise 5.7.4

Exercise 5.7.5

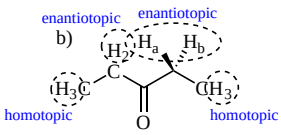
In a), the CH_2 is diastereotopic since there is another chiral center on the molecule. Both CH_3's are homotopic since replacing one of them doesn't create a chiral center.

IN b), the CH_2's are enantiotopic since it would create the only chiral center on the molecule. Both CH_3's are homotopic since replacing one of them doesn't create a chiral center.

a)



b)



Exercise 5.7.6

a. You are looking at the **si face**. The re face would be if you were facing the molecule from the back.
b. You are looking at the **re face**. The si face would be if you were facing the molecule from the back.

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5.8: Resolution: Separation of Enantiomers

Objectives

After completing this section, you should be able to

1. describe a common process for separating a mixture of enantiomers.
2. explain why racemic mixtures do not rotate plane-polarized light.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- racemic mixture (or racemate)
- resolve

Study Notes

A *racemic mixture* is a 50:50 mixture of two enantiomers. Because they are mirror images, each enantiomer rotates plane-polarized light in an equal but opposite direction and is optically inactive. If the enantiomers are separated, the mixture is said to have been *resolved*. A common experiment in the laboratory component of introductory organic chemistry involves the resolution of a racemic mixture.

The dramatic biochemical consequences of chirality are illustrated by the use, in the 1950s, of the drug Thalidomide, a sedative given to pregnant women to relieve morning sickness. It was later realized that while the (+)-form of the molecule, was a safe and effective sedative, the (–)-form was an active teratogen. The drug caused numerous birth abnormalities when taken in the early stages of pregnancy because it contained a mixture of the two forms.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used in this technique are known as 'Moscher's esters', after Harry Stone Moscher, a chemist who pioneered the method at Stanford University.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called **resolution**. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. Reversing the first reaction then leads to the separated enantiomers plus the recovered reagent.

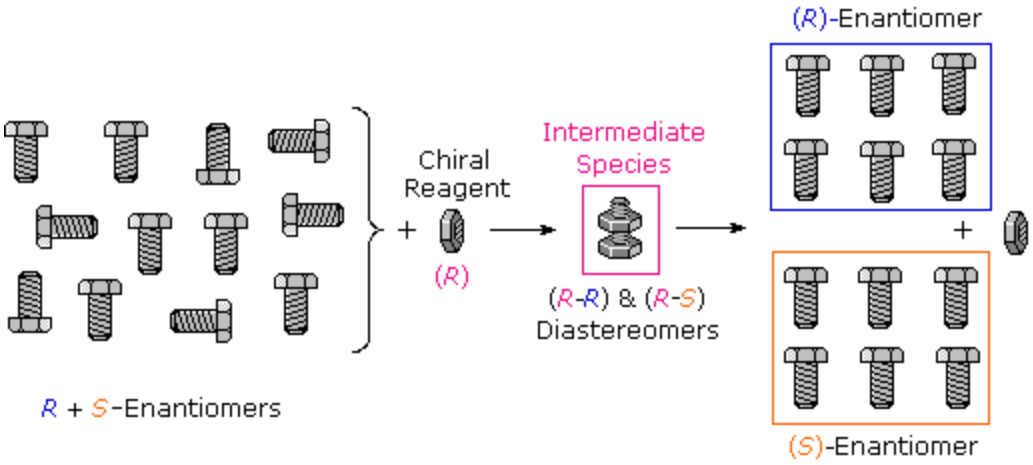


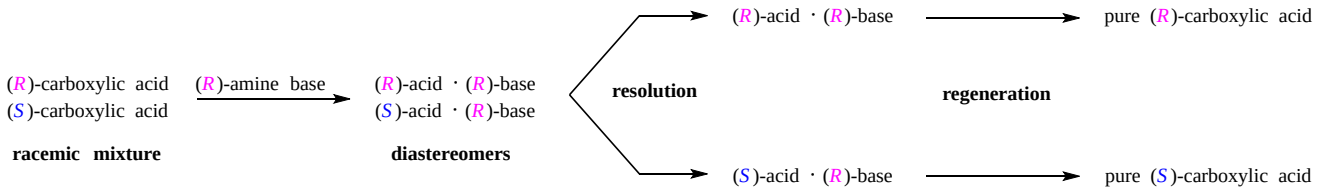
Figure 5.8.1:

Many kinds of chemical and physical reactions, including salt formation, may be used to achieve the diastereomeric intermediates needed for separation. Figure 5.8.1 illustrates this general principle by showing how a nut having a right-handed thread (R) could serve as a "reagent" to discriminate and separate a mixture of right- and left-handed bolts of identical size and weight. Only the two right-handed partners can interact to give a fully-threaded intermediate, so separation is fairly simple. The resolving moiety, i.e. the nut, is then removed, leaving the bolts separated into their right and left-handed forms. Chemical reactions of enantiomers are normally not so dramatically different, but a practical distinction is nevertheless possible.

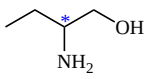
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution of enantiomers are based upon this fact. We include here a discussion of the primary methods of resolution.

Chiral Amines as Resolving Agents and Resolution of Racemic Acids

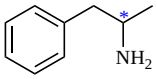
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or (*R*)/(S) mixture of enantiomers of a carboxylic acid and convert this to a salt with a chiral amine base having the (*R*) configuration, the salt will be a mixture of two diastereomers, ((*R*)-acid · (*R*)-base) and ((S)-acid · (*R*)-base). These diastereomeric salts are *not* identical and they are not mirror images. Therefore they will differ to some degree in their physical properties, and a separation by physical methods, such as crystallization, may be possible. If the diastereomeric salts can be completely separated, the carboxylic acid regenerated from each salt will be either exclusively the (*R*) or the (*S*) enantiomer.



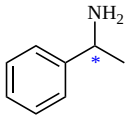
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino-1-butanol, amphetamine, and 1-phenylethanamine, also can be used, but first they must be resolved themselves.



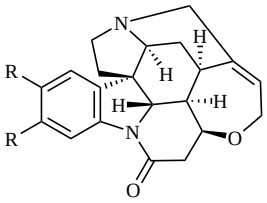
2-amino-1-butanol



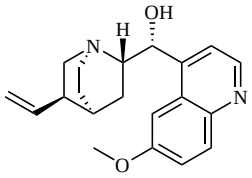
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



R = H,strychnine
R = OCH_3, brucine



quinine
(antimicrobial)
(antimalarial)

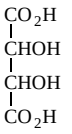
Worked Example 5.8.1

Show how (S)-1-phenylethylamine can be used to resolve a racemic mixture of lactic acid. Please draw all the structures involved.

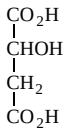
Answer available at the end of this section.

Resolution of Racemic Bases

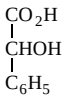
Chiral acids, such as (+)-tartaric acid, (-)-malic acid, (-)-mandelic acid, and (+)-camphor- 10-sulfonic acid, are used for the resolution of a racemic base.



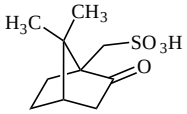
tartaric acid
(2,3-dihydroxy-
butanedioic acid)



malic acid
(2-hydroxybutane-
dioic acid)



mandelic acid
(2-hydroxy-2-
phenylethanoic acid)

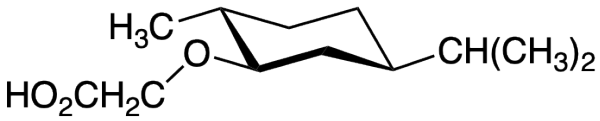


camphor-10-
sulfonic acid

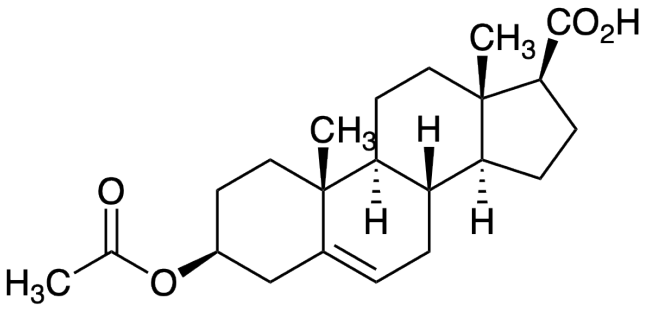
The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind can be tedious, because numerous recrystallizations in different solvents may be necessary to progressively enrich the crystals in the less-soluble diastereomer. To determine when the resolution is complete, the mixture of diastereomers is recrystallized until there is no further change in the measured optical rotation of the crystals. At this stage it is hoped that the crystalline salt is a pure diastereomer from which one pure enantiomer can be recovered. The optical rotation of this enantiomer will be a maximum value if it is "optically" pure because any amount of the other enantiomer could only reduce the magnitude of the measured rotation α.

Resolution of Racemic Alcohols

To resolve a racemic alcohol, a chiral acid can be used to convert the alcohol to a mixture of diastereomeric esters. This is not as generally useful as might be thought because esters tend to be liquids unless they are very high-molecularweight compounds. If the diastereomeric esters are not crystalline, they must be separated by some other method than fractional crystallization (for instance, by chromatography methods, Section 9-2). Two chiral acids that are useful resolving agents for alcohols are:

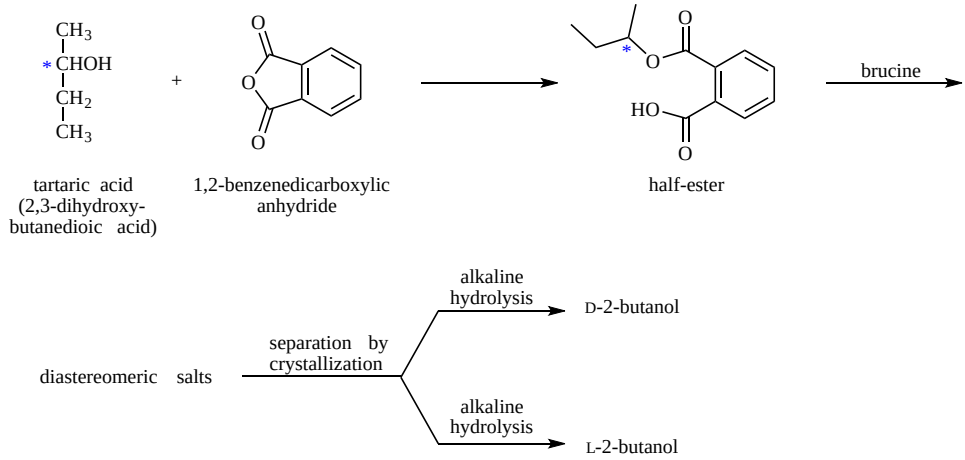


menthoxyethanoic acid



3-β-acetoxy-Δ^5-etienic acid

The most common method of resolving an alcohol is to convert it to a half-ester of a dicarboxylic acid, such as butanedioic (succinic) or 1,2-benzenedicarboxylic (phthalic) acid, with the corresponding anhydride. The resulting half-ester has a free carboxyl function and may then be resolvable with a chiral base, usually brucine:



Other Methods of Resolution

One of the major goals in the field of organic chemistry is the development of reagents with the property of "chiral recognition" such that they can affect a clean separation of enantiomers in one operation without destroying either of the enantiomers. We have not achieved that ideal yet, but it may not be far in the future. Chromatographic methods, whereby the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than the other, have been used to resolve racemic compounds, but such resolutions seldom have led to both pure enantiomers on a preparative scale. Other methods, called kinetic resolutions, are excellent when applicable. The procedure takes advantage of differences in reaction rates of enantiomers with chiral reagents. One enantiomer may react more rapidly, thereby leaving an excess of the other enantiomer behind. For example, racemic tartaric acid can be resolved with the aid of certain penicillin molds that consume the dextrorotatory enantiomer faster than the levorotatory enantiomer. As a result, almost pure (-)-tartaric acid can be recovered from the mixture:

(±)-tartaric acid + mold → (-)-tartaric acid + more mold

The crystallization procedure employed by Pasteur for his classical resolution of (±)-tartaric acid (**Section 5.4**) has been successful only in a very few cases. This procedure depends on the formation of individual crystals of each enantiomer. Thus if the crystallization of sodium ammonium tartrate is carried out below 27", the usual racemate salt does not form; a mixture of crystals of the (+) and (-) salts forms instead. The two different kinds of crystals, which are related as an object to its mirror image, can be separated manually with the aid of a microscope and subsequently may be converted to the tartaric acid enantiomers by strong acid. A variation on this method of resolution is the seeding of a saturated solution of a racemic mixture with crystals of one pure enantiomer in the hope of causing crystallization of just that one enantiomer, thereby leaving the other in solution. Unfortunately, very few practical resolutions have been achieved in this way.

Predicating the Chirality of the Product of a Reaction

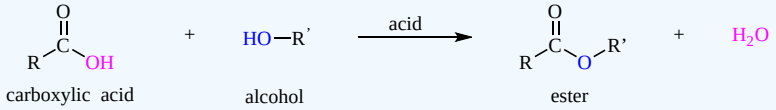
It important to understand the changes in chirality which occur during the formation of product during a reaction. A chiral reaction product, has the possibility of forming multiple stereoisomers which all need to be considered. Changes in chirality, if possible, will be discussed with each individual reaction as this textbook moves forward. Some possible situations which can occur are:

- **A new chiral carbon is formed during a reaction.** This commonly occurs when an sp^2 hybridized carbon in the reactant is converted to sp^3 hybridized chiral carbon in the product. When this occurs, a racemic mixture of the new chiral carbon is formed.
- **A chiral carbon is lost during a reaction.** This commonly occurs when an sp^3 hybridized chiral carbon in the reactant is converted to either a sp^2 or sp hybridized carbon in the product.
- **An enantiomerically pure starting material is converted to a racemic mixture in the product.** This commonly occurs when a sp^3 hybridized chiral carbon is temporarily converted to an sp^2 hybridized carbon during a reaction's mechanism. The chiral carbon is reformed as a racemic mixture.
- **Chiral carbons remain unchanged during a reaction.** If a chiral carbon is not directly involved in a reaction, it will move from a reactant to a product unchanged.

Determining if a chiral carbon is involved in a given reaction is vital for determining which of these four situations is occurring.

Worked Example 5.8.2

The following reaction involves the conversion of a carboxylic acid reacting with an alcohol to form an ester. If a pure sample of (R)-2-methylbutanoic acid is reacted with methanol to form an ester, what would be the stereochemistry of the product?



Answer available at the end of this section.

Exercise 5.8.1

Indicate the reagents you could use to resolve the following compounds. Show the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenyl-2-propanamine.

Answer available at the end of this section.

Exercise 5.8.2

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 2,3-pentadienedioic acid.

Answer available at the end of this section.

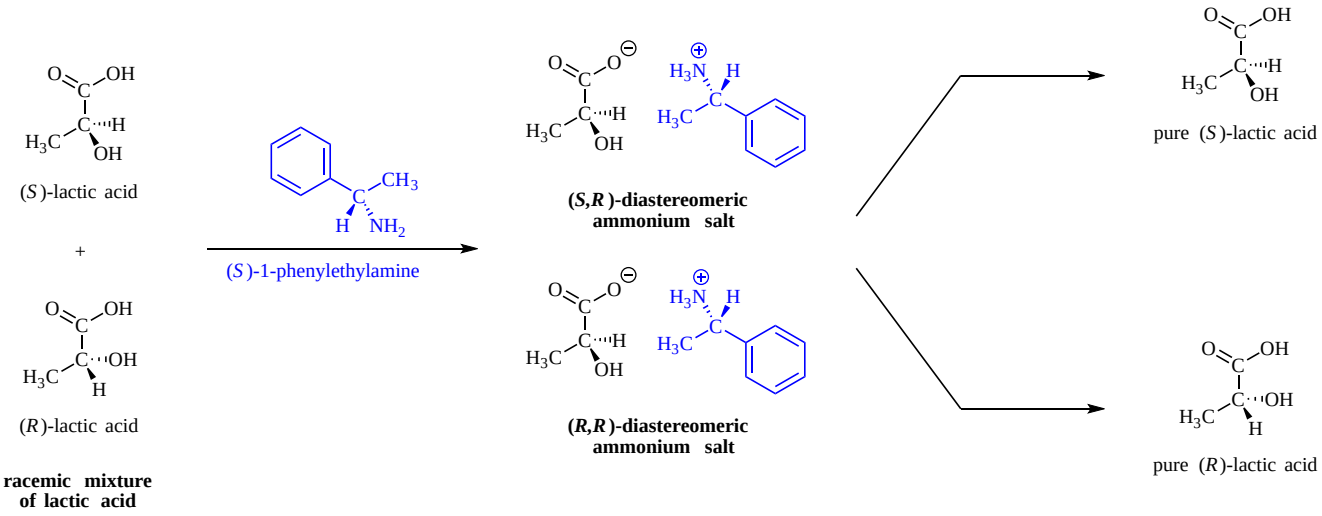
Exercise 5.8.3

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenylethanol.

Answer available at the end of this section.

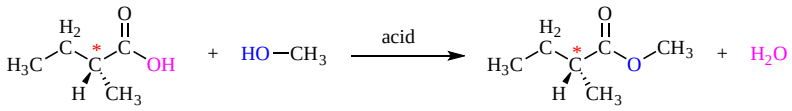
Answers

Worked Example 5.8.1



Worked Example 5.8.2

First it is important to identify the location of the chiral carbon and determine if it is directly involved in the reaction. In this case, the chiral carbon is not involved so the stereochemistry will be carried over into the product unchanged.



Exercise 5.8.1

You could react the 1-phenyl-2-propanamine racemic mixture with a chiral acid such as (+)-tartaric acid (*R*, *R*). The reaction will produce a mixture of diastereomeric salts (i.e. *R*, *R*, *R* and S, *R*, *R*). You can separate the diastereomers through crystallization and treat the salt with a strong base (e.g. KOH) to recover the pure enantiomeric amine.

Exercise 5.8.2

You could react the 2,3-pentadienedioic acid mixture with a chiral base such as (*R*)-1-phenylethylamine. The reaction will produce a mixture of diastereomeric salts.

Separate the diastereomers through crystallization and treat the resulting salt with strong acid (e.g. HCl) to recover the pure enantiomeric acid.

Exercise 5.8.3

You could react the 1-phenylethanol mixture with 1,2-benzenedicarboxylic anhydride. The reaction will produce a mixture of diastereomeric salts. You could then separate the diastereomers through crystallization and then alkaline hydrolysis treatment should recover the pure enantiomeric alcohol.

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5.E: Stereoisomers (Exercises)

5.E: Stereoisomers (Exercises)

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6: BIMOLECULAR NUCLEOPHILIC SUBSTITUTION IN HALOALKANES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy 

6.1: Physical Properties of Haloalkanes
6.2: Nucleophilic Substitution
6.3: Reaction Mechanisms Involving Polar Functional Groups: Using "Electron-Pushing"' Arrows
6.4: A Closer Look at the Nucleophilic Substitution Mechanism: Kinetics
6.5: Frontside or Backside Attack? Stereochemistry of the SN2 Reaction
6.6: Consequences of Inversion in SN2 Reactions
6.7: Structure and \(S_N2\) Reactivity: The Leaving Group
6.8: Structure and SN2 Reactivity: The Nucleophile
6.9: Keys to Success: Choosing Among Multiple Mechanistic Pathways
6.3: Reaction Mechanisms Involving Polar Functional Groups: Using "Electron-Pushing\\"' Arrows
6.10: Structure and SN2 Reactivity: The Substrate
6.11: The Sn2 Reaction at a Glance
6.E: Properties and Reactions of Haloalkanes: Bimolecular Nucleophilic Substitution (Exercises)

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6.1: Physical Properties of Haloalkanes

Objectives

After completing this section, you should be able to

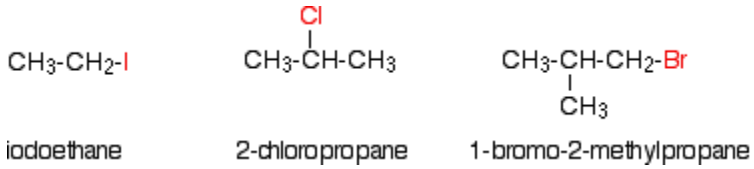
1. write the IUPAC name of a halogenated aliphatic hydrocarbon, given its Kekulé, condensed, or shorthand structure.
2. draw the Kekulé, condensed, or shorthand structure of a halogenated aliphatic hydrocarbon, given its IUPAC name.
3. write the IUPAC name and draw the Kekulé, condensed, or shorthand structure of a simple alkyl halide, given a systematic, non-IUPAC name (e.g., *sec*-butyl iodide).
4. arrange a given series of carbon-halogen bonds in order of increasing or decreasing length and strength.

Study Notes

This section contains little that is new. If you mastered the IUPAC nomenclature of alkanes, you should have little difficulty in naming alkyl halides. Notice that when a group such as CH_2Br must be regarded as a substituent, rather than as part of the main chain, we may use terms such as bromomethyl.

You will find it easier to understand the reactions of the alkyl halides if you keep the polarity of the C-X bond fixed permanently in your mind (see "The Polar C-X Bond" shown in the reading below).

Alkyl halides are also known as haloalkanes. This page explains what they are and discusses their physical properties. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). For example:

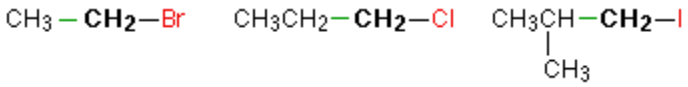


Halide Designations

Alkyl halides fall into different classes depending on how many alkyl groups are attached to the carbon which holds the halogen. There are some chemical differences between the various types. When there are **no** alkyl groups attached to the carbon holding the halogen, these are considered methyl halides (CH_3X).

Primary alkyl halides

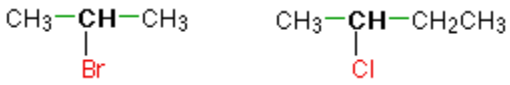
In a primary (1°) haloalkane, the carbon which carries the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

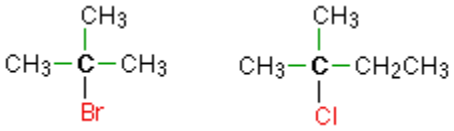
Secondary alkyl halides

In a secondary (2°) haloalkane, the carbon with the halogen attached is joined directly to two other alkyl groups, which may be the same or different. Examples:



Tertiary alkyl halides

In a tertiary (3°) haloalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



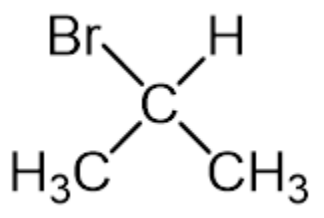
Example 6.1.1

Please indicate if the following haloalkanes are methyl, 1^o, 2^o, or 3^o:

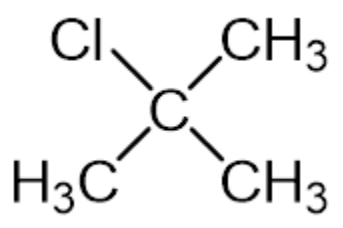
a) CH_3I

b) CH_3CH_2Br

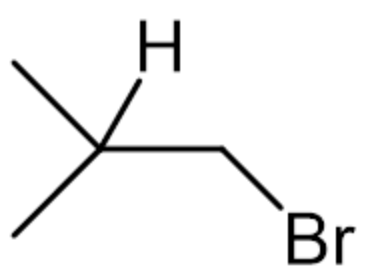
c)



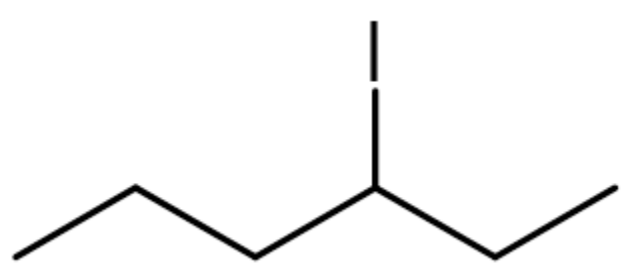
d)



e)



f)



Solution

a) methyl

b) 1^o

c) 2^o

d) 3^o

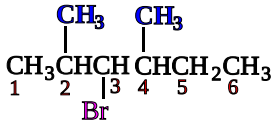
e) 1^o

f) 2^o

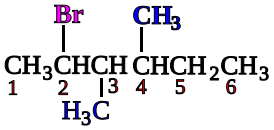
Nomenclature of Alkyl Halides

Alkyl halides are systematically named as alkanes (**Section 3-4**) where the halogen is a substituent on the parent alkane chain. To summarize the rules discussed in detail in **Section 3-4**, there are three basic steps to naming alkyl halides.

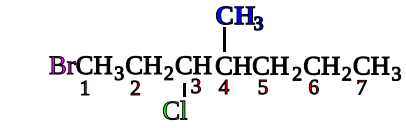
1. Find and name the longest carbon chain and name it as the parent chain. Remember is an alkene or alkyne is present, the parent chain must contain both carbons of the multiple bond.
2. Number the parent chain consecutively, starting at the end nearest a substituent group. Then assign each substituent a number. Remember the IUPAC system uses a prefix to indicate the halogen followed by the suffix -ide. The prefixes are *fluoro-* for fluorine, *chloro-* for chlorine, *bromo-* from bromine, and *iodo-* for iodine. The name of a halogen is preceded by a number indicating the substituent's location on the parent chain.



3-Bromo -2,4-Dimethyl hexane

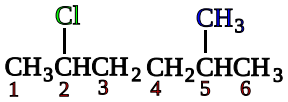


2-Bromo -3,4-Dimethyl hexane



1-Bromo -3-Chloro -4-methyl heptane

3. If there is an ambiguity in numbering the parent chain, begin on the end which is closer to the substituent which comes first alphabetically.

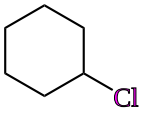


2-Chloro -5-methyl hexane
(Not 5-Chloro-2-methylhexane)

Common Names of Alkyl Halides

Alkyl halides with simple alkyl groups are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names. The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the first syllable of the name of the halogen, with the ending *-ide*. The names of common alkyl groups are listed in **Section 3.3**.





IUPAC Name:	Bromomethane	2-Iodopropane	Chlorocyclohexane
Common Name:	Methyl bromide	Isopropy iodide	Cyclohexyl chloride

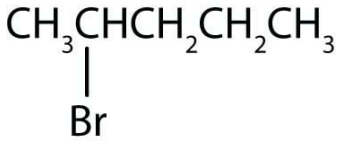
Exercise 6.1.1

1) Give the common and IUPAC names for each compound.

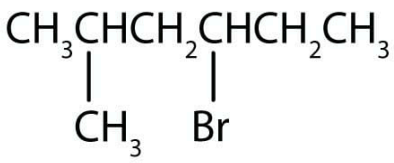
a. $CH_3CH_2CH_2Br$
b. $(CH_3)_2CHCl$
c. CH_3CH_2I
d. $CH_3CH_2CH_2CH_2F$

2) Give the IUPAC name for each compound.

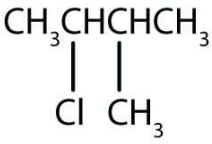
a)



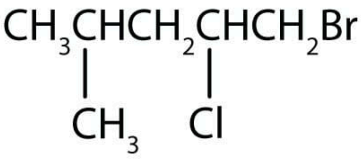
b)



c)



d)



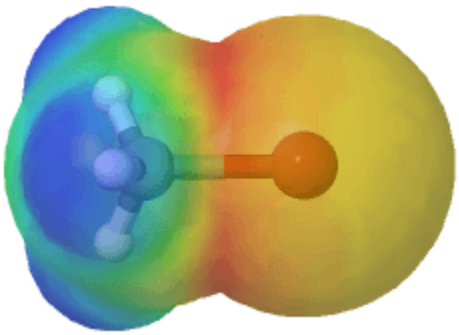
Answer available at the end of this section.

There is a fairly large distinction between the structural and physical properties of haloalkanes and the structural and physical properties of alkanes. As mentioned above, the structural differences are due to the replacement of one or more hydrogens with a halogen atom. The differences in physical properties are a result of factors such as electronegativity, bond length, bond strength, and molecular size.

Halogens and the Character of the Carbon-Halogen Bond

As discussed in Section 6.4, halogens are more electronegative than carbon. This results in a carbon-halogen bond that is polarized with the carbon atom bearing a partial positive charge and the halogen a partial negative charge. This polarity can be distinctly seen when viewing the electrostatic potential map of a methyl halide. Electron density is shown by a red/yellow color which is almost exclusively around the halogen atom. The methyl portion of the compound lacks electron density which is shown by a blue/green color.

The polar C-X bond. The dipole starts at the partially positive carbon and points towards the partially negative halogen.



The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

Electronegativity increases from left to right starting from iodine then bromine to chlorine and finally fluorine.

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases, the bonds get longer, and the strength of those bonds decreases.

Bond length increases from left to right starting from C-F then C-Cl to C-Br and finall C-I. Bond strength increases from left to right starting with C-I then C-Br to C-Cl and finall C-F. Molecular size increases from right to left starting with fluorine then chlorine to bromine and finally iodine.

Haloalkanes Have Higher Boiling Points than Alkanes

When comparing alkanes and haloalkanes, we will see that haloalkanes have higher boiling points than alkanes containing the same number of carbons. London dispersion forces are the first of two types of forces that contribute to this physical property. You might recall from general chemistry that London dispersion forces increase with molecular surface area. In comparing haloalkanes with alkanes, haloalkanes exhibit an increase in surface area due to the substitution of a halogen for hydrogen. The increase in surface area leads to an increase in London dispersion forces, which then results in a higher boiling point.

Dipole-dipole interaction is the second type of force that contributes to a higher boiling point. As you may recall, this type of interaction is a coulombic attraction between the partial positive and partial negative charges that exist between carbon-halogen bonds on separate haloalkane molecules. Similar to London dispersion forces, dipole-dipole interactions establish a higher boiling point for haloalkanes in comparison to alkanes with the same number of carbons.

Dipole-Dipole interaction between two carbon-halogens. The partially positive carbon attracts the partially negative halogen of a different molecule.

The table below illustrates how boiling points are affected by some of these properties. Notice that the boiling point increases when hydrogen is replaced by a halogen, a consequence of the increase in molecular size, as well as an increase in both London dispersion forces and dipole-dipole attractions. The boiling point also increases as a result of increasing the size of the halogen, as well as increasing the size of the carbon chain.

The boiling points of haloalkanes

Solubility

Solubility in water

The alkyl halides are at best only slightly soluble in water. For a haloalkane to dissolve in water the attractions between the haloalkane molecules (van der Waals dispersion and dipole-dipole interactions) and hydrogen bonds between water molecules must be broken. Both of these cost energy. Energy is released when new intermolecular forces are generated between the haloalkane molecules and water molecules. These will only be dispersion forces and dipole-dipole interactions. These are not as strong as the original hydrogen bonds in the water, and so not as much energy is released as was used to separate the water molecules. The energetics of the changes are sufficiently "unprofitable" such that very little dissolves.

Solubility in organic solvents

Alkyl halides tend to dissolve in organic solvents because the new intermolecular attractions have roughly the same strength as the ones being broken in the separate haloalkane and solvent.

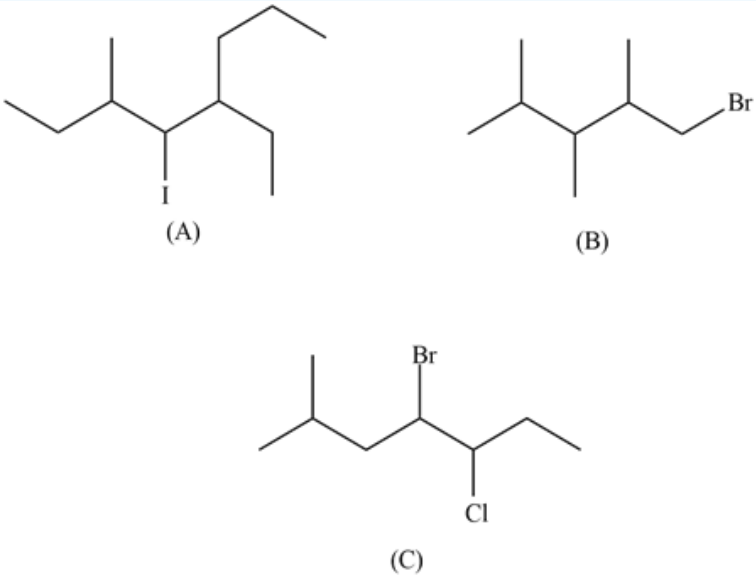
Chemical Reactivity

The pattern in chemical reactiviy lies in the strength of the bond between the carbon atom and the halogen atom. Previously

in this section, it was noted that the trend for bond strength increases from C-I to C-Br to C-Cl with C-F bonds being the strongest. To react with the alkyl halides, the carbon-halogen bond has got to be broken. Because that gets easier as you go from fluoride to chloride to bromide to iodide, the compounds get more reactive in that order. Iodoalkanes are the most reactive and fluoroalkanes are the least. In fact, fluoroalkanes are so unreactive that we will ignore them completely from now on in this section!

Exercise 6.1.2

1) Give the names of the following organohalides:



2) Draw the structures of the following compounds:

a) 2-Chloro-3,3-dimethylpentane

b) 1,1-Dichloro-4-isopropylcyclohexane

c) 3-bromo-3-ethylhexane

Answer available at the end of this section.

Answers

Exercise 6.1.1

1) a) The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.

b) The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro*-) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

c) The alkyl group (CH_3CH_2–) is a ethyl group, and the halogen is iodine (I). The common name is therefore ethyl iodide. For the IUPAC name, the prefix for iodine (iodo) is combined with the name for a two-carbon chain (ethane), preceded by a number identifying the carbon atom to which the I atom is attached, so the IUPAC name is 1-iodoethane.

d) The alkyl group ($CH_3CH_2CH_2CH_2$–) is a butyl group, and the halogen is fluorine (F). The common name is therefore butyl fluoride. For the IUPAC name, the prefix for fluorine (Fluoro) is combined with the name for a four-carbon chain (butane), preceded by a number identifying the carbon atom to which the F atom is attached, so the IUPAC name is 1-fluorobutane.

2) a) The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.

b) The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

c) 2-Chloro-3-methylbutane

d) 1-Bromo-2-chloro-4-methylpentane.

Exercise 6.1.2

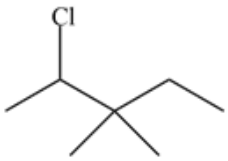
1)

a) 5-ethyl-4-iodo-3-methyloctane

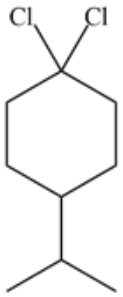
b) 1-bromo-2,3,4-trimethylpentane

c) 4-bromo-5-chloro-2-methylheptane

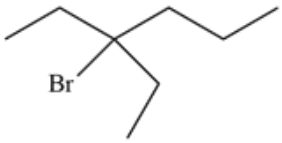
2)



(A)



(B)



(C)

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6.2: Nucleophilic Substitution

Halogens and the Character of the Carbon-Halogen Bond

With respect to electronegativity, halogens are more electronegative than carbons. This results in a carbon-halogen bond that is polarized. As shown in the image below, carbon atom has a partial positive charge, while the halogen has a partial negative charge.

Haloalkanes 0.1.bmp

The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

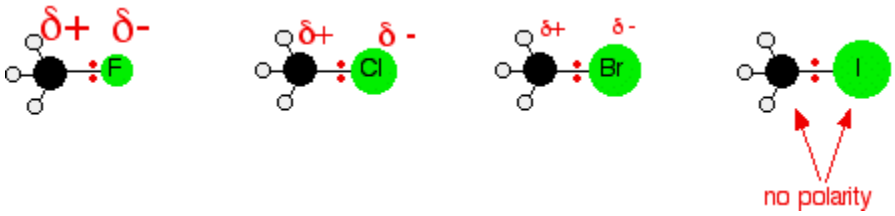
Haloalkanes 0.2.bmp

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.

Haloalkanes 0.3.bmp

The influence of bond polarity

Of the four halogens, fluorine is the most electronegative and iodine the least. That means that the electron pair in the carbon-fluorine bond will be dragged most towards the halogen end. Looking at the methyl halides as simple examples:



The electronegativities of carbon and iodine are equal and so there will be no separation of charge on the bond.

One of the important set of reactions of alkyl halides involves replacing the halogen by something else - substitution reactions. These reactions involve either:

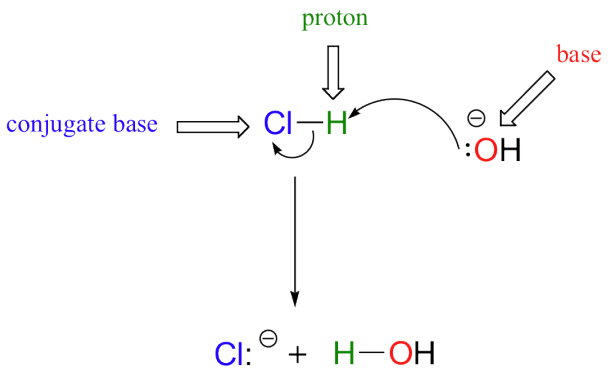
- the carbon-halogen bond breaking to give positive and negative ions. The ion with the positively charged carbon atom then reacts with something either fully or slightly negatively charged.
- something either fully or negatively charged attracted to the slightly positive carbon atom and pushing off the halogen atom.

You might have thought that either of these would be more effective in the case of the carbon-fluorine bond with the quite large amounts of positive and negative charge already present. But that's not so - quite the opposite is true! The thing that governs the reactivity is the strength of the bonds which have to be broken. If is difficult to break a carbon-fluorine bond, but easy to break a carbon-iodine one.

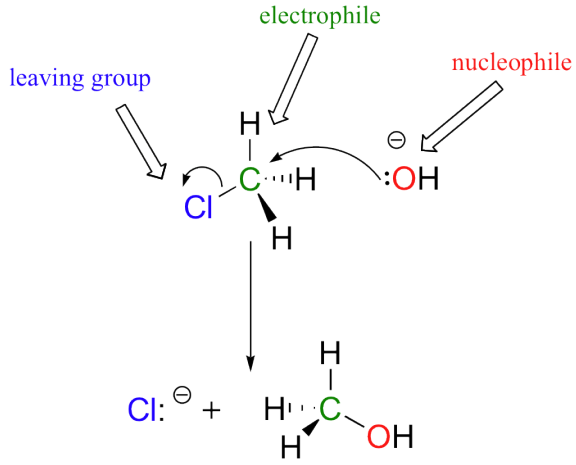
Contributors

- Rachael Curtis (UC Davis)
- Jim Clark (Chemguide.co.uk)

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



acid-base reaction



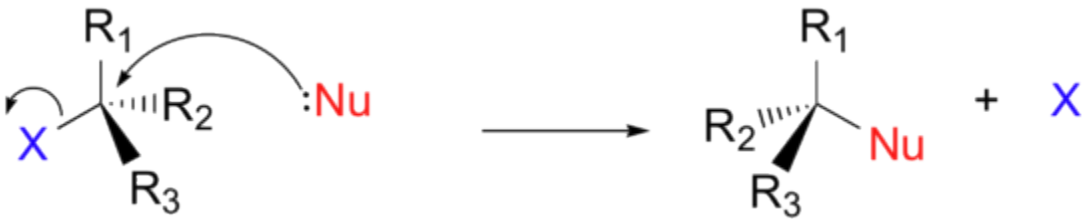
nucleophilic substitution

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

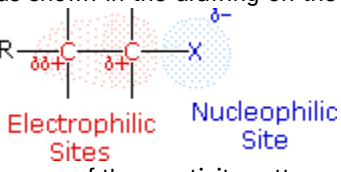
In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. In the same way, we will see later that nucleophiles and leaving groups are sometimes protonated and sometimes not, so for now, for the sake of simplicity, we will not include protons on 'Nu' or 'X'. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction:

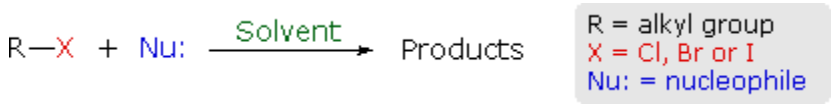


The functional group of alkyl halides is a carbon-halogen bond, the common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic, as shown in the drawing on the right. Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is covalent bond strength. The strongest of the carbon-halogen covalent bonds is that to fluorine. Remarkably, this is the strongest common single bond to carbon, being roughly 30 kcal/mole stronger than a carbon-carbon bond and about 15 kcal/mole stronger than a carbon-hydrogen bond. Because of this, **alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable**, and do not share any of the reactivity patterns



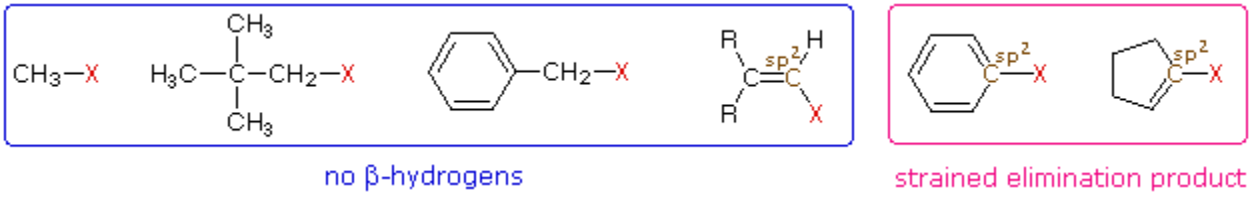
shown by the other alkyl halides. The carbon-chlorine covalent bond is slightly weaker than a carbon-carbon bond, and the bonds to the other halogens are weaker still, the bond to iodine being about 33% weaker. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF (pK_a = 3.2), all the hydrohalic acids are very strong, small differences being in the direction HCl < HBr < HI.

In order to understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation.



One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. **If R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.

It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).



Using the general reaction shown above as our reference, we can identify the following variables and observables.

Variables	**R** change α-carbon from 1° to 2° to 3° if the α-carbon is a chiral center, set as (*R*) or (S) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: **only one variable should be changed at a time**, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R–group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, C_2H_5–CN, in all cases, but the speed or rate of the reaction would increase in the order: Cl < Br < I. This reactivity order reflects both the strength of the C–X bond, and the stability of $X^{(-)}$ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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6.3: Reaction Mechanisms Involving Polar Functional Groups: Using "Electron-Pushing'" Arrows

Objectives

After completing this section, you should be able to

- explain the difference between heterolytic and homolytic bond breakage, and between heterogenic and homogenic bond formation.
- state the two reaction types involved in symmetrical and unsymmetrical processes.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- heterogenic
- heterolytic
- homogenic
- homolytic
- polar reaction
- radical reaction
- reaction mechanism

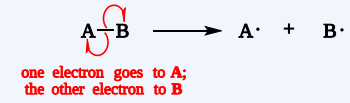
Study Notes

Upon first reading first four key terms, it is easy to be puzzled. The ending of the word tells you whether a bond is being formed (-genic) or broken (-lytic), while the root of the word describes the nature of that formation or decomposition. So hetero (meaning different) reactions involve asymmetrical bond making (or breaking) and homo (meaning same) involve symmetrical processes.

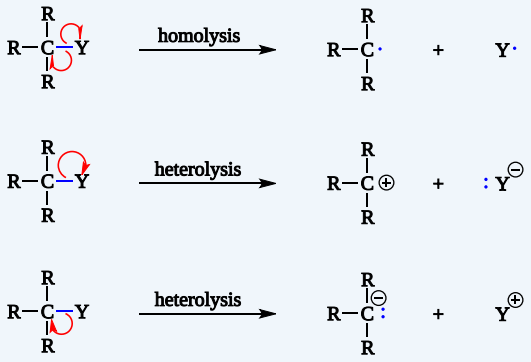
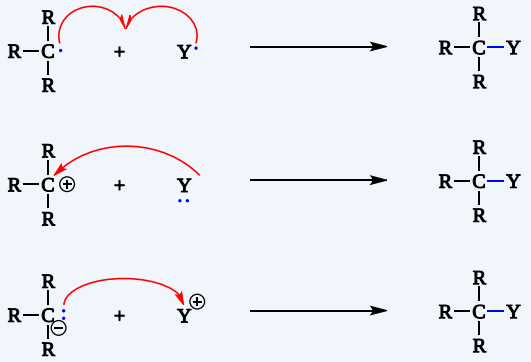
Because one pair of electrons constitutes a single bond, the unsymmetrical making or breaking of that bond in a hetero processes are described as polar reactions. Similarly, symmetrical homo processes of bond making and breaking are called radical reactions. Radicals (sometimes referred to as free radicals) are highly reactive neutral chemical species with one unpaired electron. In later sections we discuss radical and polar reactions in more detail.

The Arrow Notation in Mechanisms

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

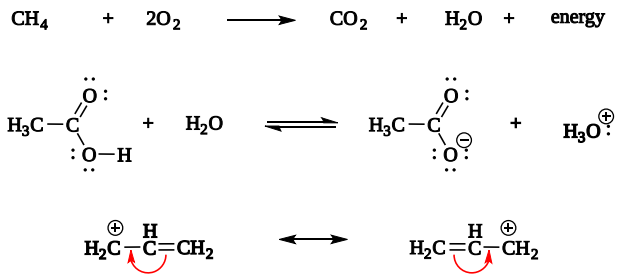
Bond-Breaking	Bond-Making
	

Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

The Reaction Arrow	The Equilibrium Arrow	The Resonance Arrow

The following equations illustrate the proper use of these symbols:



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.

Charged Intermediates	Uncharged Intermediates
 a carbocation	 a radical

Charged Intermediates	Uncharged Intermediates
 a carbanion	 a carbene

A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

- Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
- Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined below.

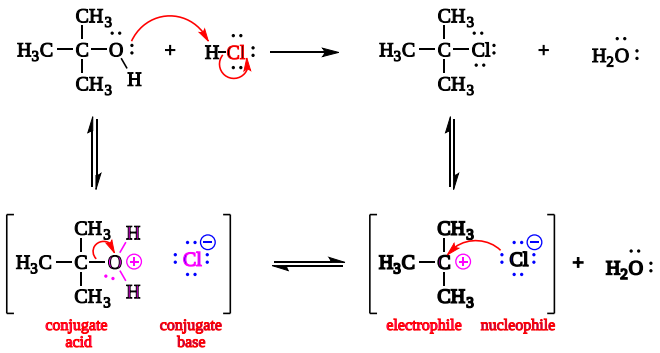
The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

Ionic Reactions

The principles and terms introduced in the previous sections can now be summarized and illustrated by the following three examples. Reactions such as these are called **ionic** or **polar** reactions, because they often involve charged species and the bonding together of **electrophiles and nucleophiles**. Ionic reactions normally take place in liquid solutions, where solvent molecules assist the formation of charged intermediates.

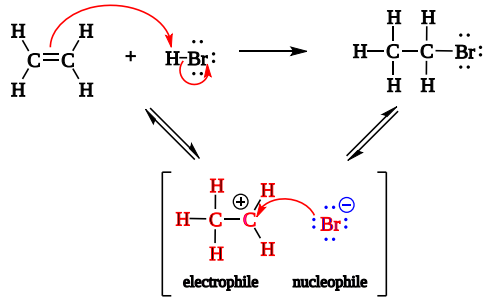
Substitution Reaction

The substitution reaction shown below can be viewed as taking place in three steps. The first is an acid-base equilibrium, in which HCl protonates the oxygen atom of the alcohol. The resulting conjugate acid then loses water in a second step to give a carbocation intermediate. Finally, this electrophile combines with the chloride anion nucleophile to give the final product.



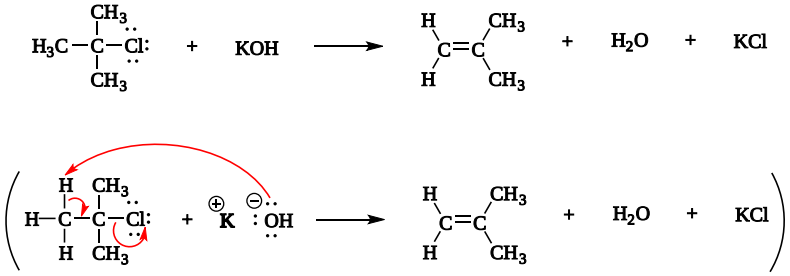
Addition Reaction

The addition reaction shown below can be viewed as taking place in two steps. The first step can again be considered an acid-base equilibrium, with the pi-electrons of the carbon-carbon double bond functioning as a base. The resulting conjugate acid is a carbocation, and this electrophile combines with the nucleophilic bromide anion.



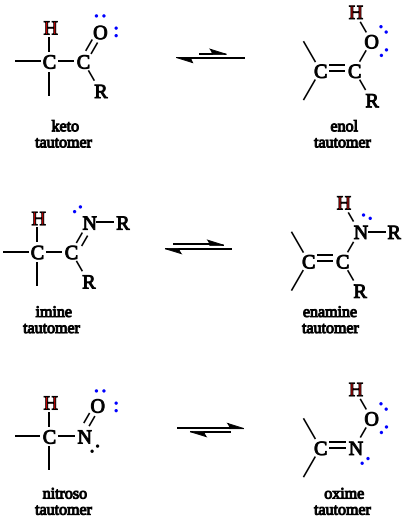
Elemination Reaction

The elimination reaction shown below takes place in one step. The bond breaking and making operations that take place in this step are described by the curved arrows. The initial stage may also be viewed as an acid-base interaction, with hydroxide ion serving as the base and a hydrogen atom component of the alkyl chloride as an acid. **rearrangement** (tautomerism)



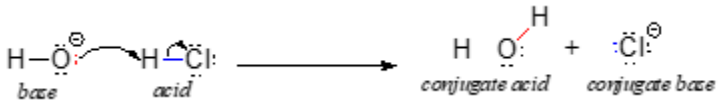
Tautomerization Reaction

There are many kinds of molecular rearrangements. The examples shown below are from an important class called **tautomerization** or, more specifically, keto-enol tautomerization. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



The Brønsted-Lowry definition of acidity

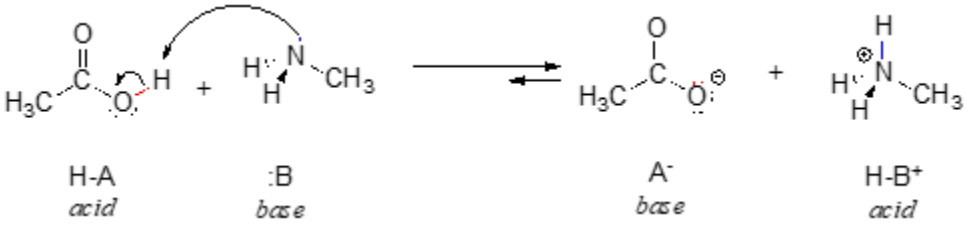
We'll begin our discussion of acid-base chemistry with a couple of essential definitions. The first of these definitions was proposed in 1923 by the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry, and has come to be known as the Brønsted-Lowry definition of acids and bases. An acid, by the Brønsted-Lowry definition, is a species which is able to donate a proton (H^+), while a base is a proton acceptor. We have already discussed in the previous chapter one of the most familiar examples of a Brønsted-Lowry acid-base reaction, between hydrochloric acid and hydroxide ion:



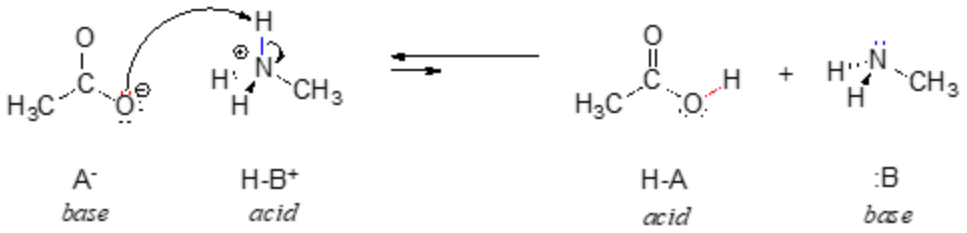
In this reaction, a proton is transferred from HCl (the acid, or proton *donor*) to hydroxide (the base, or proton *acceptor*). As we learned in the previous chapter, curved arrows depict the movement of electrons in this bond-breaking and bond-forming process.

After a Brønsted-Lowry acid donates a proton, what remains – in this case, a chloride ion – is called the **conjugate base**. Chloride is thus the conjugate base of hydrochloric acid. Conversely, when a Brønsted-Lowry base accepts a proton it is converted into its **conjugate acid** form: water is thus the conjugate acid of hydroxide.

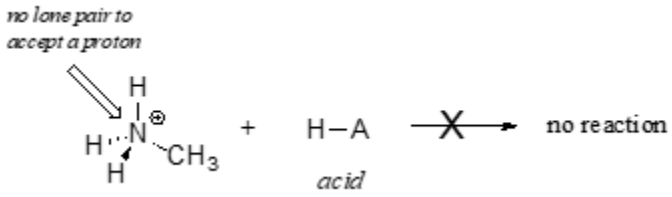
We can also talk about conjugate acid/base pairs: the two acid/base pairs involved in our first reaction are hydrochloric acid/chloride and hydroxide/water. In this next acid-base reaction, the two pairs involved are acetate/acetic acid and methyl ammonium/methylamine:



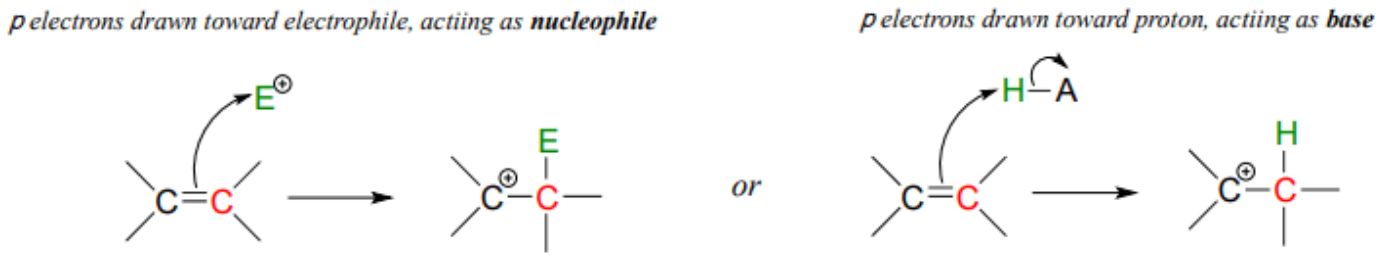
Throughout this text, we will often use the abbreviations HA and :B in order to refer in a general way to acidic and basic reactants:



In order to act as a proton acceptor, a base must have a reactive pair of electrons. In all of the examples we shall see in this chapter, this pair of electrons is a non-bonding lone pair, usually (but not always) on an oxygen, nitrogen, sulfur, or halogen atom. When acetate acts as a base in the reaction shown above, for example, one of its oxygen lone pairs is used to form a new bond to a proton. The same can be said for an amine acting as a base. Clearly, methyl ammonium ion cannot act as a base – it does not have a reactive pair of electrons with which to accept a new bond to a proton.



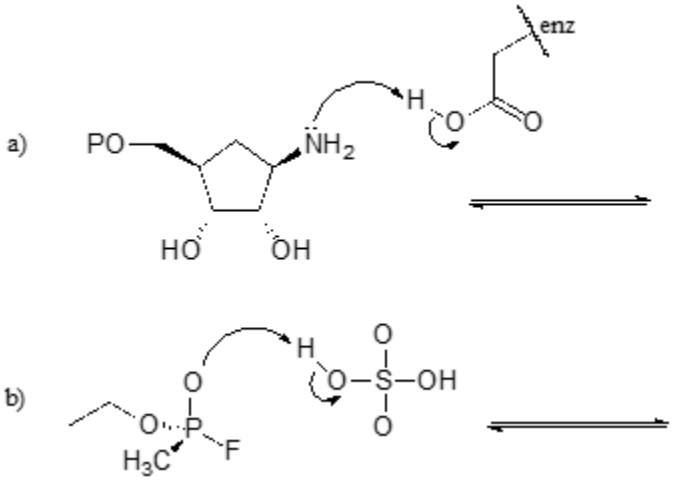
Later, in chapter 15, we will see several examples where the (relatively) reactive pair of electrons in a π bond act in a basic fashion.



In this chapter, we will concentrate on those bases with non-bonding (lone pair) electrons.

Example	

Exercise 7.1: Draw structures for the missing conjugate acids or conjugate bases in the reactions below.



Solution

Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

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6.4: A Closer Look at the Nucleophilic Substitution Mechanism: Kinetics

Objectives

After completing this section, you should be able to

1. write an expression relating reaction rate to the concentration of reagents for a second-order reaction.
2. determine the order of a chemical reaction from experimentally obtained rate data.
3. describe the essential features of the S_N2 mechanism, and draw a generalized **transition state** for such a reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- bimolecular
- kinetics
- rate coefficient
- rate equation
- reaction rate
- second-order reaction
- S_N2

Study Notes

Most of the key terms introduced in this section should already be familiar to you from your previous general chemistry course.

Reaction rate refers to the change in concentration of a reactant or product per unit of time. Using strict SI units, reaction rates are expressed in $\text{mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$, but in some textbooks you will find this value written as M/s. In general, the reaction rate of a given reaction changes with time, as it is dependent on the concentration of one or more of the reactants.

An equation which shows the relationship between the reaction rate and the concentrations of the reactants is known as the rate equation. All rate equations contain a proportionality constant, usually given the symbol *k*, which is known as the rate coefficient. Some textbooks refer to this value as the "rate constant," but this name is a little misleading as it is not a true constant. The rate coefficient of a given reaction depends on such factors as temperature and the nature of the solvent.

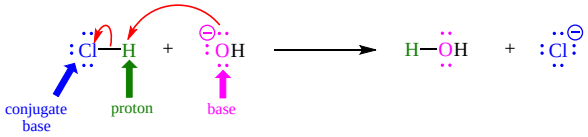
S_N2 is short for "bimolecular nucleophilic substitution." You will encounter abbreviations for other types of reactions later in this chapter.

If you are unclear on the point about the inversion of configuration during an S_N2 reaction, construct a molecular model of a chiral alkyl halide, the **transition state** formed when this substance reacts with a nucleophile in an S_N2 process, and the product obtained from this reaction.

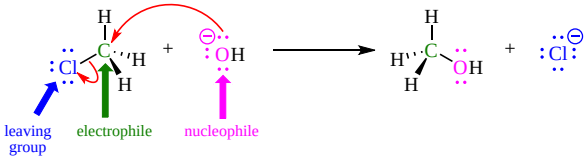
Brønsted-Lowry acid-base reactions

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.

Acid-base reaction:

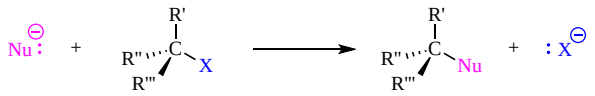


Nucleophilic substitution:



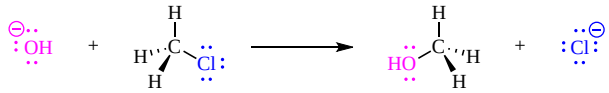
In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base. Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction.

General S_N2 Reaction



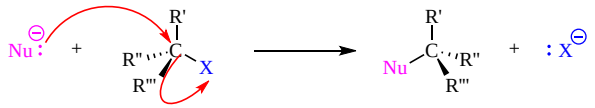
R = alkyl or H

Example



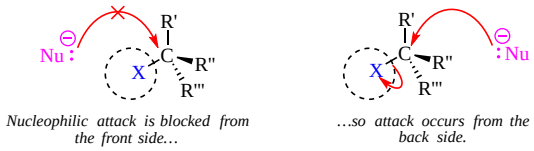
The S_N2 Mechanism

Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen. This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. The mechanism starts when lone pair electrons from the nucleophile attacks the electrophilic carbon of the alkyl halide to form a C-Nu sigma bond. Simultaneously, X-C bond is broken when the electrons are pushed onto the leaving group. Overall during this mechanism, a set of lone pair electrons are transferred from the nucleophile to the leaving groups.



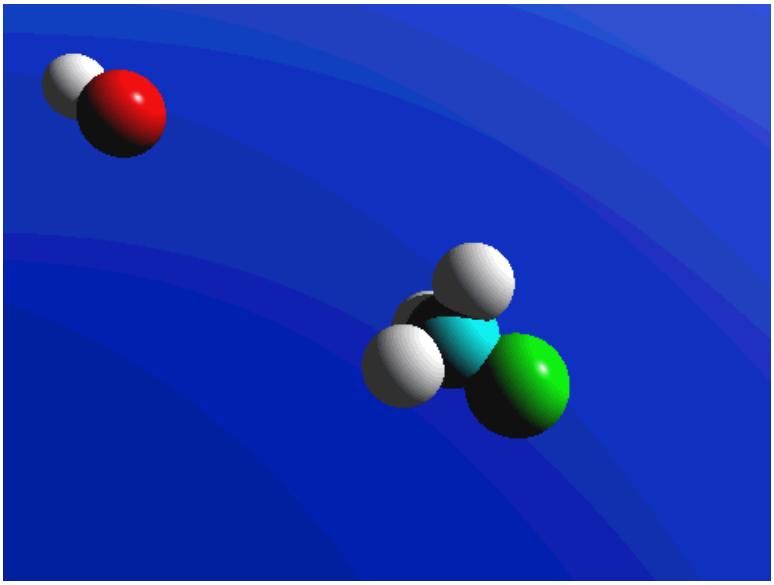
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The

nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.

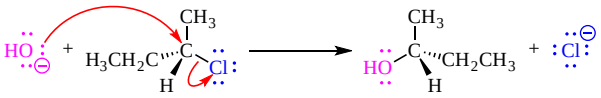


The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



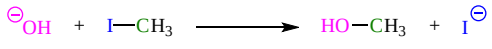
Example



(*S*)-2-chlorobutane (*R*)-2-butanol

Bimolecular Nucleophilic Substitution Reactions and Kinetics

In the term S_N2, (as previously stated) the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



$$\text{Rate} = k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 2k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 2\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$\text{Rate}_1 = k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 4k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 4\text{Rate}_1$$

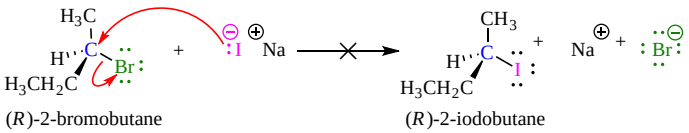
The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

S_N2 Reactions Are Stereospecific

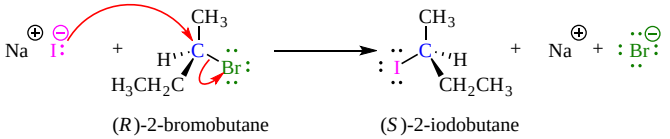
The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an (*R*) enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the (*R*) enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the (*S*) enantiomer.

Frontside attack with retention of configuration:



(*R*)-2-bromobutane (*R*)-2-iodobutane

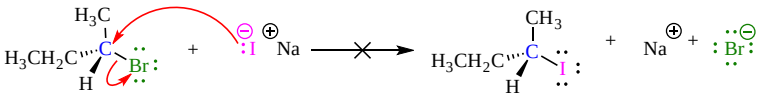
Backside attack with inversion of configuration:



(*R*)-2-bromobutane (*S*)-2-iodobutane

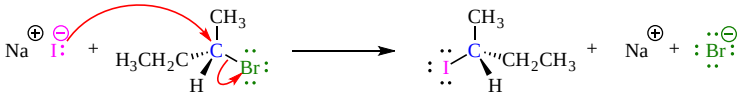
Conversely, if the substrate is an (S) enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the (S) enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the (*R*) enantiomer.

Frontside attack with retention of configuration:



(*S*)-2-bromobutane (*S*)-2-iodobutane

Backside attack with inversion of configuration:

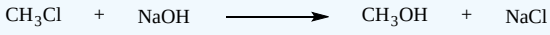


(*S*)-2-bromobutane (*R*)-2-iodobutane

In conclusion, S_N2 reactions that begin with the (*R*) enantiomer as the substrate will form the (S) enantiomer as the product. Those that begin with the (S) enantiomer as the substrate will form the (*R*) enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

Exercise 6.4.1

1) The reaction below follows the S_N2 mechanism.



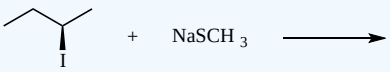
a) Write the rate law for this reaction.

b) Determine the value of the rate coefficient, k, if the initial concentrations are 0.01 M CH_3Cl, 0.01 M NaOH, and the initial reaction rate is 6 x 10^{-10} M/s.

c) Calculate the initial reaction rate if the initial reactant concentrations are changed to 0.02 M CH_3Cl and 0.0005 M NaOH.

2) Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

3) Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



4) Since everything is relative in chemistry, one reaction's nucleophile can be another reaction's leaving group. Some functional groups can only react as a nucleophile or electrophile, while other functional groups can react as either a nucleophile or electrophile depending on the reaction conditions. Classify the following compounds as nucleophile, electrophile, or leaving groups. More than one answer may be possible.

a) bromoethane

b) hydroxide

c) water

d) chlorocyclohexane

e) ethanol

f) bromide

Answer available at the end of this section.

Answers

Exercise 6.4.1

1) a) rate = k [CH_3Cl] [OH^-]

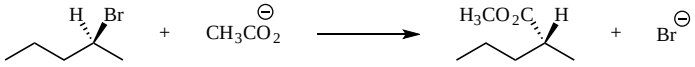
b) substitute the data into the rate expression above and apply algebra to solve for k

k = 6 x 10^{-6} $Lmol^{-1}s^{-1}$

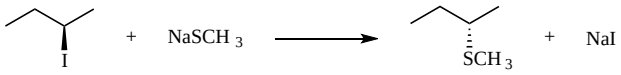
c) Using the rate law above, substitute the value for k from the previous question along with the new concentrations to determine the new initial rate.

rate = 6 x 10^{-10} M/s

2)



3)



4)

a) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

b) strong nucleophile

c) weak nucleophile and good leaving group

d) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

e) weak nucleophile, a poor electrophile without clever chemistry (stay tuned for future chapters), good leaving group

f) good nucleophile and a good leaving group

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6.5: Frontside or Backside Attack? Stereochemistry of the SN2 Reaction

7.11 The SN2 Mechanism

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6.6: Consequences of Inversion in SN2 Reactions

Objectives

After completing this section, you should be able to

1. write an equation to represent the Walden inversion.
2. write a short paragraph describing the Walden inversion.
3. describe, using equations, a series of reactions interconverting two enantiomers of 1-phenyl-2-propanol which led to the conclusion that nucleophilic substitution of primary and secondary alkyl halides proceeds with inversion of configuration.

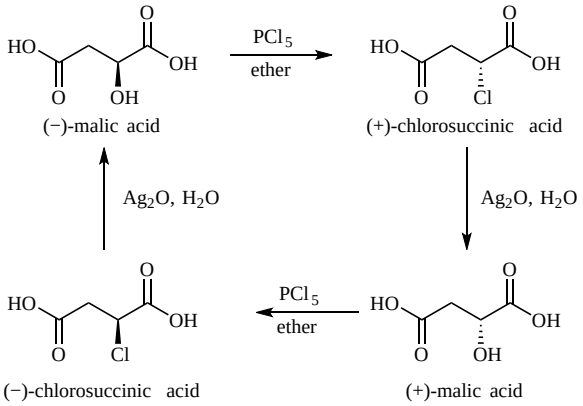
Study Notes

The IUPAC name for malic acid is 2-hydroxybutanedioic acid. This acid is produced by apples, a fact which seems to have been appreciated by the British novelist Thomas Hardy in *The Woodlanders*:

Up, upward they crept, a stray beam of the sun alighting every now and then like a star on the blades of the pomace-shovels, which had been converted to steel mirrors by the action of the malic acid.

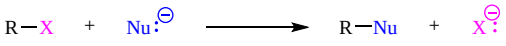
In 1896, the German chemist Paul Walden discovered that he could interconvert pure enantiomeric (+) and (-) malic acids through a series of reactions. This conversion meant that there was some kind of change in the stereochemistry made during the series of reactions. First, (−)-malic acid was reacted with **phosphorus pentachloride (PCl_5)** to provide (+)-chlorosuccinic acid.

This was reacted with **silver(I)oxide (Ag_2O)** to provide (+)-malic acid. These two combined steps caused an inversion of stereochemistry of (−)-malic acid to (+)-malic acid. The reaction series was then continued to convert (+)-malic acid back into (−)-malic acid by further reaction with PCl_5 and Ag_2O.



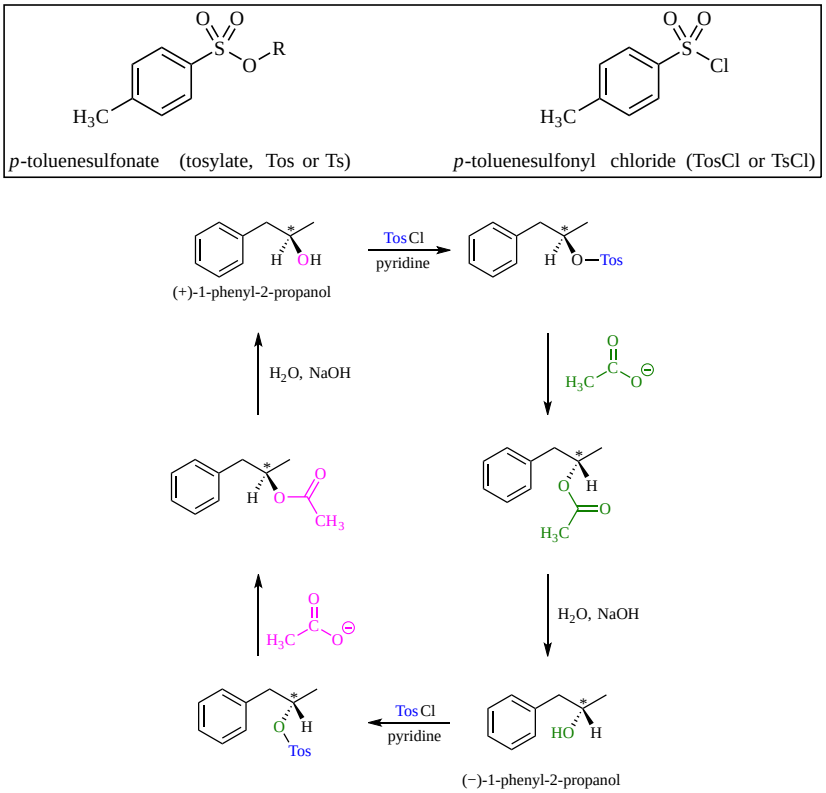
These results were considered astonishing. The fact that (−)-malic acid was converted into (+)-malic acid meant that the configuration of the chiral center has somehow been changed during the reaction series.

These reactions are currently referred to as nucleophilic substitution reactions because each step involves the substitution of one nucleophile by another. These are among the most common and versatile reaction types in organic chemistry.

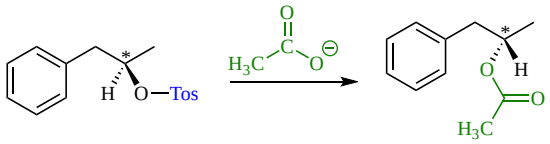


Further investigations into these reaction were undertaken during the 1920's and 1930's to clarify the mechanism and clarify how the inversion of configurations occur. These reactions involved nucleophilic substitution of an alkyl p-toluenesulfonate (called a tosylate group). For this purpose the tosylate groups act similarly to a halogen substituent. In the series of reactions

(+)-1-phenyl-2-propanol is interconverted with (-)-1-phenyl-2-propanol.



Somewhere in this three-step series of reactions the configuration at a chiral center is being inverted. In the first step the tosylate is formed without breaking the C-O bond of the chiral center, which means the configuration is unchanged. Similarly, the cleavage of the ester in step three occurs without breaking the C-O bond of the chiral center, which also means the configuration of the chiral carbon is unaffected. It was determined that the second step where acetate nucleophile undergoes a substitution with tosylate was causing the stereochemical configuration to be inverted.



inversion of configuration

Exercise 6.6.1

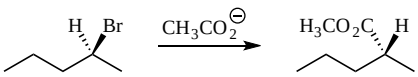
1) Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

Answer available at the end of this section.

Answers

Exercise 6.6.1

1)



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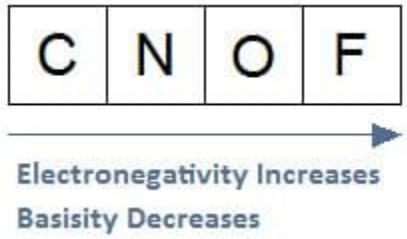
- 11.1: The Discovery of Nucleophilic Substitution Reactions by Dietmar Kennepohl, Steven Farmer is licensed CC BY-SA 4.0.

6.7: Structure and S_N2 Reactivity: The Leaving Group

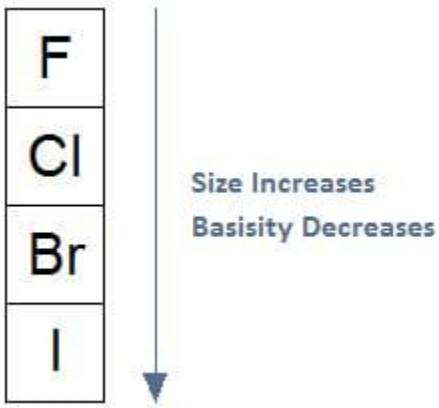
Our general discussion of nucleophilic substitution reactions, we have until now been designating the leaving group simply as “X". As you may imagine, however, the nature of the leaving group is an important consideration: if the C-X bond does not break, the new bond between the nucleophile and electrophilic carbon cannot form, regardless of whether the substitution is S_N1 or S_N2. In this module, we are focusing on substitution reactions in which the leaving group is a halogen ion, although many reactions are known, both in the laboratory and in biochemical processes, in which the leaving group is something other than a halogen.

In order to understand the nature of the leaving group, it is important to first discuss factors that help determine whether a species will be a strong base or weak base. If you remember from general chemistry, a Lewis base is defined as a species that donates a pair of electrons to form a covalent bond. The factors that will determine whether a species wants to share its electrons or not include electronegativity, size, and resonance.

As Electronegativity Increases, Basicity Decreases: In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, electronegativity increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons.



Resonance Decreases Basicity: The third factor to consider in determining whether or not a species will be a strong or weak base is resonance. As you may remember from general chemistry, the formation of a resonance stabilized structure results in a species that is less willing to share its electrons. Since strong bases, by definition, want to share their electrons, resonance stabilized structures are weak bases.Edit section

Now that we understand how electronegativity, size, and resonance affect basicity, we can combine these concepts with the fact that weak bases make the best leaving groups. Think about why this might be true. In order for a leaving group to leave, it must be able to accept electrons. A strong bases wants to donate electrons; therefore, the leaving group must be a weak base. We will now revisit electronegativity, size, and resonance, moving our focus to the leaving group, as well providing actual examples.

Note

As the Electronegativity of the group *Increases*, The propensity of the Leaving Group to Leave *Increases*

As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basisity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing $^{-}CH_3$ to be the worst leaving group and F^{-} to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that S_N2 reactions of fluoroalkanes are rarely observed.

$$^{-}CH_3 < {}^{-}NH_2 < {}^{-}OH < {}^{-}F$$

Worst Best

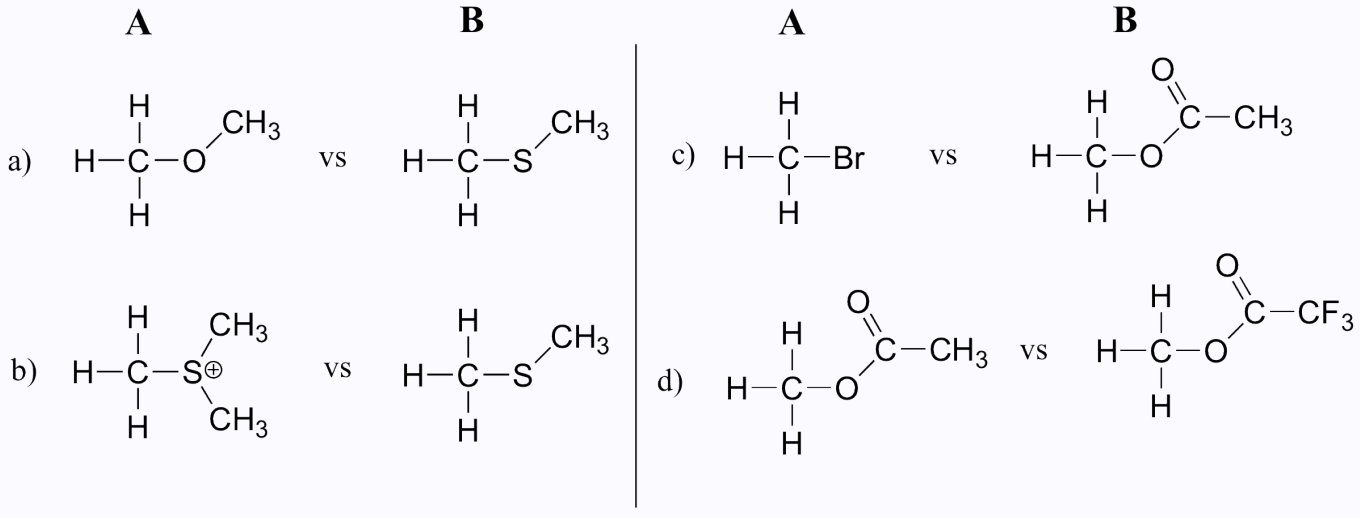
As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

$$F < Cl < Br < I$$

Worst Fair Good Excellent

Example 7.7.1

In each pair (A and B) below, which electrophile would be expected to react more rapidly in an S_N2 reaction with the thiol group of cysteine as the common nucleophile?



Solution (8.13)

Contributor

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.8: Structure and SN2 Reactivity: The Nucleophile

What is a nucleophile?

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates. More specifically in laboratory reactions, halide and azide (N_3^-) anions are commonly seen acting as nucleophiles.

Of course, carbons can also be nucleophiles - otherwise how could new carbon-carbon bonds be formed in the synthesis of large organic molecules like DNA or fatty acids? Enolate ions (section 7.5) are the most common carbon nucleophiles in biochemical reactions, while the cyanide ion (CN^-) is just one example of a carbon nucleophile commonly used in the laboratory. Reactions with carbon nucleophiles will be dealt with in chapters 13 and 14, however - in this chapter and the next, we will concentrate on non-carbon nucleophiles.

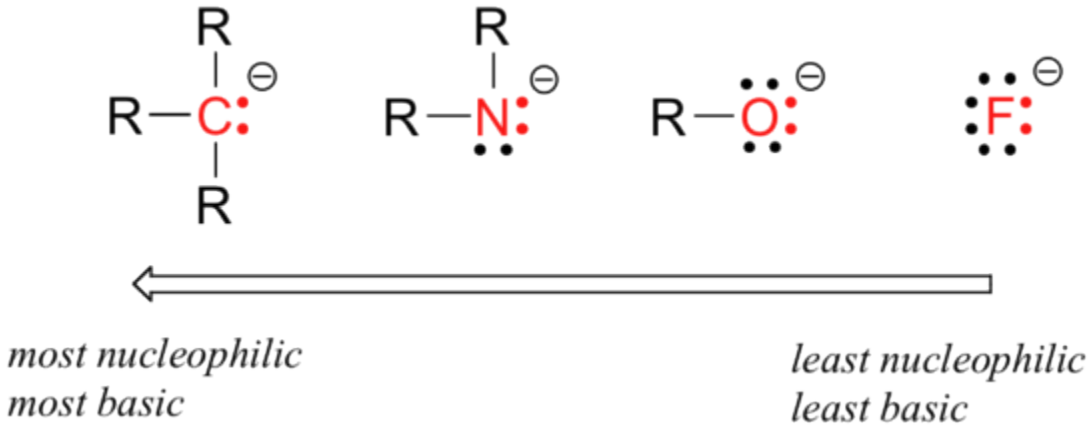
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Protonation states and nucleophilicity

The protonation state of a nucleophilic atom has a very large effect on its nucleophilicity. This is an idea that makes intuitive sense: a hydroxide ion is much more nucleophilic (and basic) than a water molecule, because the negatively charged oxygen on the hydroxide ion carries greater electron density than the oxygen atom of a neutral water molecule. In practical terms, this means that a hydroxide nucleophile will react in an S_N2 reaction with methyl bromide much faster (about 10,000 times faster) than a water nucleophile.

Periodic trends and solvent effects in nucleophilicity

There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:

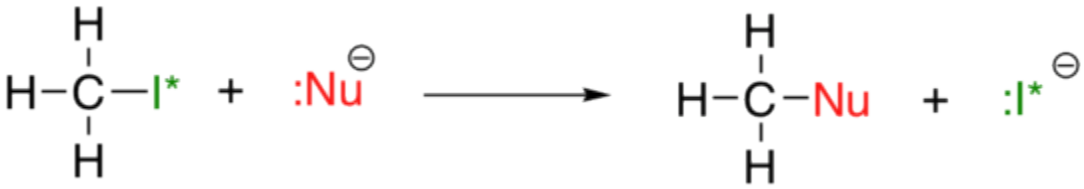


The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond.

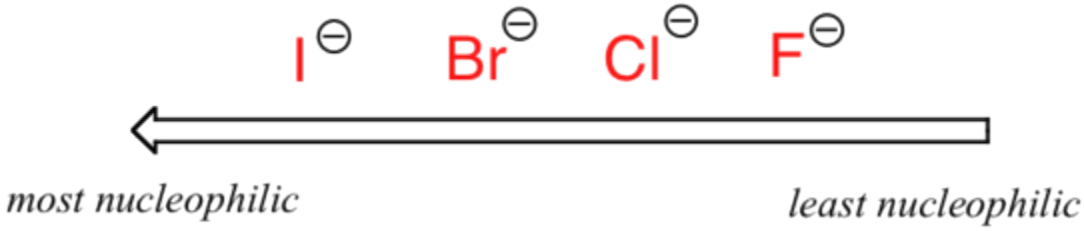
This horizontal trends also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

The vertical periodic trend for nucleophilicity is somewhat more complicated that that for basicity: depending on the solvent that the reaction is taking place in, the nucleophilicity trend can go in either direction. Let's take the simple example of the SN2 reaction below:



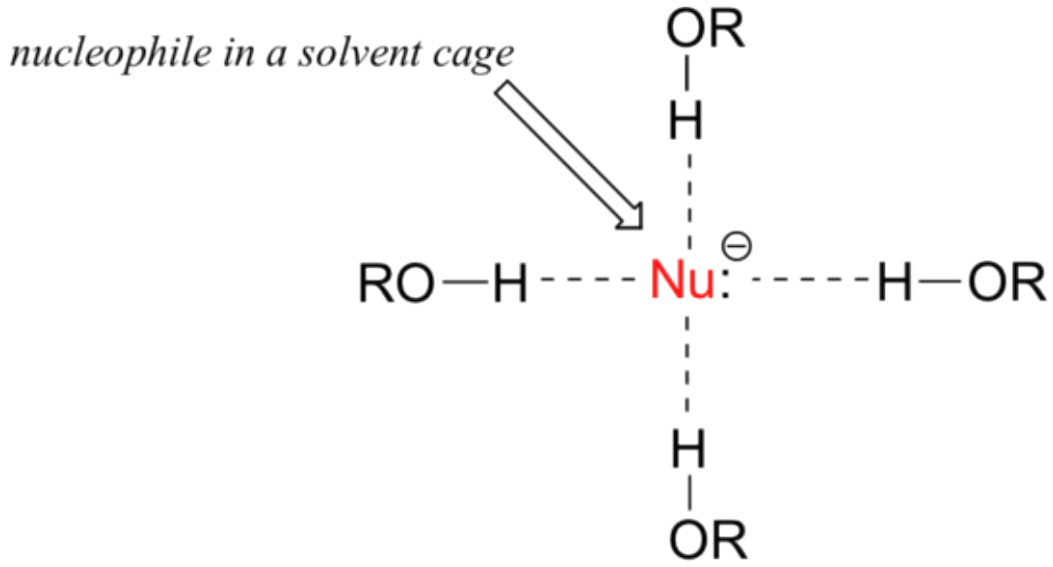
. . .where Nu^- is one of the halide ions: fluoride, chloride, bromide, or iodide, and the leaving group I* is a radioactive isotope of iodine (which allows us to distinguish the leaving group from the nucleophile in that case where both are iodide). If this reaction is occurring in a **protic solvent** (that is, a solvent that has a hydrogen bonded to an oxygen or nitrogen - water, methanol and ethanol are the most important examples), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.



Relative nucleophilicity in a protic solvent

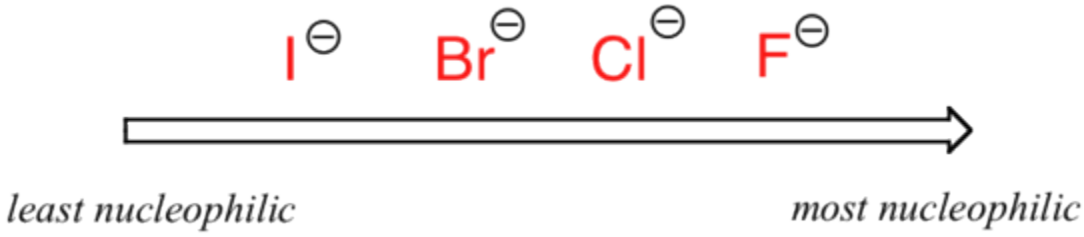
This of course, is opposite that of the vertical periodic trend for basicity, where iodide is the *least* basic. What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction running in a *protic* solvent like ethanol. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile:



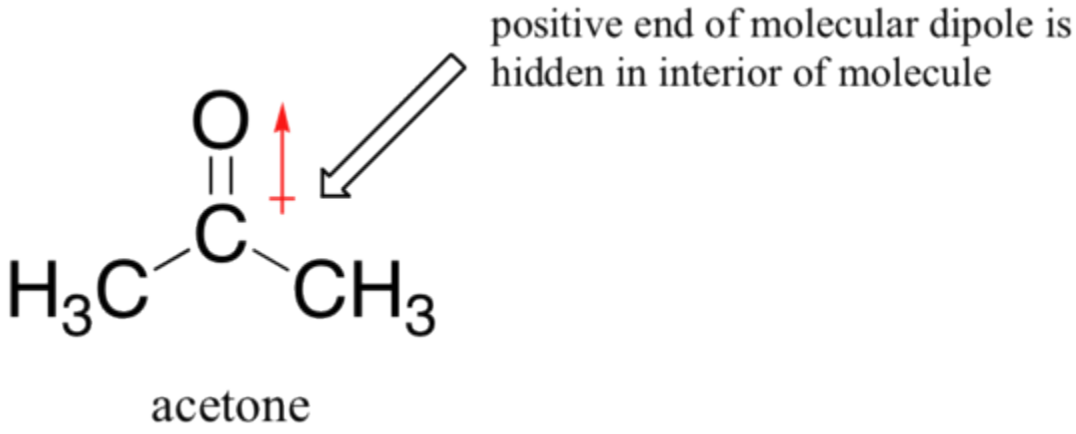
In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. The lone pair electrons on the larger, less basic iodide ion interact less tightly with the protons on the protic solvent molecules - thus the iodide nucleophile is better able to break free from its solvent cage compared the smaller, more basic fluoride ion, whose lone pair electrons are bound more tightly to the protons of the cage.

The picture changes if we switch to a **polar aprotic solvent**, such as acetone, in which there is a molecular dipole but *no hydrogens bound to oxygen or nitrogen*. Now, fluoride is the best nucleophile, and iodide the weakest.



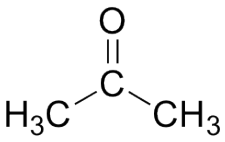
Relative nucleophilicity in a polar aprotic solvent

The reason for the reversal is that, with an aprotic solvent, the ion-dipole interactions between solvent and nucleophile are much weaker: the positive end of the solvent's dipole is hidden in the interior of the molecule, and thus it is shielded from the negative charge of the nucleophile.

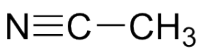


A weaker solvent-nucleophile interaction means a weaker solvent cage for the nucleophile to break through, so the solvent effect is much less important, and the more basic fluoride ion is also the better nucleophile.

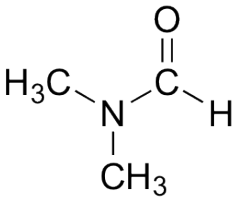
Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate an a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).



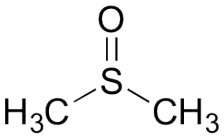
acetone



acetonitrile



dimethylformamide (DMF)

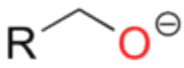


dimethylsulfoxide (DMSO)

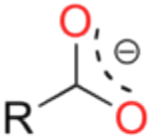
In biological chemistry, where the solvent is protic (water), the most important implication of the periodic trends in nucleophilicity is that thiols are more powerful nucleophiles than alcohols. The thiol group in a cysteine amino acid, for example, is a powerful nucleophile and often acts as a nucleophile in enzymatic reactions, and of course negatively-charged thiolates (RS^-) are even more nucleophilic. This is not to say that the hydroxyl groups on serine, threonine, and tyrosine do not also act as nucleophiles - they do.

Resonance effects on nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.

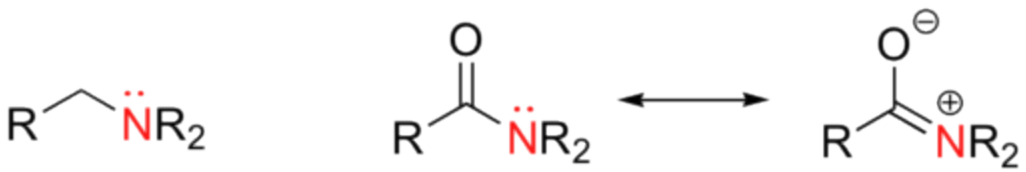


alkoxide ion:
charge is localized
more nucleophilic



carboxylate ion:
charge is spread over both oxygens
less nucleophilic

The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



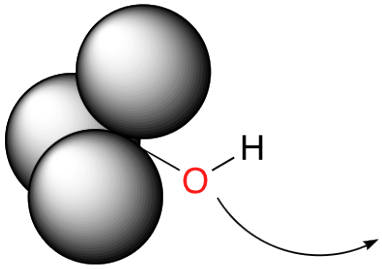
amine
more nucleophilic

amide
less nucleophilic

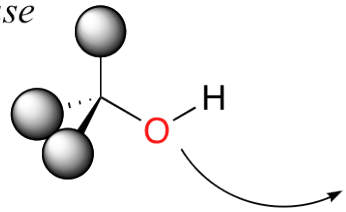
Steric effects on nucleophilicity

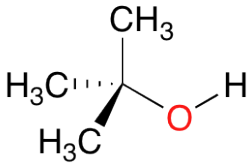
Steric hindrance is an important consideration when evaluating nucleophility. For example, *tert*-butanol is less potent as a nucleophile than methanol. This is because the comparatively bulky methyl groups on the tertiary alcohol effectively block the route of attack by the nucleophilic oxygen, slowing the reaction down considerably (imagine trying to walk through a narrow doorway while carrying three large suitcases!).

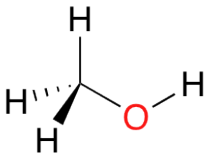
large methyl groups hinder nucleophlic attack



small hydrogens cause far less hindance







It is not surprising that it is more common to observe serines acting as nucleophiles in enzymatic reactions compared to threonines - the former is a primary alcohol, while the latter is a secondary alcohol.

Example 7.8.1

Which is the better nucleophile - a cysteine side chain or a methionine side chain? Explain.

Example 7.8.2

In each of the following pairs of molecules/ions, which is the better nucleophile in a reaction with CH_3Br in acetone solvent? Explain your choice.

a. phenolate ion (deprotonated phenol) or benzoate ion (deprotonated benzoic acid)
b. water and hydronium ion
c. trimethylamine and triethylamine
d. chloride anion and iodide anion
e. CH_3NH^- and CH_3CH_2NH

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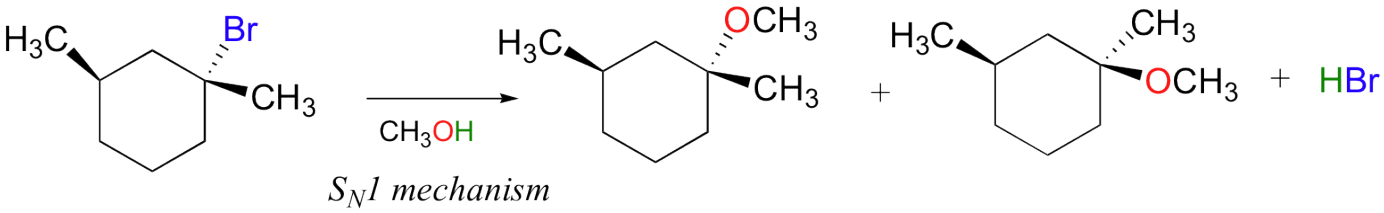
6.9: Keys to Success: Choosing Among Multiple Mechanistic Pathways

Predicting S_N1 vs. S_N2 mechanisms; competition between nucleophilic substitution and elimination reactions

When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

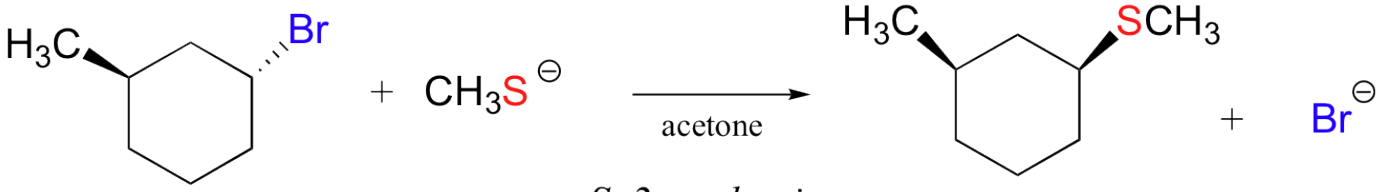
1. **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.
2. **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.
3. **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.



S_N1 mechanism

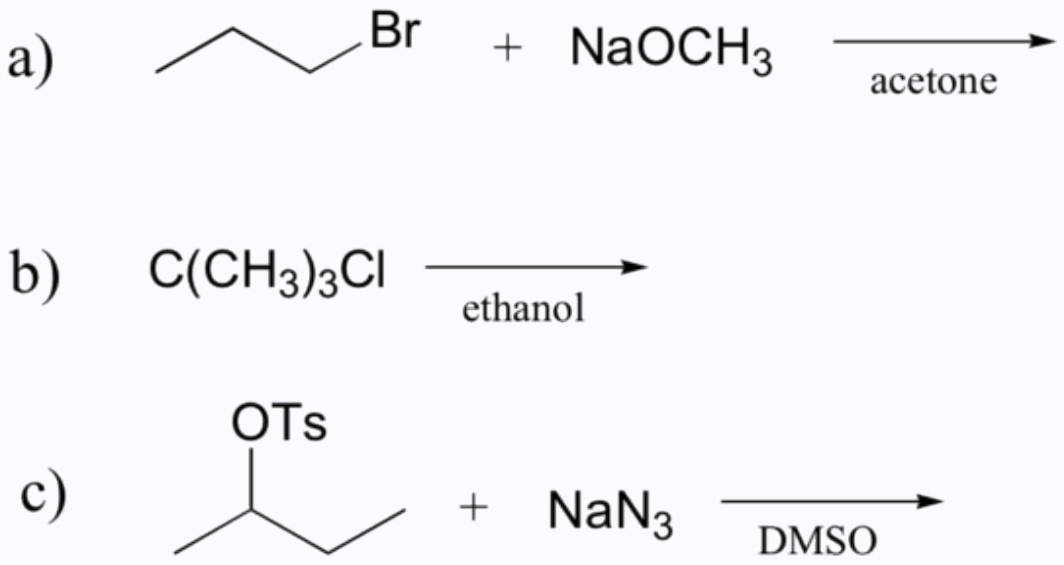
In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar protic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



S_N2 mechanism

Example 7.17.1

Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism.



Solution

Contributors

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.3: Reaction Mechanisms Involving Polar Functional Groups: Using "Electron-Pushing\'" Arrows

Objectives

After completing this section, you should be able to

- explain the difference between heterolytic and homolytic bond breakage, and between heterogenic and homogenic bond formation.
- state the two reaction types involved in symmetrical and unsymmetrical processes.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- heterogenic
- heterolytic
- homogenic
- homolytic
- polar reaction
- radical reaction
- reaction mechanism

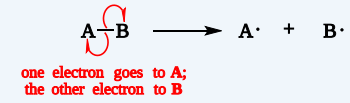
Study Notes

Upon first reading first four key terms, it is easy to be puzzled. The ending of the word tells you whether a bond is being formed (-genic) or broken (-lytic), while the root of the word describes the nature of that formation or decomposition. So hetero (meaning different) reactions involve asymmetrical bond making (or breaking) and homo (meaning same) involve symmetrical processes.

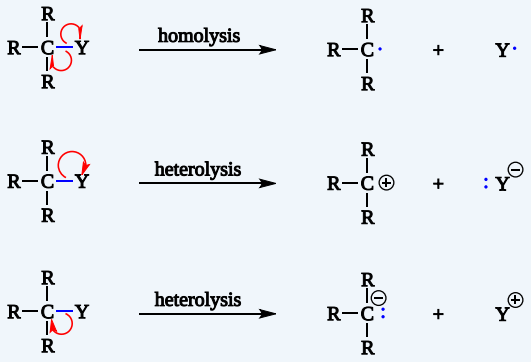
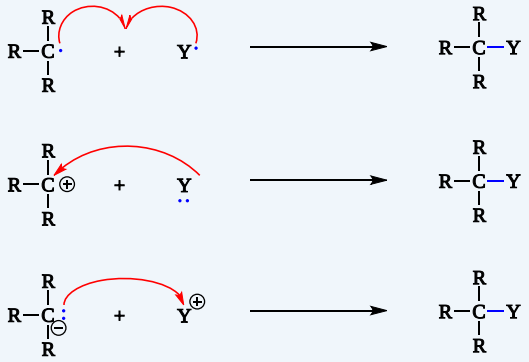
Because one pair of electrons constitutes a single bond, the unsymmetrical making or breaking of that bond in a hetero processes are described as polar reactions. Similarly, symmetrical homo processes of bond making and breaking are called radical reactions. Radicals (sometimes referred to as free radicals) are highly reactive neutral chemical species with one unpaired electron. In later sections we discuss radical and polar reactions in more detail.

The Arrow Notation in Mechanisms

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

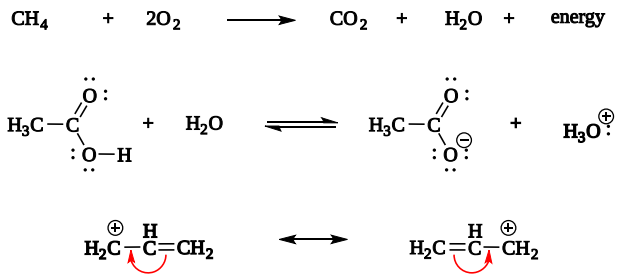
Bond-Breaking	Bond-Making
	

Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

The Reaction Arrow	The Equilibrium Arrow	The Resonance Arrow

The following equations illustrate the proper use of these symbols:



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.

Charged Intermediates	Uncharged Intermediates
 a carbocation	 a radical

Charged Intermediates	Uncharged Intermediates
 a carbanion	 a carbene

A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

- Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
- Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined below.

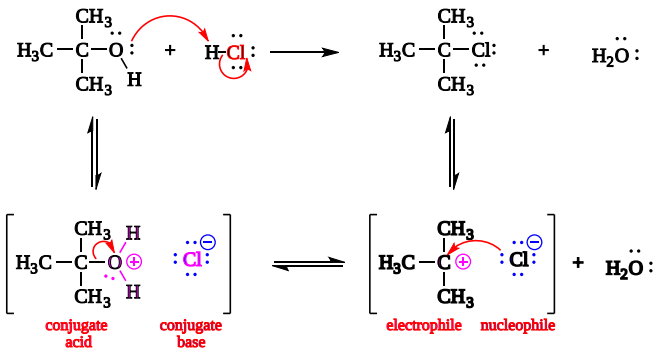
The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

Ionic Reactions

The principles and terms introduced in the previous sections can now be summarized and illustrated by the following three examples. Reactions such as these are called **ionic** or **polar** reactions, because they often involve charged species and the bonding together of **electrophiles and nucleophiles**. Ionic reactions normally take place in liquid solutions, where solvent molecules assist the formation of charged intermediates.

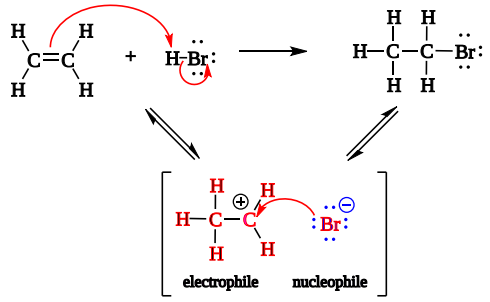
Substitution Reaction

The substitution reaction shown below can be viewed as taking place in three steps. The first is an acid-base equilibrium, in which HCl protonates the oxygen atom of the alcohol. The resulting conjugate acid then loses water in a second step to give a carbocation intermediate. Finally, this electrophile combines with the chloride anion nucleophile to give the final product.



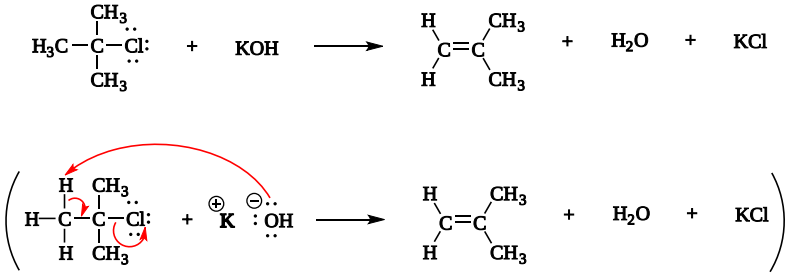
Addition Reaction

The addition reaction shown below can be viewed as taking place in two steps. The first step can again be considered an acid-base equilibrium, with the pi-electrons of the carbon-carbon double bond functioning as a base. The resulting conjugate acid is a carbocation, and this electrophile combines with the nucleophilic bromide anion.



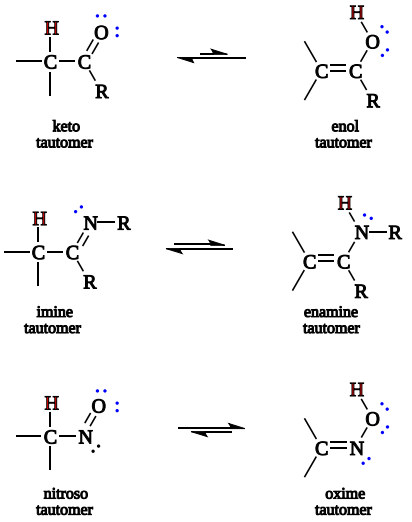
Elemination Reaction

The elimination reaction shown below takes place in one step. The bond breaking and making operations that take place in this step are described by the curved arrows. The initial stage may also be viewed as an acid-base interaction, with hydroxide ion serving as the base and a hydrogen atom component of the alkyl chloride as an acid. **rearrangement** (tautomerism)



Tautomerization Reaction

There are many kinds of molecular rearrangements. The examples shown below are from an important class called **tautomerization** or, more specifically, keto-enol tautomerization. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



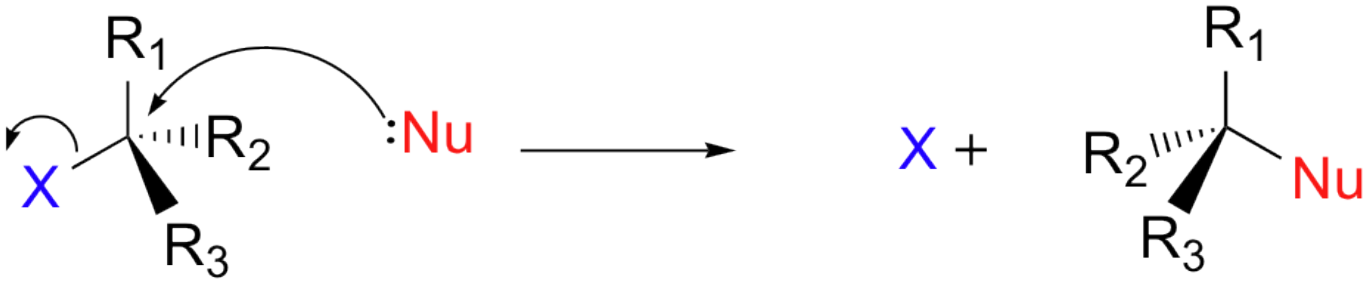
This page titled 6.3: Reaction Mechanisms Involving Polar Functional Groups: Using "Electron-Pushing\\'" Arrows is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

- 6.2: How Organic Reactions Occur - Mechanisms by Dietmar Kennepohl, Krista Cunningham, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

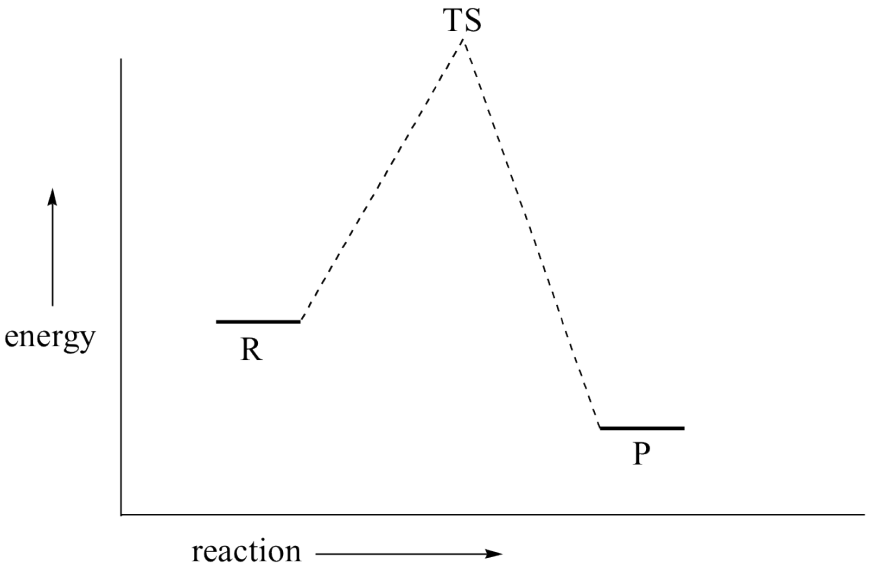
6.10: Structure and SN2 Reactivity: The Substrate

The S_N2 mechanism

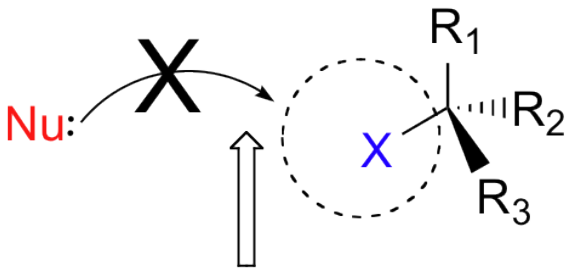
There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution. In the first picture, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



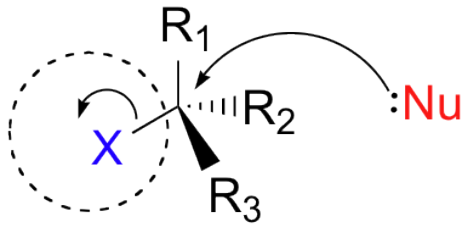
This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.

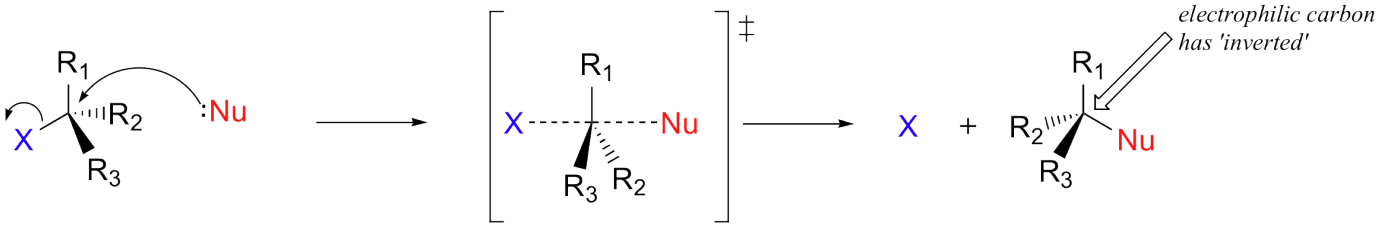


nucleophilic attack is blocked from the front side . . .



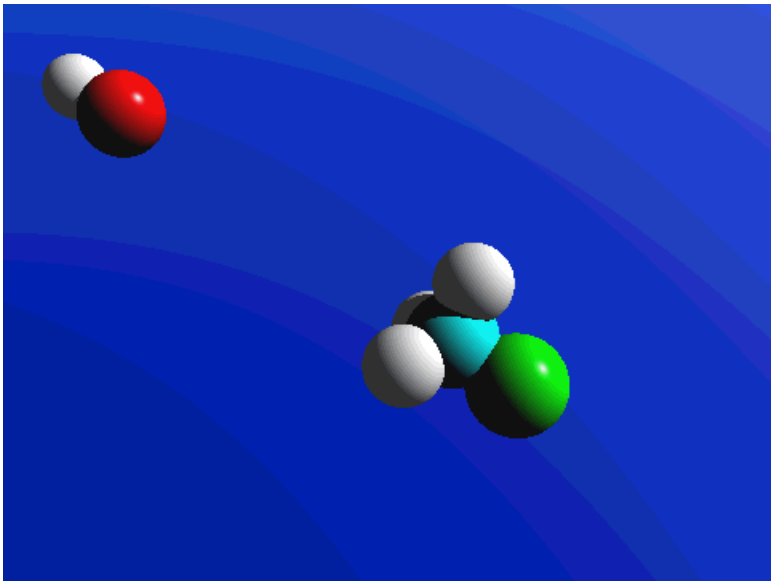
. . .so attack occurs from the back side

The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.



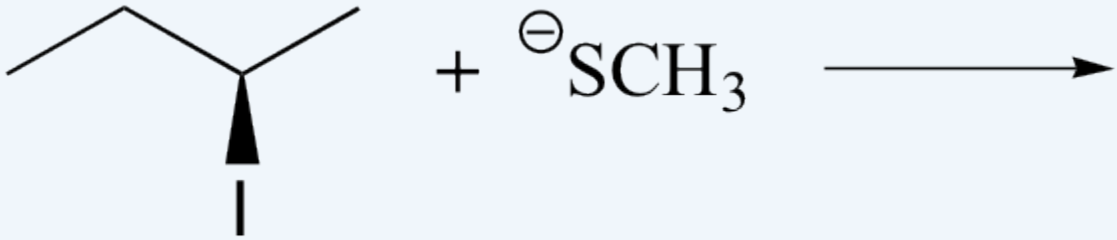
transition state

What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



Exercise

Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



We will be contrasting about two types of nucleophilic substitution reactions. One type is referred to as **unimolecular nucleophilic substitution (S_N1)**, whereby the rate determining step is unimolecular and **bimolecular nucleophilic substitution (S_N2)**, whereby the rate determining step is bimolecular. We will begin our discussion with S_N2 reactions, and discuss S_N1 reactions elsewhere.

Biomolecular Nucleophilic Substitution Reactions and Kinetics

In the term S_N2, the S stands for substitution, the N stands for nucleophilic, and the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.

Haloalkanes 05.bmp

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

Haloalkanes 06.bmp

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

Haloalkanes 07.bmp

The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

Bimolecular Nucleophilic Substitution Reactions Are Concerted

Bimolecular nucleophilic substitution (SN_2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electophilic carbon and the halogen.

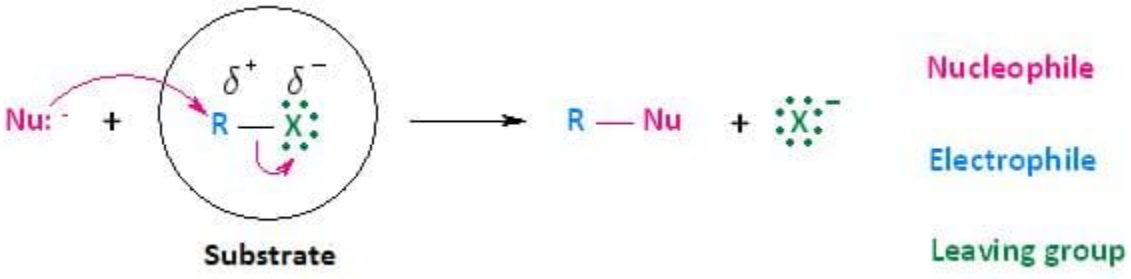
The potential energy diagram for an SN_2 reaction is shown below. Upon nucleophilic attack, a single transition state is formed. A

transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. Again, this is a single-step, concerted process with the occurrence of a single transition state.

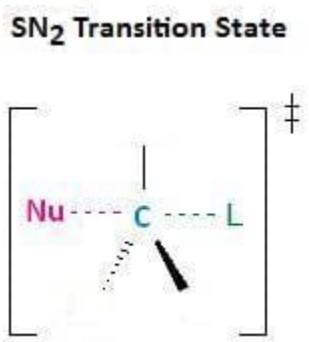
Haloalkanes 10.bmp

Sterrically Hindered Substrates Will Reduce the S_N2 Reaction Rate

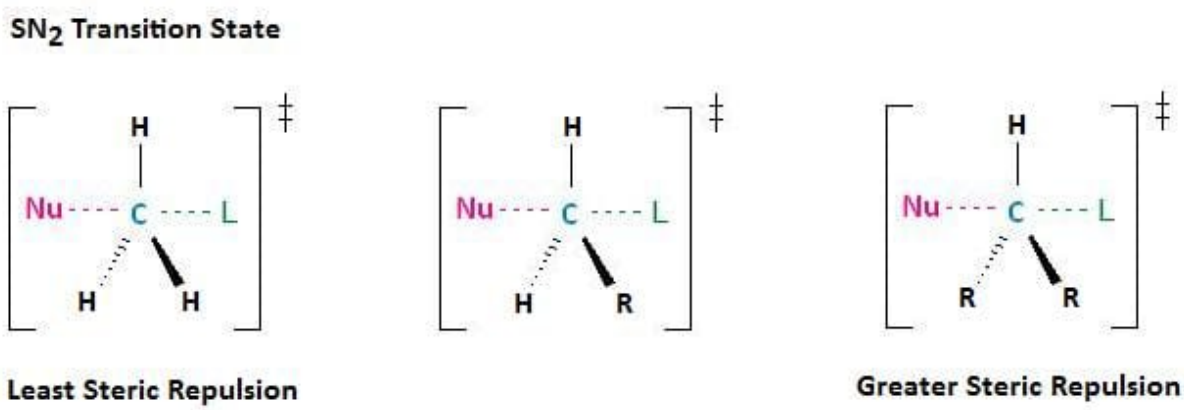
Now that we have discussed the effects that the leaving group, nucleophile, and solvent have on biomolecular nucleophilic substitution (S_N2) reactions, it's time to turn our attention to how the substrate affects the reaction. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below, we will be paying particular attention to the alkyl portion of the substrate. In other words, we are most interested in the electrophilic center that bears the leaving group.



In the section Kinetics of Nucleophilic Substitution Reactions, we learned that the SN_2 transition state is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

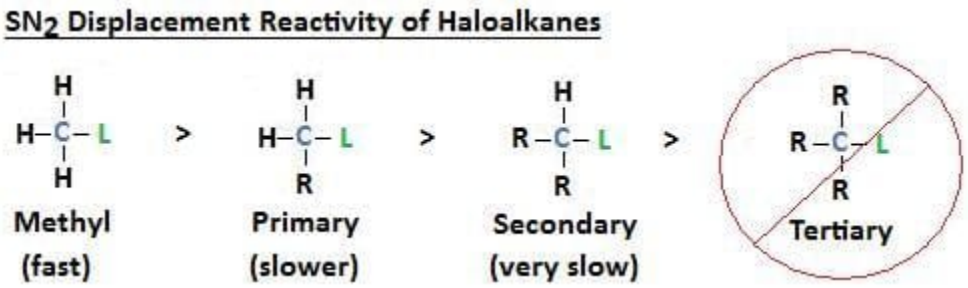


If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the SN_2 reaction to occur, the nucleophile must be able to attack the electrophilic center, resulting in the expulsion of the leaving group. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.



How does steric hindrance affect the rate at which an SN_2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. This is because the addition of one or two R groups shields the backside of the electrophilic carbon, impeding nucleophilic attack.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.



Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

Frontside vs. Backside Attacks

A biomolecular nucleophilic substitution (S_N2) reaction is a type of nucleophilic substitution whereby a lone pair of electrons on a nucleophile attacks an electron deficient electrophilic center and bonds to it, resulting in the expulsion of a leaving group. It is possible for the nucleophile to attack the electrophilic center in two ways.

- **Frontside Attack:** In a frontside attack, the nucleophile attacks the electrophilic center on the same side as the leaving group. When a frontside attack occurs, the stereochemistry of the product remains the same; that is, we have retention of configuration.
- **Backside Attack:** In a backside attack, the nucleophile attacks the electrophilic center on the side that is opposite to the leaving group. When a backside attack occurs, the stereochemistry of the product does not stay the same. There is inversion of configuration.

The following diagram illustrates these two types of nucleophilic attacks, where the frontside attack results in retention of configuration; that is, the product has the same configuration as the substrate. The backside attack results in inversion of configuration, where the product's configuration is opposite that of the substrate.

Haloalkanes 08.bmp

Experimental Observation: All S_N2 Reactions Proceed With Nucleophilic Backside Attacks

Experimental observation shows that all S_N2 reactions proceed with inversion of configuration; that is, the nucleophile will always attack from the backside in all S_N2 reactions. To think about why this might be true, remember that the nucleophile has a lone pair of electrons to be shared with the electrophilic center, and the leaving group is going to take a lone pair of electrons with it upon leaving. Because like charges repel each other, the nucleophile will always proceed by a backside displacement mechanism.

S_N2 Reactions Are Stereospecific

The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an R enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the S enantiomer.

Haloalkanes 11.bmp

Conversely, if the substrate is an S enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the S enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the R enantiomer.

Haloalkanes 12.bmp

In conclusion, S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

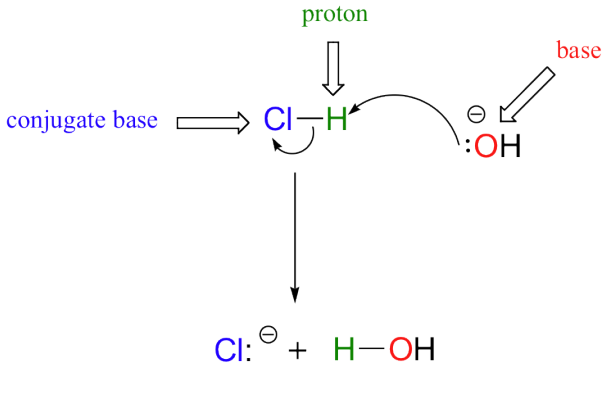
John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition*. W. A. Benjamin, Inc. ,

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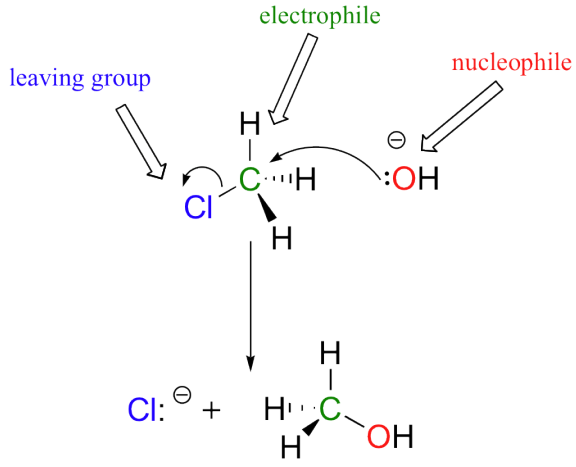
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6.11: The Sn2 Reaction at a Glance

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



acid-base reaction



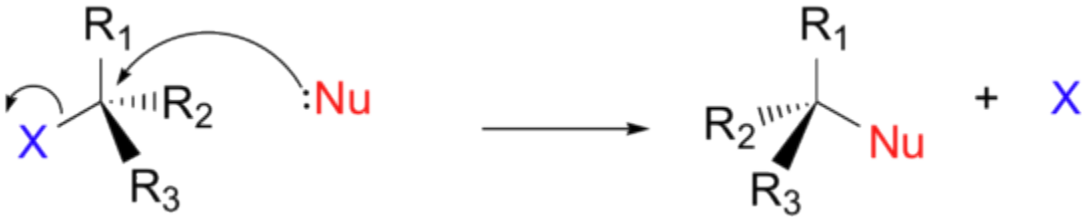
nucleophilic substitution

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

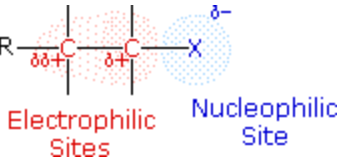
Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. In the same way, we will see later that nucleophiles and leaving groups are sometimes protonated and sometimes not, so for now, for the sake of simplicity, we will not include protons on 'Nu' or 'X'. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction:

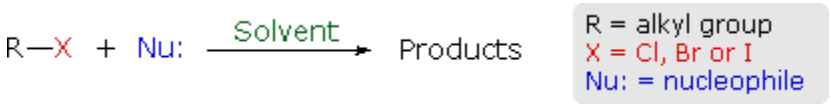


The functional group of alkyl halides is a carbon-halogen bond, the common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic, as shown in the drawing on the

right. Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is covalent bond strength. The strongest of the carbon-halogen covalent bonds is that to fluorine. Remarkably, this is the strongest common single bond to carbon, being roughly 30 kcal/mole stronger than a carbon-carbon bond and about 15 kcal/mole stronger than a carbon-hydrogen bond. Because of this, **alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable**, and do not share any of the reactivity patterns shown by the other alkyl halides. The carbon-chlorine covalent bond is slightly weaker than a carbon-carbon bond, and the bonds to the other halogens are weaker still, the bond to iodine being about 33% weaker. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF (pK_a = 3.2), all the hydrohalic acids are very strong, small differences being in the direction HCl < HBr < HI.

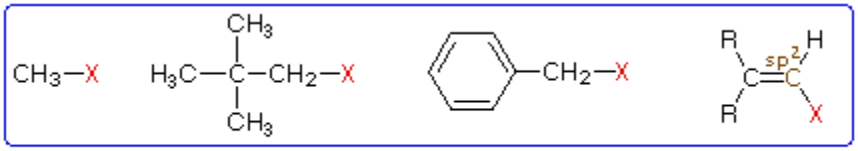


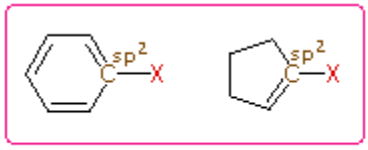
In order to understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation.



One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. **If R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.

It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).





Using the general reaction shown above as our reference, we can identify the following variables and observables.

Variables	**R** change α-carbon from 1° to 2° to 3° if the α-carbon is a chiral center, set as (*R*) or (S) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: **only one variable should be changed at a time**, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R–group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, C_2H_5–CN, in all cases,

but the speed or rate of the reaction would increase in the order: Cl < Br < I. This reactivity order reflects both the strength of the C–X bond, and the stability of $X^{(-)}$ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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6.E: Properties and Reactions of Haloalkanes: Bimolecular Nucleophilic Substitution (Exercises)

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7: FURTHER REACTIONS OF HALOALKANES: UNIMOLECULAR SUBSTITUTION AND PATHWAYS OF ELIMINATION

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

7.1: Solvolysis of Tertiary and Secondary Haloalkanes
7.2: Unimolecular Nucleophilic Substitution
7.3: Stereochemical Consequences of SN1 Reactions
7.4: Effects of Solvent, Leaving Group, and Nucleophile on Unimolecular Substitution
7.5: Effect of the Alkyl Group on the SN 1 Reaction: Carbocation Stability
7.6: Unimolecular Elimination: E1
7.7: Bimolecular Elimination: E2
7.8: Keys to Success: Substitutin Versus Elimination-Structure Determines Function
7.9: Summary of Reactivity of Haloalkanes
7.E: Further Reactions of Haloalkanes: Unimolecular Substitution (Exercises)

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7.1: Solvolysis of Tertiary and Secondary Haloalkanes

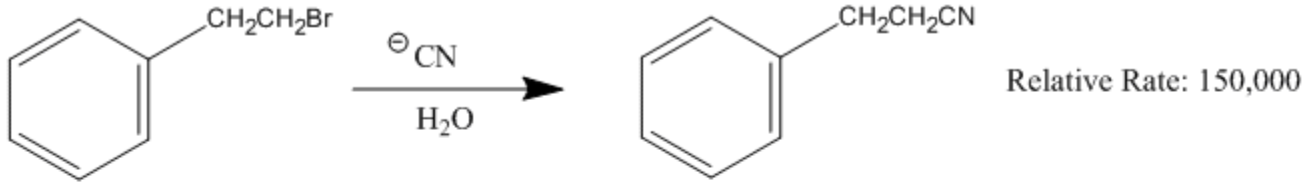
Just as with S_N2 reactions, the nucleophile, solvent and leaving group also affect S_N1 (Unimolecular Nucleophilic Substitution) reactions. Polar protic solvents have a hydrogen atom attached to an electronegative atom so the hydrogen is highly polarized. Polar aprotic solvents have a dipole moment, but their hydrogen is not highly polarized. Polar aprotic solvents are not used in S_N1 reactions because some of them can react with the carbocation intermediate and give you an unwanted product. Rather, polar protic solvents are preferred.

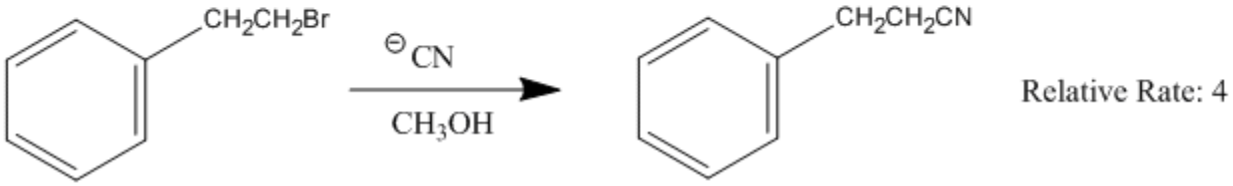
Introduction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an SN2, but it does not affect an S_N1 reaction because the nucleophile is not a part of the rate-determining step (See S_N2 Nucleophile). Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment of the solvent helps to stabilize the transition state. The highly positive and highly negative parts interact with the substrate to lower the energy of the transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction. Sometimes in an S_N1 reaction the solvent acts as the nucleophile. This is called a solvolysis reaction (see example below). The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for the solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

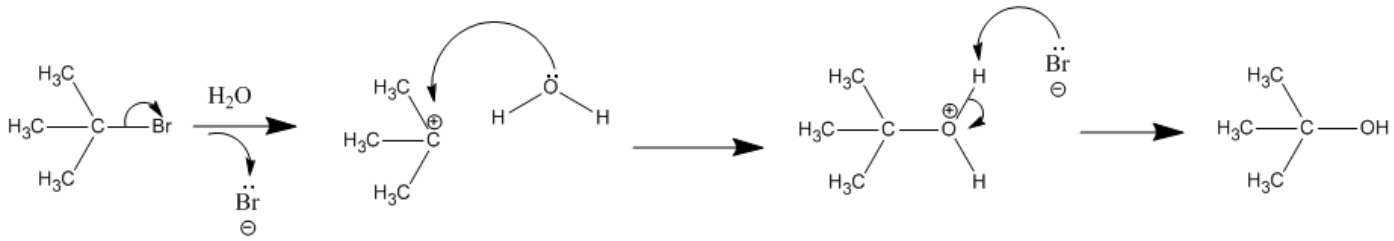
Solvent	Dielectric Constant	Relative Rate
• CH_3CO_2H	• 6	• 1
• CH_3OH	• 33	• 4
• H_2O	• 78	• 150,000

Below is the same reaction conducted in two different solvents and the relative rate that corresponds with it.





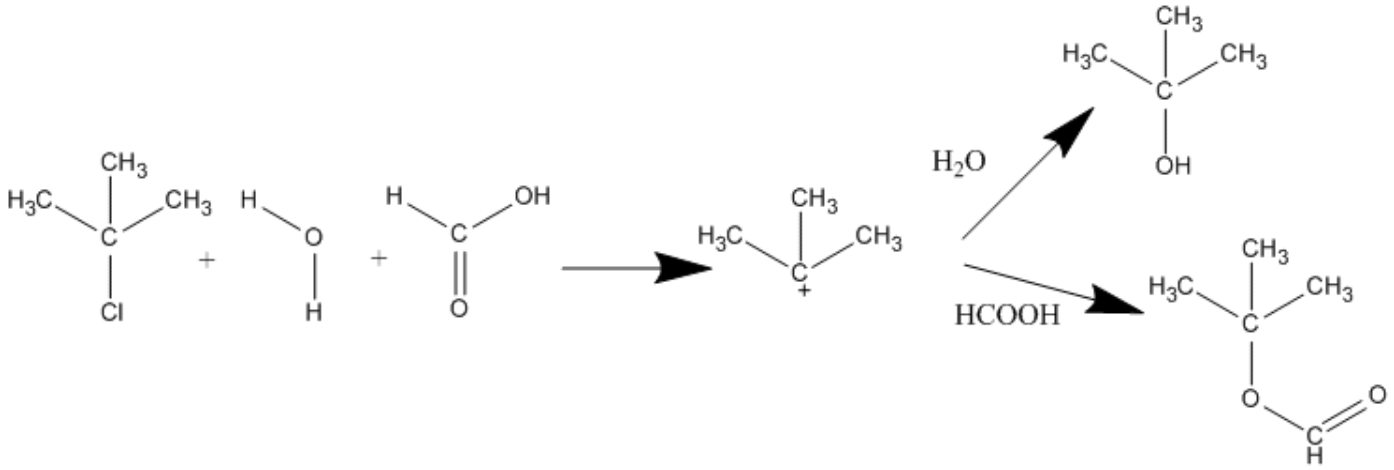
The figure below shows the mechanism of an S_N1 reaction of an alkyl halide with water. Since water is also the solvent, this is an example of a solvolysis reaction.



Examples of polar protic solvents are: acetic acid, isopropanol, ethanol, methanol, formic acid, water, etc.

Effects of Nucleophile

The strength of the nucleophile does not affect the reaction rate of SN1 because, as stated above, the nucleophile is not involved in the rate-determining step. However, if you have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affects the distribution of products that you will get. For example, if you have $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: (CH3)3COH and $(CH_3)_3$3COCOH. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.



Effects of Leaving Group



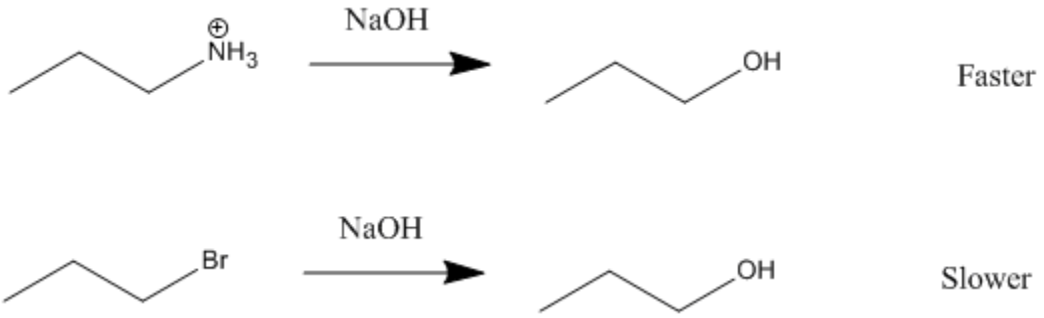
An S_N1 reaction speeds up with a good leaving group. This is because the leaving group is involved in the rate-determining step. A good leaving group wants to leave so it breaks the C-Leaving Group bond faster. Once the bond breaks, the carbocation is formed

and the faster the carbocation is formed, the faster the nucleophile can come in and the faster the reaction will be completed.

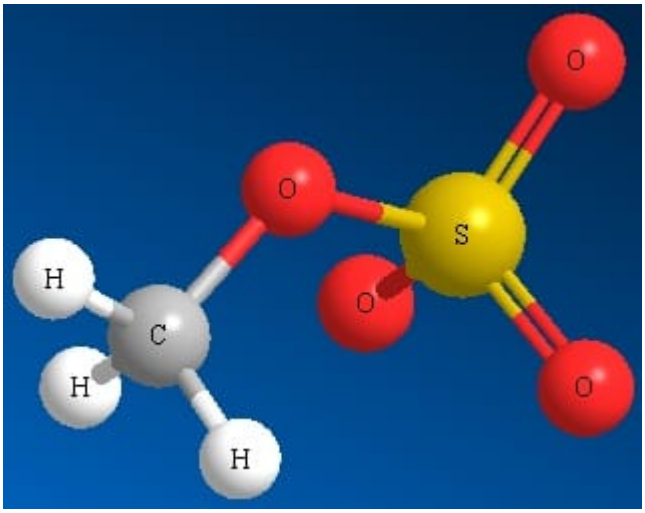
A good leaving group is a weak base because weak bases can hold the charge. They're happy to leave with both electrons and in order for the leaving group to leave, it needs to be able to accept electrons. Strong bases, on the other hand, donate electrons which is why they can't be good leaving groups. As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whos leaving-group ability increases as you go down the column.

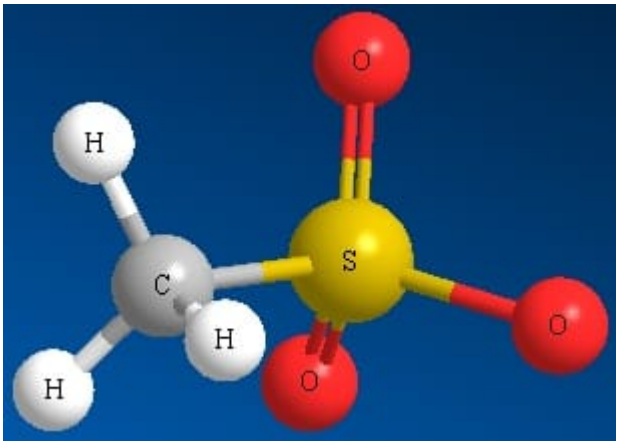


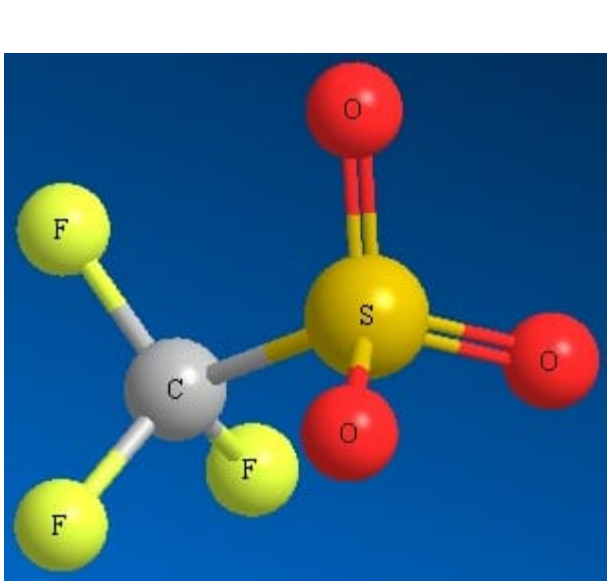
The two reactions below is the same reaction done with two different leaving groups. One is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.

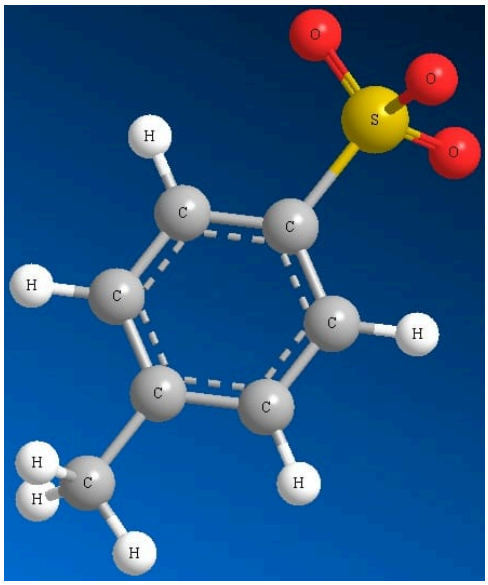


Other examples of good leaving groups are sulfur derivatives such as methyl sulfate ion and other sulfonate ions (See Figure below)









Methyl Sulfate Ion Mesylate Ion Triflate Ion Tosylate Ion

References

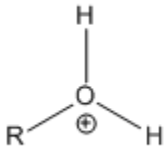
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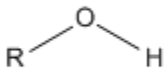
Outside Links

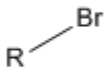
- http://en.Wikipedia.org/wiki/Sn1
- http://www.youtube.com/watch?v=FuFpjx_ZeT0 (Pretty good summary of SN1 reaction)

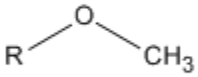
Problems

1. Put the following leaving groups in order of decreasing leaving group ability





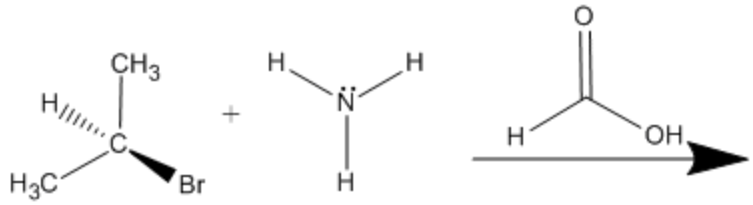




2. Which solvent would an SN1 reaction occur faster in? H2O or CH3CN

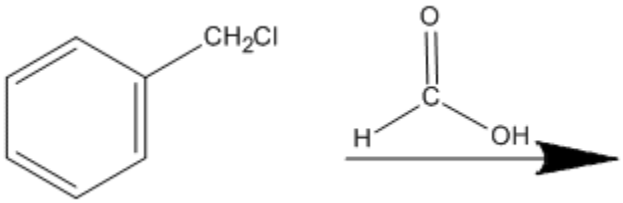
3. What kind of conditions disfavor SN1 reactions?

4. What are the products of the following reaction and does it proceed via SN1 or SN2?



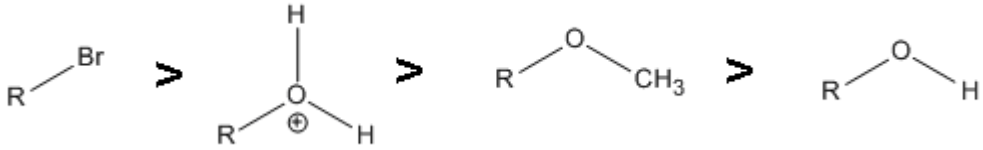
5. How could you change the reactants in the problem 4 to favor the other substitution reaction?

6. Indicate the expected product and list why it occurs through SN1 instead of SN2?



Answers

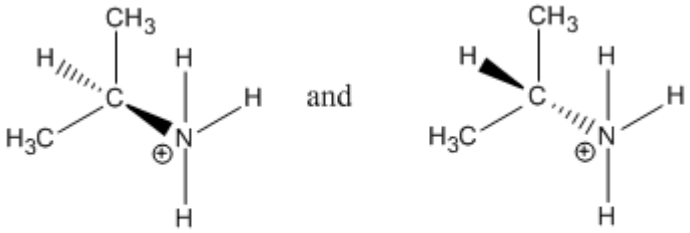
1.



2. An SN1 reaction would occur faster in H2O because it's polar protic and would stailize the carbocation and CH3CN is polar aprotic.

3. Polar aprotic solvents, a weak leaving group and primary substrates disfavor SN1 reactions.

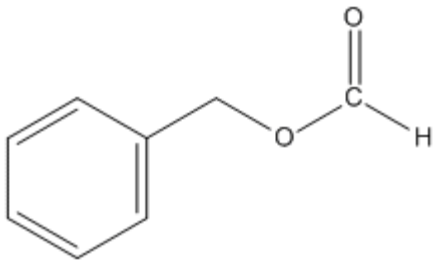
4.



Racemic Mixture

Reaction proceeds via SN1 because a tertiary carbocation was formed, the solvent is polar protic and Br- is a good leaving group.

5. You could change the solvent to something polar aprotic like CH3CN or DMSO and you could use a better base for a nucleophile such as NH2- or OH-.

6. 

This reaction occurs via SN1 because Cl- is a good leaving group and the solvent is polar protic. This is an example of a solvolysis reaction because the nucleophile is also the solvent.

Contributors

- Ashiv Sharma

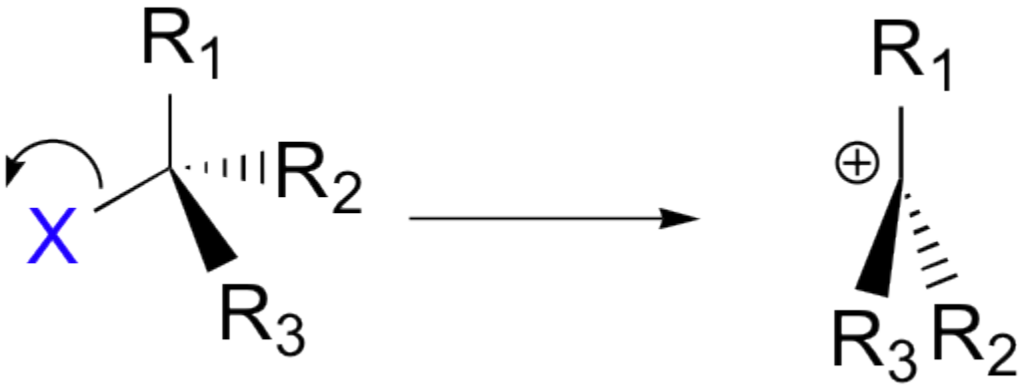
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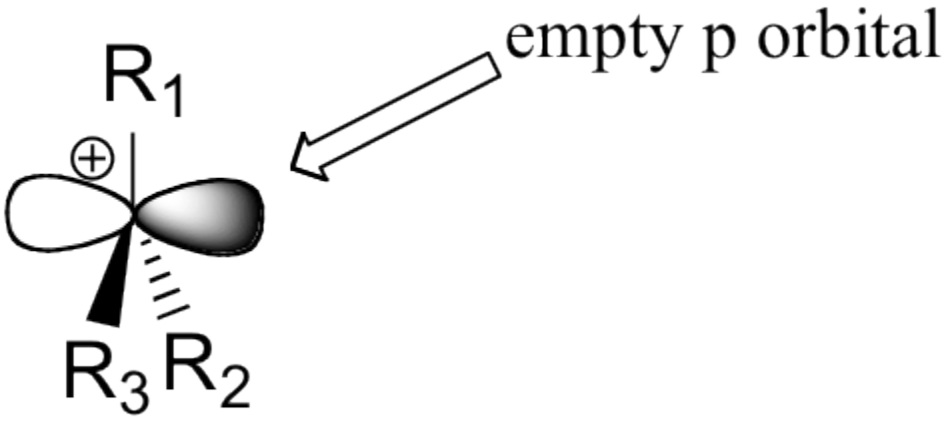
7.2: Unimolecular Nucleophilic Substitution

The S_N1 mechanism

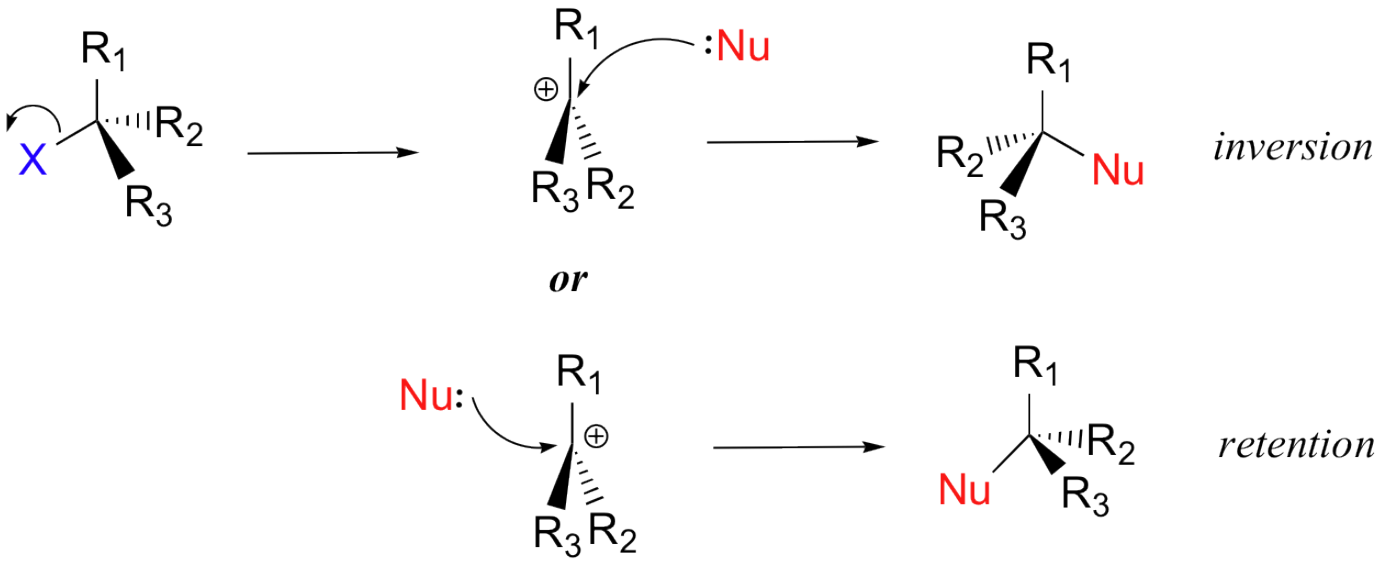
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



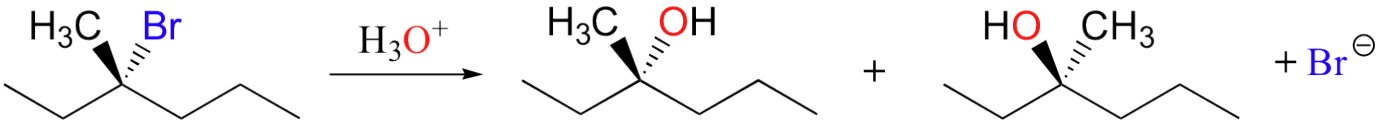
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.

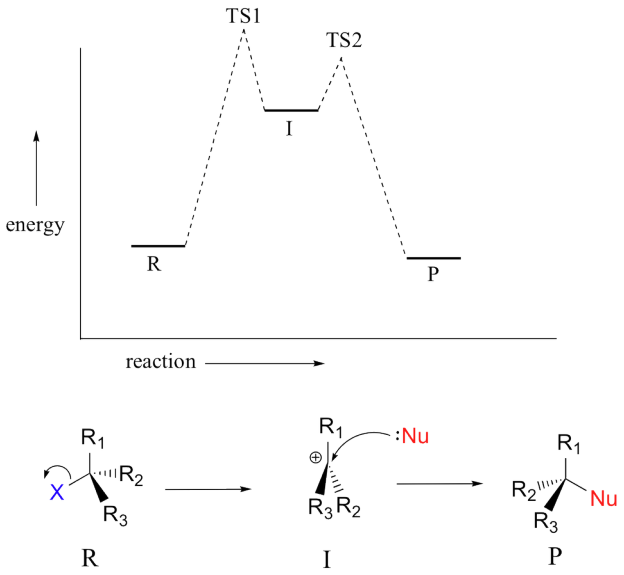


We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



Exercise
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

The S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.

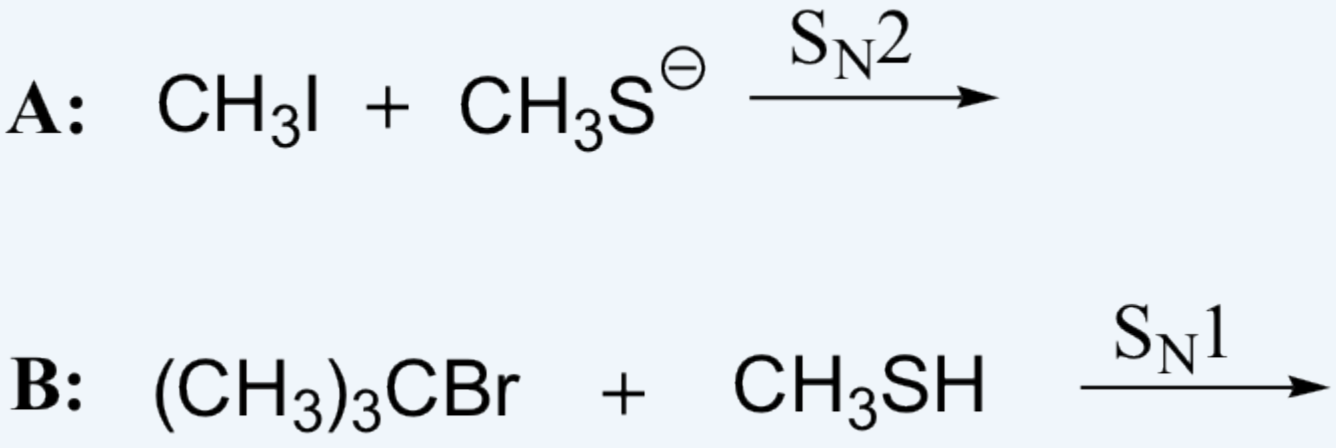


Exercise
Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding.

Exercise

Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

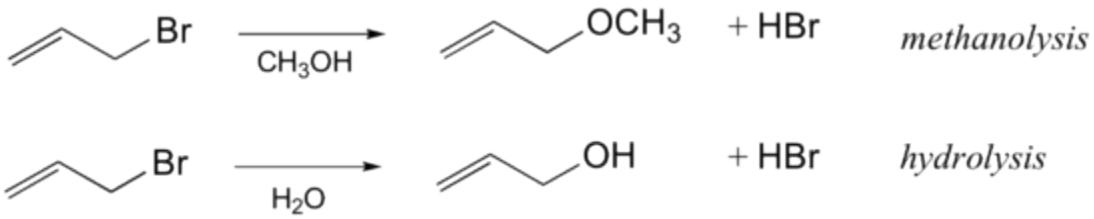


Influence of the solvent in an SN1 reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an SN2, but it does not affect an SN1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment

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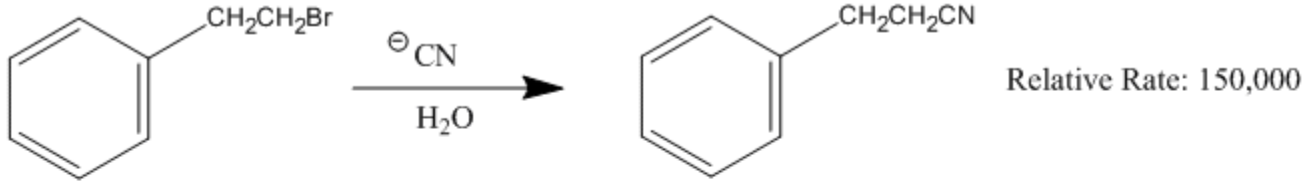
Sometimes in an SN1 reaction the solvent acts as the nucleophile. This is called a solvolysis reaction.The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:

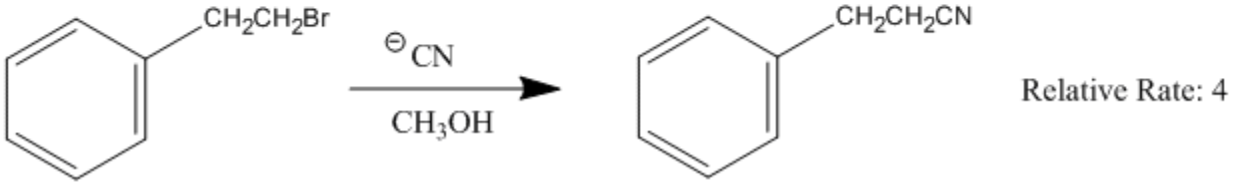


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Solvent	Dielectric Constant	Relative Rate
• CH_3CO_2H • CH_3OH • H_2O	• 6 • 33 • 78	• 1 • 4 • 150,000

Below is the same reaction conducted in two different solvents and the relative rate that corresponds with it.

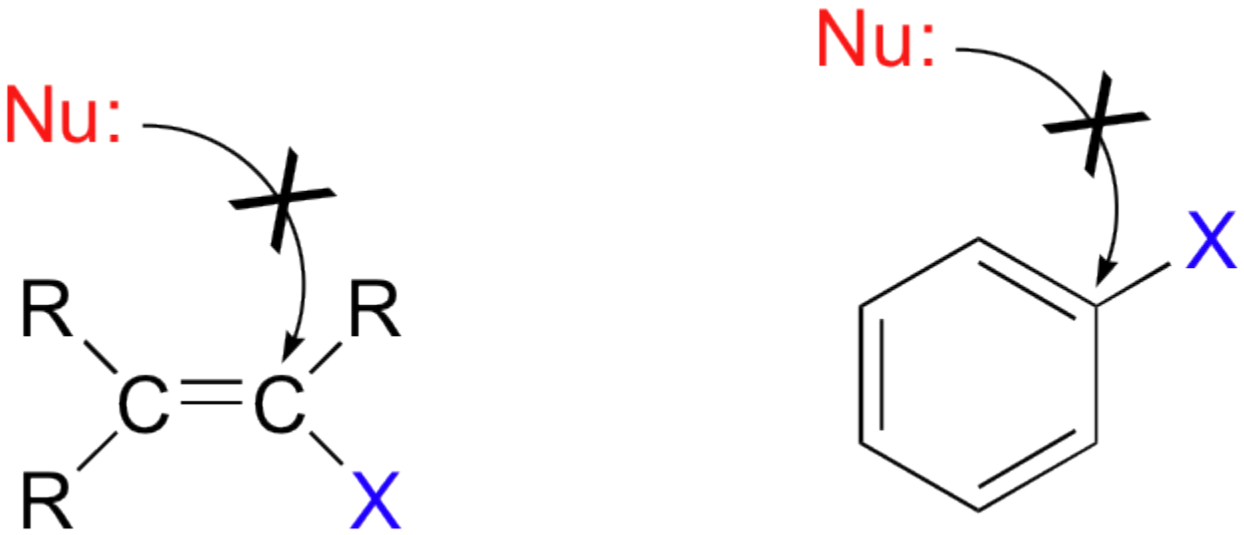




Exercise
Draw a complete curved-arrow mechanism for the methanolysis reaction of allyl bromide shown above.

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3-hybridized carbons,

and *not* where the leaving group is attached to an sp^2-hybridized carbon::



Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable (we'll discuss the relative stability of carbocation intermediates in a later section of this module).

Before we look at some real-life nucleophilic substitution reactions in the next chapter, we will spend some time in the remainder of this module focusing more closely on the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group.

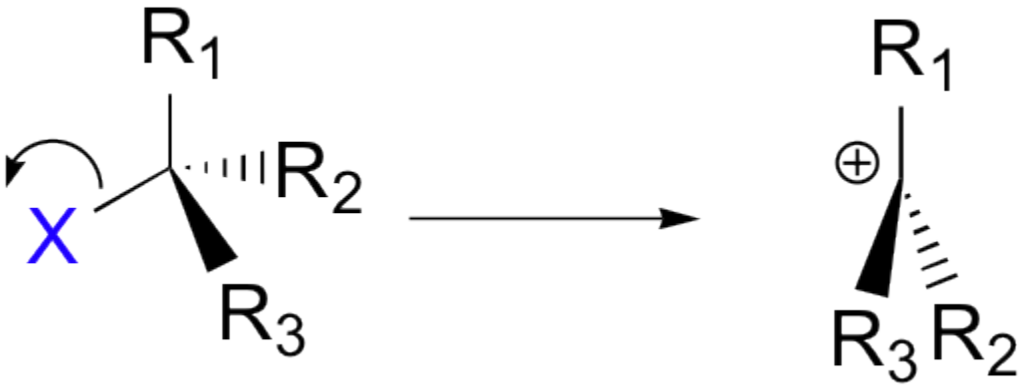
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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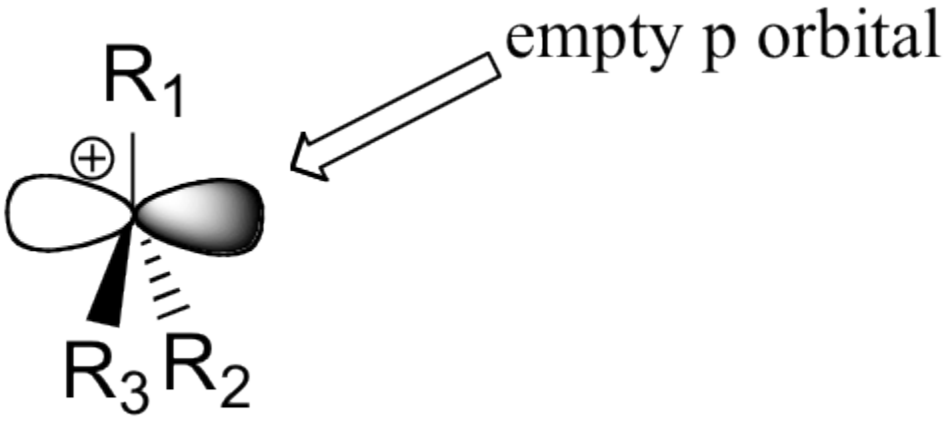
7.3: Stereochemical Consequences of SN1 Reactions

The S_N1 mechanism

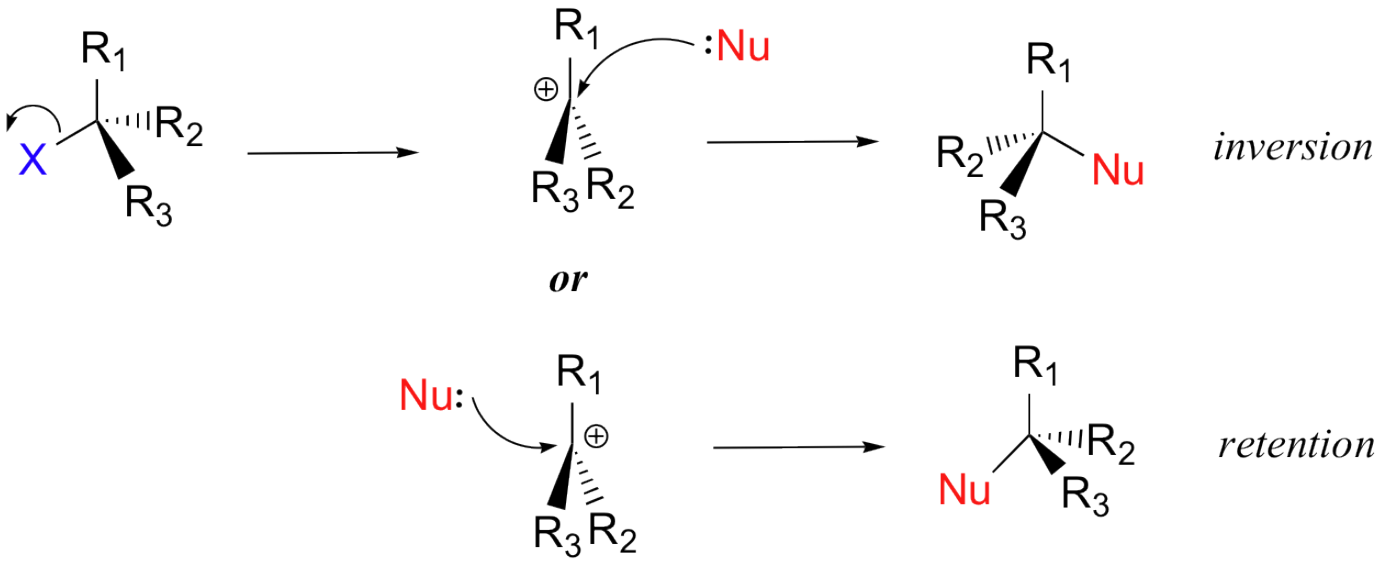
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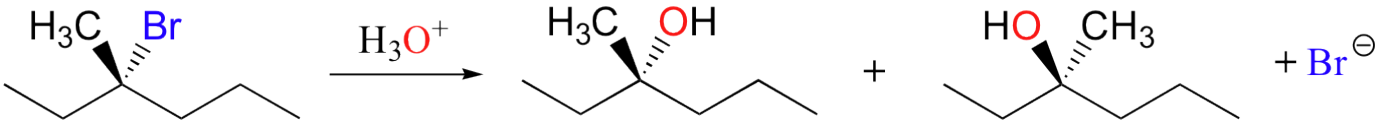
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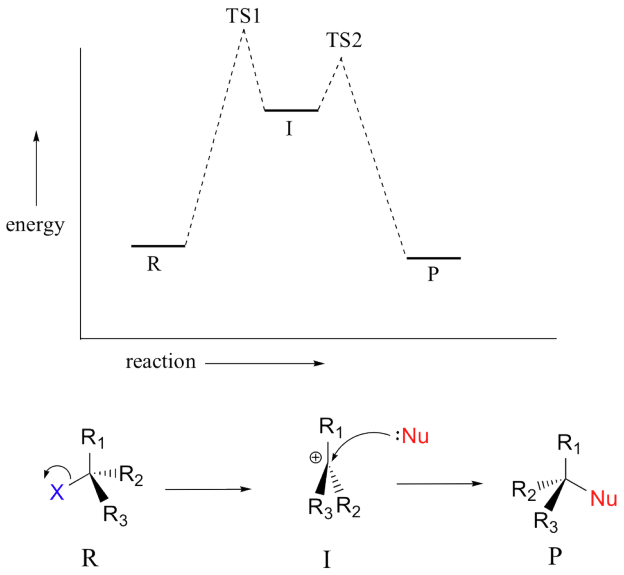


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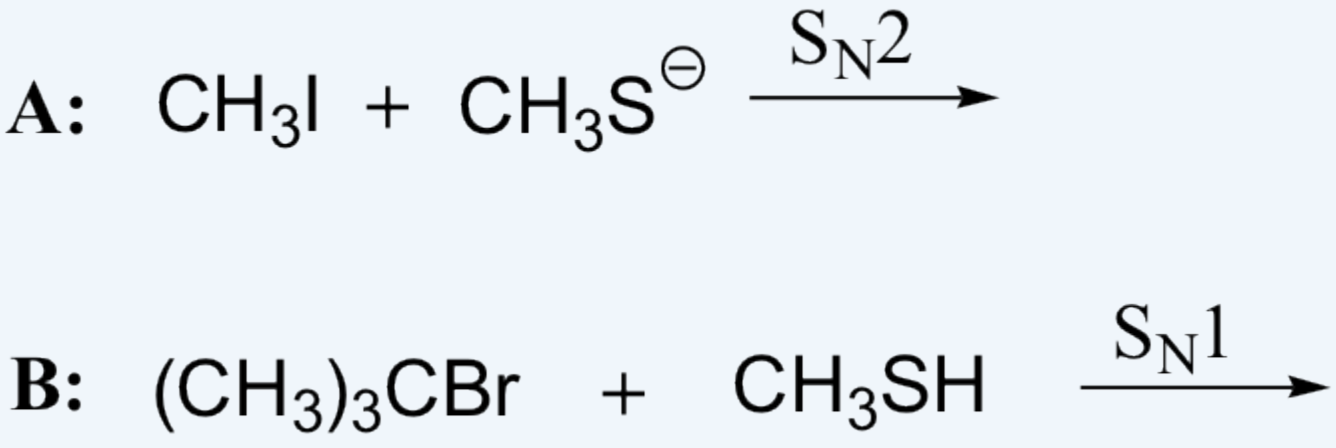


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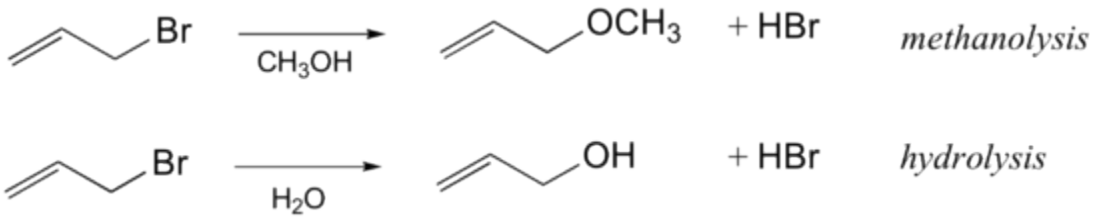


Influence of the solvent in an SN1 reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an SN2, but it does not affect an SN1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment

of the solvent helps to stabilize the transition state. The highly positive and highly negative parts interact with the substrate to lower the energy of the transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.

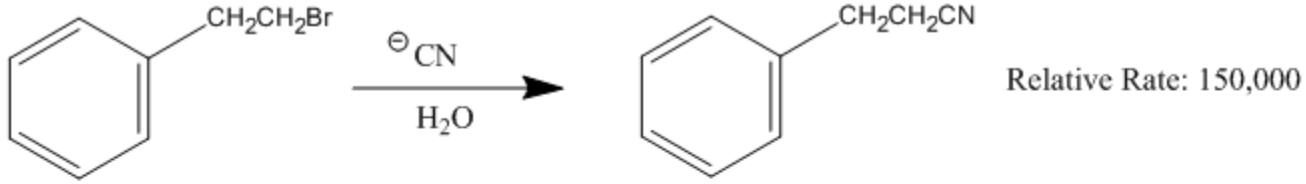
Sometimes in an SN1 reaction the solvent acts as the nucleophile. This is called a solvolysis reaction.The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:

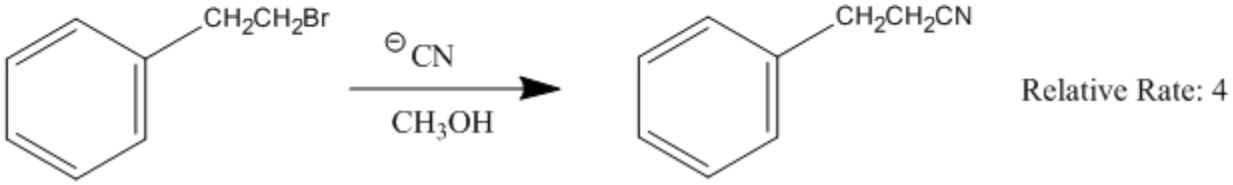


The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for the solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

Solvent	Dielectric Constant	Relative Rate
• CH_3CO_2H	• 6	• 1
• CH_3OH	• 33	• 4
• H_2O	• 78	• 150,000

Below is the same reaction conducted in two different solvents and the relative rate that corresponds with it.

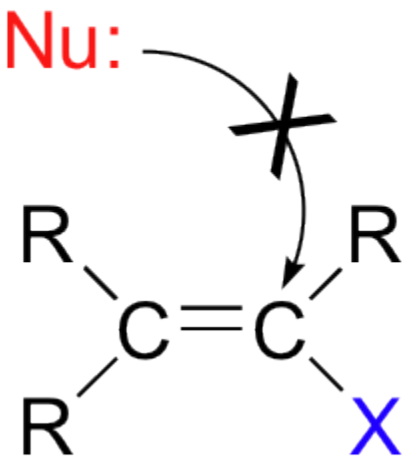


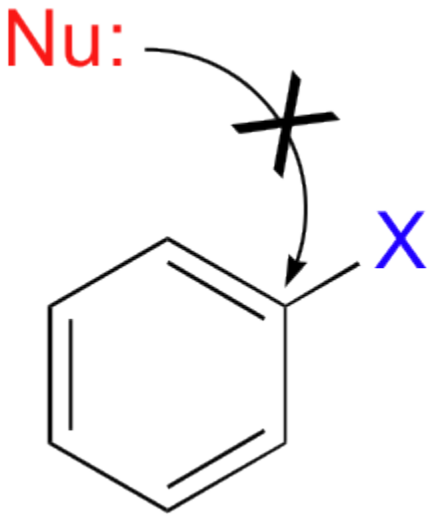


Exercise
Draw a complete curved-arrow mechanism for the methanolysis reaction of allyl bromide shown above.

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3-hybridized carbons,

and *not* where the leaving group is attached to an sp^2-hybridized carbon::





Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable (we'll discuss the relative stability of carbocation intermediates in a later section of this module).

Before we look at some real-life nucleophilic substitution reactions in the next chapter, we will spend some time in the remainder of this module focusing more closely on the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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7.4: Effects of Solvent, Leaving Group, and Nucleophile on Unimolecular Substitution

Objectives

After completing this section, you should be able to

1. discuss how the structure of the substrate affects the rate of a reaction occurring by the S_N1 mechanism.
2. arrange a given list of carbocations (including benzyl and allyl) in order of increasing or decreasing stability.
3. explain the high stability of the allyl and benzyl carbocations.
4. arrange a given series of compounds in order of increasing or decreasing reactivity in S_N1 reactions, and discuss this order in terms of the Hammond postulate.
5. discuss how the nature of the leaving group affects the rate of an S_N1 reaction, and in particular, explain why S_N1 reactions involving alcohols are carried out under acidic conditions.
6. explain why the nature of the nucleophile does not affect the rate of an S_N1 reaction.
7. discuss the role played by the solvent in an S_N1 reaction, and hence determine whether a given solvent will promote reaction by this mechanism.
8. compare the roles played by the solvent in S_N1 and in S_N2 reactions.
9. determine which of two S_N1 reactions will occur faster, by taking into account factors such as the structure of the substrate and the polarity of the solvent.
10. determine whether a given reaction is most likely to occur by an S_N1 or S_N2 mechanism, based on factors such as the structure of the substrate, the solvent used, etc.

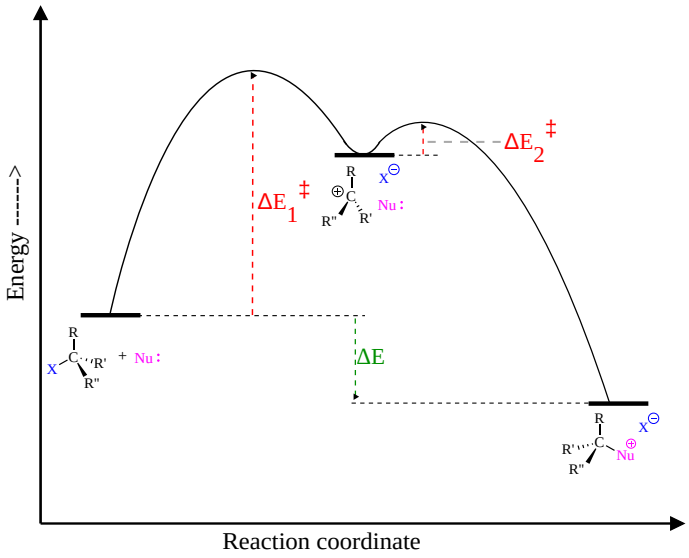
Key Terms

Make certain that you can define, and use in context, the key terms below.

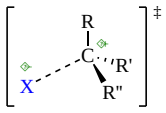
- benzylic
- dielectric constant
- polarity

The Substrate in S_N1Reactions

As discussed in the previous section S_N1 reactions follow first order kinetics due to a multi-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide to form a carbocation.



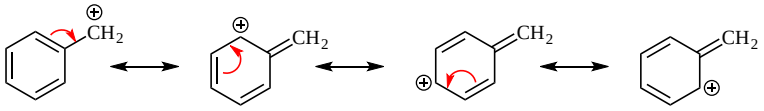
The transition state for the rate determining step shows the transition of an alkyl halide to a carbocation. Because the rate determining step is endothermic, the Hammond postulate says that the transition state more closely resembles the carbocation intermediate. Factors which stabilize this intermediate will lower the energy of activation for the rate determining step and cause the rate of reaction to increase. In general, a more stable carbocation intermediate formed during the reaction allows for a faster the S_N1 reaction rate.



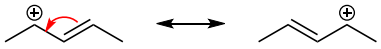
Transition State 1

($TS_1^{\ddagger}$)

In Section 7-9, the stability of alky carbocations was shown to be $3^o > 2^o > 1^o >$ methyl. Two special cases of resonance-stabilized carbocations, allyl and benzyl, must be considered and added to the list. The delocalization of the positive charge over an extended p orbital system allows for allyl and benzyl carbocations to be exceptionally stable. The resonance hybrid of an allyic cation is made up of two resonance forms while the resonance hybrid of the benzylic carbocation is made up of five.

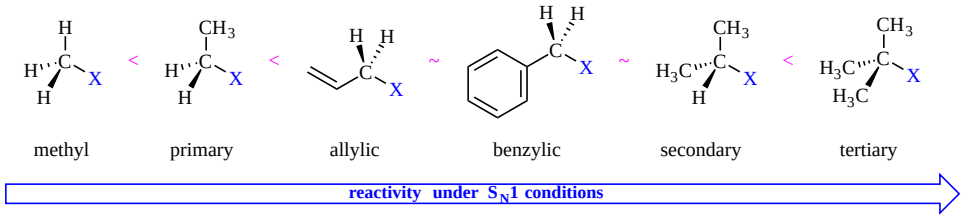


Resonance Structures for a Benzyl Carbocation



Resonance Structures for an Allylic Carbocation

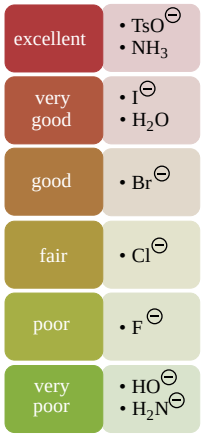
Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	CH_2=CH-$CH_2^{(+)}$	≈	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

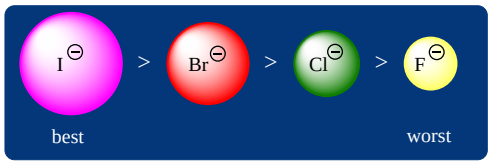


Effects of Leaving Group

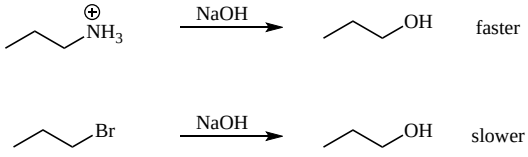
Since leaving group removal is involved in the rate-determining step of the S_N1 mechanism, reaction rates increase with a good leaving group. A good leaving group can stabilize the electron pair it obtains after the breaking of the C-Leaving Group bond faster. Once the bond breaks, the carbocation is formed and the faster the carbocation is formed, the faster the nucleophile can come in and the faster the reaction will be completed.

Because weak bases tend to strongly hold onto their electrons, they are lower energy molecules and they tend to make good leaving groups. Strong bases, on the other hand, donate electrons readily because they are high energy, reactive molecules. Therefore, they are not typically good leaving groups. As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whose leaving-group ability increases as you go down the halogen column of the periodic table.



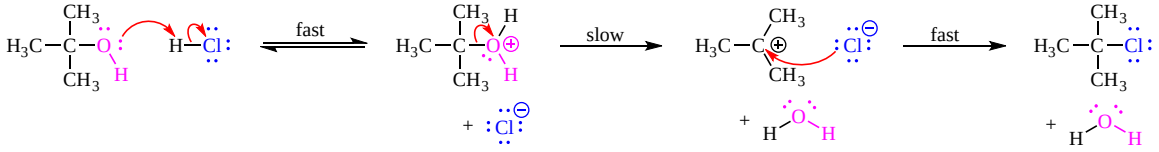


The two reactions below only vary by the different leaving groups in each reaction. The reaction with a more stable leaving group is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.



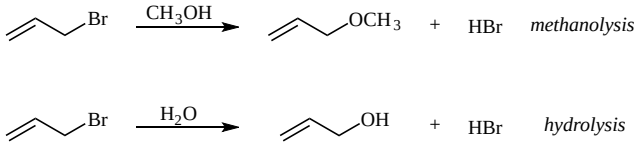
Under acidic conditions, the -OH group of an alcohol can be converted into a neutral water leaving group through protonation. As discussed in **Section 10-5**, this occurs during the conversion of a tertiary alcohol to an alkyl halide through reaction with HCl or HBr. Because the -OH group itself is a poor nucleophile, the mechanism starts with protonation to form a hydronium ion. Neutral water is then lost as a leaving group to create the carbocation intermediate which then reacts with the halide ion nucleophile to

provide the alkyl halide product. This reaction works best when a tertiary alcohol is used because it produces a stable carbocation intermediate.

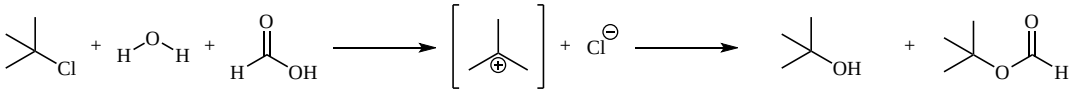


The Nucleophile

Since nucleophiles only participate in the fast second step, their relative molar concentrations rather than their nucleophilicities should be the primary product-determining factor. If a nucleophilic solvent such as water is used, its high concentration will assure that alcohols are the major product. While recombination of the halide anion with the carbocation intermediate can occur, it simply reforms the starting compound. Also this is less likely since there are less molecules of the leaving group in solution than there are of the solvent. Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:



The strength of the nucleophile does not affect the reaction rate of S_N1 because, as described previously, the nucleophile is not involved in the rate-determining step. However, if you have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affects the distribution of products that you will get. For example, if you have $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.

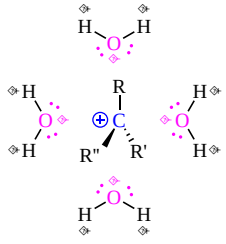


(product if water acts as a nucleophile)

(product if formic acid acts as a nucleophile)

Solvent Effects on the S_N1 Reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an S_N2 reaction which depends on nucleophilic attack during the rate-determining step of the reaction. However, this does not affect an S_N1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment of the solvent helps to stabilize the carbocation-like transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.



The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for a solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

Solvent	Dielectric Constant	Relative Rate
CH_3CO_2H	6	1
CH_3OH	33	4
H_2O	78	150,000

(note that even though acetic acid is a highly polar molecule, it tends to make a dimer with itself greatly reducing its dielectric constant)

Predicting S_N1 vs. S_N2 mechanisms

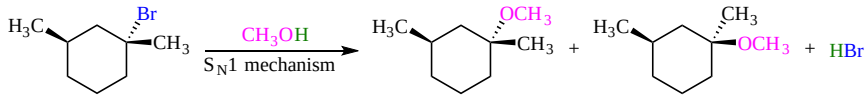
When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.

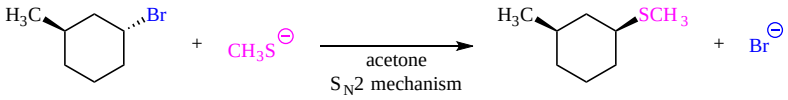
2) **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.

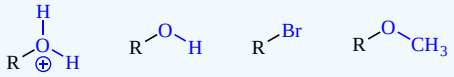


In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar aprotic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



Exercise 7.4.1

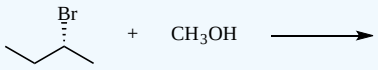
1. Put the following leaving groups highlighted in blue in order of decreasing leaving group ability



2. Which solvent would an S_N1 reaction occur faster in? H_2O or CH_3CN

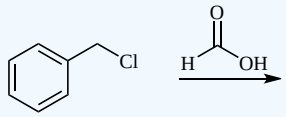
3. What kind of conditions disfavor S_N1 reactions?

4. What are the products of the following reaction and does it proceed via S_N1 or S_N2?

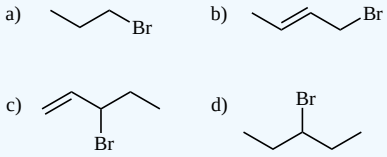


5. How could you change the reactants in the problem 4 to favor the other substitution reaction?

6. Indicate the expected product and list why it occurs through S_N1 instead of S_N2?

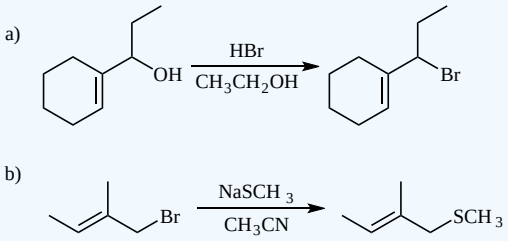


7. Rank the following by increasing reactivity in an S_N1 reaction.

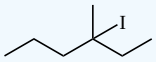


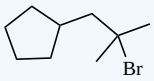
8. 3-bromo-1-pentene and 1-bromo-2-pentene undergo S_N1 reaction at almost the same rate, but one is a secondary halide while the other is a primary halide. Explain why this is.

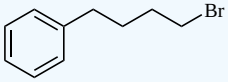
9. Label the following reactions as most likely occuring by an S_N1 or S_N2 mechanism. Suggest why.

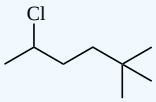


10. Give the solvolysis product expected when the compound is heated in methanol.

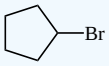
a) 

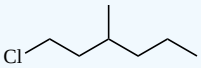
b) 

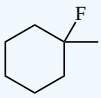
c) 

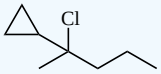
d) 

11. Predict whether each compound below would be more likely to undergo a S_N2 or S_N1 reaction.

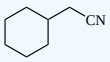
a) 

b) 

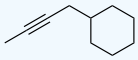
c) 

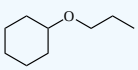
d) 

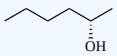
12. Show how each compound may be synthesized using nucleophilic substitution reactions.

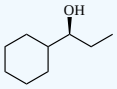
a) 

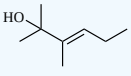
b) 

c) 

d) 

e) 

f) 

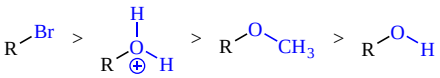
g) 

Answers available at the end of this section.

Answers

Exercise 7.4.1

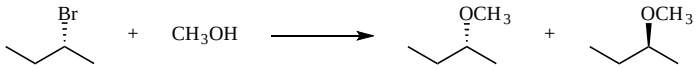
1.



2. An S_N1 reaction would occur faster in H_2O because it's polar protic and would stabilize the carbocation and CH_3CN is polar aprotic.

3. Polar aprotic solvents, a weak leaving group and primary substrates disfavor S_N1 reactions.

4.

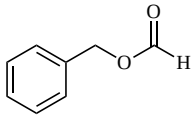


racemic mixture

Reaction proceeds via S_N1 because a secondary carbocation was formed, the solvent is polar protic and Br- is a good leaving group.

5. You could change the solvent to something polar aprotic like CH_3CN or DMSO, and you could use a stronger nucleophile such as $NaOCH_3$. Note that this would give only the inverted product, and not a racemic mixture.

6.

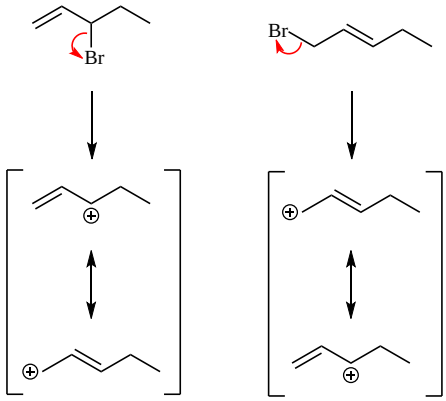


This reaction occurs via S_N1 because Cl^- is a good leaving group, the intermediate carbocation is a stable benzylic cation, and the solvent is polar protic. This is an example of a solvolysis reaction because the nucleophile is also the solvent.

7. Consider the stability of the intermediate, the carbocation.

A < D < B < C (most reactive)

8. They have the same intermediates when you look at the resonance forms.

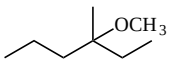


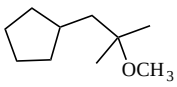
9.

A – S_N1 *poor leaving group, protic solvent, secondary cation intermediate

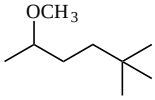
B – S_N2 *good leaving group, polar solvent, primary position.

10.

a) 

b) 

c) no reaction

d) 

11.

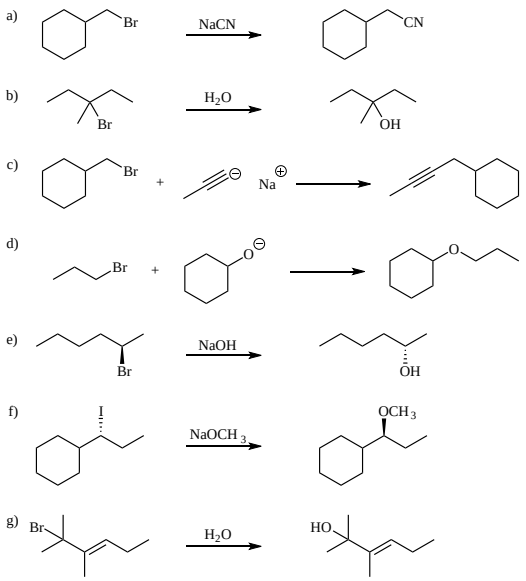
a) Can undergo S_N1 or S_N2, depending on reaction conditions

b) S_N2

c) S_N1

d) S_N1

12.



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- 11.5: Characteristics of the SN1 Reaction by Ashiv Sharma, Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

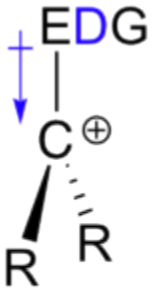
7.5: Effect of the Alkyl Group on the SN 1 Reaction: Carbocation Stability

Stability of carbocation intermediates

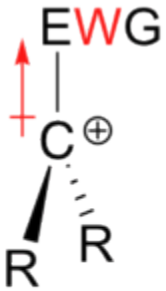
We know that the rate-limiting step of an S_N1 reaction is the first step - formation of the this carbocation intermediate. The rate of this step – and therefore, the rate of the overall substitution reaction – depends on the activation energy for the process in which the bond between the carbon and the leaving group breaks and a carbocation forms. According to Hammond's postulate (section 6.2B), the more stable the carbocation intermediate is, the faster this first bond-breaking step will occur. In other words, the likelihood of a nucleophilic substitution reaction proceeding by a dissociative (S_N1) mechanism depends to a large degree on the stability of the carbocation intermediate that forms.

The critical question now becomes, *what stabilizes a carbocation?*

So if it takes an electron *withdrawing* group to stabilize a negative charge, what will stabilize a positive charge? An electron *donating* group!



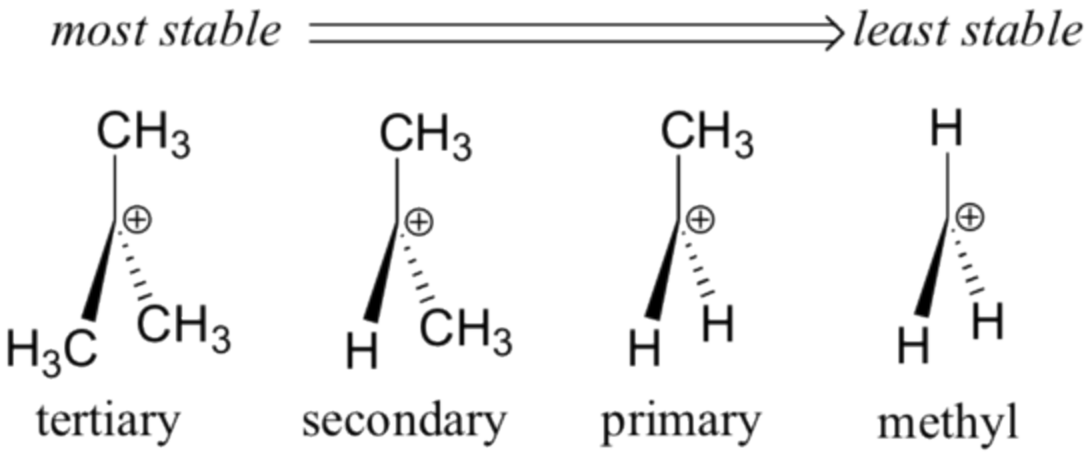
Electron Donating Group:
stabilizes a carbocation



Electron Withdrawing Group:
*de*stabilizes a carbocation

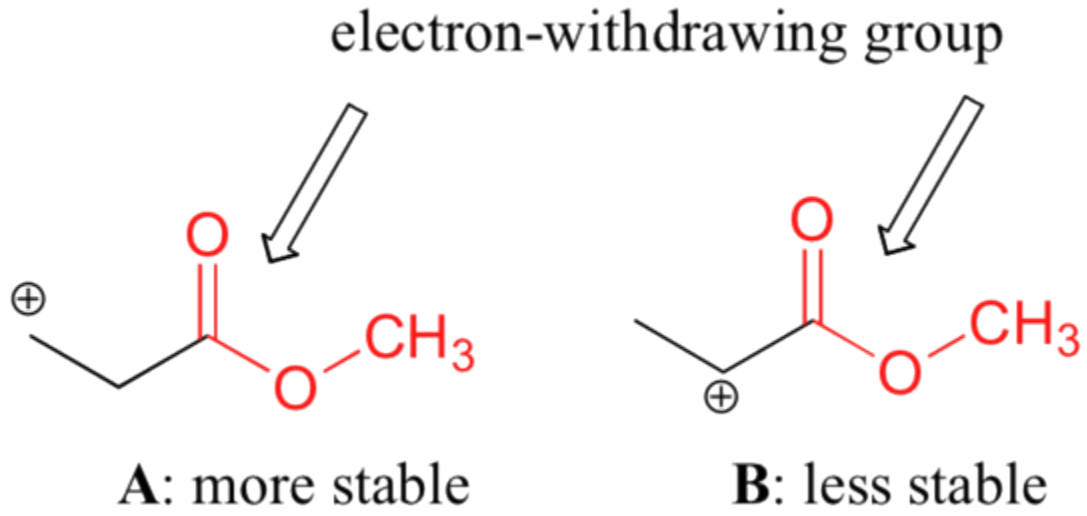
A positively charged species such as a carbocation is very electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.

Alkyl groups – methyl, ethyl, and the like – are weak electron donating groups, and thus stabilize nearby carbocations. What this means is that, in general, *more substituted carbocations are more stable*: a tert-butyl carbocation, for example, is more stable than an isopropyl carbocation. Primary carbocations are highly unstable and not often observed as reaction intermediates; methyl carbocations are even less stable.



Alkyl groups are electron donating and carbocation-stabilizing because the electrons around the neighboring carbons are drawn towards the nearby positive charge, thus slightly reducing the electron poverty of the positively-charged carbon.

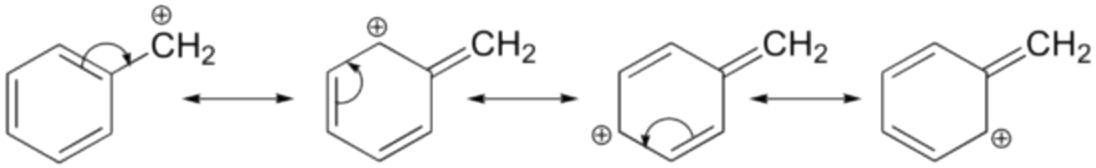
It is not accurate to say, however, that carbocations with higher substitution are *always* more stable than those with less substitution. Just as electron-donating groups can stabilize a carbocation, electron-withdrawing groups act to destabilize carbocations. Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the C=O double bond. It is possible to demonstrate in the laboratory (see section 16.1D) that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.



The difference in stability can be explained by considering the electron-withdrawing inductive effect of the ester carbonyl. Recall that inductive effects - whether electron-withdrawing or donating - are relayed through covalent bonds and that the strength of the effect decreases rapidly as the number of intermediary bonds increases. In other words, the effect decreases with distance. In species B the positive charge is closer to the carbonyl group, thus the destabilizing electron-withdrawing effect is stronger than it is in species A.

In the next chapter we will see how the carbocation-destabilizing effect of electron-withdrawing fluorine substituents can be used in experiments designed to address the question of whether a biochemical nucleophilic substitution reaction is S_N1 or S_N2.

Stabilization of a carbocation can also occur through resonance effects, and as we have already discussed in the acid-base chapter, resonance effects as a rule are more powerful than inductive effects. Consider the simple case of a **benzylic** carbocation:

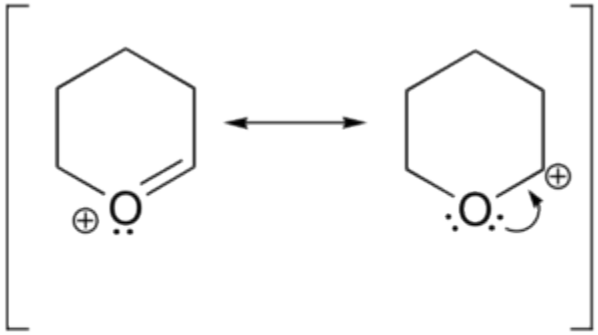


This carbocation is comparatively stable. In this case, electron donation is a resonance effect. Three additional resonance structures can be drawn for this carbocation in which the positive charge is located on one of three aromatic carbons. The positive charge is not isolated on the benzylic carbon, rather it is delocalized around the aromatic structure: this delocalization of charge results in significant stabilization. As a result, benzylic and **allylic** carbocations (where the positively charged carbon is conjugated to one or more non-aromatic double bonds) are significantly more stable than even tertiary alkyl carbocations.

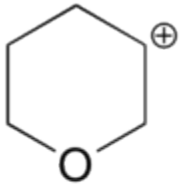


an allylic carbocation

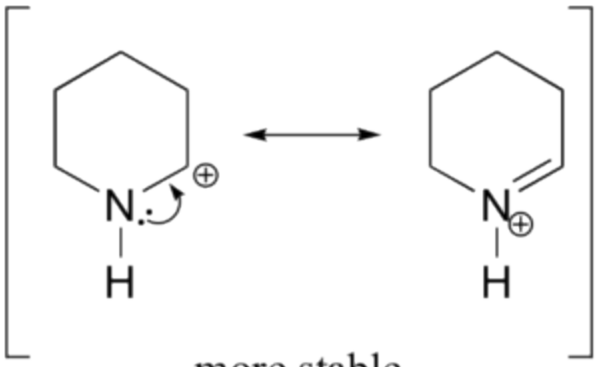
Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall effect is carbocation stabilization. This is due to the fact that although these heteroatoms are electron *withdrawing* groups by induction, they are electron *donating* groups by resonance, and it is this resonance effect which is more powerful. (We previously encountered this same idea when considering the relative acidity and basicity of phenols and aromatic amines in section 7.4). Consider the two pairs of carbocation species below:



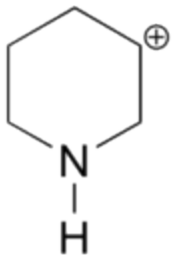
more stable



less stable
(no resonance delocalization)



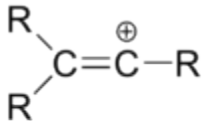
more stable



less stable
(no resonance delocalization)

In the more stable carbocations, the heteroatom acts as an electron donating group by resonance: in effect, the lone pair on the heteroatom is available to delocalize the positive charge. In the less stable carbocations the positively-charged carbon is more than one bond away from the heteroatom, and thus no resonance effects are possible. In fact, in these carbocation species the heteroatoms actually *destabilize* the positive charge, because they are electron withdrawing by induction.

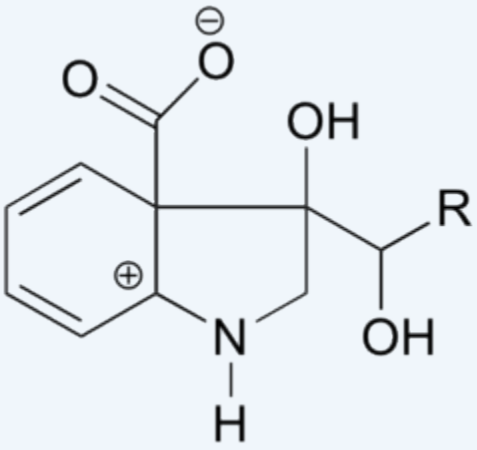
Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.

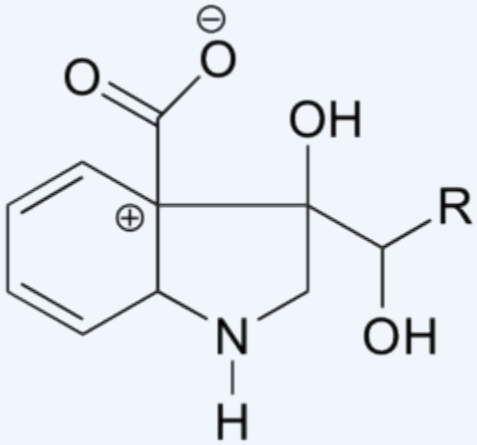


a vinylic carbocation
(very unstable)

Example 8.10

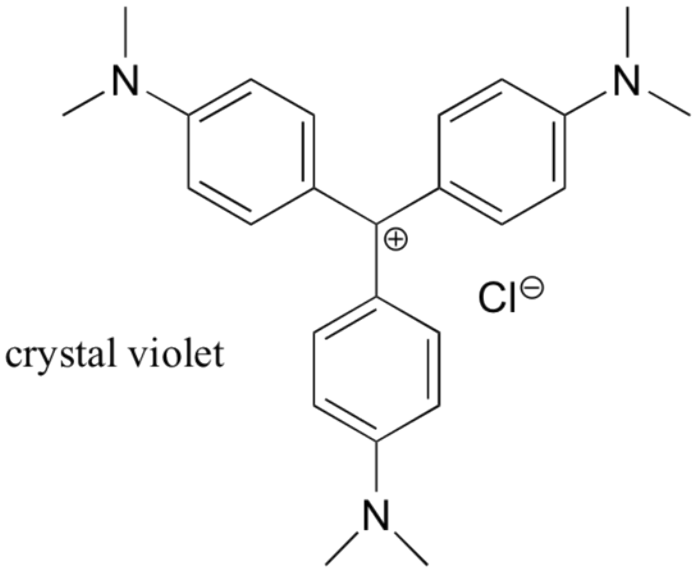
Exercise 8.10: In which of the structures below is the carbocation expected to be more stable? Explain.





Solution

For the most part, carbocations are very high-energy, transient intermediate species in organic reactions. However, there are some unusual examples of very stable carbocations that take the form of organic salts. Crystal violet is the common name for the chloride salt of the carbocation whose structure is shown below. Notice the structural possibilities for extensive resonance delocalization of the positive charge, and the presence of three electron-donating amine groups.



crystal violet

Example 8.11

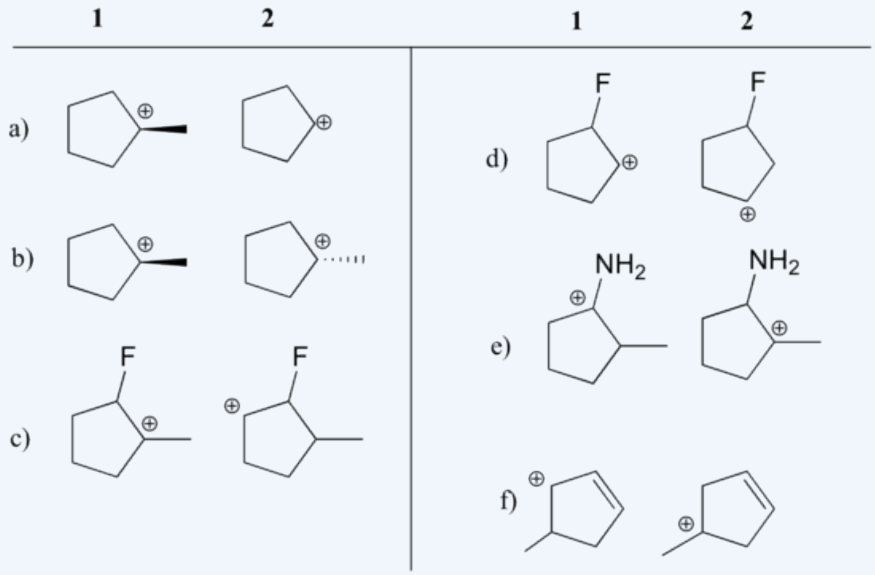
Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.

Solution

When considering the possibility that a nucleophilic substitution reaction proceeds *via* an S_N1 pathway, it is critical to evaluate the stability of the hypothetical carbocation intermediate. If this intermediate is not sufficiently stable, an S_N1 mechanism must be considered unlikely, and the reaction probably proceeds by an S_N2 mechanism. In the next chapter we will see several examples of biologically important S_N1 reactions in which the positively charged intermediate is stabilized by inductive and resonance effects inherent in its own molecular structure.

Example 8.12

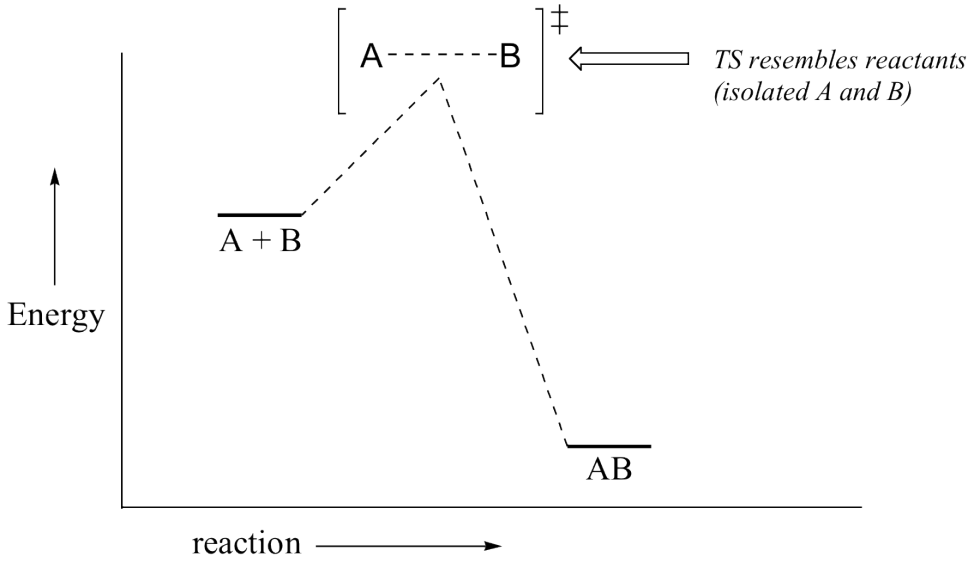
State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.



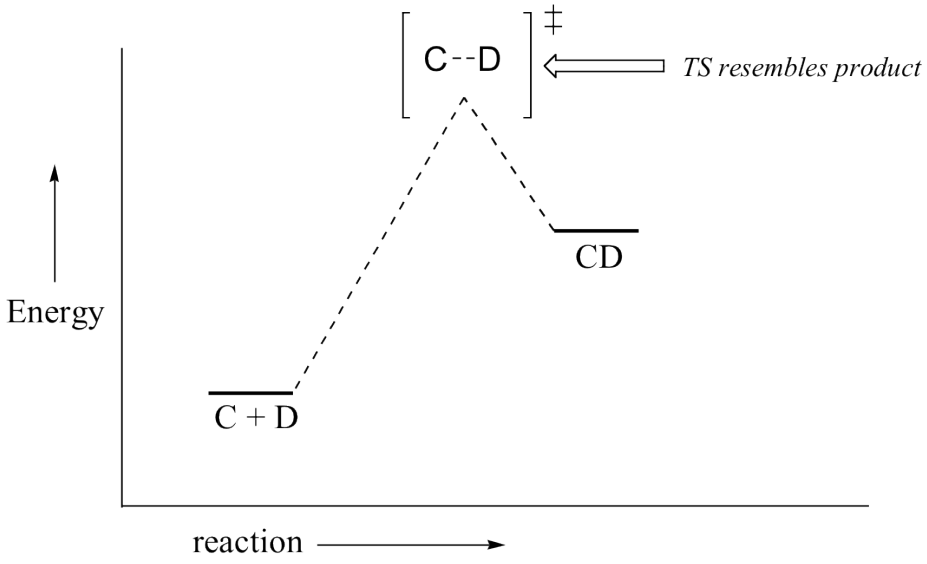
Solution

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Now, back to transition states. Chemists are often very interested in trying to learn about what the transition state for a given reaction looks like, but addressing this question requires an indirect approach because the transition state itself cannot be observed. In order to gain some insight into what a particular transition state looks like, chemists often invoke the **Hammond postulate**, which states that *a transition state resembles the structure of the nearest stable species*. For an exergonic reaction, therefore, the transition state resembles the reactants more than it does the products.



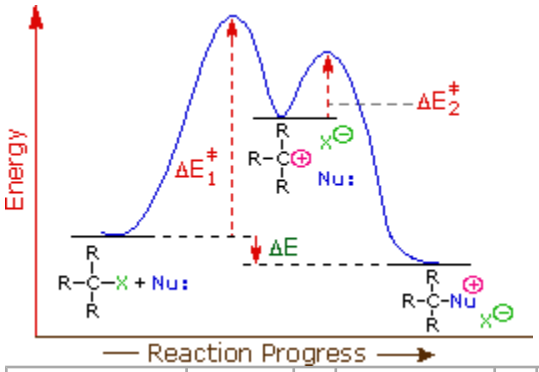
If we consider a hypothetical exergonic reaction between compounds A and B to form AB, the distance between A and B would be relatively large at the transition state, resembling the starting state where A and B are two isolated species. In the hypothetical endergonic reaction between C and D to form CD, however, the bond formation process would be much further along at the TS point, resembling the product.



The Hammond Postulate is a very simplistic idea, which relies on an assumption that potential energy surfaces are parabolic. Although such an assumption is not rigorously true, it is fairly reliable and allows chemists to make energetic arguments about transition states by employing arguments about the stability of a related species. Since the formation of a reactive intermediate is very reliably **endergonic**, arguments about the stability of reactive intermediates can serve as proxy arguments about transition state stability.

The Hammond Postulate and the S_N1 Reaction

the Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate. The stability of carbocations was discussed earlier, and a qualitative relationship is given below:



Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	CH_2=CH-$CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

Consequently, we expect that 3°-alkyl halides will be more reactive than their 2° and 1°-counterparts in reactions that follow an S_N1 mechanism. This is opposite to the reactivity order observed for the S_N2 mechanism. Allylic and benzylic halides are exceptionally reactive by either mechanism.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

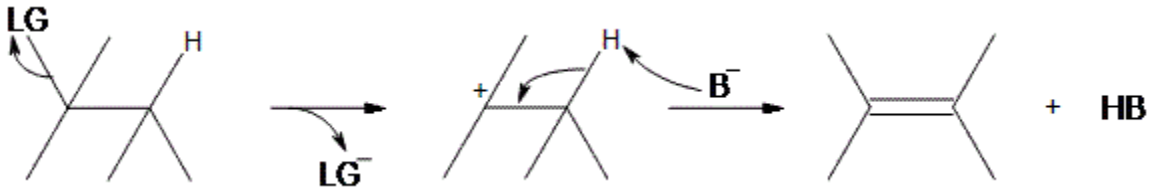
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7.6: Unimolecular Elimination: E1

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control. Although Elimination entails two types of reactions, E1 and E2, we will focus mainly on E1 reactions with some reference to E2.

General Reaction

An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (B^-) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Reactivity

Due to the fact that E1 reactions create a carbocation intermediate, rules present in S_N1 reactions still apply.

ranking_E1.bmp

As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good / strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2 / S_n2 from occurring.

Acid catalyzed dehydration of secondary / tertiary alcohols

We'll take a look at a mechanism involving solvolysis during an E1 reaction of Propanol in Sulfuric Acid.

E1 mechanism 2 hydration image.bmp

- Step 1: The OH group on the pentanol is hydrated by H_2SO_4. This allows the OH to become an H_2O, which is a better leaving group.
- Step 2: Once the OH has been hydrated, the H_2O molecule leaves, taking its electrons with it. This creates a carbocation intermediate on the attached carbon.
- Step 3: Another H_2O molecule comes in to deprotonate the beta carbon, which then donates its electrons to the neighboring C-C bond. The carbons are rehybridized from sp^3 to sp^2, and thus a pi bond is formed between them.

Mechanism for Alkyl Halides

This mechanism is a common application of E1 reactions in the synthesis of an alkene.

alkyl halides.bmp

Once again, we see the basic 2 steps of the E1 mechanism.

1. The leaving group leaves along with its electrons to form a carbocation intermediate.
2. A base deprotonates a beta carbon to form a pi bond.

In this case we see a mixture of products rather than one discrete one. This is the case because the carbocation has two nearby carbons that are capable of being deprotonated, but that only one forms a major product (more stable).

How are Regiochemistry & Stereochemistry involved?

In terms of regiochemistry, Zaitsev's rule states that although more than one product can be formed during alkene synthesis, the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

Unlike E2 reactions, E1 is not stereospecific. Thus, a hydrogen is not required to be anti-periplanar to the leaving group.

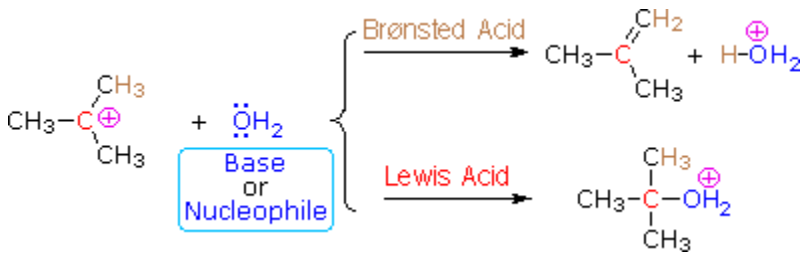
zaitsev mechanism img.bmp

In this mechanism, we can see two possible pathways for the reaction. One in which the methyl on the right is deprotonated, and another in which the CH_2 on the left is deprotonated. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by **Zaitsev's rule**, deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.

Contributors

- Satish Balasubramanian

The E1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as it does in the S_N1 reaction, or a Brønsted acid, as in the E1 reaction.



Thus, hydrolysis of tert-butyl chloride in a mixed solvent of water and acetonitrile gives a mixture of 2-methyl-2-propanol (60%)

and 2-methylpropene (40%) at a rate independent of the water concentration. The alcohol is the product of an S_N1 reaction and the alkene is the product of the E1 reaction. The characteristics of these two reaction mechanisms are similar, as expected. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.

$$(CH_3)_3C\text{–}Cl + H_2O \longrightarrow [\ (CH_3)_3C(+)\ ] + Cl^{(-)} + H_2O \longrightarrow (CH_3)_3C\text{–}OH + (CH_3)_2C{=}CH_2 + HCl + H_2O$$

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a beta-proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

Since the S_N1 and E1 reactions proceed via the same carbocation intermediate, the product ratios are difficult to control and both substitution and elimination usually take place.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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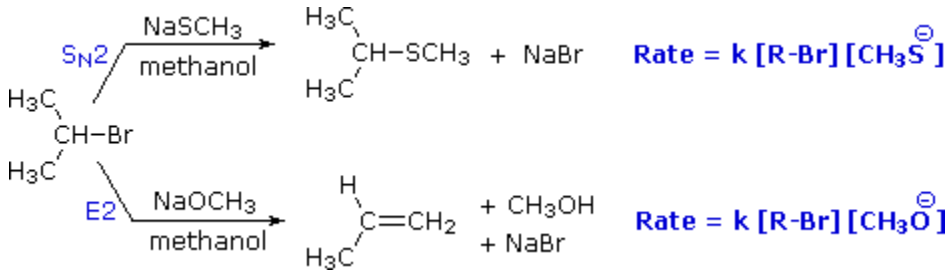
7.7: Bimolecular Elimination: E2

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. Unlike E1 reactions, E2 reactions remove two subsituents with the addition of a strong base, resulting in an alkene.

Introduction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

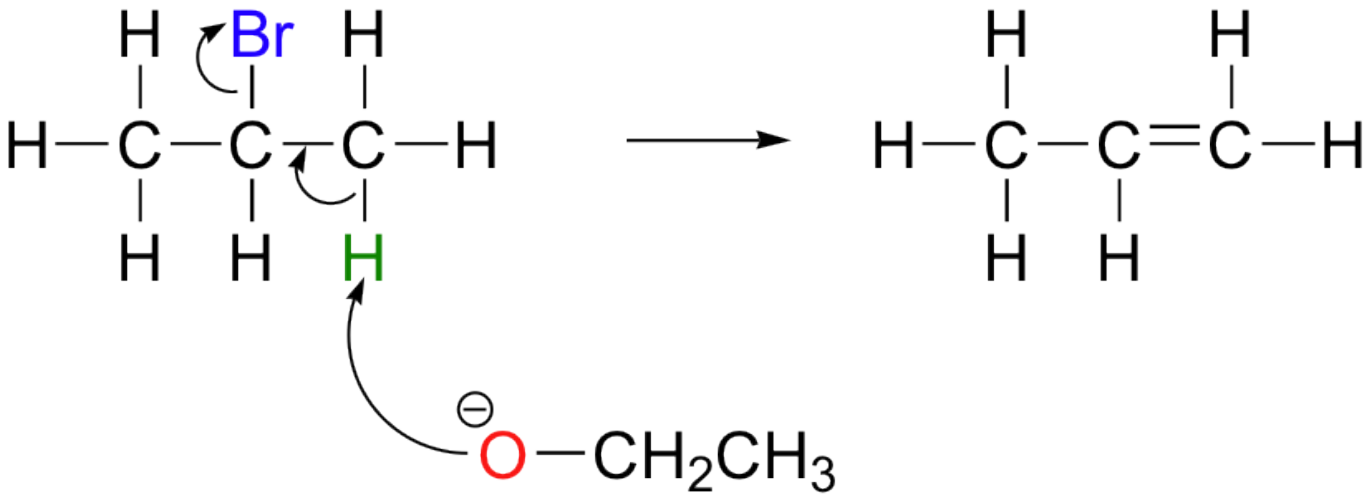
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2°-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.



General Reaction

Below is a mechanistic diagram of an elimination reaction by the E2 pathway:

.



In this reaction Ba represents the base and Br representents a leaving group, typically a halogen. There is one transition state

that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond. The product be both eclipse and staggered depending on the transition states. Eclipsed products have a synperiplanar transition states, while staggered products have antiperiplanar transition states. Staggered conformation is usually the major product because of its lower energy confirmation.

An E2 reaction has certain requirements to proceed:

- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertirary primary halides will procede with E2 in the precesence of a base (OH-, RO-, R_2N-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
- Hoffman Rule, if a strically hindered base will result in the least substituted product.

E2 Reaction Coordinate

Reaction Coordinate.bmp

The Leaving Group Effect in E2 Reactions

As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

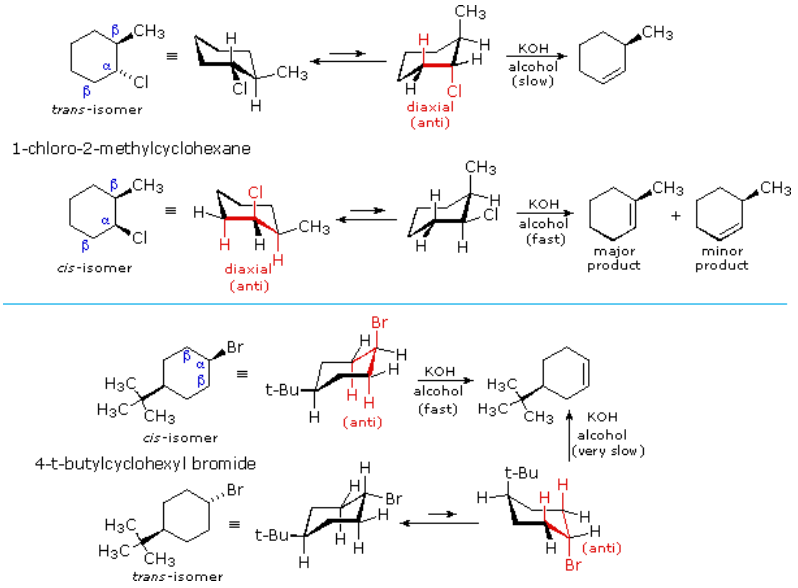


Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

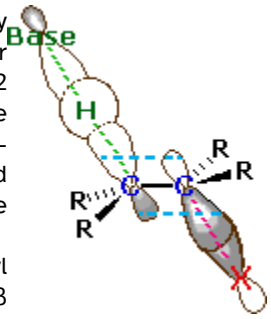
Stereochemistry of the E_2 Reaction

E2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product. These differences are described by the first two equations in the following diagram.

Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. Consequently, reactions conducted on such substrates often provide us with information about the preferred orientation of reactant species in the transition state. Stereoisomers are particularly suitable in this respect, so the results shown here contain important information about the E2 transition state.



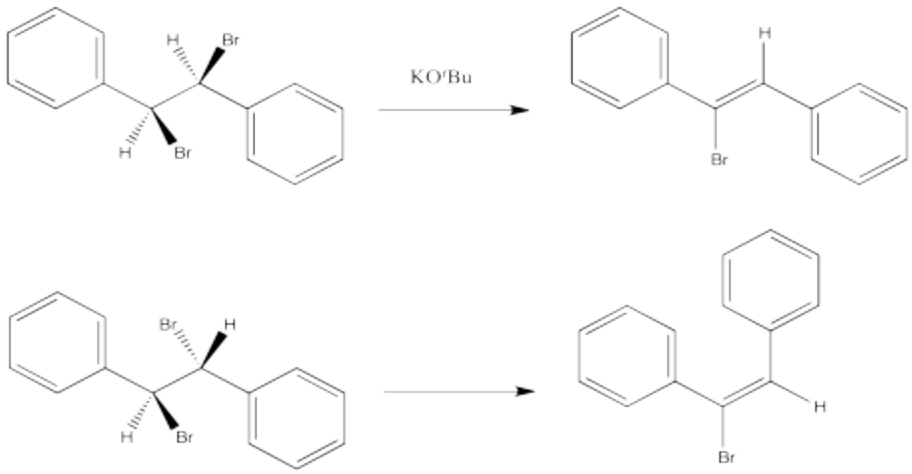
The most sensible interpretation of the elimination reactions of 2- and 4-substituted halocyclohexanes is that this reaction prefers an **anti orientation** of the halogen and the beta-hydrogen which is attacked by the base. These anti orientations are colored in red in the above equations. The compounds used here all have six-membered rings, so the anti orientation of groups requires that they assume a diaxial conformation. The observed differences in rate are the result of a steric preference for equatorial orientation of large substituents, which reduces the effective concentration of conformers having an axial halogen. In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that it will always assume an equatorial orientation, leaving the bromine to be axial in the cis-isomer and equatorial in the trans. Because of symmetry, the two axial beta-hydrogens in the cis-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the chlorine atom. To assume a conformation having an axial bromine the trans-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, substitution by hydroxide anion predominates.



A similar analysis of the 1-chloro-2-methylcyclohexane isomers explains both the rate and regioselectivity differences. Both the chlorine and methyl groups may assume an equatorial orientation in a chair conformation of the trans-isomer, as shown in the top equation. The axial chlorine needed for the E2 elimination is present only in the less stable alternative chair conformer, but this structure has only one axial beta-hydrogen (colored red), and the resulting elimination gives 3-methylcyclohexene. In the cis-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two axial beta hydrogens. The more stable 1-methylcyclohexene is therefore the predominant product, and the overall rate of elimination is relatively fast.
An orbital drawing of the anti-transition state is shown on the right. Note that the base attacks the alkyl halide from the side opposite the halogen, just as in the S_N2 mechanism. In this drawing the α and β carbon atoms are undergoing a rehybridization from sp^3 to sp^2 and the developing π-bond is drawn as dashed light blue lines. The symbol **R** represents an alkyl group or hydrogen. Since both the base and the alkyl halide are present in this transition state, the reaction is bimolecular and should exhibit second order kinetics. We should note in passing that a syn-transition state would also provide good orbital overlap for elimination, and in some cases where an anti-orientation is prohibited by structural constraints *syn*-elimination has been observed.

Instead, in an E_2 reaction, stereochemistry of the double bond -- that is, whether the *E* or *Z* isomer results -- is dictated by the stereochemistry of the starting material, if it is diastereomeric. In other words, if the carbon with the hydrogen and the carbon with the halogen are both chiral, then one diastereomer will lead to one product, and the other diastereomer will lead to the other product.

The following reactions of potassium ethoxide with dibromostilbene (1,2-dibromo-1,2-diphenylethane) both occurred via an E_2 mechanism. Two different diastereomers were used. Two different stereoisomers (*E* vs. *Z*) resulted.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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7.8: Keys to Success: Substitutin Versus Elimination- Structure Determines Function

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**.In general, in order for an SN1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible; and that low dielectric solvents (e.g. acetone, ethanol, tetrahydrofuran & ethyl acetate) are used. When a high dielectric solvent would significantly influence the reaction this is noted in red. **Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents**.

Nucleophile **Alkyl Group**	**Anionic Nucleophiles** (Weak Bases: I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^- etc.) pK_a's from -9 to 10 (left to right)	**Anionic Nucleophiles** (Strong Bases: HO^-, RO^-) pK_a's > 15	**Neutral Nucleophiles** (H_2O, ROH, RSH, R_3N) pK_a's ranging from -2 to 11
Primary RCH_2–	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl$ + KOH ⟶ CH_2=CHCl	S_N2 substitution. (N ≈ S >>O)
Secondary R_2CH–	S_N2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK_a = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S_N2 substitution. (N ≈ S >>O) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be formed slowly.
Tertiary R_3C–	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be expected.	E2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	E2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E1 products may be formed.

Allyl $H_2C=CHCH_2–$	Rapid S_N2 substitution for 1° and 2°-halides. For 3°-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1° halides. E2 elimination will compete with substitution in 2°-halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2°-halides. 3°-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2° & 3°-halides.
Benzyl $C_6H_5CH_2–$	Rapid S_N2 substitution for 1° and 2°-halides. For 3°-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1° halides (note there are no β hydrogens). E2 elimination will compete with substitution in 2°-halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2°-halides. 3°-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2° & 3°-halides.

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7.9: Summary of Reactivity of Haloalkanes

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**.In general, in order for an SN1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

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William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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7.E: Further Reactions of Haloalkanes: Unimolecular Substitution (Exercises)

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8: HYDROXY OF FUNCTIONAL GROUP: ALCOHOLS: PROPERTIES, PREPARATION, AND STRATEGY OF SYNTHESIS

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

8.1: Naming the Alcohols
8.2: Structural and Physical Properties of Alcohols
8.3: Alcohols as Acids and Bases
8.4: Industrial Sources of Alcohols: Carbon Monoxide and Ethene
8.5: Synthesis of Alcohols by Nucleophilic Substitution
8.6: Synthesis of Alcohols: Oxidation-Reduction Relation Between Alcohols and Carbonyl Compounds
8.7: Organometallic Reagents: Sources of Nucleophilic Carbon for Alcohol Synthesis
8.8: Organometallic Reagents in the Synthesis of Alcohols
8.9: Keys to Success: An Introduction to Synthetic Strategy

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8.1: Naming the Alcohols

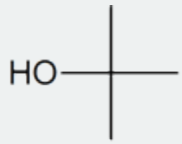
Objectives

After completing this section, you should be able to

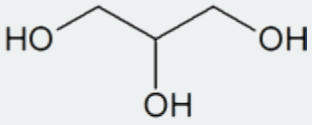
1. identify an alcohol as being primary, secondary or tertiary, given its structure, its IUPAC name or its trivial name.
2. write the IUPAC name of an alcohol or phenol given its Kekulé, condensed or shorthand structure.
3. draw the structure of an alcohol or phenol given its IUPAC name.
4. identify a number of commonly occurring alcohols (e.g., benzyl alcohol, *tert*-butyl alcohol) by their trivial names.

Study Notes

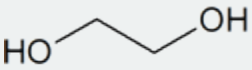
The following are common names of some alcohols (with IUPAC name).



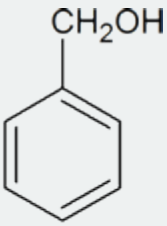
tert-butyl alcohol
(2-methyl-2-propanol)



gycerol
(1,2,3-propanetriol)



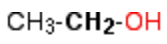
ethylene glycol
(1,2-ethanediol)



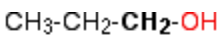
benzyl alcohol
(phenylmethanol)

Primary alcohols

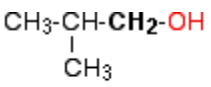
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



ethanol



propan-1-ol

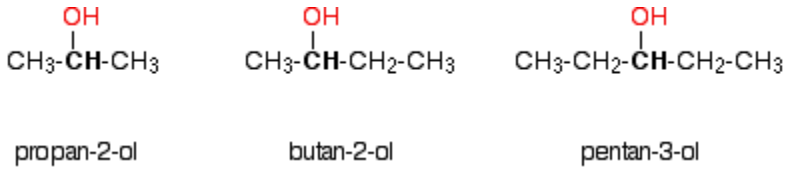


2-methylpropan-1-ol

Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH2 group holding the -OH group. There is an exception to this. Methanol, CH3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the carbon with the -OH group on it.

Secondary alcohols

In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



propan-2-ol butan-2-ol pentan-3-ol

Tertiary alcohols

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



2-methylpropan-2-ol 2-methylbutan-2-ol

Naming Alcohols

1. Find the longest chain containing the hydroxy group (OH). If there is a chain with more carbons than the one containing the OH group it will be named as a subsitutent.
2. Place the OH on the lowest possible number for the chain. With the exception of carbonyl groups such as ketones and aldehydes, the alcohol or hydroxy groups have first priority for naming.
3. When naming a cyclic structure, the -OH is assumed to be on the first carbon unless the carbonyl group is present, in which case the later will get priority at the first carbon.
4. When multiple -OH groups are on the cyclic structure, number the carbons on which the -OH groups reside.
5. Remove the final **e** from the parent alkane chain and add -**ol**. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. ex. 2,3-hexan**diol.** If a carbonyl group is present, the -OH group is named with the prefix "hydroxy," with the carbonyl group attached to the parent chain name so that it ends with -**al** or -**one.**

Examples

Ethan**e**: CH_3CH_3 ----->Ethan**ol**: (the alcohol found in beer, wine and other consumed sprits)

Secondary alcohol: 2-propanol

Other functional groups on an alcohol: 3-bromo-2-pentanol

Cyclic alcohol (two -OH groups): cyclohexan-1,4-diol

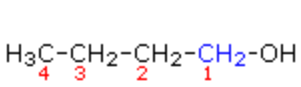
Other functional group on the cyclic structure: 3-hex**ene**ol (the alkene is in **bold** and indicated by numbering the carbon closest to the alcohol)

A complex alcohol:4-ethyl-3hexanol (the parent chain is in red and the substituent is in blue)

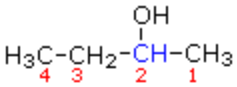
In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes -**ene** and -**yne**. Halogens, on the other hand, do not have a suffix and are named as

substituents, for example: $(CH_3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene.

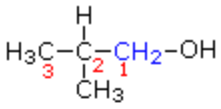
Alcohols are usually named by the first procedure and are designated by an **-ol** suffix, as in ethanol, CH_3CH_2OH (note that a locator number is unnecessary on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(CH_3)_2C{=}CHCH(OH)CH_3$ is 4-methyl-3-penten-2-ol. Other examples of IUPAC nomenclature are shown below, together with the common names often used for some of the simpler compounds. For the mono-functional alcohols, this common system consists of naming the **alkyl group** followed by the word **alcohol**. Alcohols may also be classified as primary, **1°**, secondary, **2°**, and tertiary, **3°**, in the same manner as alkyl halides. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group (colored blue in the illustration).



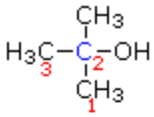
1-butanol
(butyl alcohol)
a 1°-alcohol



2-butanol
(*sec*-butyl alcohol)
a 2°-alcohol



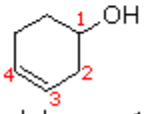
2-methyl-1-propanol
(isobutyl alcohol)
a 1°-alcohol



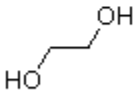
2-methyl-2-propanol
(*tert*-butyl alcohol)
a 3°-alcohol



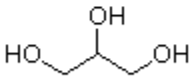
2-propen-1-ol
(allyl alcohol)



3-cyclohexen-1-ol



1,2-ethanediol
(ethylene glycol)

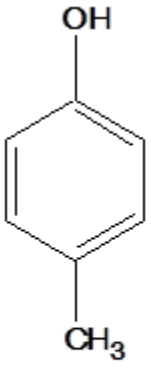


1,2,3-propanetriol
(glycerol)

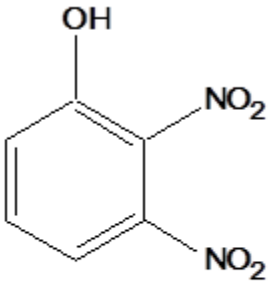
Many functional groups have a characteristic suffix designator, and only one such suffix (other than "-ene" and "-yne") may be used in a name. When the hydroxyl functional group is present together with a function of higher nomenclature priority, it must be cited and located by the prefix **hydroxy** and an appropriate number. For example, lactic acid has the IUPAC name 2-hydroxypropanoic acid.

Naming phenols

Phenols are named using the rules for aromatic compounds discussed in Section 15.1 Note! that *-phenol* is used rather than *-benzene*.



p-Metylphenol



2,3-Dinitrophenol

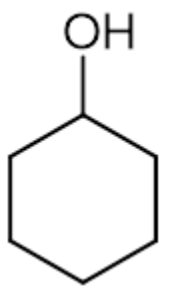
Exercises

Exercise 17.1.1

Indicate if the following molecules are 1^{o}, 2^{o}, or 3^{o} alcohols:

1)

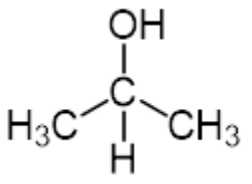
a)



b) $(CH_3)_3COH$

c) $CH_3CH_2CH_2OH$

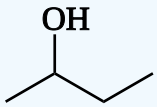
d)

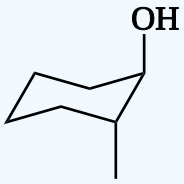


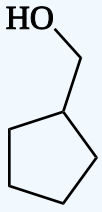
Answer available at the end of this section.

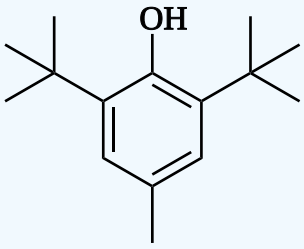
Exercise 17.1.2

Give IUPAC names for the following structures.





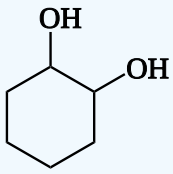


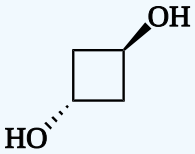


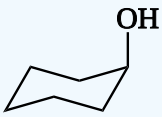
Answer available at the end of this section.

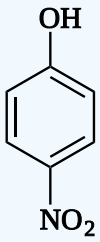
Exercise 17.1.3

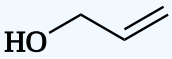
Name the following structures.

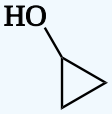












Answer available at the end of this section.

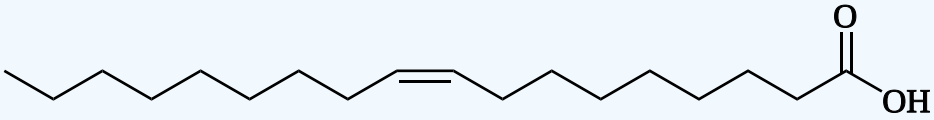
Exercise 17.1.4

Draw and name all the alcohol isomers of C_3H_9O

Answer available at the end of this section.

Exercise 17.1.5

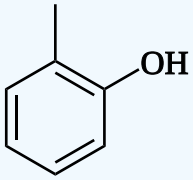
Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

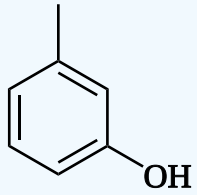


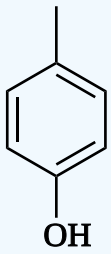
Answer available at the end of this section.

Exercise 17.1.6

Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.







Answer available at the end of this section.

Questions

Q17.1.1

Give IUPAC names for the following structures.

(a) 17.20aq.png (b) 17.20bq.png Indicate stereochemistry (c) 17.20cq.png (d) 17.20dq.png

Q17.1.2

Name the following structures.

17.25q.png

Q17.1.3

Draw and name all the alcohol isomers of C_3H_9O

Q17.1.4

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

17.28q..png

Q17.1.5

Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.

17.29q.png

Solutions

S17.1.1

(a) 17.20aa.png (b) 17.20ba.png (c) 17.20ca.png (d) 17.20da.png

S17.1.2

S171.2

S17.1.3

17.26a.png or, 1-propanol and 2-propanol

S17.1.4

(9*Z*)-Octadec-9-enoic acid

S17.1.5

17.29a.png

Contributors and Attributions

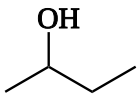
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

Answers

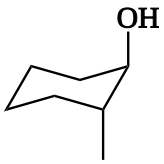
Exercise 17.1.1

1)
a) Secondary
b) Tertiary
c) Primary
d) Secondary

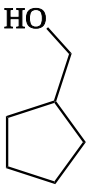
Exercise 17.1.2



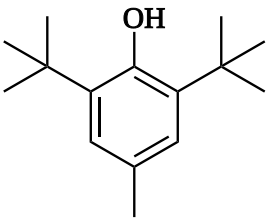
butan-2-ol



(1*R*, 2*R*)-2-mthylcyclohexan-1-ol

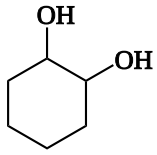


cyclopentylmethanol

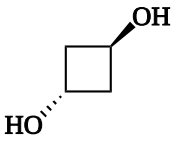


2,6-di-tert-butyl-4-methylphenol

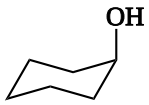
Exercise 17.1.3



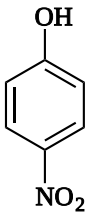
cyclohexane-1,2,-diol



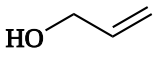
trans-cyclobutane-1,3-diol



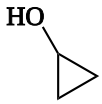
cyclohexanol



4-nitrophenol



prop-2-en-1-ol



cycloproanol

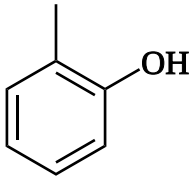
Exercise 17.1.4

Add texts here. Do not delete this text first.

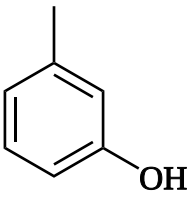
Exercise 17.1.5

(9*Z*)-Octadec-9-enoic acid

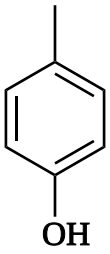
Exercise 17.1.6



2-methylphenol



3-methylphenol



4-methylphenol

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8.2: Structural and Physical Properties of Alcohols

Objectives

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

Study Notes

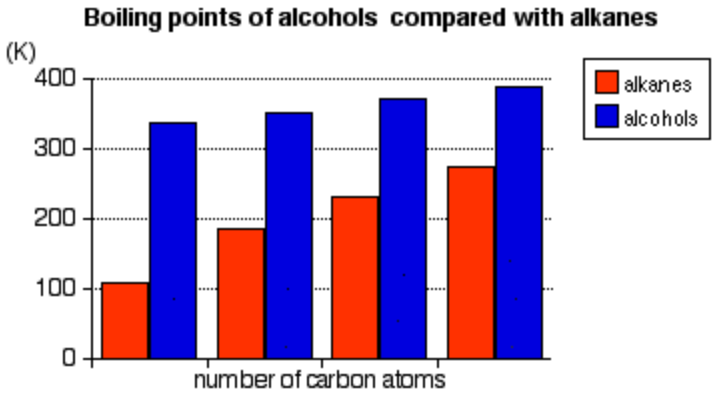
You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

Boiling Points

The chart below shows the boiling points of the following simple primary alcohols with up to 4 carbon atoms:

CH_3OH	CH_3CH_2OH	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2CH_2OH$
methanol	ethanol	propan-1-ol	butan-1-ol

These boiling points are compared with those of the equivalent alkanes (methane to butane) with the same number of carbon atoms.



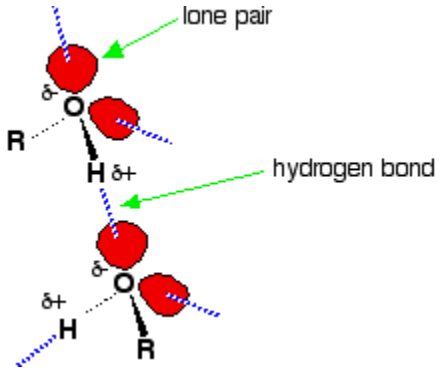
Notice that:

- The boiling point of an alcohol is always significantly higher than that of the analogous alkane.
- The boiling points of the alcohols increase as the number of carbon atoms increases.

The patterns in boiling point reflect the patterns in intermolecular attractions.

Hydrogen bonding

Hydrogen bonding occurs between molecules in which a hydrogen atom is attached to a strongly electronegative element: fluorine, oxygen or nitrogen. In the case of alcohols, hydrogen bonds occur between the partially-positive hydrogen atoms and lone pairs on oxygen atoms of other molecules.



The hydrogen atoms are slightly positive because the bonding electrons are pulled toward the very electronegative oxygen atoms. In alkanes, the only intermolecular forces are van der Waals dispersion forces. Hydrogen bonds are much stronger than these, and therefore it takes more energy to separate alcohol molecules than it does to separate alkane molecules. This the main reason for higher boiling points in alcohols.

The effect of van der Waals forces

- **Boiling points of the alcohols**: Hydrogen bonding is not the only intermolecular force alcohols experience. There are also van der Waals dispersion forces and dipole-dipole interactions. The hydrogen bonding and dipole-dipole interactions are much the same for all alcohols, but dispersion forces increase as the alcohols get bigger. These attractions get stronger as the molecules get longer and have more electrons. This increases the sizes of the temporary dipoles formed. This is why the boiling points increase as the number of carbon atoms in the chains increases. It takes more energy to overcome the dispersion forces, and thus the boiling points rise.
- **Comparison between alkanes and alcohols**: Even without any hydrogen bonding or dipole-dipole interactions, the boiling point of the alcohol would be higher than the corresponding alkane with the same number of carbon atoms.

Compare ethane and ethanol:

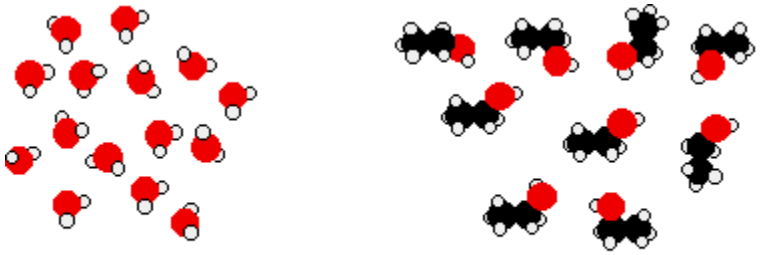


Ethanol is a longer molecule, and the oxygen atom brings with it an extra 8 electrons. Both of these increase the size of the van der Waals dispersion forces, and subsequently the boiling point. A more accurate measurement of the effect of the hydrogen bonding on boiling point would be a comparison of ethanol with propane rather than ethane. The lengths of the two molecules are more similar, and the number of electrons is exactly the same.

Solubility of alcohols in water

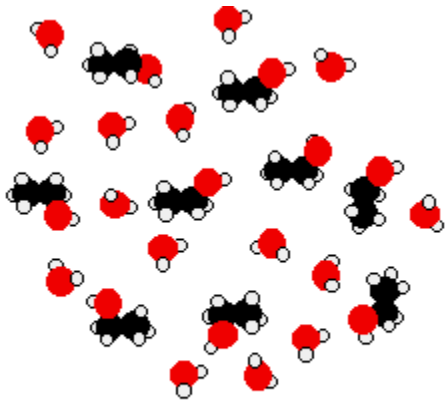
Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

Consider ethanol as a typical small alcohol. In both pure water and pure ethanol the main intermolecular attractions are hydrogen bonds.



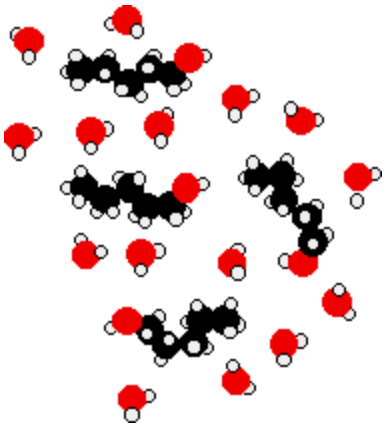
Both of these are held together mainly by hydrogen bonding.

In order to mix the two, the hydrogen bonds between water molecules and the hydrogen bonds between ethanol molecules must be broken. Energy is required for both of these processes. However, when the molecules are mixed, new hydrogen bonds are formed between water molecules and ethanol molecules.



New hydrogen bonds are set up between ethanol and water molecules.

The energy released when these new hydrogen bonds form approximately compensates for the energy needed to break the original interactions. In addition, there is an increase in the disorder of the system, an increase in entropy. This is another factor in deciding whether chemical processes occur. Consider a hypothetical situation involving 5-carbon alcohol molecules.



The hydrocarbon chains are forced between water molecules, breaking hydrogen bonds between those water molecules. The -OH ends of the alcohol molecules can form new hydrogen bonds with water molecules, but the hydrocarbon "tail" does not form hydrogen bonds. This means that many of the original hydrogen bonds being broken are never replaced by new ones.

In place of those original hydrogen bonds are merely van der Waals dispersion forces between the water and the hydrocarbon "tails." These attractions are much weaker, and unable to furnish enough energy to compensate for the broken hydrogen bonds. Even allowing for the increase in disorder, the process becomes less feasible. As the length of the alcohol increases, this situation becomes more pronounced, and thus the solubility decreases.

Acid/Base properties of alcohols

Several important chemical reactions of alcohols involving the O-H bond or oxygen-hydrogen bond only and leave the carbon-oxygen bond intact. An important example is salt formation with acids and bases. Alcohols, like water, are both weak bases and weak acids. The acid ionization constant (Ka) of ethanol is about 10~18, slightly less than that of water. Ethanol can be converted to its conjugate base by the conjugate base of a weaker acid such as ammonia {Ka — 10~35), or hydrogen (Ka ~ 10-38). It is convenient to employ sodium metal or sodium hydride, which react vigorously but controllably with alcohols:

$$\underset{\text{sodium amide (sodamide)}}{C_2H_5OH + Na^{\oplus}NH_2^{\ominus}} \rightleftharpoons \underset{\text{sodium ethoxide}}{C_2H_5O^{\ominus}Na^{\oplus}} + NH_3$$

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

$$C_2H_5OH + Na^{\oplus}H^{\ominus} \longrightarrow C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the equilibrium position for the proton-transfer reaction (Equation 15-1) lies more on the side of ROH and OHe as R is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered less acidic than ethanol:

$$ROH + OH^- \rightleftharpoons RO^- + HOH \tag{8.2.1}$$

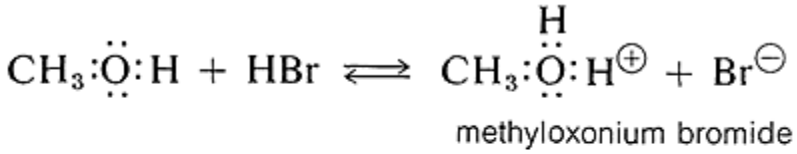
However, in the gas phase the order of acidity is reversed, and the equilibrium position for Equation 15-1 lies increasingly on the side of ROGas R is changed from primary to secondary to tertiary, terf-Butyl alcohol is therefore more acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria expressed by Equation 15-1. In solution, the larger anions of alcohols, known as alkoxide ions, probably are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions:

$CH_3O^{\ominus}$	$C_2H_5O^{\ominus}$	$(CH_3)_2CHO^{\ominus}$	$(CH_3)_3CO^{\ominus}$
methoxide	ethoxide	isopropoxide	*tert*-butoxide

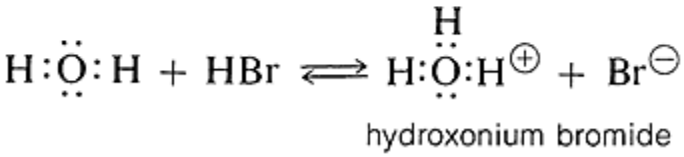
Acidity of alcohols therefore decreases as the size of the conjugate base increases. However, “naked” gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is. (Also see Section 11-8A, which deals with the somewhat similar situation encountered with respect to the relative acidities of ethyne and water.)

Chemical Reactions of Alcohols involving the O-H bond of Compounds with Basic Properties

Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:



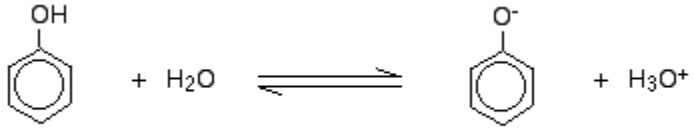
methyloxonium bromide



hydroxonium bromide

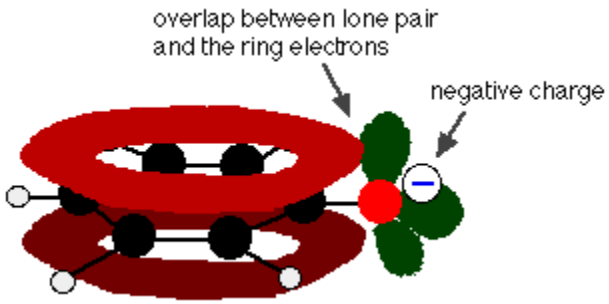
Acidity of Phenol

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in solution in water:



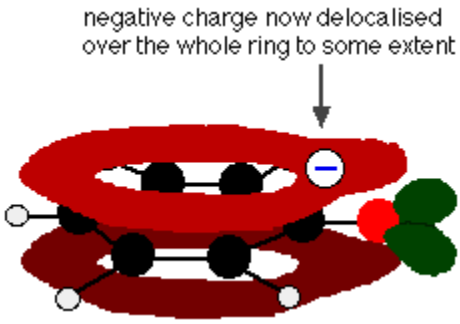
a **phenoxide** ion

Phenol is a very weak acid and the position of equilibrium lies well to the left. Phenol can lose a hydrogen ion because the phenoxide ion formed is stabilised to some extent. The negative charge on the oxygen atom is delocalised around the ring. The more stable the ion is, the more likely it is to form. One of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is

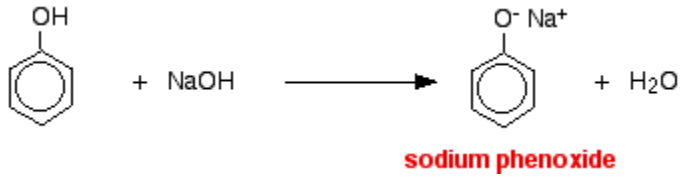
no longer entirely localized on the oxygen, but is spread out around the whole ion.



Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

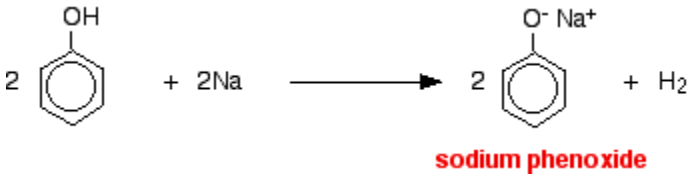
Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.



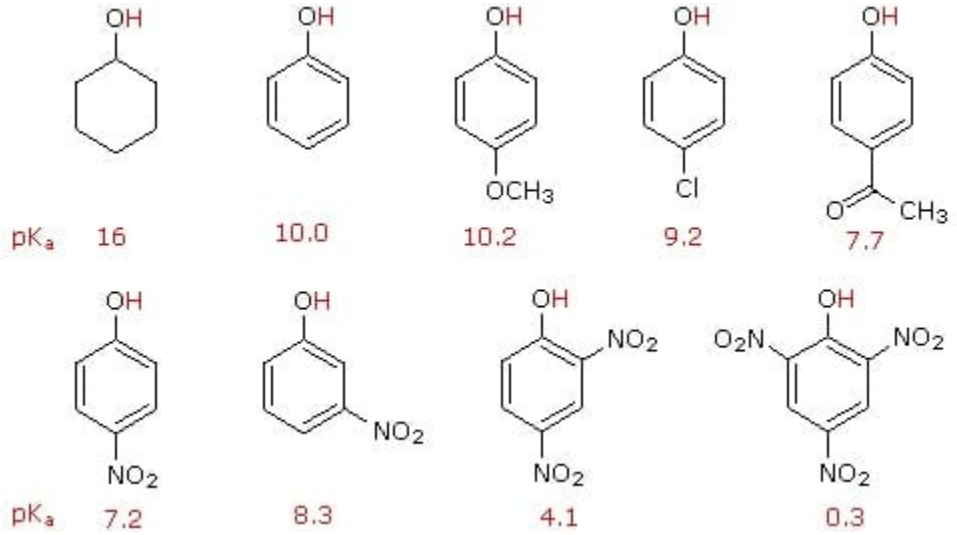
In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

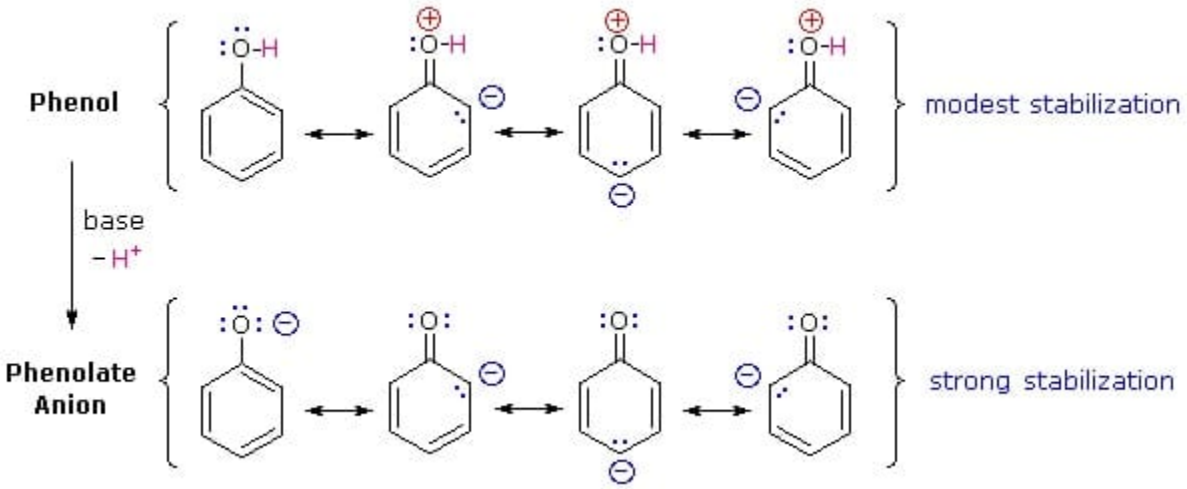
Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off. The mixture left in the tube will contain sodium phenoxide.

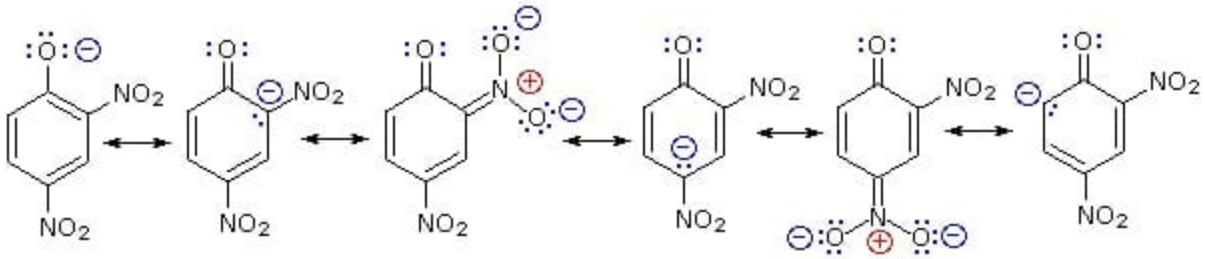


Acidity of Substituted Phenols

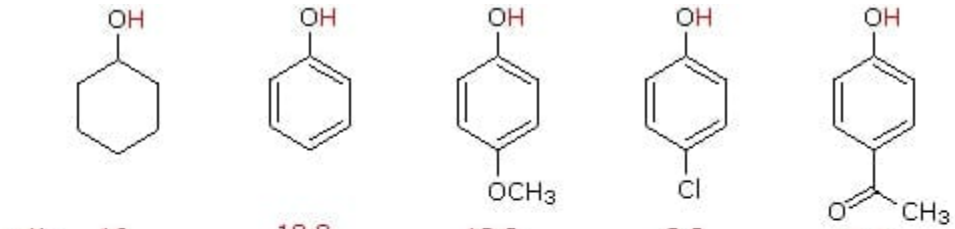
Substitution of the hydroxyl hydrogen atom is even more facile with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. The alcohol cyclohexanol is shown for reference at the top left. It is noteworthy that the influence of a nitro substituent is over ten times stronger in the para-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. Furthermore additional nitro groups have an additive influence if they are positioned in ortho or para locations. The trinitro compound shown at the lower right is a very strong acid called picric acid.

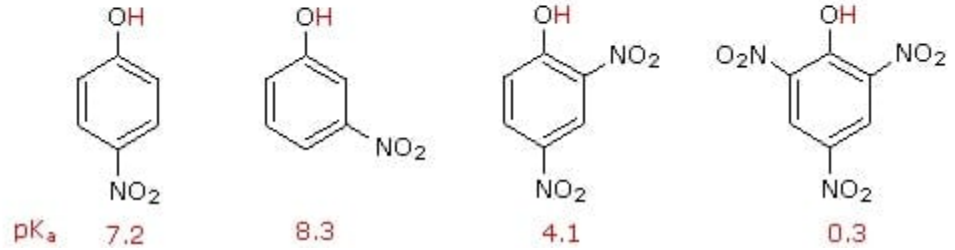






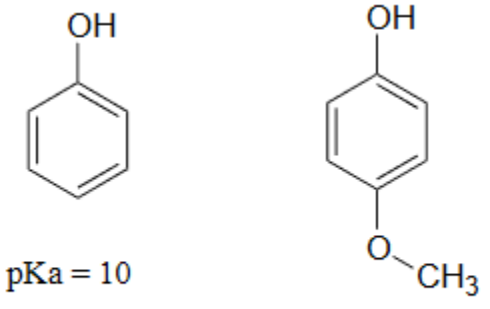
Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents





Worked Example 17.2.1

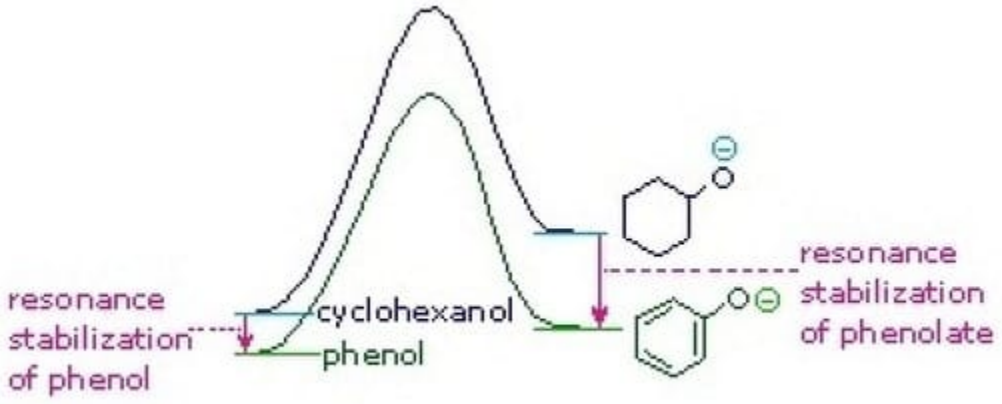
Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer available at the end of this section.

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that

resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

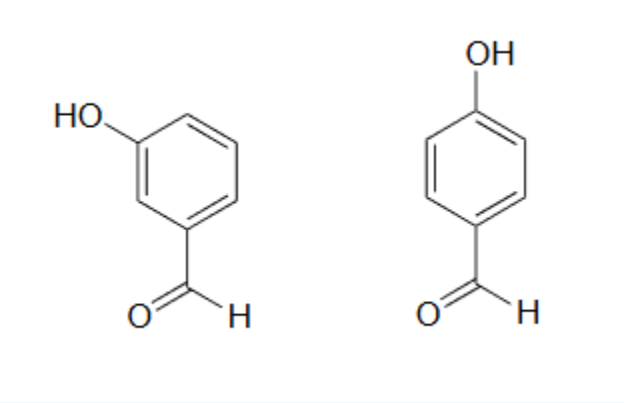


The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

Exercises

Exercise 17.2.1

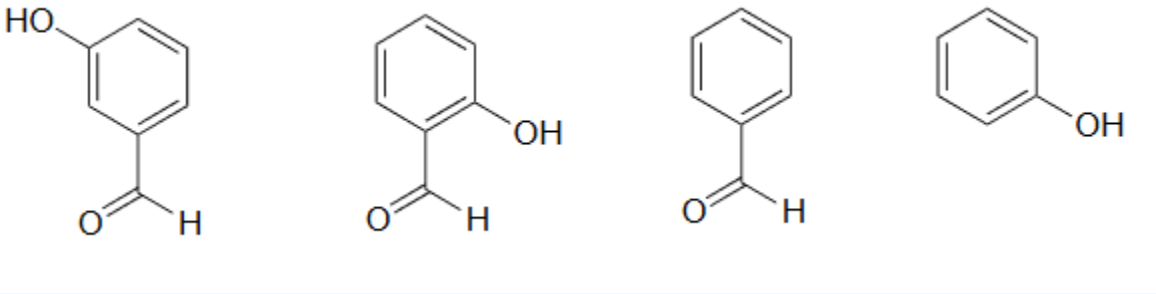
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



Answer available at the end of this section.

Exercise 17.2.2

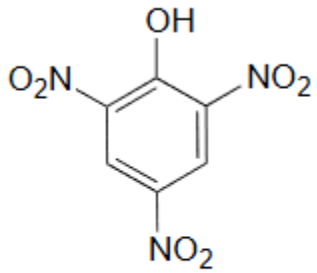
Rank the four compounds below from most acidic to least.



Answer available at the end of this section.

Exercise 17.2.3

Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

Answer available at the end of this section.

Exercise 17.2.4

Predict which compound of each pair is more soluble in water and explain your reasoning.

a) Butan-1-ol or pentan-1-ol

b) Phenol or cyclohexanol

c) Octan-1,3-diol or octan-1-ol

d) 1-Chlorohexane or hexan-1-ol

5) Predict which compound has the higher boiling point and explain your reasoning.

a) Water or ethanol

b) Butan-1-ol or octan-1-ol

c) Hexan-2-ol or hexan-2-one

Answer available at the end of this section.

Contributors and Attributions

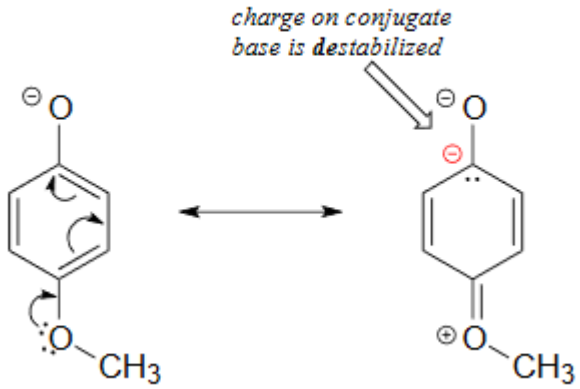
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition*. W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

Answers

Worked Example 17.2.1

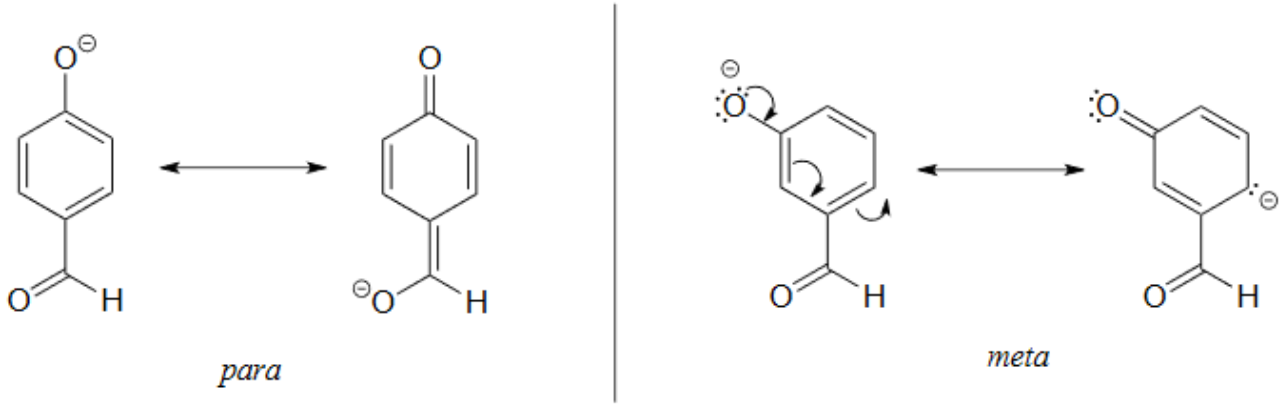
The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

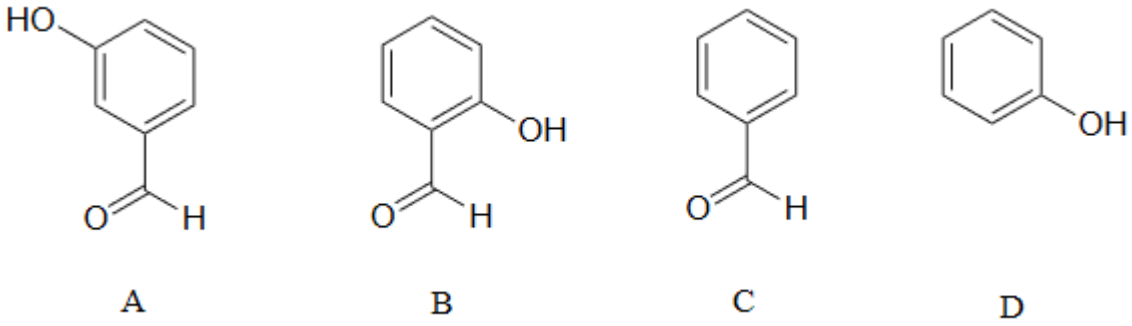
Exercise 17.2.1

The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position.



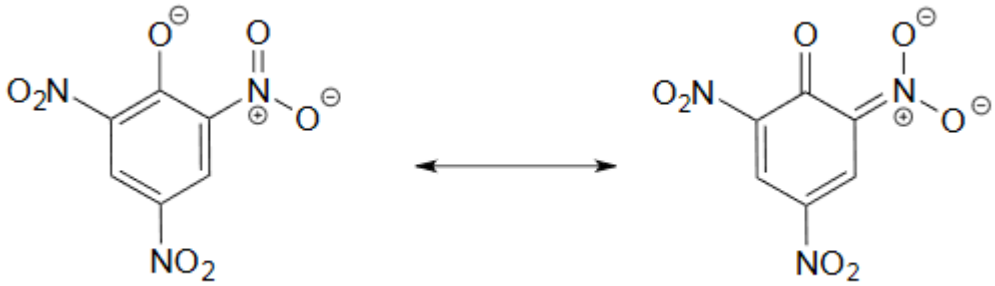
Exercise 17.2.2

Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



Exercise 17.2.3

The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



Exercise 17.2.4

a) Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.

b) Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.

c) Octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.

d) Hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

5) a) Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.

b) Octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.

c) Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

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8.3: Alcohols as Acids and Bases

Alcohols are very weak Brønsted acids with pK_a values generally in the range of 15 - 20. Because the hydroxyl proton is the most electrophilic site, proton transfer is the most important reaction to consider with nucleophiles. There are small differences in the acidities of aliphatic alcohols in aqueous solution, which are due to differences in structure and, more importantly, solvation.

General Assessment of Acidities

When considering alcohols as organic reagents, pK_as are often used because they reflect reactivity in aqueous solution. In general, alcohols in aqueous solution are slightly less acidic than water. However, the differences among the pK_as of the alcohols are not large. This is not surprising because all alcohols are oxy-acids (OH), and the differences in acidities are due to the effect of substituents in the 1-position removed from the acidic site. Moreover, the more highly substituted alcohols vary only in the structure two positions removed from the acidic site. The marginal effects of additional substituents at the carbon tow positions removed from the acidic site are even evident in the gas-phase enthalpies of reaction for the reaction

$$ROH \rightarrow RO^- + H^+ \tag{1}$$

The pK_as and gas-phase enthalpies of reaction for various alcohols, ROH, with various substituents (R) are shown in Table 1 below.

Table 1: *pK_as and gas-phase enthalpies of reaction*

R	Name	pKa1	ΔH_{acid} kJ/mol^2
H	water	14.0	1633.1
CH_3	methanol	15.5	1597 ± 6
CH_3CH_2	ethanol	15.9	1587 ± 4
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5	1569 ± 4
$(CH_3)_3C$	2-methylpropan-2-ol (t-butanol)	17	1568 ± 4
C_6H_5 (phenyl)	phenol	9.95	1462 ± 10

Interpretation of the Relative Acidities of Alcohols

There are many sites on the internet with explanations of the relative ordering of alcohol acidities **in aqueous solution**. The general explanation is that the larger substituents are better electron donors, which destabilize the resulting alkoxide anions. Because hydrogen is least donating of the substituents, water is the strongest acid. Unfortunately, although this belief persists, it is incomplete because it does not account for the gas-phase results. The problem with the electron donation explanation is that it suggests that the order of acidity is due solely to the intrinsic electronic effects of the substituents. However, if that were the case, the electron donating effect should also be evident in the gas-phase data. However, the relative acidities in the gas phase are opposite to those in aqueous solution. Consequently, any interpretation of the acidities of alcohols must take the gas phase data into account.

The inversion of the acidities of alcohols between the gas phase and aqueous solution was pointed out by Brauman and Blair in 1968.[3] They proposed that the ordering of acidities of alcohols **in solution** is predominantly due to the combination of a) polarizibility and b) solvation, and that the electron donating ability of the substituent does not play a significant role.[4]

Polarizibility almost completely accounts for the trend in gas-phase acidities. As the size of the substituent increases, the acid becomes stronger due to the ability for the charge to be distributed over a larger volume, thereby reducing the charge density and, consequently, the Coulombic repulsion. Therefore, in the gas-phase, t-butanol is the most acidic alcohol, more acidic than isopropanol, followed by ethanol and methanol. In the gas phase, water is much less acidic than methanol, which is consistent with the difference in polarizibility between a proton and a methyl group. As before, the fact that water is less acidic than methanol in the gas phase is not consistent with the expected electronic donating capabilities of the two substituents. Given the absence

of a solvent, the gas-phase properties reflect the instrinsic effects on the acidities.

In solution, however, the ions can be stabilized by solvation, and this is what leads to the inversion of acidity ordering. Brauman and Blair[3] showed that smaller ions are better stabilized by solvation, which is consistent with the Born equation. Therefore, methanol is more acidic than t-butanol because the smaller methoxide ion has a shorter radius of solvation, leading to a larger solvation energy, which overcomes the stabilization that results from polarization of the charge. Because the solvation energy of hydroxide is even larger than that of methoxide, water is more acidic than methanol.

Note: Phenol

Discussions of acidities of alcohols usually include phenol in which the enhanced acidity is generally attributed to stabilization of the phenoxide ion by resonance delocalization. In this case, the gas-phase results agree with the solution trend that phenol is a much stronger acid than the aliphatic alcohols, and the difference is certainly due to electronic effects. However, this commonly encountered explanation is incomplete because it ignores the role that inductive effects have on acidities of oxy-acids. However, it is true that the acidity of phenol is much more a result of resonance stabilization than, for example, the acidities of carboxylic acids.

Practical Considerations

With pK_a values in the 15.5 - 20.0 range, useful concentrations of alkoxides cannot be formed by proton transfer with hydroxide:

$$ROH + OH^- \rightarrow RO^- + H_2O \tag{2}$$

The equilibrium constant for the proton transfer reaction is on the order of 10^{-2}-10^{-5}. Phenoxide can be formed almost completely by reaction with aqueous alkaline base because the value of the equilibrium constant is roughly 10^4. The acidity of alcohols also indicates that it will react by proton transfer with any base more basic than hydroxide, which includes most organic bases, such as acetylide ions, cyanide, and vinyl/phenyl/alkyl anions. Therefore, alcohols will protonate most organic nucleophiles and effectively destroy most organometallic reagents, including Grignard or organolithium reagents.

Formation of alkoxide ions

Alkoxide ions can be formed by deprotonating alcohols with an extremely strong base such as an amide ion, NH_2^-. However, this method is rarely used. Alkoxides are more often formed by reaction of an alkali metal such as sodium with the pure alcohol:

$$2ROH + 2Na \rightarrow 2RO^- + 2Na^+ + H_2 \tag{3}$$

Conclusions

Relative acidities of all acids depend on many factors, including intrinsic electronic factors such as electronegativity, inductive and resonance effects, and polarizibility, as well as extrinsic factors such as solvation. For aliphatic alcohols, the most important effects are polarizibility and solvation, not electronic donation, as is generally assumed. In systems where the intrinsic factors are large, their effects are manifested in the overall properties, regardless of the medium.

References

1. http://research.chem.psu.edu/brpgrou...ompilation.pdf with correction for pK_a of water
2. http://webbook.nist.gov/chemistry/ accessing Reaction Thermochemistry Data for each compound
3. Brauman,J.I.; Blair,L.K. *J. Am. Chem. Soc.* **1968**, *90*, 6561.
4. Brauman,J.I.; Blair,L.K. *J. Am. Chem. Soc.* **1970**, *92*, 5986.

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8.4: Industrial Sources of Alcohols: Carbon Monoxide and Ethene

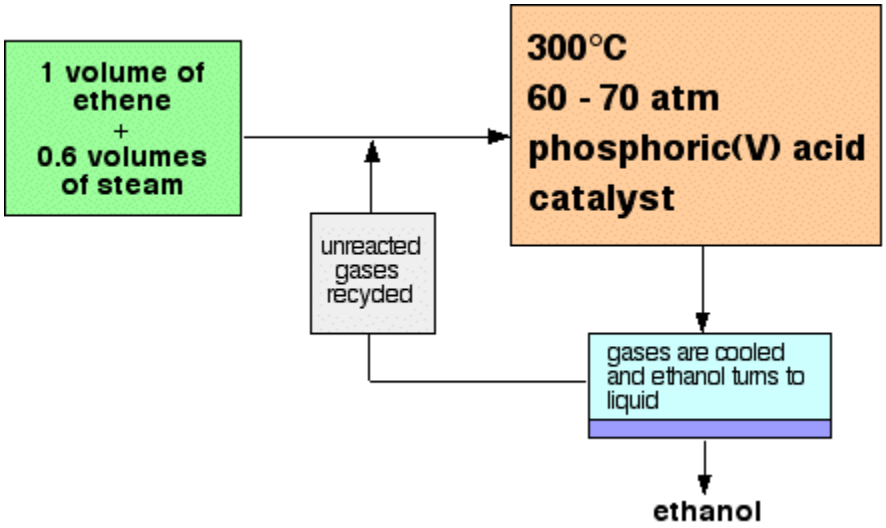
This page looks at the manufacture of alcohols by the direct hydration of alkenes, concentrating mainly on the hydration of ethene to make ethanol. It then compares that method with making ethanol by fermentation.

Manufacturing alcohols from alkenes

Ethanol is manufactured by reacting ethene with steam. The catalyst used is solid silicon dioxide coated with phosphoric(V) acid. The reaction is reversible.

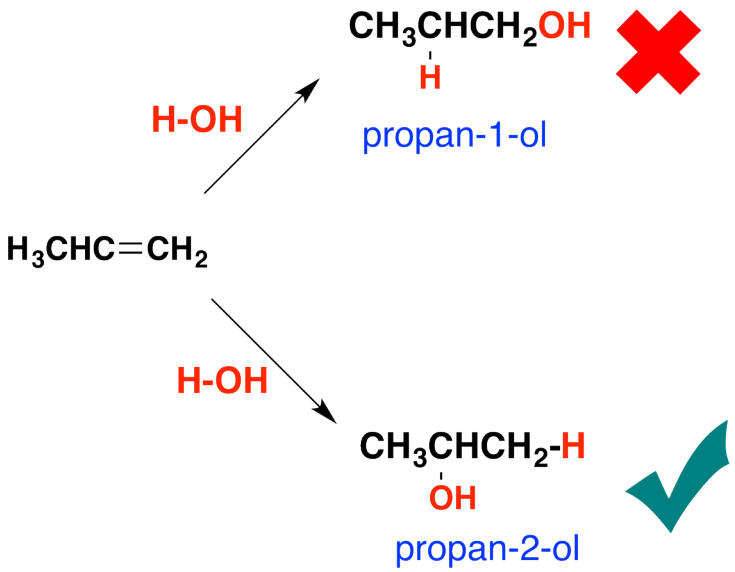
$$H_2C{=}CH_2(g) + H_2O(g) \underset{}{\overset{H_3PO_4}{\rightleftharpoons}} CH_3CH_2OH(g)$$

Only 5% of the ethene is converted into ethanol at each pass through the reactor. By removing the ethanol from the equilibrium mixture and recycling the ethene, it is possible to achieve an overall 95% conversion. A flow scheme for the reaction looks like this:



The manufacture of other alcohols from alkenes

Some - but not all - other alcohols can be made by similar reactions. The catalyst used and the reaction conditions will vary from alcohol to alcohol. The reason that there is a problem with some alcohols is well illustrated with trying to make an alcohol from propene, $CH_3CH{=}CH_2$. In principle, there are two different alcohols which might be formed:



You might expect to get either propan-1-ol or propan-2-ol depending on which way around the water adds to the double bond. In practice what you get is propan-2-ol. If you add a molecule H-X across a carbon-carbon double bond, the hydrogen nearly always gets attached to the carbon with the most hydrogens on it already - in this case the CH_2 rather than the CH. The effect of this is that there are bound to be some alcohols which it is impossible to make by reacting alkenes with steam because the addition would be the wrong way around.

Making ethanol by fermentation

This method only applies to ethanol and you cannot make any other alcohol this way. The starting material for the process varies widely, but will normally be some form of starchy plant material such as maize (US: corn), wheat, barley or potatoes. Starch is a complex carbohydrate, and other carbohydrates can also be used - for example, in the lab sucrose (sugar) is normally used to produce ethanol. Industrially, this wouldn't make sense. It would be silly to refine sugar if all you were going to use it for was fermentation. There is no reason why you should not start from the original sugar cane, though.

The first step is to break complex carbohydrates into simpler ones. For example, if you were starting from starch in grains like wheat or barley, the grain is heated with hot water to extract the starch and then warmed with malt. Malt is germinated barley which contains enzymes which break the starch into a simpler carbohydrate called maltose, $C_{12}H_{22}O_{11}$. Maltose has the same molecular formula as sucrose but contains two glucose units joined together, whereas sucrose contains one glucose and one fructose unit.

Yeast is then added and the mixture is kept warm (say 35°C) for perhaps several days until fermentation is complete. Air is kept out of the mixture to prevent oxidation of the ethanol produced to ethanoic acid (vinegar). Enzymes in the yeast first convert carbohydrates like maltose or sucrose into even simpler ones like glucose and fructose, both $C_6H_{12}O_6$, and then convert these in turn into ethanol and carbon dioxide. You can show these changes as simple chemical equations, but the biochemistry of the reactions is much, much more complicated than this suggests.

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2C_6H_{12}O_6 \tag{8.4.1}$$

$$C_6H_{12}O_6 \longrightarrow 2CH_3CH_2OH + 2CO2 \tag{8.4.2}$$

Yeast is killed by ethanol concentrations in excess of about 15%, and that limits the purity of the ethanol that can be produced. The ethanol is separated from the mixture by fractional distillation to give 96% pure ethanol. For theoretical reasons (minimum boiling point azeotrope), it is impossible to remove the last 4% of water by fractional distillation.

Table 1.1.1: *A comparison of fermentation with the direct hydration of ethene*

	Fermentation	Hydration of ethene
Type of process	A batch process. Everything is put into a container and then left until fermentation is complete. That batch is then cleared out and a new reaction set up. This is inefficient.	A continuous flow process. A stream of reactants is passed continuously over a catalyst. This is a more efficient way of doing things.
Rate of reaction	Very slow.	Very rapid.
Quality of product	Produces very impure ethanol which needs further processing	Produces much purer ethanol.
Reaction conditions	Uses gentle temperatures and atmospheric pressure.	Uses high temperatures and pressures, needing lots of energy input.
Use of resources	Uses renewable resources based on plant material.	Uses finite resources based on crude oil.

Contributors

- Jim Clark (Chemguide.co.uk)

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8.5: Synthesis of Alcohols by Nucleophilic Substitution

Synthesis of Alcohols by Substitution of Alkyl Halides

Synthesis of alcohols from alkyl halides

Formation of alcohols from alkenes

Additional Resources

Carey 4th Edition On-Line Activity

Hydration of alkenes

Hydroboration-Oxidation of Alkenes

Oxymercuration-Demercuration of Alkenes

Hydrolysis of Alkyl halides

Cliffs Notes

Synthesis of alcohols

Slide Presentations

Properties and preps of alcohols

Synthesis and structure of alcohol presentation

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8.6: Synthesis of Alcohols: Oxidation-Reduction Relation Between Alcohols and Carbonyl Compounds

Objectives

After completing this section, you should be able to

1. determine whether a given reaction should be classified as an oxidation or a reduction.
2. write an equation to represent the reduction of an aldehyde or ketone using sodium borohydride or lithium aluminum hydride.
   a. discuss the relative advantages and disadvantages of using sodium borohydride or lithium aluminum hydride to reduce aldehydes or ketones to alcohols.
   b. identify the product formed from the reduction of a given aldehyde or ketone.
   c. identify the aldehyde or ketone that should be used to produce a given alcohol in a reduction reaction.
   d. identify the best reagent to carry out the reduction of a given aldehyde or ketone.
3. write an equation to represent the reduction of an ester or a carboxylic acid to an alcohol.
   a. identify the product formed from the reduction of a given ester or carboxylic acid.
   b. identify the esters or carboxylic acids that could be reduced to form a given alcohol.

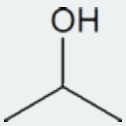
Key Terms

Make certain that you can define, and use in context, the key terms below.

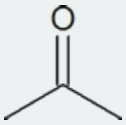
- (organic) oxidation
- (organic) reduction

Study Notes

In your course in first-year general chemistry, you probably discussed oxidation-reduction reactions in terms of the transfer of electrons and changes in oxidation numbers (oxidation states). In organic chemistry, it is often more convenient to regard reduction as the gain of hydrogen or loss of oxygen, and oxidation as the gain of oxygen or the loss of hydrogen. There is no contradiction in using these various definitions. For example, when hydrogen is added across the double bond of ethene to reduce it to ethane, the oxidation number of the doubly bonded carbon atoms decreases from –II to –III. Similarly, when 2-propanol



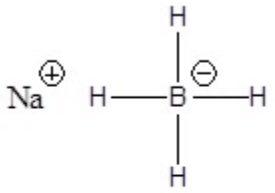
is oxidized to acetone



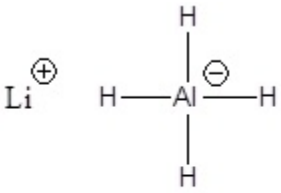
hydrogen is removed from the compound and the oxidation number of the central carbon atom increases from 0 to +II. If necessary, review the concept of oxidation number.

Reduction of Aldehydes and Ketones

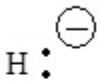
The most common sources of the hydride Nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



Sodium Borohydride

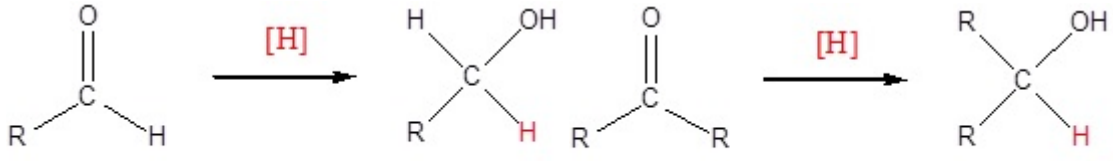


Lithium Aluminum Hydride



Hydride Nucleophile

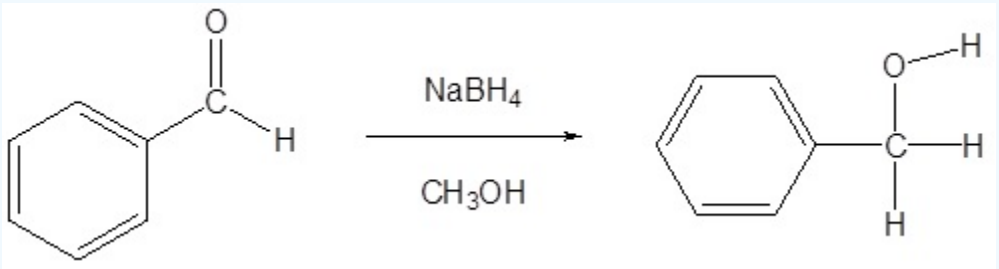
Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols.

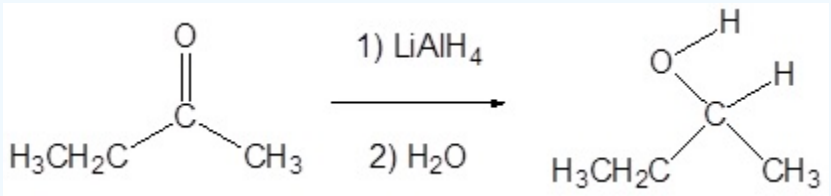


Aldehyde **1° Alcohol** **Ketone** **2° Alcohol**

In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

Example 17.4.1

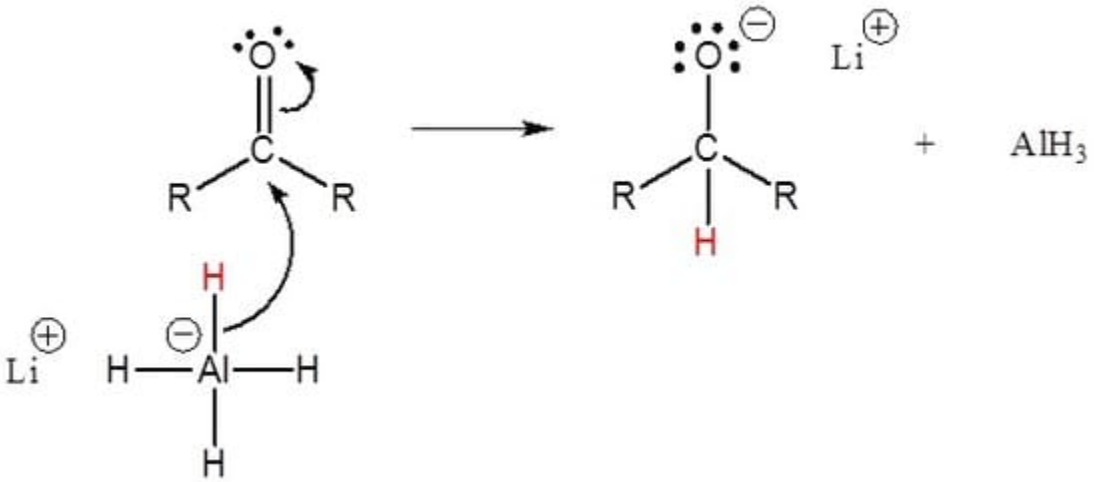




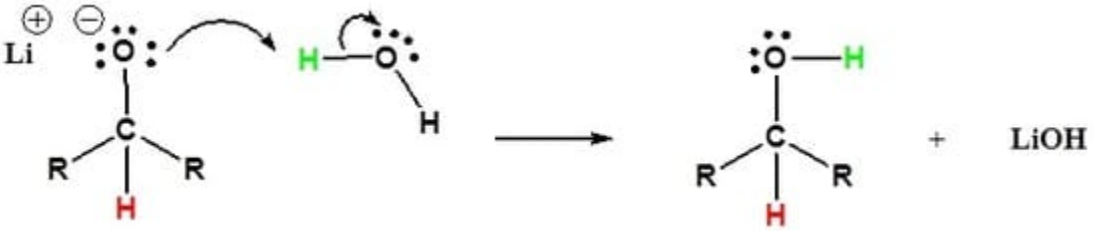
Mechanism

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

1) Nucleopilic attack by the hydride anion

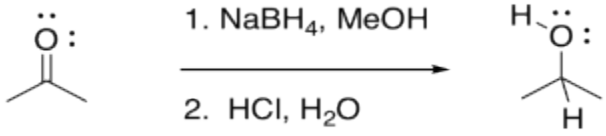


2) The alkoxide is protonated



Biological Reduction

Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.

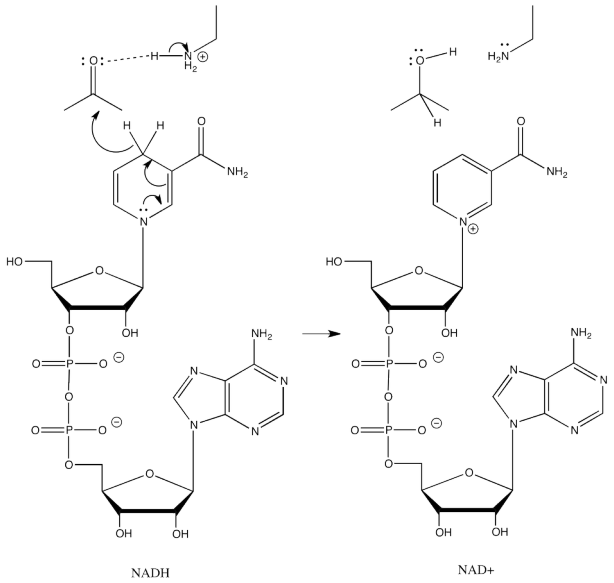


Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. An aldehyde plus two electrons and two protons becomes an alcohol.

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

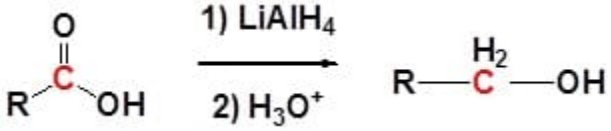
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an

anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

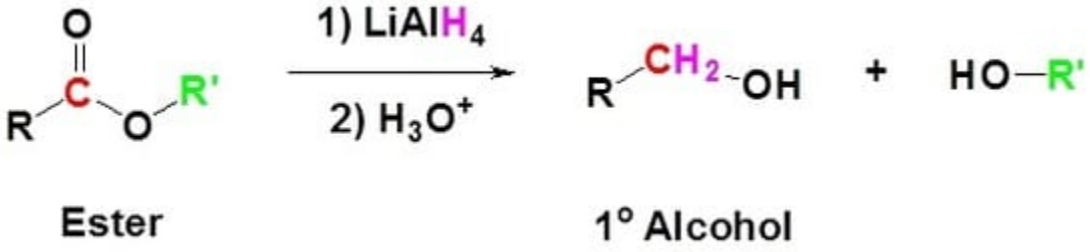


Reduction of Carboxylic Acids and Esters

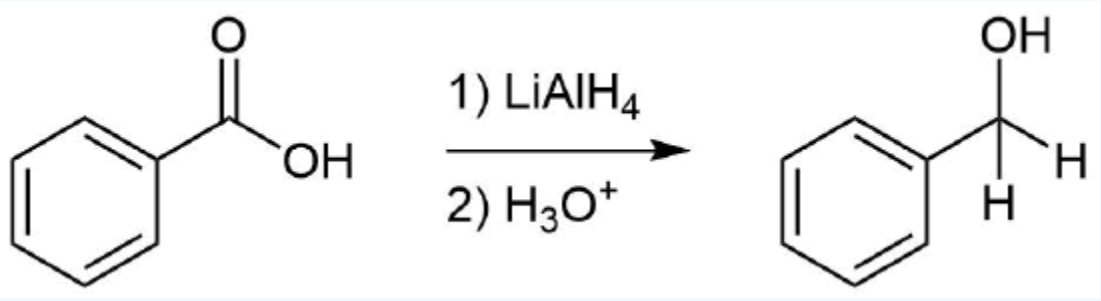
Carboxylic acids can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.

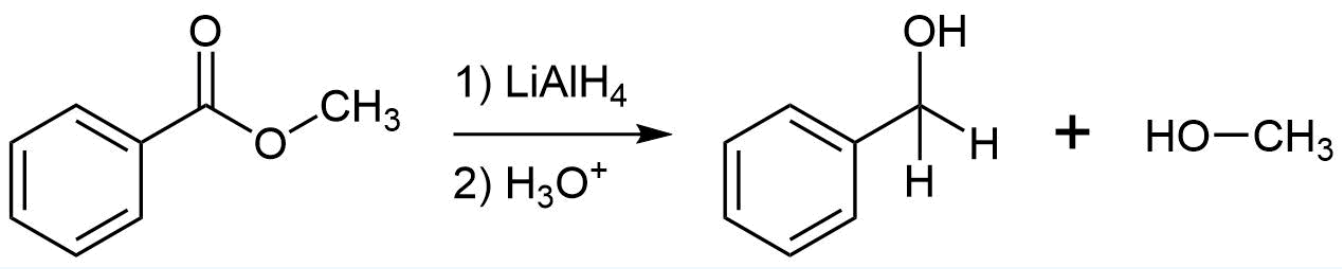


Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride ($NaBH_4$) is not a strong enough reducing agent to perform this reaction.



Example 17.4.2

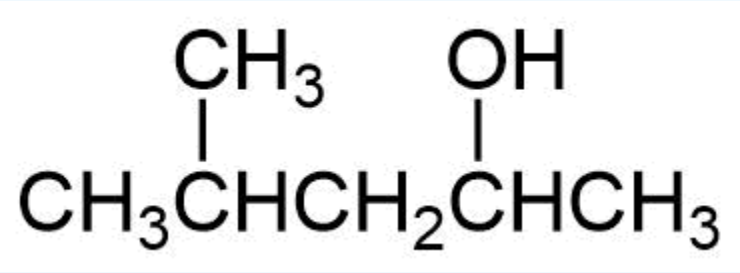




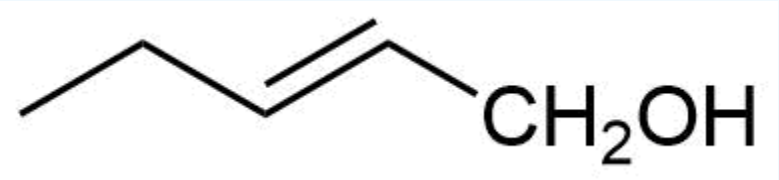
Worked Example 17.4.1

How would you prepare the following molecules using a hydride reduction?

a)



b)

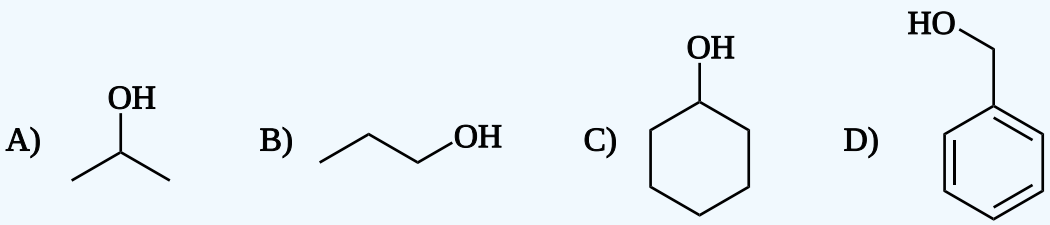


Answer available at the end of this section.

Exercises

Exercise 17.4.1

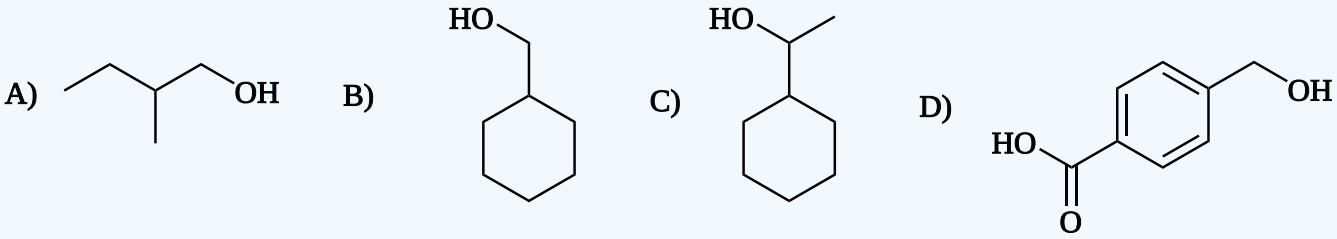
Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.



Answer available at the end of this section.

Exercise 17.4.2

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$.



Answer available at the end of this section.

Questions

Q17.4.1

Give the aldehyde, ketone, or carboxyllic acid (there can be multiple answers) that could be reduced to form the following alcohols.

(a) 17.31aq.png (b) 17.31bq.png (c) 17.31cq.png (d) 17.31dq.png

Q17.4.2

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

(a) 17.32aq.png (b) 17.32bq.png (c) 17.32cq.png (d) 17.32dq.png

Solutions

S17.4.1

(a) 17.31aa.png (b) 17.31ba.png (c) 17.31ca.png (d) 17.31da.png

S17.4.2

Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.

(a) 17.32aa.png (b) 17.32ba.png (c) 17.32ca.png (d) 17.32da.png

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

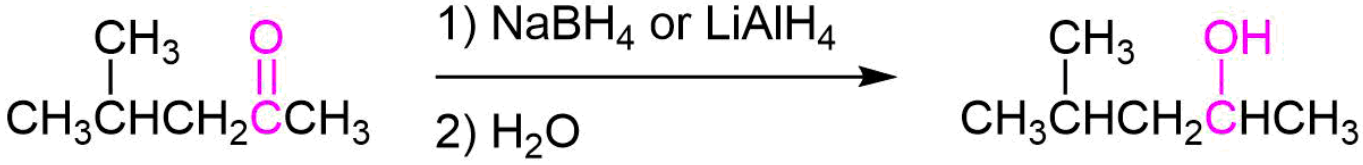
17.07 Oxidation of Alcohols

Answers

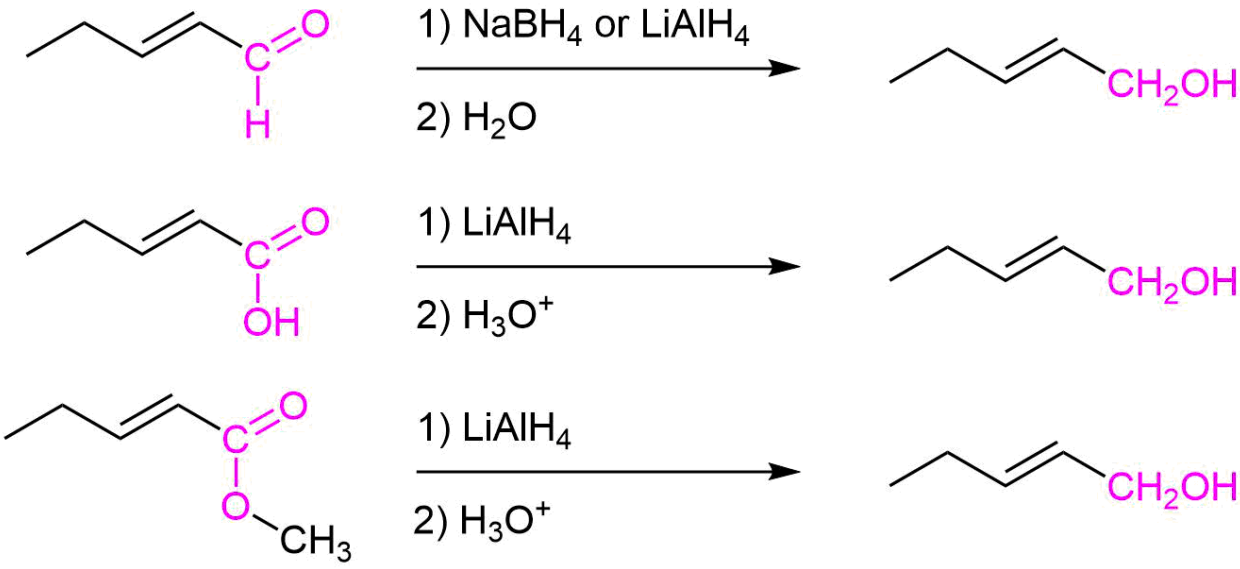
Worked Example 17.4.1

Analysis: The first step is to note if the target molecule is a 1^o or 2^o alcohol. Primary alcohols can be made by the hydride reduction of an aldehyde, carboxylic acid, or ester while secondary alcohols are made by the reduction of ketones. A 3^o alcohol cannot be made by a hydride reduction. Also, it is important to remember than aldehydes and ketones can be reduced by both $NaBH^4$ and $LiAlH_4$ whereas carboxylic acids and ester can only be reduced by $LiAlH_4$.

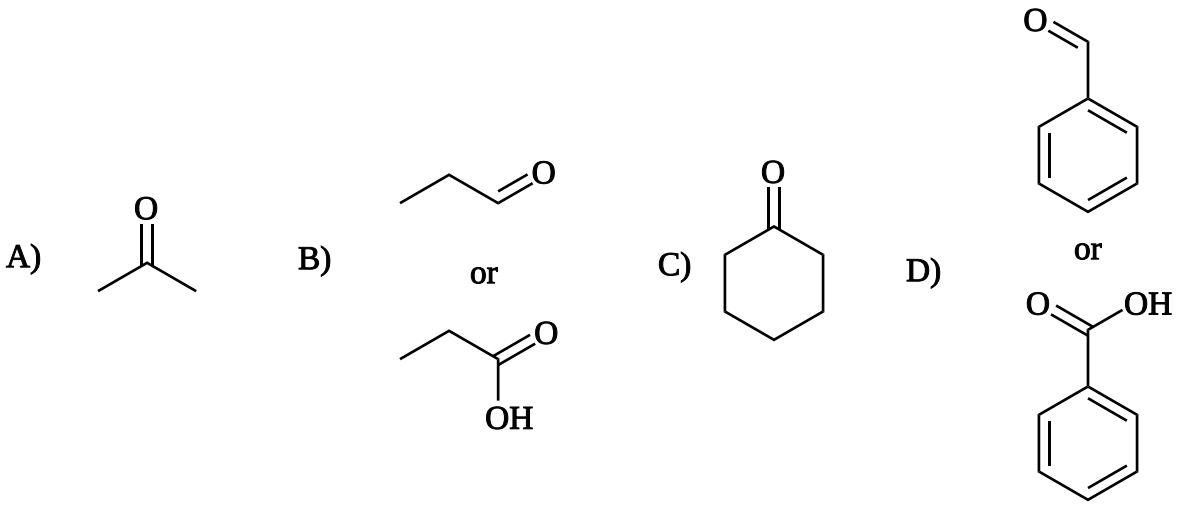
a) Because the target molecule is a secondary alcohol the starting material must be a ketone.



b) Because the target molecule is a primary alcohol the starting material could be an aldehyde, a carboxylic acid, or an ester.

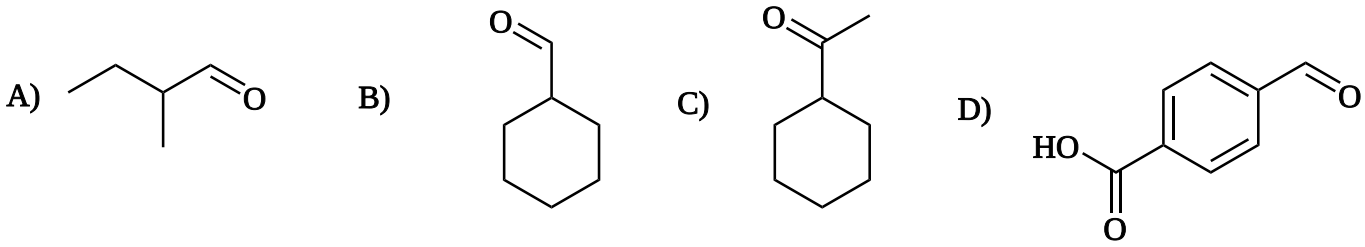


Exercise 17.4.1



Exercise 17.4.2

Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



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8.7: Organometallic Reagents: Sources of Nucleophilic Carbon for Alcohol Synthesis

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal which has characteristics similar to a carbanion (R:-).

Formation of Organometallic Reagents

Many organometallic reagents are commercially available, however, it is often necessary to make then. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination).

- **An Alkyl Lithium Reagent**

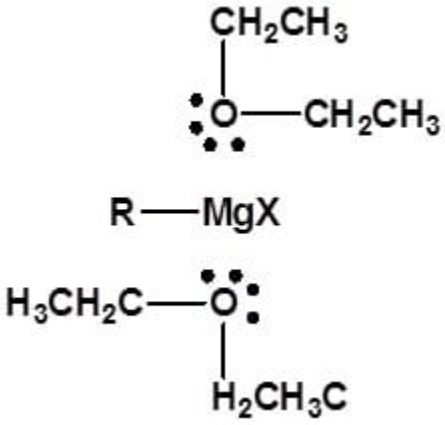
$$\mathrm{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{8.7.1}$$

- **A Grignard Regent**

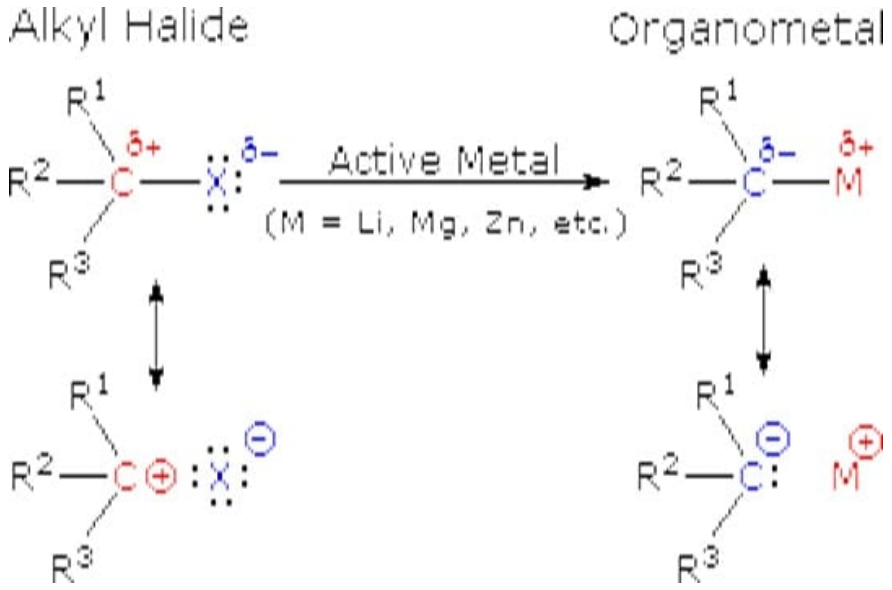
$$\mathrm{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{8.7.2}$$

Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used. The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The other metals mentioned above react in a similar manner, but Grignard and Alky Lithium Reagents most widely used. Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

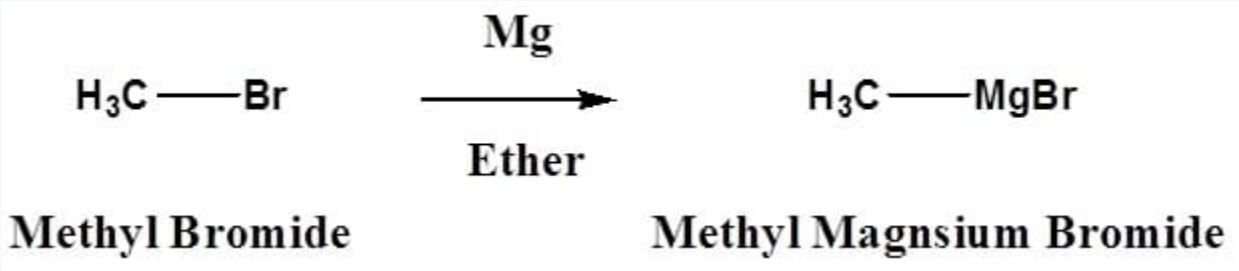
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (As pictured below). This complex helps stabilize the organometallic and increases its ability to react.

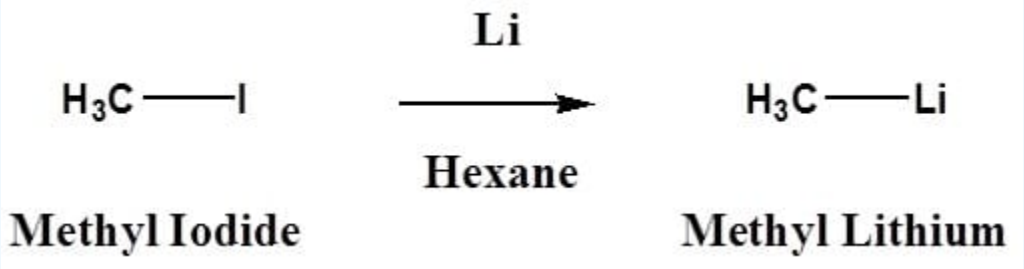


These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

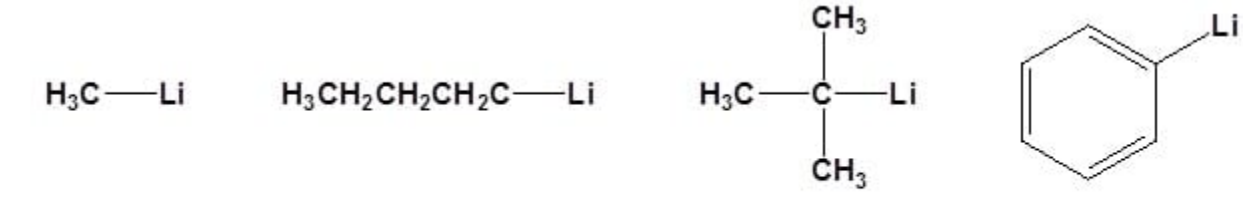


Example 8.7.1:

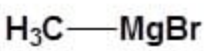


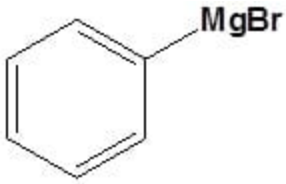


Common Organometallic Reagents



Methyl Lithium | Butyl Lithium | *t*-Butyl Lithium | Phenyl Lithium



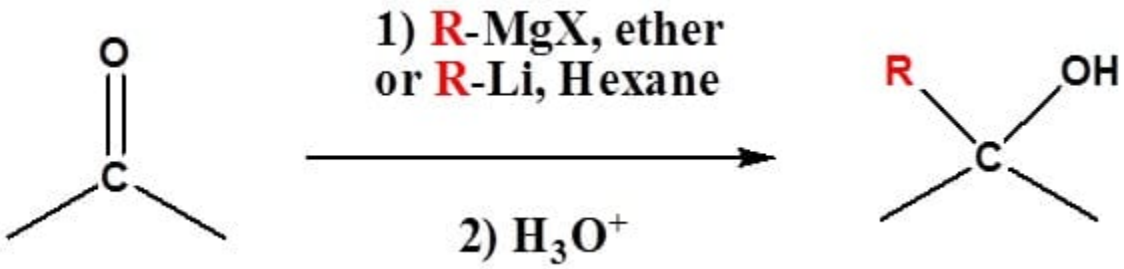


Methyl Magnesium Bromide

Phenylmagnesium Bromide

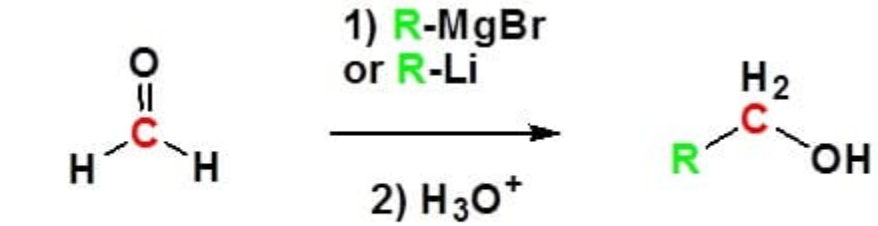
Reaction of Organometallic Reagents with Various Carbonyls

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.



Both Grignard and Organolithium Reagents will perform these reactions.

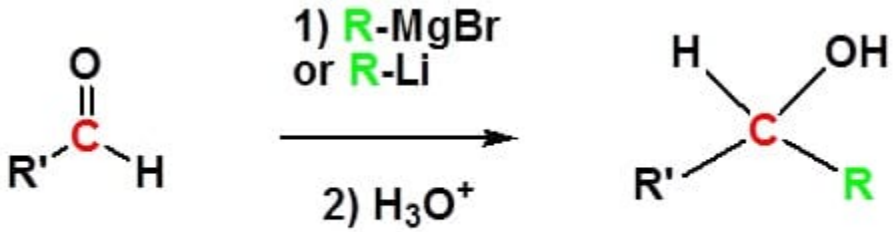
Addition to formaldehyde gives 1° alcohols



Formaldehyde

1° Alcohol

Addition to aldehydes gives 2° alcohols



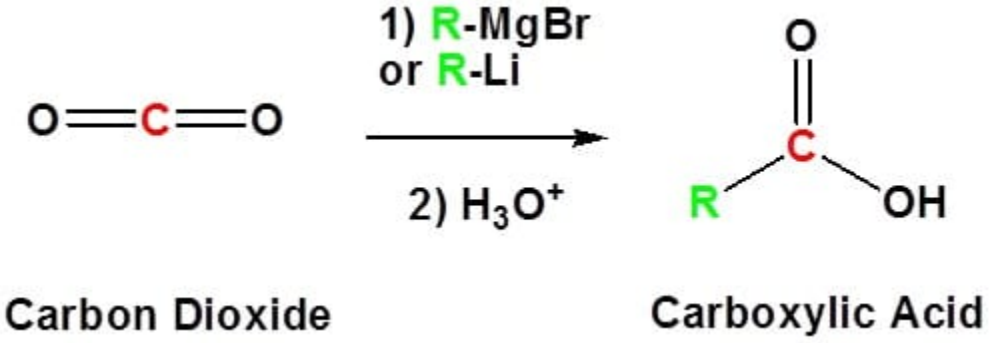
Aldehyde

2° Alcohol

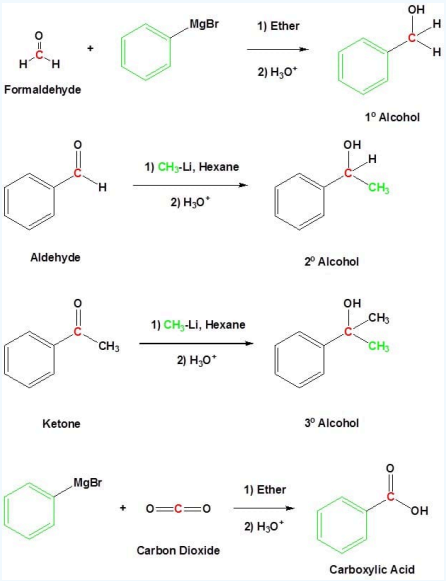
Addition to ketones gives 3° alcohols



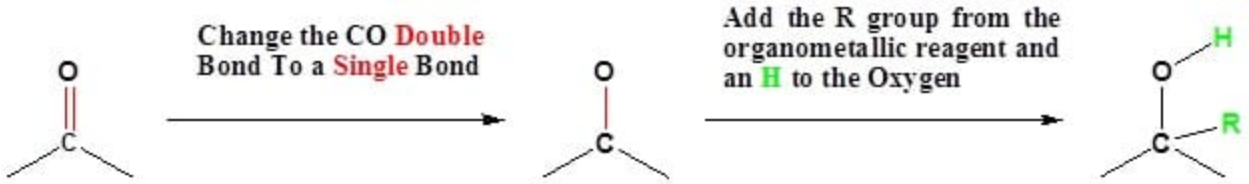
Addition to carbon dioxide (CO_2) forms a carboxylic acid



Example 8.7.1:



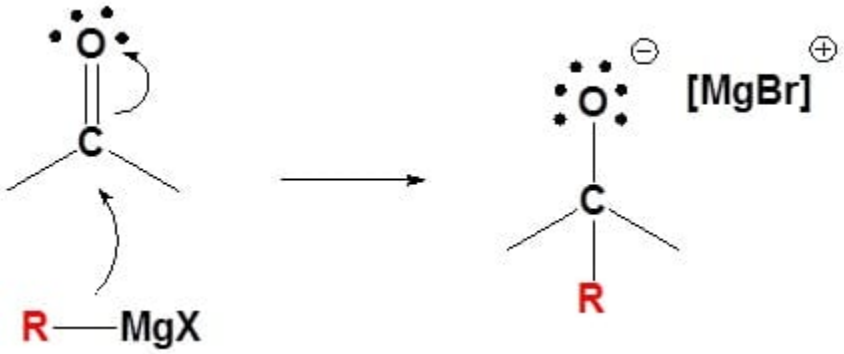
Going from Reactants to Products Simplified



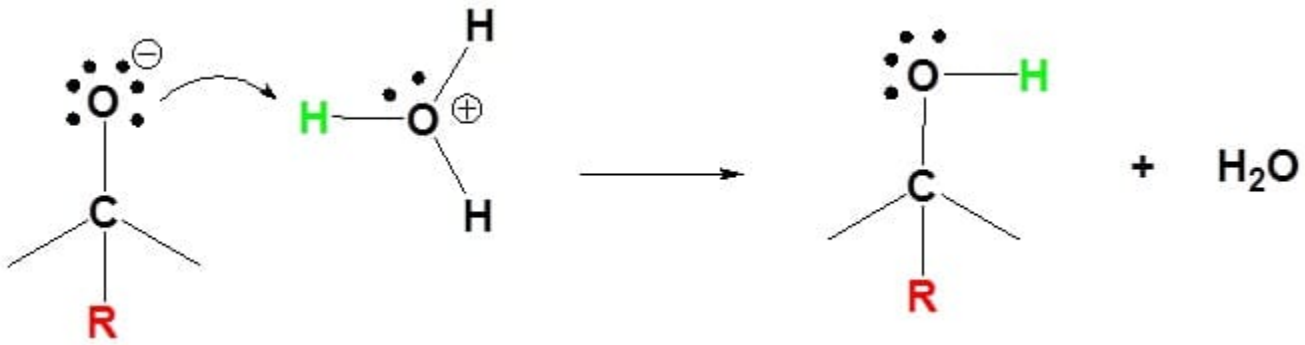
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown; the mechanism for an organometallic reagent is the same.

1) Nucleophilic attack



2) Protonation



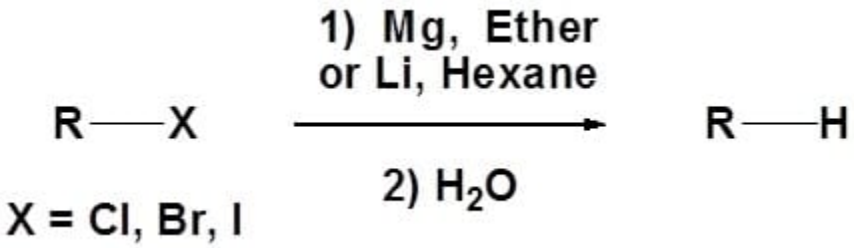
Organometallic Reagents as Bases

These reagents are very strong bases (pKa's of saturated hydrocarbons range from 42 to 50). Although not usually done with Grignard reagents, organolithium reagents can be used as strong bases. Both Grignard reagents and organolithium reagents react with water to form the corresponding hydrocarbon. This is why so much care is needed to insure dry glassware and solvents when working with organometallic reagents.



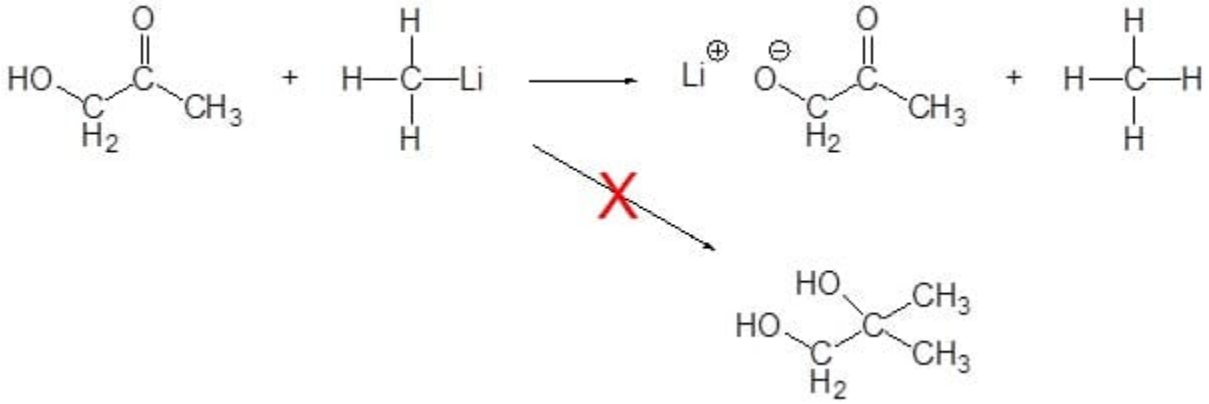
In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion

of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



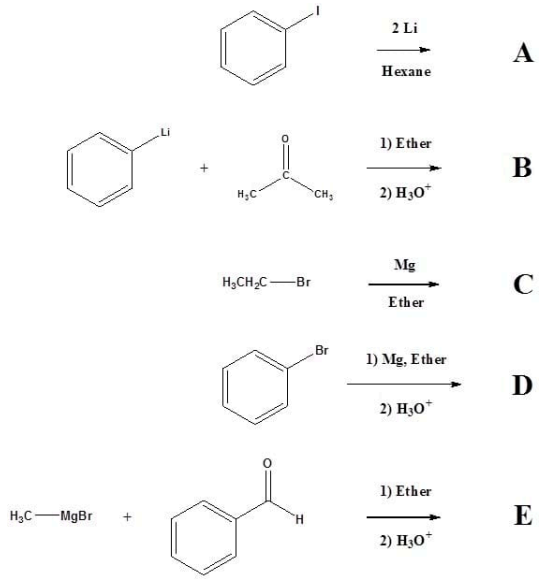
Limitation of Organometallic Reagents

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1o amines, 2o amines, carboxylic acids, and terminal alkynes.

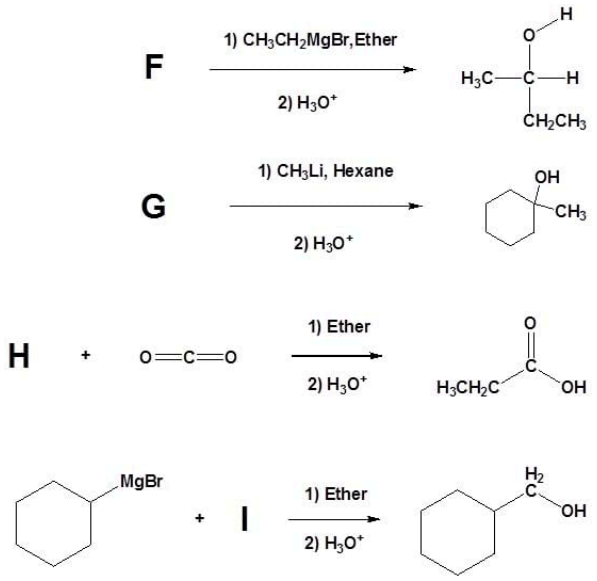


Problems

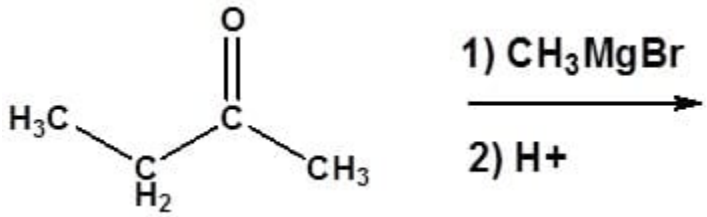
1) Please write the product of the following reactions.



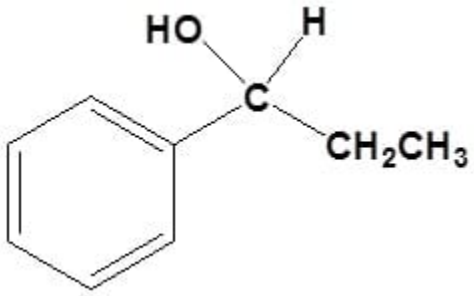
2) Please indicate the starting material required to produce the product.



3) Please give a detailed mechanism and the final product of this reaction

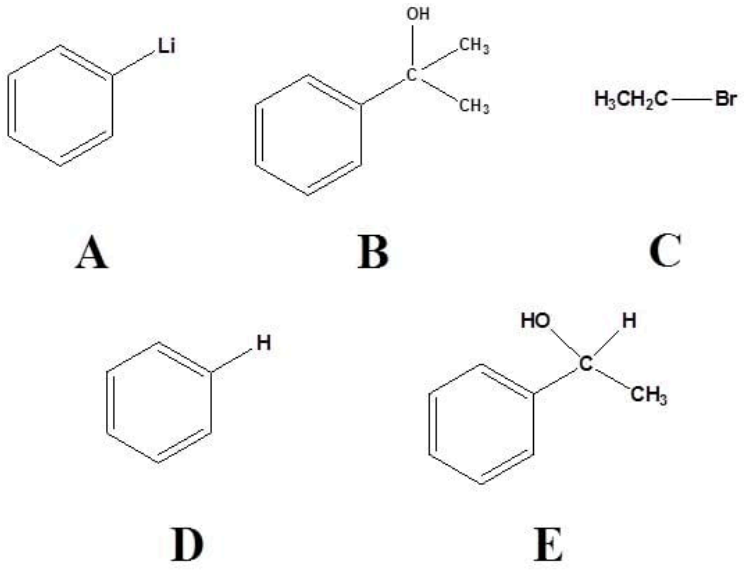


4) Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.

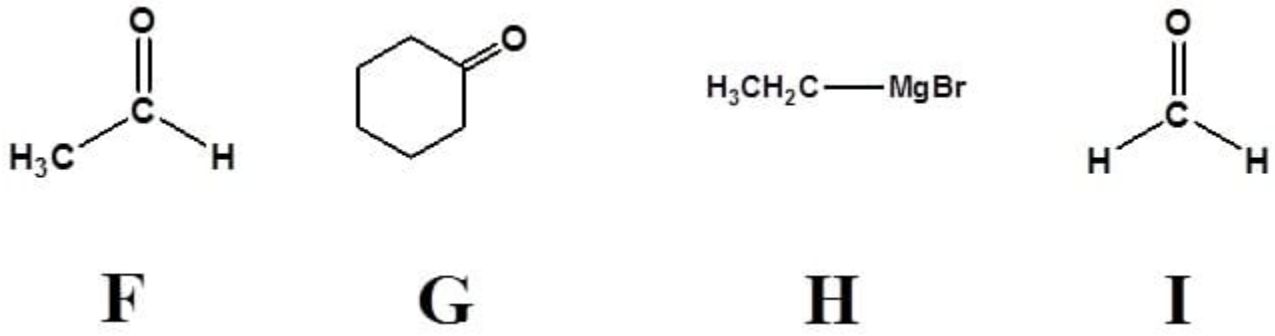


Answers

1)

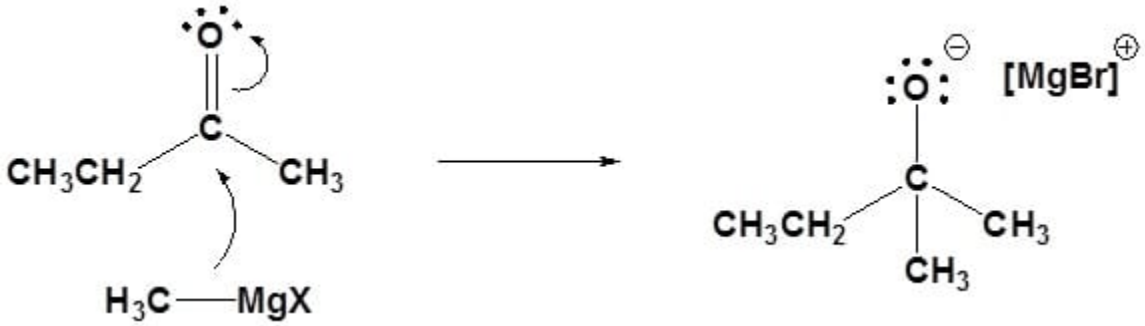


2)

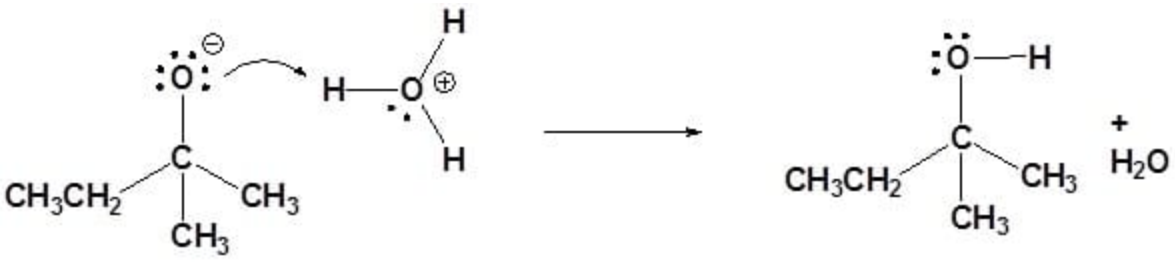


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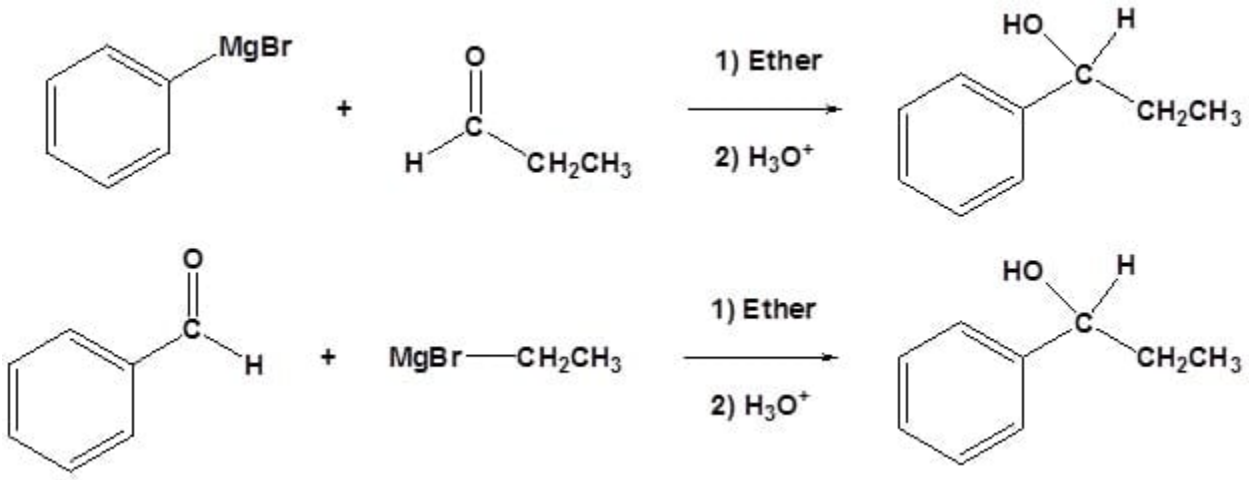
Nucleophilic attack



Protonation



4)



Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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8.8: Organometallic Reagents in the Synthesis of Alcohols

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal which has characteristics similar to a carbanion (R:-).

Formation of Organometallic Reagents

Many organometallic reagents are commercially available, however, it is often necessary to make then. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination).

- **An Alkyl Lithium Reagent**

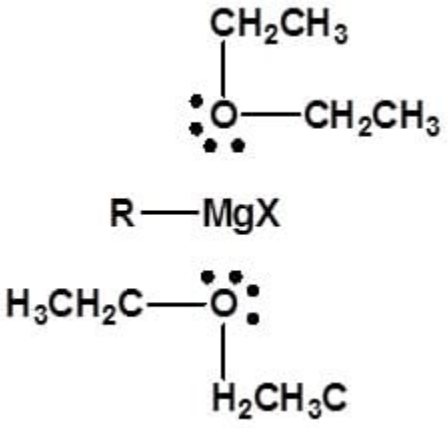
$$\mathrm{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{8.8.1}$$

- **A Grignard Regent**

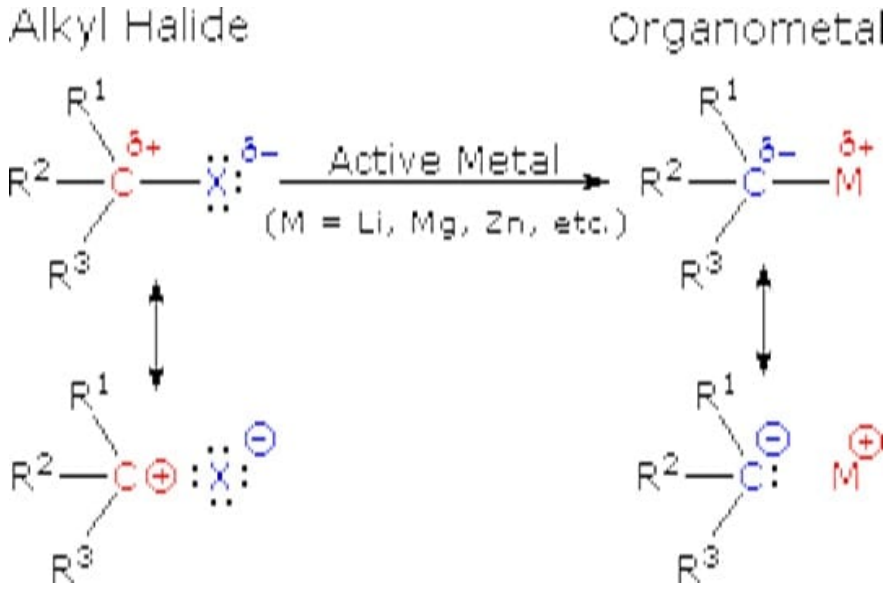
$$\mathrm{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{8.8.2}$$

Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used. The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The other metals mentioned above react in a similar manner, but Grignard and Alky Lithium Reagents most widely used. Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

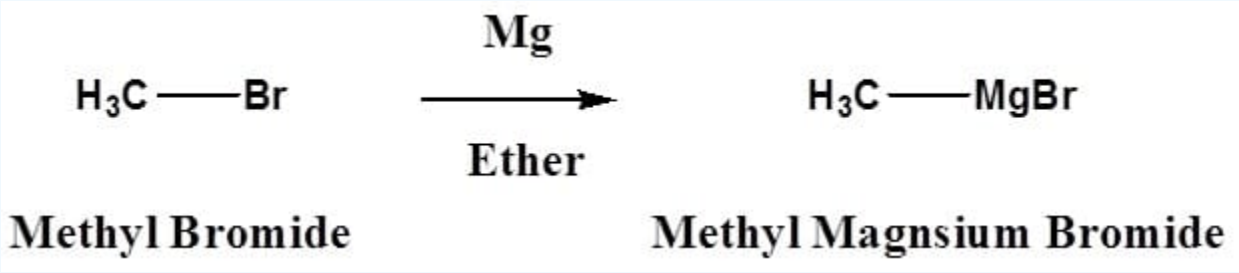
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (As pictured below). This complex helps stabilize the organometallic and increases its ability to react.

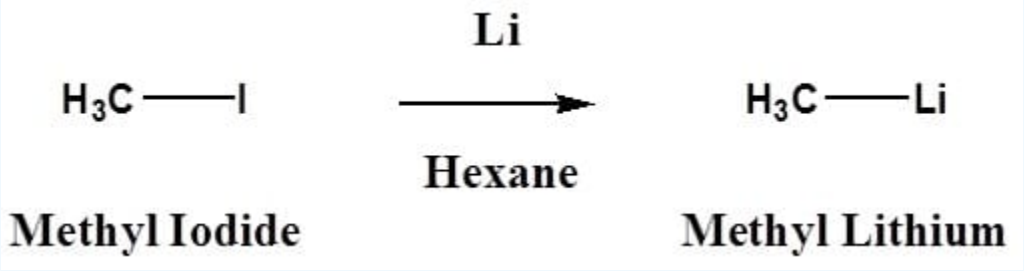


These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

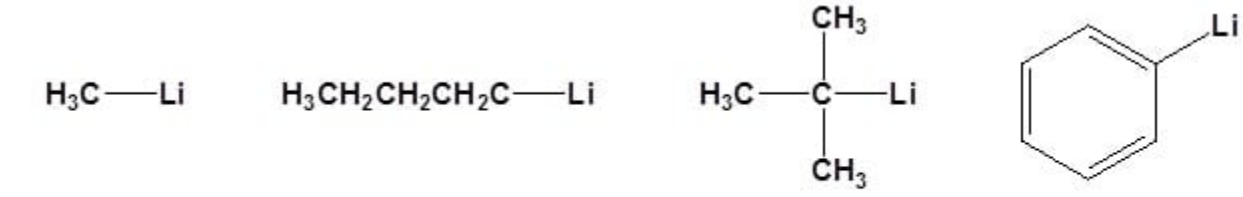


Example 8.8.1:





Common Organometallic Reagents



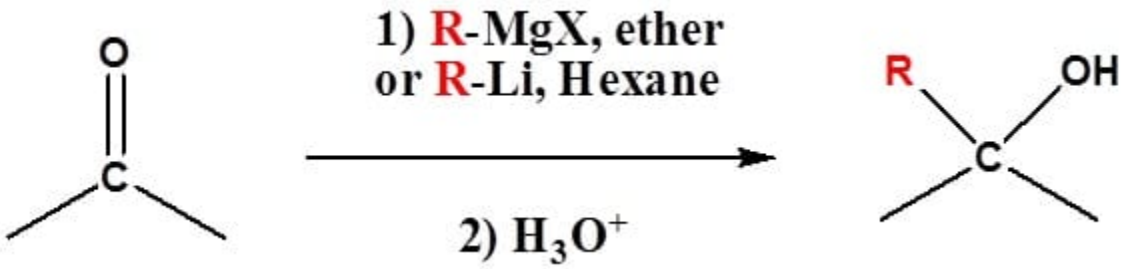
Methyl Lithium | Butyl Lithium | *t*-Butyl Lithium | Phenyl Lithium



Methyl Magnesium Bromide Phenylmagnesium Bromide

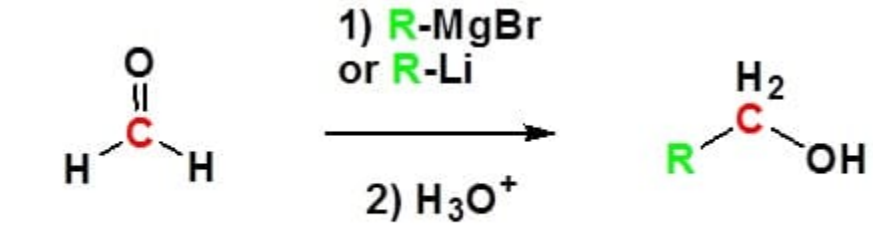
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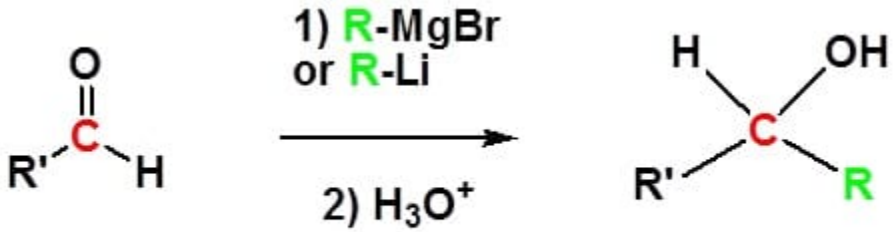
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Addition to formaldehyde gives 1° alcohols



Formaldehyde 1° Alcohol

Addition to aldehydes gives 2° alcohols

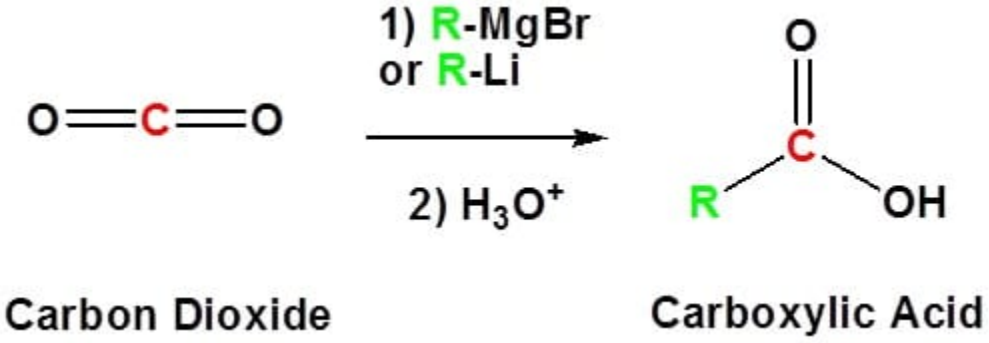


Aldehyde 2° Alcohol

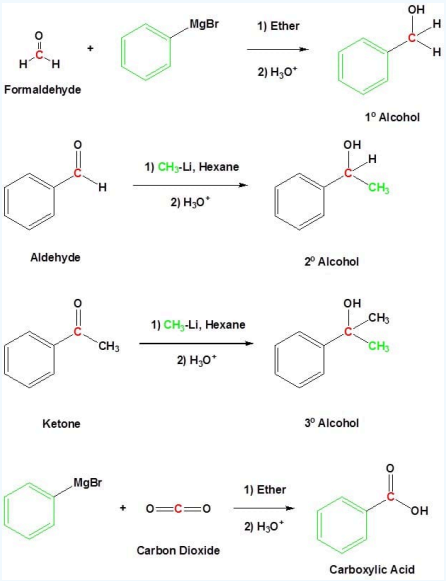
Addition to ketones gives 3° alcohols



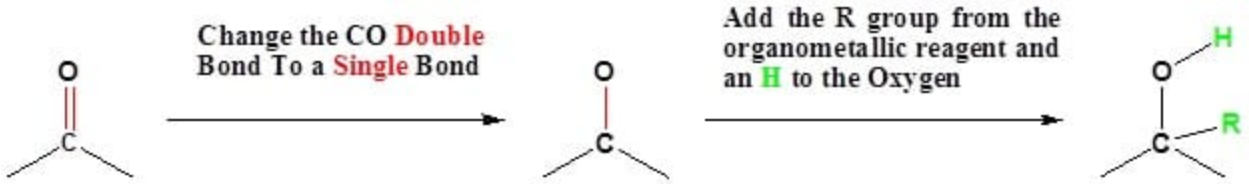
Addition to carbon dioxide (CO_2) forms a carboxylic acid



Example 8.8.1:



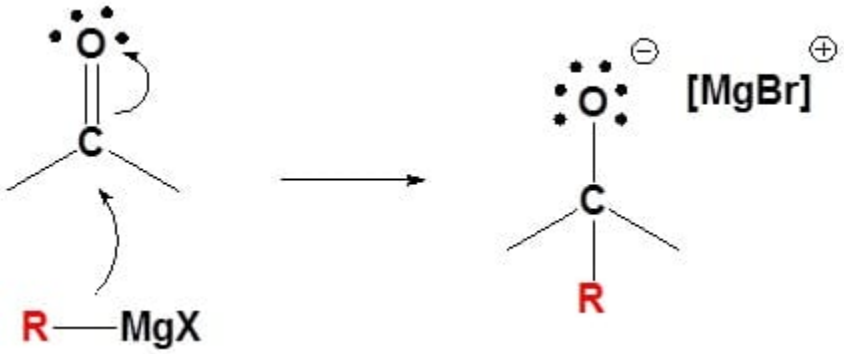
Going from Reactants to Products Simplified



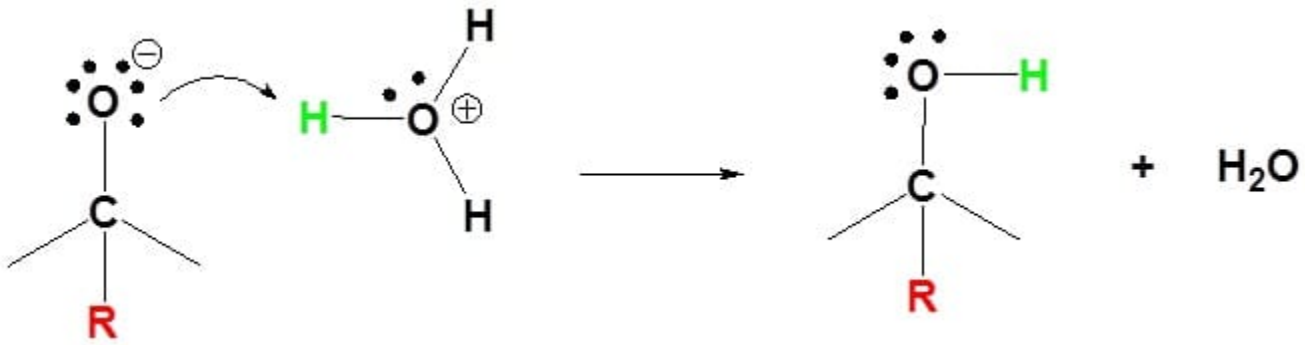
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown; the mechanism for an organometallic reagent is the same.

1) Nucleophilic attack



2) Protonation



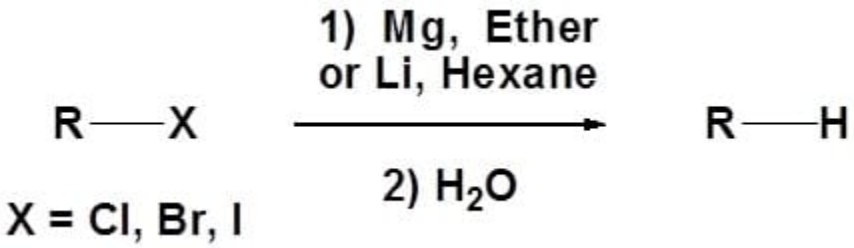
Organometallic Reagents as Bases

These reagents are very strong bases (pKa's of saturated hydrocarbons range from 42 to 50). Although not usually done with Grignard reagents, organolithium reagents can be used as strong bases. Both Grignard reagents and organolithium reagents react with water to form the corresponding hydrocarbon. This is why so much care is needed to insure dry glassware and solvents when working with organometallic reagents.



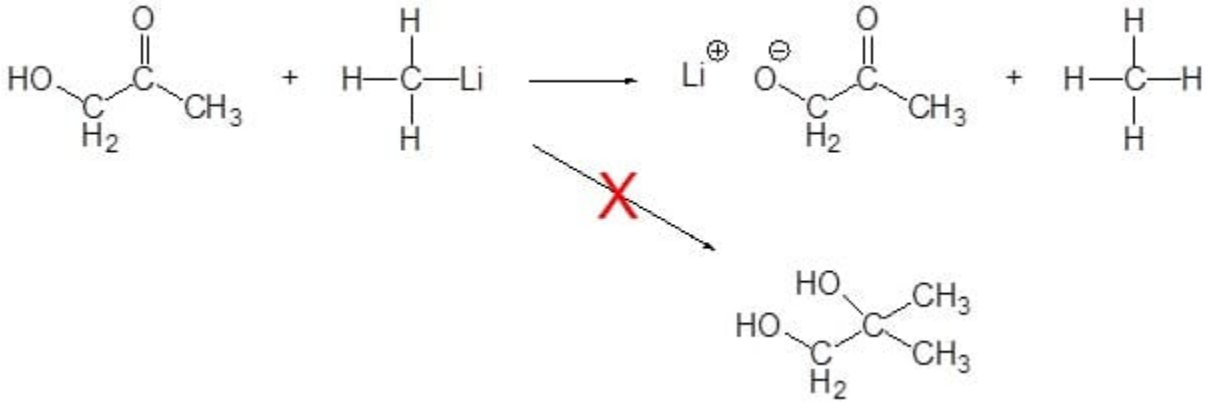
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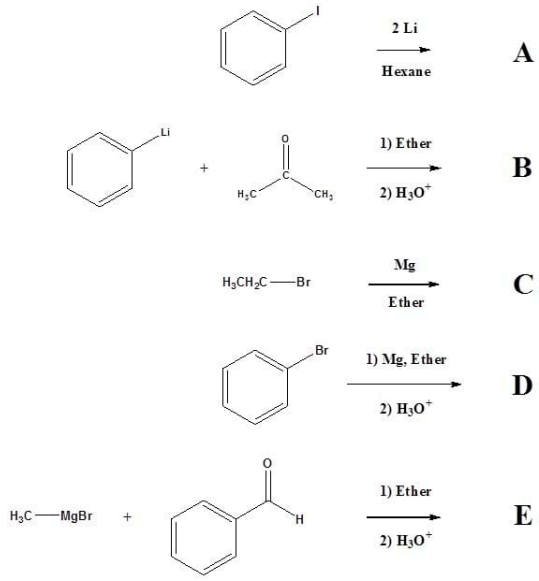
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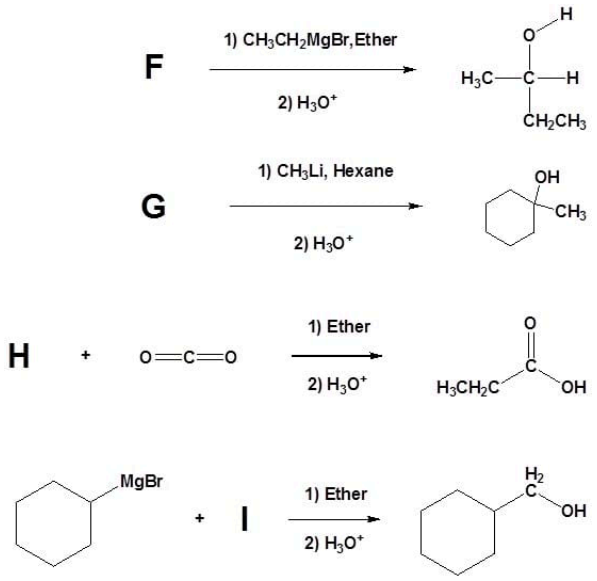


Problems

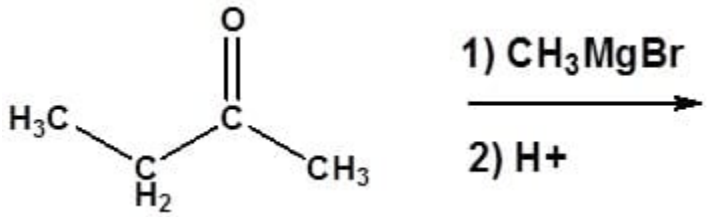
1) Please write the product of the following reactions.



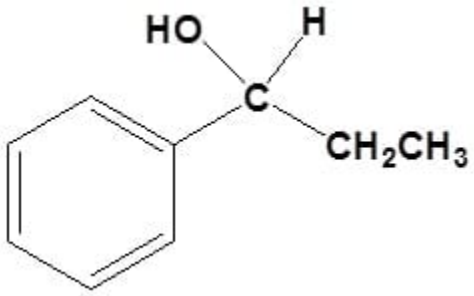
2) Please indicate the starting material required to produce the product.



3) Please give a detailed mechanism and the final product of this reaction

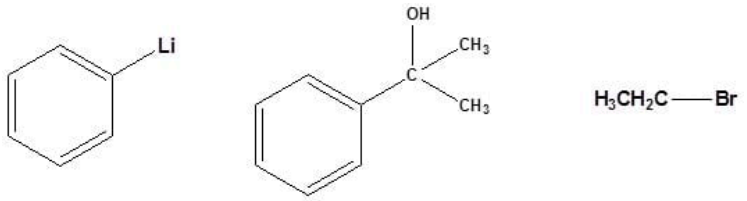


4) Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.

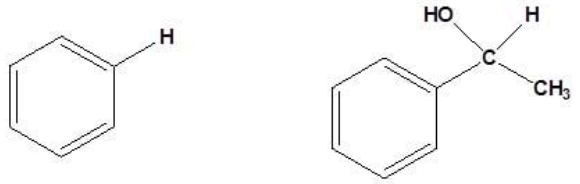


Answers

1)

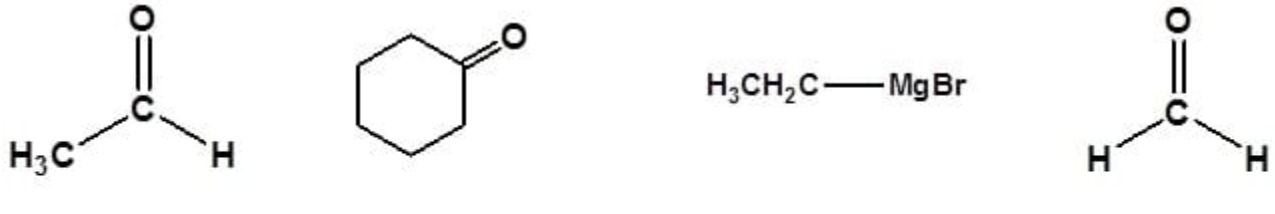


A B C



D E

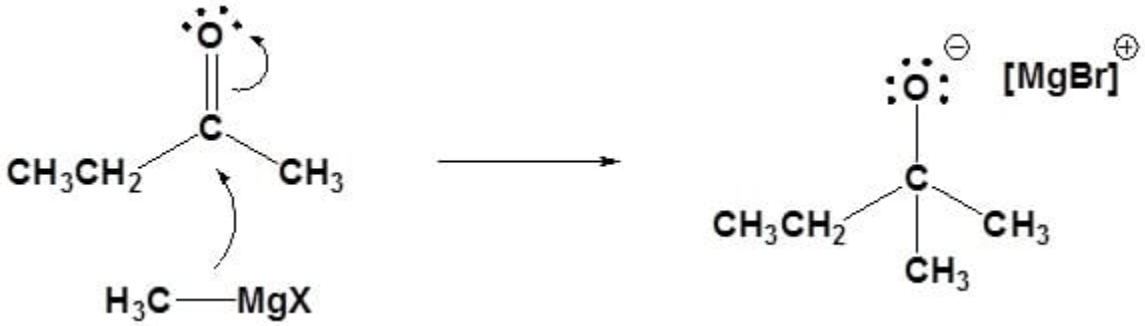
2)



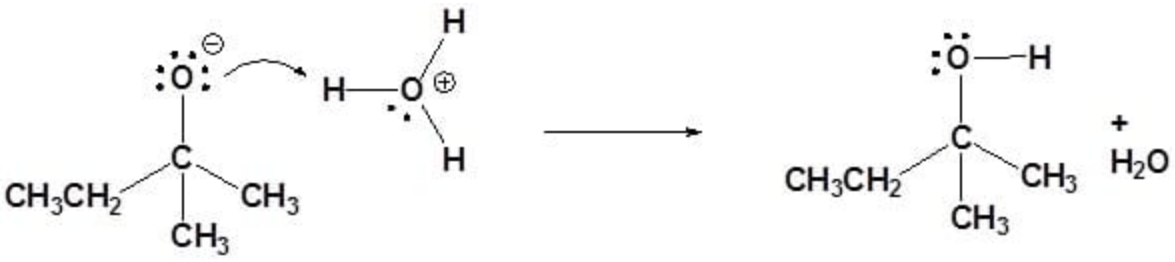
F G H I

3)

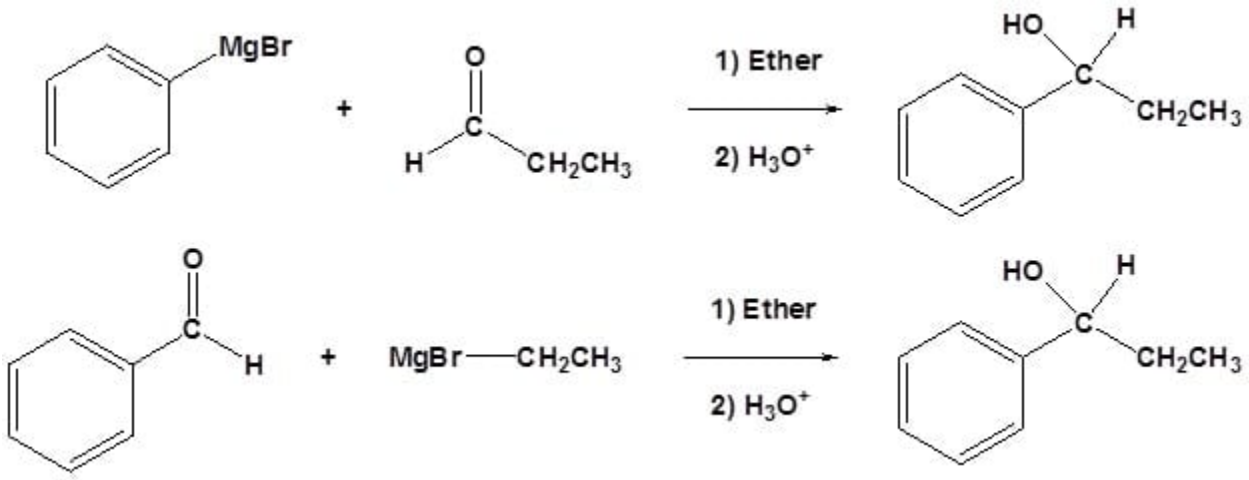
Nucleophilic attack



Protonation



4)



Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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8.9: Keys to Success: An Introduction to Synthetic Strategy

Objective

After completing this section, you should be able to design a multistep synthesis to prepare a given product from a given starting material, using any of the reactions introduced in the textbook up to this point.

Study Notes

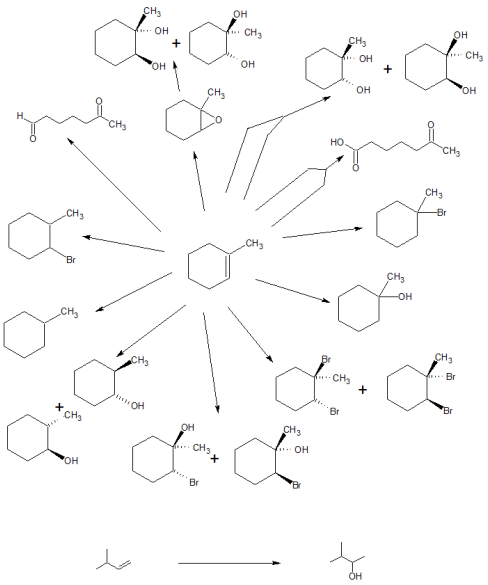
You should have noticed that some of the assigned problems have required that you string together a number of organic reactions to convert one organic compound to another when there is no single reaction to achieve this goal. Such a string of reactions is called an "organic synthesis." One of the major objectives of this course is to assist you in designing such syntheses. To achieve this objective, you will need to have all of the reactions described in the course available in your memory. You will need to recall some reactions much more frequently than others, and the only way to master this objective is to practise. The examples given in this chapter will be relatively simple, but you will soon see that you can devise some quite sophisticated syntheses using a limited number of basic reactions.

Introduction

The study of organic chemistry introduces students to a wide range of interrelated reactions. Alkenes, for example, may be converted to structurally similar alkanes, alcohols, alkyl halides, epoxides, glycols and boranes; cleaved to smaller aldehydes, ketones and carboxylic acids; and enlarged by carbocation and radical additions as well as cycloadditions. Most of these reactions are shown in the Alkene Reaction Map below. All of these products may be subsequently transformed into a host of new compounds incorporating a wide variety of functional groups. Consequently, the logical conception of a multi-step synthesis for the construction of a designated compound from a specified starting material becomes one of the most challenging problems that may be posed. Functional group reaction maps like the one below for alkenes can be helpful in designing multi-step syntheses. It can be helpful to build and design your own reaction maps for each functional group studied.

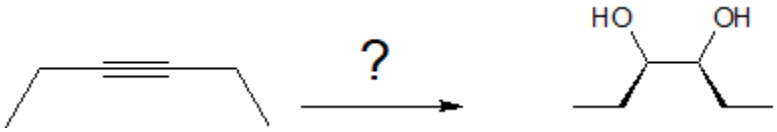
Alkene Reaction Map

Please note: The reagents for each chemical transformation have been intentionally omitted so that this map can be used as a study tool. The answers are provided at the end of this section as part of the exercises.

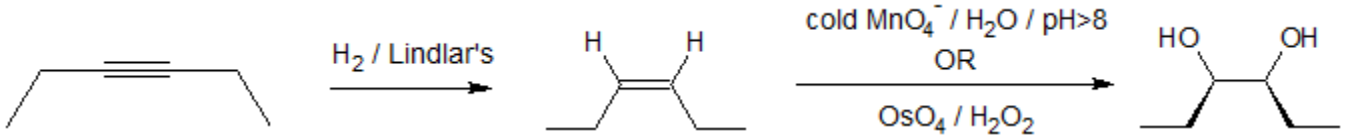


Simple Multi-Step Syntheses

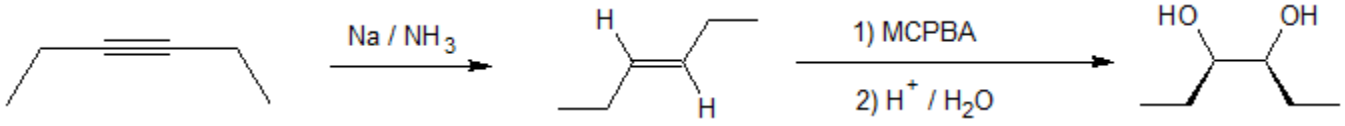
A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.



One approach would be to reduce the alkyne to cis or trans-3-hexene before undertaking glycol formation. Permanaganate or osmium tetroxide hydroxylation of cis-3-hexene would form the desired meso isomer.



From trans-3-hexene, it would be necessary to first epoxidize the alkene with a peracid followed by ring opening with acidic or basic hydrolysis.



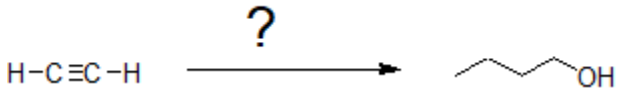
Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope and limitations constraining each of the individual reactions being employed. The skill is acquired by practice, experience, and often trial and error.

Thinking it Through with 3 Examples

The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. Retro-synthesis is the approach of working backwards from the product to the

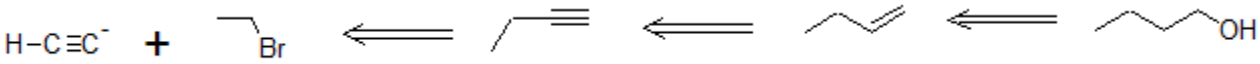
starting material.

In the first example, we are asked to synthesize 1-butanol from acetylene.

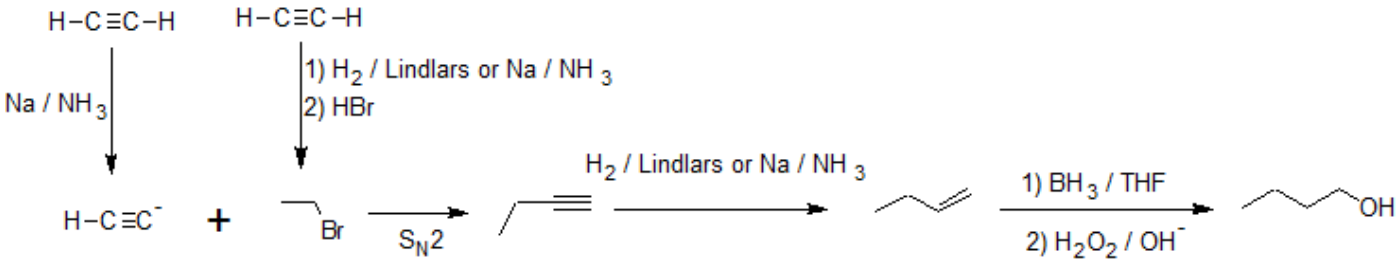


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.

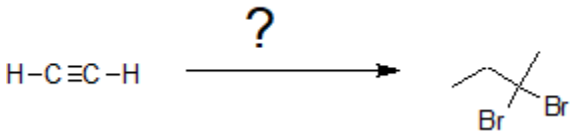
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation identified from the retro-synthesis. The ethylbromide must also be derived from acetylene so multiple reaction pathways are combined as shown below.

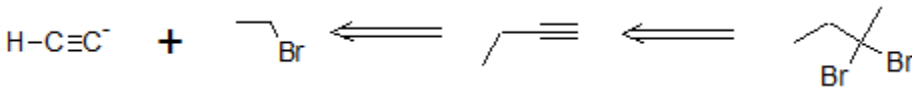


In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.

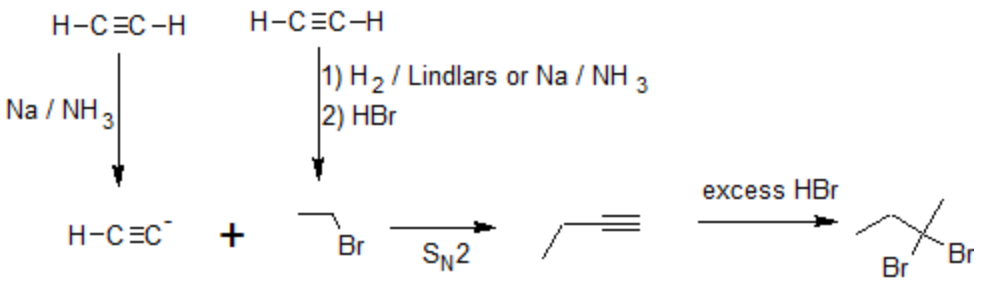


Once again there is an increase in the carbon chain length indicating an acetylide S_N2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne with 1,2-dibromobutane, there is a difference of two H atoms and two Br atoms indicating hydrohalogenation and not halogenation. The addition of both bromine atoms to the same carbon atom also supports the idea that hydrohalogenation occurs on an alkyne and not an alkene. The formation of the geminal dihalide also indicates hydrohalogenation instead of halogenation because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

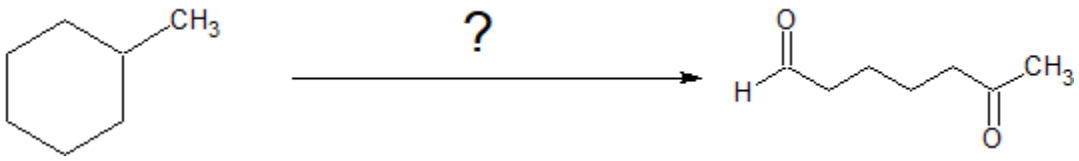
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.

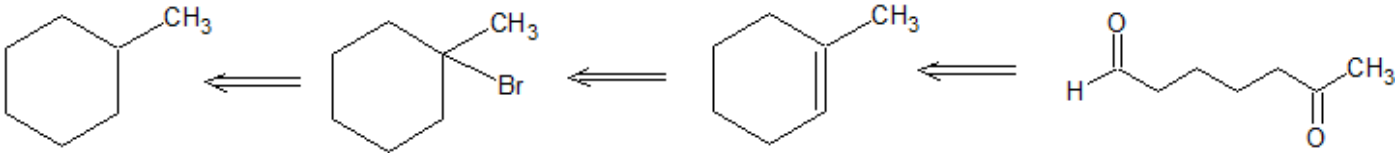


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.

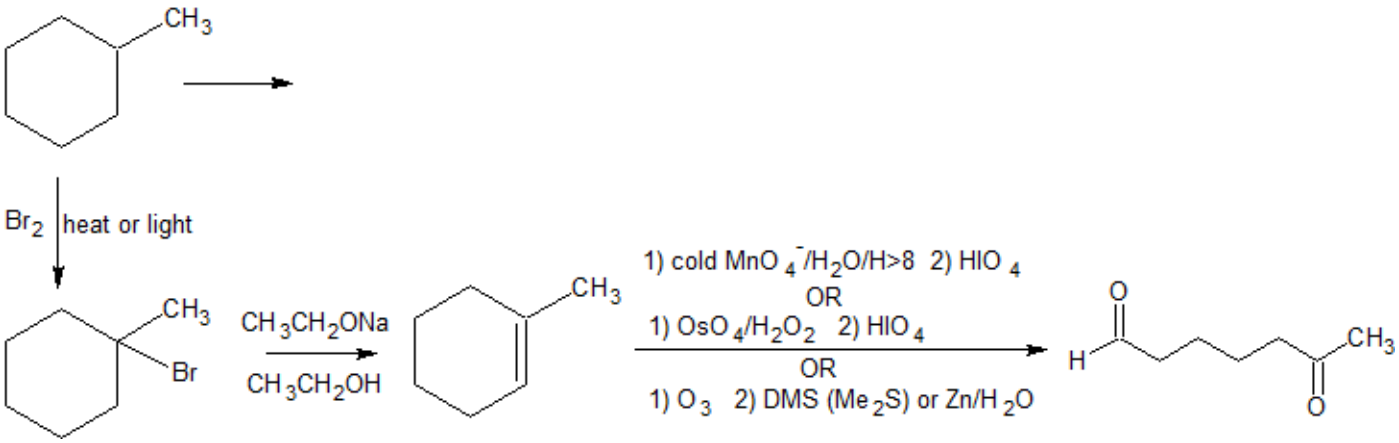


Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or perform free-radical halogenation to create alkyl halides with excellent leaving groups. With these observations, the following retro-synthesis is reasonable.

Retro-Synthesis



Working forwards, we specify the reagents needed for each reaction. For the initial free-radical halogenation of the alkane, we have the option of chlorine (Cl_2) or bromine (Br_2). Because methylcyclohexane has several different classifications of carbons, the selectivity of Br_2 is more important than the faster reactivity of Cl_2. A strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldehyde group on the final product indicates gentle oxidative cleavage by any of several reaction pathways. These reactions can be combined in to the following multi-step synthesis.

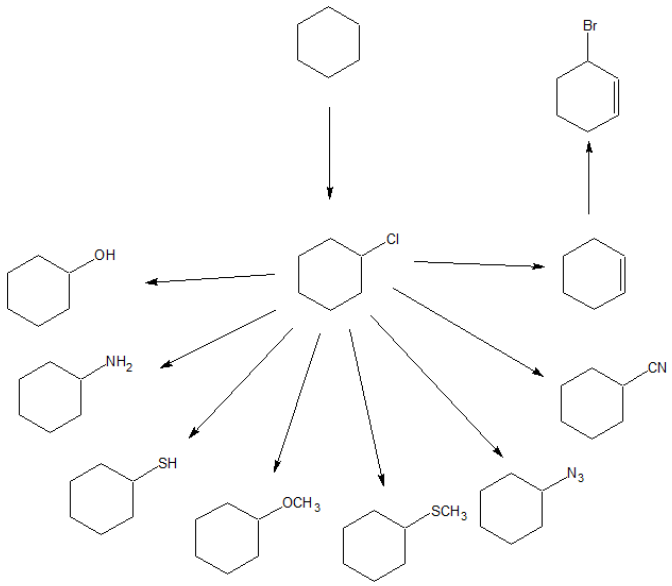


Reaction Maps to Build Functional Group Conversion Mastery

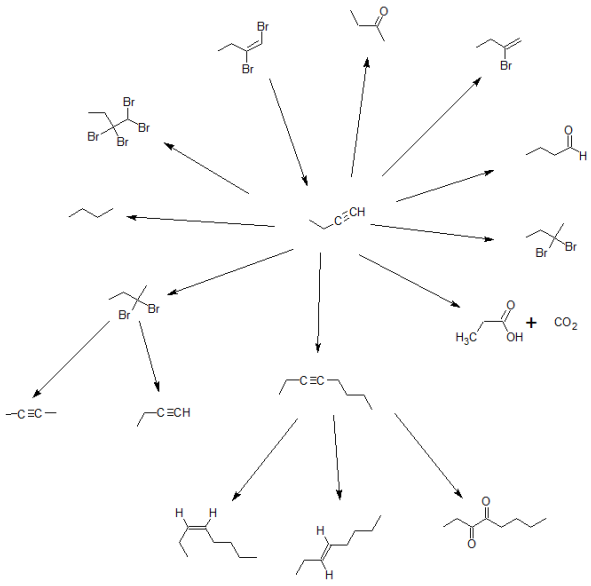
After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

Please note: The reagents for each chemical transformation have been intentionally omitted so that these maps can be used as a study tools. The answers are provided at the end of this section as part of the exercises.

Alkane and Alkyl Halide Reaction Map



Alkyne Reaction Map



Exercise

1) Starting at 3-hexyne predict synthetic routes to achieve:

a) trans-3-hexene

b) 3,4-dibromohexane

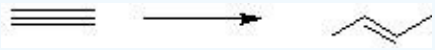
c) 3-hexanol.

2) Starting with acetylene and any alkyl halides propose a synthesis to make

a) pentanal

b) hexane.

3) Show how you would accomplish the following synthetic transformations.

a) 

b) 

Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise

1)

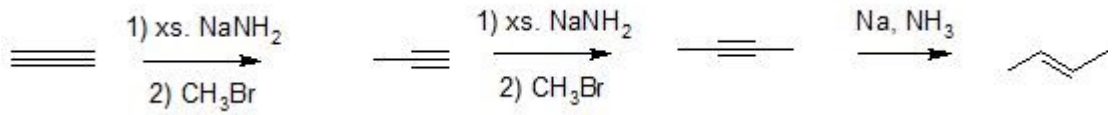
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2)

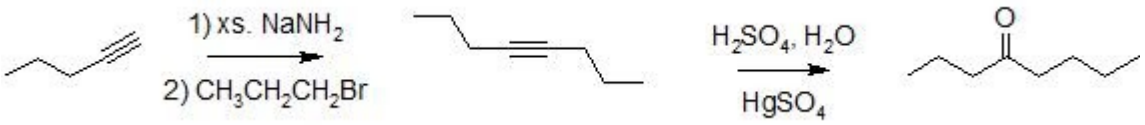
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3)

a)



b)



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9: FURTHER REACTIONS OF ALCOHOLS AND THE CHEMISTRY OF ETHERS

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

9.1: Reactions of Alcohols with Base: Preparation of Alkoxides

9.2: Reactions of Alcohols with Strong Acids: Alkyloxonium Ions in Substitution and Elimination Reactions of Alcohols

9.3: Carbocation Rearrangements

9.4: Organic and Inorganic Esters from Alcohols

9.5: Names and Physical Properties of Ethers

9.6: Williamson Ether Synthesis

9.7: Synthesis of Ethers: Alcohols and Mineral Acids

9.8: Reactions of Ethers

9.9: Reactions of Oxacyclopropanes

9.10: Sulfur Analogs of Alcohols and Ethers

9.11: Physiological Properties and Uses of Alcohols and Ethers

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9.1: Reactions of Alcohols with Base: Preparation of Alkoxides

This page describes the reaction between alcohols and metallic sodium,and introduces the properties of the alkoxide that is formed. We will look at the reaction between sodium and ethanol as being typical, but you could substitute any other alcohol and the reaction would be the same.

The Reaction between Sodium Metal and Ethanol

If a small piece of sodium is dropped into ethanol, it reacts steadily to give off bubbles of hydrogen gas and leaves a colorless solution of sodium ethoxide: $\mathrm{CH_3CH_2ONa}$. The anion component is an *alkoxide*.

If the solution is evaporated carefully to dryness, then sodium ethoxide ($\mathrm{CH_3CH_2ONa}$) is left behind as a white solid.

$$2\,\mathrm{CH_3CH_2OH} + 2\,\mathrm{Na} \longrightarrow 2\,\mathrm{CH_3CH_2ONa} + \mathrm{H_2} \tag{9.1.1}$$

> The solution formed from Equation 1 only initially a colorless solution, as the ionic sodium ethoxide is only sparingly soluble in liquid ethanol, and quickly becomes cloudy, with precipitation of the sodium ethoxide ($\mathrm{CH_3CH_2ONa\,(s)}$).

Although initially this appears as something new and complicated, in fact, it is exactly the same (apart from being a more gentle reaction) as the reaction between sodium and water - something you have probably known about for years.

Compare the two:

$$2_{32}\mathrm{CHCHOH} + 2\,\mathrm{Na} \longrightarrow 2\mathrm{CH_3CH_2ONa} + \mathrm{H_2}$$

$$2\mathrm{HOH} + 2\,\mathrm{Na} \longrightarrow 2\mathrm{HONa} + \mathrm{H_2}$$

We normally, of course, write the sodium hydroxide formed as NaOH rather than HONa - but that's the only difference. Sodium ethoxide is just like sodium hydroxide, except that the hydrogen has been replaced by an ethyl group. Sodium hydroxide contains $\mathrm{OH^-}$ ions; sodium ethoxide contains $\mathrm{CH_3CH_2O^-}$ ions.

> **Note**
>
> The reason that the ethoxide formula is written with the oxygen on the right unlike the hydroxide ion is simply a matter of clarity. If you write it the other way around, it doesn't immediately look as if it comes from ethanol. You will find the same thing happens when you write formulae for organic salts like sodium ethanoate, for example.

There are two simple uses for this reaction:

- **To safely dispose of small amounts of sodium:** If you spill some sodium on the bench or have a small amount left over from a reaction you cannot simply dispose of it in the sink. It tends to react explosively with the water - and comes flying back out at you again! It reacts much more gently with ethanol. Ethanol is, therefore, used to dissolve small quantities of waste sodium. The solution formed can be washed away without problems (provided you remember that sodium ethoxide is strongly alkaline - see below).
- **To test for the -OH group in alcohols:** Because of the dangers involved in handling sodium, this is not the best test for an alcohol at this level. Because sodium reacts violently with acids to produce a salt and hydrogen, you would first have to be sure that the liquid you were testing was neutral. You would also have to be confident that there was no trace of water present because sodium reacts with the -OH group in water even better than with the one in an alcohol. With those provisos, if you add a tiny piece of sodium to a neutral liquid free of water and get bubbles of hydrogen produced, then the liquid is an alcohol.

Ethoxide Ions are Strongly Basic

If you add water to sodium ethoxide, it dissolves to give a colorless solution with a high pH. The solution is strongly alkaline because ethoxide ions are Brønsted-Lowry bases and remove hydrogen ions from water molecules to produce hydroxide ions, which increase the pH.

$$CH_3CH_2O^- + H_2O \longrightarrow CH_3CH_2OH + OH^-$$

Ethoxide Ions are Good Nucleophiles

A nucleophile is a chemical species that carries a negative or partial negative charge that it uses to attack positive centers in other molecules or ions. Hydroxide ions are good nucleophiles, and you may have come across the reaction between a halogenoalkane (also called a haloalkane or alkyl halide) and sodium hydroxide solution. The hydroxide ions replace the halogen atom.

$$CH_3CH_2CH_2Br + OH^- \longrightarrow CH_3CH_2CH_2OH + Br^-$$

In this case, an alcohol is formed. The ethoxide ion behaves in exactly the same way. If you knew the mechanism for the hydroxide ion reaction, you could work out exactly what happens in the reaction between a halogenoalkane and ethoxide ion.

Compare this equation with the last one.

$$CH_3CH_2CH_2Br + CH_3CH_2O^- \longrightarrow CH_3CH_2CH_2OCH_2CH_3 + Br^-$$

$$CH_3CH_2CH_2Br + OH^- \longrightarrow CH_3CH_2CH_2OH + Br^-$$

The only difference is that where there was a hydrogen atom at the right-hand end of the product molecule, you now have an alkyl group.

Two alkyl (or other hydrocarbon) groups bridged by an oxygen atom is called an ether. This particular one is 1-ethoxypropane or ethyl propyl ether. This reaction is known as the Williamson Ether Synthesis and is a good method of synthesizing ethers in the lab.

Note

There are all sorts of ways of naming ethers. For UK A level purposes, the problem doesn't arise - you almost certainly won't have to name them.
If you have looked at the chemistry of halogenoalkanes, you may be aware that there is a competition between substitution and elimination when they react with hydroxide ions. Exactly the same competition occurs in their reactions with ethoxide ions. Just as the hydroxide ion can act as either a base or a nucleophile, exactly the same is true of alkoxide ions like the ethoxide ion.

You could read about the reactions of halogenoalkanes with hydroxide ions and work out for yourself what is going to happen in the possible elimination reaction if you used sodium ethoxide rather than sodium hydroxide. Because this is getting well beyond UK A level, I haven't given any detail for this anywhere on the site. The whole point about understanding chemistry (and especially mechanisms!) is that you can work things out for yourself when you need to!

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9.2: Reactions of Alcohols with Strong Acids: Alkyloxonium Ions in Substitution and Elimination Reactions of Alcohols

	Purdue CHM 26100: Organic Chemistry for Engineers (1st Semester) Fall 2014: Prof. Paul Wenthold	

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9.3: Carbocation Rearrangements

09.9 Carbocation Rearrangements

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9.4: Organic and Inorganic Esters from Alcohols

9.12 Conversion of Alcohols to Alkyl Halides with $SOCl2$ and $PBr3$

Nucleophilic Substitution of the Hydroxyl Group

The chemical behavior of alkyl halides can be used as a reference in discovering analogous substitution and elimination reactions of alcohols. The chief difference, of course, is a change in the leaving anion from halide to hydroxide. Because oxygen is slightly more electronegative than chlorine (3.5 vs. 2.8 on the Pauling scale), the C-O bond is expected to be more polar than a C-Cl bond. Furthermore, an independent measure of the electrophilic characteristics of carbon atoms from their NMR chemical shifts (both ^{13}C and alpha protons) indicates that oxygen and chlorine substituents exert a similar electron-withdrawing influence when bonded to sp^3 hybridized carbon atoms. Despite this promising background evidence, alcohols do not undergo the same S_N2 reactions commonly observed with alkyl halides. For example, the rapid S_N2 reaction of 1-bromobutane with sodium cyanide, shown below, has no parallel when 1-butanol is treated with sodium cyanide. In fact, ethyl alcohol is often used as a solvent for alkyl halide substitution reactions such as this.

$CH_3CH_2CH_2CH_2–Br + Na^{(+)}\ CN^{(-)} \longrightarrow CH_3CH_2CH_2CH_2–CN + Na^{(+)}\ Br^{(-)}$
$CH_3CH_2CH_2CH_2–OH + Na^{(+)}\ CN^{(-)} \longrightarrow$ No Reaction

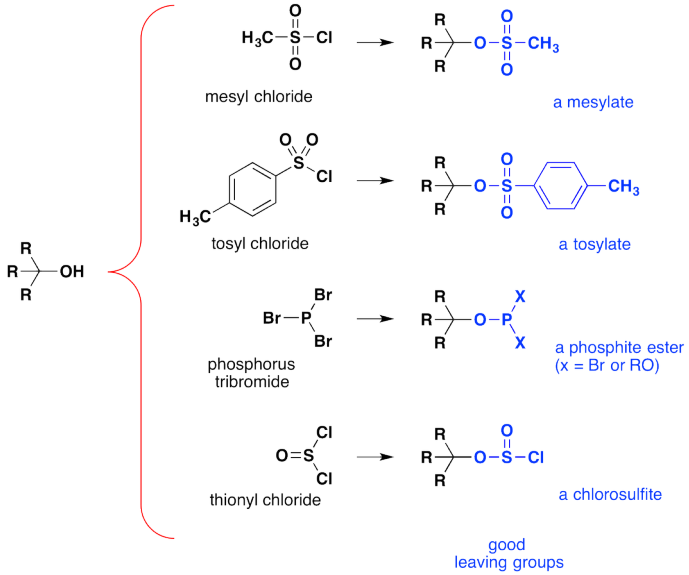
The key factor here is the stability of the leaving anion (bromide vs. hydroxide). HBr is a much stronger acid than water (by more than 18 orders of magnitude), and this difference is reflected in reactions that generate their respective conjugate bases. The weaker base, bromide, is more stable, and its release in a substitution or elimination reaction is much more favorable than that of hydroxide ion, a stronger and less stable base.

A clear step toward improving the reactivity of alcohols in S_N2 reactions would be to modify the –OH functional group in a way that improves its stability as a leaving anion. One such modification is to conduct the substitution reaction in a strong acid, converting –OH to $–OH_2^{(+)}$. Because the hydronium ion ($H_3O^{(+)}$) is a much stronger acid than water, its conjugate base (H_2O) is a better leaving group than hydroxide ion. The only problem with this strategy is that many nucleophiles, including cyanide, are deactivated by protonation in strong acids, effectively removing the nucleophilic co-reactant required for the substitution. The strong acids HCl, HBr and HI are not subject to this difficulty because their conjugate bases are good nucleophiles and are even weaker bases than alcohols. The following equations illustrate some substitution reactions of alcohols that may be affected by these acids. As with alkyl halides, the nucleophilic substitution of 1°-alcohols proceeds by an S_N2 mechanism, whereas 3°-alcohols react by an S_N1 mechanism. Reactions of 2°-alcohols may occur by both mechanisms and often produce some rearranged products. The numbers in parentheses next to the mineral acid formulas represent the weight percentage of a concentrated aqueous solution, the form in which these acids are normally used.

$CH_3CH_2CH_2CH_2–OH + HBr\ (48\%) \rightleftharpoons CH_3CH_2CH_2CH_2–OH_2^{(+)}\ Br^{(-)} \longrightarrow CH_3CH_2CH_2CH_2–Br + H_2O\ S_N2$
$(CH_3)_3C–OH + HCl\ (37\%) \rightleftharpoons (CH_3)_3C–OH_2^{(+)}\ Cl^{(-)} \rightleftharpoons (CH_3)_3C^{(+)}\ Cl^{(-)} + H_2O \longrightarrow (CH_3)_3C–Cl + H_2O\ S_N1$

Although these reactions are sometimes referred to as "acid-catalyzed," this is not strictly correct. In the overall transformation, a strong HX acid is converted to water, a very weak acid, so at least a stoichiometric quantity of HX is required for a complete conversion of alcohol to alkyl halide. The necessity of using equivalent quantities of very strong acids in this reaction limits its usefulness to simple alcohols of the type shown above. Alcohols with acid-sensitive groups do not, of course, tolerate such treatment. Nevertheless, the idea of modifying the -OH functional group to improve its stability as a leaving anion can be pursued in other directions. The following diagram shows some modifications that have proven effective. In each case the hydroxyl group is converted to an ester of a strong acid. The first two examples show the sulfonate esters described earlier. The third and fourth examples show the formation of a phosphite ester (X represents the remaining bromines or additional alcohol substituents) and a chlorosulfite ester, respectively. All of these leaving groups (colored blue) have conjugate acids that are much stronger than water (by 13 to 16 powers of ten); thus, the leaving anion is correspondingly more stable than the hydroxide ion. The mesylate and tosylate compounds are particularly useful because they may be used in substitution reactions with a wide variety of nucleophiles. The intermediates produced in reactions of alcohols with phosphorus tribromide and thionyl chloride (last two examples) are

seldom isolated, and these reactions continue to produce alkyl bromide and chloride products.

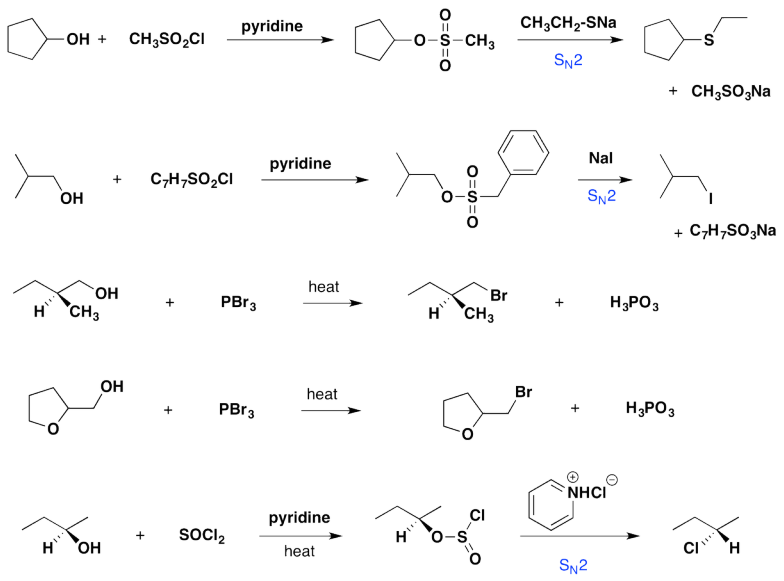


The importance of sulfonate ester intermediates in general nucleophilic substitution reactions of alcohols may be illustrated by the following conversion of 1-butanol to pentanenitrile (butyl cyanide), a reaction that does not occur with the alcohol alone. The phosphorus and thionyl halides, on the other hand, only act to convert alcohols to the corresponding alkyl halides.

$CH_3CH_2CH_2CH_2$–OH + CH_3SO_2Cl	pyridine ⟶	$CH_3CH_2CH_2CH_2$–OSO_2CH_3	$Na^{(+)}$ $CN^{(-)}$ ⟶	$CH_3CH_2CH_2CH_2$–CN + $CH_3SO_2O^{(-)}$ $Na^{(+}$

Some examples of alcohol substitution reactions using this approach to activating the hydroxyl group are shown in the following diagram. The first two cases serve to reinforce the fact that sulfonate ester derivatives of alcohols may replace alkyl halides in a variety of S_N2 reactions. The next two cases demonstrate the use of phosphorus tribromide in converting alcohols to bromides. This reagent may be used without added base (e.g. pyridine) because the phosphorous acid product is a weaker acid than HBr. Phosphorus tribromide is best used with 1°-alcohols because 2°-alcohols often yield rearrangement by-products resulting from competing S_N1 reactions. Note that the ether oxygen in reaction **4** is not affected by this reagent, whereas the alternative synthesis using concentrated HBr cleaves ethers. Phosphorus trichloride (PCl_3) converts alcohols to alkyl chlorides in a similar manner, but thionyl chloride is usually preferred for this transformation because the inorganic products are gases (SO_2 & HCl). Phosphorus triiodide is not stable but may be generated *in situ* from a mixture of red phosphorus and iodine and acts to convert alcohols to alkyl iodides. The last example shows the reaction of thionyl chloride with a chiral 2°-alcohol. The presence of an organic base such as pyridine is important because it provides a substantial concentration of chloride ion required for the final S_N2 reaction of the chlorosufite intermediate. In the absence of a base, chlorosufites decompose upon heating to yield the expected alkyl chloride with **retention of configuration**

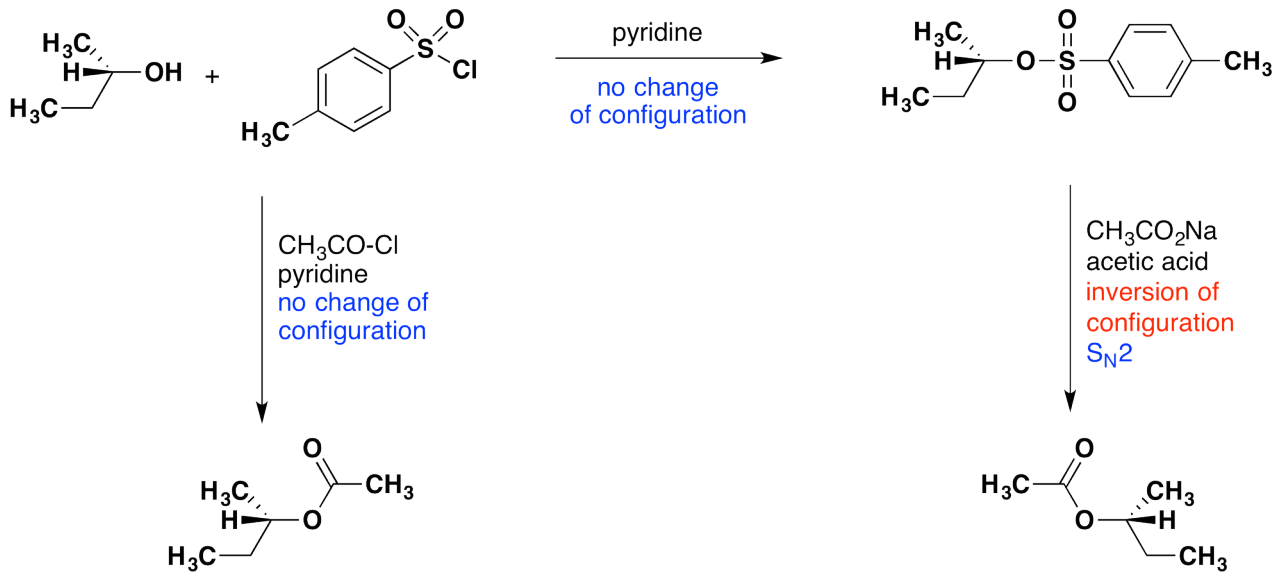
Tertiary alcohols are not commonly used for substitution reactions of the type discussed here because S_N1 and E1 reaction paths are dominant and are difficult to control.



The importance of sulfonate esters as intermediates in many substitution reactions cannot be overstated. A rigorous proof of the configurational inversion that occurs at the substitution site in S_N2 reactions makes use of such reactions. An example of such a proof is displayed below. Abbreviations for the more commonly used sulfonyl derivatives are given in the following table.

Sulfonyl Group	CH_3SO_2–	$CH_3C_6H_4SO_2$–	$BrC_6H_4SO_2$–	CF_3SO_2–
Name & Abbrev.	Mesyl or Ms	Tosyl or Ts	Brosyl or Bs	Trifyl or Tf

Inversion Proof



For a more complete discussion of hydroxyl substitution reactions and a description of other selective methods for this transformation, Click Here.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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9.5: Names and Physical Properties of Ethers

Ethers are compounds having two alkyl or aryl groups bonded to an oxygen atom, as in the formula R^1–O–R^2. The ether functional group does not have a characteristic IUPAC nomenclature suffix, so it is necessary to designate it as a substituent. To do so the common alkoxy substituents are given names derived from their alkyl component (below):

Alkyl Group	Name		Alkoxy Group	Name
CH_3–	Methyl		CH_3O–	Methoxy
CH_3CH_2–	Ethyl		CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl		$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl		$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl		C_6H_5O–	Phenoxy

Ethers can be named by naming each of the two carbon groups as a separate word followed by a space and the word ether. The -OR group can also be named as a substituent using the group name, alkox

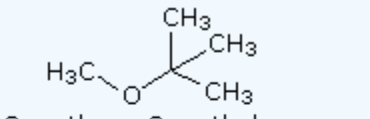
Example 9.5.1

CH_3-CH_2-O-CH_3 is called ethyl methyl ether or methoxyethane.

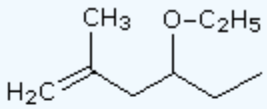
The smaller, shorter alkyl group becomes the alkoxy substituent. The larger, longer alkyl group side becomes the alkane base name. Each alkyl group on each side of the oxygen is numbered separately. The numbering priority is given to the carbon closest to the oxgen. The alkoxy side (shorter side) has an "-oxy" ending with its corresponding alkyl group. For example, $CH_3CH_2CH_2CH_2CH_2$-O-$CH_2CH_2CH_3$ is 1-propoxypentane. If there is cis or trans stereochemistry, the same rule still applies.

Examples 9.5.2

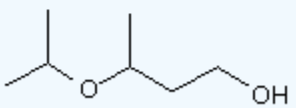
- $CH_3CH_2OCH_2CH_3$, diethyl ether (sometimes referred to as just ether)
- $CH_3OCH_2CH_2OCH_3$, ethylene glycol dimethyl ether (glyme).



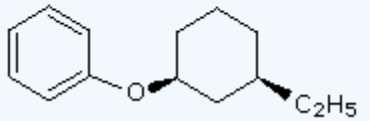
2-methoxy-2-methylpropane
tert-butyl methyl ether



4-ethoxy-2-methyl-1-hexene



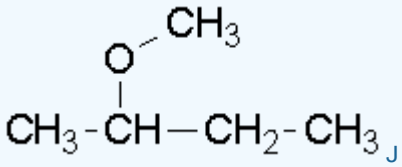
3-isopropoxy-1-butanol



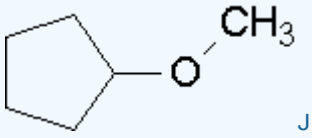
cis-1-ethyl-3-phenoxycyclohexane

Exercises 9.5.2

Try to name the following compounds using these conventions:



J



J

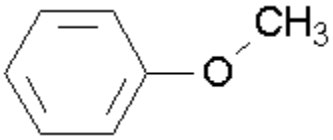
Try to draw structures for the following compounds:

- 2-pentyl 1-propyl ether J
- 1-(2-propoxy)cyclopentene J

Common names

Simple ethers are given common names in which the alkyl groups bonded to the oxygen are named in alphabetical order followed by the word "ether". The top left example shows the common name in blue under the IUPAC name. Many simple ethers are symmetrical, in that the two alkyl substituents are the same. These are named as "dialkyl ethers".

- **anisole** (try naming anisole by the other two conventions. J)



- **oxirane**

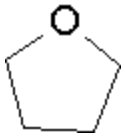


1,2-epoxyethane, ethylene oxide, dimethylene oxide, oxacyclopropane,

- **furan (this compound is aromatic)**

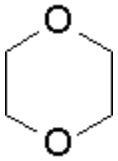


tetrahydrofuran



oxacyclopentane, 1,4-epoxybutane, tetramethylene oxide,

- **dioxane**



1,4-dioxacyclohexane

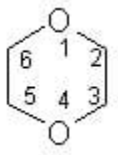
Exercise 9.5.2

Try to draw structures for the following compounds-

- 3-bromoanisole J
- 2-methyloxirane J
- 3-ethylfuran J

Heterocycles

In cyclic ethers (heterocycles), one or more carbons are replaced with oxygen. Often, it's called heteroatoms, when carbon is replaced by an oxygen or any atom other than carbon or hydrogen. In this case, the stem is called the oxacycloalkane, where the prefix "oxa-" is an indicator of the replacement of the carbon by an oxygen in the ring. These compounds are numbered starting at the oxygen and continues around the ring. For example,



1,4-dioxacyclohexane



1-oxacyclopentane

If a substituent is an alcohol, the alcohol has higher priority. However, if a substituent is a halide, ether has higher priority. If there is both an alcohol group and a halide, alcohol has higher priority. The numbering begins with the end that is closest to the higher priority substituent. There are ethers that are contain multiple ether groups that are called cyclic polyethers or crown ethers. These are also named using the IUPAC system.

Sulfides

Sulfur analogs of ethers (R–S–R') are called **sulfides**, e.g., $(CH_3)_3C–S–CH_3$ is tert-butyl methyl sulfide. Sulfides are chemically more reactive than ethers, reflecting the greater nucleophilicity of sulfur relative to oxygen.

References

1. Schore, Neil E. and Vollhardt, K. Peter C. Organic Chemistry: Structure and Function. New York: Bleyer, Brennan, 2007.
2. Winter, Arthur. Organic Chemistry for Dummies. Hoboken, New Jersey: Wiley, 2005.
3. Pellegrini, Frank. Cliffs QuickReview Organic Chemistry II. Foster City, CA: Wiley, 2000

Problems

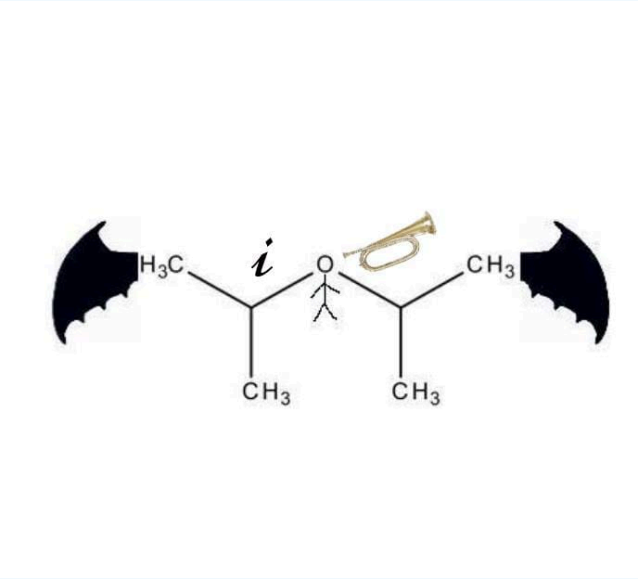
Name the following ethers:

ETHER PROBS.bmp

(Answers to problems above: 1. diethyl ether; 2. 2-ethoxy-2-methyl-1-propane; 3. cis-1-ethoxy-2-methoxycyclopentane; 4. 1-ethoxy-1-methylcyclohexane; 5. oxacyclopropane; 6. 2,2-Dimethyloxacyclopropane)

Exercise 9.5.3

What would you call



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Answer available at the end of this section.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Richard Banks (Boise State University)

09.4 Physical Properties

Objectives

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

Key Terms

Make certain that you can define, and use in context, the key term below.

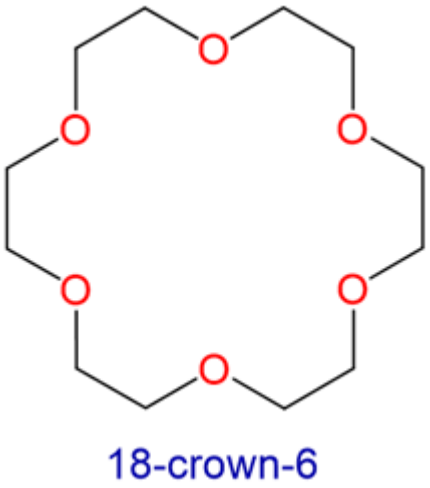
- crown ether

Study Notes

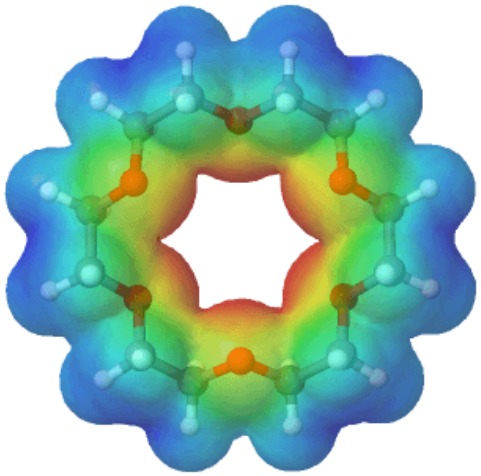
A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

Crown Ethers

Crown ethers are cyclic polyethers with four or more oxygen atoms each separated by two or three carbon atoms. Crown ethers have the general formula of $(OCH_2CH_2)_n$ or $(OCH_2CH_2CH_2)_n$ and are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms. All crown ethers have a cavity in the center this is lined with oxygen atoms and can accommodate a alkali metal ion, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. The negative character of center cavity of 18-crown-6 can be seen by looking at its electrostatic potential map shown below. The presence of high electron density is shown by a red color.



18-crown-6



Crown ethers are useful for dissolving ionic substances in organic solvents, such as $KMnO_4$ dissolving in toluene, by sequestering the cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic.

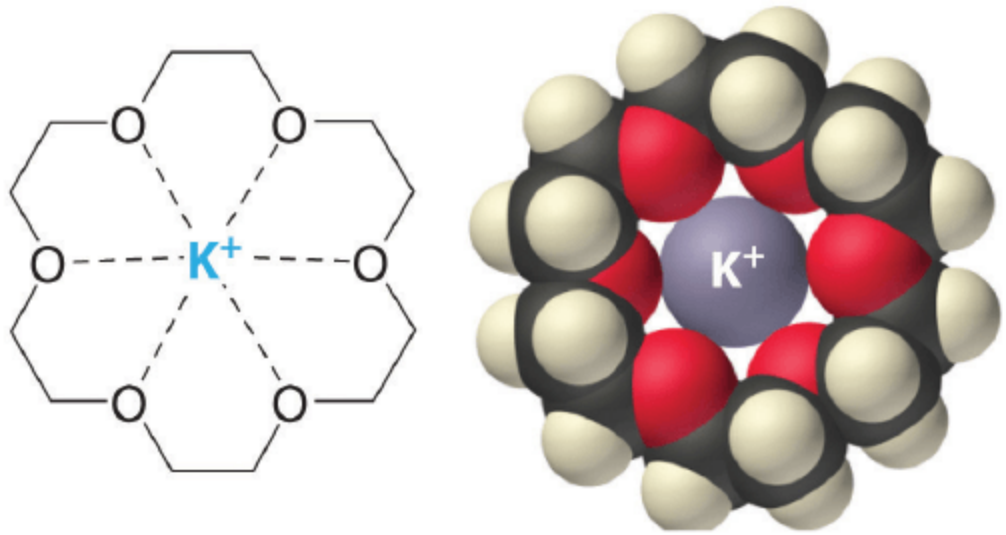
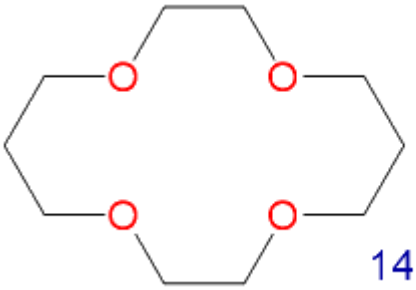
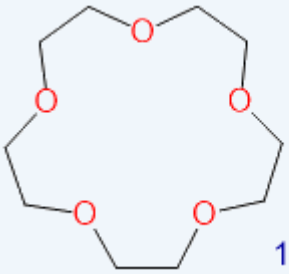
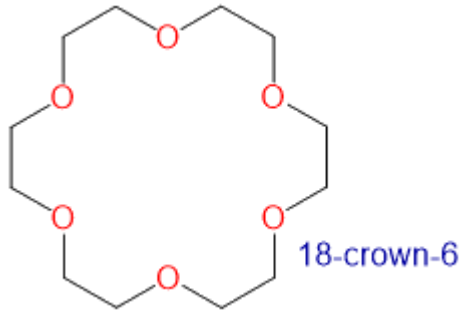
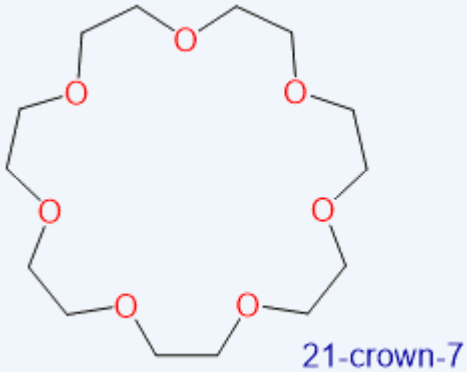


Figure 9.5.1: Potassium complex of the crown ether 18-crown-6. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity. Crown ethers prefer to bind alkali metal cations with sizes that match that of their binding cavity. For instance, as shown in Table 9.5.1, 14-crown-4 preferentially binds to Li^+, 15-crown-5 preferentially binds to Na^+, 18-crown-6 preferentially binds to K^+, and 21-crown-7 preferentially binds to Cs^+.

Table 9.5.1: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter (A°)	Preferred Cation	Cation Diameter (A°)
	1.2-1.5	Li^+	1.36
	1.7-2.2	Na^+	1.94

Crown Ether	Cavity Diameter (A°)	Preferred Cation	Cation Diameter (A°)
	2.6-3.2	K^+	2.66
	3.4-4.3	Cs^+	3.34

Cryptands

Cryptands (from the Greek *kryptós*, meaning “hidden”) are variations of crown ethers comprised of two nitrogens connected by three polyether strands. A common nomenclature is used where the numbers preceding the word cryptan indicate the number of oxygen atoms in each strand of the molecule.

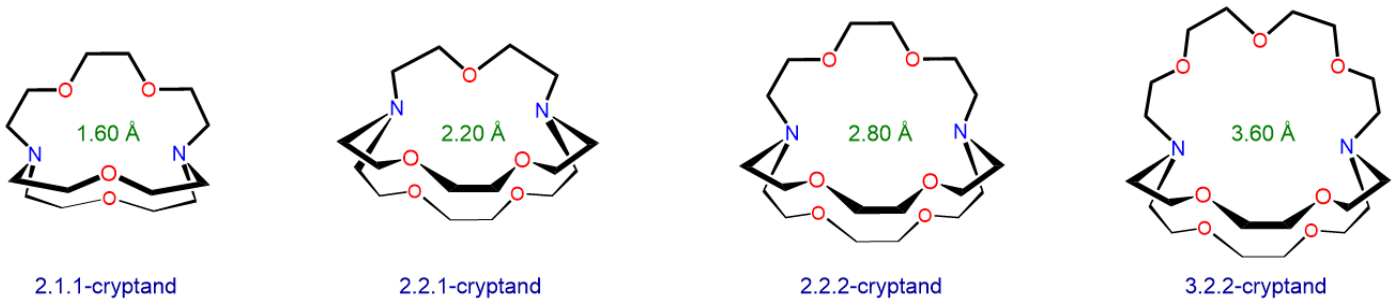


Figure 9.5.2: Structures and approximate binding cavity diameters for several cryptands.

Like crown ethers, cryptands are compounds that contains a central cavity that can completely surround a cation with lone pair electrons from oxygen and nitrogen atoms. Also, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them. Similar to crown ethers, cryptands prefer to bind with alkali metal cations whose diameter matches the size of their binding cavity.

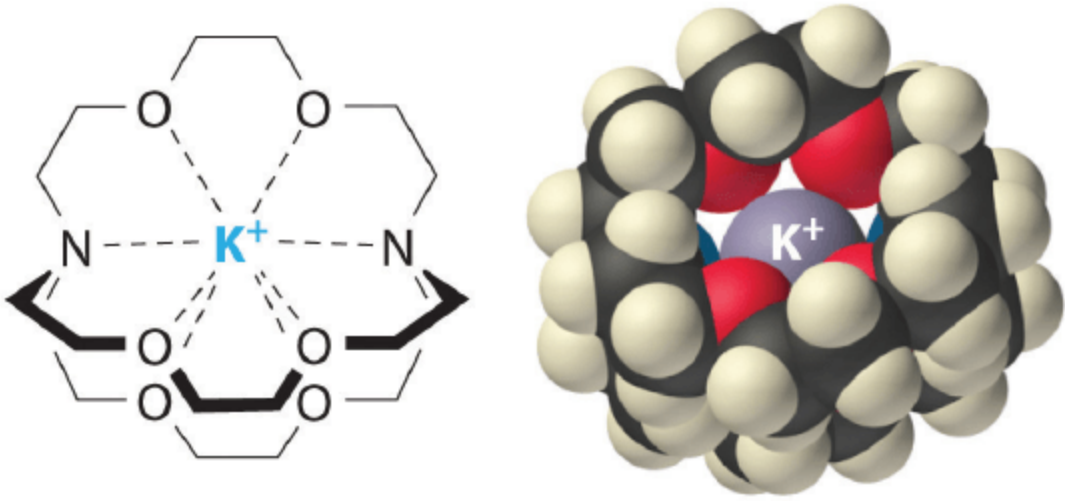


Figure 9.5.3: Potassium complex of 2,2,2-cryptand. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Exercise 9.5.1

Cryptand ligands also preferentially bind alkali metal ions with sizes that match the size of their binding cavities. The structure and approximate cavity sizes of several cryptands are shown above. Use the information in Table 9.5.1 to predict which alkali metal ion each cryptand will preferentially bind.

Answer available at the end of this section.

Answers

Exercise 9.5.3

A one-eyed one-horned flying propyl people ether

Exercise 9.5.1

The cryptands might be expected to selectively bind the largest ion which fits within the cavity. Predicted selectivity of crown ethers for alkali metal cations based on the hypothesis that they will selectively bind the largest ion which fits their binding cavity are listed below.

Cryptand	Cavity Diameter of (Å)	Preferred Cation	Cation Diameter (Å)
2.1.1-cryptand	1.60	Li^+	1.36
2.2.1-cryptand	2.20	Na^+	1.96
2.2.2-cryptand	2.80	K^+	2.66
3.2.2-cryptand	3.60	Cs^+	3.34

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9.6: Williamson Ether Synthesis

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	**oxymercuration**	**alkoxymercuration**
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

Ether Formation Though Dehydration

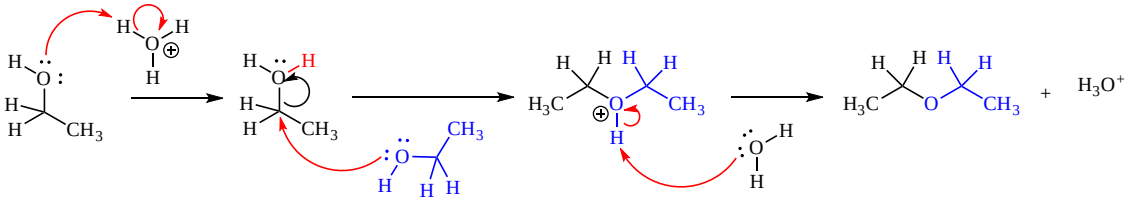
Acid-catalyzed dehydration of small 1°-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2°

and 3° alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \qquad (18.2.1)$$

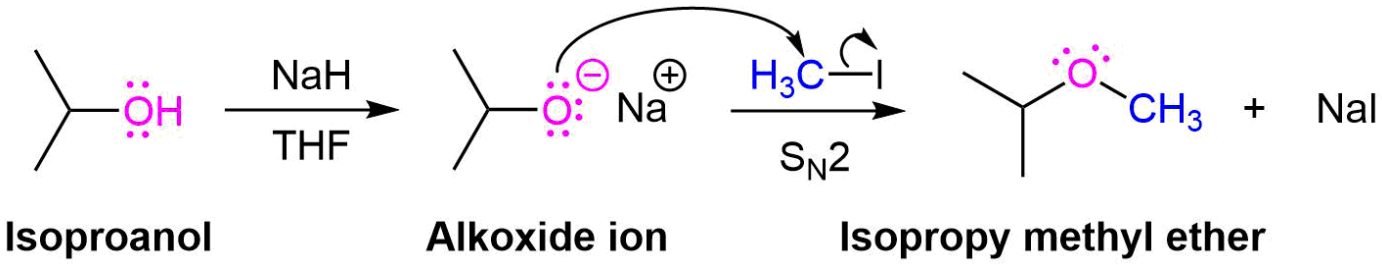
Mechanism

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



Williamson Ether Synthesis

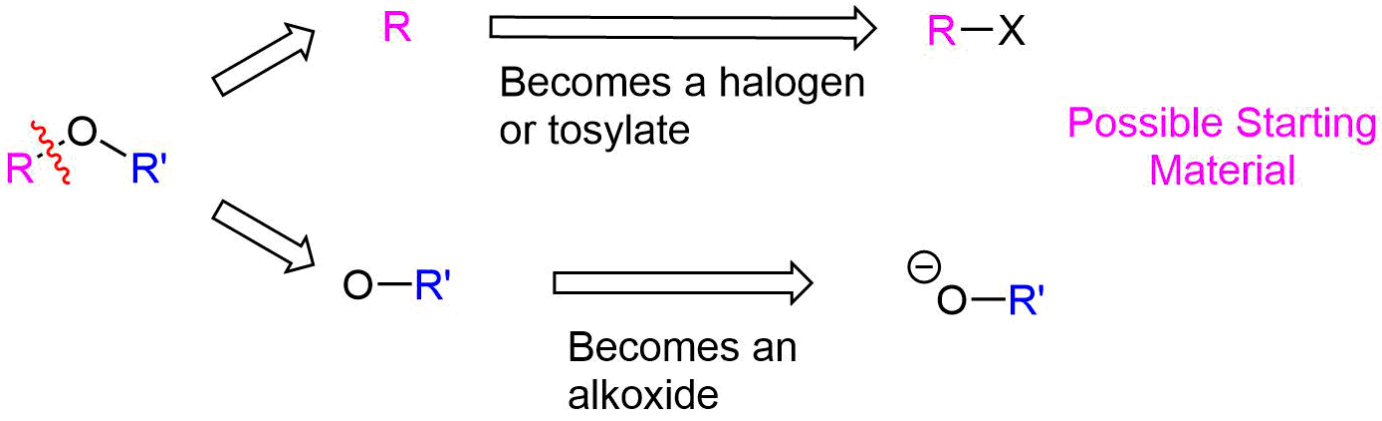
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in **Section 17-2**, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).



Planning a Williamson Ether Synthesis

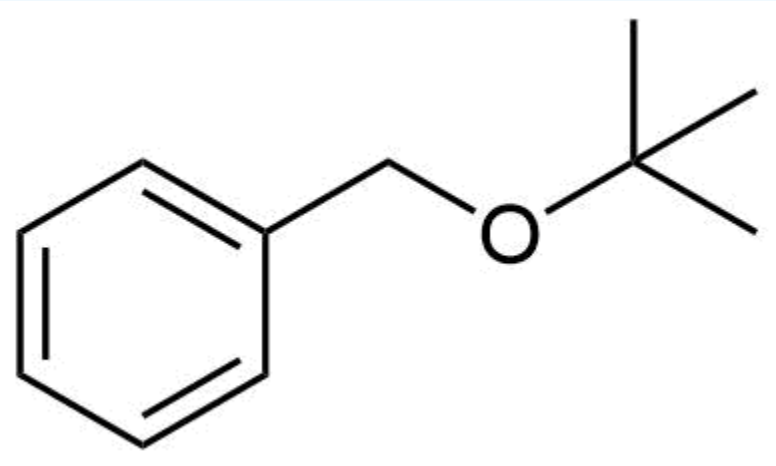
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



Worked Example 9.6.1

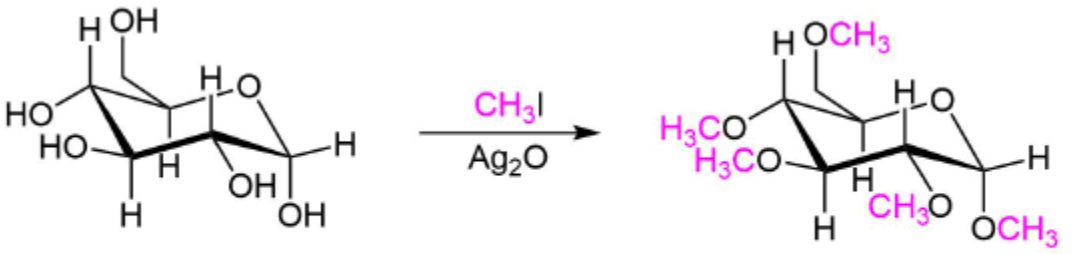
How would you prepare the following molecule using a Williamson Ether Synthesis?



Answer available at the end of this section.

Ether Synthesis Using Silver Oxide

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.

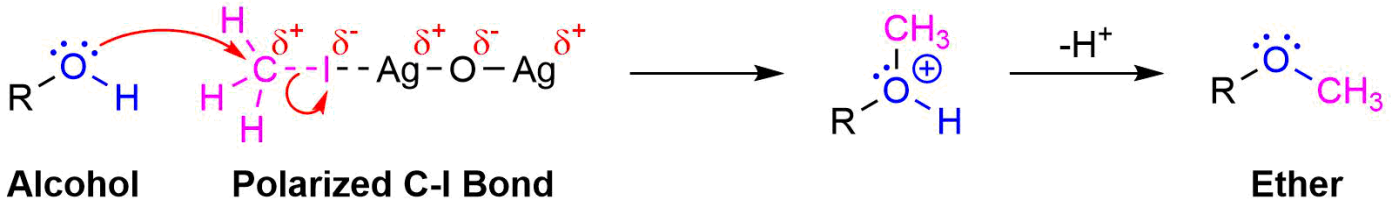


α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

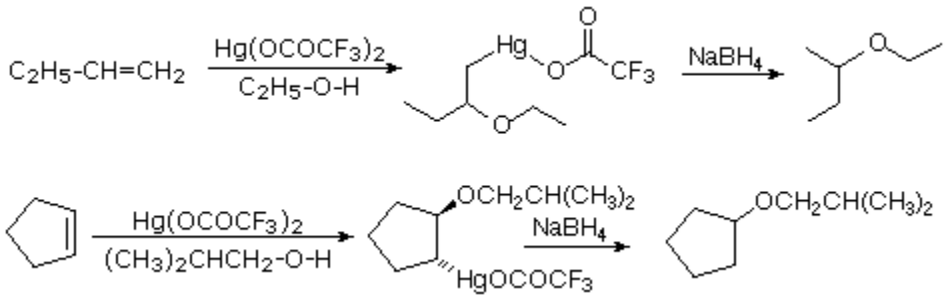
Mechanism

During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



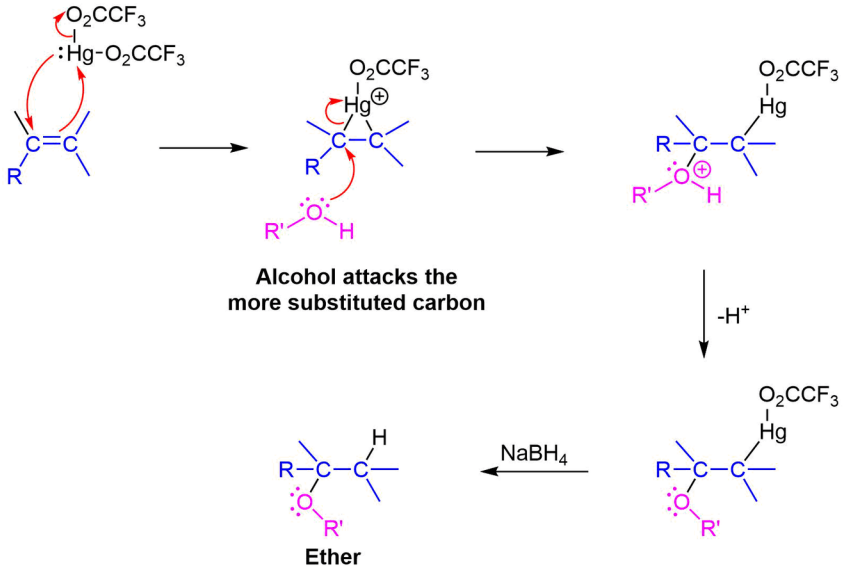
Ether Synthesis Using Alkoxymercuration

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in **Section 8-4**. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1^o, 2^o, 3^o alcohols can be successfully used for this reaction.



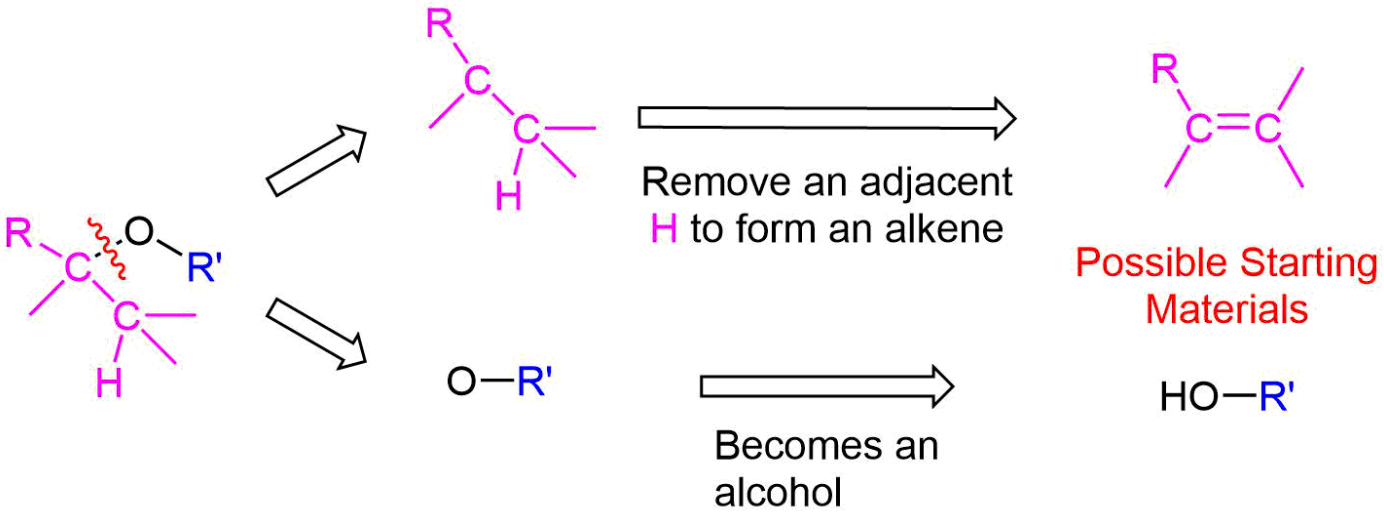
Mechanism

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



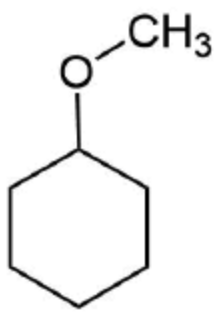
Planning the Synthesis of an Ether using Alkoxymercuration

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



Worked Example 9.6.2

How would you prepare the following molecule using a alkoxymercuration?



Answer available at the end of this section.

Exercise 9.6.1

When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

Answer available at the end of this section.

Exercise 9.6.2

How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 18.26Qa.png (b) 18.26Qb1.png (c) 18.26Qc.png (d) 18.26Qd.png (e) 18.26Qe.png

Answer available at the end of this section.

Exercise 9.6.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer available at the end of this section.

Exercise 9.6.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

Answer available at the end of this section.

Exercise 9.6.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)

18.29Q.png

Answer available at the end of this section.

Exercise 9.6.6

What reagents would you use to perform the following transformations?

(a) 18.30Qa.png

(b) 18.30Qb.png

(c) 18.30Qc.png

Answer available at the end of this section.

Exercise 9.6.7

Predict the product of the following.

18.31Q.png

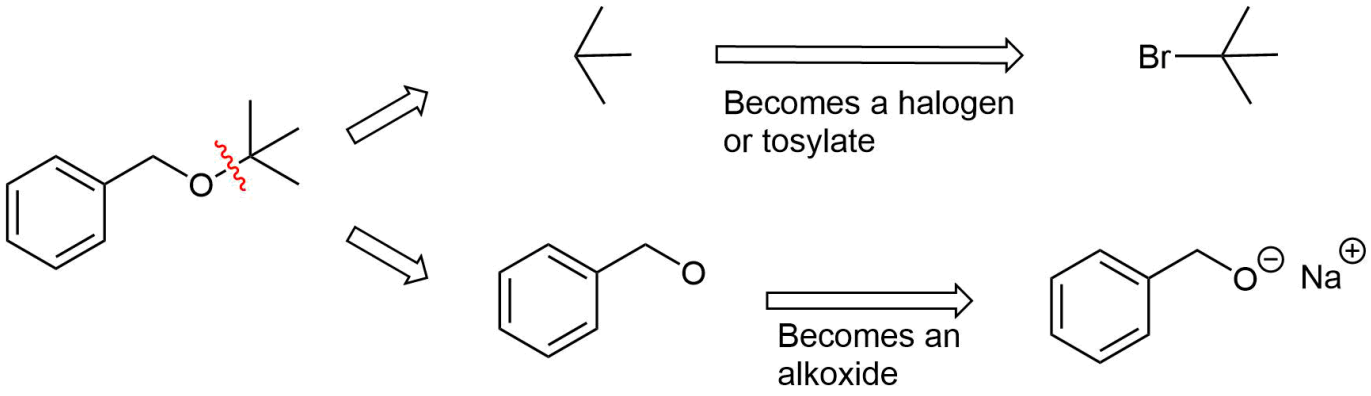
Answer available at the end of this section.

Answers

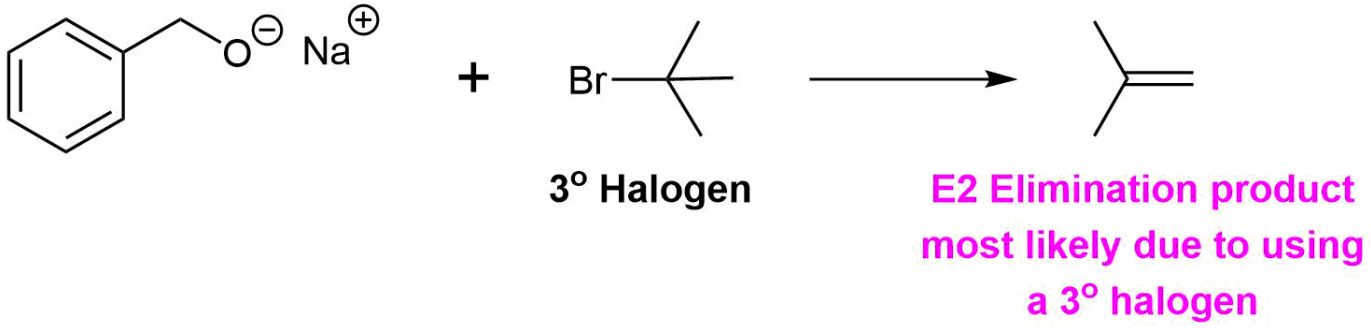
Worked Example 9.6.1

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3° halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3° halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1° halogen as a starting material which is favorable for S_N2 reactions.

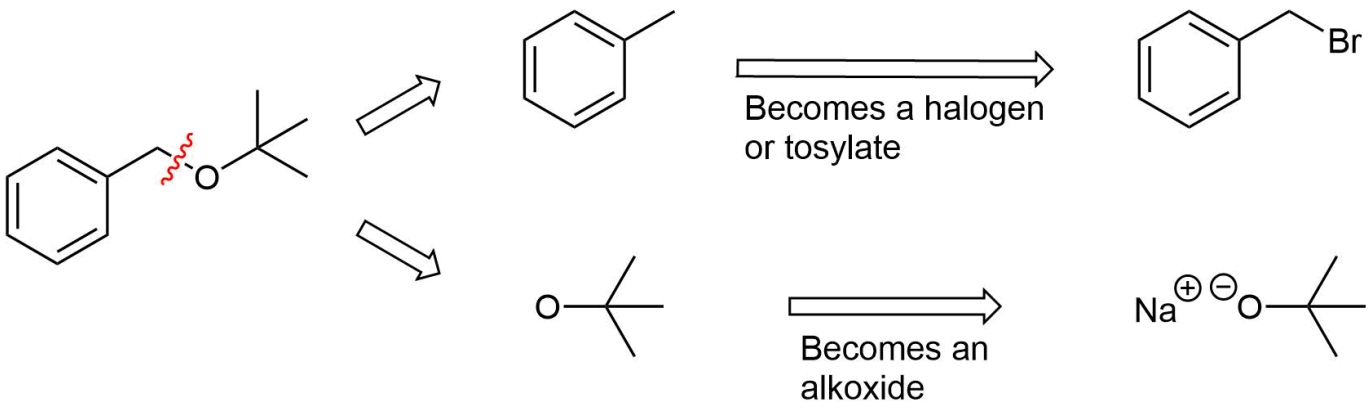
Pathway 1



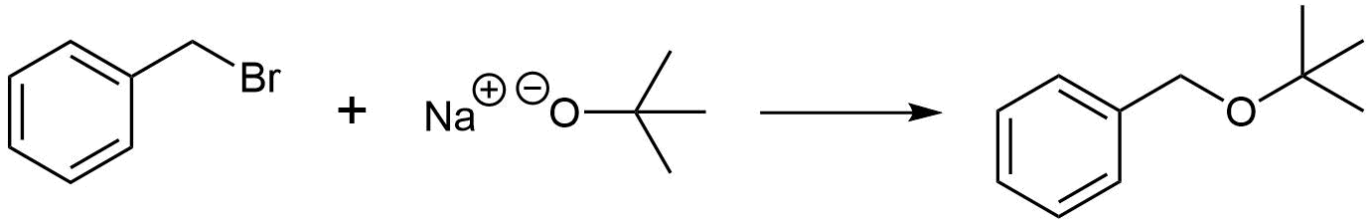
Solution 1



Pathway 2



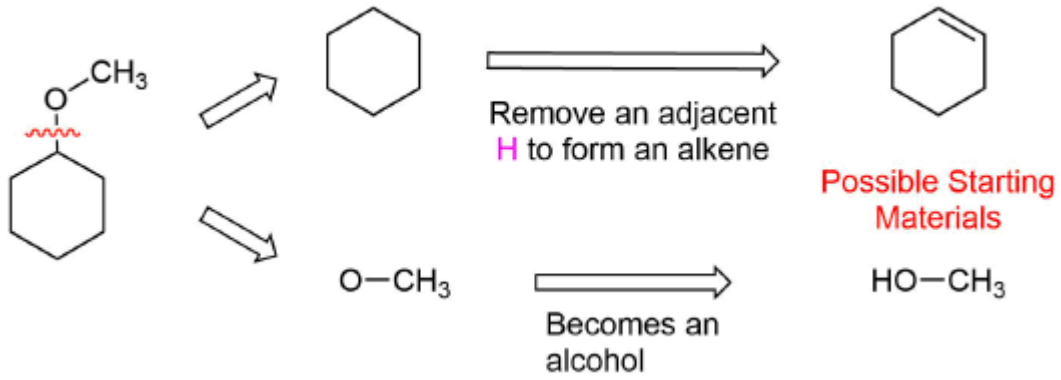
Solution 2



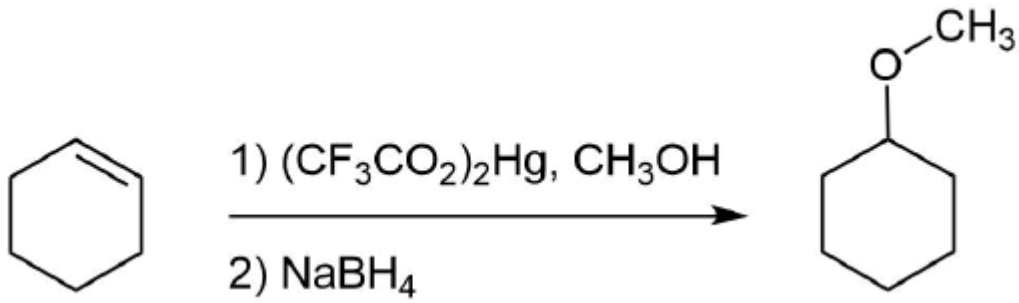
Worked Example 9.6.2

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

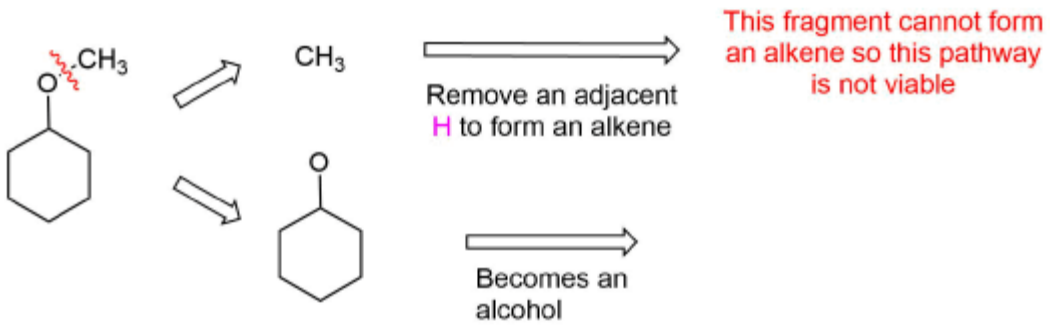
Pathway 1



Solution 1



Pathway 2



Exercise 9.6.1

The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

Exercise 9.6.2

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

(a) 18.26Aa.png

(b) 18.26Ab.png

(c) 18.26Ac.png

(d) 18.26Ad.png

Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 18.26Ae.png

Exercise 9.6.3

.18.27A.png

Exercise 9.6.4

18.28A.png

While both are possible, the top route is likely easier because both starting materials are a liquid.

Exercise 9.6.5

18.29A.png

Exercise 9.6.6

(a) 18.30Aa.png

(b) 18.30Ab.png Note the cis addition

(c) 18.30Ac.png

An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

Exercise 9.6.7

18.31A.png

The result is the production of dioxane, a common solvent.

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9.7: Synthesis of Ethers: Alcohols and Mineral Acids

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	**oxymercuration**	**alkoxymercuration**
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

Ether Formation Though Dehydration

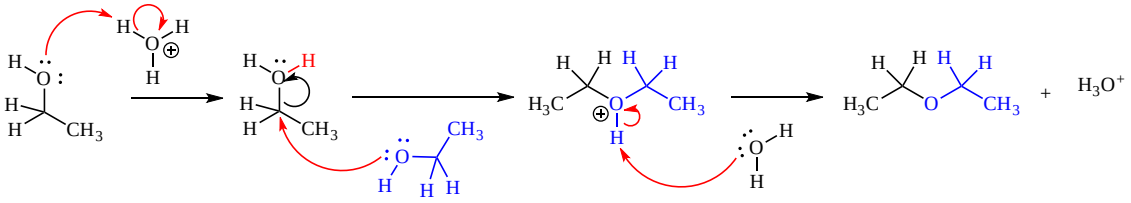
Acid-catalyzed dehydration of small 1°-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2°

and 3° alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \qquad (18.2.1)$$

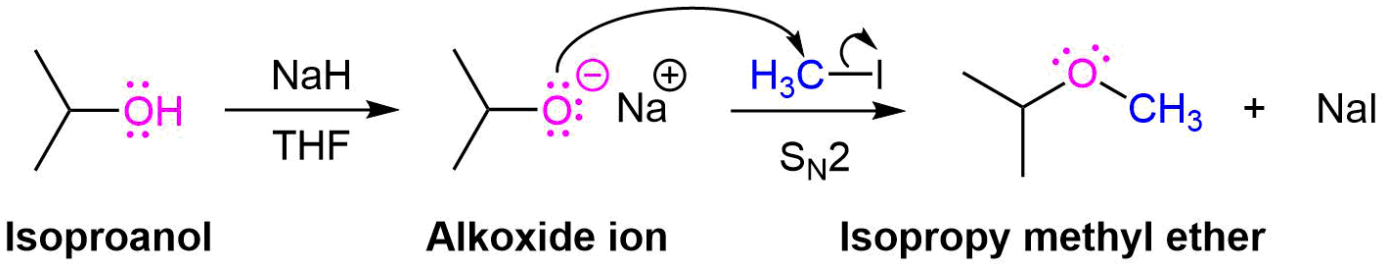
Mechanism

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



Williamson Ether Synthesis

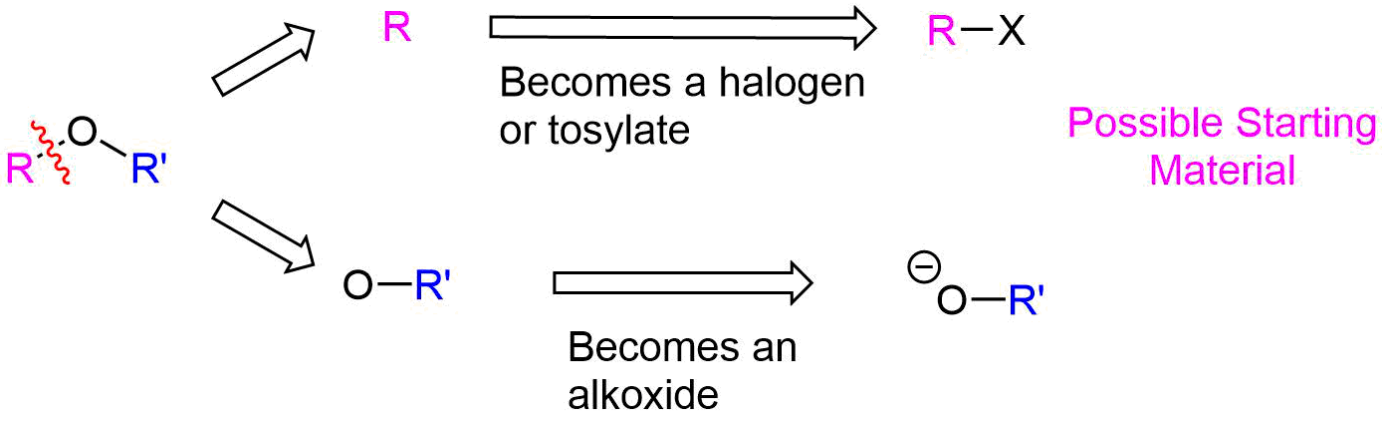
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Planning a Williamson Ether Synthesis

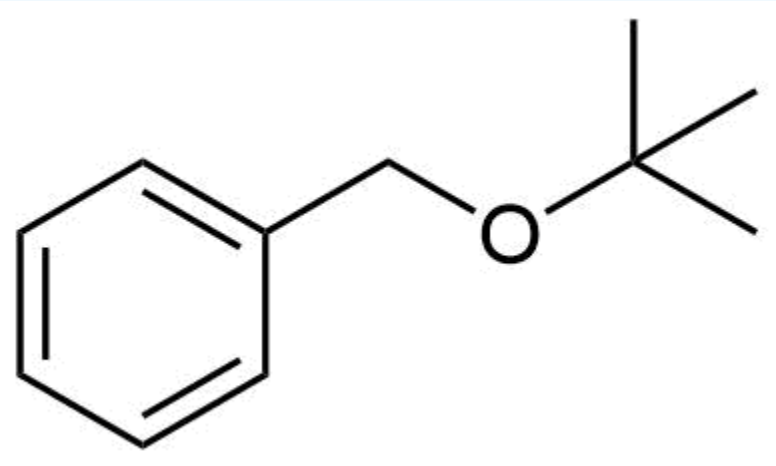
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



Worked Example 9.7.1

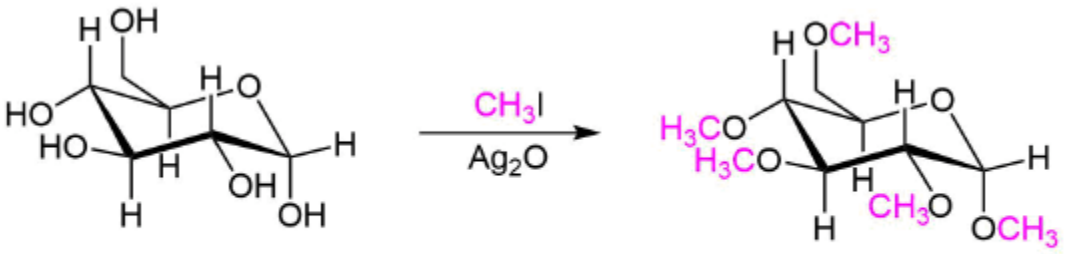
How would you prepare the following molecule using a Williamson Ether Synthesis?



Answer available at the end of this section.

Ether Synthesis Using Silver Oxide

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.

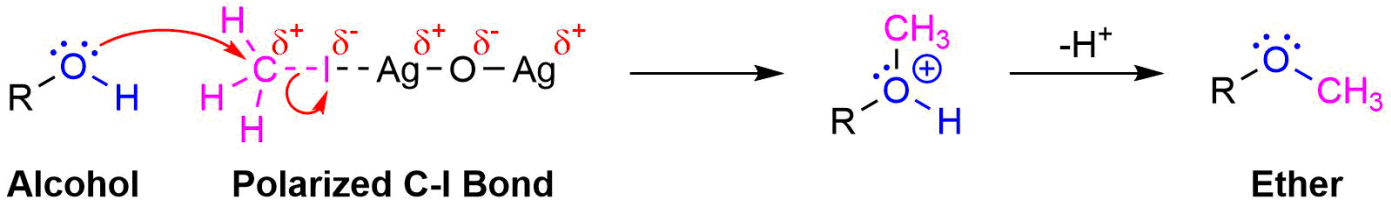


α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

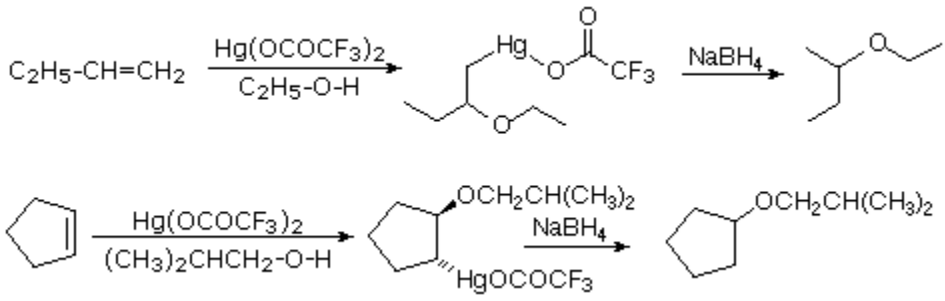
Mechanism

During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



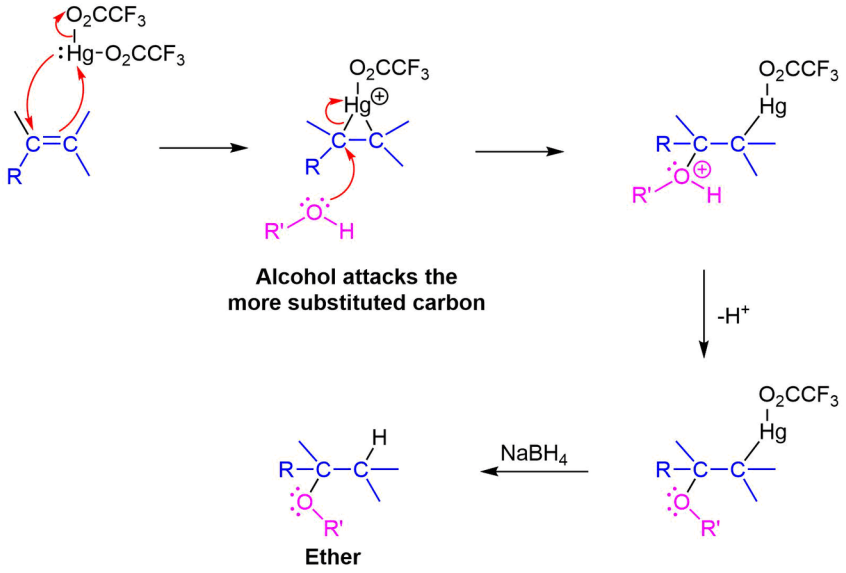
Ether Synthesis Using Alkoxymercuration

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in **Section 8-4**. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1^o, 2^o, 3^o alcohols can be successfully used for this reaction.



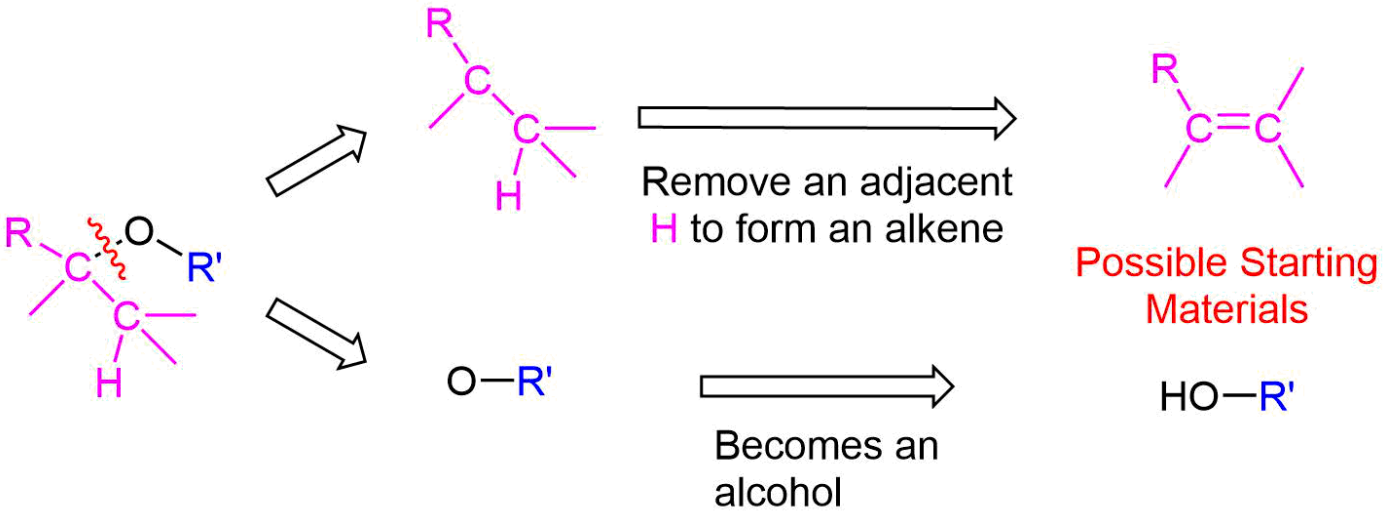
Mechanism

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



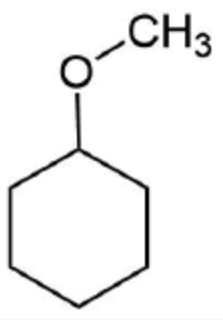
Planning the Synthesis of an Ether using Alkoxymercuration

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



Worked Example 9.7.2

How would you prepare the following molecule using a alkoxymercuration?



Answer available at the end of this section.

Exercise 9.7.1

When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

Answer available at the end of this section.

Exercise 9.7.2

How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 18.26Qa.png (b) 18.26Qb1.png (c) 18.26Qc.png (d) 18.26Qd.png (e) 18.26Qe.png

Answer available at the end of this section.

Exercise 9.7.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer available at the end of this section.

Exercise 9.7.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

Answer available at the end of this section.

Exercise 9.7.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)

18.29Q.png

Answer available at the end of this section.

Exercise 9.7.6

What reagents would you use to perform the following transformations?

(a) 18.30Qa.png

(b) 18.30Qb.png

(c) 18.30Qc.png

Answer available at the end of this section.

Exercise 9.7.7

Predict the product of the following.

18.31Q.png

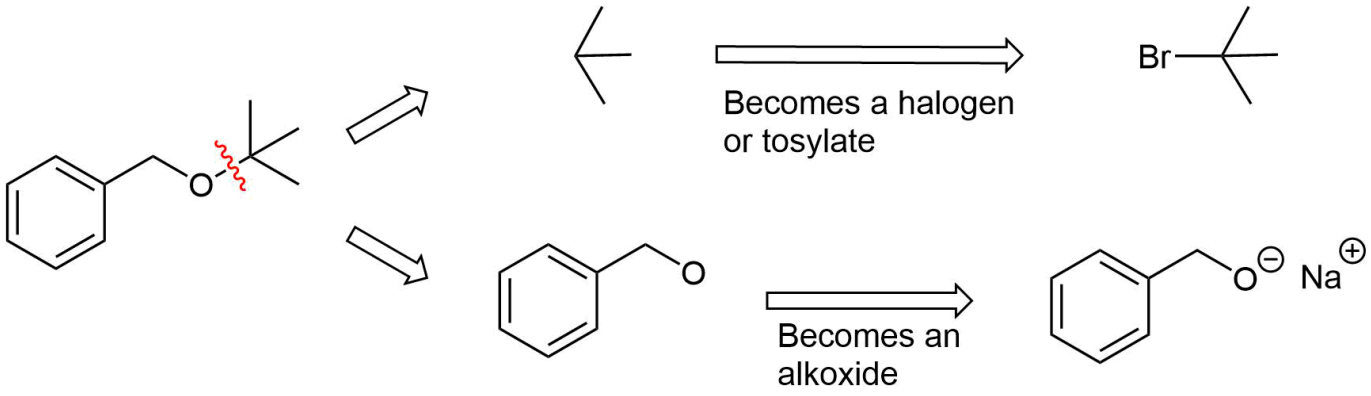
Answer available at the end of this section.

Answers

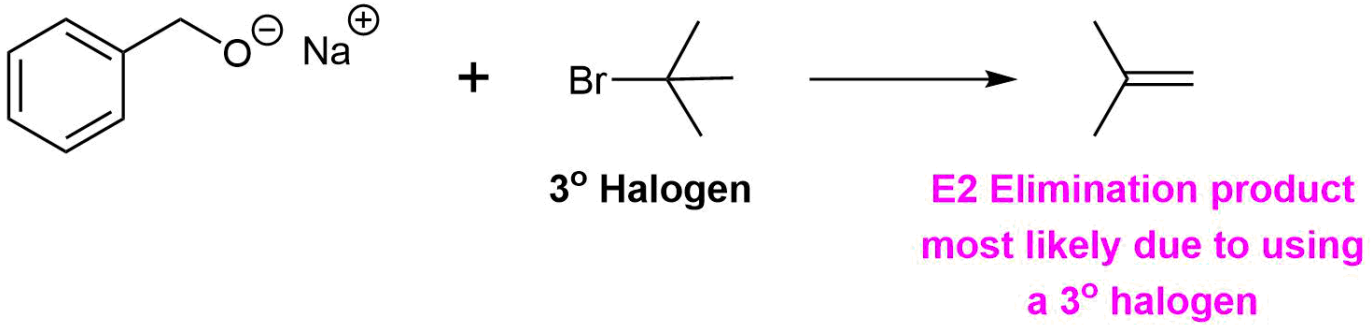
Worked Example 9.7.1

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3^{o} halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3^{o} halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1^{o} halogen as a starting material which is favorable for S_N2 reactions.

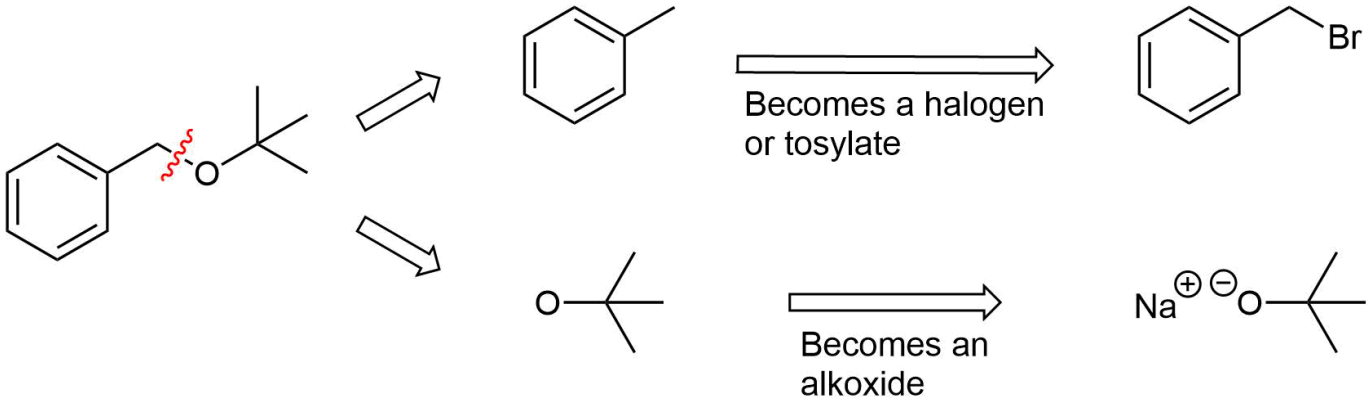
Pathway 1



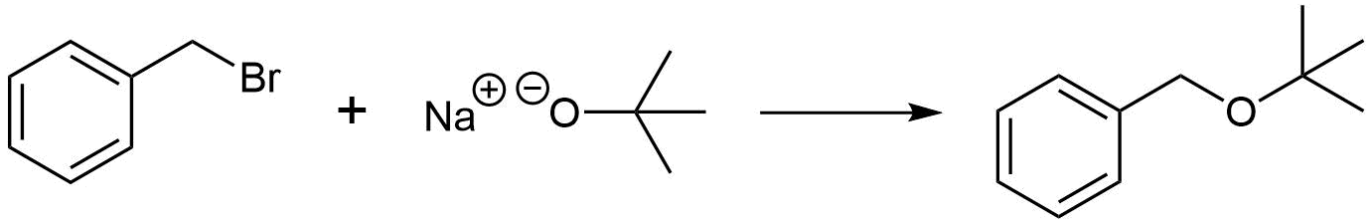
Solution 1



Pathway 2



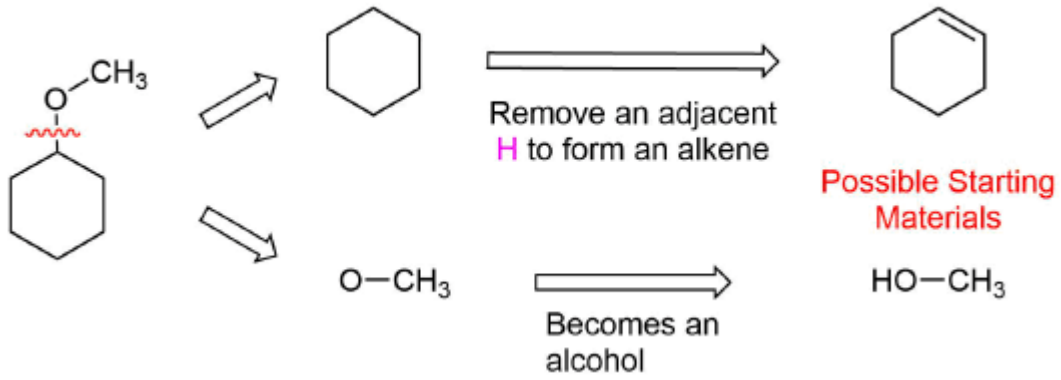
Solution 2



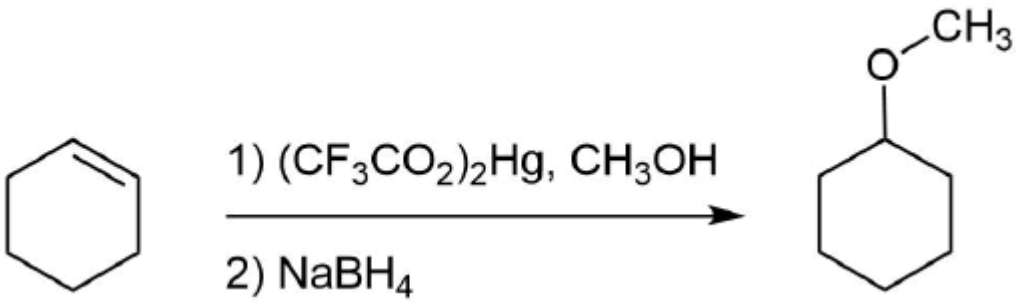
Worked Example 9.7.2

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

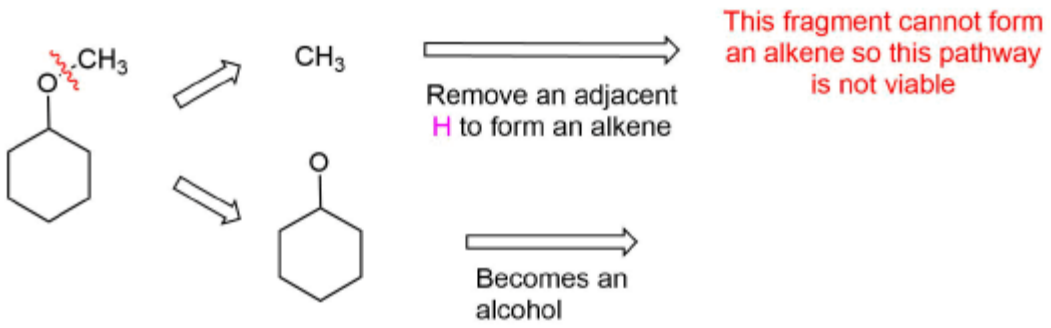
Pathway 1



Solution 1



Pathway 2



Exercise 9.7.1

The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

Exercise 9.7.2

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

(a) 18.26Aa.png

(b) 18.26Ab.png

(c) 18.26Ac.png

(d) 18.26Ad.png

Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 18.26Ae.png

Exercise 9.7.3

.18.27A.png

Exercise 9.7.4

18.28A.png

While both are possible, the top route is likely easier because both starting materials are a liquid.

Exercise 9.7.5

18.29A.png

Exercise 9.7.6

(a) 18.30Aa.png

(b) 18.30Ab.png Note the cis addition

(c) 18.30Ac.png

An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

Exercise 9.7.7

18.31A.png

The result is the production of dioxane, a common solvent.

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9.8: Reactions of Ethers

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

Study Notes

There are a number of points in this section that require additional explanations.

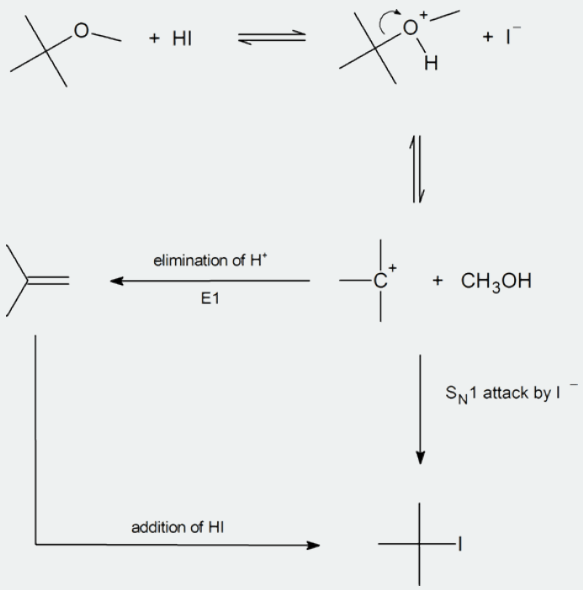
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$\mathrm{ROH + HI \longrightarrow RI + H_2O}$$

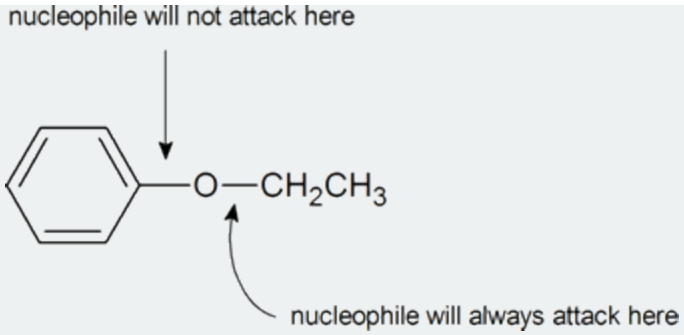
In view of this substitution, some textbooks simplify the overall cleavage process as:

$$\mathrm{R{-}O{-}R' + 2\,HI \longrightarrow RI + R'I + H_2O}$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

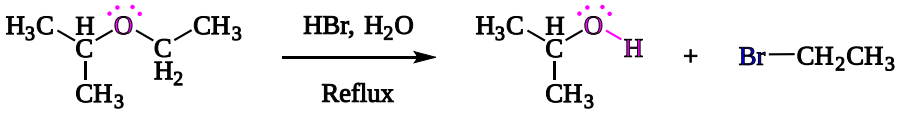


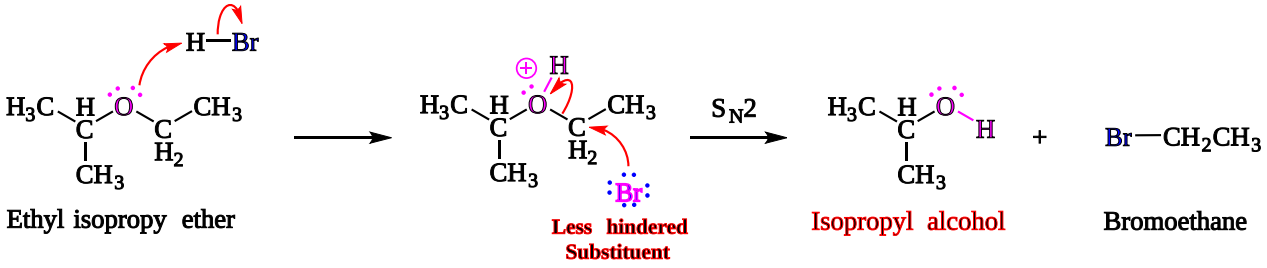
As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

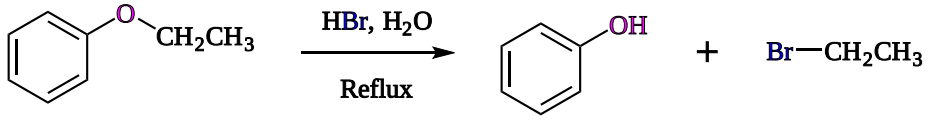
Acidic Cleavage of Ethers

Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below show that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1^o) than the isopropyl substituent (2^o).



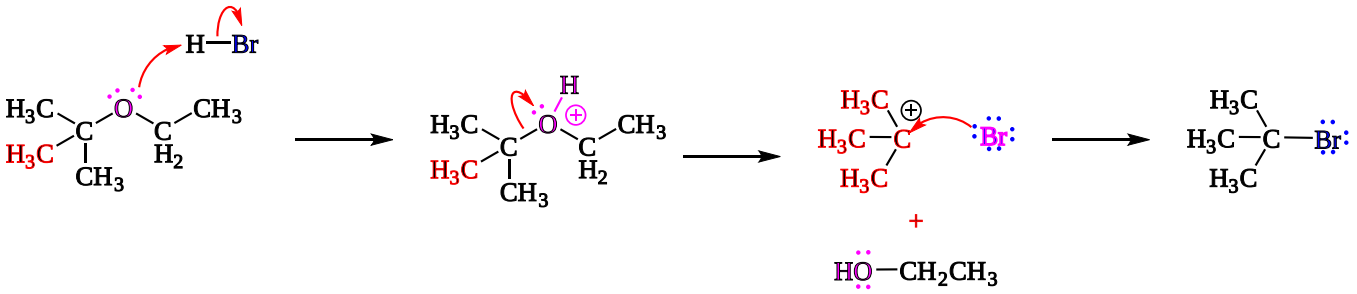


It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.

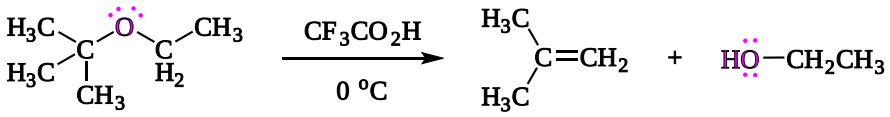


When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change

in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

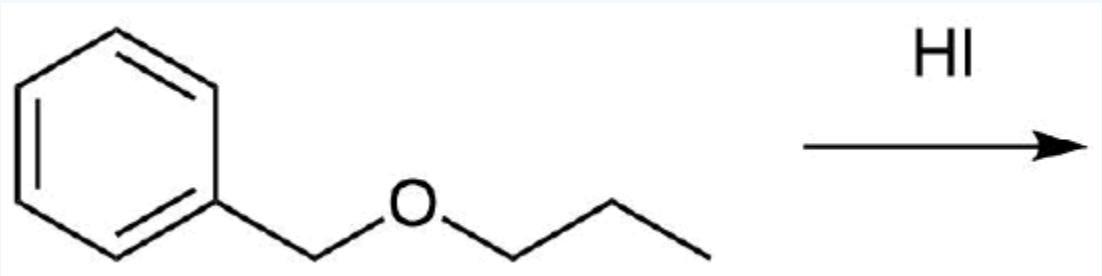


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



Worked Example 9.8.1

Predict the products of the following reaction:

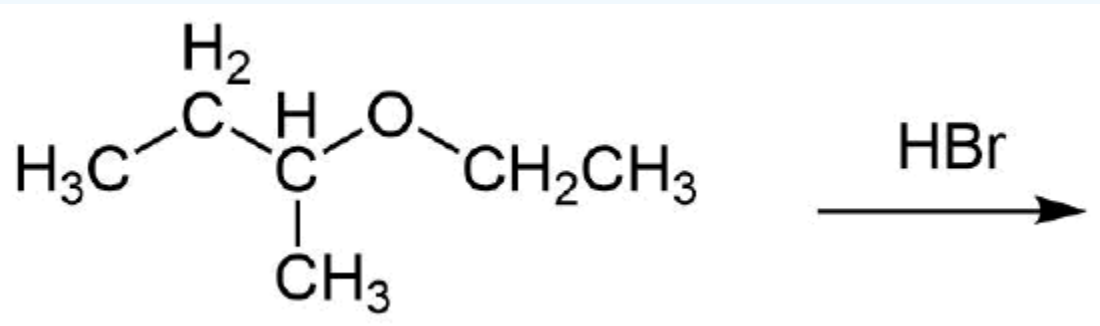


Answer available at the end of this section.

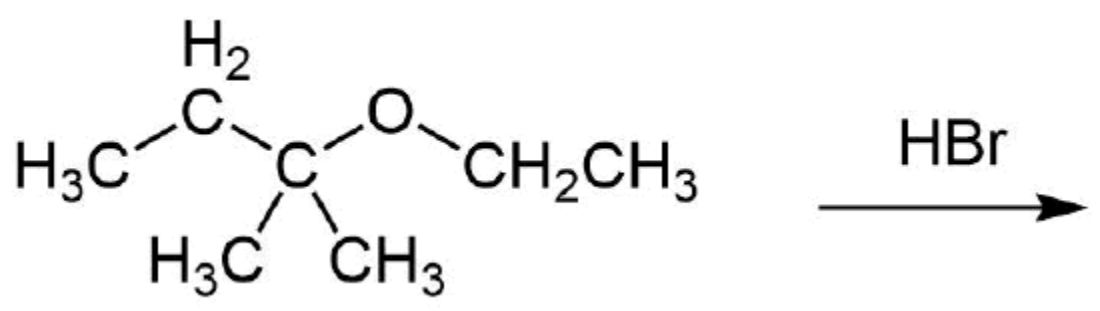
Exercises 9.8.1

1) Predict the product of the following reactions:

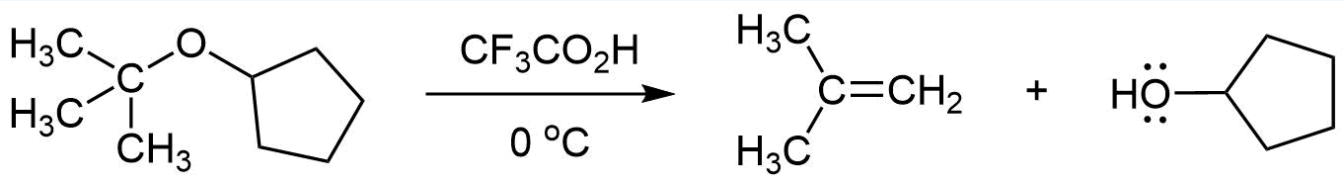
a)



b)



2) Please draw the mechanism for the following reaction:



3) Why is HCl less effective at cleaving ethers than HBr or HI?

Answer available at the end of this section.

Objectives

After completing this section, you should be able to:

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

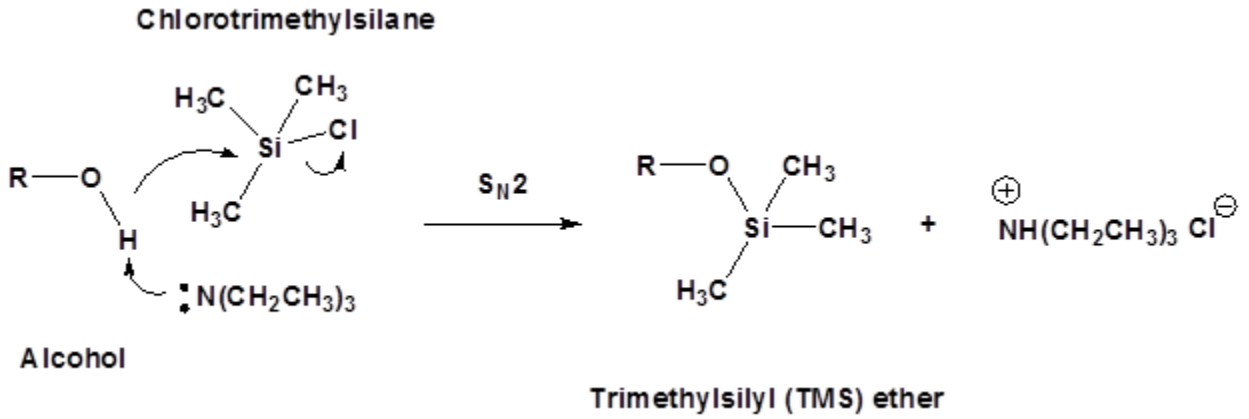
Often during the synthesis of complex molecules on functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.

When situations like this occurs chemists circumvent eh problem by protecting the interfering functional group. Functional group protection involves three steps:

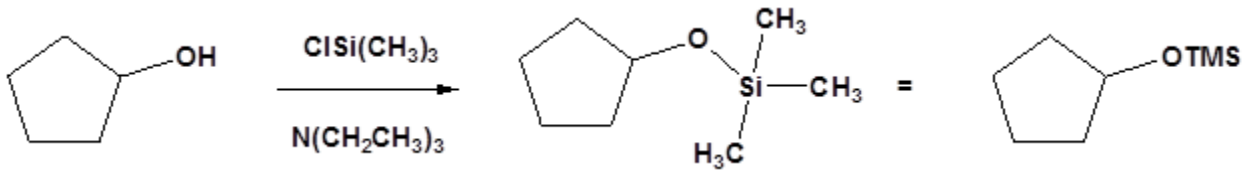
1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'-O-SiR_3. Chlorotrimethylsilane is often used in conjuction with a base, such as triethylamine, The base helps to form the alkoxide anion and remove the HCl produced by the reaction.

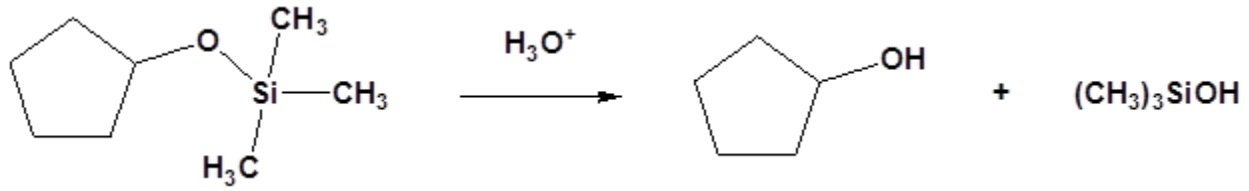
General Reaction



Example

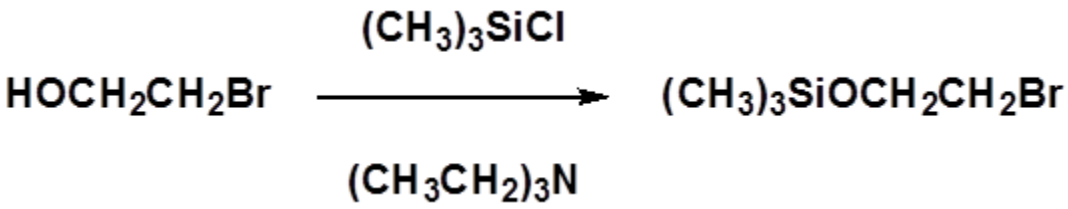


The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.

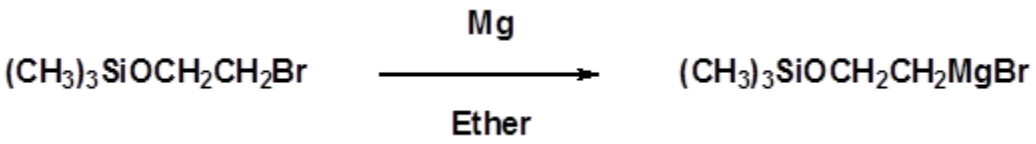


By utilizing a protecting group a Grignard reagent can be formed and reacted on a halo alcohol.

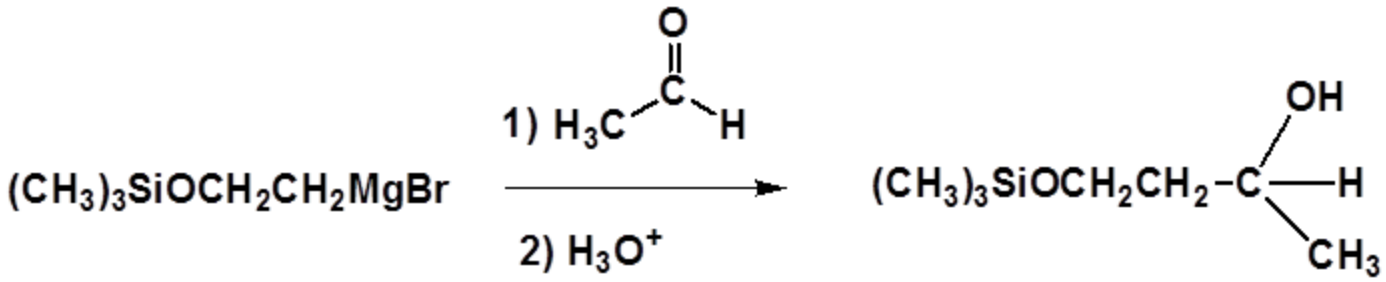
1) Protect the Alcohol



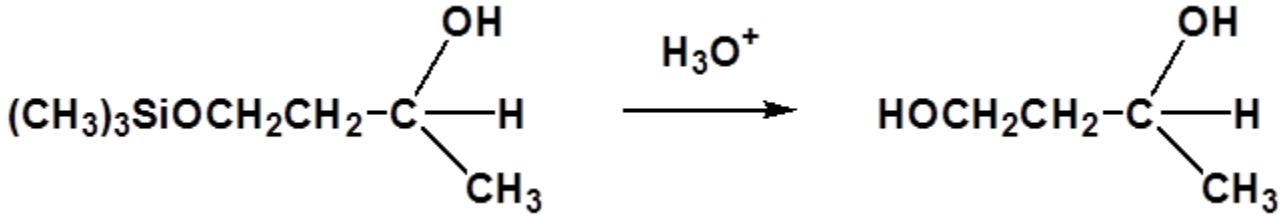
2) Form the Grignard Reagent

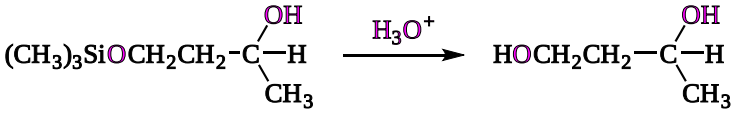


3) Perform the Grignard Reaction



4) Deprotection





Exercise

Exercise 17.8.1

Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 2-methylhexane-2,6-diol.

Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

Answers

Worked Example 9.8.1

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

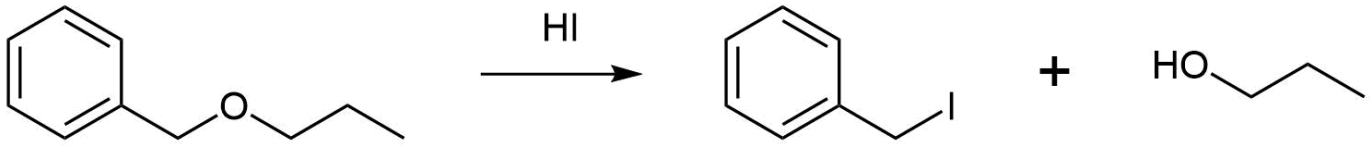
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

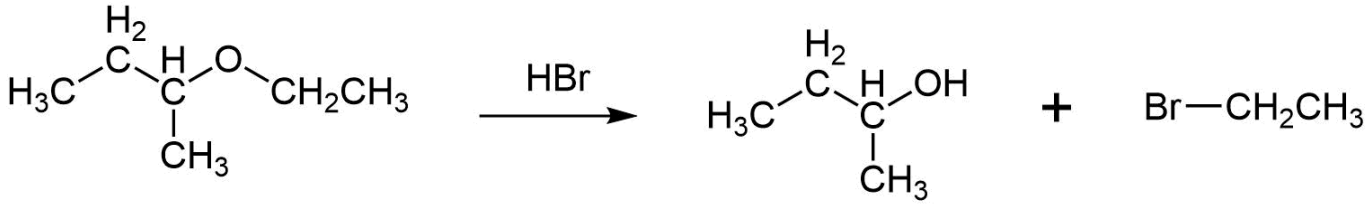
Solution



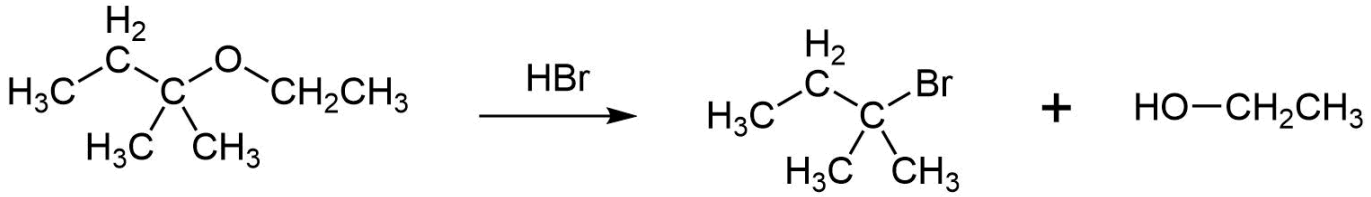
Exercises 9.8.1

1)

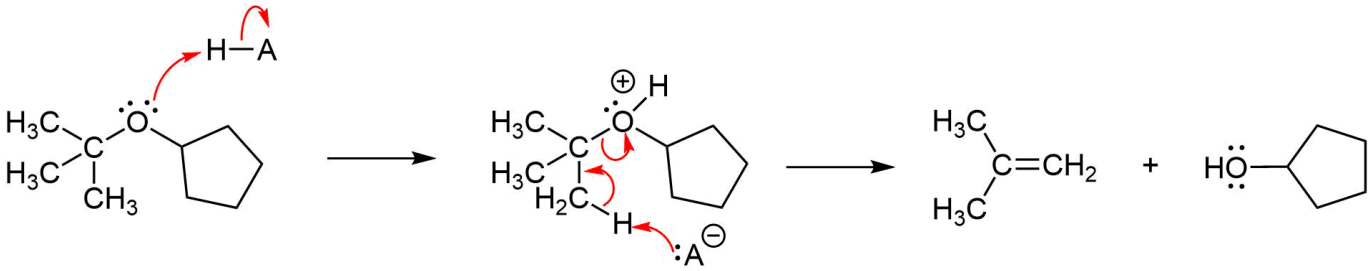
a)



b)

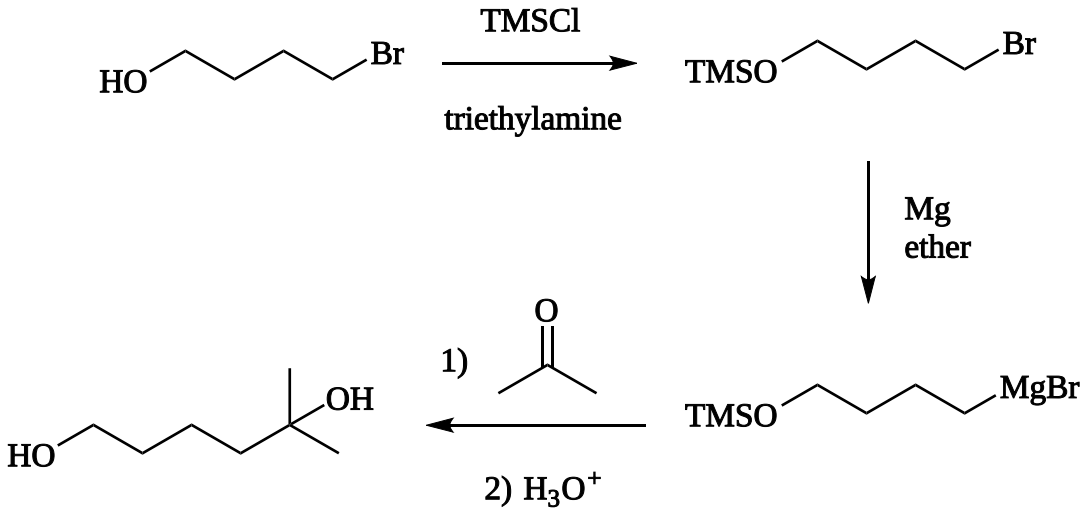


2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

Exercise 17.8.1



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9.9: Reactions of Oxacyclopropanes

Objectives

After completing this section, you should be able to

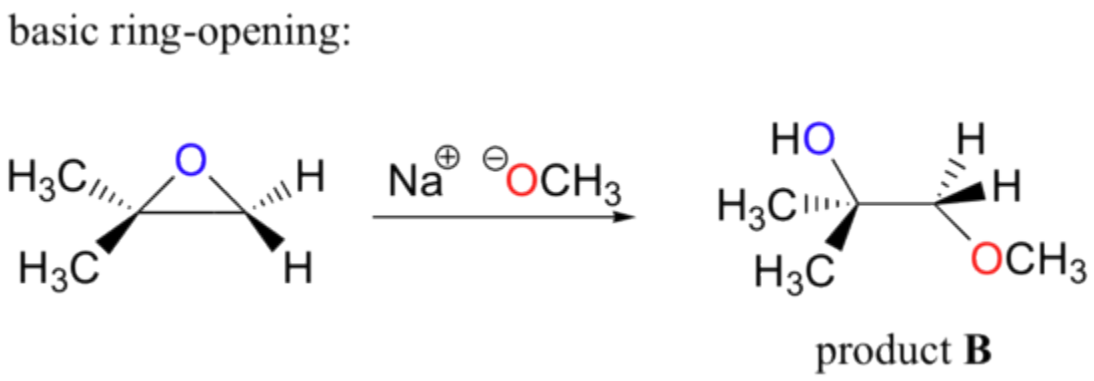
1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

Study Notes

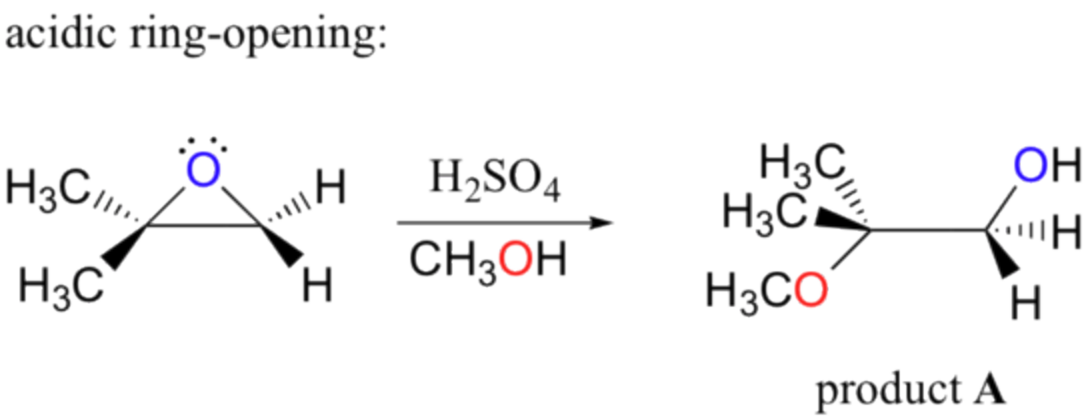
In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

Epoxide Ring-Opening by Alcoholysis

The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes alcoholysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:



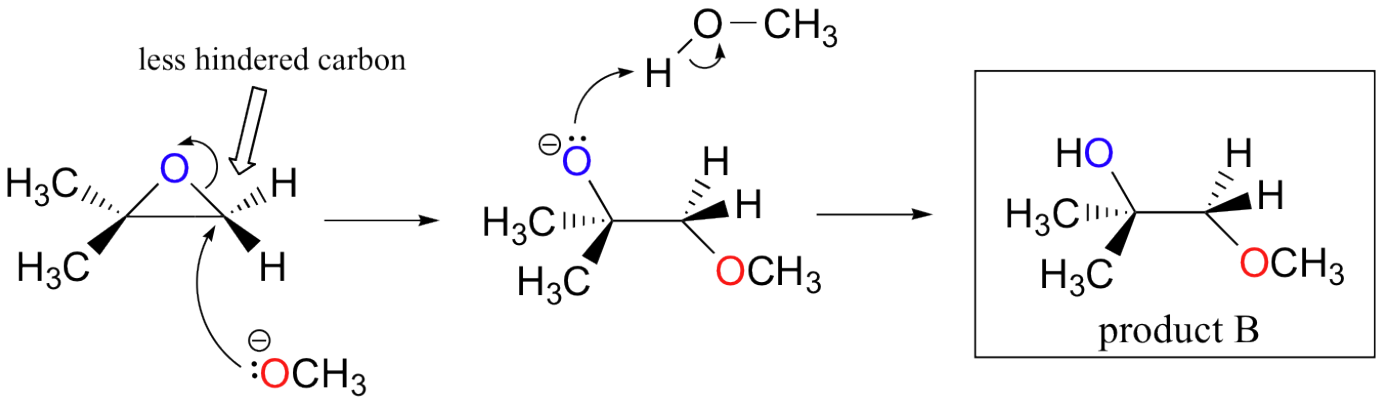
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.



These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

Basic Epoxide Ring-Opening by Alcoholysis

In the basic, S_N2 reaction, the leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group (**Section 11-3**), and thus the ring is unlikely to open without a 'push' from the nucleophile.

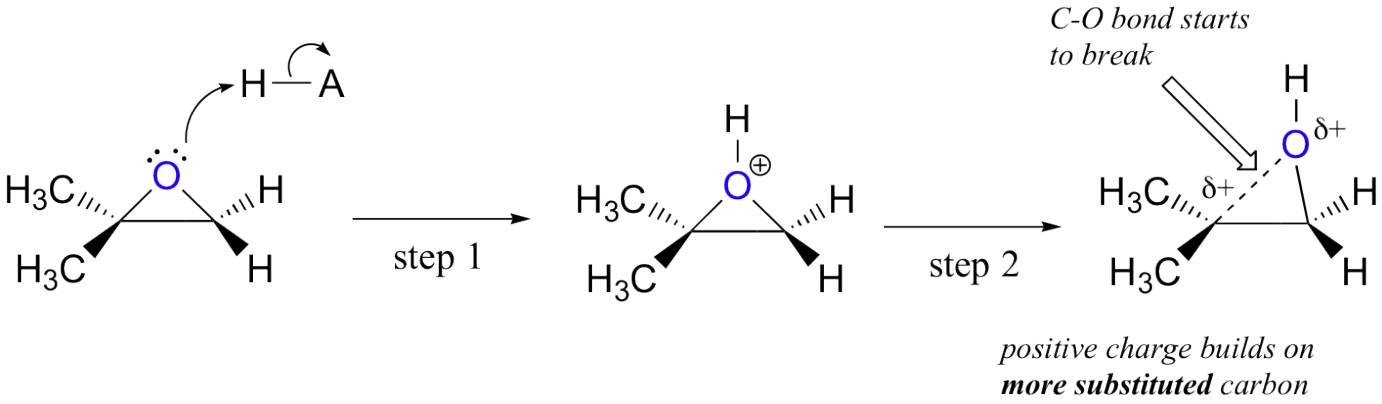


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

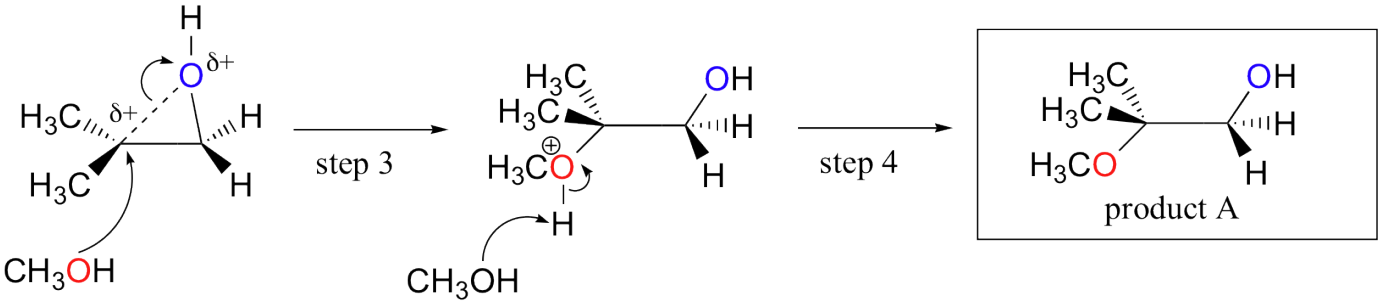
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Acid-Catalyzed Epoxide Ring-Opening by Alcoholysis

The best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon. Recall that alkyl substituents can donate electron density through hyper conjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

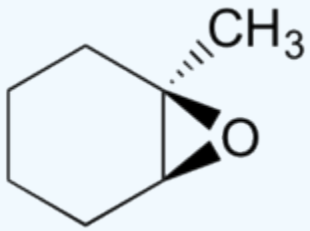


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

Example 18.6.1

Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry **and** stereochemistry!

Answer available at the end of this section.

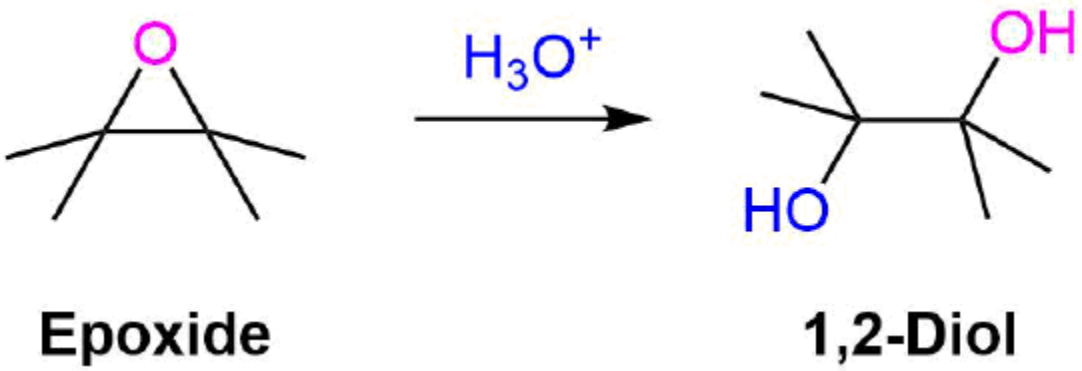
Epoxide Ring-Opening by Hydrolysis

Epoxides may be cleaved by hydrolysis to give ***trans*-1,2-diols** (1,2 diols are also called **vicinal diols or vicinal glycols)**. The reaction can be preformed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

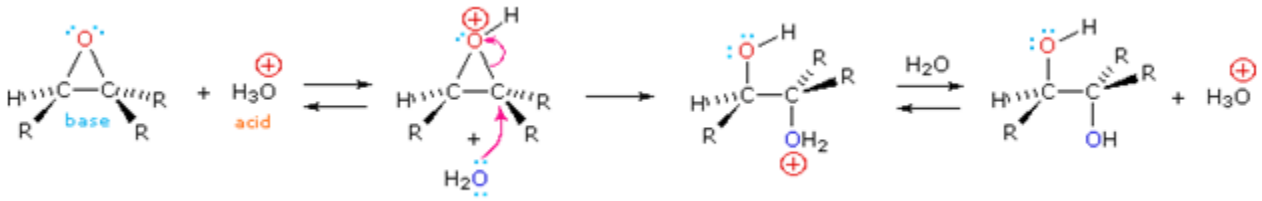
Acid Catalyzed Hydrolysis

Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

General Reaction



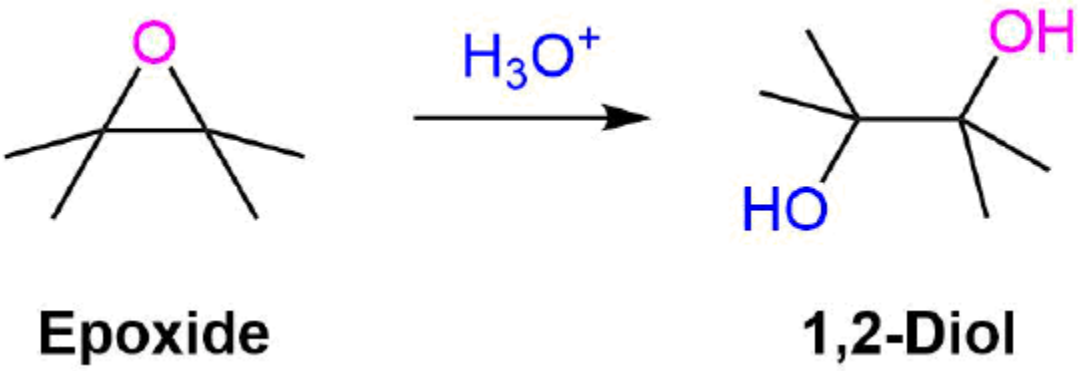
Mechanism



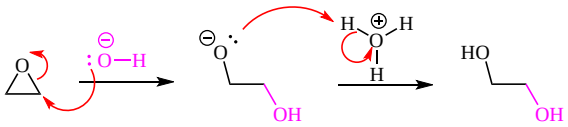
Basic Hydrolysis

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferable attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

General Reaction



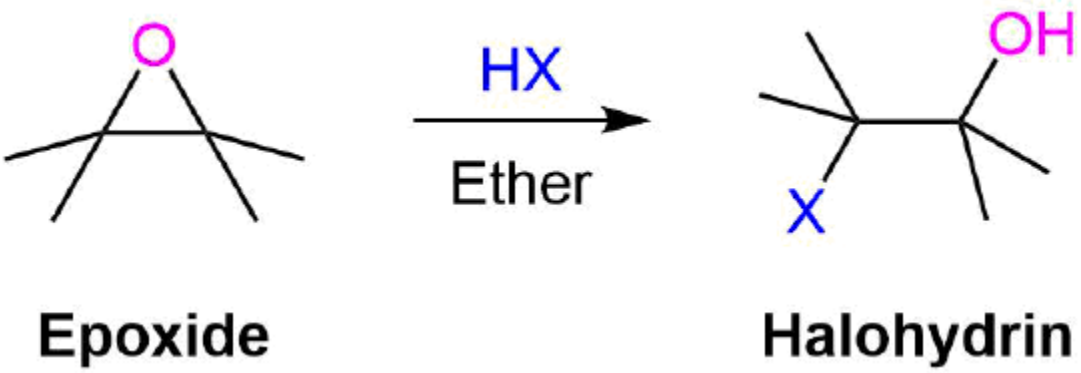
Mechanism



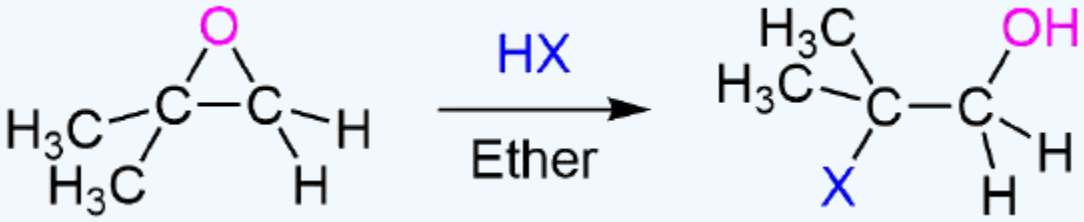
Epoxide Ring-Opening by HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

General Reaction

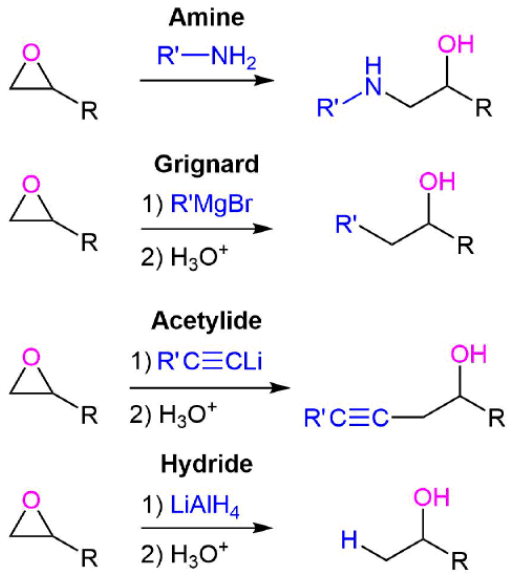


Example 18.6.2

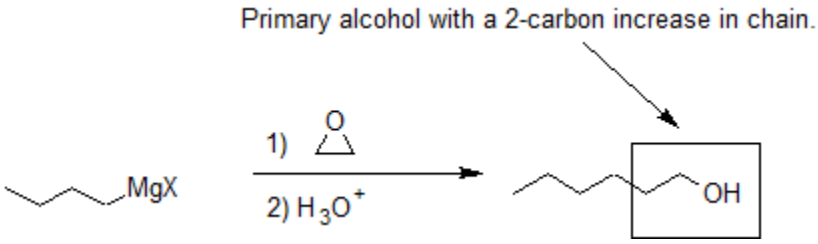


Epoxide Ring-Opening by Other Basic Nucleophiles

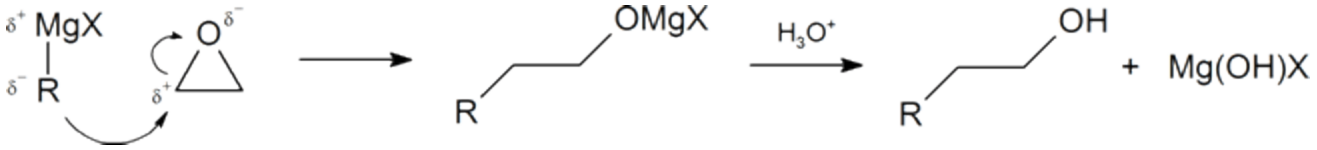
A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.



Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.

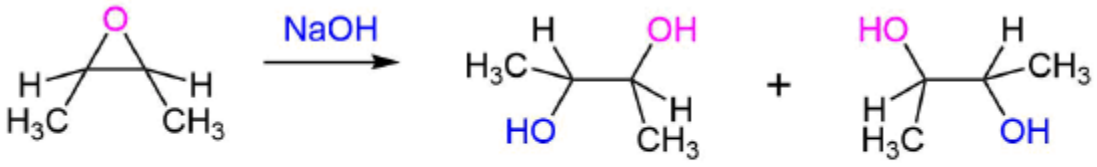


This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



Additional Stereochemical Considerations of Ring-Opening

During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.



Symmetrical Epoxide **Enantiomers**

Exercises

Exercise 9.9.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)

Q17.20.png

Answer available at the end of this section.

Exercise 9.9.2

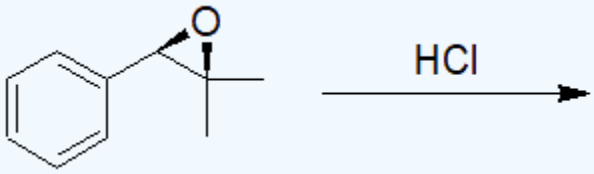
Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

Q17.21.png

Answer available at the end of this section.

Exercise 9.9.3

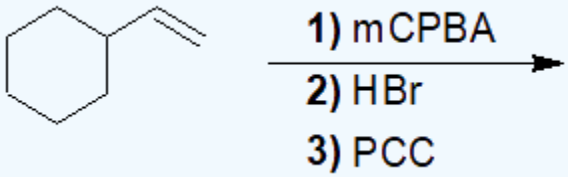
Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



Answer available at the end of this section.

Exercise 9.9.4

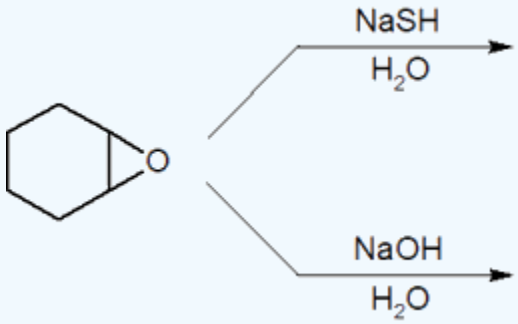
Predict the product of the following reaction.



Answer available at the end of this section.

Exercise 9.9.5

Provide the final products of the following reactions.

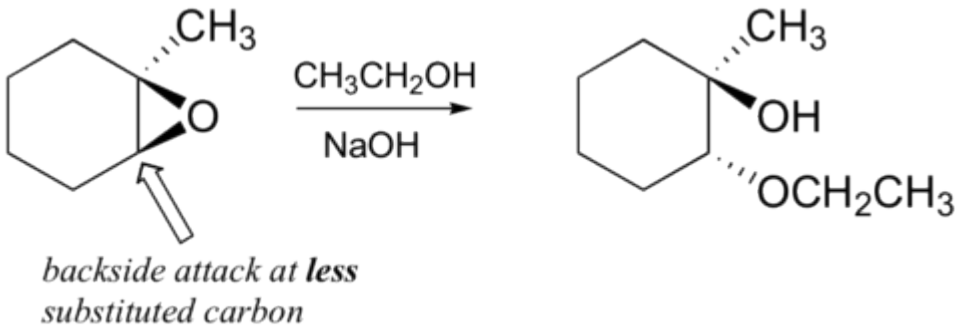


Answer available at the end of this section.

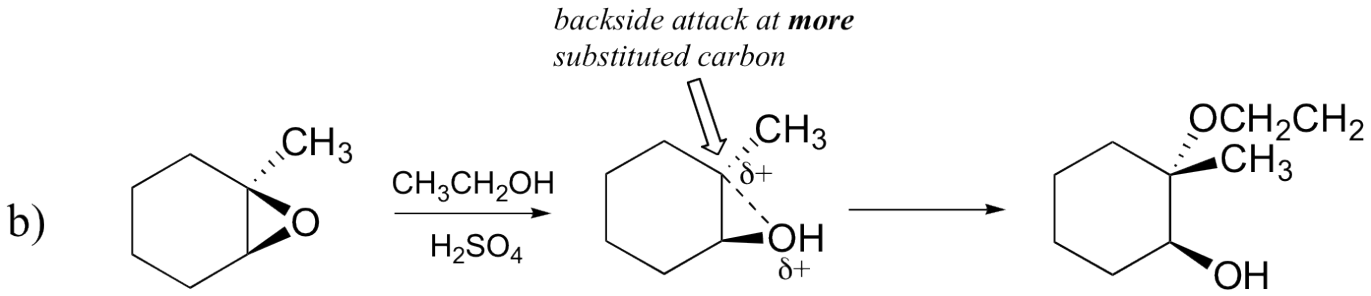
Answers

Example 18.6.1

a)



*backside attack at **less** substituted carbon*



Exercise 9.9.1

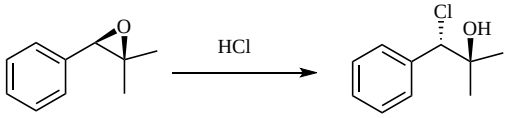
A17.20.png

Note that the stereochemistry has been inverted

Exercise 9.9.2

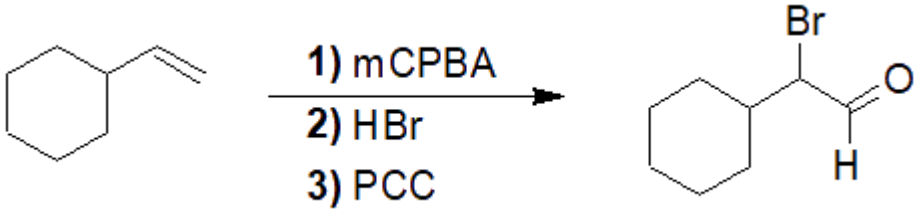
A17.21.png

Exercise 9.9.3

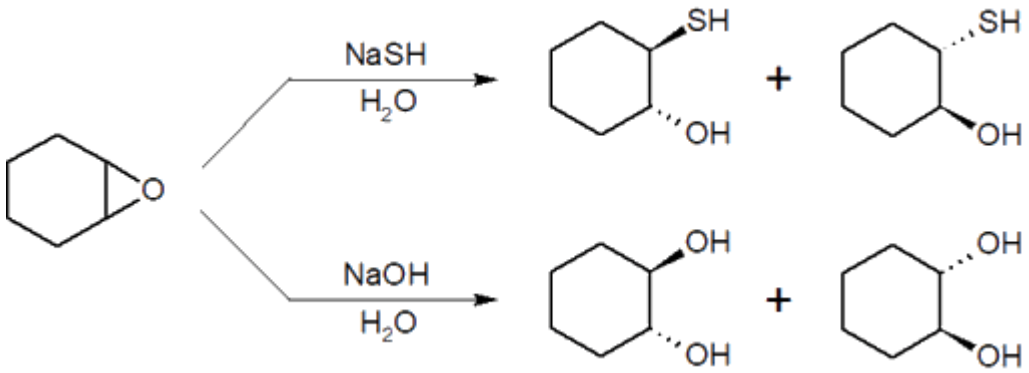


The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

Exercise 9.9.4



Exercise 9.9.5



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9.10: Sulfur Analogs of Alcohols and Ethers

Objectives

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

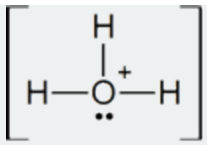
Study Notes

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

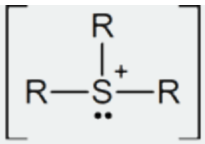
A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



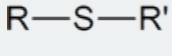
hydronium ion



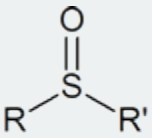
trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

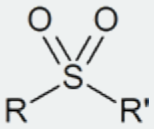
Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide



sulfoxide



sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table 9.10.1*: Comparison of compounds containing oxygen and sulfur*

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

Oxidation States of Sulfur Compounds

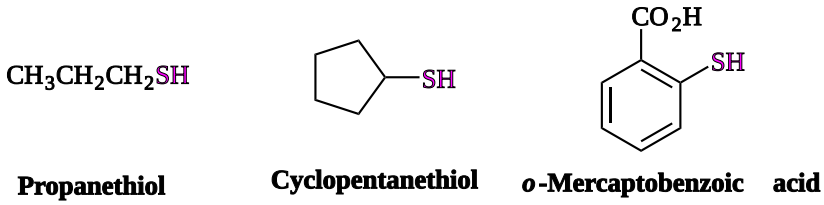
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

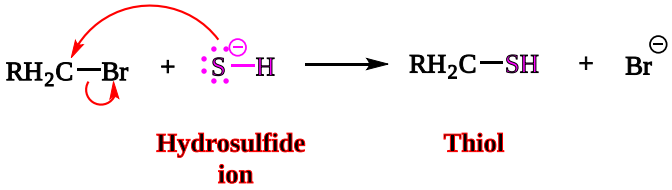
-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(⊕)(R)–R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R-O–S(=O)–O-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

Thiols

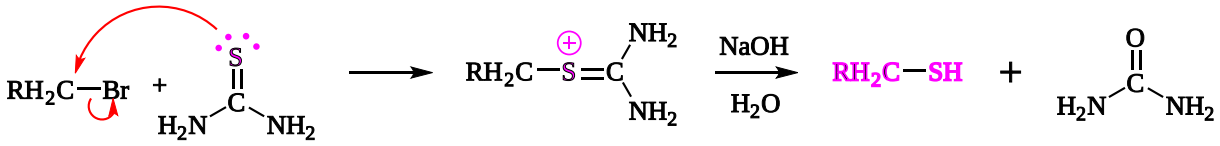
Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.

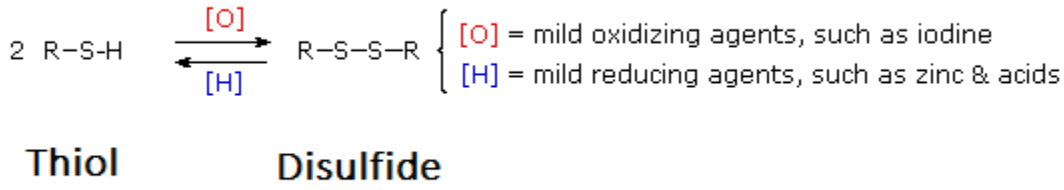


One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



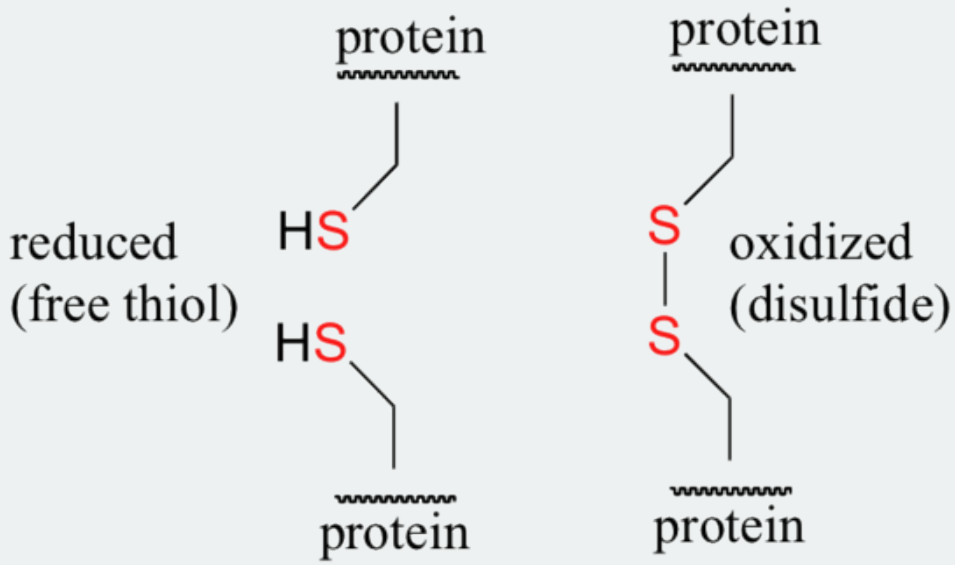
Disulfides

Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.

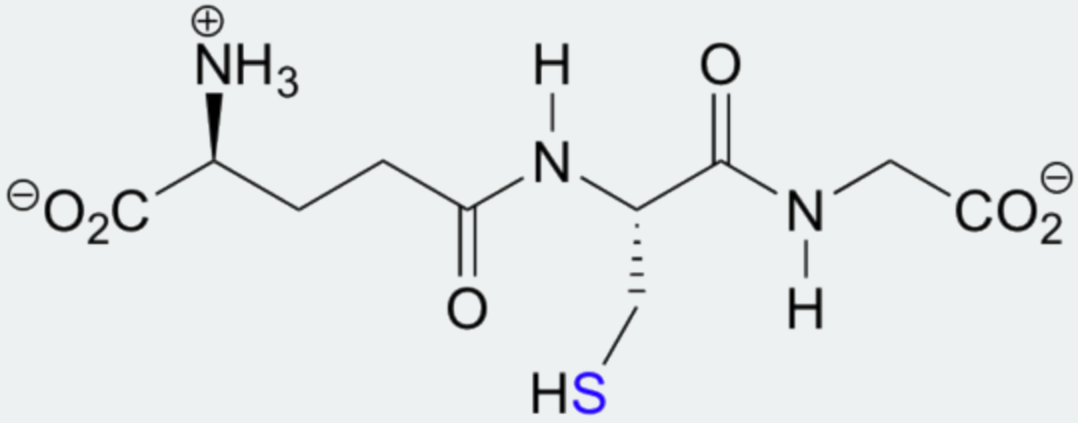


Disulfide bridges in proteins

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

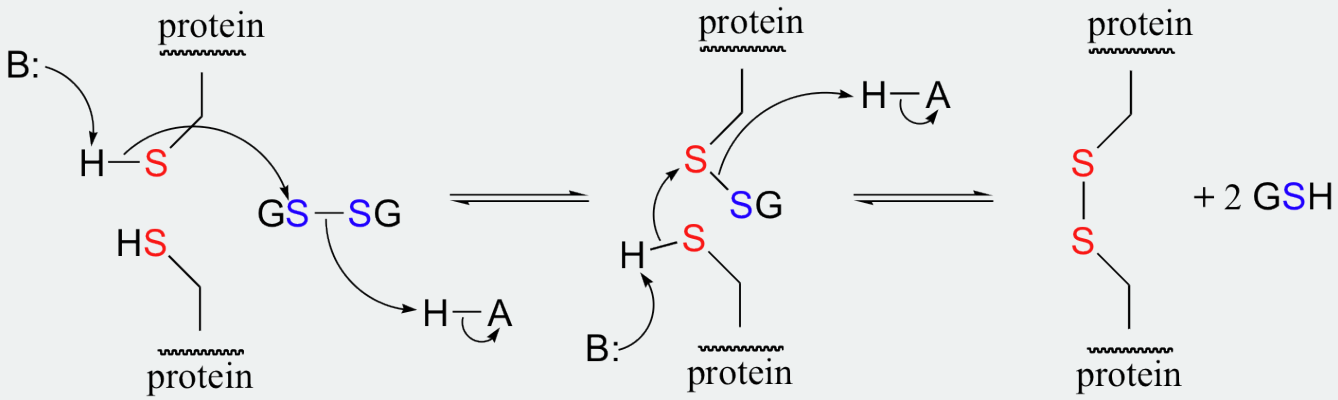


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

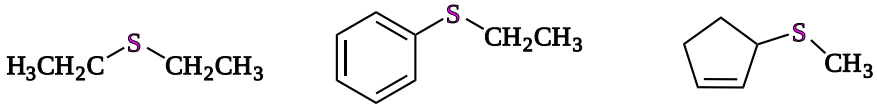
In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Sulfides

Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.

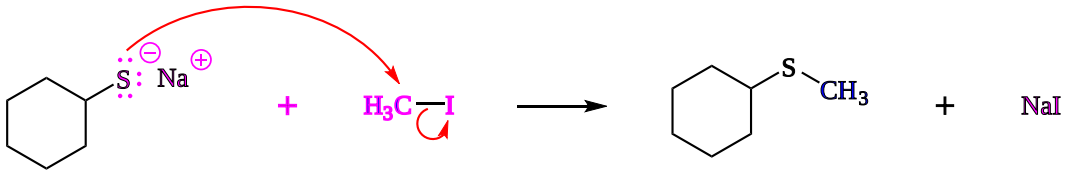


Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

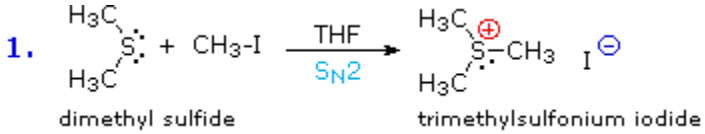
Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base

such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



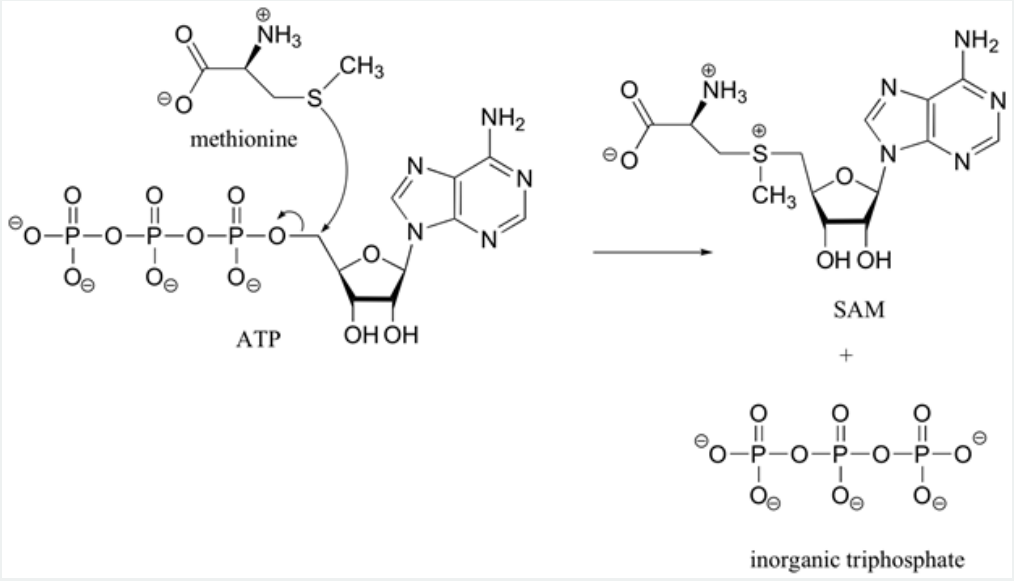
Cyclohexanethiolate **Cyclohexyl methyl sulfide**

The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3°-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

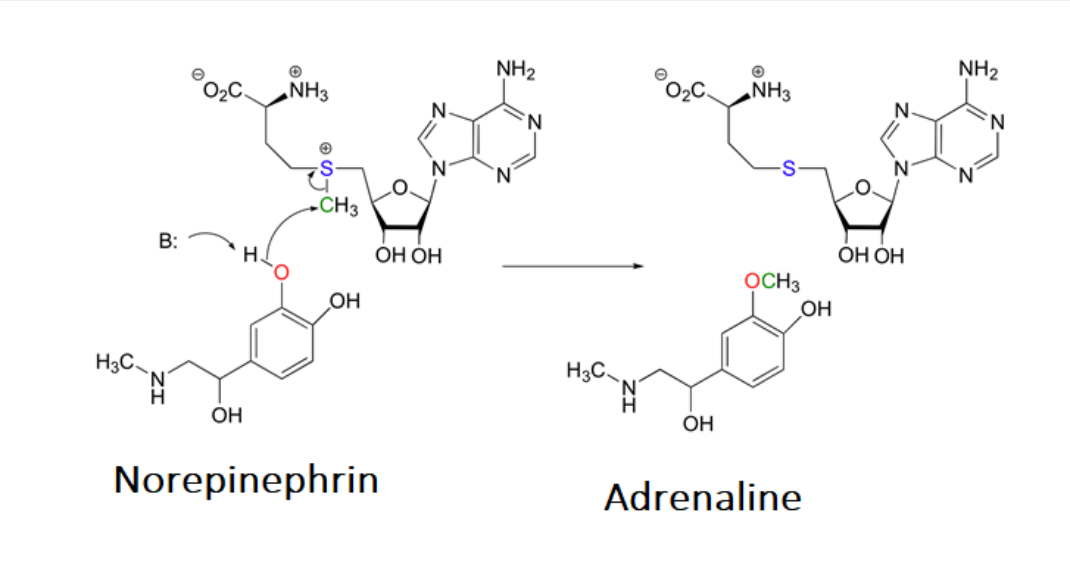


Biological Sulfonium Ion Formation

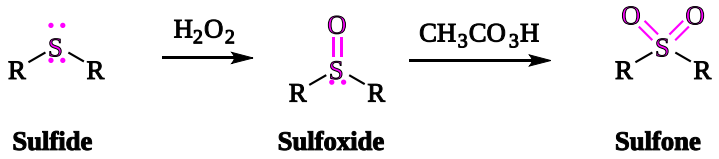
In biological systems the sulfonium ion, S-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



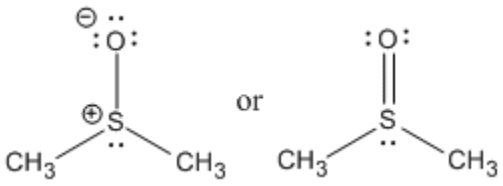
The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.



Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.

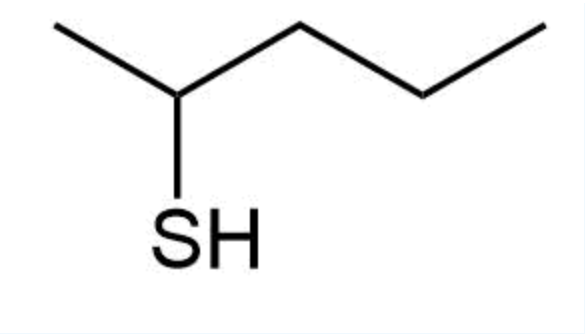


DMSO is a very polar, aprotic solvent

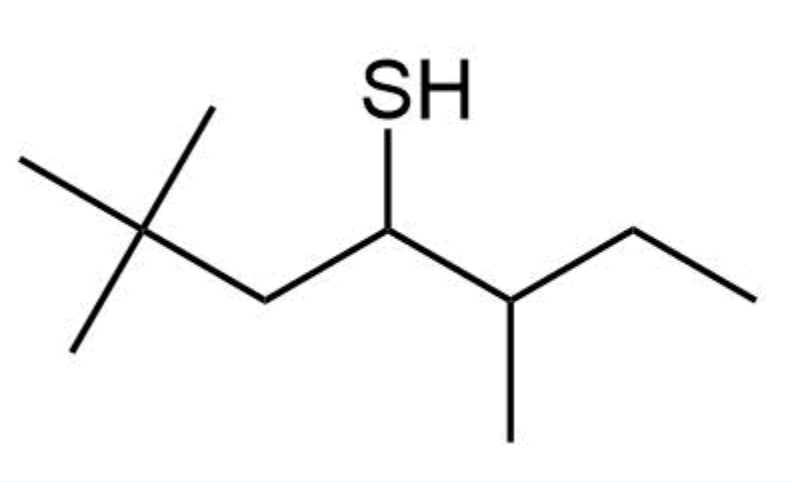
Exercise 9.10.1

Give IUPAC names the following compounds:

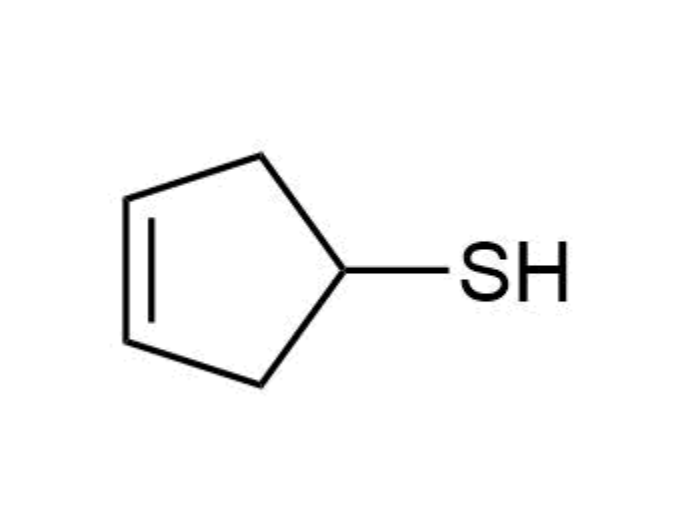
a)



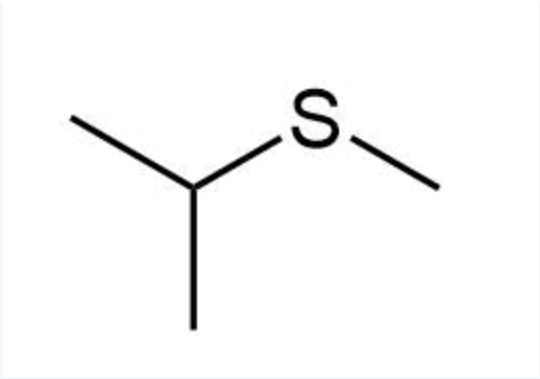
b)



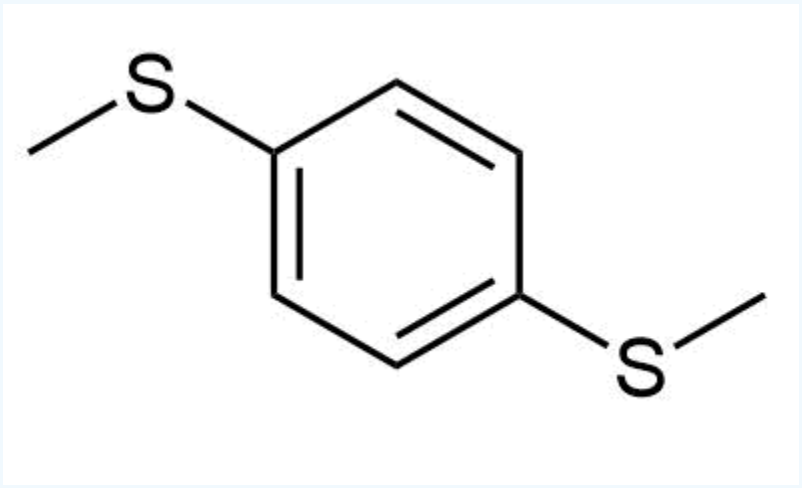
c)



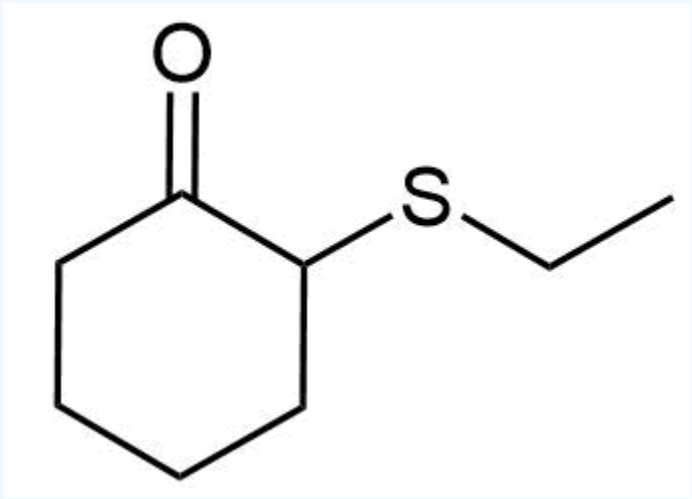
d)



e)



f)

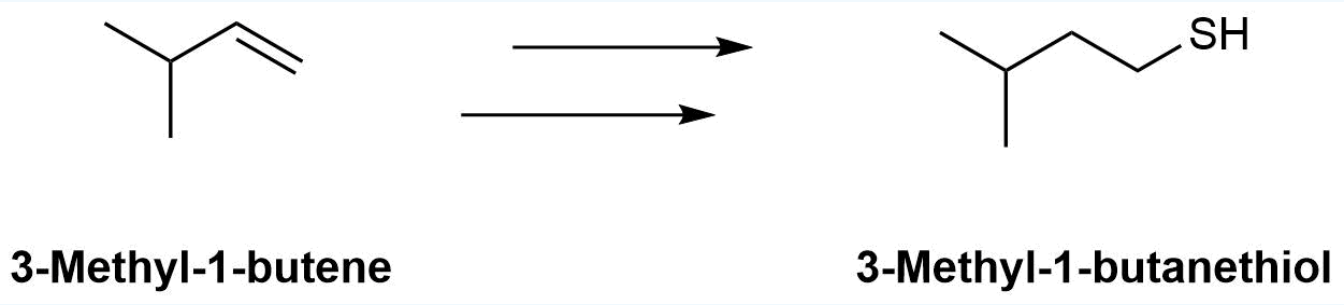


Answer available at the end of this section.

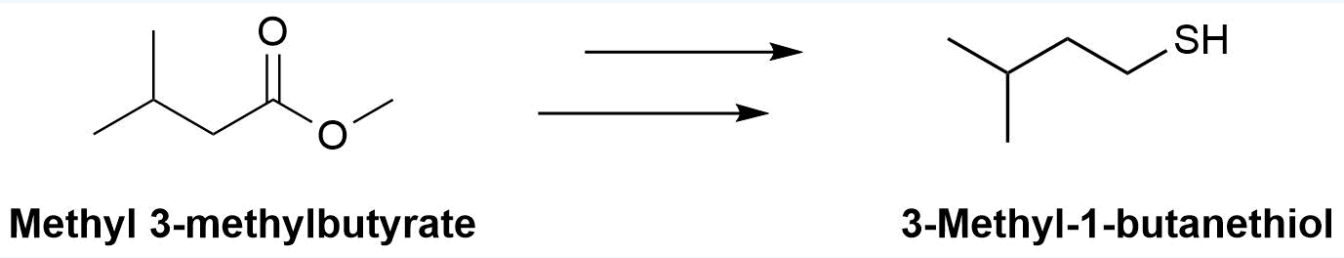
Exercise 9.10.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers available at the end of this section.

Answers

Exercise 9.10.1

a) 2-Pentanethiol
b) 2,2,5-Trimethyl-4-heptanethiol
c) 3-Cyclopentene-1-thiol
d) Methyl isopropyl sulfide
e) *p*-Di(methylthio)benzene
f) 2-(Ethylthio)cyclohexanone

Exercise 9.10.2

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O
b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

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9.11: Physiological Properties and Uses of Alcohols and Ethers

09.5 Interesting Alcohols, Ethers, and Epoxides

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10: USING NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY TO DEDUCE STRUCTURE

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy 

10.1: Physical and Chemical Tests
10.2: Defining Spectroscopy
10.3: Hydrogen Nuclear Magnetic Resonance
10.4: Using NMR Spectra to Analyze Molecular Structure: The Proton Chemical Shift
10.5: Tests for Chemical Equivalence
10.6: Integration
10.7: Spin-Spin Splitting: The Effect of Nonequivalent Neighboring Hydrogens
10.8: Spin-Spin Splitting: Some Complications
10.9: Carbon-13 Nuclear Magnetic Resonance
Index

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10.1: Physical and Chemical Tests

This page explains what structural isomerism is, and looks at some of the various ways that structural isomers can arise.

What is structural isomerism?

Isomers are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. That excludes any different arrangements which are simply due to the molecule rotating as a whole, or rotating about particular bonds. For example, both of the following are the same molecule. They are not isomers. Both are butane.

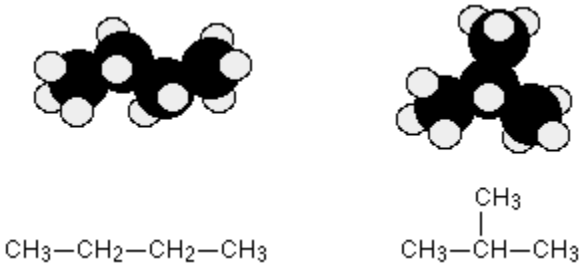


There are also endless other possible ways that this molecule could twist itself. There is completely free rotation around all the carbon-carbon single bonds. If you had a model of a molecule in front of you, you would have to take it to pieces and rebuild it if you wanted to make an isomer of that molecule. If you can make an apparently different molecule just by rotating single bonds, it's not different - it's still the same molecule.

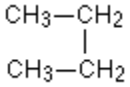
In structural isomerism, the atoms are arranged in a completely different order. This is easier to see with specific examples. What follows looks at some of the ways that structural isomers can arise. The names of the various forms of structural isomerism probably don't matter all that much, but you must be aware of the different possibilities when you come to draw isomers.

Chain Isomerism

These isomers arise because of the possibility of branching in carbon chains. For example, there are two isomers of butane, C_4H_{10}. In one of them, the carbon atoms lie in a "straight chain" whereas in the other the chain is branched.



Be careful not to draw "false" isomers which are just twisted versions of the original molecule. For example, this structure is just the straight chain version of butane rotated about the central carbon-carbon bond.

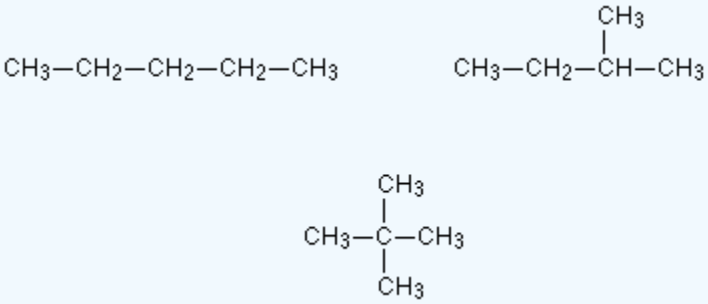


You could easily see this with a model. This is the example we've already used at the top of this page.



Example 1: Chain Isomers in Pentane

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

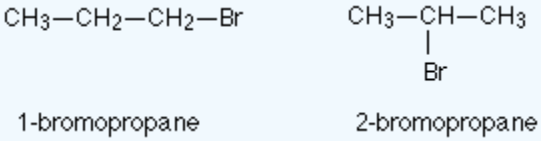


Position isomerism

In position isomerism, the basic carbon skeleton remains unchanged, but important groups are moved around on that skeleton.

Example 2: Positional Isomers in C_5H_{12}

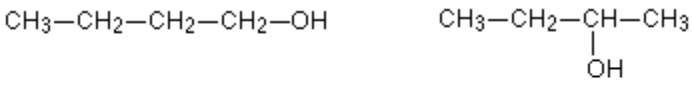
For example, there are two structural isomers with the molecular formula C3H7Br. In one of them the bromine atom is on the end of the chain, whereas in the other it's attached in the middle.



1-bromopropane 2-bromopropane

If you made a model, there is no way that you could twist one molecule to turn it into the other one. You would have to break the bromine off the end and re-attach it in the middle. At the same time, you would have to move a hydrogen from the middle to the end.

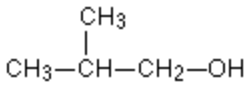
Another similar example occurs in alcohols such as C_4H_9OH



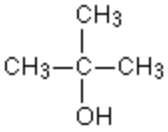
butan-1-ol butan-2-ol

These are the only two possibilities provided you keep to a four carbon chain, but there is no reason why you should do that. You can easily have a mixture of chain isomerism and position isomerism - you aren't restricted to one or the other.

So two other isomers of butanol are:

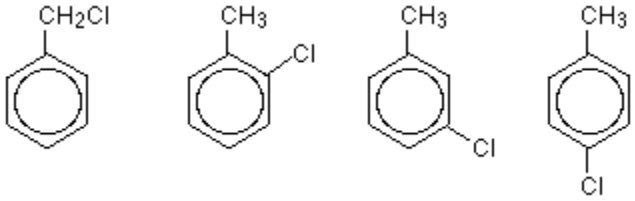


2-methylpropan-1-ol



2-methylpropan-2-ol

You can also get position isomers on benzene rings. Consider the molecular formula C_7H_7Cl. There are four different isomers you could make depending on the position of the chlorine atom. In one case it is attached to the side-group carbon atom, and then there are three other possible positions it could have around the ring - next to the CH_3 group, next-but-one to the CH_3 group, or opposite the CH_3 group.

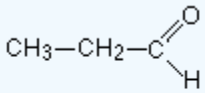


Functional group isomerism

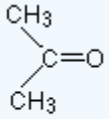
In this variety of structural isomerism, the isomers contain different functional groups - that is, they belong to different families of compounds (different homologous series).

Example 3: Isomers in C_3H_6O

A molecular formula C_3H_6O could be either propanal (an aldehyde) or propanone (a ketone).

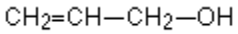


propanal

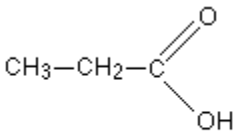


propanone

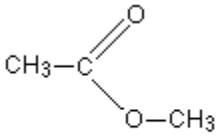
There are other possibilities as well for this same molecular formula - for example, you could have a carbon-carbon double bond (an alkene) and an -OH group (an alcohol) in the same molecule.



Another common example is illustrated by the molecular formula $C_3H_6O_2$. Amongst the several structural isomers of this are propanoic acid (a carboxylic acid) and methyl ethanoate (an ester).



propanoic acid



methyl ethanoate

Contributors

Jim Clark (Chemguide.co.uk)

Further Reading

Khan Academy

Constitutional Isomers

Cliffs Notes

Structural Isomers and Stereoisomers

Web Pages

Information on Isomers

Organizing Isomers

Difference Between Isomers and Resonance Structures

Lewis Formulas, Structural Isomerism, Resonance

Structural Isomerism

Videos

Isomers Video

Isomers Video

Tutorial

Drawing Isomers

Drawing Isomers tutorial

Practice Problems

Isomer quiz

Isomer quiz

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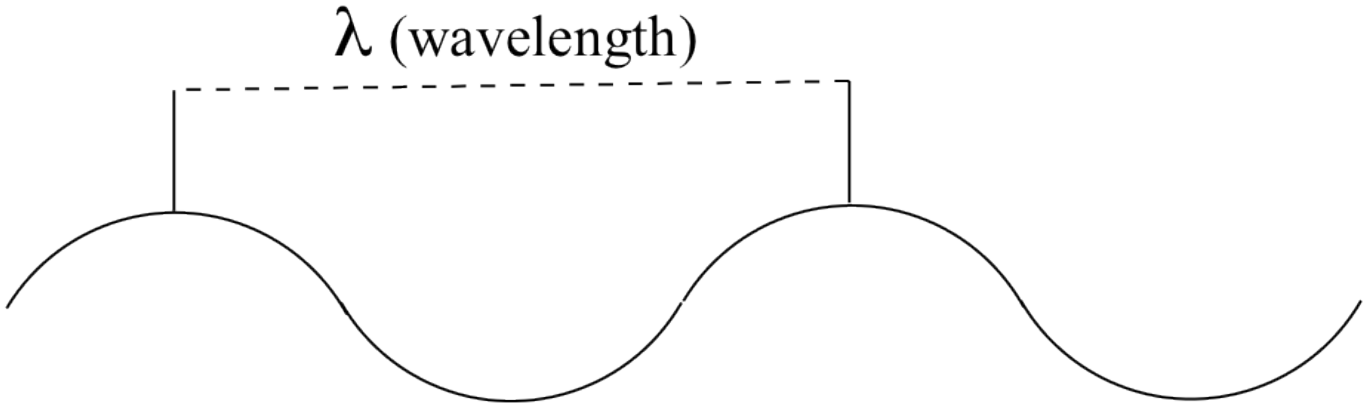
- Structural Isomerism in Organic Molecules by Jim Clark is licensed CC BY-NC 4.0.

10.2: Defining Spectroscopy

The electromagnetic spectrum

Electromagnetic radiation, as you may recall from a previous chemistry or physics class, is composed of electrical and magnetic waves which oscillate on perpendicular planes. Visible light is electromagnetic radiation. So are the gamma rays that are emitted by spent nuclear fuel, the x-rays that a doctor uses to visualize your bones, the ultraviolet light that causes a painful sunburn when you forget to apply sun block, the infrared light that the army uses in night-vision goggles, the microwaves that you use to heat up your frozen burritos, and the radio-frequency waves that bring music to anybody who is old-fashioned enough to still listen to FM or AM radio.

Just like ocean waves, electromagnetic waves travel in a defined direction. While the speed of ocean waves can vary, however, the speed of electromagnetic waves – commonly referred to as the speed of light – is essentially a constant, approximately 300 million meters per second. This is true whether we are talking about gamma radiation or visible light. Obviously, there is a big difference between these two types of waves – we are surrounded by the latter for more than half of our time on earth, whereas we hopefully never become exposed to the former to any significant degree. The different properties of the various types of electromagnetic radiation are due to differences in their wavelengths, and the corresponding differences in their energies: *shorter wavelengths correspond to higher energy.*



High-energy radiation (such as gamma- and x-rays) is composed of very short waves – as short as 10^{-16} meter from crest to crest. Longer waves are far less energetic, and thus are less dangerous to living things. Visible light waves are in the range of 400 – 700 nm (nanometers, or 10^{-9} m), while radio waves can be several hundred meters in length.

The notion that electromagnetic radiation contains a quantifiable amount of energy can perhaps be better understood if we talk about light as a stream of *particles*, called **photons**, rather than as a wave. (Recall the concept known as 'wave-particle duality': at the quantum level, wave behavior and particle behavior become indistinguishable, and very small particles have an observable 'wavelength'). If we describe light as a stream of photons, the energy of a particular wavelength can be expressed as:

$$E = \frac{hc}{\lambda} \tag{4.1.1}$$

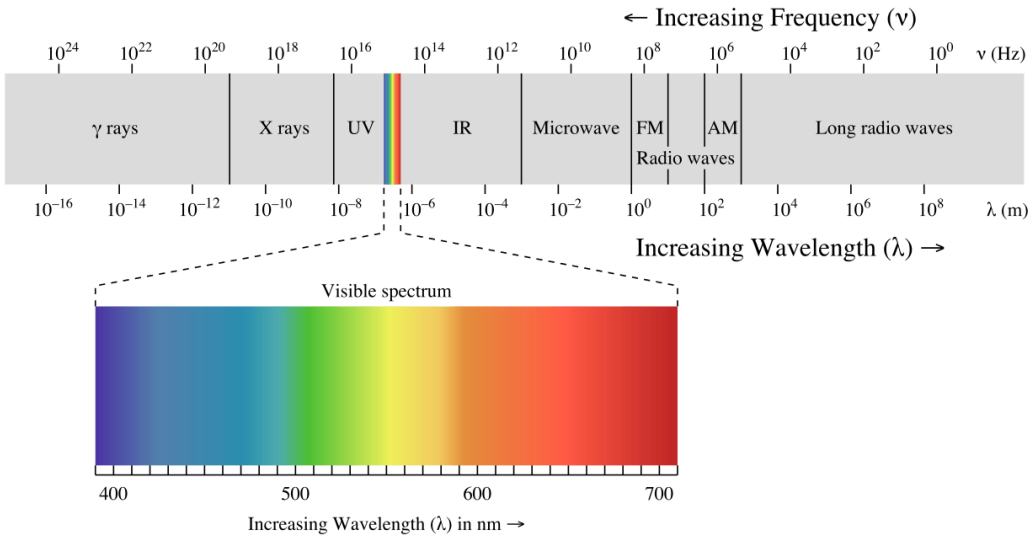
where E is energy in kJ/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^{8} m/s (the speed of light), and *h* is 3.99 x 10^{-13} kJ·s·mol^{-1}, a number known as **Planck's constant**.

Because electromagnetic radiation travels at a constant speed, each wavelength corresponds to a given frequency, which is the number of times per second that a crest passes a given point. Longer waves have lower frequencies, and shorter waves have higher frequencies. Frequency is commonly reported in hertz (Hz), meaning 'cycles per second', or 'waves per second'. The standard unit for frequency is s^{-1}.

When talking about electromagnetic waves, we can refer either to wavelength or to frequency - the two values are interconverted using the simple expression:

$$\lambda\nu = c \tag{4.1.2}$$

where **ν** (the Greek letter '*nu*') is frequency in s^{-1}. Visible red light with a wavelength of 700 nm, for example, has a frequency of 4.29 x 10^{14} Hz, and an energy of 40.9 kcal per mole of photons. The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



(Image from Wikipedia commons)

Notice that visible light takes up just a narrow band of the full spectrum. White light from the sun or a light bulb is a mixture of all of the visible wavelengths. You see the visible region of the electromagnetic spectrum divided into its different wavelengths every time you see a rainbow: violet light has the shortest wavelength, and red light has the longest.

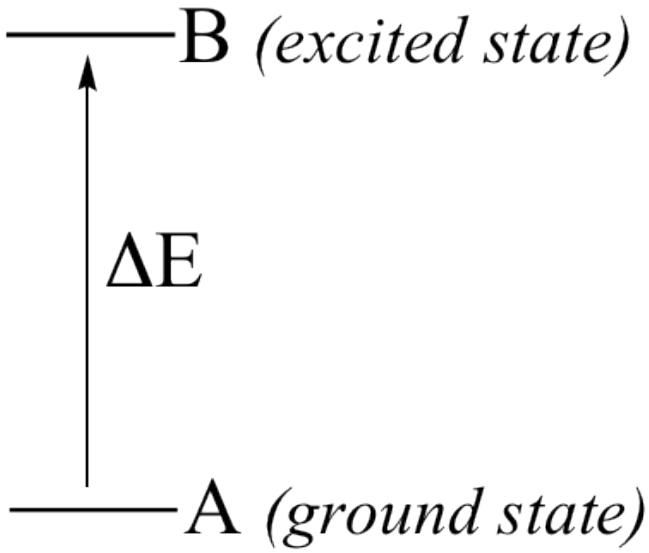
Exercise 4.4: Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kJ/mol of photons?

Solutions

Overview of a molecular spectroscopy experiment

In a spectroscopy experiment, electromagnetic radiation of a specified range of wavelengths is allowed to pass through a sample containing a compound of interest. The sample molecules absorb energy from some of the wavelengths, and as a result jump from a low energy 'ground state' to some higher energy 'excited state'. Other wavelengths are *not* absorbed by the sample molecule, so they pass on through. A detector on the other side of the sample records which wavelengths were absorbed, and to what extent they were absorbed.

Here is the key to molecular spectroscopy: *a given molecule will specifically absorb only those wavelengths which have energies that correspond to the energy difference of the transition that is occurring.* Thus, if the transition involves the molecule jumping from ground state A to excited state B, with an energy difference of **Δ**E, the molecule will specifically absorb radiation with wavelength that corresponds to **Δ**E, while allowing other wavelengths to pass through unabsorbed.



By observing which wavelengths a molecule absorbs, and to what extent it absorbs them, we can gain information about the nature of the energetic transitions that a molecule is able to undergo, and thus information about its structure.

These generalized ideas may all sound quite confusing at this point, but things will become much clearer as we begin to discuss specific examples.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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10.3: Hydrogen Nuclear Magnetic Resonance

Objectives

After completing this section, you should be able to

1. discuss the principles of NMR spectroscopy.
2. identify the two magnetic nuclei that are most important to an organic chemist.

Key Terms

Make certain that you can define, and use in context, the key term below.

- resonance

Study Notes

Notice that the word “resonance” has a different meaning when we are discussing nuclear magnetic resonance spectroscopy than it does when discussing molecular structures.

Introduction

Some types of atomic nuclei act as though they spin on their axis similar to the Earth. Since they are positively charged they generate an electromagnetic field just as the Earth does. So, in effect, they will act as tiny bar magnetics. Not all nuclei act this way, but fortunately both ^{1}H and ^{13}C do have nuclear spins and will respond to this technique.



NMR Spectrometer

In the absence of an external magnetic field the direction of the spin of the nuclei will be randomly oriented (see figure below left). However, when a sample of these nuclei is place in an external magnetic field, the nuclear spins will adopt specific orientations much as a compass needle responses to the Earth’s magnetic field and aligns with it. Two possible orientations are possible, with

the external field (*i.e.* parallel to and in the same direction as the external field) or against the field (*i.e.* antiparallel to the external field) - see Figure 10.3.1.

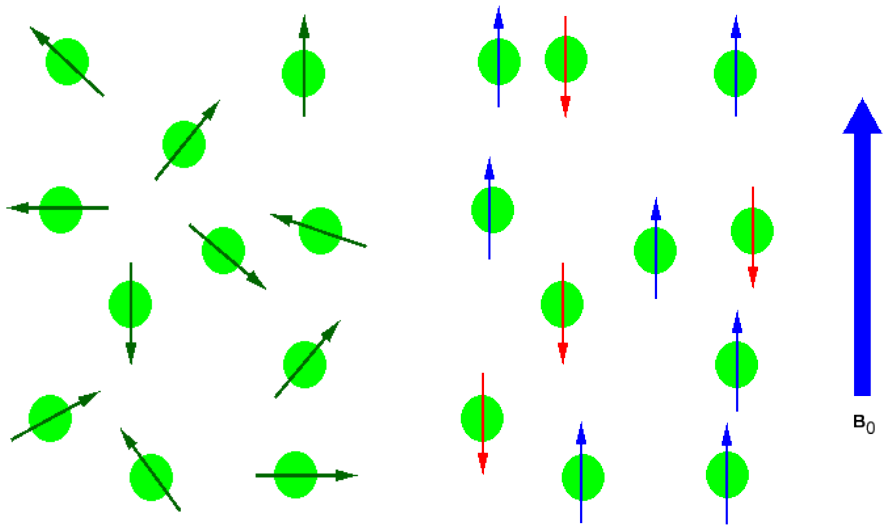
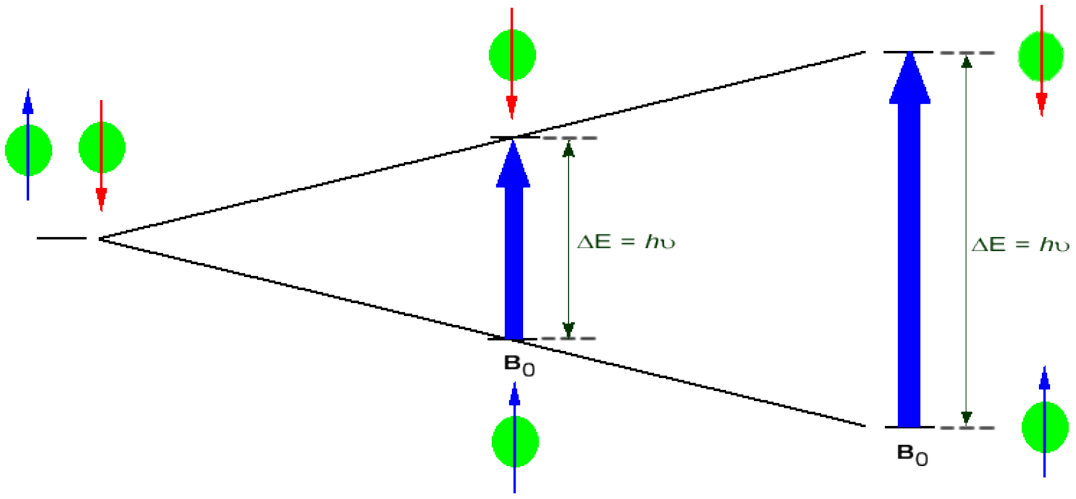


Figure 10.3.1: (Left) Random nuclear spin without an external magnetic field. (Right) Ordered nuclear spin in an external magnetic field

If the ordered nuclei are now subjected to EM radiation of the proper frequency the nuclei aligned with the field will absorb energy and "spin-flip" to align themselves against the field, a higher energy state. When this spin-flip occurs the nuclei are said to be in "resonance" with the field, hence the name for the technique, **N**uclear **M**agentic **R**esonance or NMR.

The amount of energy, and hence the exact frequency of EM radiation required for resonance to occur is dependent on both the strength of the magnetic field applied and the type of the nuclei being studied. As the strength of the magnetic field increases the energy difference between the two spin states increases and a higher frequency (more energy) EM radiation needs to be applied to achieve a spin-flip (see image below).



Superconducting magnets can be used to produce very strong magnetic field, on the order of 21 tesla (T). Lower field strengths can also be used, in the range of 4 - 7 T. At these levels the energy required to bring the nuclei into resonance is in the MHz range and corresponds to radio wavelength energies, *i.e.* at a field strength of 4.7 T 200 MHz bring ^{1}H nuclei into resonance and 50 MHz bring ^{13}C into resonance. This is considerably less energy then is required for IR spectroscopy, ~10^{-4} kJ/mol versus ~5 - ~50 kJ/mol.

^{1}H and ^{13}C are not unique in their ability to undergo NMR. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P ...) or nuclei with an odd number of neutrons (*i.e.* ^{13}C) show the magnetic properties required for NMR. Only nuclei with even number of both protons and neutrons (^{12}C and ^{16}O) do not have the required magnetic properties.

Exercise 10.3.1

If in a field strength of 4.7 T, H^{1} requires 200 MHz of energy to maintain resonance. If atom X requires 150 MHz, calculate the amount of energy required to spin flip atom X's nucleus. Is this amount greater than the energy required for hydrogen?

Answer available at the end of this section.

Exercise 10.3.1

Calculate the energy required to spin flip at 400 MHz. Does changing the frequency to 500 MHz decrease or increase the energy required? What about 300 MHz.

Answer available at the end of this section.

Answers

Exercise 10.3.1

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(150\ MHz)$

$E = 9.93 \times 10^{-26}\ J$

The energy is equal to $9.93x10^{-26}$ J. This value is smaller than the energy required for hydrogen (1.324×10^{-25} J).

Exercise 10.3.1

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(400\ MHz)$

$E = 2.648 \times 10^{-25}\ J$

The energy would increase if the frequency would increase to 500 MHz, and decrease if the frequency would decrease to 300 MHz.

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10.4: Using NMR Spectra to Analyze Molecular Structure: The Proton Chemical Shift

Objectives

After completing this section, you should be able to

1. explain, in general terms, the origin of shielding effects in NMR spectroscopy.
2. explain the number of peaks occurring in the ^{1}H or ^{13}C NMR spectrum of a simple compound, such as methyl acetate.
3. describe, and sketch a diagram of, a simple NMR spectrometer.
4. explain the difference in time scales of NMR and infrared spectroscopy.
5. predict the number of peaks expected in the ^{1}H or ^{13}C NMR spectrum of a given compound.

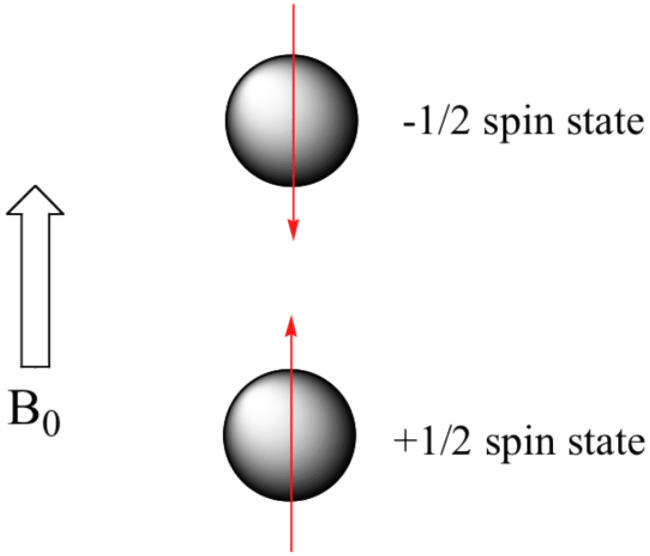
Study Notes

Before you go on, make sure that you understand that each signal in the ^{1}H NMR spectrum shown for methyl acetate is due to a different proton environment. The three protons on the same methyl group are equivalent and appear in the spectrum as one signal. However, the two methyl groups are in two different environments (one is more deshielded) and so we see two signals in the whole spectrum (aside from the TMS reference peak).

Methyl acetate has a very simple ^{1}H NMR spectrum, because there is no proton-proton coupling, and therefore no splitting of the signals. In later sections, we discuss splitting patterns in ^{1}H NMR spectra and how they help a chemist determine the structure of organic compounds.

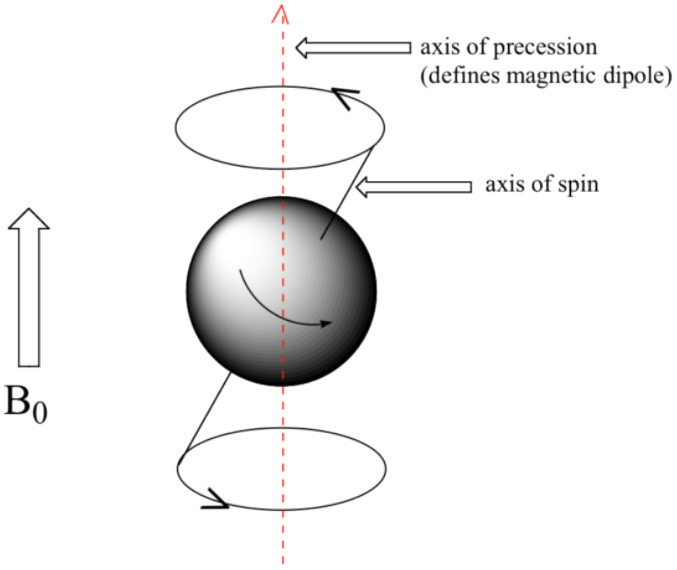
Nuclear precession, spin states, and the resonance condition

When a sample of an organic compound is sitting in a flask on a laboratory benchtop, the magnetic moments of its hydrogen atoms are randomly oriented. When the same sample is placed within the field of a very strong magnet in an NMR instrument (this field is referred to by NMR spectroscopists as the **applied field**, abbreviated $\mathbf{B_0}$) each hydrogen will assume one of two possible **spin states**. In what is referred to as the +½ spin state, the hydrogen's magnetic moment is aligned *with* the direction of B_0, while in the -½ spin state it is aligned *opposed to* the direction of B_0.



Because the +½ spin state is slightly lower in energy, in a large population of organic molecules slightly more than half of the hydrogen atoms will occupy this state, while slightly less than half will occupy the –½ state. *The difference in energy between the two spin states increases with increasing strength of* B_0.This last statement is in italics because it is one of the key ideas in NMR spectroscopy, as we shall soon see.

At this point, we need to look a little more closely at how a proton spins in an applied magnetic field. You may recall playing with spinning tops as a child. When a top slows down a little and the spin axis is no longer completely vertical, it begins to exhibit **precessional motion**, as the spin axis rotates slowly around the vertical. In the same way, hydrogen atoms spinning in an applied magnetic field also exhibit precessional motion about a vertical axis. It is this axis (which is either parallel or antiparallel to B_0) that defines the proton's magnetic moment. In the figure below, the proton is in the +1/2 spin state.



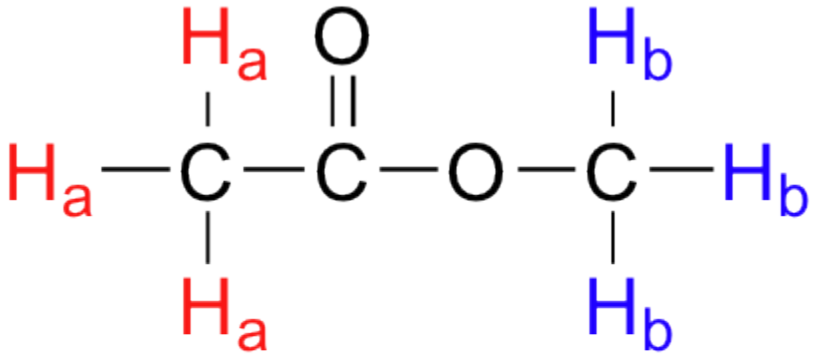
The **frequency of precession** (also called the **Larmour frequency,** abbreviated ω_L) is simply the number of times per second that the proton precesses in a complete circle. A proton`s precessional frequency increases with the strength of B_0.

If a proton that is precessing in an applied magnetic field is exposed to electromagnetic radiation of a frequency ν that matches its precessional frequency ω_L, we have a condition called **resonance**. *In the resonance condition, a proton in the lower-energy +½ spin state (aligned with* B_0*) will transition (flip) to the higher energy –½ spin state (opposed to* B_0*). In doing so, it will absorb radiation at this resonance frequency* $\nu = \omega_L$. This frequency, as you might have already guessed, corresponds to the energy

difference between the proton's two spin states. With the strong magnetic fields generated by the superconducting magnets used in modern NMR instruments, the resonance frequency for protons falls within the radio-wave range, anywhere from 100 MHz to 800 MHz depending on the strength of the magnet.

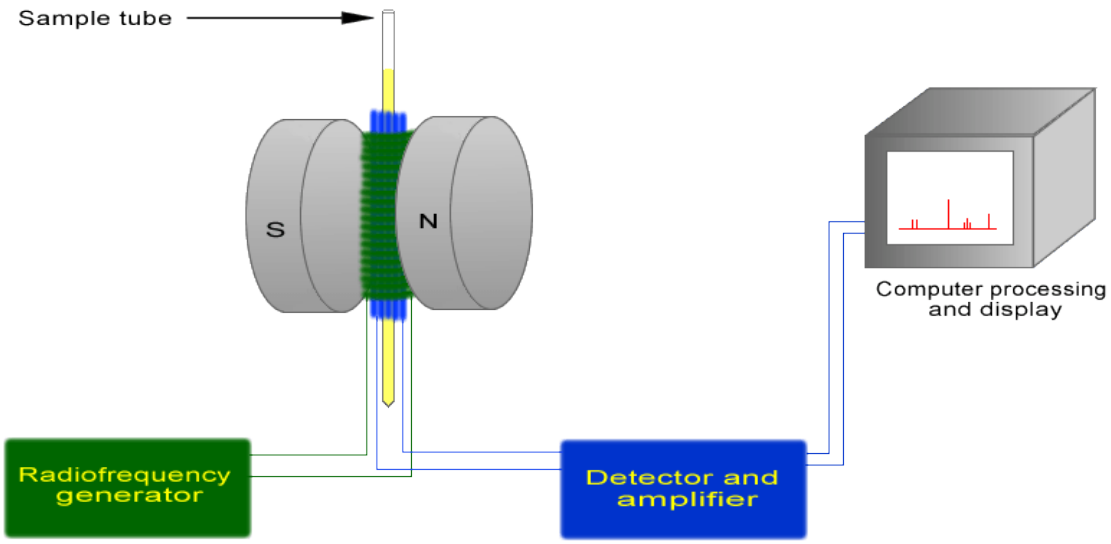
The basics of an NMR experiment

So far, you may have the impression that all ^{1}H nuclei in a molecule would absorb the same frequency. However, this would be of little use to organic chemists if that were the case. It turns out that not all ^{1}H nuclei absorb the same frequency and this is the same for all other NMR active nuclei. It turns out that chemically nonequivalent protons (or other nuclei) have different resonance frequencies in the same applied magnetic field. Nonequivalent protons are in different chemical environments. This allows NMR spectroscopy to provide us with useful information about the structure of an organic molecule. A full explanation of how a modern NMR instrument functions is beyond the scope of this text, but here is what happens. First, a sample compound (we'll use methyl acetate) is placed inside a very strong applied magnetic field (B_0). There are two types of protons in methyl acetate. H_a are bonded to a C that is then bonded to a carbonyl, whereas H_b are bonded to a carbon that is then bonded to an oxygen atom. This difference in bonding leads to different types of environments for H_a and H_b. All the H_a protons are the same since they all have the same type of bonding and will be in the same chemical environment and the same is true for H_b.



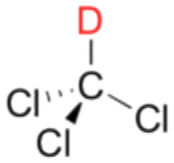
methyl acetate

The basic arrangement of an NMR spectrometer is displayed below. A sample (in a small glass tube, where the methyl acetate is in solution) is placed between the poles of a strong magnet. A radio frequency generator pulses the sample and excites the nuclei causing a spin-flip. The spin flip is detected by the detector and the signal sent to a computer where it is processed.

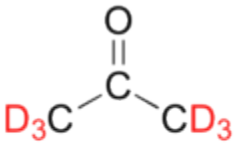


In the magnet, all of the protons begin to precess: the H_a protons at precessional frequency ω_a, the H_b protons at ω_b. At first, the magnetic moments of (slightly more than) half of the protons are aligned with B_0, and half (slightly less than half) are aligned against B_0. Then, the sample is hit with electromagnetic radiation in the radio frequency range. The two specific frequencies which match ω_a and ω_b (i.e. the resonance frequencies) cause those H_a and H_b protons which are aligned *with* B_0 to 'flip' so that they are now aligned *against* B_0. In doing so, the protons absorb radiation at the two resonance frequencies. The NMR instrument records which frequencies were absorbed, as well as the intensity of each absorbance.

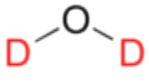
In most cases, a sample being analyzed by NMR is in solution. If we used a common laboratory solvent (diethyl ether, acetone, dichloromethane, ethanol, water, etc.) to dissolve our NMR sample, however, we run into a problem – there many more solvent protons in solution than there are sample protons, therefore the signals from the sample protons will be overwhelmed. To get around this problem, we use special NMR solvents in which all protons have been replaced by deuterium. Recall that deuterium is NMR-active, but its resonance frequency is very different from that of protons, and thus it is `invisible` in ^{1}H-NMR. Some common NMR solvents are shown below. There are multiple deuterated solvents since molecules have different solubilities, so one molecule may dissolve in deuterated chloroform while others may not.



deuterated chloroform ($CDCl_3$)



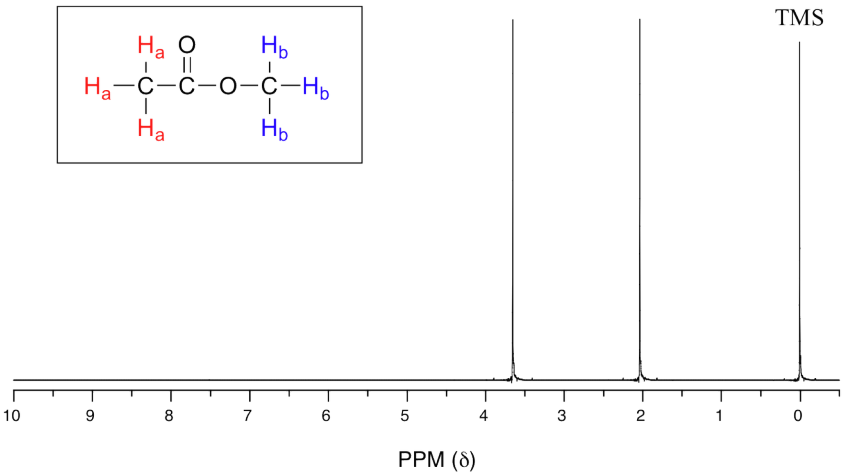
d_6-acetone



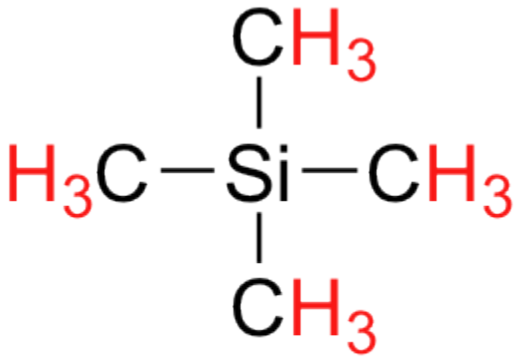
D_2O

The Chemical Shift

Let's look at an actual ^{1}H-NMR plot for methyl acetate. Just as in IR and UV-vis spectroscopy, the vertical axis corresponds to intensity of absorbance, the horizontal axis to frequency (typically the vertical axis is not shown in an NMR spectrum).



We see three absorbance signals: two of these correspond to H_a and H_b, while the peak at the far right of the spectrum corresponds to the 12 chemically equivalent protons in tetramethylsilane (TMS), a standard reference compound that was added to our sample.



tetramethylsilane (TMS)

You may be wondering about a few things at this point - why is TMS necessary, and what is the meaning of the `ppm (δ)` label on the horizontal axis? Shouldn't the frequency units be in Hz? Keep in mind that NMR instruments of many different applied field strengths are used in organic chemistry laboratories, and that the proton's resonance frequency range depends on the strength of the applied field. The spectrum above was generated on an instrument with an applied field of approximately 7.1 Tesla, at which strength protons resonate in the neighborhood of 300 million Hz (chemists refer to this as a 300 MHz instrument). If our colleague in another lab takes the NMR spectrum of the same molecule using an instrument with a 2.4 Tesla magnet, the protons will resonate at around 100 million Hz (so we'd call this a 100 MHz instrument). It would be inconvenient and confusing to always have to convert NMR data according to the field strength of the instrument used. Therefore, chemists report resonance frequencies not as absolute values in Hz, but rather as values *relative to a common standard*, generally the signal generated by the protons in TMS. This is where the ppm – parts per million – term comes in. Regardless of the magnetic field strength of the instrument being used, the resonance frequency of the 12 equivalent protons in TMS is defined as a zero point. The resonance frequencies of protons in the sample molecule are then reported in terms of how much higher they are, in ppm, relative to the TMS signal (almost all protons in organic molecules have a higher resonance frequency than those in TMS, for reasons we shall explore quite soon).

The two proton groups in our methyl acetate sample are recorded as resonating at frequencies 2.05 and 3.67 ppm higher than

TMS. One-millionth (1.0 ppm) of 300 MHz is 300 Hz. Thus 2.05 ppm, on this instrument, corresponds to 615 Hz, and 3.67 ppm corresponds to 1101 Hz. If the TMS protons observed by our 7.1 Tesla instrument resonate at exactly 300,000,000 Hz, this means that the protons in our ethyl acetate samples are resonating at 300,000,615 and 300,001,101 Hz, respectively. Likewise, if the TMS protons in our colleague's 2.4 Tesla instrument resonate at exactly 100 MHz, the methyl acetate protons in her sample resonate at 100,000,205 and 100,000,367 Hz (on the 100 MHz instrument, 1.0 ppm corresponds to 100 Hz). The absolute frequency values in each case are not very useful – they will vary according to the instrument used – but the *difference* in resonance frequency from the TMS standard, expressed in parts per million, should be the same regardless of the instrument.

Expressed this way, the resonance frequency for a given proton in a molecule is called its **chemical shift**. A frequently used symbolic designation for chemical shift in ppm is the lower-case Greek letter *delta* (δ). Most protons in organic compounds have chemical shift values between 0 and 12 ppm from TMS, although values below zero and above 12 are occasionally observed. By convention, the left-hand side of an NMR spectrum (higher chemical shift) is called **downfield**, and the right-hand direction is called **upfield**.

In our methyl acetate example we included for illustrative purposes a small amount of TMS standard directly in the sample, as was the common procedure for determining the zero point with older NMR instruments . That practice is generally no longer necessary, as modern NMR instruments are designed to use the deuterium signal from the solvent as a standard reference point, then to extrapolate the 0 ppm baseline that corresponds to the TMS proton signal (in an applied field of 7.1 Tesla, the deuterium atom in $CDCl_3$ resonates at 32 MHz, compared to 300 MHz for the protons in TMS). In the remaining NMR spectra that we will see in this text we will not see an actual TMS signal, but we can always assume that the 0 ppm point corresponds to where the TMS protons *would* resonate if they were present.

Example

A proton has a chemical shift (relative to TMS) of 4.56 ppm.

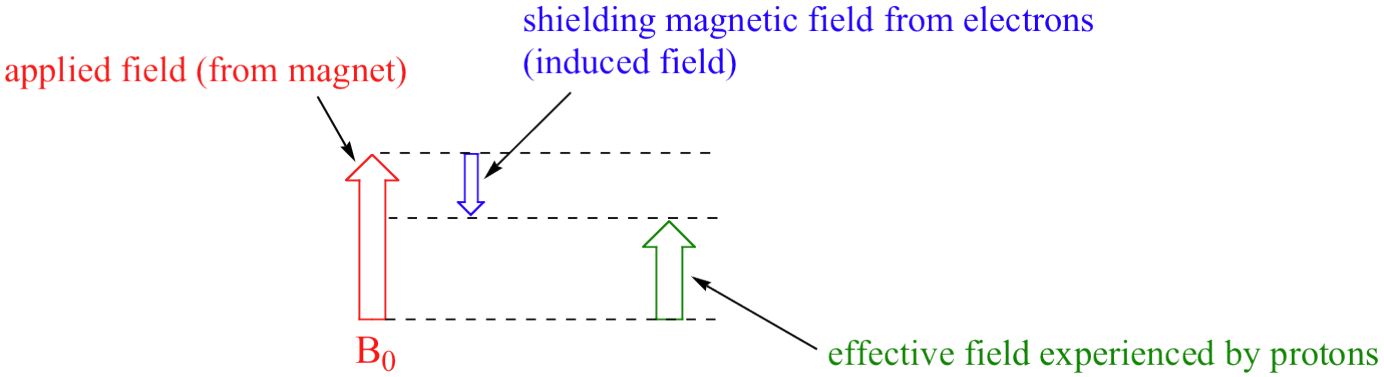
a. a) What is its chemical shift, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?
b. b) What is its resonance frequency, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?

(Assume that in these instruments, the TMS protons resonate at exactly 300 or 200 MHz, respectively)

Solution

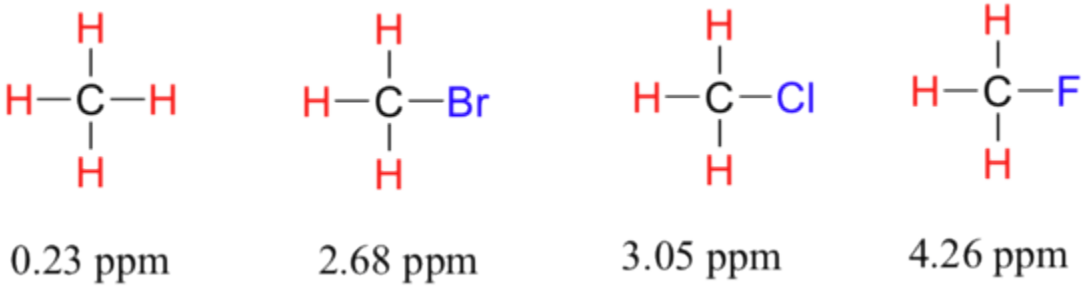
Diamagnetic shielding and deshielding

We come now to the question of *why* nonequivalent protons have different chemical shifts. The chemical shift of a given proton is determined primarily by its immediate electronic environment. Consider the methane molecule (CH_4), in which the protons have a chemical shift of 0.23 ppm. The valence electrons around the methyl carbon, when subjected to B_0, are induced to circulate and thus generate their own very small magnetic field that *opposes* B_0. This **induced field**, to a small but significant degree, *shields* the nearby protons from experiencing the full force of B_0, an effect known as **local diamagnetic shielding**. The methane protons therefore do not experience the full force of B_0 - what they experience is called B_{eff}, or the **effective field**, which is slightly *weaker* than B_0.

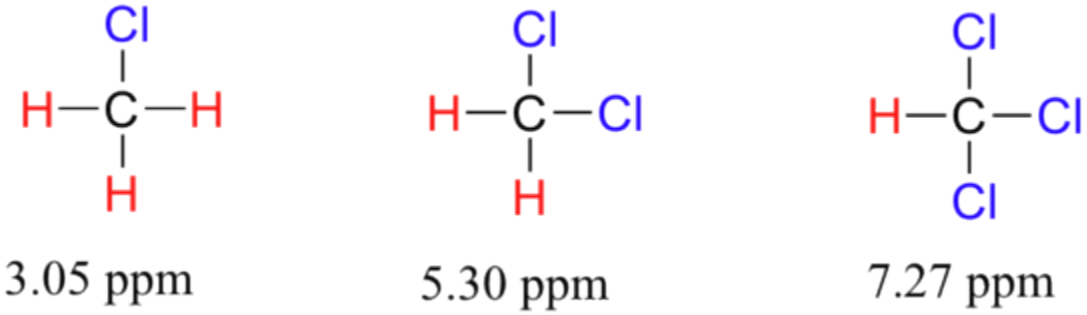


Therefore, their resonance frequency is slightly lower than what it would be if they did not have electrons nearby to shield them.

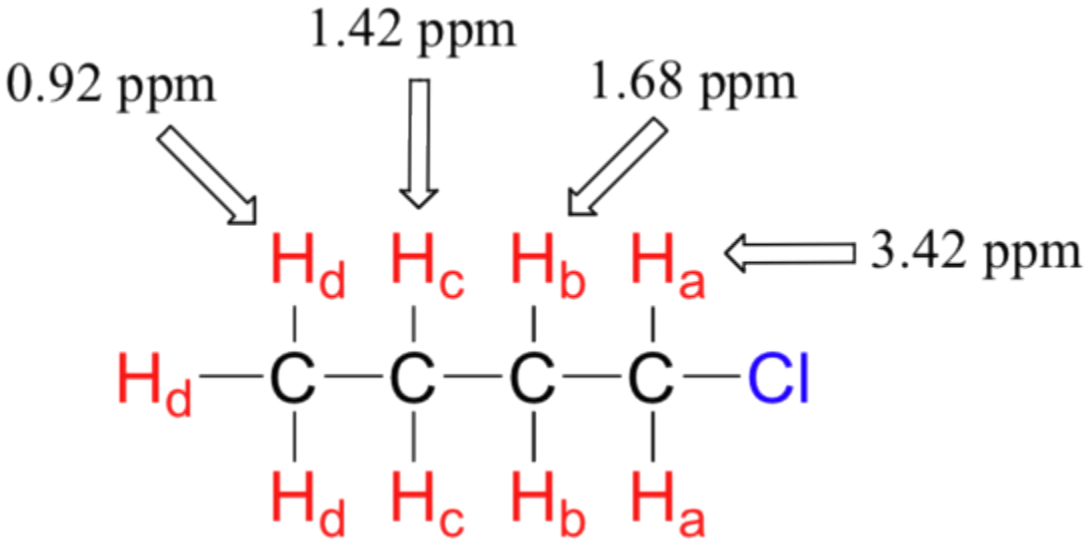
Now consider methyl fluoride, CH_3F, in which the protons have a chemical shift of 4.26 ppm, significantly higher than that of methane. This is caused by something called the **deshielding effect**. Because fluorine is more electronegative than carbon, it pulls valence electrons away from the carbon, effectively *decreasing* the electron density around each of the protons. For the protons, lower electron density means less diamagnetic shielding, which in turn means a greater overall exposure to B_0, a stronger B_{eff}, and a higher resonance frequency. Put another way, the fluorine, by pulling electron density away from the protons, is *deshielding* them, leaving them more exposed to B_0. As the electronegativity of the substituent increases, so does the extent of deshielding, and so does the chemical shift. This is evident when we look at the chemical shifts of methane and three halomethane compounds (remember that electronegativity increases as we move up a column in the periodic table).



To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton. The chemical shift of trichloromethane is, as expected, higher than that of dichloromethane, which is in turn higher than that of chloromethane.



The deshielding effect of an electronegative substituent diminishes sharply with increasing distance:



The presence of an electronegative oxygen, nitrogen, sulfur, or sp^2-hybridized carbon also tends to shift the NMR signals of nearby protons slightly downfield:

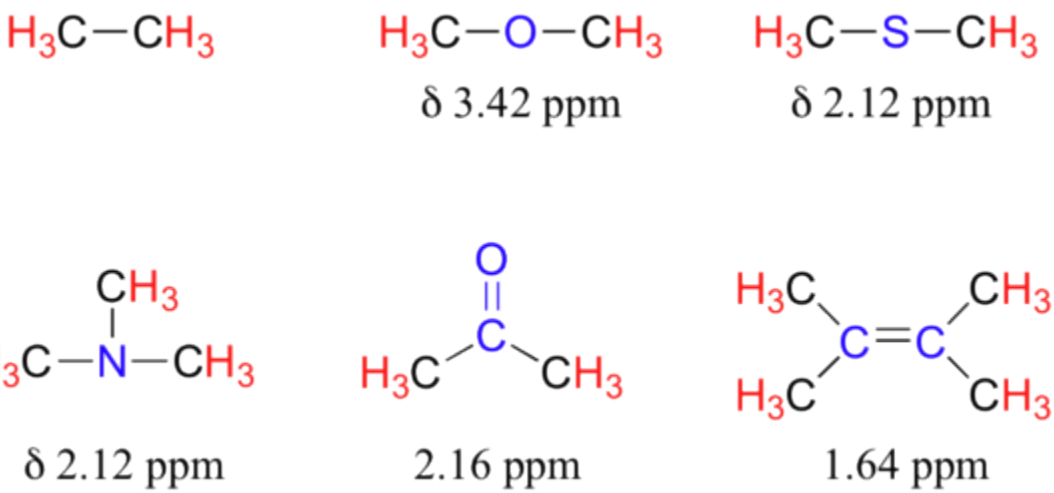
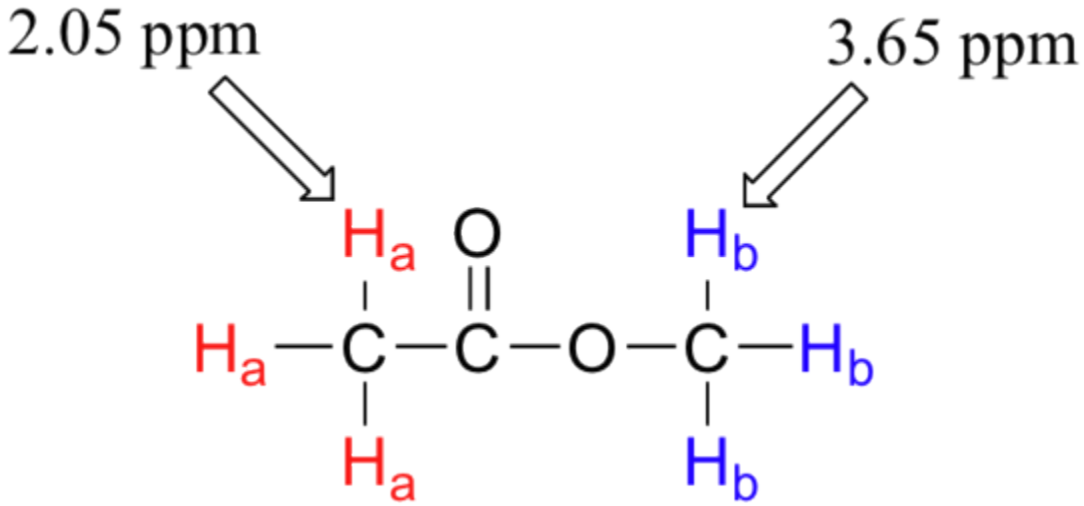
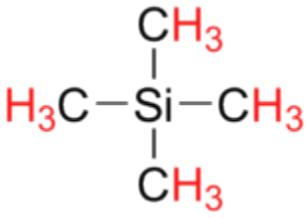


Table 2 lists typical chemical shift values for protons in different chemical environments.

Armed with this information, we can finally assign the two peaks in the the ^{1}H-NMR spectrum of methyl acetate that we saw a few pages back. The signal at 3.65 ppm corresponds to the methyl ester protons (H_b), which are deshielded by the adjacent oxygen atom. The upfield signal at 2.05 ppm corresponds to the acetate protons (H_a), which is deshielded - but to a lesser extent - by the adjacent carbonyl group.



Finally, a note on the use of TMS as a standard in NMR spectroscopy: one of the main reasons why the TMS proton signal was chosen as a zero-point is that the TMS protons are highly shielded: silicon is slightly *less* electronegative than carbon, and therefore *donates* some additional shielding electron density. Very few organic molecules contain protons with chemical shifts that are negative relative to TMS.



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10.5: Tests for Chemical Equivalence

Objectives

After completing this section, you should be able to

- identify those protons which are equivalent in a given chemical structure.
- use the ^{1}H NMR spectrum of a simple organic compound to determine the number of equivalent sets of protons present.

Key Terms

Make certain that you can define, and use in context, the key terms below.

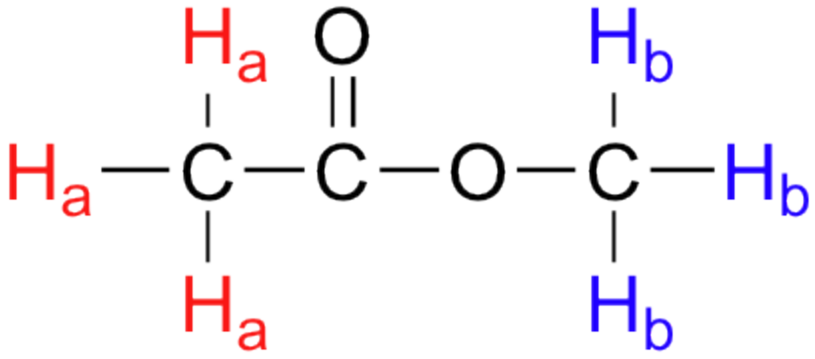
- diastereotopic
- enantiotopic
- homotopic

Study Notes

It is important at this stage to be able to identify equivalent protons in any organic compound given the structure of that compound. Once you know the number of different groups of equivalent protons in a compound, you can predict the number (before coupling) and relative strength of signals. Look at the following examples and make sure you understand how the number and intensity ratio of signals are derived from the structure shown.

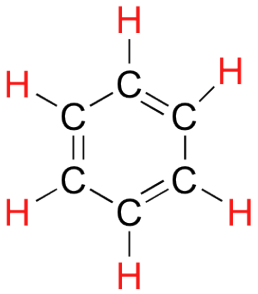
Structure	**Number of Signals**	**Ratio of Signals**	
CH3OCH2CH2Br	3	A : B : C	3 : 2 : 2
cyclopentane	1		
2,2-dimethyloxetane	3	A : B : C	2 : 2 : 6 (or 1 : 1 : 3)
1,3-cyclohexadiene	3	A : B : C	2 : 4 : 2 (or 1 : 2 : 1)
1-methoxy-2-butanone	4	A : B : C : D	3 : 2 : 2 : 3
3-methylpyridine	5	A : B : C : D : E	3 : 1 : 1 : 1 : 1

Proton equivalence in proton NMR refers to the concept that not all hydrogen atoms in a molecule produce distinct signals in the NMR spectrum. Instead, chemically equivalent protons, meaning those that occupy identical environments within a molecule, yield the same NMR signal. This concept is essential for interpreting NMR spectra accurately. Chemical equivalence is determined by the molecular structure and symmetry of a molecule. If all protons in all organic molecules had the same resonance frequency in an external magnetic field of a given strength, the information in the previous paragraph would be interesting from a theoretical standpoint, but would not be terribly useful to organic chemists. Fortunately for us, however, resonance frequencies are not uniform for all protons in a molecule. *In an external magnetic field of a given strength, protons in different locations in a molecule have different resonance frequencies, because they are in non-identical electronic environments.* In methyl acetate, for example, there are two 'sets' of protons. The three protons labeled H_a have a different - and easily distinguishable – resonance frequency than the three H_b protons, because the two sets of protons are in non-identical environments: they are, in other words, chemically nonequivalent.

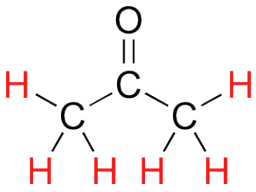


On the other hand, the three H_a protons are all in the same electronic environment, and are chemically equivalent to one another. They have identical resonance frequencies. The same can be said for the three H_b protons. These protons are considered to be homotopic. Homotopic protons are chemically identical, so electronically equivalent, thus show up as identical NMR absorptions.

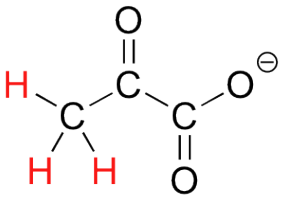
The ability to recognize chemical equivalency and nonequivalency among atoms in a molecule will be central to understanding NMR. In each of the molecules below, all protons are chemically equivalent, and therefore will have the same resonance frequency in an NMR experiment.



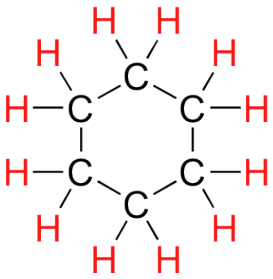
benzene



acetone



pyruvate



cyclohexane

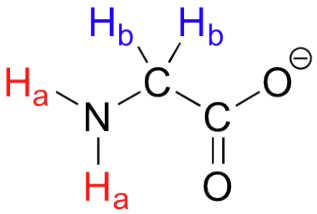
You might expect that the equatorial and axial hydrogens in cyclohexane would be non-equivalent, and would have different resonance frequencies. In fact, an axial hydrogen *is* in a different electronic environment than an equatorial hydrogen. Remember, though, that the molecule rotates rapidly between its two chair conformations, meaning that any given hydrogen is rapidly moving back and forth between equatorial and axial positions. It turns out that, except at extremely low temperatures, this rotational motion occurs on a time scale that is much faster than the time scale of an NMR experiment.



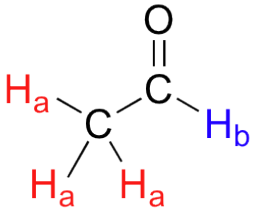
ring-flip process is *fast* compared to the NMR time-scale

In this sense, NMR is like a camera that takes photographs of a rapidly moving object with a slow shutter speed - the result is a blurred image. In NMR terms, this means that all 12 protons in cyclohexane are equivalent.

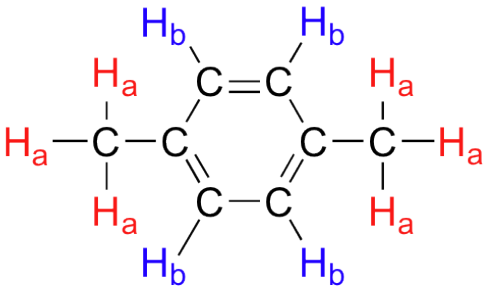
Each the molecules in the next figure contains *two* sets of protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



glycine



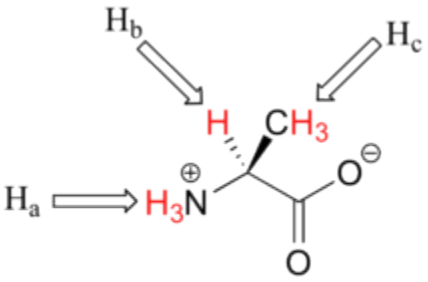
acetaldehyde



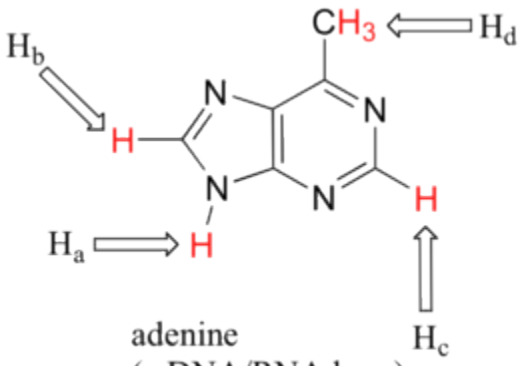
para-xylene

Notice how the symmetry of *para*-xylene results in there being only two different sets of protons.

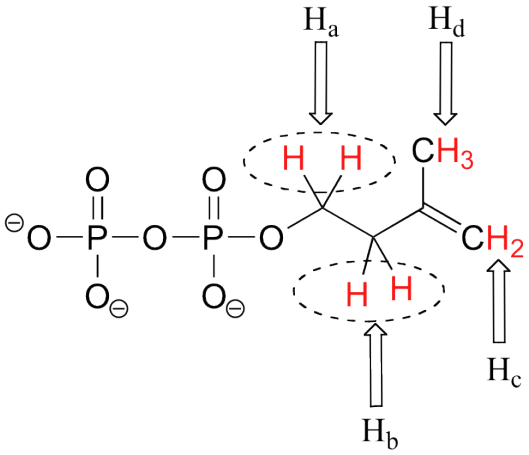
Most organic molecules have several sets of protons in different chemical environments, and each set, in theory, will have a different resonance frequency in ^{1}H-NMR spectroscopy.



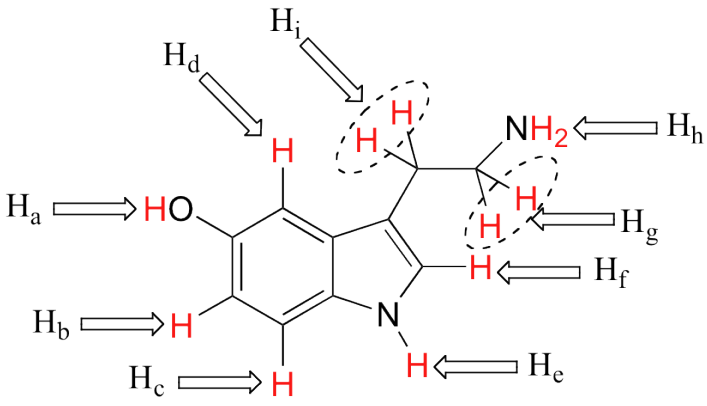
alanine
(an amino acid)



adenine
(a DNA/RNA base)

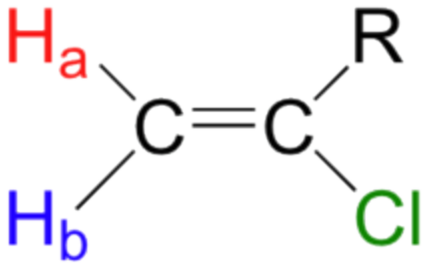


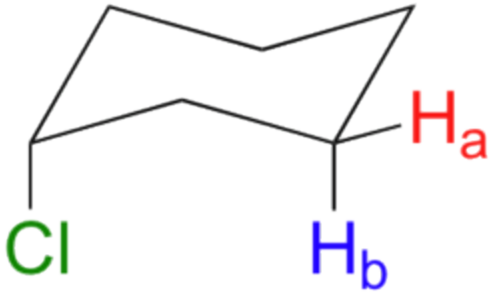
isopentenyl diphosphate
(a lipid building block)



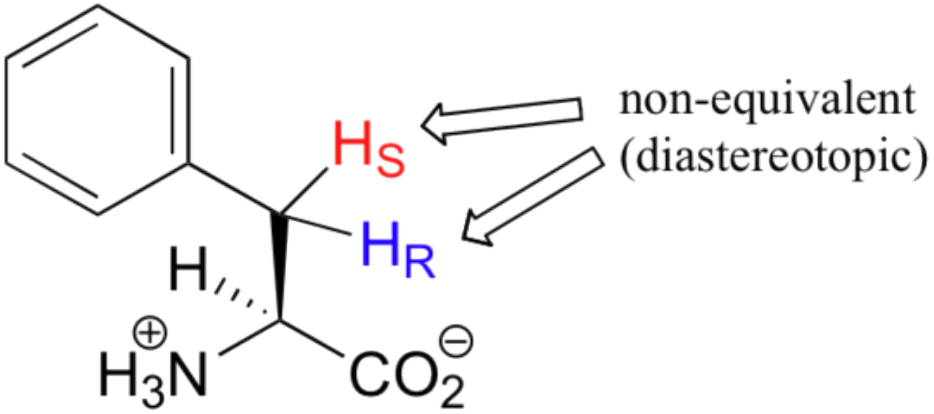
seratonin (a neurotransmitter)

When stereochemistry is taken into account, the issue of equivalence vs nonequivalence in NMR starts to get a little more complicated. It should be fairly intuitive that hydrogens on different sides of asymmetric ring structures and double bonds are in different electronic environments, and thus are non-equivalent and have different resonance frequencies. In the alkene and cyclohexene structures below, for example, H_a is *trans* to the chlorine substituent, while H_b is *cis* to chlorine.



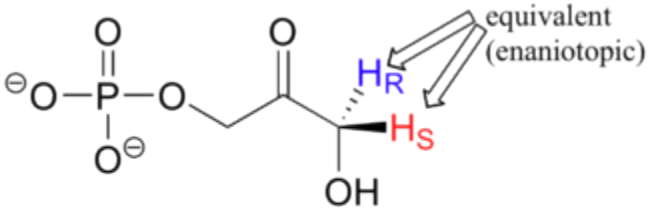


What is not so intuitive is that diastereotopic hydrogens (section 3.10) on chiral molecules are also non-equivalent:

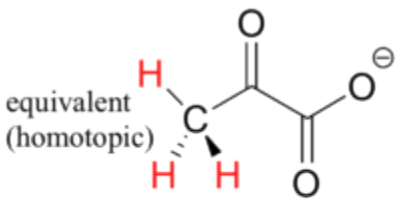


phenylalanine

However, enantiotopic and homotopic hydrogens are chemically equivalent. To determine if protons are homotopic or enantiotopic, you can do a thought experiment by replacing one H with X followed by the other H by X. In pyruvate below, if you replace any of the Hs with an X, then you would get the same molecule. These protons are homotopic. In dihydroxyacetone phosphate, this is not quite the case. If you exchange H_R for X, then you would create a stereocenter with R configuration. If you exchange H_S for X, then you would create a stereocenter with S configuration. The two "new molecules" would have the relationship of being enantiomers. Therefore H_R and H_S are enantiotopic protons. The only way these protons will show up different under NMR experimental conditions would be if you used a solvent that was chiral. Since most common solvents are all achiral, the enantiotopic protons are NMR equivalent and will show up as if they were the same proton.



dihydroxyacetone phosphate

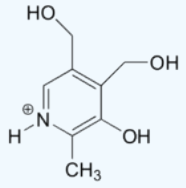


pyruvate

Example 13.6.1

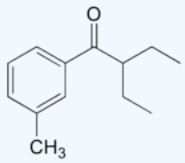
How many different sets of protons do the following molecules contain? (count diastereotopic protons as non-equivalent).

a)



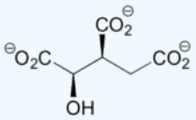
pyridoxine
(vitamin B_6)

b)



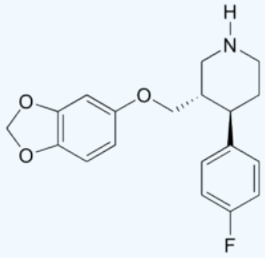
DEET
(an insect repellent)

c)



isocitrate
(a citric acid cycle intermediate)

d)



paroxetine
(an antianxietry drug, trade name Paxil)

Solution

Exercise 10.5.1

How many non-equivalent hydrogen are in the following molecules; how many different signals will you see in a H^1 NMR spectrum.

a. $CH_3CH_2CH_2Br$
b. $CH_3OCH_2C(CH_3)_3$
c. Ethyl Benzene
d. 2-methyl-1-hexene

Answer available at the end of this section.

Answers

Exercise 10.5.1

A. 3; B. 3; C. 5; D. 7

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10.6: Integration

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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10.7: Spin-Spin Splitting: The Effect of Nonequivalent Neighboring Hydrogens

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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10.8: Spin-Spin Splitting: Some Complications

Objectives

After completing this section, you should be able to

- explain how multiple coupling can give rise to complex-looking ^{1}H NMR spectra.
- predict the splitting pattern expected in the ^{1}H NMR spectrum of an organic compound in which multiple coupling is possible.
- interpret ^{1}H NMR spectra in which multiple coupling is evident.

Key Terms

Make certain that you can define, and use in context, the key term below.

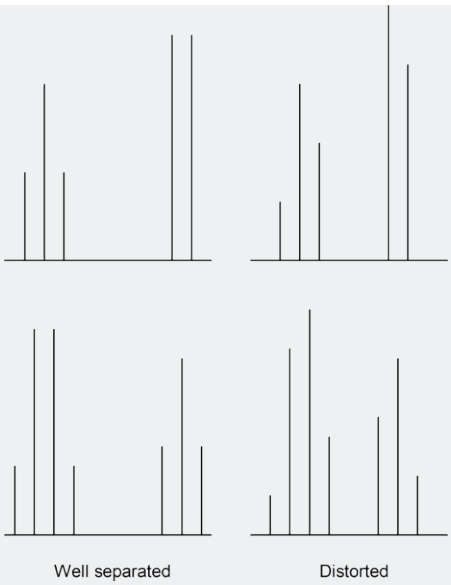
- tree diagram

Study Notes

We saw the effects of spin-spin coupling on the appearance of a ^{1}H NMR signal. These effects can be further complicated when that signal is coupled to several different protons. For example, $BrCH_2CH_2CH_2Cl$ would produce three signals. The hydrogens at C_1 and C_3 would each be triplets because of coupling to the two hydrogens on C_2. However, the hydrogen on C_2 "sees" two different sets of neighboring hydrogens, and would therefore produce a triplet of triplets.

Another effect that can complicate a spectrum is the "closeness" of signals. If signals accidently overlap they can be difficult to identify. In the example above, we expected a triplet of triplets. However, if the coupling is identical (or almost identical) between the hydrogens on C_2 and the hydrogens on both C_1 and C_3, one would observe a quintet in the ^{1}H NMR spectrum. [You can try this yourself by drawing a tree diagram of a triplet of triplets assuming, first, different coupling constants, and then, identical coupling constants.] Keep this point in mind when interpreting real ^{1}H NMR spectra.

Also, when multiplets are well separated, they form patterns. However, when multiplets approach each other in the spectrum they sometimes become distorted. Usually, the inner peaks become larger than the outer peaks. Note the following examples:



Aromatic ring protons quite commonly have overlapping signals and multiplet distortions. Sometimes you cannot distinguish between individual signals, and one or more messy multiplets often appear in the aromatic region.

It is much easier to rationalize the observed ^{1}H NMR spectrum of a known compound than it is to determine the structure of an unknown compound from its ^{1}H NMR spectrum. However, rationalizations can be a useful learning technique as you try to improve your proficiency in spectral interpretation. Remember that when a chemist tries to interpret the ^{1}H NMR spectrum of an unknown compound, he or she usually has additional information available to make the task easier. For example, the chemist will almost certainly have an infrared spectrum of the compound and possibly a mass spectrum too. Details of how the compound was synthesized may be available, together with some indication of its chemical properties, its physical properties, or both.

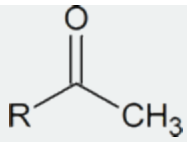
In examinations, you will be given a range of information (IR, MS, UV data and empirical formulae) to aid you with your structural determination using ^{1}H NMR spectroscopy. For example, you may be asked to determine the structure of $C_6H_{12}O$ given the following spectra:

Infrared spectrum: 3000 cm^{-1} and 1720 cm^{-1} absorptions are both strong

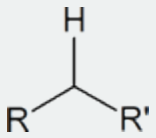
^{1}H NMR

δ (ppm)	Protons	Multiplicity
0.87	6	doublet
1.72	1	broad multiplet
2.00	3	singlet
2.18	2	doublet

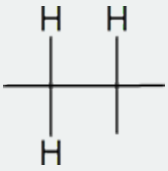
To answer this question, you note that the infrared spectrum of $C_6H_{12}O$ shows $\mathrm{C{-}H}$ stretching (3000 cm^{-1}) and $\mathrm{C{-}O}$ stretching (1720 cm^{-1}). Now you have to piece together the information from the ^{1}H NMR spectrum. Notice the singlet with three protons at 2.00 ppm. This signal indicates a methyl group that is not coupled to other protons. It could possibly mean the presence of a methyl ketone functional group.



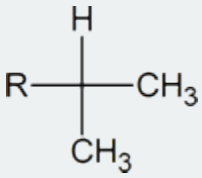
The signal at 1.72 ppm is a broad multiplet, suggesting that a carbon with a single proton is beside carbons with several different protons.



The doublet signal at 2.18 ppm implies that a $-CH_2-$ group is attached to a carbon having only one proton.

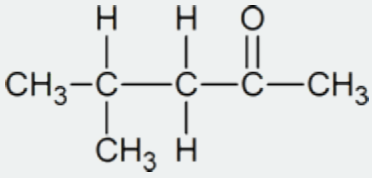


The six protons showing a doublet at 0.87 ppm indicate two equivalent methyl groups attached to a carbon with one proton.



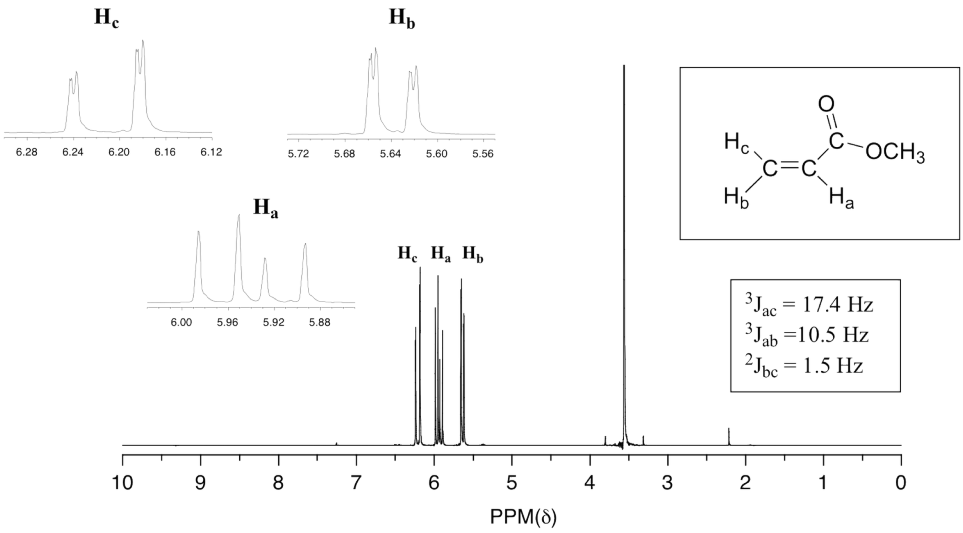
Whenever you see a signal in the 0.7-1.3 ppm range that is a multiplet of three protons (3, 6, 9) it is most likely caused by equivalent methyl groups.

Using trial and error, and with the above observations, you should come up with the correct structure.

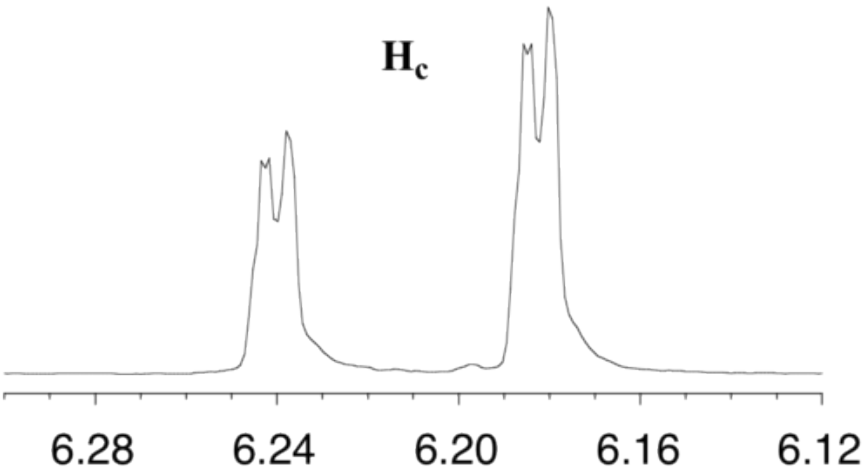


Complex Coupling

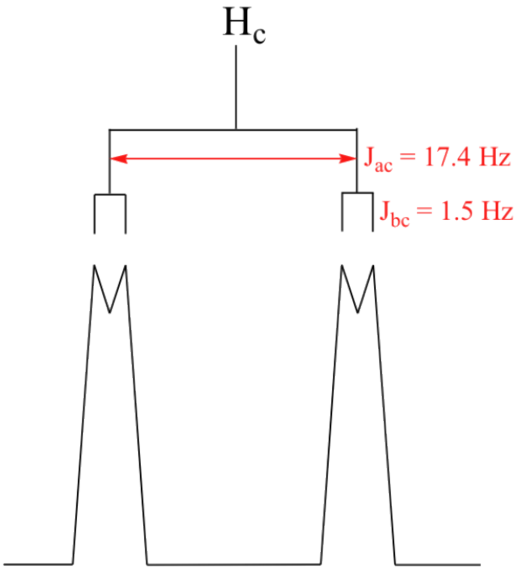
In all of the examples of spin-spin coupling that we have seen so far, the observed splitting has resulted from the coupling of one set of hydrogens to *just one* neighboring set of hydrogens. When a set of hydrogens is coupled to *two or more* sets of nonequivalent neighbors, the result is a phenomenon called **complex coupling**. A good illustration is provided by the ^{1}H-NMR spectrum of methyl acrylate:



First, let's first consider the H_c signal, which is centered at 6.21 ppm. Here is a closer look:

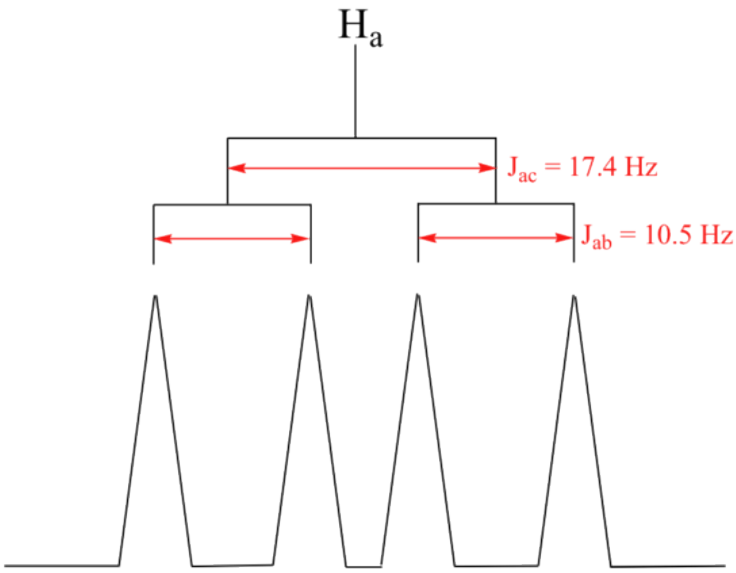


With this enlargement, it becomes evident that the Hc signal is actually composed of four sub-peaks. Why is this? H_c is coupled to both H_a and H_b , but with *two different coupling constants*. Once again, a splitting diagram (or tree diagram) can help us to understand what we are seeing. H_a is *trans* to H_c across the double bond, and splits the H_c signal into a doublet with a coupling constant of $^3J_{ac}$ = 17.4 Hz. In addition, each of these H_c doublet sub-peaks is split again by H_b (*geminal* coupling) into two more doublets, each with a much smaller coupling constant of $^2J_{bc}$ = 1.5 Hz.

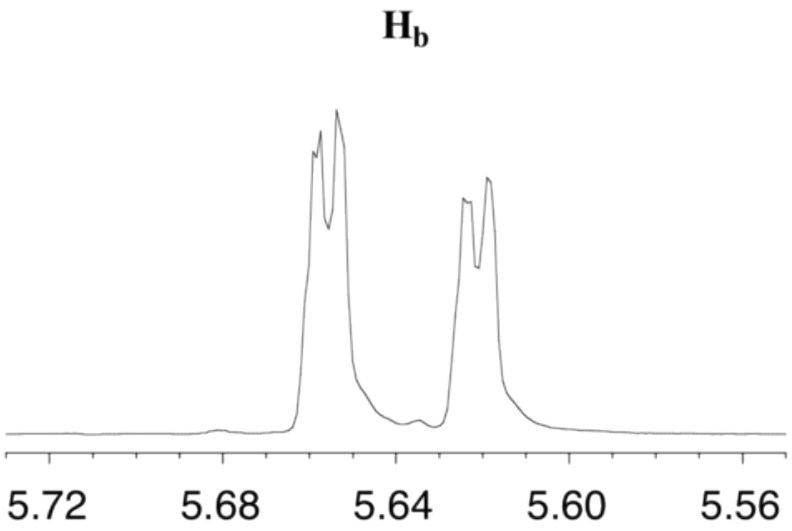


The result of this `double splitting` is a pattern referred to as a **doublet of doublets**, abbreviated `**dd**`.

The signal for H_a at 5.95 ppm is also a doublet of doublets, with coupling constants $^3J_{ac}$= 17.4 Hz and $^3J_{ab}$ = 10.5 Hz.



The signal for H_b at 5.64 ppm is split into a doublet by H_a, a *cis* coupling with $^3J_{ab}$ = 10.4 Hz. Each of the resulting sub-peaks is split again by H_c, with the same *geminal* coupling constant $^2J_{bc}$ = 1.5 Hz that we saw previously when we looked at the H_c signal. The overall result is again a doublet of doublets, this time with the two `sub-doublets` spaced slightly closer due to the smaller coupling constant for the *cis* interaction. Here is a blow-up of the actual $H_b$signal:



Example 10.8.1

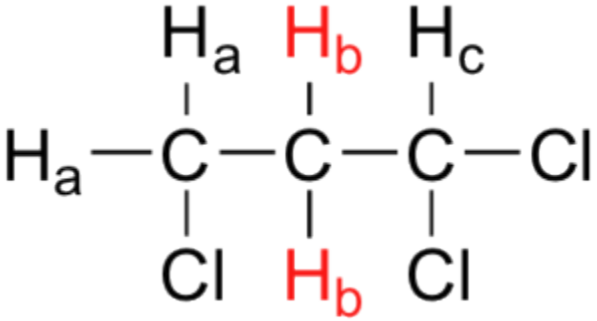
Construct a splitting diagram for the H_b signal in the ^{1}H-NMR spectrum of methyl acrylate. Show the chemical shift value for each sub-peak, expressed in Hz (assume that the resonance frequency of TMS is exactly 300 MHz).

Solution

Note

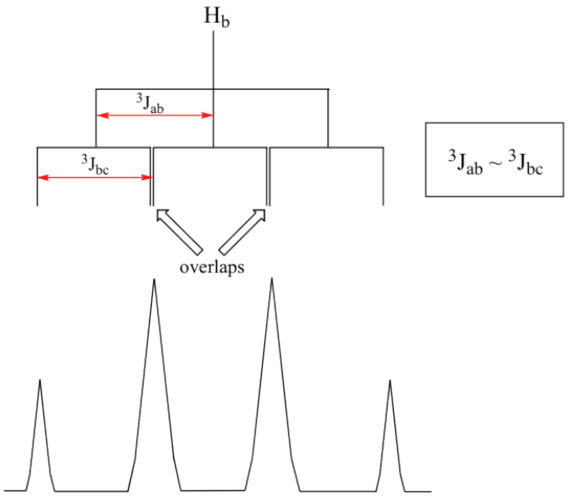
When constructing a splitting diagram to analyze complex coupling patterns, it is usually easier to show the larger splitting first, followed by the finer splitting (although the reverse would give the same end result).

When a proton is coupled to two different neighboring proton sets with identical or very close coupling constants, the splitting pattern that emerges often appears to follow the simple `*n* + 1 rule` of non-complex splitting. In the spectrum of 1,1,3-trichloropropane, for example, we would expect the signal for H_b to be split into a triplet by H_a, and again into doublets by H_c, resulting in a 'triplet of doublets'.

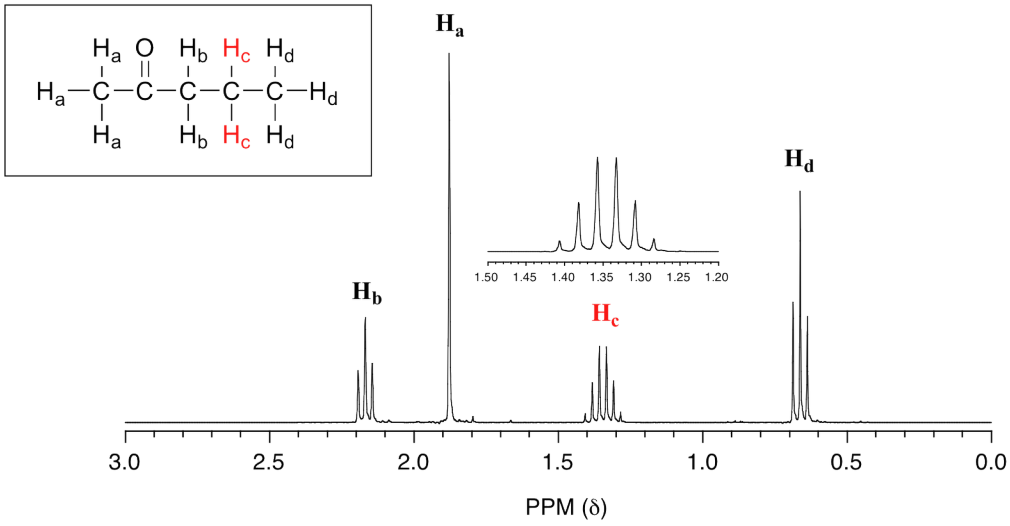


$$^3J_{ab} \sim {}^3J_{bc}$$

H_a and H_c are not equivalent (their chemical shifts are different), but it turns out that $^3J_{ab}$ is very close to $^3J_{bc}$. If we perform a splitting diagram analysis for H_b, we see that, due to the overlap of sub-peaks, the signal appears to be a quartet, and for all intents and purposes follows the *n* + 1 rule.

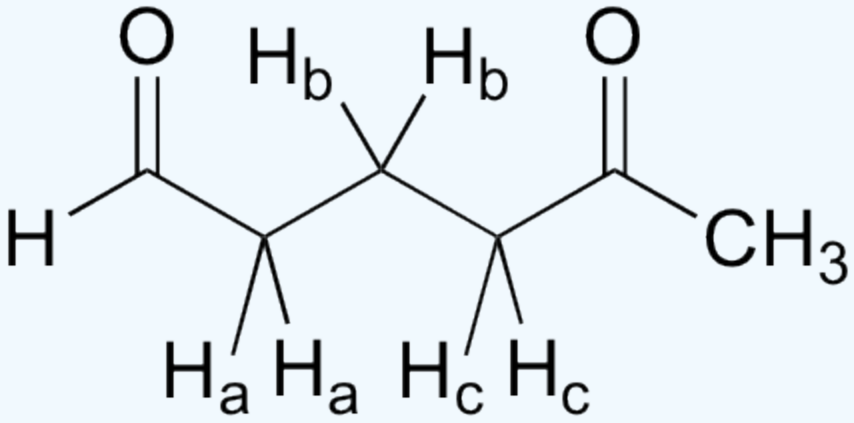


For similar reasons, the H_c peak in the spectrum of 2-pentanone appears as a sextet, split by the five combined H_b and H_d protons. Technically, this 'sextet' could be considered to be a 'triplet of quartets' with overlapping sub-peaks.



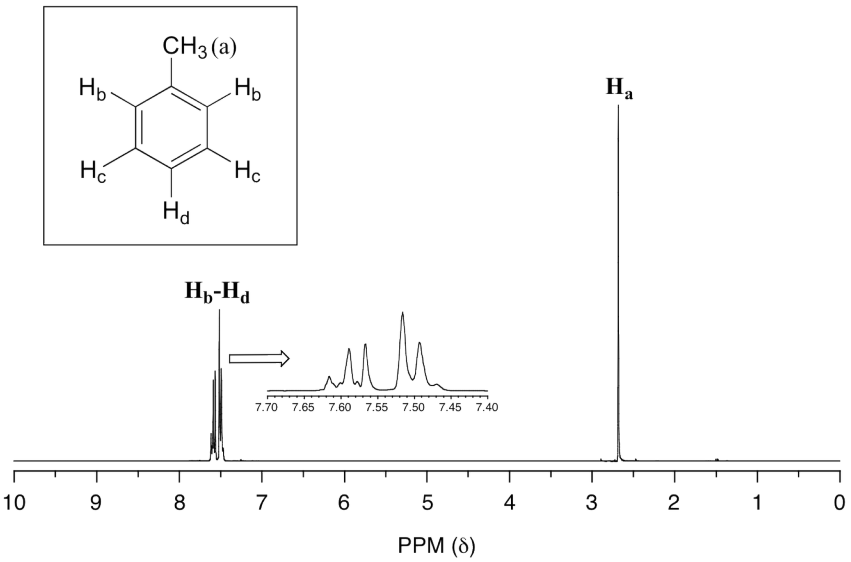
Example 10.8.2

What splitting pattern would you expect for the signal corresponding to H_b in the molecule below? Assume that $J_{ab} \sim J_{bc}$. Draw a splitting diagram for this signal, and determine the relative integration values of each subpeak.



Solution

In many cases, it is difficult to fully analyze a complex splitting pattern. In the spectrum of toluene, for example, if we consider only 3-bond coupling we would expect the signal for H_b to be a doublet, H_d a triplet, and H_c a triplet.



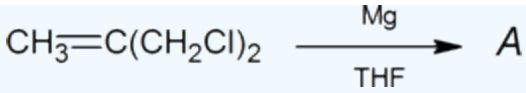
In practice, however, all three aromatic proton groups have very similar chemical shifts and their signals overlap substantially, making such detailed analysis difficult. In this case, we would refer to the aromatic part of the spectrum as a **multiplet**.

When we start trying to analyze complex splitting patterns in larger molecules, we gain an appreciation for why scientists are willing to pay large sums of money (hundreds of thousands of dollars) for higher-field NMR instruments. Quite simply, the stronger our magnet is, the more resolution we get in our spectrum. In a 100 MHz instrument (with a magnet of approximately 2.4 Tesla field strength), the 12 ppm frequency 'window' in which we can observe proton signals is 1200 Hz wide. In a 500 MHz (~12 Tesla) instrument, however, the window is 6000 Hz - five times wider. In this sense, NMR instruments are like digital cameras and HDTVs: better resolution means more information and clearer pictures (and higher price tags!)

Exercise 10.8.1

Draw the structures of compound given the information.

An unknown compound *A* was prepared as follows:



Mass spectrum

base peak *m/e* = 39
parent peak *m/e* = 54

^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
1.0	2	triplet
5.4	1	quintet

Answer available at the end of this section.

Exercise 10.8.2

Draw the structures of compound given the information.

Unknown compound *B* has the molecular formula $C_7H_6O_2$.

Infrared spectrum

3200 cm^{-1} (broad) and 1747 cm^{-1} (strong) absorptions

^{1}H NMR spectrum

δ (ppm)	Protons
6.9	2
7.4	2
9.8	1
10.9	1

Hint: Aromatic ring currents deshield all proton signals just outside the ring.

Answer available at the end of this section.

Exercise 10.8.3

Draw the structures of compound given the information.

Unknown compound *C* shows no evidence of unsaturation and contains only carbon and hydrogen.

Mass spectrum

parent peak *m/e* = 68

^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
1.84	3	triplet
2.45	1	septet

Hint: Think three dimensionally!

Answer available at the end of this section.

Exercise 10.8.4

Draw the structures of compound given the information.

Unknown compound *D* ($C_{15}H_{14}O$) has the following spectral properties.

Infrared spectrum

3010 cm^{-1} (medium)
1715 cm^{-1} (strong)
1610 cm^{-1} (strong)
1500 cm^{-1} (strong)

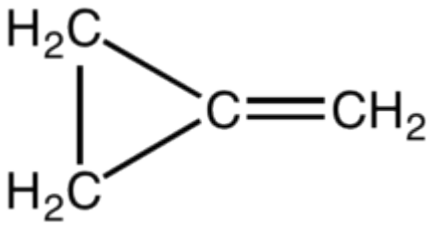
^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
3.00	2	triplet
3.07	2	triplet
7.1-7.9	10	Multiplets

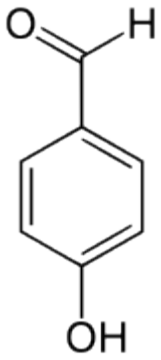
Answer available at the end of this section.

Answers

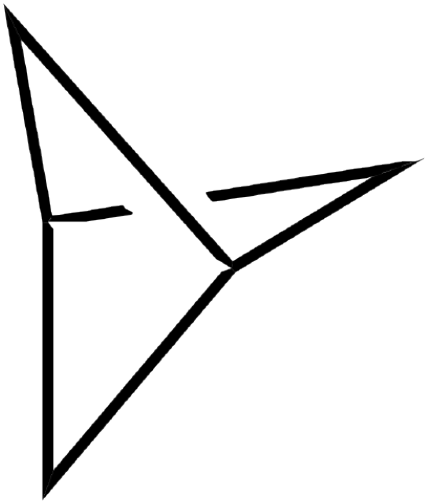
Exercise 10.8.1



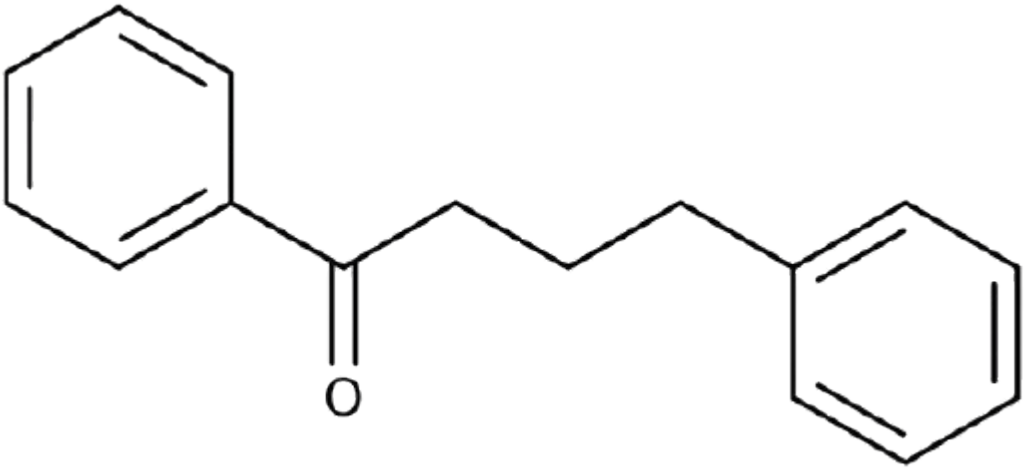
Exercise 10.8.2



Exercise 10.8.3



Exercise 10.8.4



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10.9: Carbon-13 Nuclear Magnetic Resonance

Objectives

After completing this section, you should be able to

- Determine the number of distinct C atoms in a molecule.
- Use the chemical shifts table to determine functional groups present in a molecule.
- Assign a chemical shift to each carbon in a given molecule.

The Basics of ^{13}C-NMR spectroscopy

Unlike ^{1}H-NMR signals, the area under a ^{13}C-NMR signal cannot be used to determine the number of carbons to which it corresponds. This is because the signals for some types of carbons are inherently weaker than for other types – peaks corresponding to carbonyl carbons, for example, are much smaller than those for methyl or methylene (CH_2) peaks. Peak integration is generally not useful in ^{13}C-NMR spectroscopy, except when investigating molecules that have been enriched with ^{13}C isotope.

The resonance frequencies of ^{13}C nuclei are lower than those of protons in the same applied field - in a 7.05 Tesla instrument, protons resonate at about 300 MHz, while carbons resonate at about 75 MHz. This is fortunate, as it allows us to look at ^{13}C signals using a completely separate 'window' of radio frequencies. This means you will only see the ^{13}C nuclei in a ^{13}C NMR experiment like in the ^{1}H NMR experiments we just looked at, we only saw hydrogens. Just like in ^{1}H-NMR, the standard used in ^{13}C-NMR experiments to define the 0 ppm point is tetramethylsilane (TMS), although of course in ^{13}C-NMR it is the signal from the four equivalent *carbons* in TMS that serves as the standard. Chemical shifts for ^{13}C nuclei in organic molecules are spread out over a much wider range than for protons – up to 200 ppm for ^{13}C compared to 12 ppm for protons (see Table 3 for a list of typical ^{13}C-NMR chemical shifts). This is also fortunate, because it means that the signal from each carbon in a compound can almost always be seen as a distinct peak, without the overlapping that often plagues ^{1}H-NMR spectra. The chemical shift of a ^{13}C nucleus is influenced by essentially the same factors that influence a proton's chemical shift: bonds to electronegative atoms and diamagnetic anisotropy effects tend to shift signals downfield (higher resonance frequency). In addition, sp^2 hybridization results in a large downfield shift. The ^{13}C-NMR signals for carbonyl carbons are generally the furthest downfield (170-220 ppm), due to both sp^2 hybridization and to the double bond to oxygen.

Example 10.9.1

a. How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 5.1?
b. How many sets of non-equivalent carbons are there in:
    - toluene
    - 2-pentanone
    - para-xylene
    - triclosan

(all structures are shown earlier in this chapter)

Solution

a

a) 8 signals (each carbon is different)

b) 11 signals (the two enantiotopic CH_2CH_3 groups are NMR-equivalent)

c) 6 signals (each carbon is different)

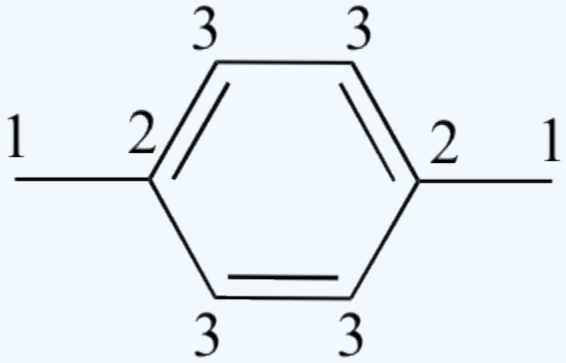
d) 16 signals (the fluorobenzene group only contributes 4 signals due to symmetry)

b

a) 5 signals

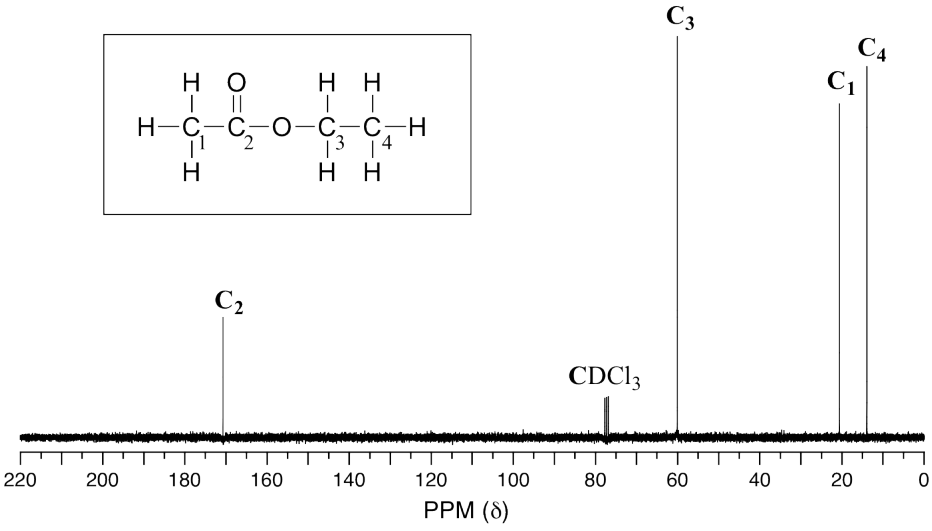
b) 5 signals

c) 3 signals

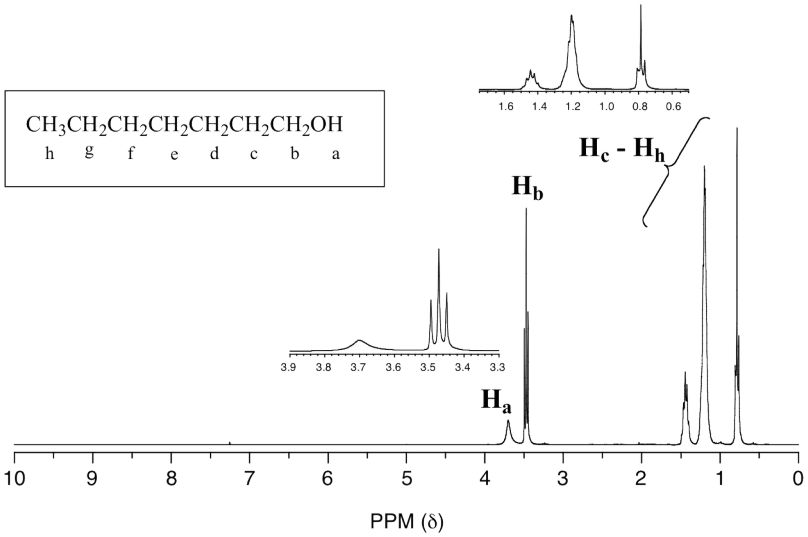


d) 6 signals

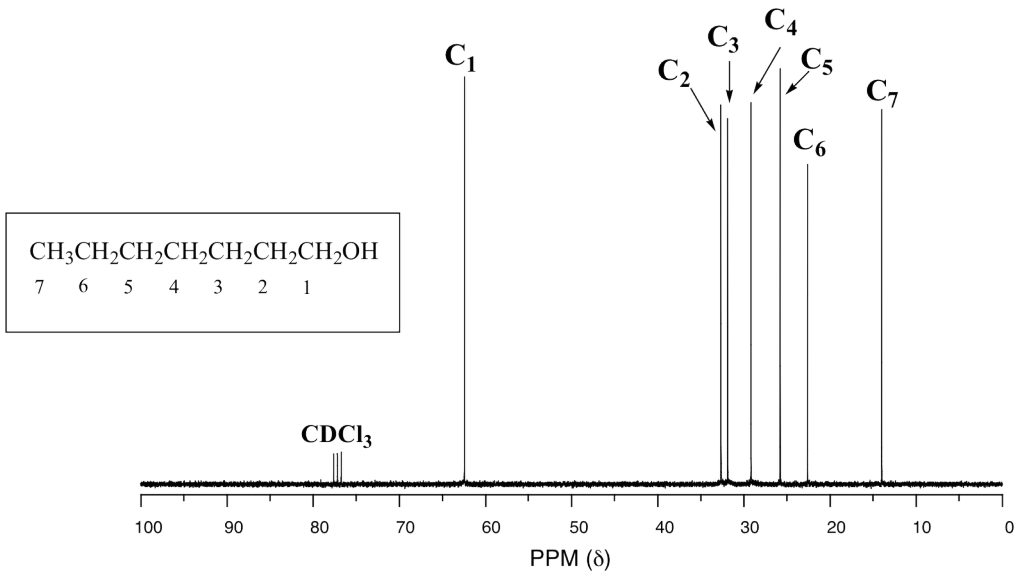
Because of the low natural abundance of ^{13}C nuclei, it is very unlikely to find two ^{13}C atoms near each other in the same molecule, and thus *we do not see spin-spin coupling between neighboring carbons in a ^{13}C-NMR spectrum*. There is, however, **heteronuclear coupling** between ^{13}C carbons and the hydrogens to which they are bound. Carbon-proton coupling constants are very large, on the order of 100 – 250 Hz. For clarity, chemists generally use a technique called **broadband decoupling**, which essentially 'turns off' C-H coupling, resulting in a spectrum in which all carbon signals are singlets. Below is the proton-decoupled ^{13}C-NMR spectrum of ethyl acetate, showing the expected four signals, one for each of the carbons.



One of the greatest advantages of ^{13}C-NMR compared to ^{1}H-NMR is the breadth of the spectrum - recall that carbons resonate from 0-220 ppm relative to the TMS standard, as opposed to only 0-12 ppm for protons. Because of this, ^{13}C signals rarely overlap, and we can almost always distinguish separate peaks for each carbon, even in a relatively large compound containing carbons in very similar environments. In the proton spectrum of 1-heptanol, for example, only the signals for the alcohol proton (H_a) and the two protons on the adjacent carbon (H_b) are easily analyzed. The other proton signals overlap, making analysis difficult.



In the ^{13}C spectrum of the same molecule, however, we can easily distinguish each carbon signal, and we know from this data that our sample has seven non-equivalent carbons. (Notice also that, as we would expect, the chemical shifts of the carbons get progressively smaller as they get farther away from the deshielding oxygen.)



This property of ^{13}C-NMR makes it very helpful in the elucidation of larger, more complex structures.

^{13}C NMR Chemical Shifts

The Carbon NMR is used for determining functional groups using characteristic shift values. ^{13}C chemical shifts are greatly affected by electronegative effects. If a H atom in an alkane is replaced by substituent X, electronegative atoms (O, N, halogen),

^{13}C signals for nearby carbons shift downfield (left; increase in ppm) with the effect diminishing with distance from the electron withdrawing group. Figure 13.11.1 shows typical ^{13}C chemical shift regions of the major chemical class.

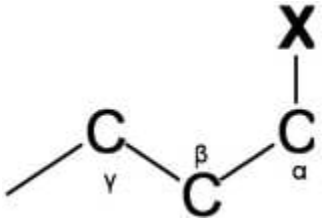


Fig9.bmp

Figure 10.9.1: ^{13}C Chemical shift range for organic compound

Spin-Spin Splitting

Comparing the ^{1}H NMR, there is a big difference thing in the ^{13}C NMR. The ^{13}C-^{13}Cspin-spin splitting rarely exit between adjacent carbons because ^{13}C is naturally lower abundant (1.1%)

- **^{13}C-^{1}H Spin coupling**: ^{13}C-^{1}H Spin coupling provides useful information about the number of protons attached a carbon atom. In case of one bond coupling ($^{1}J_{CH}$), -CH, -CH_2, and CH_3 have respectively doublet, triplet, quartets for the ^{13}C resonances in the spectrum. However, ^{13}C-^{1}H Spin coupling has an disadvantage for ^{13}C spectrum interpretation. ^{13}C-^{1}H Spin coupling is hard to analyze and reveal structure due to a forest of overlapping peaks that result from 100% abundance of ^{1}H.
- **Decoupling**: Decoupling is the process of removing ^{13}C-^{1}H coupling interaction to simplify a spectrum and identify which pair of nuclei is involved in the J coupling. The decoupling ^{13}C spectra shows only one peak(singlet) for each unique carbon in the molecule (Fig 13.11.2). Decoupling is performed by irradiating at the frequency of one proton with continuous low-power RF.

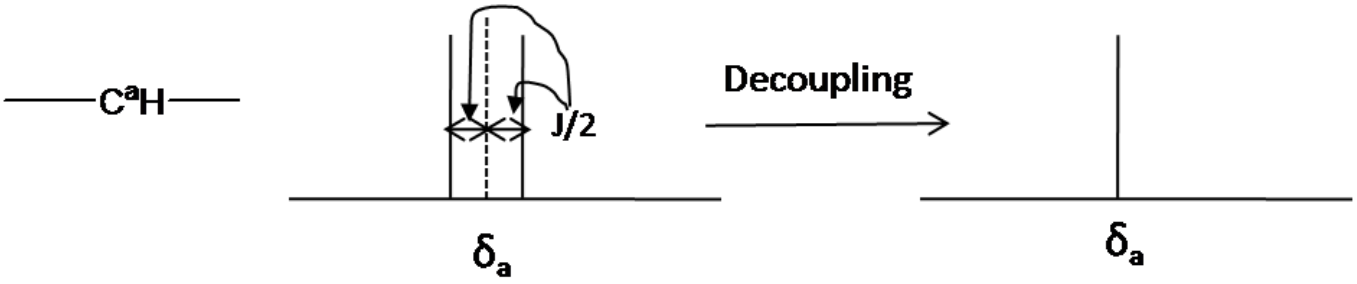


Figure 10.9.2: Decoupling in the ^{13}C NMR

Summary

^{13}C NMR (Carbon-13 Nuclear Magnetic Resonance) Spectroscopy is a powerful analytical technique used to study the structure and connectivity of organic molecules. Unlike proton NMR, which detects hydrogen nuclei, ^{13}C NMR specifically targets the carbon nuclei within a molecule. In ^{13}C NMR spectroscopy, carbon atoms resonate at characteristic frequencies based on their local chemical environment, which is influenced by neighboring atoms and functional groups. These resonances appear as peaks in the NMR spectrum, providing valuable information about the types of carbon atoms present and their surroundings. By analyzing the chemical shifts, intensities, and coupling patterns of these peaks, chemists can deduce crucial structural details such as the number and types of carbon atoms, their connectivity, and the presence of certain functional groups. This information is essential for determining the molecular structure and understanding chemical properties and reactivities.

Objectives

After completing this section, you should be able to use data from ^{13}C NMR spectra to distinguish between two (or more) possible structures for an unknown organic compound.

Features of a ^{13}C NMR spectrum

Butane shows two different peaks in the ^{13}C NMR spectrum, below. Note that: the chemical shifts of these peaks are not very different from methane. The carbons in butane are in a similar environment to the one in methane.

- there are two distinct carbons in butane: the methyl, or CH_3, carbon, and the methylene, or CH_2, carbon.
- the methyl carbon absorbs slightly upfield, or at lower shift, around 10 ppm.
- the methylene carbon absorbs at slightly downfield, or at higher shift, around 20 ppm.
- other factors being equal, methylene carbons show up at slightly higher shift than methyl carbons.

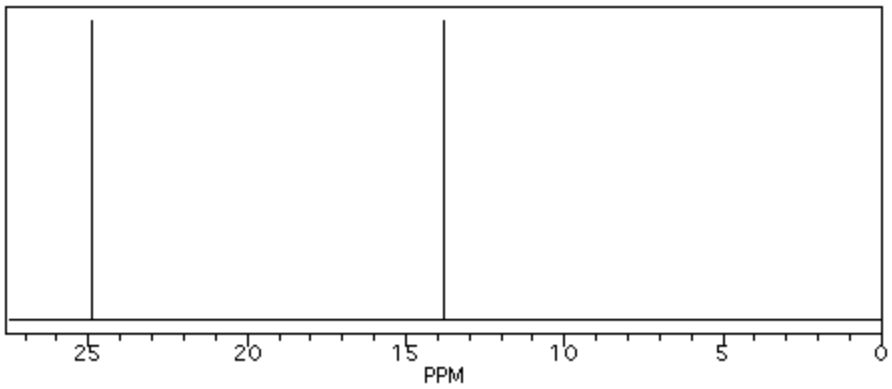


Figure 10.9.1. *Simulated ^{13}C NMR spectrum of butane (showing only the upfield portion of the spectrum).*

In the ^{13}C NMR spectrum of pentane (below), you can see three different peaks, even though pentane just contains methyl carbons and methylene carbons like butane. As far as the NMR spectrometer is concerned, pentane contains three different kinds of carbon, in three different environments. That result comes from symmetry.

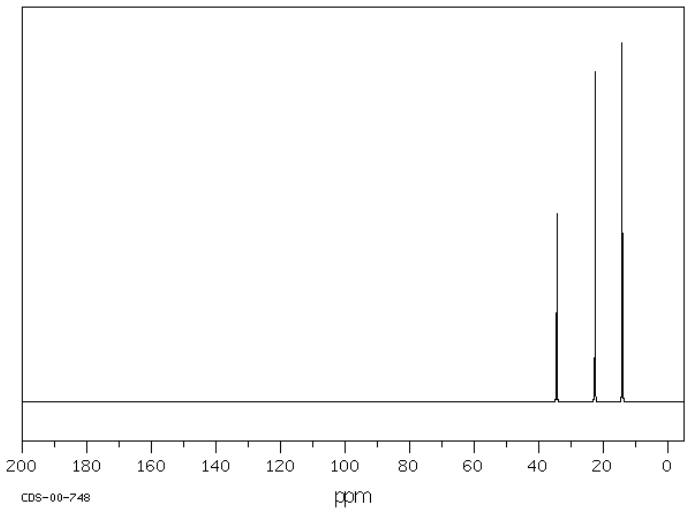


Figure 10.9.2. *^{13}C NMR spectrum of pentane. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 15 August 2008)*

Symmetry is an important factor in spectroscopy. Nature says:

- atoms that are symmetry-inequivalent can absorb at different shifts.
- atoms that are symmetry-equivalent must absorb at the same shift.

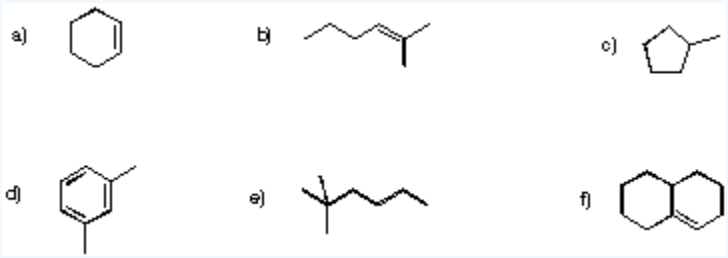
To learn about symmetry, take a model of pentane and do the following:

- make sure the model is twisted into the most symmetric shape possible: a nice "W".
- choose one of the methyl carbons to focus on.
- rotate the model 180 degrees so that you are looking at the same "W" but from the other side.
- note that the methyl you were focusing on has simply switched places with the other methyl group. These two carbons are symmetry-equivalent via two-fold rotation.

By the same process, you can see that the second and fourth carbons along the chain are also symmetry-equivalent. However, the middle carbon is not; it never switches places with the other carbons if you rotate the model. There are three different sets of inequivalent carbons; these three groups are not the same as each other according to symmetry.

Example 10.9.1

Determine how many inequivalent carbons there are in each of the following compounds. How many peaks do you expect in each ^{13}C NMR spectrum?



Practically speaking, there is only so much room in the spectrum from one end to the other. At some point, peaks can get so crowded together that you can't distinguish one from another. You might expect to see ten different peaks in eicosane, a twenty-carbon alkane chain, but when you look at the spectrum you can only see seven different peaks. That may be frustrating, because the experiment does not seem to agree with your expectation. However, you will be using a number of methods together to minimize the problem of misleading data.

Solution

a) Three inequivalent carbons/three peaks. There is a plane of symmetry that bisects the cyclohexene horizontally. The three different carbons are one of the alkene (C1), the CH_2 next to alkene (C3) and C4.

b) Six inequivalent carbons/six peaks. The two methyl groups attached to the alkene are identical.

c) Four inequivalent carbons/four peaks. This molecule has a plane of symmetry through the molecule, including the methyl group. The two carbons adjacent to the methyl group are equivalent (C2 and C5). C3 and C4 are also equivalent.

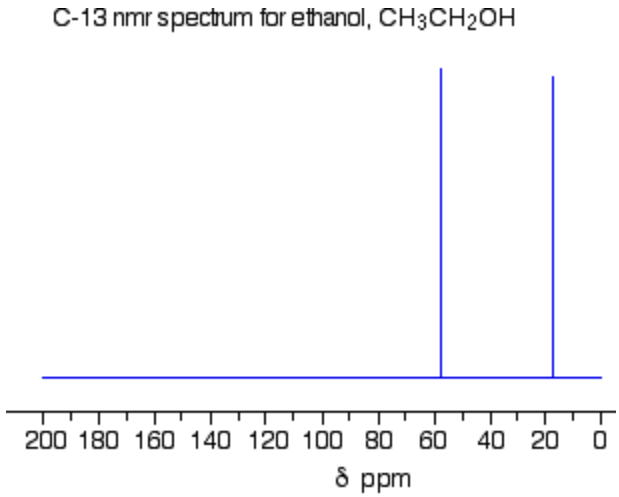
d) Five inequivalent carbons/five peaks. This molecule has a plane of symmetry that passes through the ring carbon between the two methyl groups. The two methyl carbons are identical. The two ring carbons with the methyl groups attached are identical (C1 and C3). C4 and C6 are also equivalent.

e) Six inequivalent carbons/six peaks. The three methyl groups at the end of the molecule are equivalent.

f) Ten inequivalent carbons/ten peaks. There is no symmetry for the carbons in this molecule.

The ^{13}C NMR spectrum for ethanol

This is a simple example of a ^{13}C NMR spectrum. Don't worry about the scale for now - we'll look at that in a minute.



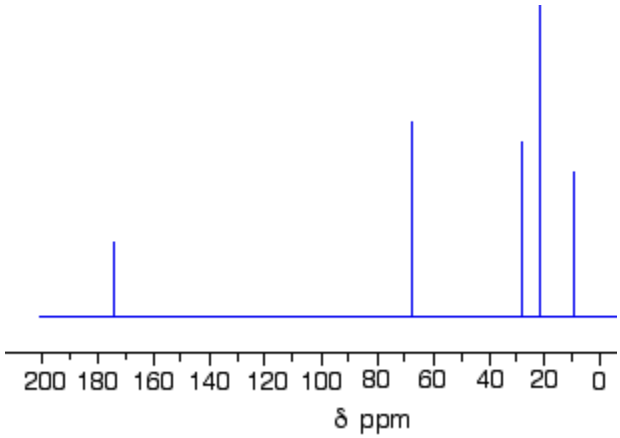
Note

Note: The NMR spectra on this page have been produced from graphs taken from the Spectral Data Base System for Organic Compounds (SDBS) at the National Institute of Materials and Chemical Research in Japan.

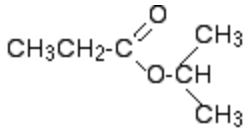
There are two peaks because there are two different environments for the carbons. The carbon in the CH_3 group is attached to 3 hydrogens and a carbon. The carbon in the CH_2 group is attached to 2 hydrogens, a carbon and an oxygen. The two lines are in different places in the NMR spectrum because they need different external magnetic fields to bring them in to resonance at a particular radio frequency.

The ^{13}C NMR spectrum for a more complicated compound

This is the ^{13}C NMR spectrum for 1-methylethyl propanoate (also known as isopropyl propanoate or isopropyl propionate).



This time there are 5 lines in the spectrum. That means that there must be 5 different environments for the carbon atoms in the compound. Is that reasonable from the structure?



If you count the carbon atoms, there are 6 of them. So why only 5 lines? In this case, two of the carbons are in exactly the same environment. They are attached to exactly the same things. Look at the two CH_3 groups on the right-hand side of the molecule.

You might reasonably ask why the carbon in the CH_3 on the left is not also in the same environment. Just like the ones on the right, the carbon is attached to 3 hydrogens and another carbon. But the similarity is not exact - you have to chase the similarity along the rest of the molecule as well to be sure.

The carbon in the left-hand CH_3 group is attached to a carbon atom which in turn is attached to a carbon with two oxygens on it - and so on down the molecule. That's not exactly the same environment as the carbons in the right-hand CH_3 groups. They are attached to a carbon which is attached to a single oxygen - and so on down the molecule. We'll look at this spectrum again in detail on the next page - and look at some more similar examples as well. This all gets easier the more examples you look at.

For now, all you need to realize is that each line in a ^{13}C NMR spectrum recognizes a carbon atom in one particular environment in the compound. If two (or more) carbon atoms in a compound have exactly the same environment, they will be represented by a single line.

Note

You might wonder why all this works, since only about 1% of carbon atoms are ^{13}C. These are the only ones picked up by this form of NMR. If you had a single molecule of ethanol, then the chances are only about 1 in 50 of there being one ^{13}C atom in it, and only about 1 in 10,000 of both being ^{13}C.

But you have got to remember that you will be working with a sample containing huge numbers of molecules. The instrument can pick up the magnetic effect of the ^{13}C nuclei in the carbon of the CH_3 group and the carbon of the CH_2 group even if they are in separate molecules. There's no need for them to be in the same one.

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11: ALKENES: INFRARED SPECTROSCOPY AND MASS SPECTROMETRY

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

11.1: Naming the Alkenes
11.2: Structure and Bonding in Ethene: The Pi Bond
11.3: Physical Properties of Alkenes
11.4: Nuclear Magnetic Resonance of Alkenes
11.5: Catalytic hydrogenatin of Alkenes: Relative Stability of Double Bonds
11.6: Preparation of Alkenes from Haloalkanes and Alkyl Sufonates: Bimolecular Elimination Revisited
11.7: Preparation of Alkenes by Dehydration of Alcohols
11.8: Infrared Spectroscopy
11.9: Measuring the Molecular Mass of Organic Compounds: Mass Spectrometry
11.10: Fragmentation Patterns of Organic Molecules
11.11: Degree of Unsaturation: Another Aid to Identifying Molecular Structure

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11.1: Naming the Alkenes

Objectives

After completing this section, you should be able to

- provide the correct IUPAC name for an acyclic or cyclic alkene, given its Kekulé, condensed or shorthand structure.
- draw the Kekulé, condensed or shorthand structure of an alkene (cyclic or acyclic), given its IUPAC name.
- give the IUPAC equivalent of the following trivial names: ethylene, propylene, isobutylene and isoprene.
- draw the structure of a vinyl (ethenyl) and allyl (2-propenyl) group, and use these names in alkene nomenclature.

Study Notes

This course uses IUPAC nomenclature; therefore, you need not usually memorize a large number of trivial names. However, you will encounter some trivial names so frequently in books and articles that they soon become familiar.

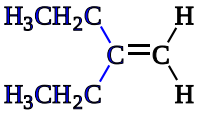
An alkene that can exhibit geometric isomerism has not been properly named unless its name specifies whether the double bond (or bonds) is (or are) cis or trans. The most effective way of giving this information is discussed, and more details of cis and trans follow in Section 7.4.

Alkenes contain carbon-carbon double bonds and are unsaturated hydrocarbons with the molecular formula is C_nH_{2n}; this is also the same molecular formula as cycloalkanes. The parent chain of an alkene is the longest chain containing both carbon atoms of the double bond. Alkenes are named by dropping the **-ane** ending of the parent and adding **-ene**. Also, the position of double bond in the parent chain of the alkene is indicated with a number.

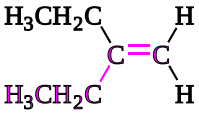
The Basic Rules for Naming Alkenes

For straight chain alkenes, it is the same basic rules as nomenclature of alkanes apply except the **-ane** suffix is changed to **-ene**.

1) Find the longest carbon chain that contains both carbons of the double bond.

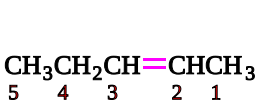


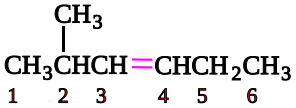
This compound is NOT named as an pentene



This compound is named as a butene because the double bond is contained in the four carbon chain

2) Start numbering from the end of the parent chain which gives the lowest possible number to the double bond. If the double bond is equidistant from both ends of the parent chain, number from the end which gives the substituents the lowest possible number. The double bond in cycloalkenes do not need to number because it is understood that they are in the one position.





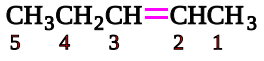
3) Place the location number of the double bond directly before the parent name. The location number indicates the position of the first carbon of the double bond. Add substituents and their position to the alkene as prefixes. Remember substituents are

written in alphabetical order.

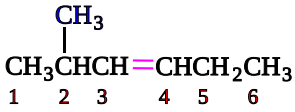
The presence of multiple double bonds is indicated by using the appropriate suffix such as **-diene**, **-triene**, ect. Each of the multiple bonds receives a location number. Also, only **-ne** is removed from the parent alkane chain name leaving an "a" in the name.

Overall, the name of an alkene should look like:

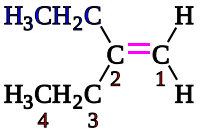
(Location number of substituent)-(Name of substituent)-(Location number of double bond)-(Name of parent chain) + ene



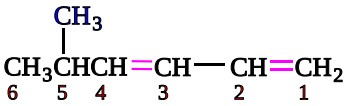
2-Pent ene



2-Methyl -3-hex ene



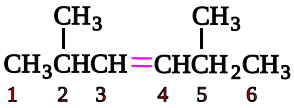
3-Ethyl -1-but ene

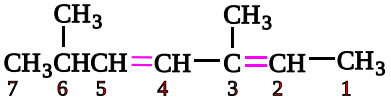


5-Methyl -1,3- hexa diene

Newer IUPAC Nomenclature

In 1993 IUPAC updated their naming recommendation to place the location number of the double bond before the -ene suffix of alkene names. The provides names such as hex-2-ene rather than 2-hexene. The newer system is slowly being accepted so it may occasionally be encountered.

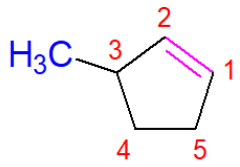




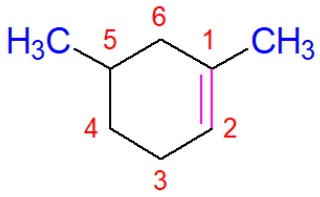
Older Numbering System:	**2,5-Dimethyl -3-hex ene**	**5-Methyl -1,3- hexa diene**
Newer Numbering System:	**2,5-Dimethylhex -3-ene**	**5-Methylhexa -1,3-diene**

Naming Cycloalkenes

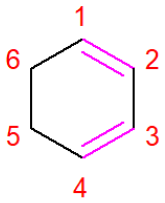
Because there are no chain ends in cycloalkenes, the double bond is assumed to numbered C1 and C2 and its location number is not required in the name. The direction of the numbering is determined by which will give the substituent closest to the double bond the lowest number. If multiple double bonds are present, it may be necessary to include their location numbers in the name. One of the double bonds will be number C1 and C2 and the numbering direction is determined by which gives the remaining double bonds the lowest possible number.



3-Methylcyclopent-1-ene



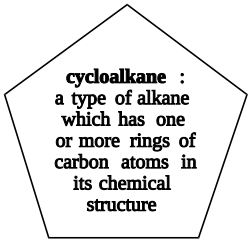
1,5-Dimethylcyclohexene



1,3-Cyclohexadiene
(New:Cyclohexa-1,3-diene)

Endocyclic vs. Exocyclic Alkenes

Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.



Cyclopentene is an example of an endocyclic double bond.



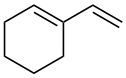
Methylenecylopentane is an example of an exocyclic double bond.



Name the following compounds...



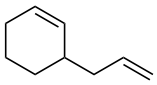
1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.



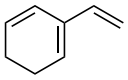
1-ethenylcyclohexene, the methyl group places the double bond. It is correct to also name this compound as 1-ethenylcyclohex-1-ene. A common name would be 1-vinylcyclohexene.

Try to draw structures for the following compounds...

- 3-allylcyclohex-1-ene

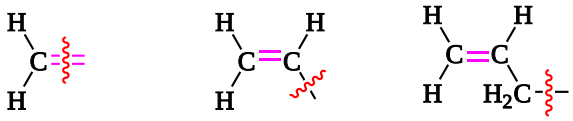


- 2-vinyl-1,3-cyclohexadiene



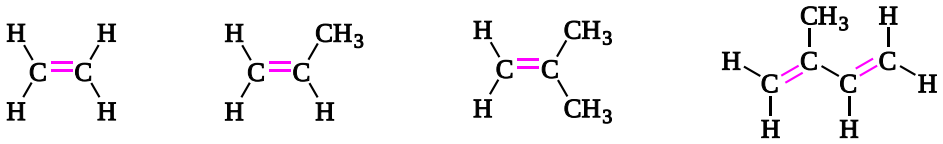
Common Names of Alkene Fragments

Some alkene containing fragments have common names which should be recognized. These common names can be used to simplify naming much the alkyl fragments discussed in **Section: 3.3**. Some of these fragments are the methylene group (H_2C=), the vinyl group (H_2C=CH-), and the allyl group (H_2C=CH-CH_2-).



Methylene Group **Vinyl Group** **Allyl Group**

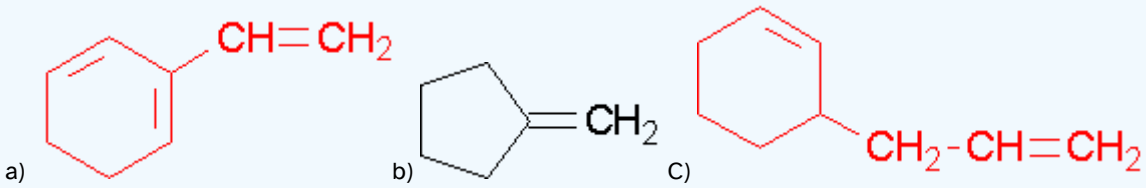
In addition, the common name some small alkene compounds are still accepted by IUPAC. It is important to be able to identify them.



Common Name:	**Ethylene**	**Propylene**	**Isobutylene**	**Isoprene**
IUPAC Name:	**Ethene**	**Propene**	**2-Methylpropene**	**2-Methyl-1,3-butadiene**

Exercise 11.1.1

Name the following compounds using common fragment names.

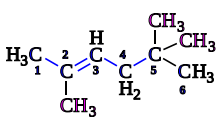


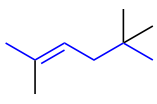
a) b) C)

Answer available at the end of this section.

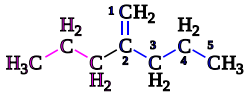
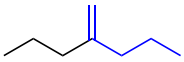
Examples

(1)



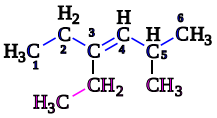
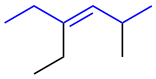


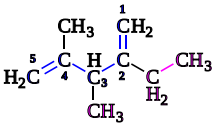
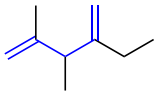
$(CH_3)_2C$=$CHCH_2C(CH_3)_3$
2,5,5-trimethyl-2-hexene

(2)   $(CH_3CH_2CH_2)_2C{=}CH_2$
2-propyl-1-pentene

Both these compounds have double bonds, making them alkenes. In example (1) the longest chain consists of six carbons, so the root name of this compound will be hexene. Three methyl substituents (colored red) are present. Numbering the six-carbon chain begins at the end nearest the double bond (the left end), so the methyl groups are located on carbons 2 & 5. The IUPAC name is therefore: 2,5,5-trimethyl-2-hexene.

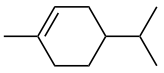
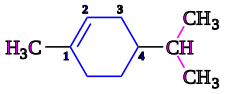
In example (2) the longest chain incorporating both carbon atoms of the double bond has a length of five. There is a seven-carbon chain, but it contains only one of the double bond carbon atoms. Consequently, the root name of this compound will be pentene. There is a propyl substituent on the inside double bond carbon atom (#2), so the IUPAC name is: 2-propyl-1-pentene.

(3)   $(CH_3CH_2)_2C{=}CHCH(CH_3)_2$
4-ethyl-2-methyl-3-hexene

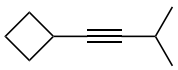
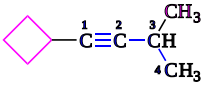
(4)   $CH_2{=}C(CH_3)CH(CH_3)C(C_2H_5){=}CH_2$
2-ethyl-3,4-dimethyl-1,4-pentadiene

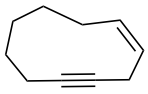
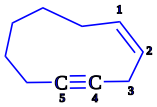
The double bond in example (3) is located in the center of a six-carbon chain. The double bond would therefore have a locator number of 3 regardless of the end chosen to begin numbering. The right hand end is selected because it gives the lowest first-substituent number (2 for the methyl as compared with 3 for the ethyl if numbering were started from the left). The IUPAC name is assigned as shown.

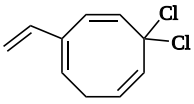
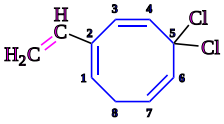
Example (4) is a diene (two double bonds). Both double bonds must be contained in the longest chain, which is therefore five- rather than six-carbons in length. The second and fourth carbons of this 1,4-pentadiene are both substituted, so the numbering begins at the end nearest the alphabetically first-cited substituent (the ethyl group).

(5)   4-isopropyl-1-methylcyclohexene

4-isopropyl-1-methylcyclohex-1-ene

(6)   1-cyclobutyl-3-methyl-1-butyne

(7)   1-cyclodecen-4-yne

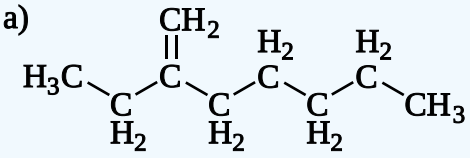
(8)   5,5-dichloro-2-vinyl-1,3,6-cyclooctatriene

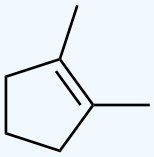
These examples include rings of carbon atoms as well as some carbon-carbon triple bonds. Example (6) is best named as an alkyne bearing a cyclobutyl substituent. Example (7) is simply a ten-membered ring containing both a double and a triple bond. The double bond is cited first in the IUPAC name, so numbering begins with those two carbons in the direction that gives the triple bond carbons the lowest locator numbers. Because of the linear geometry of a triple bond, a-ten membered ring is the smallest ring in which this functional group is easily accommodated. Example (8) is a cyclooctatriene (three double bonds in an eight-membered ring). The numbering must begin with one of the end carbons of the conjugated diene moiety (adjacent double

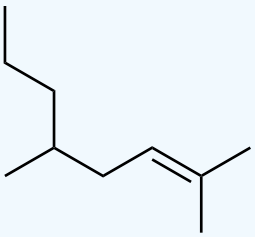
bonds), because in this way the double bond carbon atoms are assigned the smallest possible locator numbers (1, 2, 3, 4, 6 & 7). Of the two ways in which this can be done, we choose the one that gives the vinyl substituent the lower number.

Exercise 11.1.2

Name the following alkenes.

a) 

b) 

c) 

Answer available at the end of this section.

Exercise 11.1.3

Draw structures for the following compounds from the given names.

a. 3-butylhept-2-ene (3-butyl-2-heptene)
b. 1,4-pentadiene (penta-1,4-diene)
c. 3-vinyl-1,4-cyclohexadiene (cyclohexa-1,4-diene)

Answer available at the end of this section.

References

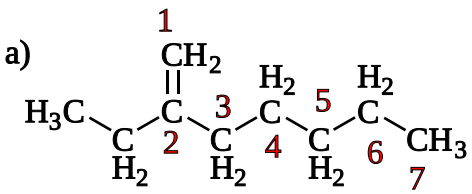
1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

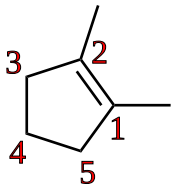
Answers

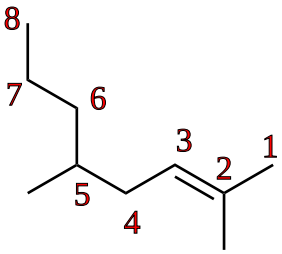
Exercise 11.1.1

a) 2-Vinyl-cyclohexa-1,3-diene
b) Methylenecylopentane
c) 3-Allylcyclohex-1-ene

Exercise 11.1.2

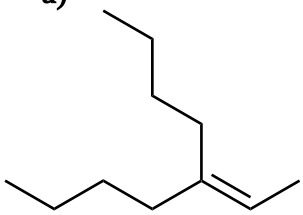
a) 

b) 

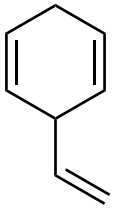
c) 

a) 2-ethylhept-1-ene or 2-ethyl-1-heptene
b) 1,2-dimethylcyclohept-1-ene
c) 2,5-dimethyloct-2-ene or 2,5-dimethyl-1-octene

Exercise 11.1.3

a) 

b) 

c) 

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11.2: Structure and Bonding in Ethene: The Pi Bond

This is an introductory page about alkenes such as ethene, propene and the rest. It deals with their formulae and isomerism, their physical properties, and an introduction to their chemical reactivity.

What are alkenes?

Alkenes are a family of hydrocarbons (compounds containing carbon and hydrogen only) containing a carbon-carbon double bond. The first two are:

ethene	C_2H_4
propene	C_3H_6

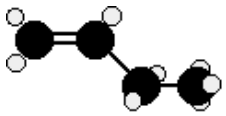
You can work out the formula of any of them using: C_nH_{2n} The table is limited to the first two, because after that there are isomers which affect the names.

Isomerism in the alkenes

Structural isomerism

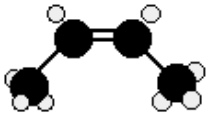
All the alkenes with 4 or more carbon atoms in them show structural isomerism. This means that there are two or more different structural formulae that you can draw for each molecular formula.

For example, with C_4H_8, it isn't too difficult to come up with these three structural isomers:



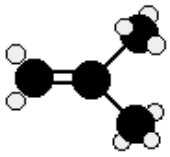
$CH_2=CH-CH_2-CH_3$

but-1-ene



$CH_3-CH=CH-CH_3$

but-2-ene



$CH_2=C(CH_3)-CH_3$

2-methylpropene

There is, however, another isomer. But-2-ene also exhibits geometric isomerism.

Geometric (cis-trans) isomerism

The carbon-carbon double bond doesn't allow any rotation about it. That means that it is possible to have the CH_3 groups on either end of the molecule locked either on one side of the molecule or opposite each other.

These are called cis-but-2-ene (where the groups are on the same side) or trans-but-2-ene (where they are on opposite sides).



cis-but-2-ene trans-but-2-ene

Cis-but-2-ene is also known as (Z)-but-2-ene; trans-but-2-ene is also known as (E)-but-2-ene. For an explanation of the two ways of naming these two compounds, follow the link in the box below..

Chemical Reactivity

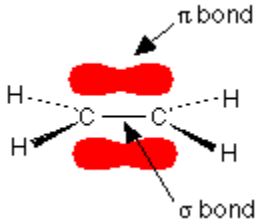
Bonding in the alkenes

We just need to look at ethene, because what is true of C=C in ethene will be equally true of C=C in more complicated alkenes. Ethene is often modeled like this:



The double bond between the carbon atoms is, of course, two pairs of shared electrons. What the diagram doesn't show is that the two pairs aren't the same as each other.

One of the pairs of electrons is held on the line between the two carbon nuclei as you would expect, but the other is held in a molecular orbital above and below the plane of the molecule. A molecular orbital is a region of space within the molecule where there is a high probability of finding a particular pair of electrons.



In this diagram, the line between the two carbon atoms represents a normal bond - the pair of shared electrons lies in a molecular orbital on the line between the two nuclei where you would expect them to be. This sort of bond is called a sigma bond.

The other pair of electrons is found somewhere in the shaded part above and below the plane of the molecule. This bond is called a pi bond. The electrons in the pi bond are free to move around anywhere in this shaded region and can move freely from one half to the other.

The pi electrons are not as fully under the control of the carbon nuclei as the electrons in the sigma bond and, because they lie exposed above and below the rest of the molecule, they are relatively open to attack by other things.

Contributors

Jim Clark (Chemguide.co.uk)

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11.3: Physical Properties of Alkenes

Physical state

Ethene, Propene, and Butene exists as colorless gases. Members of the 5 or more carbons such as Pentene, Hexene, and Heptene are liquid, and members of the 15 carbons or more are solids.

Density

Alkenes are lighter than water, therefore, are insoluble in water. Alkenes are only soluble in nonpolar solvent.

Solubility

Alkenes are virtually insoluble in water, but dissolve in organic solvents. The reasons for this are exactly the same as for the alkanes.

Boiling Points

The boiling point of each alkene is very similar to that of the alkane with the same number of carbon atoms. Ethene, propene and the various butenes are gases at room temperature. All the rest that you are likely to come across are liquids.

Boiling points of alkenes depends on more molecular mass (chain length). The more intermolecular mass is added, the higher the boiling point. Intermolecular forces of alkenes gets stronger with increase in the size of the molecules.

Compound	Boiling points (oC)
Ethene	-104
Propene	-47
Trans-2-Butene	0.9
Cis-2-butene	3.7
Trans 1,2-dichlorobutene	155
Cis 1,2-dichlorobutene	152
1-Pentene	30
Trans-2-Pentene	36
Cis-2-Pentene	37
1-Heptene	115
3-Octene	122
3-Nonene	147
5-Decene	170

In each case, the alkene has a boiling point which is a small number of degrees lower than the corresponding alkane. The only attractions involved are Van der Waals dispersion forces, and these depend on the shape of the molecule and the number of electrons it contains. Each alkene has 2 fewer electrons than the alkane with the same number of carbons.

Melting Points

Melting points of alkenes depends on the packaging of the molecules. Alkenes have similar melting points to that of alkanes, however, in cis isomers molecules are package in a U-bending shape, therefore, will display a lower melting points to that of the trans isomers.

Compound	Melting Points (0C)
Ethene	-169
Propene	-185
Butene	-138
1-Pentene	-165
Trans-2-Pentene	-135
Cis-2-Pentene	-180
1-Heptene	-119
3-Octene	-101.9
3-Nonene	-81.4
5-Decene	-66.3

Polarity

Chemical structure and fuctional groups can affect the polarity of alkenes compounds. The sp^2 carbon is much more electron-withdrawing than the sp3 hybridize orbitals, therefore, creates a weak dipole along the substituent weak alkenly carbon bond. The two individual dipoles together form a net molecular dipole. In trans-subsituted alkenes, the dipole cancel each other out. In cis-subsituted alkenes there is a net dipole, therefore contributing to higher boiling in cis-isomers than trans-isomers.

dipole dipole (8).bmp

dipole 3.bmp

dipole 5 (1).bmp

dipole 7 (1).bmp

Contributors

- Trung Nguyen
- Jim Clark (Chemguide.co.uk)

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11.4: Nuclear Magnetic Resonance of Alkenes

Nuclear Magnetic Resonance (NMR) of Alkenes

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11.5: Catalytic hydrogenatin of Alkenes: Relative Stability of Double Bonds

Catalytic Hydrogenation of Alkenes

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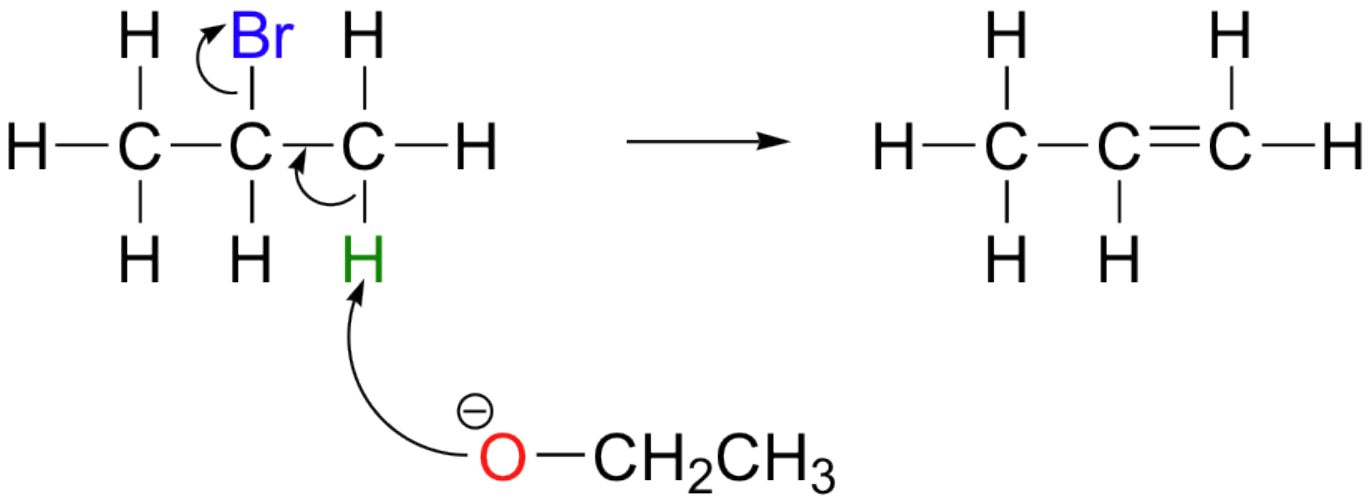
11.6: Preparation of Alkenes from Haloalkanes and Alkyl Sufonates: Bimolecular Elimination Revisited

E2 Reaction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

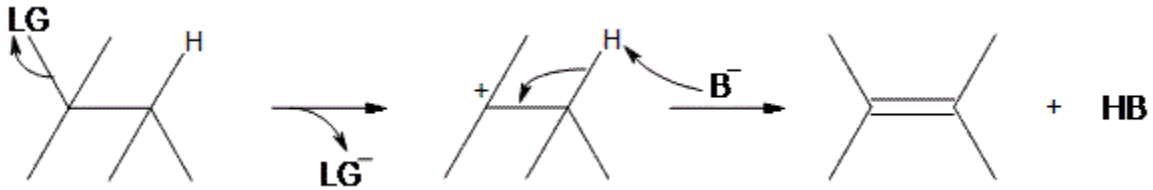
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2°-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.

.



E1 Reaction

An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



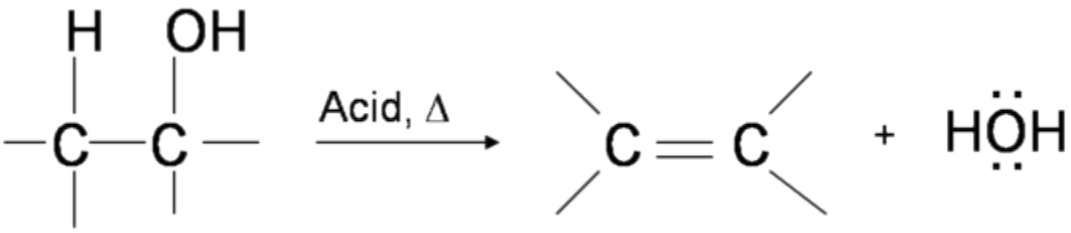
As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond

along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base ( ) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Dehydration

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond.

The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



Primary alcohol dehydrates through the E2 mechanism

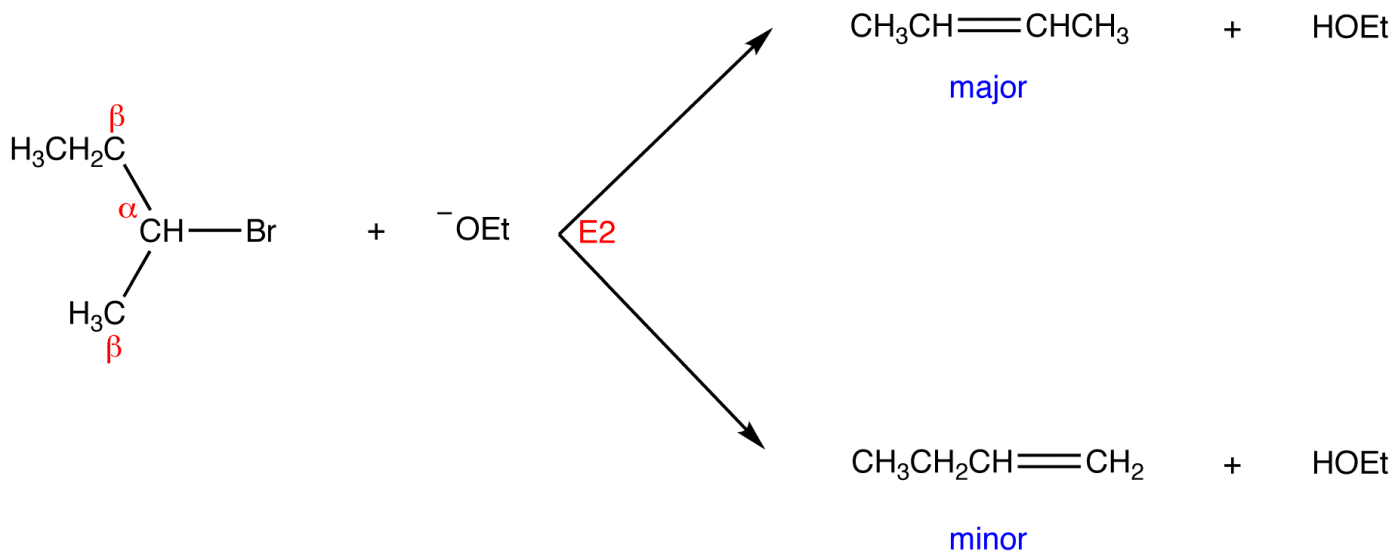
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.

Secondary and tertiary alcohols dehydrate through the E1 mechanism

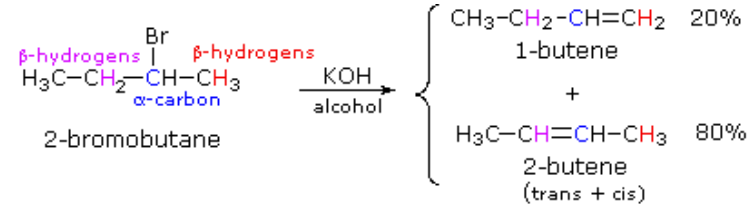
Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

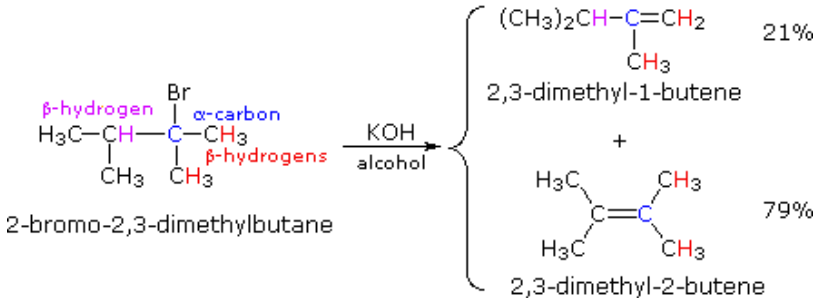
Zaitsev's Rule

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

Objectives

After completing this section, you should be able to

1. write the mechanism of a typical E2 reaction.
2. sketch the transition state of a typical E2 reaction.

3. discuss the kinetic evidence that supports the proposed E2 mechanism.
4. discuss the stereochemistry of an E2 reaction, and explain why the anti periplanar geometry is preferred.
5. determine the structure of the alkene produced from the E2 reaction of a substrate containing two chiral carbon atoms.
6. describe the deuterium isotope effect, and discuss how it can be used to provide evidence in support of the E2 mechanism.

Key Terms

Make certain that you can define, and use in context, the key terms below.

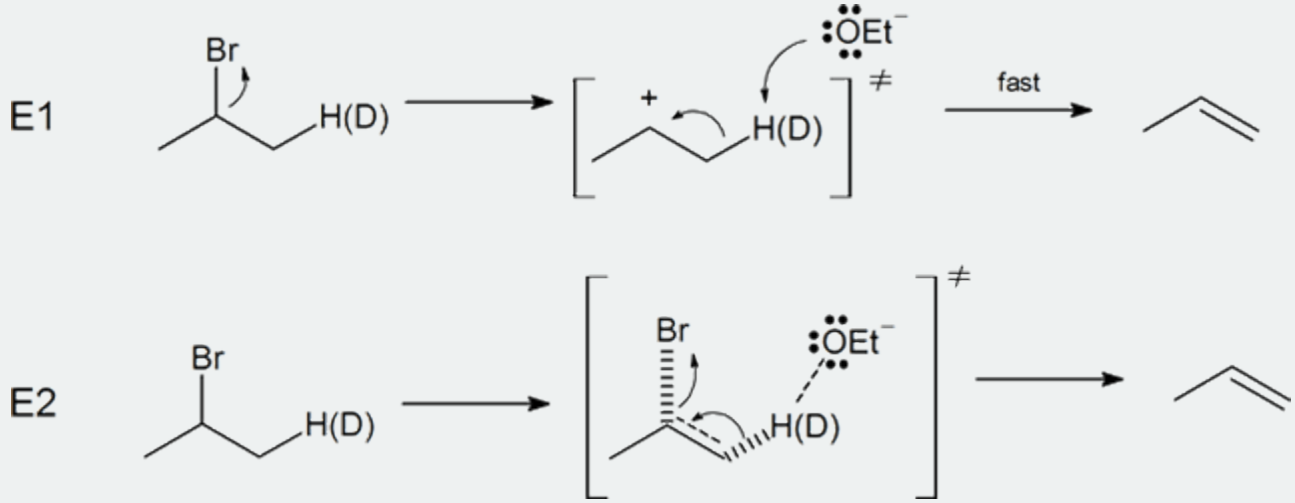
- anti periplanar
- deuterium isotope effect
- E2 reaction
- periplanar
- syn periplanar

Study Notes

An *E2 reaction* is a bimolecular elimination reaction; thus, two molecules are involved in the rate-limiting step. In this section, we are concerned with E2 reactions involving an alkyl halide and a base.

Use molecular models to assist you to understand the difference between syn periplanar and anti periplanar, and to appreciate why E2 eliminations are stereospecific.

Note that when deuterium is used the kinetic isotope effect (KIE) is referred to as the deuterium isotope effect. A C–H bond is about 5 kJ/mol weaker than a C–D bond. So if the rate-limiting step involves a breaking of this bond as it does at the E2 transition state there will be a substantial difference in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence consistent with an E2 mechanism.

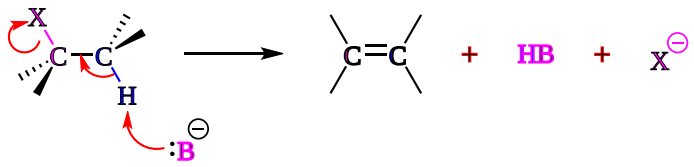


Introduction

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. E2 reactions are typically seen with secondary and tertiary alkyl halides, in the presence of a base (OH-, RO-, R_2N-). For a primary halide to undergo an E2 reaction a strong sterically hindered base is usually required. The products of an E2 reaction follow Zaitsev's rule, the most substituted alkene is usually the major product.

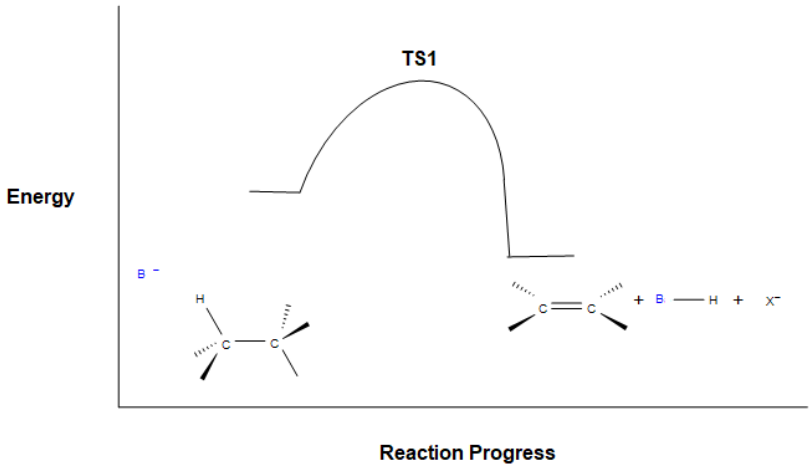
E2 Mechanism

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the carbon with the leaving group. The electrons of the broken H-C bond move to form the pi bond of the neutral product alkene. In doing this, the C-X bond is broken causing the removal of the leaving group. Overall during this reaction an electron pair is transferred from the base to the leaving group.

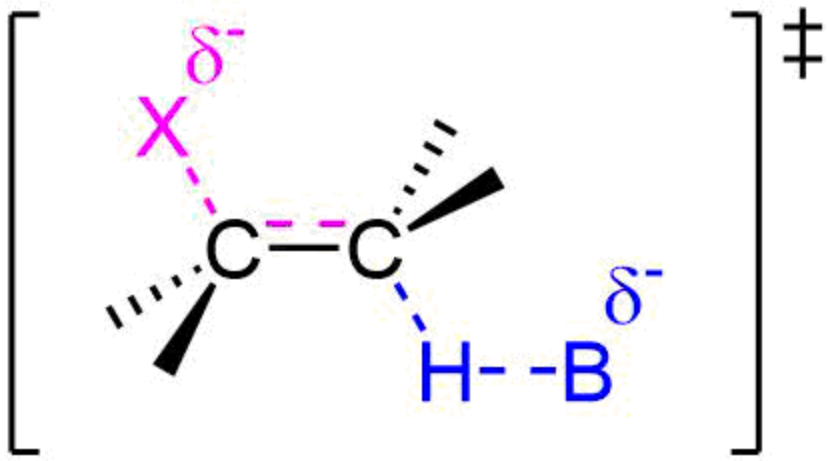


E2 Reaction Transition State

Because the E2 reaction is predicted to follow a concerted mechanism only one transition state is expected in its energy coordinate diagram.



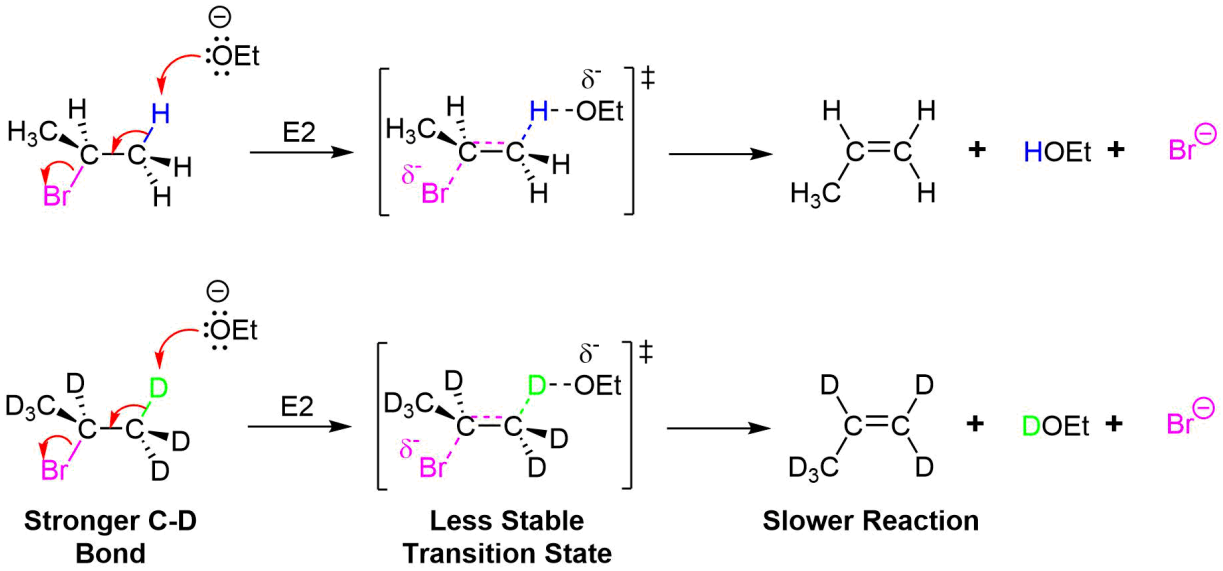
As the base begins to remove a hydrogen adjacent to the leaving group an H-B is starting to form and an H-C bond is in the process of breaking. Simultaneously, a C=C pi bond forms and the C-X bond breaks. During this reaction a set of electrons and a negative charge are transferred from the base to the leaving group. This is represented by a partial negative charge being present on both the base and the leaving group in the transition state.



Evidence for the E2 Mechanism and Transition State

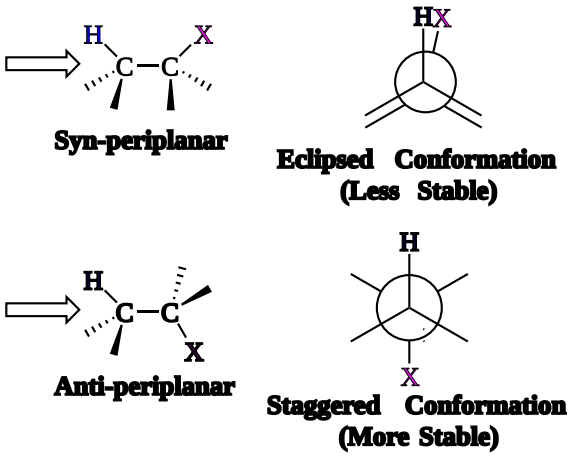
Kinetic studies of E2 reactions show that they are second order overall and follow the rate law: rate = k[RX][Base]. This data is consistent with the predicted bimolecular E2 mechanism that includes both the alkyl halide and the base participating in the mechanism's rate-determining step.

Further evidence for the predicted mechanism for the E2 reaction was provided by experiments involving the **deuterium isotope effect** (DIE). The **deuterium isotope effect** (DIE) is a phenomenon associated with molecules which have had hydrogen (H) atoms isotopically substituted with deuterium (D) atoms, exhibiting different reaction rates. The bond dissociation energy for C-D bonds is about 5 kJ/mol stronger than the bond dissociation energy of C-H bonds. This difference in energy results in a reduction in the rate of reaction, if the deuterium replacement occurs at a site of bond breaking in the rate determining step of a reaction. So if the rate-limiting step involves a breaking of this bond, as it does at the E2 transition state, there will be a substantial decrease in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence that the C-H bond is broken during the rate determining step of the E2 mechanism. This is consistent with the predicted mechanism of the E2 reaction consisting of a single concerted step. If the rate-determining step was the leaving group bond breaking first (as in an E1 reaction) the deuterium substitution would not have caused an observable change in reaction rate.

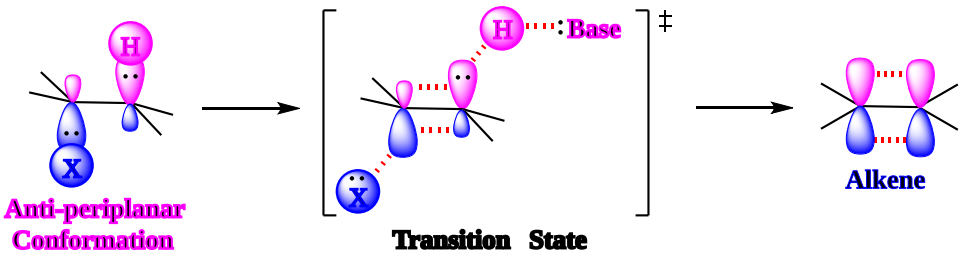


Yet another piece of evidence which supports the E2 mechanism comes when considering the stereochemistry of the elimination products. In the transition state of the E2 mechanism there are two carbons rehybridization from sp^3 to sp^2 while forming a π-

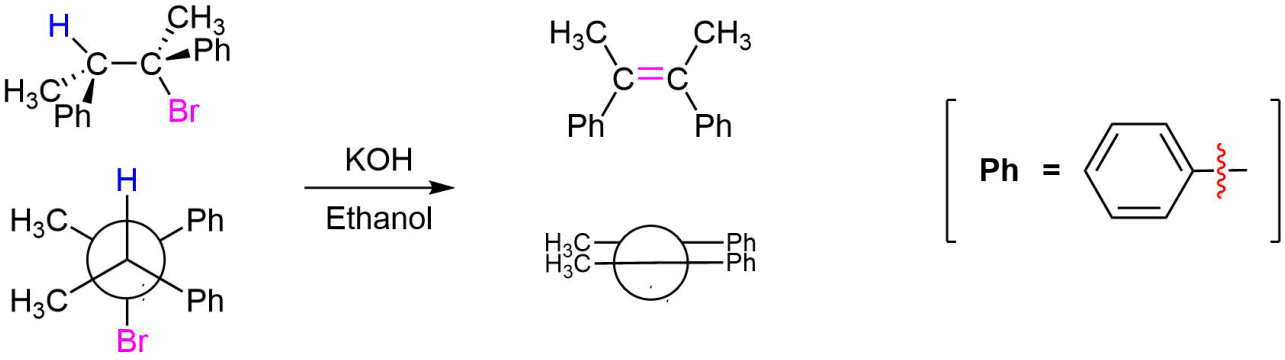
bond. For good orbital overlap to occur during this change all the atoms involved in the reaction, the two carbons, the hydrogen, and the leaving group need to all lie in the same plane or **periplanar**. There are two possible ways this geometry can be achieved: **syn-periplanar** where the hydrogen and the leaving group are on the same side of the C-C bond and **anti-periplanar** where the hydrogen and the leaving group are on opposite sides of the C-C bond. To obtain a syn-periplanar geometry the substituents attached to the C-C bond must adopt an energetically unfavorable eclipsed conformation. The energy barrier to syn-orientation is such that syn-elimination is rarely observed in E2 reactions. E2 eliminations typically take place from the anti-periplanar conformation, as this is the most stable conformation due to the substituents attached to the C-C bond being staggered.



When viewing the transition state of the E2 mechanism when in the anti-periplanar conformation, the two sp^3 hybridized orbitals making up the C-H and C-X sigma bonds are in the same plane. When these two carbons rehybridization from sp^3 to sp^2, the p orbitals forming the π-bond will also have good overlap.

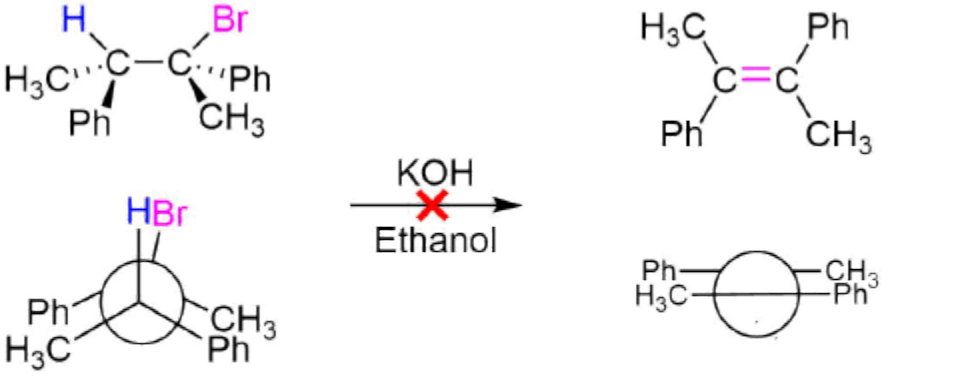


The stereochemical consequences of reactant molecules obtaining anti-periplanar geometry prior to E2 reactions has been observed in numerous experiments and provides further evidence of the proposed mechanism. For example, (2S, 3R)-2-bromo-2,3-diphenylbutane only forms (Z)-2,3-diphenyl-2-butene as a product of E2 elimination. To form the Z alkene isomer, the starting material must obtain the anti-periplanar geometry preferred for E2 reactions.



2-Bromo-2,3-diphenylbutane (Anti-periplanar geometry) **(Z)-2,3-Diphenyl-2-butene**

No isomeric E alkene product is formed because the starting materials would need to obtain a staggard, syn-periplanar geometry. The syn-periplanar geometry would be transferred to the transition state making it higher in energy and harder to form. The fact that only the Z alkene isomer forms provides further evidence that the E2 mechanism takes place by a single bimolecular step.

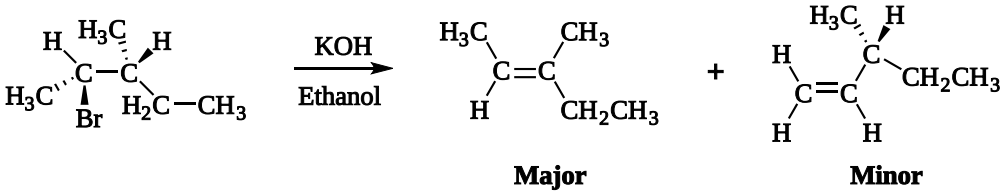


2-Bromo-2,3-diphenylbutane (Syn-periplanar geometry) **(E)-2,3-Diphenyl-2-butene (Not Formed!)**

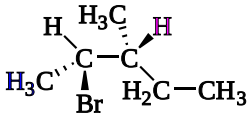
Predicting the Stereochemical Product of E2 Reactions

E2 reactions have the requirements of a leaving group and a hydrogen on a carbon adjacent to the leaving group carbon. For non-ringed compounds, the C-C can usually undergo free rotation to place the C-X and C-H bonds anti-periplaner to each other. Stereochemical considerations usually come into play when both of the carbons in the C-C bond are chiral. When these carbons are achiral but contain the other requirements for an E2 reaction, products lacking stereochemistry are usually produced.

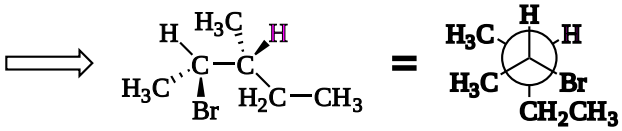
When both of the carbons in the C-C bond are chiral, one carbon will have a leaving group and the other carbon will have a single hydrogen. To consider the stereochemistry of an E2 product, start by creating a Newman projection looking down the C-C bond. Then rotate the C-C bond until the C-X and C-H bonds are in the anti position. The Newman projection now shows the relative positioning of the substituents on the C-C bond as they will appear in the double bond formed. It should be noted that if syn elimination was possible, a positional isomer of the double bond will be created. Consider the elimination products for (2R, 3R)-2-bromo-3-methylpentane.



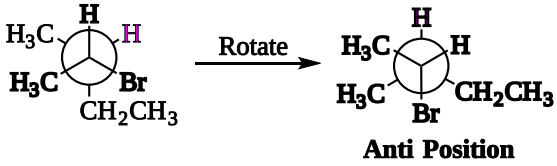
First, locate hydrogens on carbons adjacent to the leaving group. The compound used in this example has two unique sets of hydrogens.



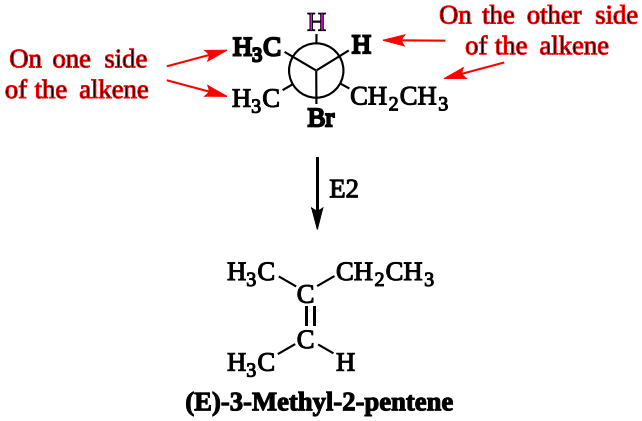
Because the adjacent hydrogen colored fuchsia is attached to a chiral carbon it require special consideration. Convert the structure into a Newman projection along the C-C bond that will for the alkene elimination product. The C-C bond can be view down either direction and still product the correct product.



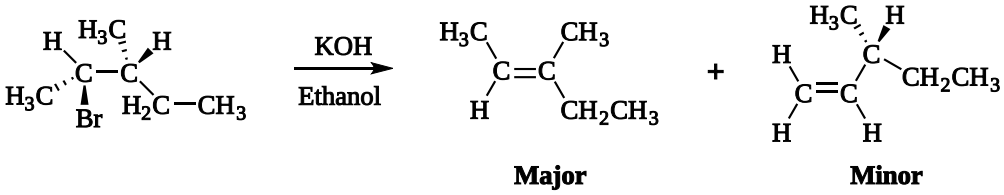
Then rotate such the the adjacent H and the leaving group are in the anti position.



This Newman projection shows the relative positioning of the substituents on the double bond formed. Note, none of the Z isomer is formed because it would require syn orientation of the H and Br.

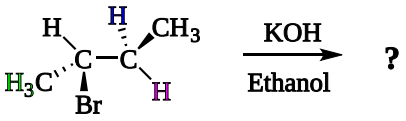


Lastly, consider the products made by other adjacent hydrogens and apply Zaitsev's rule to predict the preferred product.

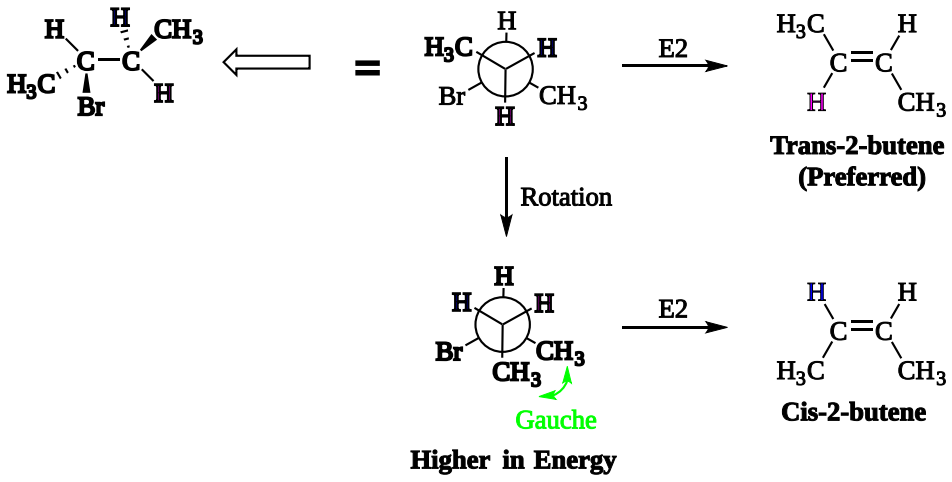


Determining *Cis* and *Trans* Products in Elimination Reaction

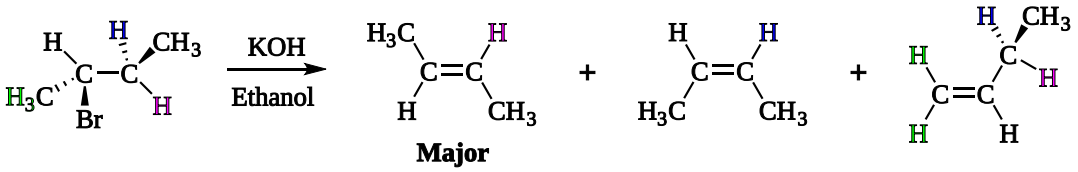
Understanding that E2 reactions require an anti-periplanar geometry can explain cis and trans alkene isomers can form as products. This occurs as an important exception to the rule that stereoisomers only form as elimination products when both of the carbons in the C-C bond forming the alkene are chiral. When considering the E2 reaction products of (R)-2-butane, there are two groups of hydrogens on carbons adjacent to the leaving group a CH_3 and a CH_2.



The carbon in the CH_2 group is achiral so both the H's appear to be equivalent. However, when the anti-periplanar geometry requirement is applied each hydrogen will produce its own unique product. Once the reactant is converted into a Newman projection it can be seen that the Br leaving group and the hydrogen colored blue are in the anti orientation and are ready to be eliminated. It should also be noted that the two CH_3 groups are also in the anti position which gives them the least amount of steric interaction possible. Because the CH_3 groups are on opposite sides of the Newman projection the CH_3 groups will be on opposite sides of the alkene thus creating the product *trans*-2-butene. When the Newman projection is rotated such that the fuchsia colored hydrogen is anti to the Br leaving group, the two CH_3 groups are now on the same. This orientation creates the isomer *cis*-2-butene. However, to obtain this orientation the two CH_3 groups must overcome the steric strain associated with a gauche conformation. This makes the transition state leading the cis isomer higher in energy and more difficult to form. Because of this, the trans isomer will be the major product. It is clear that the two hydrogens of the CH_2 group are not equivalent despite their not being attached to a chiral carbon.

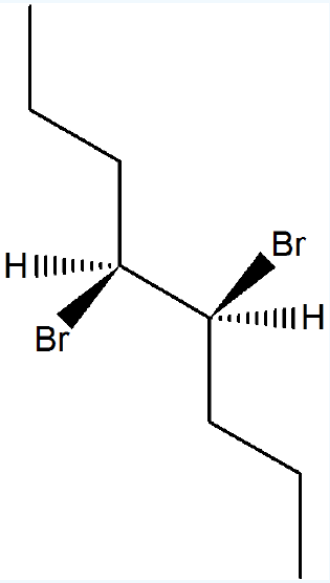


After considering all the products made during this E2 reaction the preferred product can be determined. The *cis* and *trans* isomer both have two alkene substituents while the third product only has one. Of the *cis* and *trans* isomer, the *trans* isomer is expected to be easier to form. Zaitsev's rule says that trans-2-butene will be the major product of this reaction.



Exercise 11.6.1

1) What is the product of the following molecule in an E2 reaction? What is the stereochemistry?

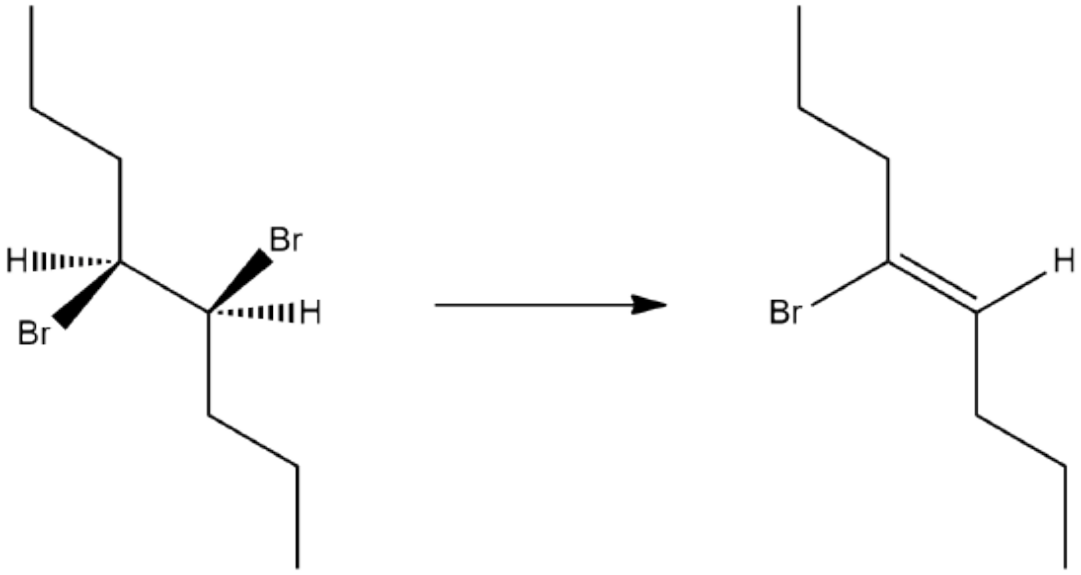


Answer available at the end of this section.

Answers

Exercise 11.6.1

The stereochemistry is (*Z*) for the reaction.



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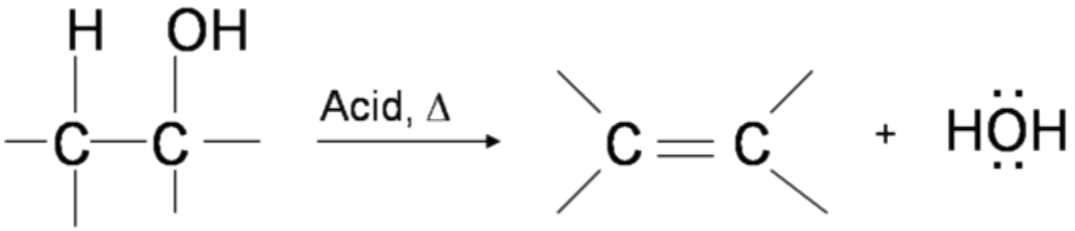
- 11.8: The E2 Reaction and the Deuterium Isotope Effect by Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

11.7: Preparation of Alkenes by Dehydration of Alcohols

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond.

Introduction

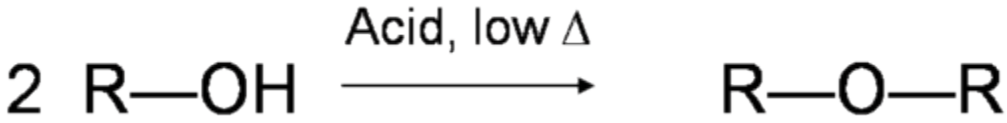
The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



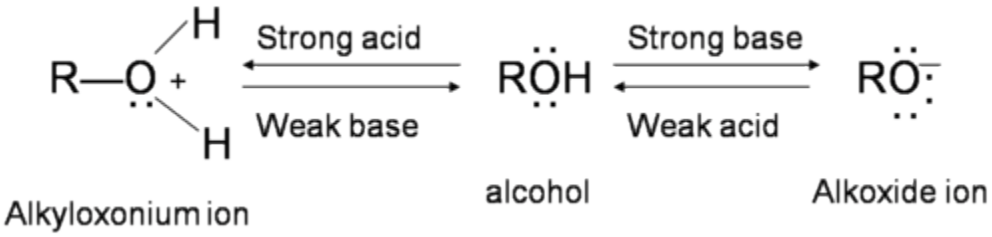
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).



Alcohols are amphoteric; they can act both as acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. Oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion $^{+}OH_2$ (The pKa value of a tertiary protonated alcohol can go as low as -3.8). This basic characteristic of alcohol is essential for its dehydration reaction with an acid to form alkenes.



Mechanism for the Dehydration of Alcohol into Alkene

Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H^+ from the acid reagent, forming an

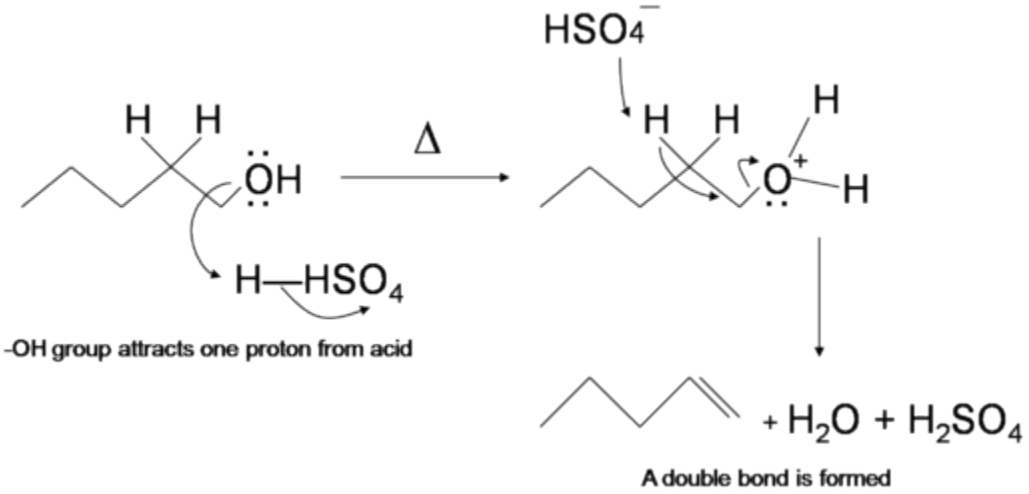
alkyloxonium ion. This ion acts as a very good leaving group which leaves to form a carbocation. The deprotonated acid (the nucleophile) then attacks the hydrogen adjacent to the carbocation and form a double bond.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

Methanol < primary < secondary < tertiary

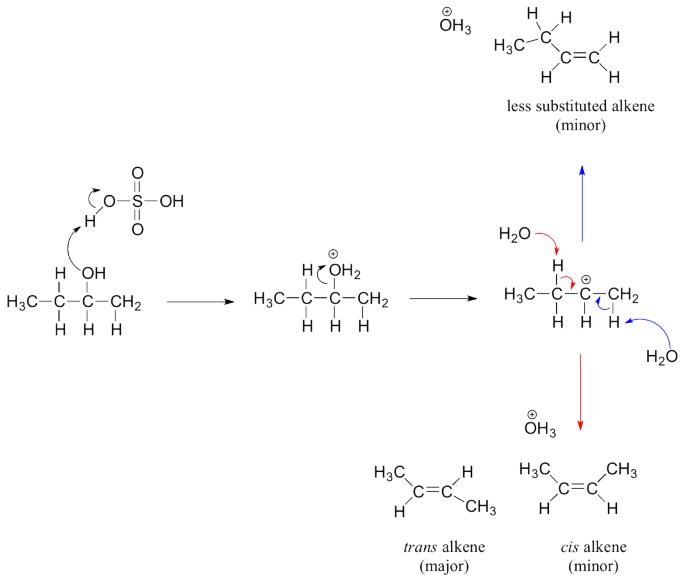
Primary alcohol dehydrates through the E2 mechanism

Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.



Secondary and tertiary alcohols dehydrate through the E1 mechanism

Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Therefore, the *trans* diastereomer of the 2-butene product is most abundant.



Dehydration reaction of secondary alcohol: *The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.*

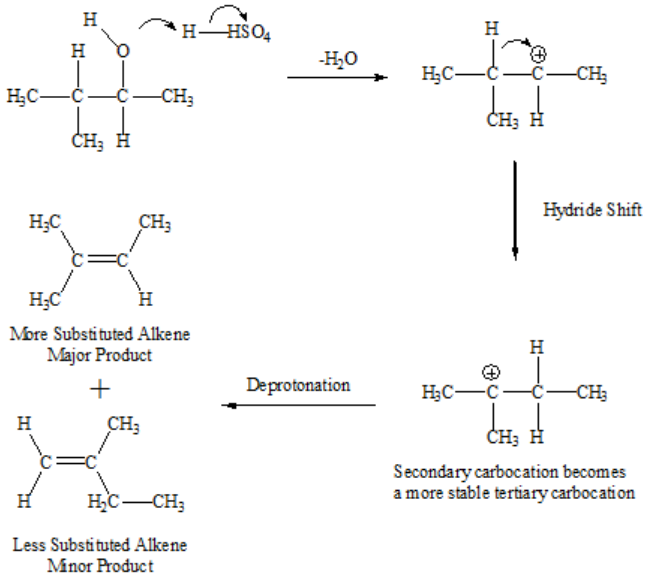
When more than one alkene product are possible, the favored product is usually the thermodynamically most stable alkene. More-substituted alkenes are favored over less-substituted ones; and trans-substituted alkenes are preferred compared to cis-substituted ones.

1. Since the C=C bond is not free to rotate, cis-substituted alkenes are less stable than trans-subsituted alkenes because of steric hindrance (spatial interfererence) between two bulky substituents on the same side of the double bond (as seen in the cis product in the above figure). Trans-substituted alkenes reduce this effect of spatial interference by separating the two bulky substituents on each side of the double bond (for further explanation on the rigidity of C=C bond, see Structure and Bonding in Ethene- The pi Bond).
2. Heats of hydrogenation of differently-substituted alkene isomers are lowest for more-substituted alkenes, suggesting that they are more stable than less-substituted alkenes and thus are the major products in an elimination reaction. This is partly because in more --substituted alkenes, the p orbitals of the pi bond are stabilized by neighboring alkyl substituents, a phenomenon similar to hyperconjugation.

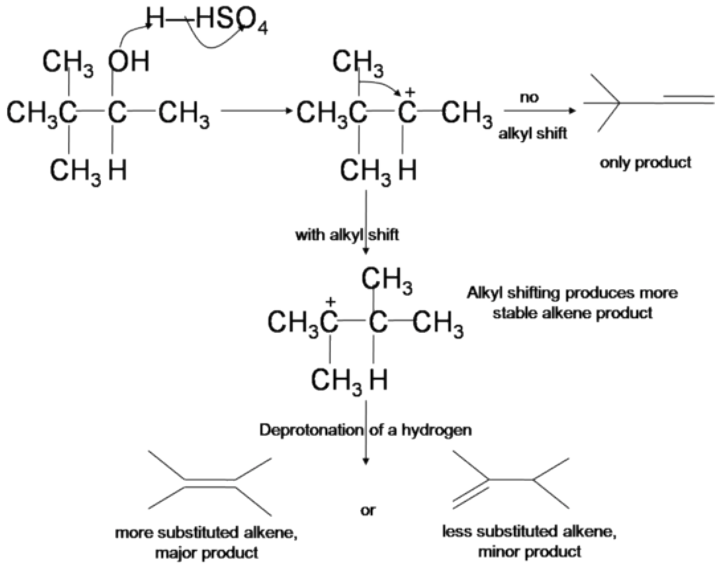
Hydride and Alkyl Shifts

Since the dehydration reaction of alcohol has a carbocation intermediate, hydride or alkyl shifts can occur which relocates the carbocation to a more stable position. The dehydrated products therefore are a mixture of alkenes, with and without carbocation rearrangement. Tertiary cation is more stable than secondary cation, which in turn is more stable than primary cation due to a phenomenon known as hyperconjugation, where the interaction between the filled orbitals of neighboring carbons and the singly occupied p orbital in the carbocation stabilizes the positive charge in carbocation.

- In hydride shifts, a secondary or tertiary hydrogen from a carbon next to the original carbocation takes both of its electrons to the cation site, swapping place with the carbocation and renders it a more stable secondary or tertiary cation.



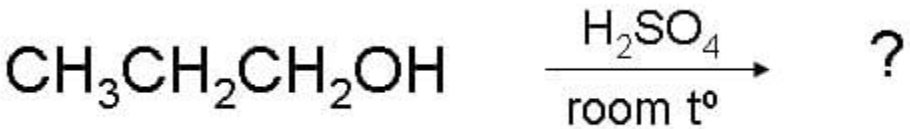
Similarly, when there is no hydride available for hydride shifting, an alkyl group can take its bonding electrons and swap place with an adjacent cation, a process known as alkyl shift.



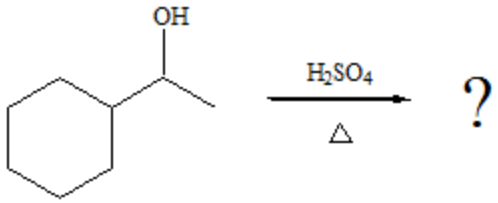
Practice Problems

Test your understanding by predicting what product(s) will be formed in each of the following reactions:

1.

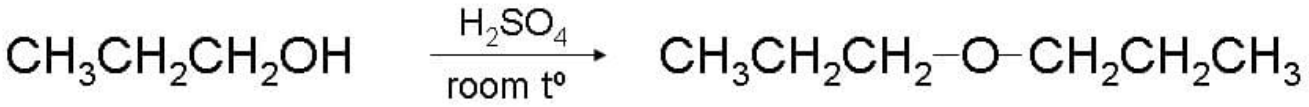


2.

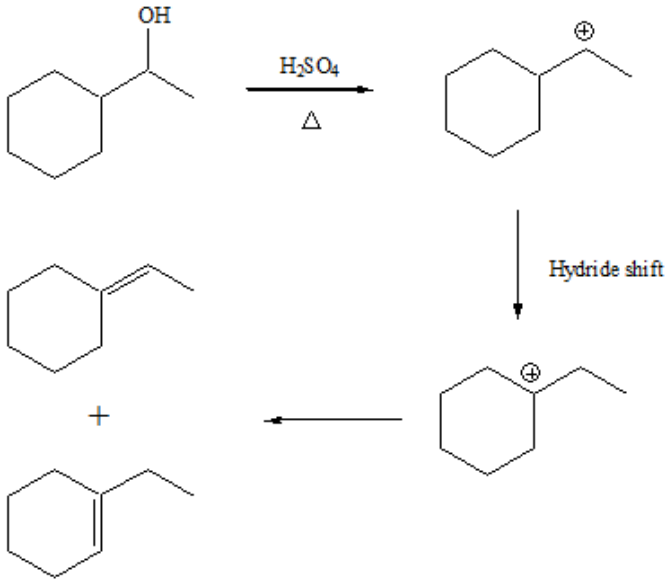


Solutions

1. Did you notice the reaction temperature? It is only 25°, which is much lower than the required temperature of 170°C for dehydration of primary alcohol. This reaction will not produce any alkene but will form ether.



2. . Notice that the reactant is a secondary -OH group, which will form a relatively unstable secondary carbocation in the intermediate. Thus hydride shift from an adjacent hydrogen will occur to make the carbocation tertiary, which is much more stable. The products are a mixture of alkenes that are formed with or without carbocation rearrangement (A number of products are formed faster than hydride shift can occur).



References

1. Vollhart, K. Peter C. and Neil Schore. Organic Chemistry, Structure and Function. 5th Ed. W. H. Freeman and Company, 2007
2. McMurry, John. Fundamentals of Organic Chemistry. 3rd Ed. Cornell University. Pacific Grove, CA: Brooks/ Cole Publishing Company, 1994.

Contributors

- Thuy Hoang

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11.8: Infrared Spectroscopy

Objectives

After completing this section, you should be able to

1. identify (by wavelength, wavenumber, or both) the region of the electromagnetic spectrum which is used in infrared (IR) spectroscopy.
2. interconvert between wavelength and wavenumber.
3. discuss, in general terms, the effect that the absorption of infrared radiation can have on a molecule.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- infrared spectrum
- wavenumber (reciprocal centimetres)

Study Notes

Notice that the scale at the bottom of the infrared spectrum for 2-hexanone shown is calibrated in wavenumbers (cm^{-1}). A wavenumber is the reciprocal of a wavelength (1/λ); thus, a wavenumber of 1600 cm^{-1} corresponds to a wavelength of

$$\frac{1}{1600\,\mathrm{cm}^{-1}} = 6.25 \times 10^{-4}\mathrm{cm\ or} 6.25\,\mu\,\mathrm{m}$$

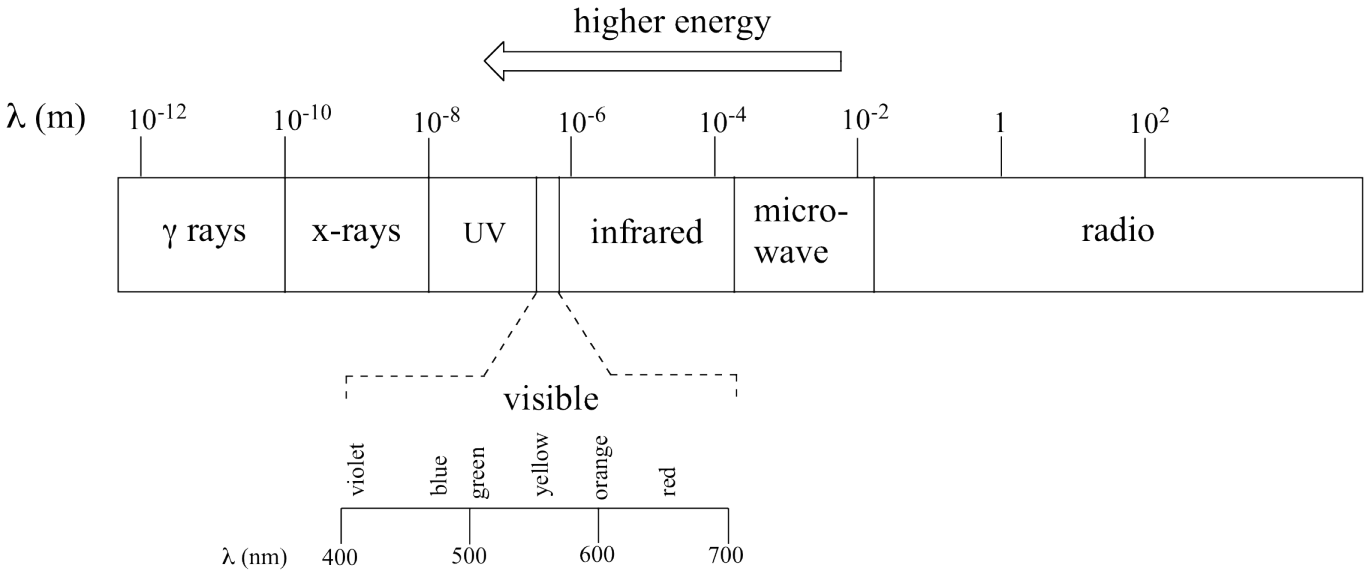
Organic chemists find it more convenient to deal with wavenumbers rather than wavelengths when discussing infrared spectra.

You will obtain infrared spectra for a number of the compounds you will synthesize in the laboratory component of this course.

The inverted peaks observed in the spectra correspond to molecular stretching and bending vibrations that only occur at certain quantized frequencies. When infrared radiation matching these frequencies falls on the molecule, the molecule absorbs energy and becomes excited. Eventually the molecule returns to its original (ground) state, and the energy which was absorbed is released as heat.

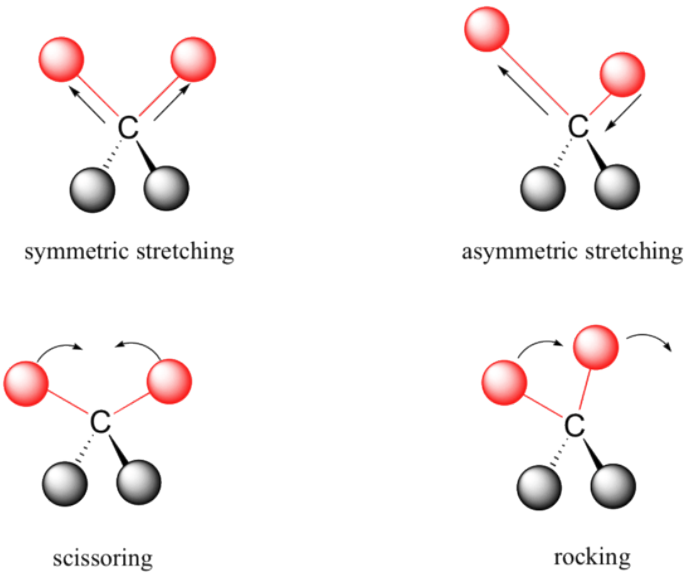
Infrared Spectroscopy

The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



Notice in the figure above that infrared light is lower energy than visible light. The wavelengths of infrared radiation are between 0.8 and 250 μm. The units that are typically used for infrared spectroscopy are wavenumbers (which is cm^{-1}). IR spectroscopy analyzes radiation between 40 to 13,000 cm^{-1}. But what type of excitation is occurring when infrared radiation is absorbed by a molecule?

Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few of which are illustrated below.

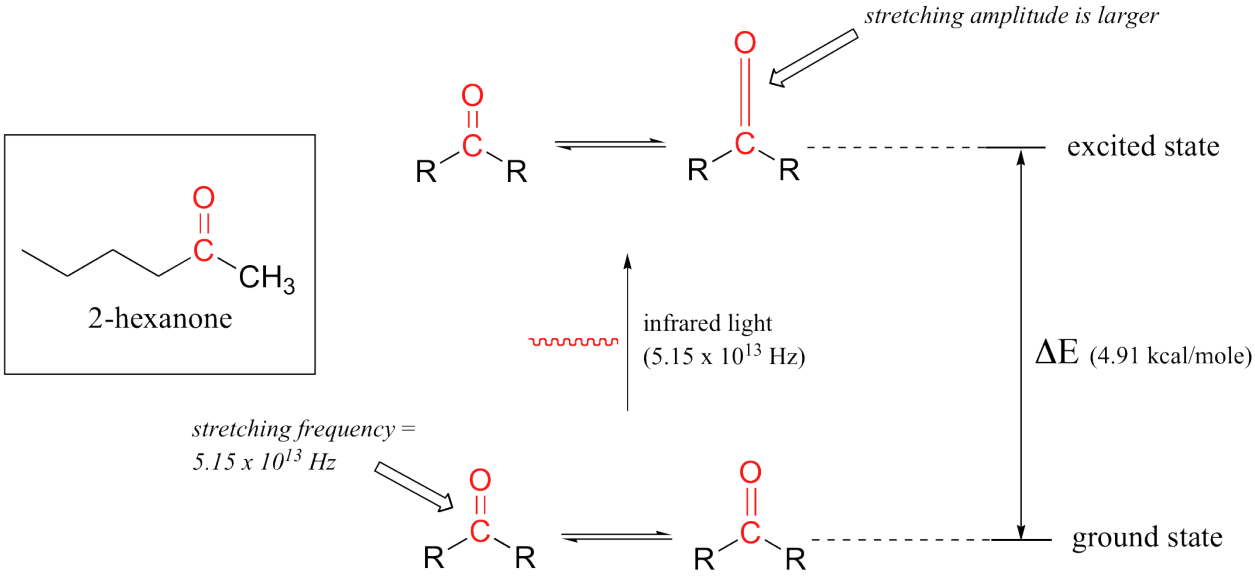


The energy of molecular vibration is *quantized* rather than continuous, meaning that a molecule can only stretch and bend at certain 'allowed' frequencies. If a molecule is exposed to electromagnetic radiation that matches the frequency of one of its vibrational modes, it will in most cases absorb energy from the radiation and jump to a higher vibrational energy state - what this means is that the *amplitude* of the vibration will increase, but the vibrational *frequency* will remain the same. The difference in energy between the two vibrational states is equal to the energy associated with the wavelength of radiation that was absorbed. It turns out that it is the *infrared* region of the electromagnetic spectrum which contains frequencies corresponding to the vibrational frequencies of organic bonds.

Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring. This spring is constantly

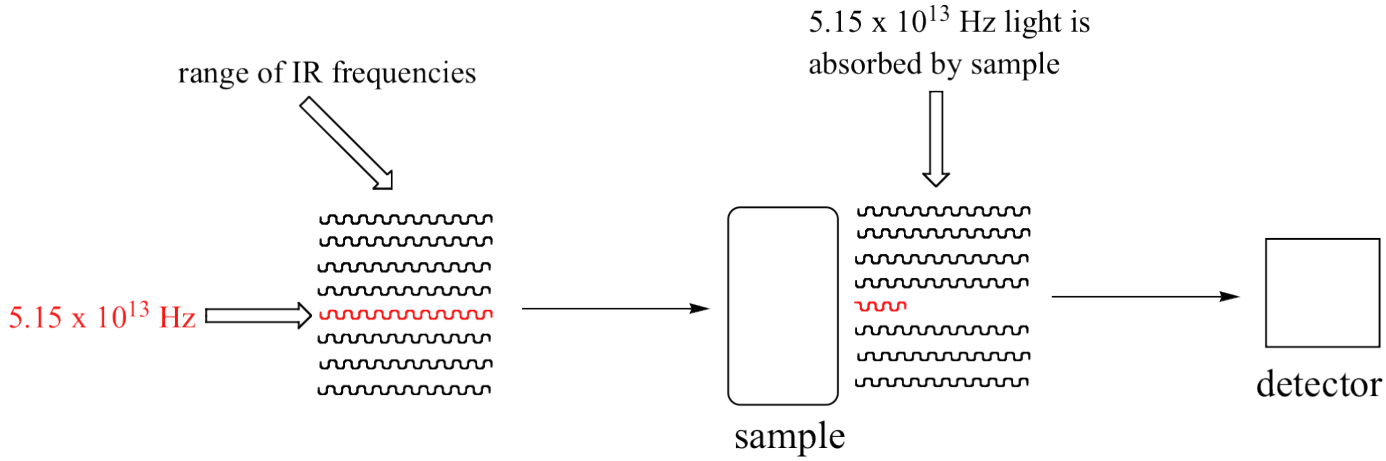
bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond. In the space of one second, the spring 'bounces' back and forth 5.15 x 10^{13} times - in other words, the ground-state frequency of carbonyl stretching for a the ketone group is about 5.15 x 10^{13} Hz.

If our ketone sample is irradiated with infrared light, the carbonyl bond will specifically absorb light with this same frequency, which by equations 4.1 and 4.2 corresponds to a wavelength of 5.83 x 10^{-6} m and an energy of 4.91 kcal/mol. When the carbonyl bond absorbs this energy, it jumps up to an excited vibrational state.



The value of **Δ**E - the energy difference between the low energy (ground) and high energy (excited) vibrational states - is equal to 4.91 kcal/mol, the same as the energy associated with the absorbed light frequency. The molecule does not remain in its excited vibrational state for very long, but quickly releases energy to the surrounding environment in form of heat, and returns to the ground state.

With an instrument called an infrared spectrophotometer, we can 'see' this vibrational transition. In the spectrophotometer, infrared light with frequencies ranging from about 10^{13} to 10^{14} Hz is passed though our sample of cyclohexane. Most frequencies pass right through the sample and are recorded by a detector on the other side.



Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

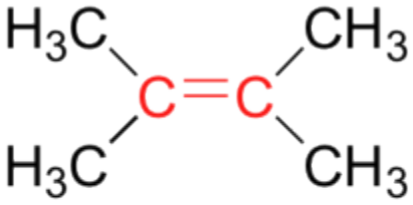
The vibrations of a 2-hexanone molecule are not, of course, limited to the simple stretching of the carbonyl bond. The various

carbon-carbon bonds also stretch and bend, as do the carbon-hydrogen bonds, and all of these vibrational modes also absorb different frequencies of infrared light.

The power of infrared spectroscopy arises from the observation that *different functional groups have different characteristic absorption frequencies*. The carbonyl bond in a ketone, as we saw with our 2-hexanone example, typically absorbs in the range of 5.11 - 5.18 x 10^{13} Hz, depending on the molecule. The carbon-carbon triple bond of an alkyne, on the other hand, absorbs in the range 6.30 - 6.80 x 10^{13} Hz. The technique is therefore very useful as a means of identifying which functional groups are present in a molecule of interest. If we pass infrared light through an unknown sample and find that it absorbs in the carbonyl frequency range but not in the alkyne range, we can infer that the molecule contains a carbonyl group but not an alkyne.

Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule*. Such vibrations are said to be **infrared active**. In general, the greater the polarity of the bond, the stronger its IR absorption. The carbonyl bond is very polar, and absorbs very strongly. The carbon-carbon triple bond in most alkynes, in contrast, is much less polar, and thus a stretching vibration does not result in a large change in the overall dipole moment of the molecule. Alkyne groups absorb rather weakly compared to carbonyls.

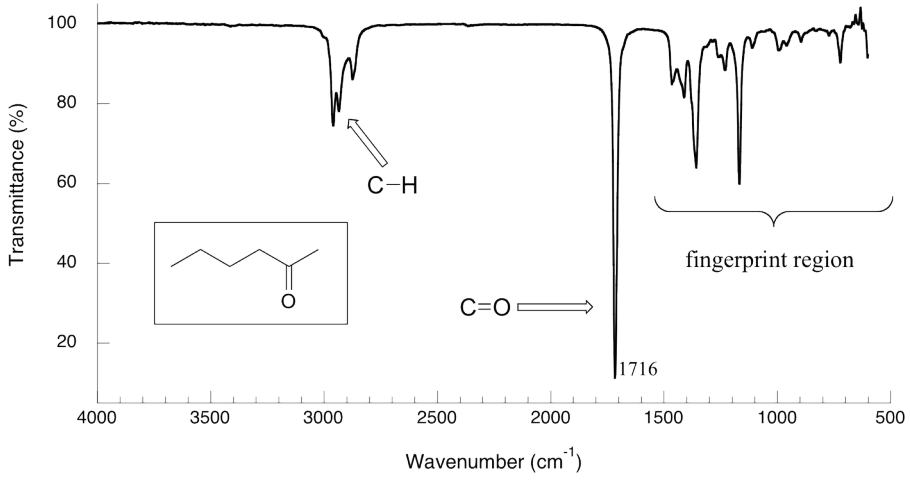
Some kinds of vibrations are **infrared inactive**. The stretching vibrations of completely symmetrical double and triple bonds, for example, do not result in a change in dipole moment, and therefore do not result in any absorption of light (but other bonds and vibrational modes in these molecules *do* absorb IR light).





infrared-inactive double and triple bonds

Now, let's look at some actual output from IR spectroscopy experiments. Below is the IR spectrum for 2-hexanone.



There are a number of things that need to be explained in order for you to understand what it is that we are looking at. On

the horizontal axis we see IR wavelengths expressed in terms of a unit called **wavenumber** (cm^{-1}), which tells us how many waves fit into one centimeter. On the vertical axis we see '**% transmittance**', which tells us how strongly light was absorbed at each frequency (100% transmittance means no absorption occurred at that frequency). The solid line traces the values of % transmittance for every wavelength – the 'peaks' (which are actually pointing down) show regions of strong absorption. For some reason, it is typical in IR spectroscopy to report wavenumber values rather than wavelength (in meters) or frequency (in Hz). The 'upside down' vertical axis, with absorbance peaks pointing down rather than up, is also a curious convention in IR spectroscopy. We wouldn't want to make things too easy for you!

Objectives

After completing this section, you should be able to

1. describe how the so-called "fingerprint region" of an infrared spectrum can assist in the identification of an unknown compound.
2. identify the functional group or groups present in a compound, given a list of the most prominent absorptions in the infrared spectrum and a table of characteristic absorption frequencies.
3. identify the broad regions of the infrared spectrum in which occur absorptions caused by
   a. N — H, C — H, and O — H
   b. You can't use 'macro parameter character #' in math mode and
      You can't use 'macro parameter character #' in math mode
   c. C = O, C = N$, and$C = C

Key Terms

Make certain that you can define, and use in context, the key term below.

- fingerprint region

Study Notes

When answering assignment questions, you may use this IR table to find the characteristic infrared absorptions of the various functional groups. However, you should be able to indicate in broad terms where certain characteristic absorptions occur. You can achieve this objective by memorizing the following table.

Region of Spectrum (cm^{-1})	**Absorption**
2500-4000	$\ce{\sf{N–H}}$, $\ce{\sf{O–H}}$, $\ce{\sf{C–H}}$
2000-2500	$\ce{\sf{C#C}}$, $\ce{\sf{C#N}}$
1500-2000	$\ce{\sf{C=O}}$, $\ce{\sf{C=N}}$, $\ce{\sf{C=C}}$
below 1500	Fingerprint region

The Origin of Group Frequencies

An important observation made by early researchers is that many functional group absorb infrared radiation at about the same wavenumber, regardless of the structure of the rest of the molecule. For example, C-H stretching vibrations usually appear between 3200 and 2800cm^{-1} and carbonyl(C=O) stretching vibrations usually appear between 1800 and 1600cm^{-1}. This makes these bands diagnostic markers for the presence of a functional group in a sample. These types of infrared bands are called group frequencies because they tell us about the presence or absence of specific functional groups in a sample.

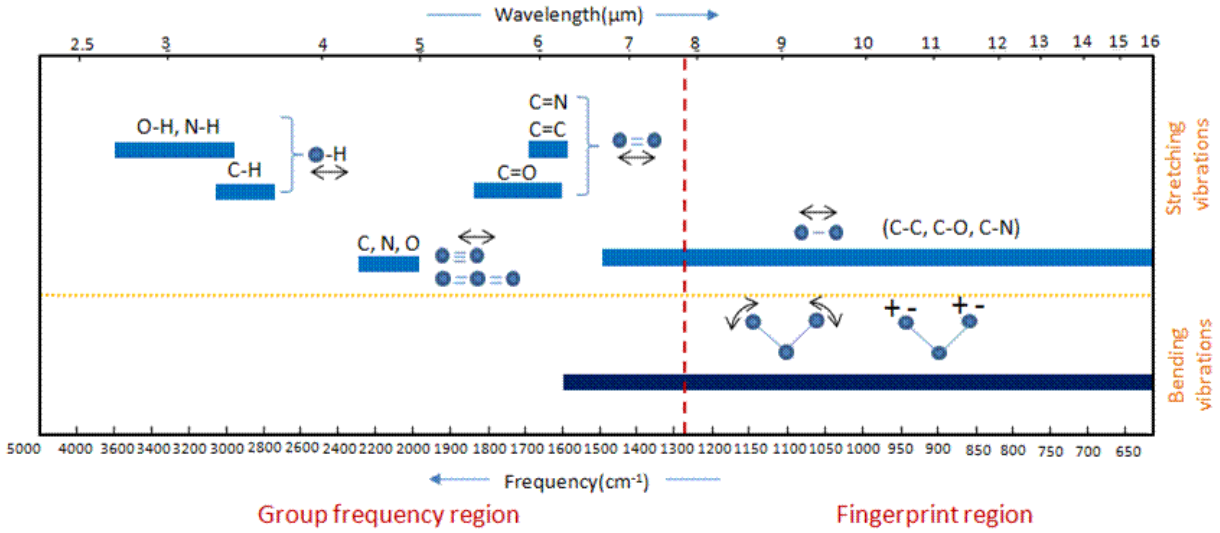
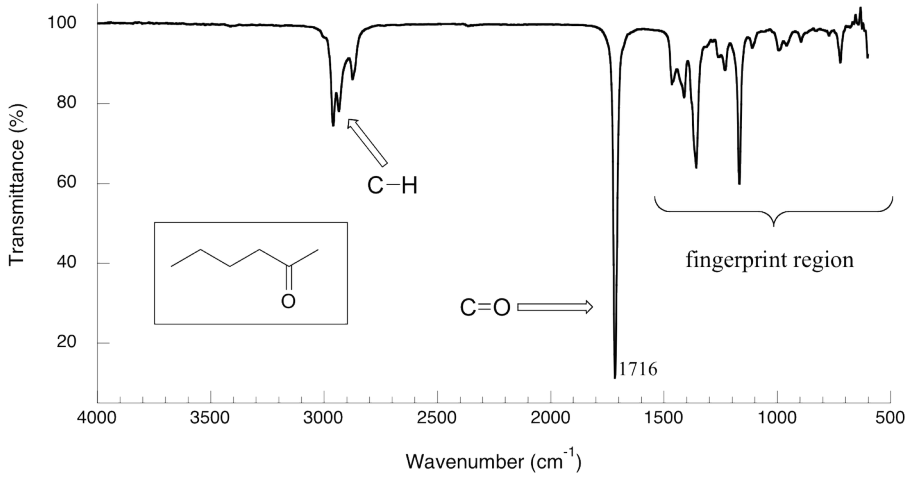


Figure 2. Group frequency and fingerprint regions of the mid-infrared spectrum

The region of the infrared spectrum from 1200 to 700 cm^{-1} is called the fingerprint region. This region is notable for the large number of infrared bands that are found there. Many different vibrations, including C-O, C-C and C-N single bond stretches, C-H bending vibrations, and some bands due to benzene rings are found in this region. The fingerprint region is often the most complex and confusing region to interpret, and is usually the last section of a spectrum to be interpreted. However, the utility of the fingerprint region is that the many bands there provide a fingerprint for a molecule.

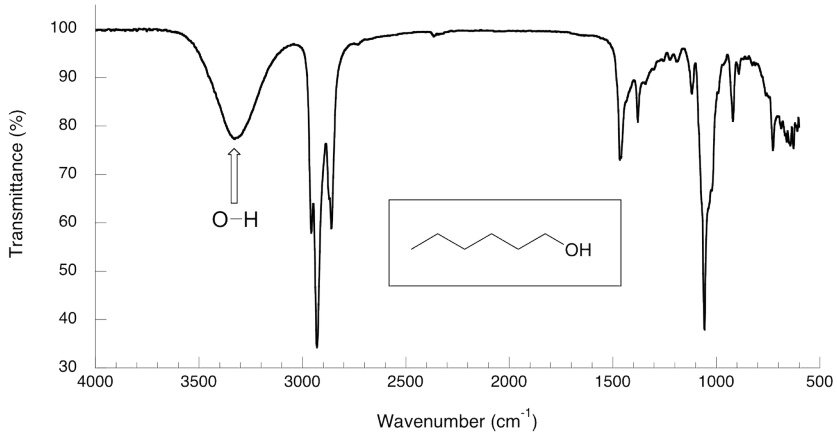


The key absorption peak in this spectrum is that from the carbonyl double bond, at 1716 cm^{-1} (corresponding to a wavelength of 5.86 mm, a frequency of 5.15 x 10^{13} Hz, and a ΔE value of 4.91 kcal/mol). Notice how strong this peak is, relative to the others on the spectrum: *a strong peak in the 1650-1750 cm^{-1} region is a dead giveaway for the presence of a carbonyl group*. Within that range, carboxylic acids, esters, ketones, and aldehydes tend to absorb in the shorter wavelength end (1700-1750 cm-1), while conjugated unsaturated ketones and amides tend to absorb on the longer wavelength end (1650-1700 cm^{-1}).

The jagged peak at approximately 2900-3000 cm^{-1} is characteristic of tetrahedral carbon-hydrogen bonds. This peak is not terribly useful, as just about every organic molecule that you will have occasion to analyze has these bonds. Nevertheless, it can serve as a familiar reference point to orient yourself in a spectrum.

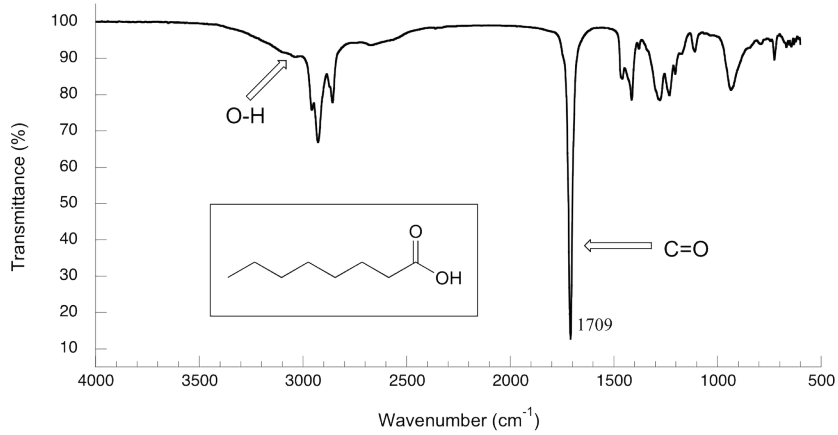
You will notice that there are many additional peaks in this spectrum in the longer-wavelength 400 -1400 cm^{-1} region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, nevertheless, contain valuable information. The reason for this is suggested by the name: just like a human fingerprint, the pattern of absorbance peaks in the fingerprint region is unique to every molecule, meaning that the data from an unknown sample can be compared to the IR spectra of known standards in order to make a positive identification. In the mid-1990's, for example, several paintings were identified as forgeries because scientists were able to identify the IR footprint region of red and yellow pigment compounds that would not have been available to the artist who supposedly created the painting (for more details see Chemical and Engineering News, Sept 10, 2007, p. 28).

Now, let's take a look at the IR spectrum for 1-hexanol.



As you can see, the carbonyl peak is gone, and in its place is a very broad 'mountain' centered at about 3400 cm^{-1}. This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen bonding between molecules.

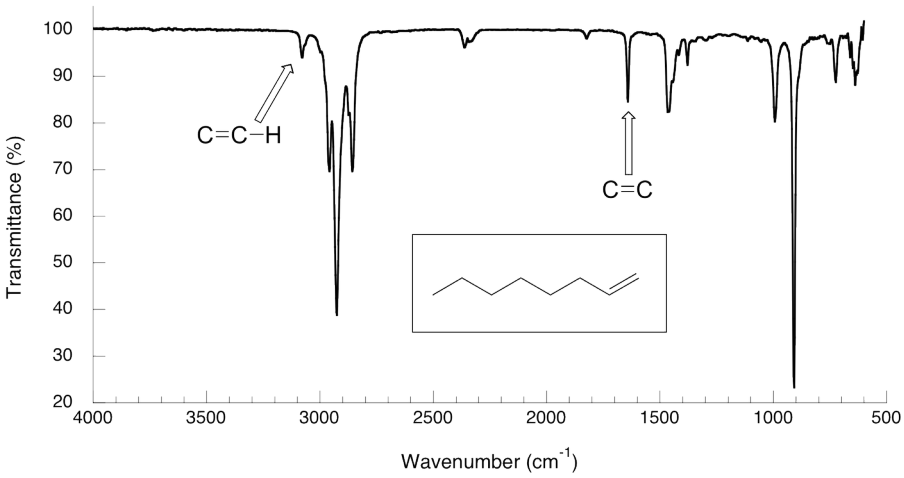
In the spectrum of octanoic acid we see, as expected, the characteristic carbonyl peak, this time at 1709 cm^{-1}.



We also see a low, broad absorbance band that looks like an alcohol, except that it is displaced slightly to the right (long-

wavelength) side of the spectrum, causing it to overlap to some degree with the C-H region. This is the characteristic carboxylic acid O-H single bond stretching absorbance.

The spectrum for 1-octene shows two peaks that are characteristic of alkenes: the one at 1642 cm^{-1} is due to stretching of the carbon-carbon double bond, and the one at 3079 cm-1 is due to stretching of the s bond between the alkene carbons and their attached hydrogens.



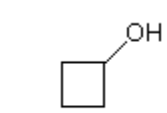
Alkynes have characteristic IR absorbance peaks in the range of 2100-2250 cm^{-1} due to stretching of the carbon-carbon triple bond, and terminal alkenes can be identified by their absorbance at about 3300 cm-1, due to stretching of the bond between the sp-hybridized carbon and the terminal hydrogen.

It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily recognized functional groups, which are summarized in this table.

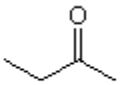
As you can imagine, obtaining an IR spectrum for a compound will not allow us to figure out the complete structure of even a simple molecule, unless we happen to have a reference spectrum for comparison. In conjunction with other analytical methods, however, IR spectroscopy can prove to be a very valuable tool, given the information it provides about the presence or absence of key functional groups. IR can also be a quick and convenient way for a chemist to check to see if a reaction has proceeded as planned. If we were to run a reaction in which we wished to convert cyclohexanone to cyclohexanol, for example, a quick comparison of the IR spectra of starting compound and product would tell us if we had successfully converted the ketone group to an alcohol.

More examples of IR spectra

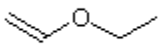
To illustrate the usefulness of infrared absorption spectra, examples for five C_4H_8O isomers are presented below their corresponding structural formulas. Try to associate each spectrum with one of the isomers in the row above it.



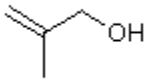
cyclobutanol



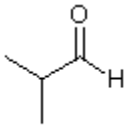
2-butanone



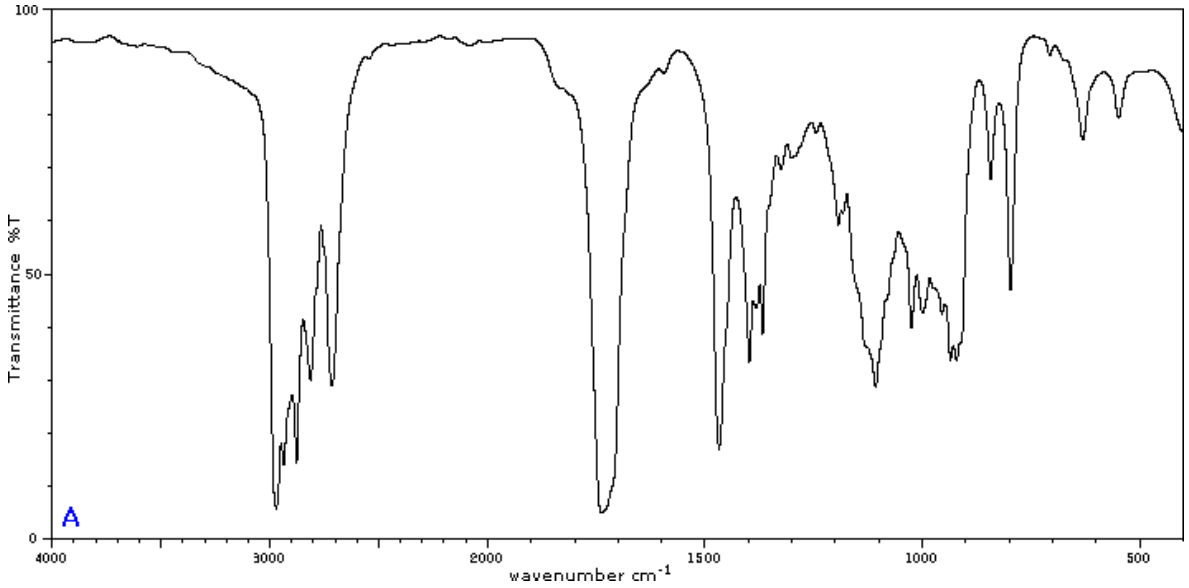
ethyl vinyl ether

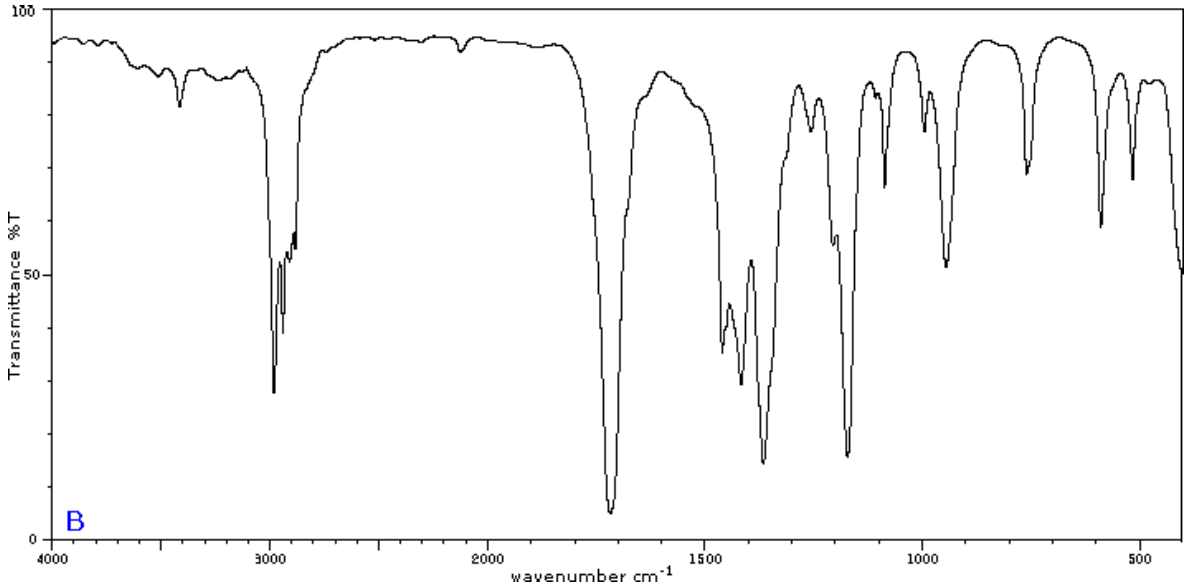


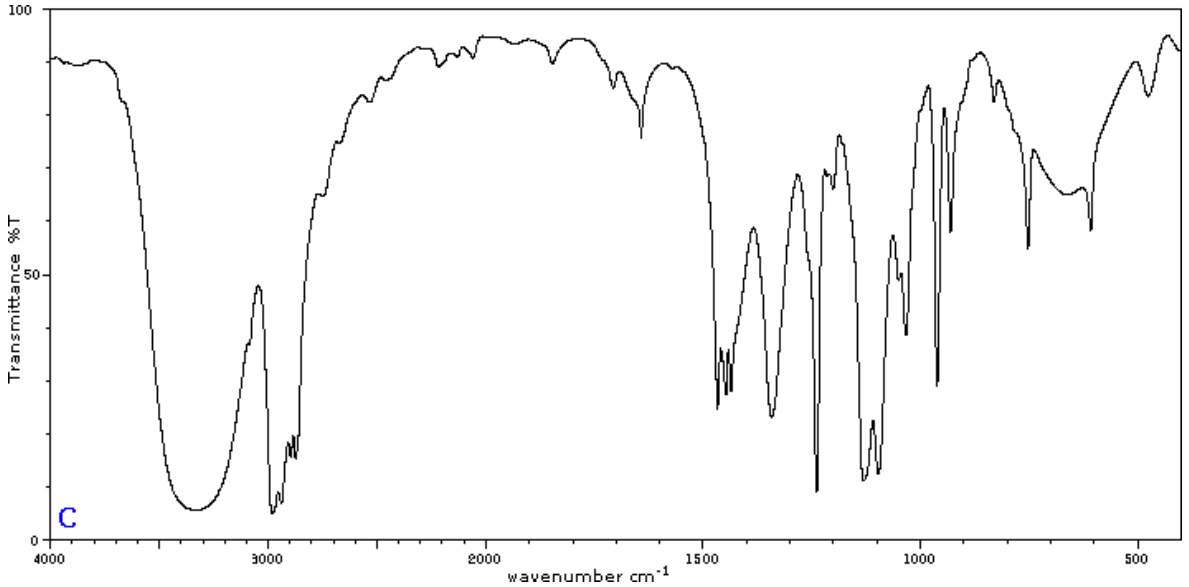
2-methyl-2-propen-1-ol

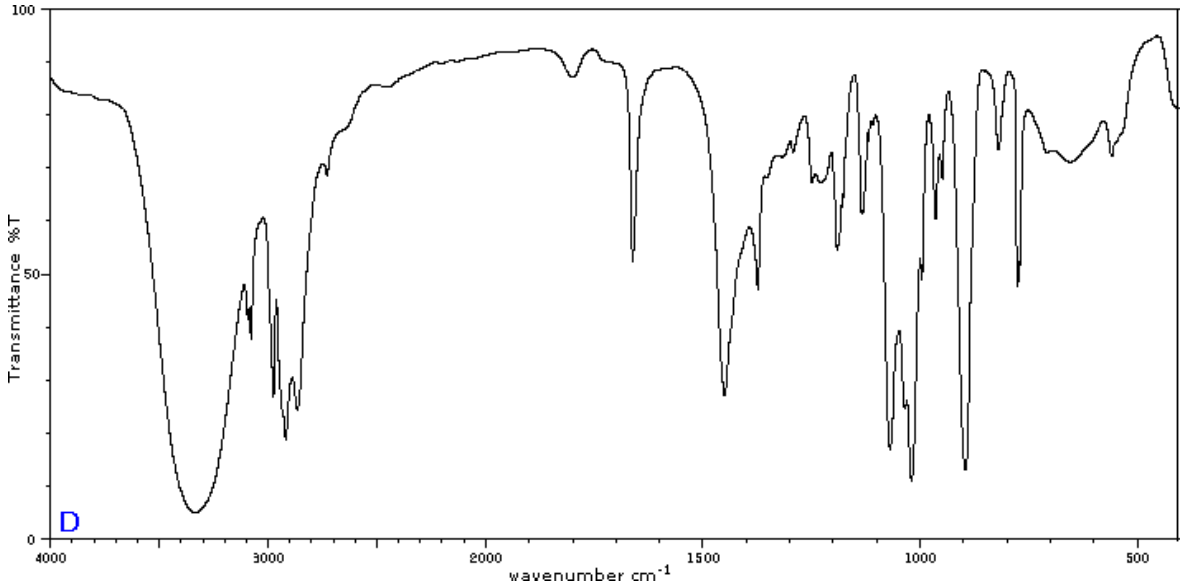


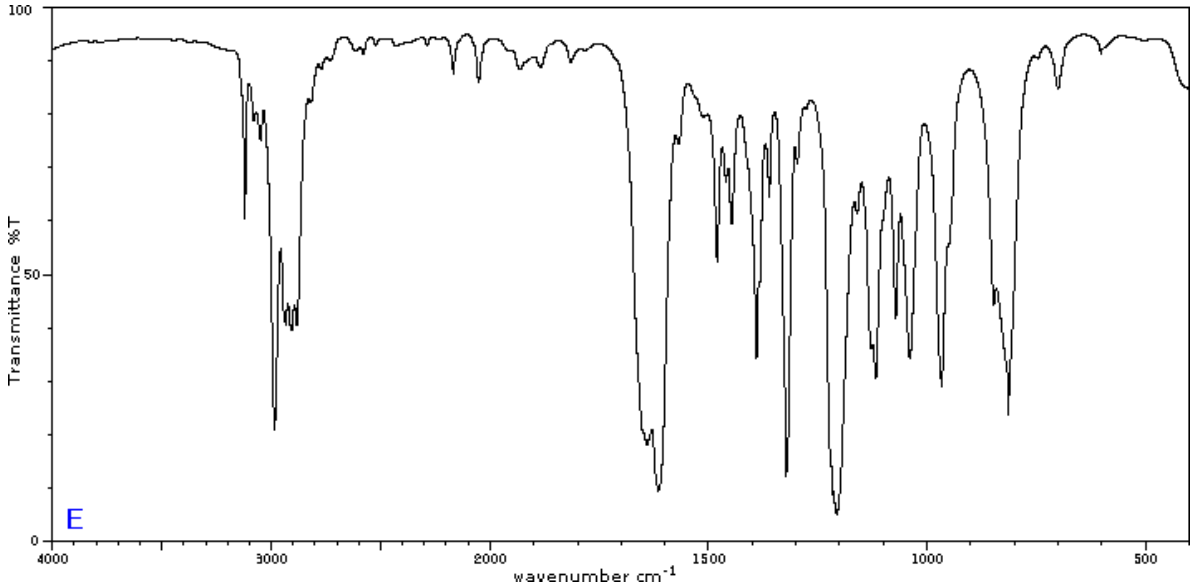
2-methylpropanal


100
50
0
Transmittance %T
A
4000
3000
2000
1500
1000
500
wavenumber cm-1


100
50
0
Transmittance %T
B
4000
3000
2000
1500
1000
500
wavenumber cm-1


100
50
0
Transmittance %T
C
4000
3000
2000
1500
1000
500
wavenumber cm-1





Exercises

Questions

Q12.7.1

What functional groups give the following signals in an IR spectrum?

A) 1700 cm^{-1}

B) 1550 cm^{-1}

C) 1700 cm^{-1} and 2510-3000 cm^{-1}

Q12.7.2

How can you distinguish the following pairs of compounds through IR analysis?

A) CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)

B) Cyclopentane and 1-pentene.

C)

12.7(2).png

Solutions

S12.7.1

12.7.png

S12.7.2

A) A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.

B) 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene

C) Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

Objective

After completing this section, you should be able to use an infrared spectrum to determine the presence of functional groups, such as alcohols, amines and carbonyl groups, in an unknown compound, given a list of infrared absorption frequencies.

Study Notes

In Chapter 12.7 you should have learned, in broad terms, where a few key absorptions occur. Otherwise, to find the characteristic infrared absorptions of the various functional groups, refer to this IR table.

Spectral Interpretation by Application of Group Frequencies

One of the most common application of infrared spectroscopy is to the identification of organic compounds. The major classes of organic molecules are shown in this category and also linked on the bottom page for the number of collections of spectral information regarding organic molecules.

Hydrocarbons

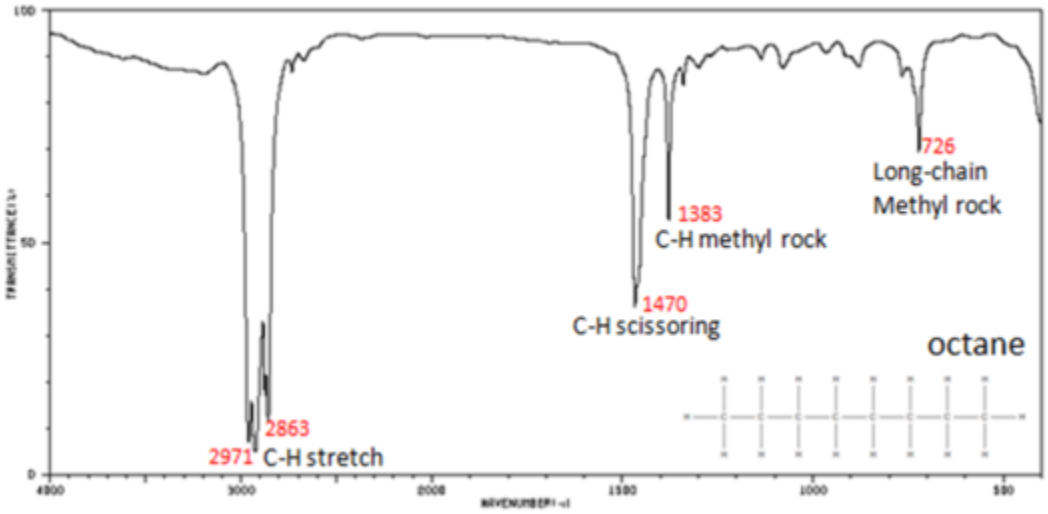
Hydrocarbons compounds contain only C-H and C-C bonds, but there is plenty of information to be obtained from the infrared spectra arising from C-H stretching and C-H bending.

In alkanes, which have very few bands, each band in the spectrum can be assigned:

- C–H stretch from 3000–2850 cm^{-1}
- C–H bend or scissoring from 1470-1450 cm^{-1}
- C–H rock, methyl from 1370-1350 cm^{-1}
- C–H rock, methyl, seen only in long chain alkanes, from 725-720 cm^{-1}

Figure 11.8.1 shows the IR spectrum of octane. Since most organic compounds have these features, these C-H vibrations are

usually not noted when interpreting a routine IR spectrum. Note that the change in dipole moment with respect to distance for the C-H stretching is greater than that for others shown, which is why the C-H stretch band is the more intense.



11.8.1: Infrared Spectrum of Octane

In alkenes compounds, each band in the spectrum can be assigned:

- C=C stretch from 1680-1640 cm^{-1}
- =C–H stretch from 3100-3000 cm^{-1}
- =C–H bend from 1000-650 cm^{-1}

Figure 11.8.2 shows the IR spectrum of 1-octene. As alkanes compounds, these bands are not specific and are generally not noted because they are present in almost all organic molecules.

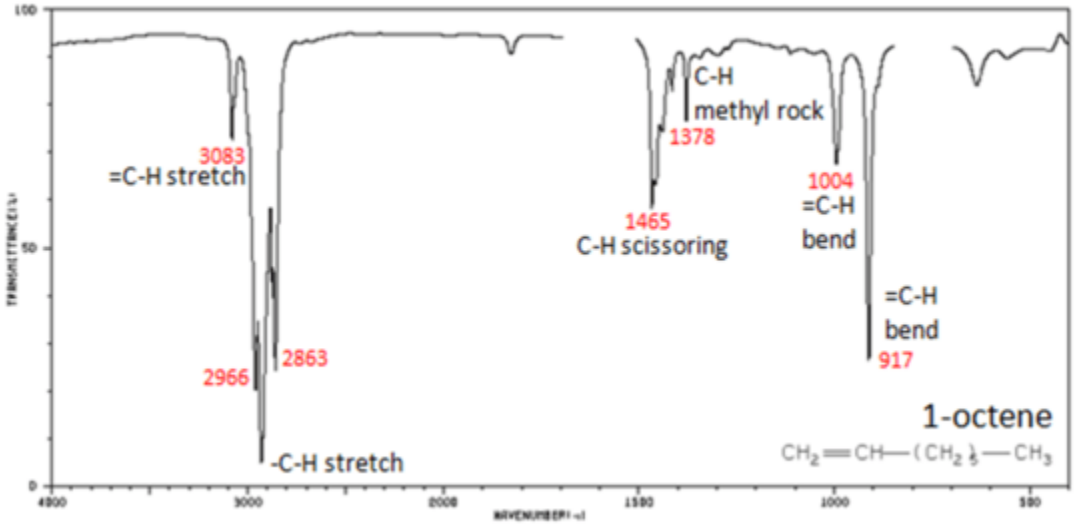


Figure 11.8.2: Infrared Spectrum of 1-Octene

In alkynes, each band in the spectrum can be assigned:

- –C≡C– stretch from 2260-2100 cm^{-1}
- –C≡C–H: C–H stretch from 3330-3270 cm^{-1}
- –C≡C–H: C–H bend from 700-610 cm^{-1}

The spectrum of 1-hexyne, a terminal alkyne, is shown below.

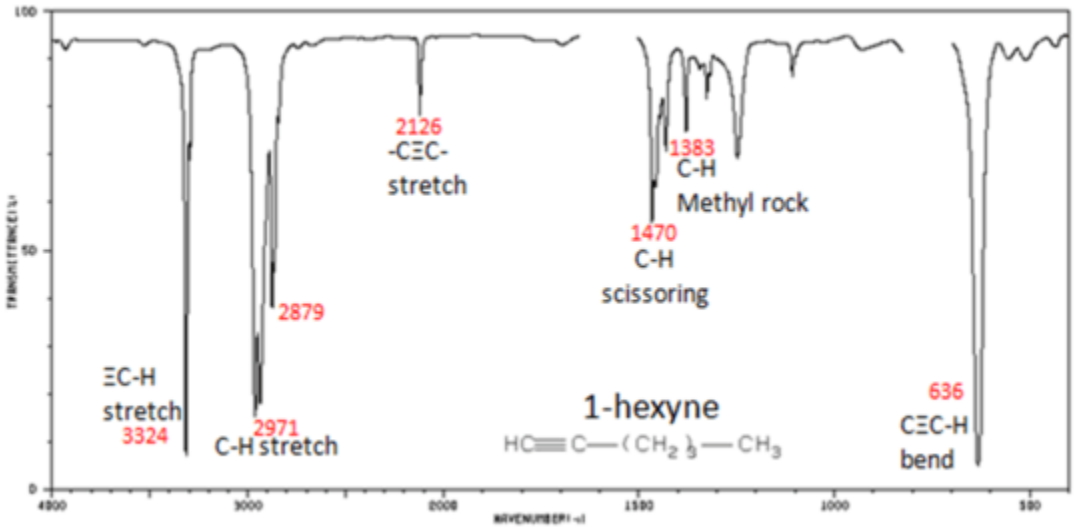


Figure 11.8.3: Infrared Spectrum of 1-Hexyne

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}. Figure 11.8.4 shows the spectrum of toluene.

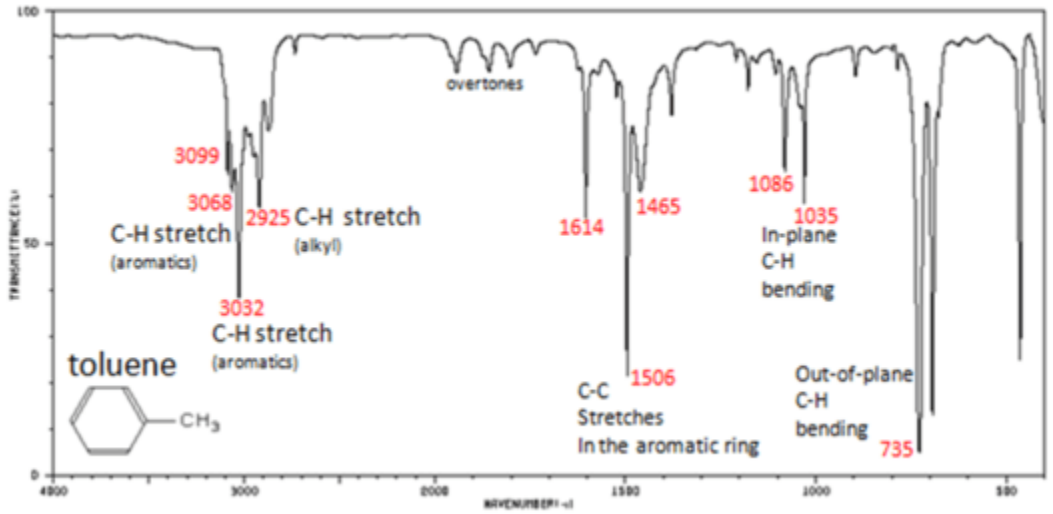


Figure 11.8.4: Infrared Spectrum of Toluene

Functional Groups Containing the C-O Bond

Alcohols have IR absorptions associated with both the O-H and the C-O stretching vibrations.

- O–H stretch, hydrogen bonded 3500-3200 cm^{-1}
- C–O stretch 1260-1050 cm^{-1} (s)

Figure 11.8.5 shows the spectrum of ethanol. Note the very broad, strong band of the O–H stretch.

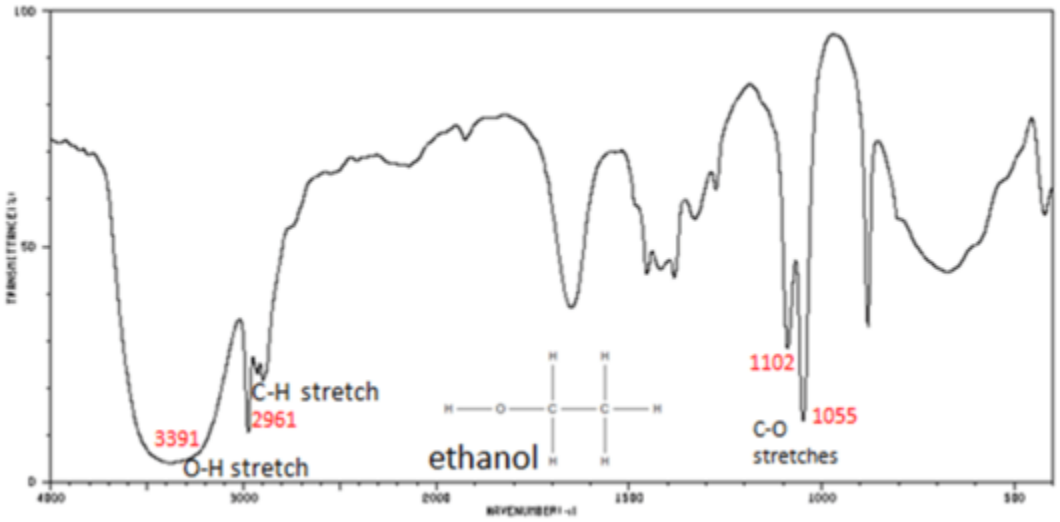


Figure 11.8.5: Infrared Spectrum of Ethanol

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

- C=O stretch - aliphatic ketones 1715 cm^{-1}
- α, β -unsaturated ketones 1685-1666 cm^{-1}

Figure 11.8.6 shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

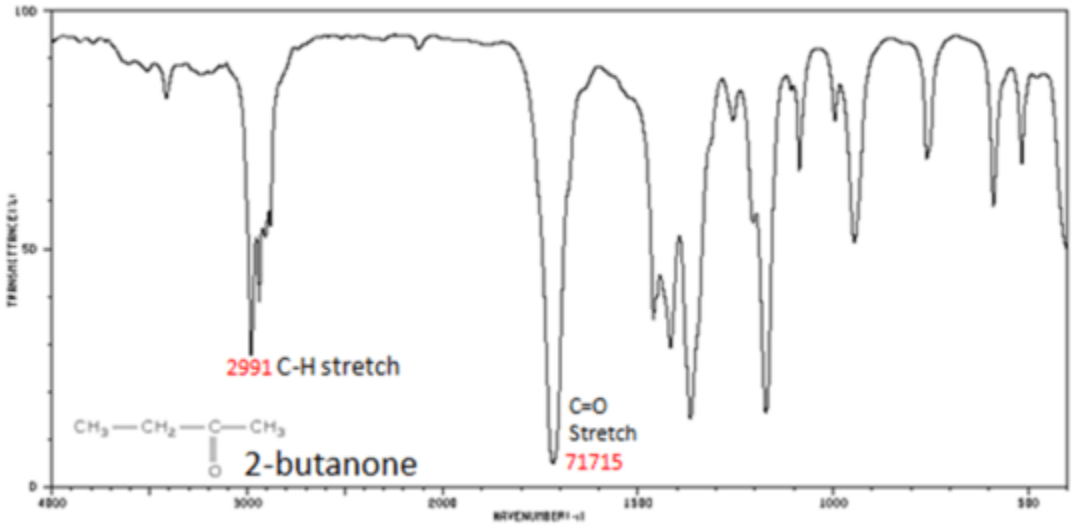


Figure 11.8.6: Infrared Spectrum of 2-Butanone

If a compound is suspected to be an aldehyde, a peak always appears around 2720 cm^{-1} which often appears as a shoulder-type

peak just to the right of the alkyl C–H stretches.

- H–C=O stretch 2830-2695 cm^{-1}
- C=O stretch:
  - aliphatic aldehydes 1740-1720 cm^{-1}
  - α, β -unsaturated aldehydes 1710-1685 cm^{-1}

Figure 11.8.7 shows the spectrum of butyraldehyde.

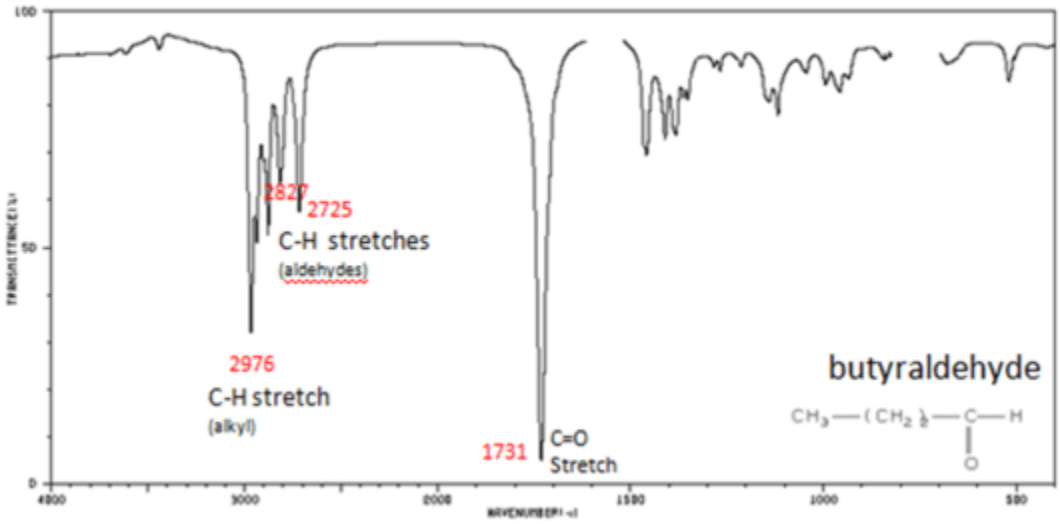


Figure 11.8.7: Infrared Spectrum of Butyraldehyde

The carbonyl stretch C=O of esters appears:

- C=O stretch
  - aliphatic from 1750-1735 cm^{-1}
  - α, β -unsaturated from 1730-1715 cm^{-1}
- C–O stretch from 1300-1000 cm^{-1}

Figure 11.8.8: shows the spectrum of ethyl benzoate.

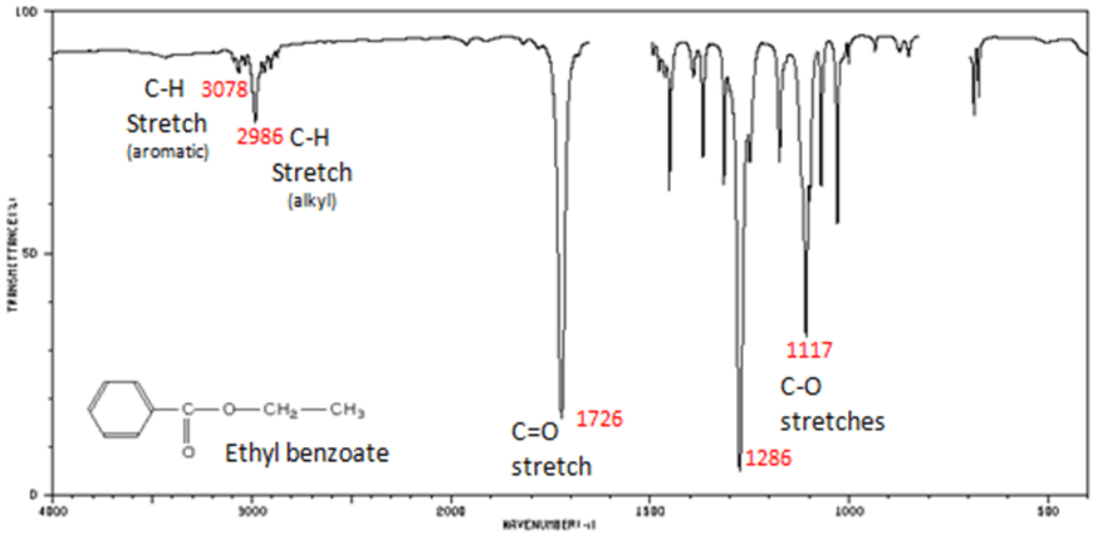


Figure 11.8.8: Infrared Spectrum of Ethyl benzoate

The carbonyl stretch C=O of a carboxylic acid appears as an intense band from 1760-1690 cm^{-1}. The exact position of this broad band depends on whether the carboxylic acid is saturated or unsaturated, dimerized, or has internal hydrogen bonding.

- O–H stretch from 3300-2500 cm^{-1}
- C=O stretch from 1760-1690 cm^{-1}
- C–O stretch from 1320-1210 cm^{-1}
- O–H bend from 1440-1395 and 950-910 cm^{-1}

Figure 11.8.9: shows the spectrum of hexanoic acid.

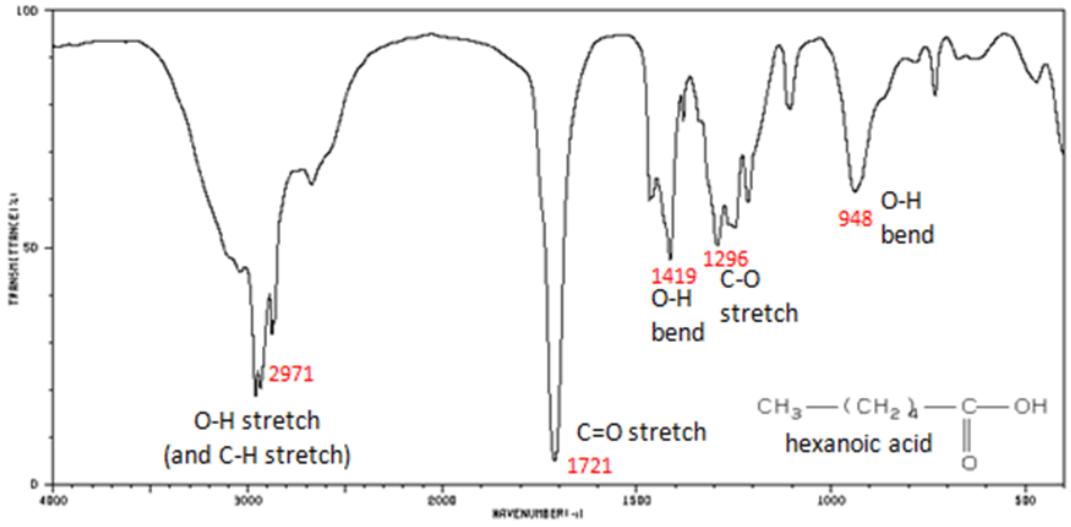


Figure 11.8.9: Infrared Spectrum of Hexanoic acid

Organic Nitrogen Compounds

- N–O asymmetric stretch from 1550-1475 cm^{-1}
- N–O symmetric stretch from 1360-1290 cm^{-1}

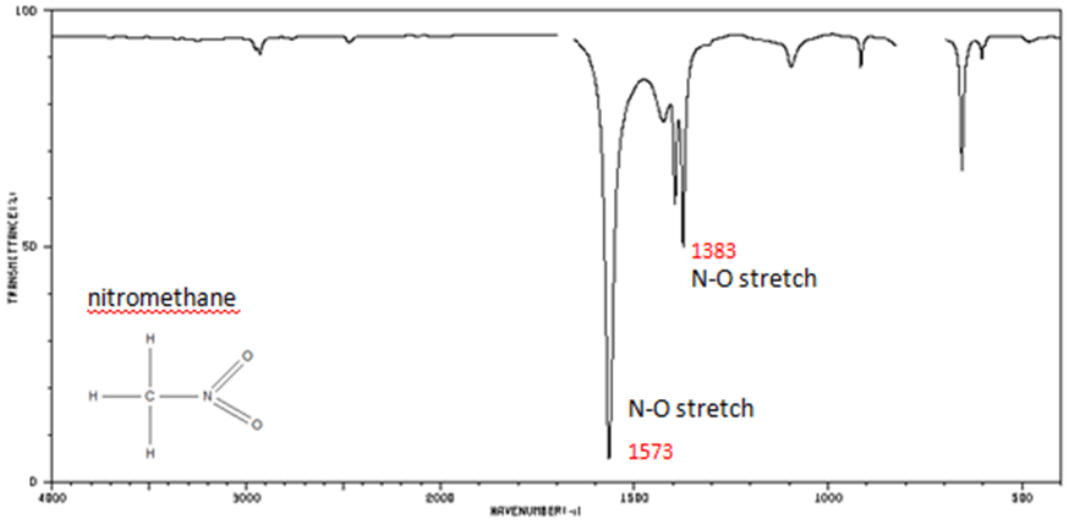


Figure 11.8.10: Infrared Spectrum of Nitomethane

Organic Compounds Containing Halogens

Alkyl halides are compounds that have a C–X bond, where X is a halogen: bromine, chlorine, fluorene, or iodine.

- C–H wag (-CH_2X) from 1300-1150 cm^{-1}
- C–X stretches (general) from 850-515 cm^{-1}
  - C–Cl stretch 850-550 cm^{-1}
  - C–Br stretch 690-515 cm^{-1}

The spectrum of 1-chloro-2-methylpropane are shown below.

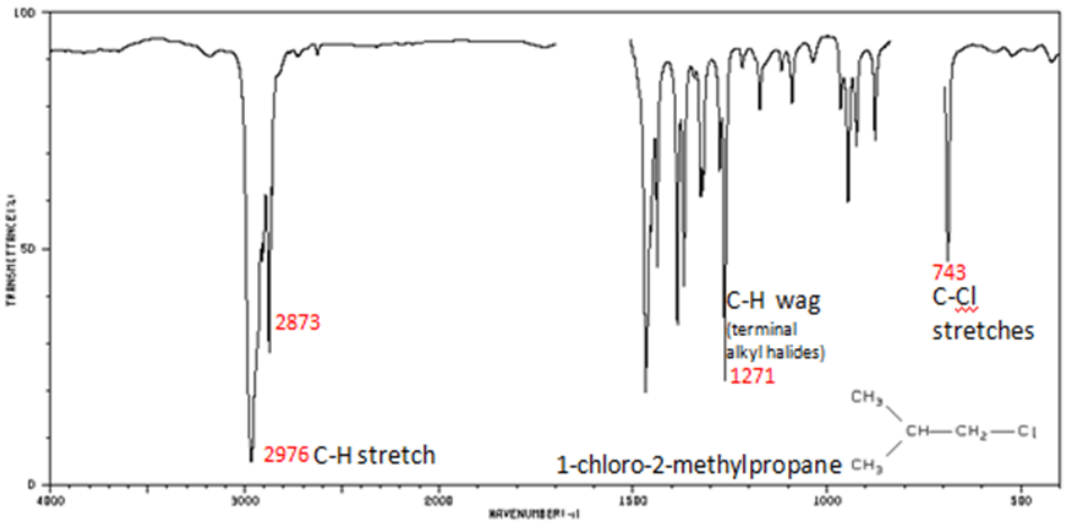


Figure 11.8.11: Infrared Spectrum of 1-chloro-2-methylpropane

For more Infrared spectra Spectral database of organic molecules is introduced to use free database. Also, the infrared spectroscopy correlation table is linked on bottom of page to find other assigned IR peaks.

Exercise 11.8.1

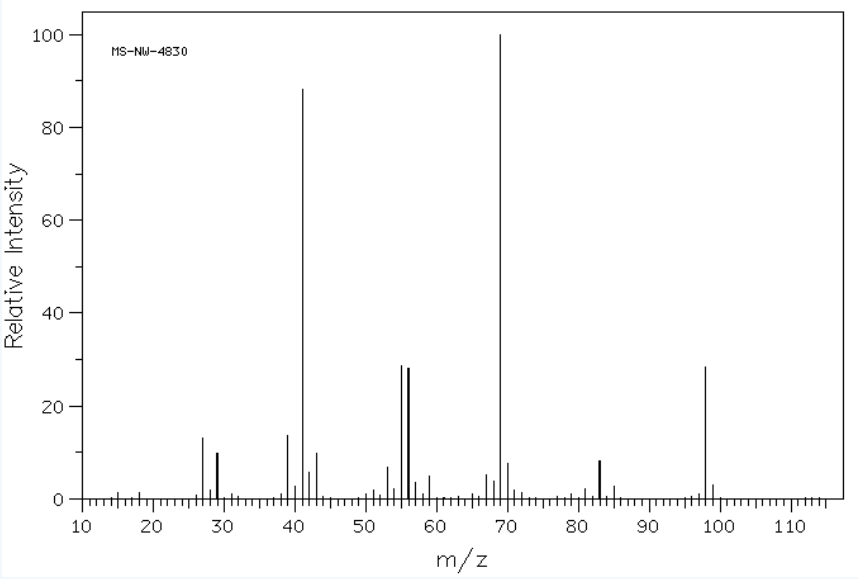
Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

Answer available at the end of this section.

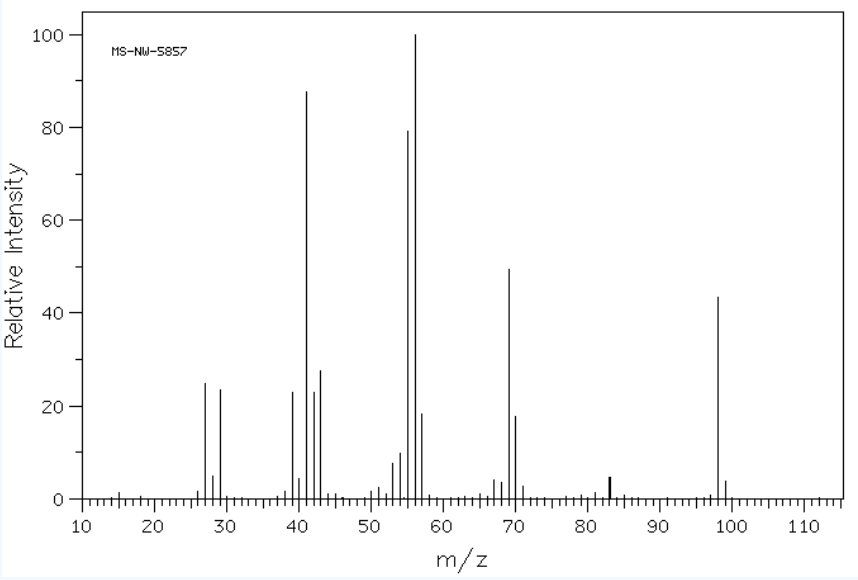
Exercise 11.8.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:



B:

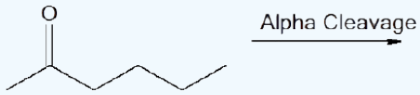


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

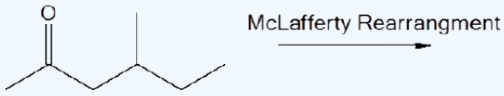
Answer available at the end of this section.

Exercise 11.8.3

What are the masses of all the components in the following fragmentations?







Answer available at the end of this section.

Exercise 11.8.4

Which of the following frequencies/wavelengths are higher energy

a. $\lambda = 2.0 \times 10^{-6}$ m or $\lambda = 3.0 \times 10^{-9}$ m
b. $\upsilon = 3.0 \times 10^{9}$ Hz or $\upsilon = 3.0 \times 10^{-6}$ Hz

Answer available at the end of this section.

Exercise 11.8.5

Calculate the energies for the following;

a. Gamma Ray $\lambda = 4.0 \times 10^{-11}$ m
b. X-Ray $\lambda = 4.0 \times 10^{-9}$ m
c. UV light $\upsilon = 5.0 \times 10^{15}$ Hz
d. Infrared Radiation $\lambda = 3.0 \times 10^{-5}$ m
e. Microwave Radiation $\upsilon = 3.0 \times 10^{11}$ Hz

Answer available at the end of this section.

Exercise 11.8.6

What functional groups give the following signals in an IR spectrum?

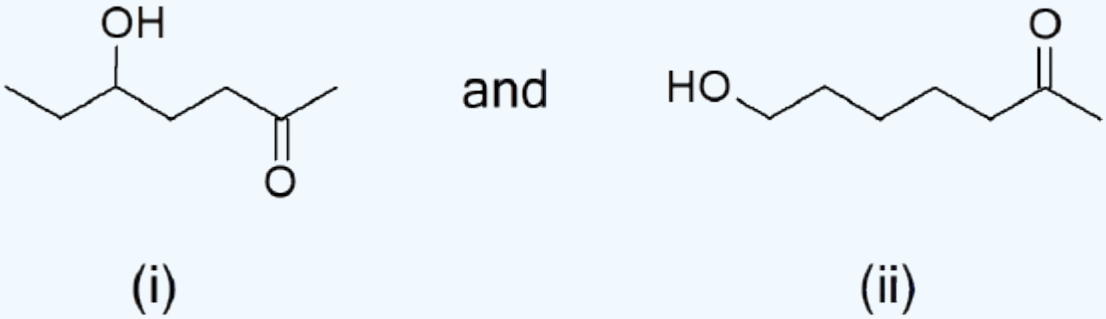
a. 1700 cm^{-1}
b. 1550 cm^{-1}
c. 1700 cm^{-1} and 2510-3000 cm^{-1}

Answer available at the end of this section.

Exercise 11.8.7

How can you distinguish the following pairs of compounds through IR analysis?

a. CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)
b. Cyclopentane and 1-pentene.
c.

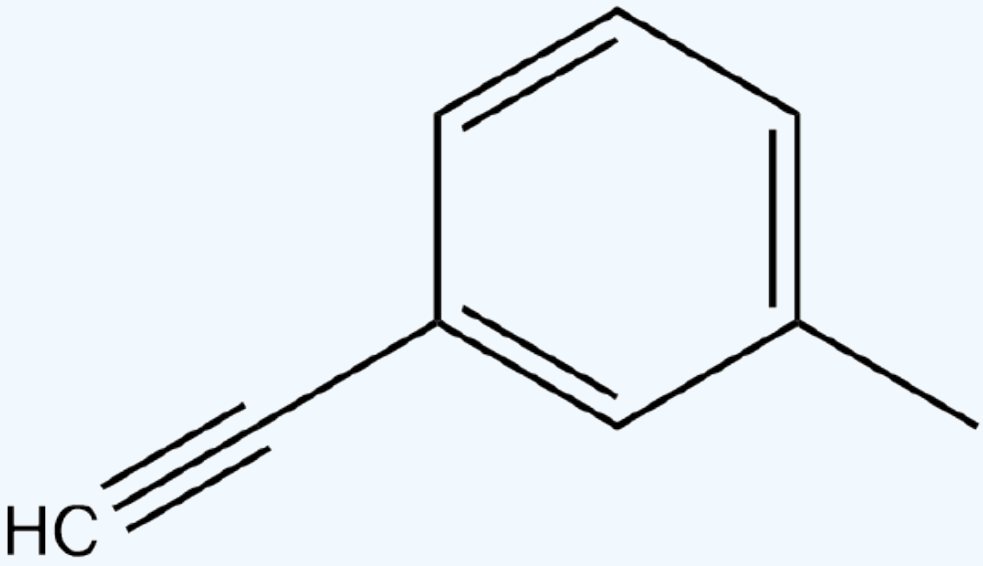


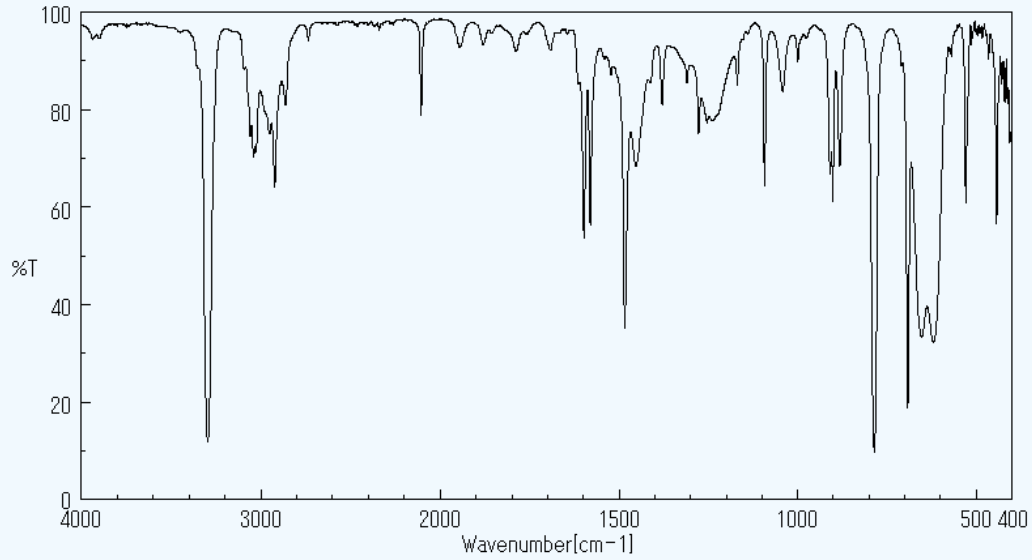
(i) (ii)

Answer available at the end of this section.

Exercise 11.8.8

The following spectra is for the accompanying compound. What are the peaks that you can I identify in the spectrum?



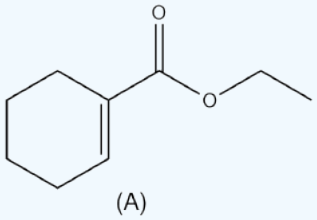


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

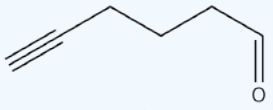
Answer available at the end of this section.

Exercise 11.8.9

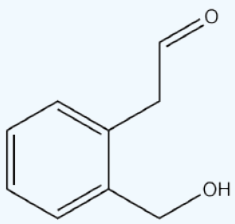
What absorptions would the following compounds have in an IR spectra?



(A)



(B)



(C)

Answer available at the end of this section.

Answers

Exercise 11.8.1

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

Exercise 11.8.2

The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

Exercise 11.8.3

12.3.png

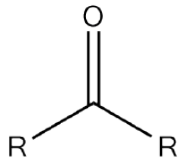
Exercise 11.8.4

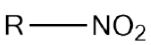
a. $\lambda = 3.00 \times 10^{-9}$ m
b. $\upsilon = 3.00 \times 10^{9}$ Hz

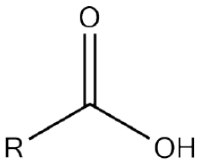
Exercise 11.8.5

a. 4.965×10^{-15} J
b. 4.965×10^{-17} J
c. 3.31×10^{-18} J
d. 6.62×10^{-21} J
e. 1.99×10^{-22} J

Exercise 11.8.6

A)  Carbonyl

B)  Nitro

C)  Carboxylic Acid

Exercise 11.8.7

a. A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.
b. 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene
c. Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

Exercise 11.8.8

Frequency (cm^{-1}) Functional Groups

3200 C≡C-H

2900-3000 C-C-H, C=C-H

2100 C≡C

1610 C=C

(There is also an aromatic undertone region between 2000-1600 which describes the substitution on the phenyl ring.)

Exercise 11.8.9

A)

Frequency (cm-1) Functional Group

2900-3000 C-C-H, C=C-H

1710 C=O

1610 C=C

1100 C-O

B)

Frequency (cm-1) Functional Group

3200 C≡C-H

2900-3000 C-C-H, C=C-H
2100 C≡C
1710 C=O

C)

Frequency (cm-1) Functional Group
3300 (broad) O-H
2900-3000 C-C-H, C=C-H
2000-1800 Aromatic Overtones
1710 C=O
1610 C=C

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11.9: Measuring the Molecular Mass of Organic Compounds: Mass Spectrometry

Objectives

After completing this section, you should be able to

1. describe, briefly, how a mass spectrometer works.
2. sketch a simple diagram to show the essential features of a mass spectrometer.
3. identify peaks in a simple mass spectrum, and explain how they arise.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- base peak
- parent peak (molecular ion peak)
- cation radical
- relative abundance
- mass spectrometer
- mass spectroscopy
- mass spectrum
- molecular ion (M+·)
- mass-to-charge ratio (*m/z*)

Study Notes

You may remember from general first-year chemistry how mass spectroscopy has been used to establish the atomic mass and abundance of isotopes.

Mass spectrometers are large and expensive, and usually operated only by fully trained personnel, so you may not have the opportunity to use such an instrument as part of this course. Research chemists often rely quite heavily on mass spectra to assist them in the identification of compounds, and you will be required to interpret simple mass spectra both in assignments and on examinations. Note that in most attempts to identify an unknown compound, chemists do not rely exclusively on the results obtained from a single spectroscopic technique. A combination of chemical and physical properties and spectral evidence is usually employed.

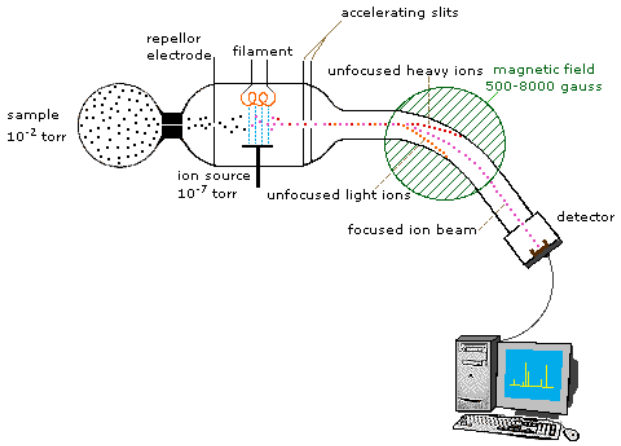
The Mass Spectrometer

In order to measure the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can be moved about and manipulated by external electric and magnetic fields. The three essential functions of a mass spectrometer, and the associated components, are:

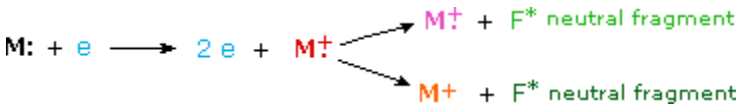
1. A small sample is ionized, usually to cations by loss of an electron. **The Ion Source**
2. The ions are sorted and separated according to their mass and charge. **The Mass Analyzer**
3. The separated ions are then measured, and the results displayed on a chart. **The Detector**

Because ions are very reactive and short-lived, their formation and manipulation must be conducted in a vacuum. Atmospheric pressure is around 760 torr (mm of mercury). The pressure under which ions may be handled is roughly 10^{-5} to 10^{-8} torr (less than a billionth of an atmosphere). Each of the three tasks listed above may be accomplished in different ways. In one common

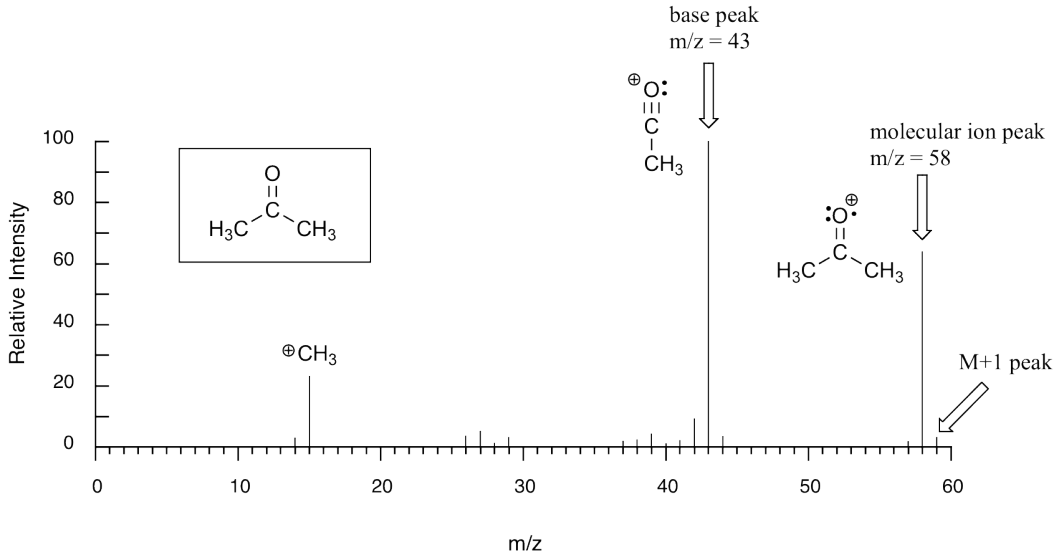
procedure, ionization is effected by a high energy beam of electrons, and ion separation is achieved by accelerating and focusing the ions in a beam, which is then bent by an external magnetic field. The ions are then detected electronically and the resulting information is stored and analyzed in a computer. A mass spectrometer operating in this fashion is outlined in the following diagram. The heart of the spectrometer is the **ion source**. Here molecules of the sample (black dots) are bombarded by electrons (light blue lines) issuing from a heated filament. This is called an **EI** (electron-ionization) source. Gases and volatile liquid samples are allowed to leak into the ion source from a reservoir (as shown). Non-volatile solids and liquids may be introduced directly. Cations formed by the electron bombardment (red dots) are pushed away by a charged repellor plate (anions are attracted to it), and accelerated toward other electrodes, having slits through which the ions pass as a beam. Some of these ions fragment into smaller cations and neutral fragments. A perpendicular magnetic field deflects the ion beam in an arc whose radius is inversely proportional to the mass of each ion. Lighter ions are deflected more than heavier ions. By varying the strength of the magnetic field, ions of different mass can be focused progressively on a detector fixed at the end of a curved tube (also under a high vacuum).



When a high energy electron collides with a molecule it often ionizes it by knocking away one of the molecular electrons (either bonding or non-bonding). This leaves behind a **molecular ion** (colored red in the following diagram). Residual energy from the collision may cause the molecular ion to fragment into neutral pieces (colored green) and smaller **fragment ions** (colored pink and orange). The molecular ion is a radical cation, but the fragment ions may either be radical cations (pink) or carbocations (orange), depending on the nature of the neutral fragment. An animated display of this ionization process will appear if you click on the ion source of the mass spectrometer diagram.



Below is typical output for an electron-ionization MS experiment (MS data below is derived from the Spectral Database for Organic Compounds, a free, web-based service provided by AIST in Japan.



The sample is acetone. On the horizontal axis is the value for m/z, which is the mass to charge ratio (as we stated above, the charge z is almost always +1, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set to 100%, and all other peaks are recorded relative to this value. For acetone, the base peak corresponds to a fragment with m/z = 43 - . The molecular weight of acetone is 58, so we can identify the peak at m/z = 58 as that corresponding to the **molecular ion peak**, or **parent peak**. Notice that there is a small peak at m/z = 59: this is referred to as the **M+1 peak**. How can there be an ion that has a greater mass than the molecular ion? Simple: a small fraction - about 1.1% - of all carbon atoms in nature are actually the ^{13}C rather than the ^{12}C isotope. The ^{13}C isotope is, of course, heavier than ^{12}C by 1 mass unit. In addition, about 0.015% of all hydrogen atoms are actually deuterium, the ^{2}H isotope. So the M+1 peak represents those few acetone molecules in the sample which contained either a ^{13}C or ^{2}H.

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11.10: Fragmentation Patterns of Organic Molecules

Objectives

After completing this section, you should be able to

1. suggest possible molecular formulas for a compound, given the *m/z* value for the molecular ion, or a mass spectrum from which this value can be obtained.
2. predict the relative heights of the M+·, (M + 1)+·, etc., peaks in the mass spectrum of a compound, given the natural abundance of the isotopes of carbon and the other elements present in the compound.
3. interpret the fragmentation pattern of the mass spectrum of a relatively simple, known compound (e.g., hexane).
4. use the fragmentation pattern in a given mass spectrum to assist in the identification of a relatively simple, unknown compound (e.g., an unknown alkane).

Study Notes

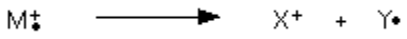
When interpreting fragmentation patterns, you may find it helpful to know that, as you might expect, the weakest carbon-carbon bonds are the ones most likely to break. You might wish to refer to the table of bond dissociation energies when attempting problems involving the interpretation of mass spectra.

This page looks at how fragmentation patterns are formed when organic molecules are fed into a mass spectrometer, and how you can get information from the mass spectrum.

The Origin of Fragmentation Patterns

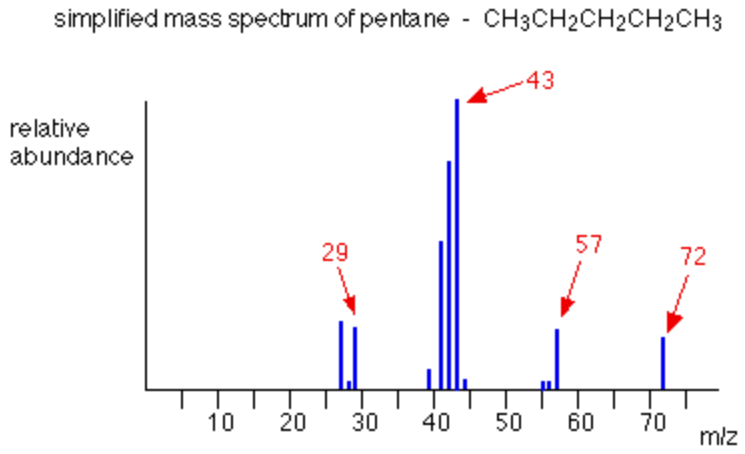
When the vaporized organic sample passes into the ionization chamber of a mass spectrometer, it is bombarded by a stream of electrons. These electrons have a high enough energy to knock an electron off an organic molecule to form a positive ion. This ion is called the **molecular ion - or sometimes the parent ion** and is often given the symbol M^+ or $M^{+\bullet}$. The dot in this second version represents the fact that somewhere in the ion there will be a single unpaired electron. That's one half of what was originally a pair of electrons - the other half is the electron which was removed in the ionization process.

The molecular ions are energetically unstable, and some of them will break up into smaller pieces. The simplest case is that a molecular ion breaks into two parts - one of which is another positive ion, and the other is an uncharged free radical.



The uncharged free radical will **not** produce a line on the mass spectrum. Only charged particles will be accelerated, deflected and detected by the mass spectrometer. These uncharged particles will simply get lost in the machine - eventually, they get removed by the vacuum pump.

The ion, X^+, will travel through the mass spectrometer just like any other positive ion - and will produce a line on the stick diagram. All sorts of fragmentations of the original molecular ion are possible - and that means that you will get a whole host of lines in the mass spectrum. For example, the mass spectrum of pentane looks like this:



Note

The pattern of lines in the mass spectrum of an *organic compound* tells you something quite different from the pattern of lines in the mass spectrum of an *element*. With an element, each line represents a different isotope of that element. With a compound, each line represents a different fragment produced when the molecular ion breaks up.

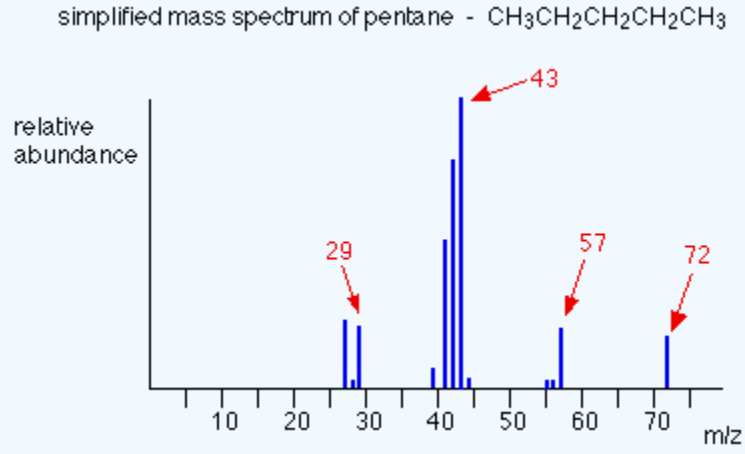
In the stick diagram showing the mass spectrum of pentane, the line produced by the heaviest ion passing through the machine (at m/z = 72) is due to the molecular ion. The tallest line in the stick diagram (in this case at m/z = 43) is called the **base peak**. This is usually given an arbitrary height of 100, and the height of everything else is measured relative to this. The base peak is the tallest peak because it represents the commonest fragment ion to be formed - either because there are several ways in which it could be produced during fragmentation of the parent ion, or because it is a particularly stable ion.

Using Fragmentation Patterns

This section will ignore the information you can get from the molecular ion (or ions). That is covered in three other pages which you can get at via the mass spectrometry menu. You will find a link at the bottom of the page.

Example 12.2.1: Pentane

Let's have another look at the mass spectrum for pentane:



What causes the line at m/z = 57?

How many carbon atoms are there in this ion? There cannot be 5 because 5 x 12 = 60. What about 4? 4 x 12 = 48. That leaves 9 to make up a total of 57. How about $C_4H_9^+$ then?

$C_4H_9^+$ would be $[CH_3CH_2CH_2CH_2]^+$, and this would be produced by the following fragmentation:

$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CH_2CH_2]^+ + \bullet CH_3$$

The methyl radical produced will simply get lost in the machine.

The line at m/z = 43 can be worked out similarly. If you play around with the numbers, you will find that this corresponds to a break producing a 3-carbon ion:

$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CH_2]^+ + \bullet CH_2CH_3$$

The line at m/z = 29 is typical of an ethyl ion, $[CH_3CH_2]^+$:

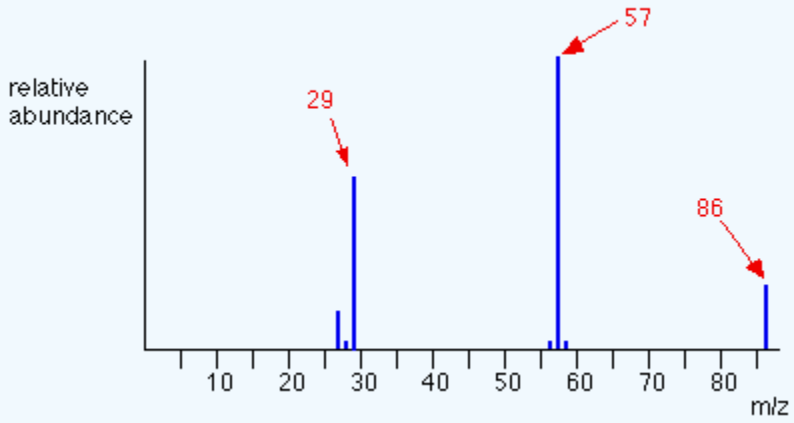
$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2]^+ + \bullet CH_2CH_2CH_3$$

The other lines in the mass spectrum are more difficult to explain. For example, lines with m/z values 1 or 2 less than one of the easy lines are often due to loss of one or more hydrogen atoms during the fragmentation process.

Example 12.2.2: Pentan-3-one

This time the base peak (the tallest peak - and so the commonest fragment ion) is at m/z = 57. But this is not produced by the same ion as the same m/z value peak in pentane.

simplified mass spectrum of pentan-3-one - $CH_3CH_2COCH_2CH_3$

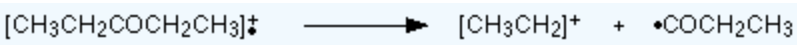


If you remember, the m/z = 57 peak in pentane was produced by $[CH_3CH_2CH_2CH_2]^+$. If you look at the structure of pentan-3-one, it's impossible to get that particular fragment from it.

Work along the molecule mentally chopping bits off until you come up with something that adds up to 57. With a small amount of patience, you'll eventually find $[CH_3CH_2CO]^+$ - which is produced by this fragmentation:

$$[CH_3CH_2COCH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CO]^+ + \bullet CH_2CH_3$$

You would get exactly the same products whichever side of the CO group you split the molecular ion. The m/z = 29 peak is produced by the ethyl ion - which once again could be formed by splitting the molecular ion either side of the CO group.



Peak Heights and Stability

The more stable an ion is, the more likely it is to form. The more of a particular sort of ion that's formed, the higher its peak height will be. We'll look at two common examples of this.

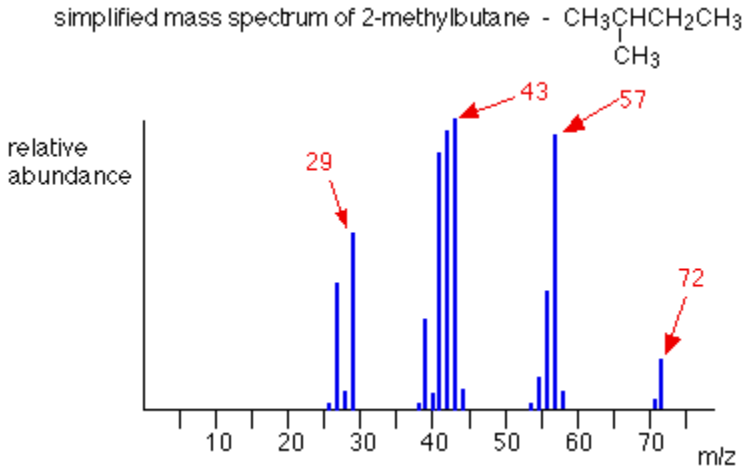
Carbocations (carbonium ions)

Summarizing the most important conclusion from the page on carbocations:

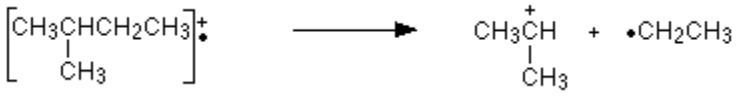
Order of stability of carbocations

primary < secondary < tertiary

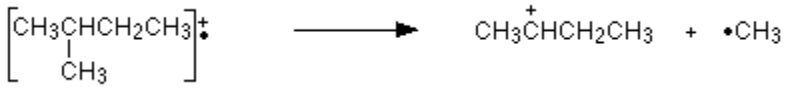
Applying the logic of this to fragmentation patterns, it means that a split which produces a secondary carbocation is going to be more successful than one producing a primary one. A split producing a tertiary carbocation will be more successful still. Let's look at the mass spectrum of 2-methylbutane. 2-methylbutane is an isomer of pentane - isomers are molecules with the same molecular formula, but a different spatial arrangement of the atoms.



Look first at the very strong peak at m/z = 43. This is caused by a different ion than the corresponding peak in the pentane mass spectrum. This peak in 2-methylbutane is caused by:



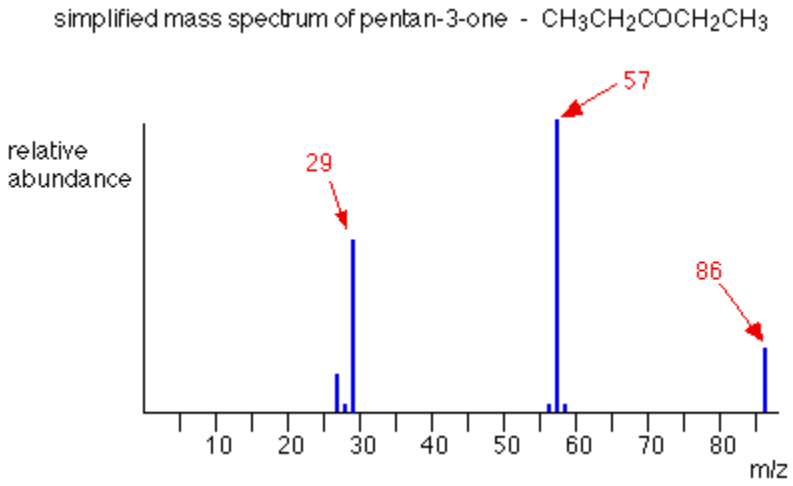
The ion formed is a secondary carbocation - it has two alkyl groups attached to the carbon with the positive charge. As such, it is relatively stable. The peak at m/z = 57 is much taller than the corresponding line in pentane. Again a secondary carbocation is formed - this time, by:



You would get the same ion, of course, if the left-hand CH_3 group broke off instead of the bottom one as we've drawn it. In these two spectra, this is probably the most dramatic example of the extra stability of a secondary carbocation.

Acylium ions, $[RCO]^+$

Ions with the positive charge on the carbon of a carbonyl group, C=O, are also relatively stable. This is fairly clearly seen in the mass spectra of ketones like pentan-3-one.



The base peak, at m/z=57, is due to the $[CH_3CH_2CO]^+$ ion. We've already discussed the fragmentation that produces this.

> **Note**
>
> The more stable an ion is, the more likely it is to form. The more of a particular ion that is formed, the higher will be its peak height.

Using mass spectra to distinguish between compounds

Suppose you had to suggest a way of distinguishing between pentan-2-one and pentan-3-one using their mass spectra.

pentan-2-one		$CH_3COCH_2CH_2CH_3$
pentan-3-one		$CH_3CH_2COCH_2CH_3$

Each of these is likely to split to produce ions with a positive charge on the CO group. In the pentan-2-one case, there are two different ions like this:

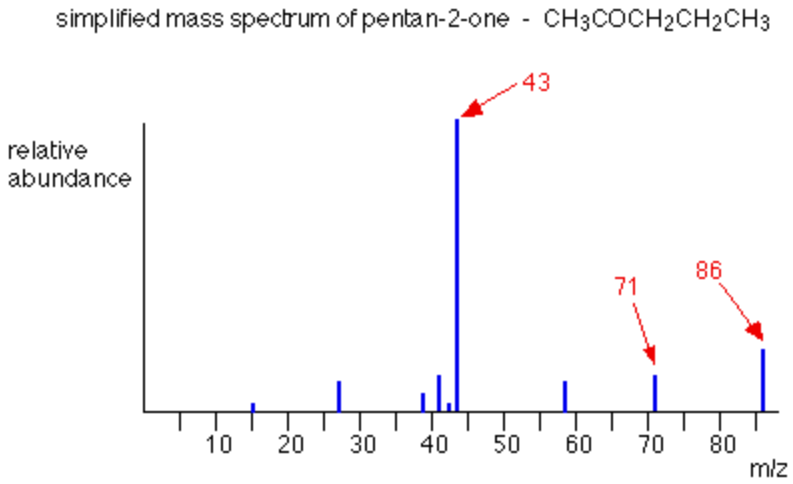
- $[CH_3CO]^+$
- $[COCH_2CH_2CH_3]^+$

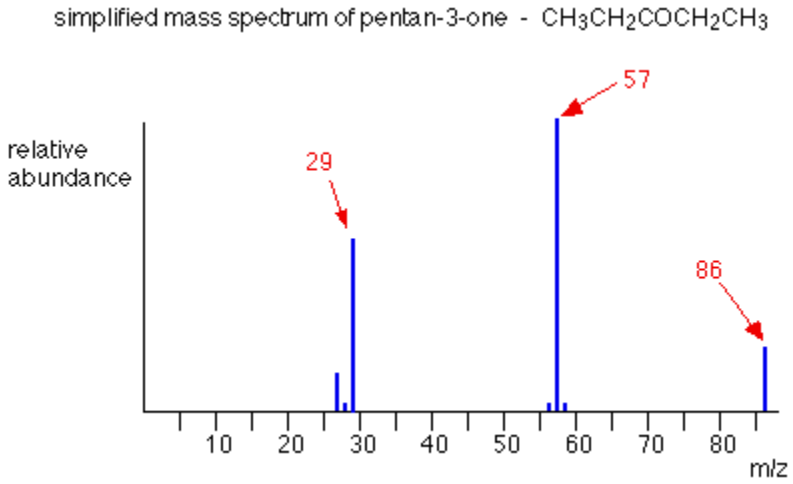
That would give you strong lines at m/z = 43 and 71. With pentan-3-one, you would only get one ion of this kind:

- $[CH_3CH_2CO]^+$

In that case, you would get a strong line at 57. You don't need to worry about the other lines in the spectra - the 43, 57 and 71 lines give you plenty of difference between the two. The 43 and 71 lines are missing from the pentan-3-one spectrum, and the 57 line is missing from the pentan-2-one one.

The two mass spectra look like this:





As you've seen, the mass spectrum of even very similar organic compounds will be quite different because of the different fragmentation patterns that can occur. Provided you have a computer data base of mass spectra, any unknown spectrum can be computer analyzed and simply matched against the data base.

Exercises

Questions

Q12.2.1

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

Q12.2.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:

12.2.gif

B:

12.2(2).gif

Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

Solutions

S12.2.1

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

S12.2.2

The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

Objective

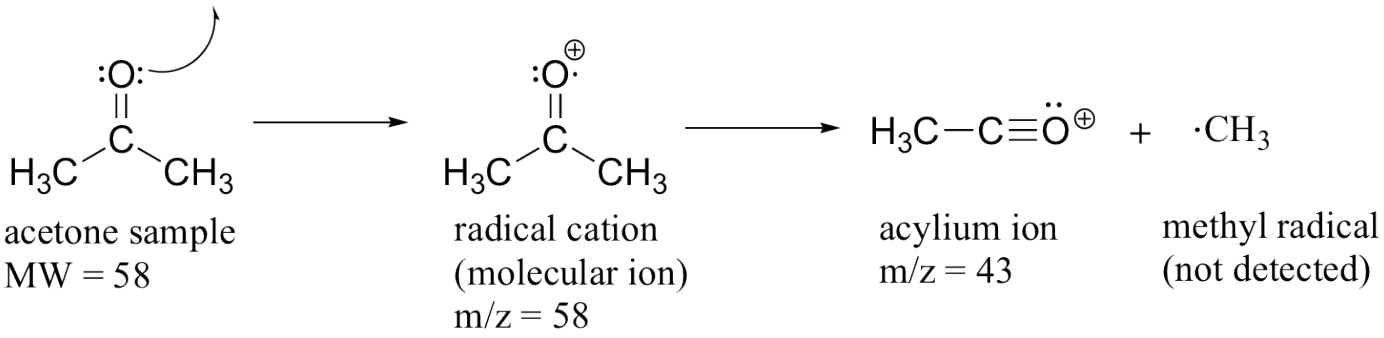
After completing this section, you should be able to predict the expected fragmentation for common functional groups, such as alcohols, amines, and carbonyl compounds.

Key Terms

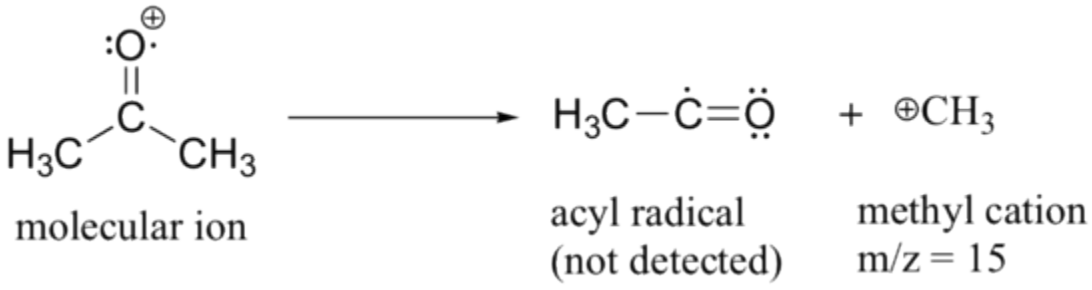
Make certain that you can define, and use in context, the key terms below.

- alpha (α) cleavage
- McLafferty rearrangement

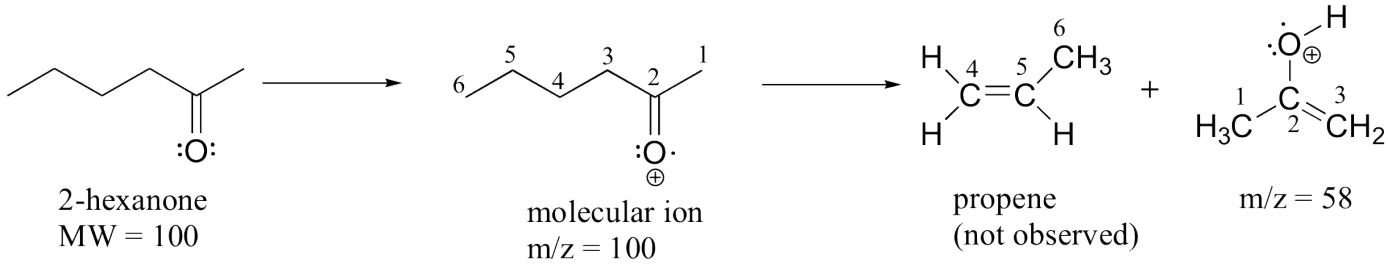
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it is worthwhile to see a few representative examples, even if we don't attempt to understand the exact process by which the fragmentation occurs. We saw, for example, that the base peak in the mass spectrum of acetone is m/z = 43. This is the result of cleavage at the 'alpha' position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



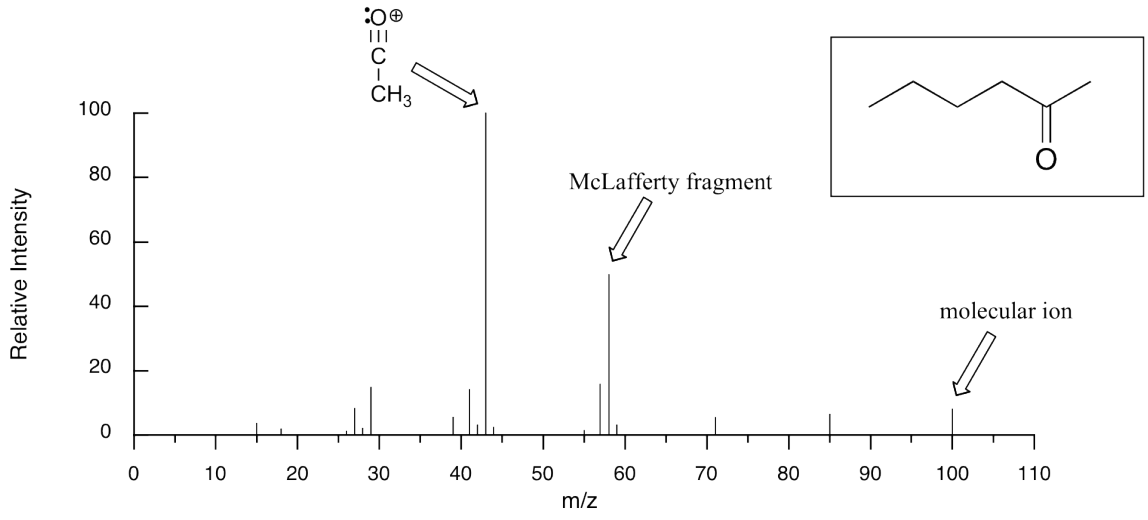
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



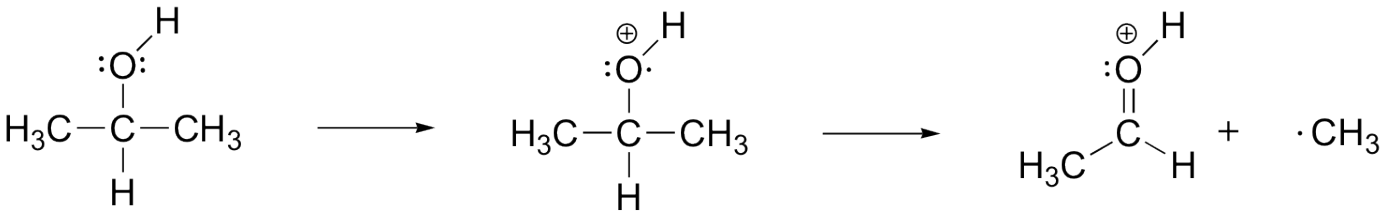
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

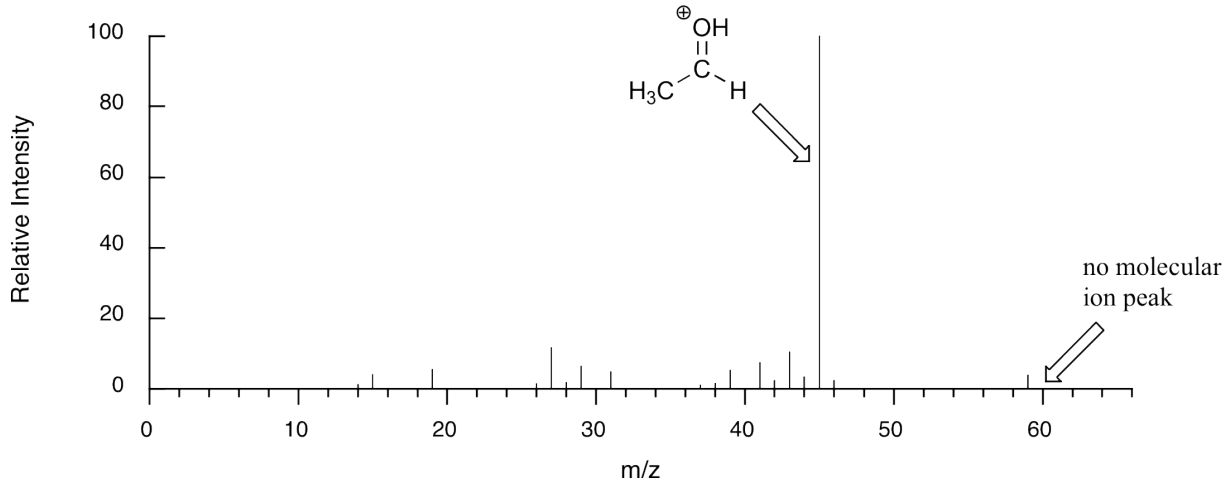


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



When alcohols are subjected to electron ionization MS, the molecular ion is highly unstable and thus a parent peak is often not detected. Often the base peak is from an ‘oxonium’ ion.





Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often 'put the puzzle together' and make some very confident predictions about the structure of the starting sample.

Click here for examples of compounds listed by functional group, which demonstrate patterns which can be seen in mass spectra of compounds ionized by electron impact ionization.

Example 12.3.1

The mass spectrum of an aldehyde gives prominent peaks at *m/z* = 59 (12%, highest value of *m/z* in the spectrum), 58 (85%), and 29 (100%), as well as others. Propose a structure, and identify the three species whose *m/z* values were listed.

Solution

Exercises

Questions

Q12.3.1

What are the masses of all the components in the following fragmentations?

12-3qu.png

Solutions

S12.3.1

12.3.png

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11.11: Degree of Unsaturation: Another Aid to Identifying Molecular Structure

Objectives

After completing this section, you should be able to

- determine the degree of unsaturation of an organic compound, given its molecular formula, and hence determine the number of double bonds, triple bonds and rings present in the compound.
- draw all the possible isomers that correspond to a given molecular formula containing only carbon (up to a maximum of six atoms) and hydrogen.
- draw a specified number of isomers that correspond to a given molecular formula containing carbon, hydrogen, and possibly other elements, such as oxygen, nitrogen and the halogens.

Key Terms

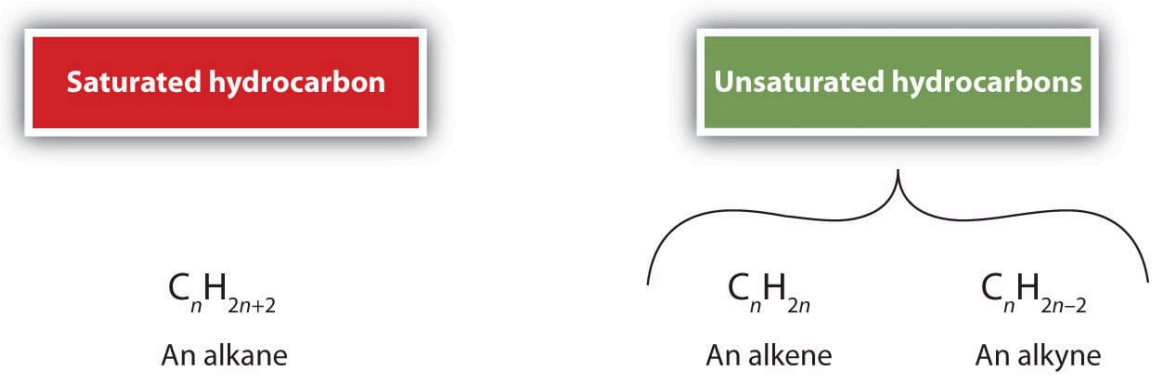
Make certain that you can define, and use in context, the key terms below.

- degree of unsaturation
- saturated
- unsaturated

There are many ways one can go about determining the structure of an unknown organic molecule. Although, nuclear magnetic resonance (NMR) and infrared radiation (IR) are the primary ways of determining molecular structures, calculating the degrees of unsaturation is useful information because it easily provides information about molecular structure.

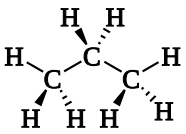
Saturated and Unsaturated Molecules

Because alkanes have the maximum number of H atoms possible according to the rules of covalent bonds, alkanes are also referred to as **saturated hydrocarbons**. The presence of a double bond causes alkenes to have less hydrogens than an alkane with the same number of carbons. Likewise, compounds containing a carbon-to-carbon triple bonds (R–C≡C–R) called alkynes (**Discussed in Chapter 9**), also have fewer hydrogens than the corresponding alkane. Collectively, compounds which have fewer hydrogen atoms than an alkane with the same number of carbon atoms are called **unsaturated hydrocarbons**. The relationship between the number of carbons (n) and hydrogens in the molecular formula for alkanes, alkenes, and alkynes are listed below.

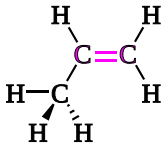


For example, the three carbon alkane, propane has the molecular formula of C_3H_8. While the unsaturated compounds propene

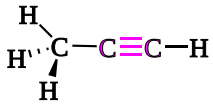
(C_3H_6) and propyne (C_3H_4) both have fewer hydrogens. Also, it is important to note that cycloalkanes with one ring have a general molecular formula of C_nH_{2n} just like alkenes. Because they also have fewer than maximum number of hydrogens possible, cyclic compounds are also considered unsaturated.



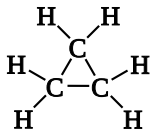
Propane (C_3H_8) Saturated



Propene (C_3H_6) Unaturated



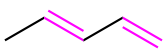
Propyne (C_3H_4) Unaturated



Cyclopropane (C_3H_6) Unaturated

Identifying Degrees of Unsaturation

Every ring or pi bond in a compound is said to represent one degree of unsaturation. Being able to determine the degrees of unsaturation in a given compound is an important skill. Each of the following compounds are isomers of C_5H_7 and contain two degrees of unsaturation.



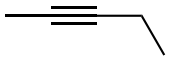
1,3-Pentadiene (Two double bonds)



Cyclopentene (One double bond and one ring)



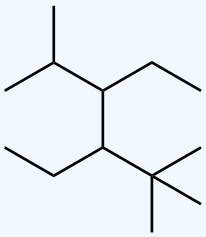
Bycyclo[2.1.0]pentane (Two rings)



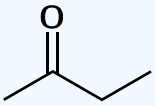
2-Pentyne (One triple bond)

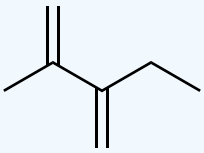
Exercise 11.11.1

How many degrees of unsaturation do the following compounds have?

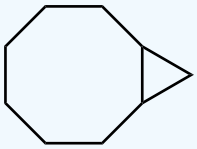
a) 

b) $CH_3CH_2CH{=}CHCF_3$

c) 

d) 

e) 3-chloro-5-octyne

f) 

Answer available at the end of this section.

Calculating the Degree of Unsaturation (DoU)

As noted above, every degree of unsaturation causes the loss of two hydrogens from a compound's molecular formula when compared to an alkane with the same number of carbons. Understanding this relationship allows for the degrees of unsaturation of a compound to be calculated from its molecular formula. First, the maximum number of hydrogens possible for a given compound **(2C + 2)** is calculated and then the actual number of hydrogens present in the compound **(H)** is subtracted**.** If this

difference is then divided by 2 the answer will be equal to the degrees of unsaturation for the compound.

For a compound which only contains carbon and hydrogen:

$$DoU = (2C + 2) - H / 2$$

As an example, for the molecular formula C_3H_4 the number of actual hydrogens needed for the compound to be saturated is 8 **[2C+2=(2x3)+2=8]**. Because the compound only has 4 hydrogens in its molecular formula, it would have to gain 4 more hydrogens in order to be fully saturated **(8-4 = 4)**. Degrees of unsaturation is equal to half the number of hydrogens the molecule needs to be fully saturated. This compound has 2 degrees of unsaturation **(4/2 = 2)**.

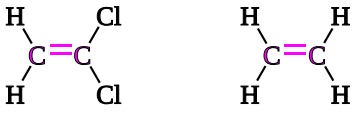
The DoU of compounds containing elements other than carbon and hydrogen can also be calculated in a similar fashion. However, different elements can affect the formula used to calculate DoU.

For a compound which contains elements other than carbon and hydrogen:

$$DoU = \frac{2C + 2 + N - X - H}{2} \tag{7.2.1}$$

- C is the number of carbons
- N is the number of nitrogens
- X is the number of halogens (F, Cl, Br, I)
- H is the number of hydrogens

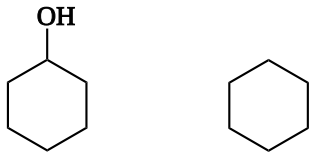
A halogen (X) replaces a hydrogen in a compound because both form one single bond. Therefore the DoU formula subtracts the number of halogens (X) present in a compound. For instance, 1,1-dichloroethene ($C_2H_2Cl_2$) has two fewer hydrogens than ethene (C_2H_4) yet they both have one degree of unsaturation.



1,1-Dichloroethene ($C_2H_2Cl_2$) **Ethene (C_2H_4)**

One Degree of Unsaturation

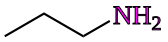
Oxygen and sulfur are not included in the DoU formula because saturation is unaffected by these elements. The inclusion of an alcohol or sulfur in a compound does not change the number of hydrogens to obtain saturation. As seen in alcohols, the number of hydrogens in cyclohexanol ($C_6H_{12}O$) matches the number of hydrogens in cyclohexane (C_6H_{12}) and they both have one degree of unsaturation.



Cyclohexanol ($C_6H_{12}O$) **Cyclohexane (C_6H_{12})**

One Degree of Unsaturation

When a nitrogen is present in a compound one more hydrogen is required to reach saturation. Therefore, we add the number of nitrogens (N). Propyl amine (C_3H_9N) has one more hydrogen compared to propane (C_3H_8) both of which are saturated compounds with 0 DoU.





Propyl Amine (C_3H_9N)

Propane (C_3H_8)

Zero Degrees of Unsaturation

With the degrees of unsaturation comes information about the possible number of rings and multiple bonds in a given compound. Remember, the degrees of unsaturation only gives the sum of pi bonds and/or rings.

- One degree of unsaturation is equivalent to 1 ring or 1 double bond (1 π bond).
- Two degrees of unsaturation is equivalent to 2 double bonds, 1 ring and 1 double bond, 2 rings, or 1 triple bond (2 π bonds).

Example 7.3.1: Benzene

What is the Degree of Unsaturation for Benzene?

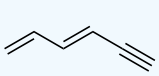
Solution

The molecular formula for benzene is C_6H_6. Thus,

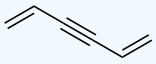
DoU= 4, where C=6, N=0,X=0, and H=6. 1 DoB can equal 1 ring or 1 double bond. This corresponds to benzene containing 1 ring and 3 double bonds.



However, when given the molecular formula C_6H_6, benzene is only one of many possible structures (isomers). The following structures all have DoB of 4 and have the same molecular formula as benzene.



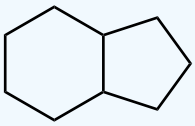




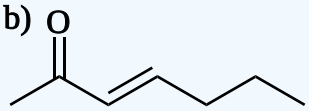
Exercise 11.11.2

Determine whether the following molecules are saturated or unsaturated.

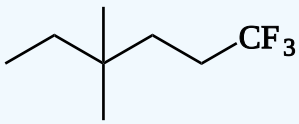
a)



b)



c)



d) $C_{10}H_6N_4$

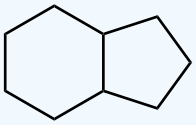
e) $C_5H_{10}O$

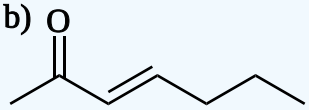
f) $C_6H_{12}F_2$

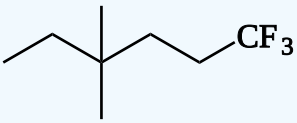
Answer available at the end of this section.

Exercise 11.11.3

Determine the degrees of unsaturation for each of the following compounds.

a) 

b) 

c) 

d) $C_{10}H_6N_4$

e) $C_5H_{10}O$

f) $C_6H_{12}F_2$

Answer available at the end of this section.

Exercise 11.11.4

Calculate the degrees of unsaturation for the following molecular formulas:

a) C_9H_{20} b) C_7H_8 c) C_5H_7Cl d) $C_9H_9NO_4$

Answer available at the end of this section.

References

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5th Ed.). New York: W. H. Freeman. (473-474)
2. Shore, N. (2007). *Study Guide and Solutions Manual for Organic Chemistry* (5th Ed.). New York: W.H. Freeman. (201)

Answers

Exercise 11.11.1

a) 0
b) 1
c) 1
d) 2
e) 2
f) 2

Exercise 11.11.2

a) **unsaturated** (*Even though the rings only contain single bonds, rings are considered unsaturated.)*
b) **unsaturated**
c) **saturated**
d) **unsaturated**
e) **unsaturated**
f) **saturated**

Exercise 11.11.3

If the molecular structure is given, the easiest way to solve is to count the number of double bonds, triple bonds and/or rings. However, you can also determine the molecular formula and solve for the degrees of unsaturation by using the formula.

a) **2** (2 rings)
b) **2** *(one double bond and the double bond from the carbonyl)*
c) **0** (no double bonds or rings)

d) **10 (2(10) + 2 + 4 - 0 - 6)/2 = 10**

e) **1 (2(5) + 2 + 0 - 0 - 10)/2 = 1**

f) **0 (2(6) + 2 + 0 - 2 - 12)/2 = 0**

Exercise 11.11.4

Use the formula to solve (O not involved in the formula)

(a.) **0 (2(9) + 2 - 20)/2 = 0**

(b.) **4 (2(7) + 2 - 8)/2 = 4**

(c.) **2 (2(5) + 2 - 1 -7)/2 = 2**

(d.) **6 (2(9) + 1 - 7)/2 = 6**

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12: REACTIONS TO ALKENES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

12.1: Why Addition Reactions Proceed: Thermodynamic Feasibility
12.2: Catalytic Hydrogenation
12.3: Nucleophilic Character of the Pi Bond: Electrophilic Addition of Hydrogen Halides
12.4: Alcohol Synthesis by Electrophilic Hydration: Thermodynamic Control
12.5: Electrophilic Addition of Halogens to Alkenes
12.6: The Generality of Electrophilic Addition
12.7: Oxymncuration-Demercuration: A Special Elcctrophilic Addition
12.8: Hydroboration-Oxidation: A Stereospecific Anti-Markovnikov Hydration
12.9: Diazomethane, Carbenes, and Cyclopropane Synthesis
12.10: Oxacyclopropane (Epoxide) Synthesis: Epoxidation by Peroxycarboxylic Acids
12.11: Vicinal SYn Dihydroxylation with Osmium Tetroxide
12.12: Oxidative Cleavage: Ozonolysis
12.13: Radical Additions: Anti-Markovnikov Product Formation
12.14: Dimerization, Oligomerization. and Polymerization of Alkenes
12.15: Synthesis of Polymers
12.16: Ethene: An Important Industrial Feedstock
12.17: Alkenes in Nature - Insect Pheromones

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12.1: Why Addition Reactions Proceed: Thermodynamic Feasibility

Addition Reactions of Alkenes

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12.2: Catalytic Hydrogenation

Objectives

After completing this section, you should be able to

- write an equation for the catalytic hydrogenation of an alkene.
- identify the product obtained from the hydrogenation of a given alkene.
- identify the alkene, the reagents, or both, required to prepare a given alkane by catalytic hydrogenation.
- describe the mechanism of the catalytic hydrogenation of alkenes.
- explain the difference between a heterogeneous reaction and a homogeneous reaction.
- recognize that other types of compounds containing multiple bonds, such as ketones, esters, nitriles and aromatic compounds, do not react with hydrogen under the conditions used to hydrogenate alkenes.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Adams' catalyst
- hydrogenation

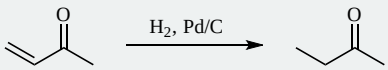
Study Notes

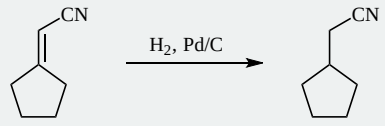
Chemical reactions that are heterogeneous have reactants that are in at least two different phases (e.g. gas with a solid), whereas homogeneous reactions occur in a single phase (e.g. gas with another gas).

Some confusion may arise from the description of the catalyst used in the reaction between alkenes and hydrogen. Three metals—nickel, platinum and palladium—are commonly used, but a chemist cannot simply place a piece of one of these metals in a mixture of the alkene and hydrogen and get a reaction. Each metal catalyst must be prepared in a special way:

- nickel is usually used in a finely divided form called "Raney nickel." It is prepared by reacting a Ni-Al alloy with NaOH.
- palladium is obtained commercially "supported" on an inert substance, such as charcoal, (Pd/C). The alkene is usually dissolved in ethanol when Pd/C is used as the catalyst.
- platinum is used as PtO_2, Adams' catalyst, although it is actually platinum metal that is the catalyst. The hydrogen used to add to the carbon-carbon double bond also reduces the platinum(IV) oxide to finely divided platinum metal. Ethanol or acetic acid is used as the solvent for the alkene.

Other types of compounds containing multiple bonds, such as ketones, esters, and nitriles, do not react with hydrogen under the conditions used to hydrogenate alkenes. The examples below show reduction of an alkene, but the ketone and nitrile groups present remain intact and are not reduced.





Aromatic rings are also not reduced under the conditions used to reduce alkenes, although these rings appear to contain three carbon-carbon double bonds. As you will see later, aromatic rings do not really contain any double bonds, and many chemists prefer to represent the benzene ring as a hexagon with a circle inside it

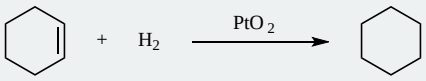


rather than as a hexagon with three alternating double bonds.

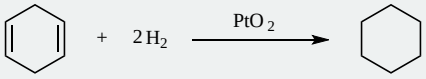


The representation of the benzene ring will be discussed further in Section 15.2.

The reaction between carbon-carbon double bonds and hydrogen provides a method of determining the number of double bonds present in a compound. For example, one mole of cyclohexene reacts with one mole of hydrogen to produce one mole of cyclohexane:



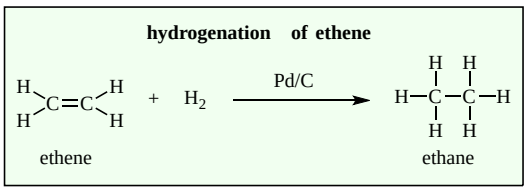
but one mole of 1,4-cyclohexadiene reacts with two moles of hydrogen to form one mole of cyclohexane:

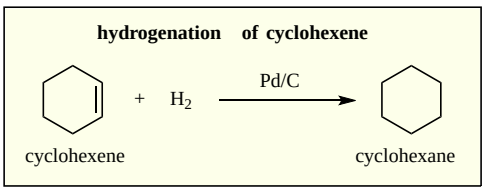


A chemist would say that cyclohexene reacts with one equivalent of hydrogen, and 1,4-cyclohexadiene reacts with two equivalents of hydrogen. If you take a known amount of an unknown, unsaturated hydrocarbon and determine how much hydrogen it will absorb, you can readily determine the number of double bonds present in the hydrocarbon (see question 2, below).

Addition of hydrogen to a carbon-carbon double bond is called hydrogenation. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst, as shown in the reaction coordinate diagram below.

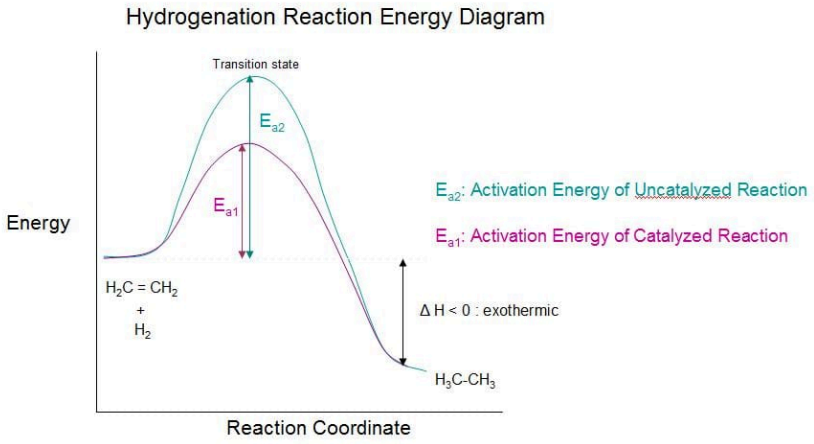
An example of an alkene addition reaction is a process called hydrogenation. In a hydrogenation reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus it is exothermic (heat is released). The heat released is called the heat of hydrogenation, which is an indicator of a molecule's stability.





Catalysts are substances that changes the rate (velocity) of a chemical reaction without being consumed or appearing as part of the product. Catalysts act by lowering the activation energy of reactions, but they do not change the relative potential energy of the reactants and products. Finely divided metals, such as platinum, palladium and nickel, are among the most widely used hydrogenation catalysts. Catalytic hydrogenation takes place in at least two stages, as depicted in the diagram. First, the alkene

must be adsorbed on the surface of the catalyst along with some of the hydrogen. Next, two hydrogens shift from the metal surface to the carbons of the double bond, and the resulting saturated hydrocarbon, which is more weakly adsorbed, leaves the catalyst surface. The exact nature and timing of the last events is not well understood.

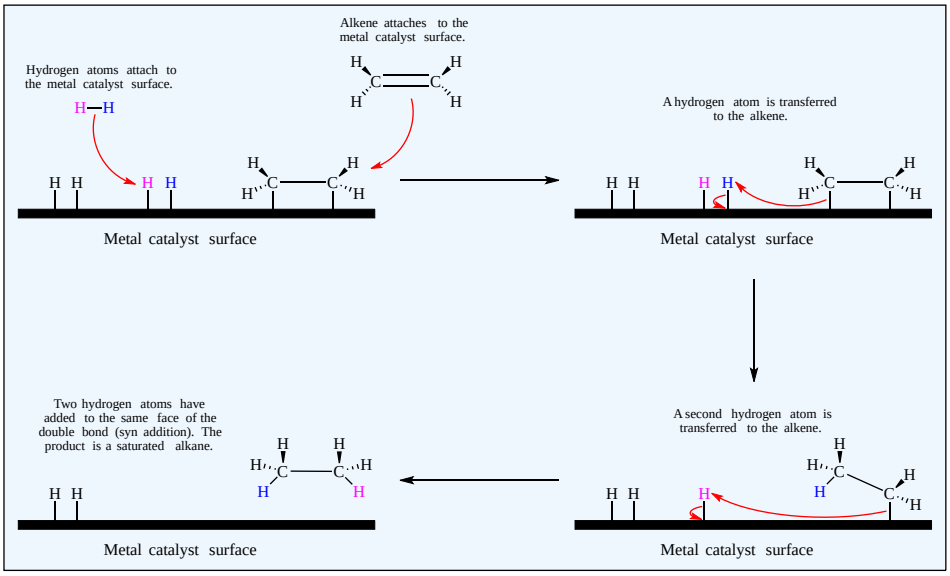


A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

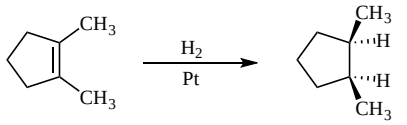
As shown in the energy diagram, the hydrogenation of alkenes is exothermic, and heat is released corresponding to the ΔH in the diagram. This heat of reaction can be used to evaluate the thermodynamic stability of alkenes having different numbers of alkyl substituents on the double bond. For example, the following table lists the heats of hydrogenation for three C_5H_{10} alkenes which give the same alkane product (2-methylbutane). Since a larger heat of reaction indicates a higher energy reactant, these heats are inversely proportional to the stabilities of the alkene isomers. To a rough approximation, we see that each alkyl substituent on a double bond stabilizes this functional group by a bit more than 1 kcal/mole.

Alkene Isomer	$(CH_3)_2CHCH{=}CH_2$ 3-methyl-1-butene	$CH_2{=}C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C{=}CHCH_3$ 2-methyl-2-butene
Heat of Reaction (ΔH°)	–30.3 kcal/mole	–28.5 kcal/mole	–26.9 kcal/mole

Catalytic Hydrogenation Mechanism



From the mechanism shown here we would expect the addition of hydrogen to occur with syn-stereoselectivity. This is often true, but the hydrogenation catalysts may also cause isomerization of the double bond prior to hydrogen addition, in which case stereoselectivity may be uncertain.



(cis product only)

Exercise 12.2.1

In the reaction

$$H_2C{=}CH_2 \quad + \quad H_2 \xrightarrow{PtO_2} H_3C{-}CH_3$$

a. 0.500 mol of ethene reacts with _____ mol of hydrogen. Thus a chemist might say that ethene reacts with one _____ of hydrogen.
b. ethene is being _____; while _____ is being oxidized.
c. the oxidation number of carbon in ethene is _____; in ethane it is _____.

Answer available at the end of this section.

Exercise 12.2.2

When 1.000 g of a certain triglyceride (fat) is treated with hydrogen gas in the presence of Adams' catalyst, it is found that the volume of hydrogen gas consumed at 99.8 kPa and 25.0°C is 162 mL. A separate experiment indicates that the molar mass of the fat is 914 g mol^{-1}. How many carbon-carbon double bonds does the compound contain?

Answer available at the end of this section.

Exercise 12.2.3

Predict the products if the following alkenes were reacted with catalytic hydrogen.

8-6qu.png

Answer available at the end of this section.

Answers

Exercise 12.2.1

a. 0.500 mol of ethene reacts with 0.500 mol of hydrogen. Thus a chemist might say that ethene reacts with one equivalent of hydrogen.
b. ethene is being reduced; while hydrogen is being oxidized.
c. the oxidation number of carbon in ethene is –2; in ethane it is –3.

Exercise 12.2.2

Amount of hydrogen consumed

$= n \text{ mol}$

$= \frac{PV}{RT}$ $^{-1} \cdot K^{-1} \times 298\ K = 6.53 \times 10^{-3}$ mol H_2

$= \frac{99.8\ \text{kPa} \times 0.162\ \text{L}}{8.31\ \text{kPa} \cdot}$ [redacted]

Amount of fat used

Math input error

Ratio of moles of hydrogen consumed to moles of fat

Math input error

Thus, the fat contains six carbon-carbon double bonds per molecule.

Exercise 12.2.3

8-6sol.png

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12.3: Nucleophilic Character of the Pi Bond: Electrophilic Addition of Hydrogen Halides

Objectives

After completing this section, you should be able to

- explain the term “electrophilic addition reaction,” using the reaction of a protic acid, HX, with an alkene as an example.
- write the mechanism for the reaction of a protic acid, HX, with an alkene.
- sketch a reaction energy diagram for the electrophilic addition of an acid, HX, to an alkene.

Key Terms

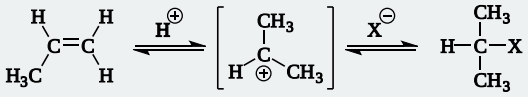
Make certain that you can define, and use in context, the key terms below.

- carbocation (carbonium ion)
- electrophilic addition reaction

Study Notes

An *electrophilic addition reaction* is a reaction in which a substrate is initially attacked by an electrophile, and the overall result is the addition of one or more relatively simple molecules across a multiple bond.

The mechanism for the addition of hydrogen halide to propene shown in the reading is quite detailed. Normally, an organic chemist would write the reaction scheme as follows:



However, the more detailed mechanism shown in the reading does allow you to see the exact fate of all the electrons involved in the reaction.

In your previous chemistry course, you were probably taught the importance of balancing chemical equations. It may come as a surprise to you that organic chemists usually do not balance their equations, and often represent reactions using a format which is quite different from the carefully written, balanced equations encountered in general chemistry courses. In fact, organic chemists are rarely interested in the inorganic products of their reactions; furthermore, most organic reactions are non-quantitative in nature.

In many of the reactions in this course, the percentage yield is indicated beneath the products: you are not expected to memorize these figures. The question of yield is very important in organic chemistry, where two, five, ten or even twenty reactions may be needed to synthesize a desired product. For example, if a chemist wishes to prepare compound D by the following reaction sequence:

$$A \rightarrow B \rightarrow C \rightarrow D$$

and each of the individual steps gives only a 50% yield, one mole of A would give only

$$1 \text{ mol} \times \frac{50\%}{100\%} \times \frac{50\%}{100\%} \times \frac{50\%}{100\%} = 0.125 \text{ mol of D}$$

You will gain first-hand experience of such situations in the laboratory component of this course.

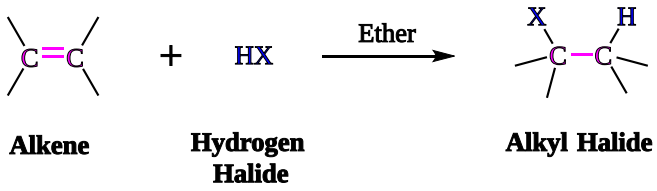
Introduction

One of the most important reactions for alkenes is called electrophilic addition. In this chapter several variations of the electrophilic addition reaction will be discussed. Each case will have aspects common among all electrophilic addition. In this section, the electrophilic addition reaction will be discussed in general to provide a better understanding of subsequent alkene reactions.

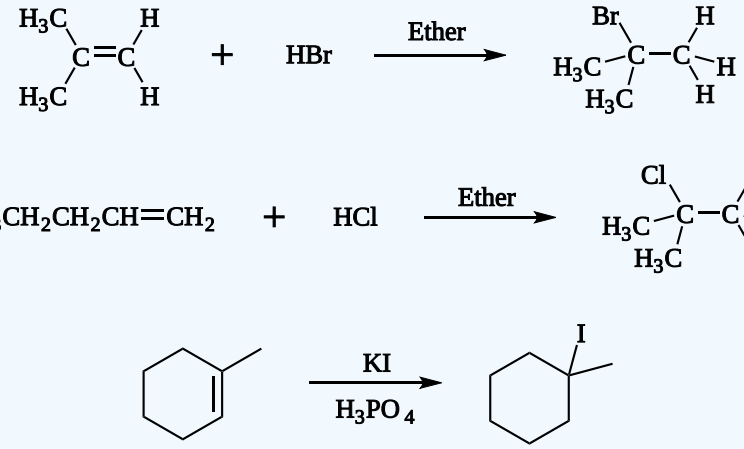
As discussed in Section 6-5, the double bond in alkenes is electron rich due to the prescience of 4 electrons instead of the two in a single bond. Also, the pi electrons are positioned above and below the double bond making them more accessibly for reactions. Overall, double bonds can easily donate lone pair electrons to act like a nucleophile (nucleus-loving, electron rich, a Lewis acid). During an electrophilic addition reactions double bonds donate lone pair electrons to an electrophile (Electron-loving, electron poor, a Lewis base). There are many types of electrophilic addition, but this section will focus on the addition of hydrogen halides (HX). Many of the basic ideas discussed will aplicable to subsequent electrophilic addition reactions.

General Reaction

Overall during this reaction the pi bond of the alkene is broken to form two single, sigma bonds. As shown in the reaction mechanism, one of these sigma bonds is connected to the H and the other to the X of the hydrogen halide. This reaction works well with HBr and HCl. HI can also but used but is is usually generated during the reaction by reacting potassium iodidie (KI) with phosphoric acid (H_3PO_4).



Example 12.3.1



Addition to symmetrical alkenes

What happens?

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other.

For example, with ethene and hydrogen chloride, you get chloroethane:



Figure 12.3.1 Electrophilic addition of HCl to ethene.

With but-2-ene you get 2-chlorobutane:

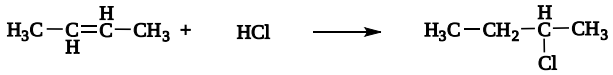


Figure 12.3.2 Electrophilic addition of HCl to but-2-ene.

What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space. That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

Mechanism

Step 1) Electrophilic Attack

During the first step of the mechanism, the 2 pi electrons from the double bond attack the H in the HBr electrophile which is shown by a curved arrow. The two pi electrons form a C-H sigma bond between the hydrogen from HBr and a carbon from the double bond. Simultaneously the electrons from the H-X bond move onto the halogen to form a halide anion. The removal of pi electrons form the double bond makes one of the carbons become an electron deficient carbocation intermediate. This carbon is sp^2 hybridized and the positive charge is contained in an unhybridized p orbital.

Step 2) Nucleophilic attack by halide anion

The formed carbocation now can act as an electrophile and accept an electron pair from the nucleophilic halide anion. The electron pair becomes a X-C sigma bond to create the neutral alkyl halide product of electrophilic addition.

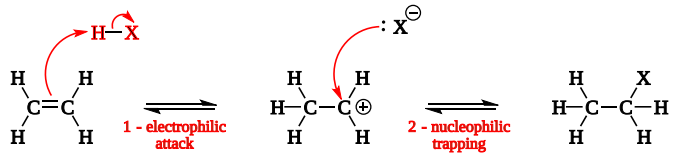


Figure 12.3.3*Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene*

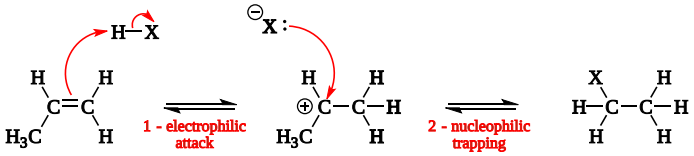


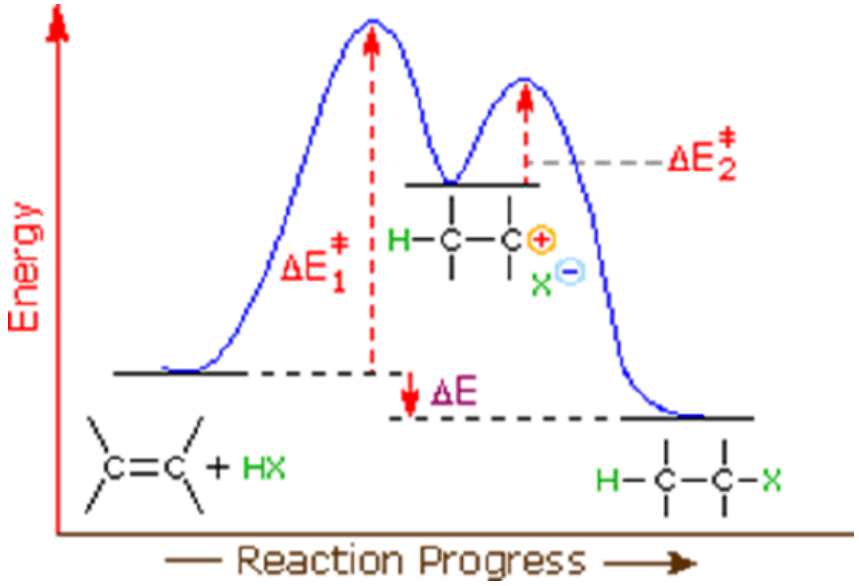
Figure 12.3.4 *Mechanism of Electrophilic Addition of Hydrogen Halide to Propene*

All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

Reaction Energy Diagram

An energy diagram for the two-step electrophilic addition mechanism is shown below. The energy diagram has two peaks which represent the transition state for each mechanistic step. The peaks are separated by a valley which represents the high energy carbocation reaction intermediate. Because the energy of activation for the first step of the mechanism ($\Delta E^{\ddagger}_1$) is much larger than the second ($\Delta E^{\ddagger}_1$), the first step of the mechanism is the rate-determining step. Both the alkene and the hydrogen halide are reactants in the first step of the mechanism, this electrophilic addition is a second order reaction and the rate law expression can be written rate = k[Alkene][HX]. Also, any structural feature which can stabilize the transition state between the reactants the carbocation intermediate will lower $\Delta E^{\ddagger}_1$ and thereby increase the reaction rate. Overall, the alkyl halide product of this reaction

more stable than the reactants making the reaction exothermic.



Reaction rates

Variation of rates when you change the halogen

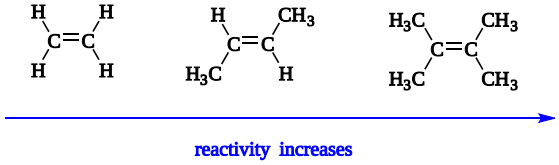
Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions.

When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

Variation of rates when you change the alkene

This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be.

Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:

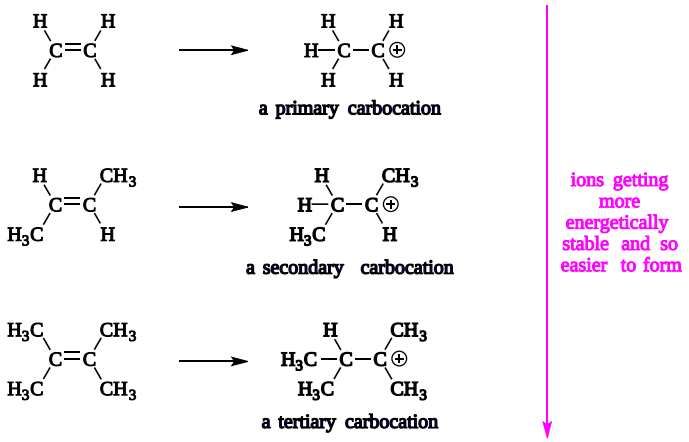


There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this.

Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes. The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride.

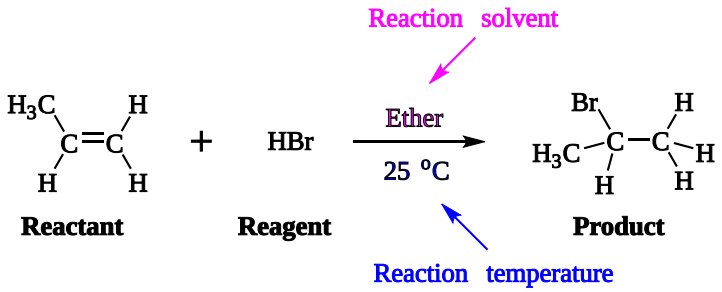
The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



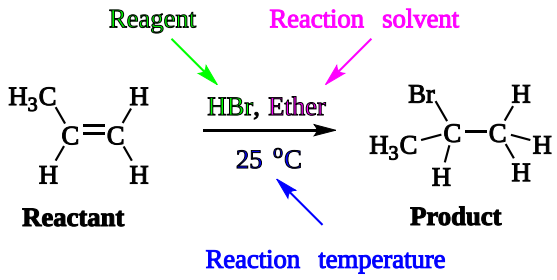
The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

Representing Organic Reactions

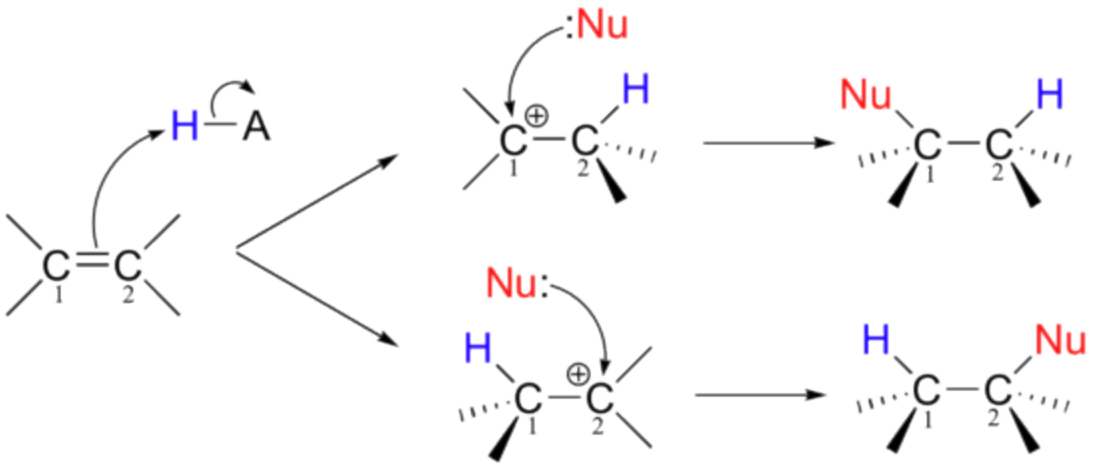
Organic reaction equations are often written in one of two ways. The reactant for the reaction is written to the left of the reaction arrow. The products are written to the right of the arrow. The reagent for the reaction is written above the arrow. Other reaction conditions such as the solvent or the temperature can be written above or below the reaction arrow.



Alternatively the reactant and reagent can both be written to the left of the reaction arrow. This is typically done to highlight the importance of the reactant. The solvent and reaction temperature are still written above or below the reaction arrow. The reaction products are still written to the right of the reaction arrow.

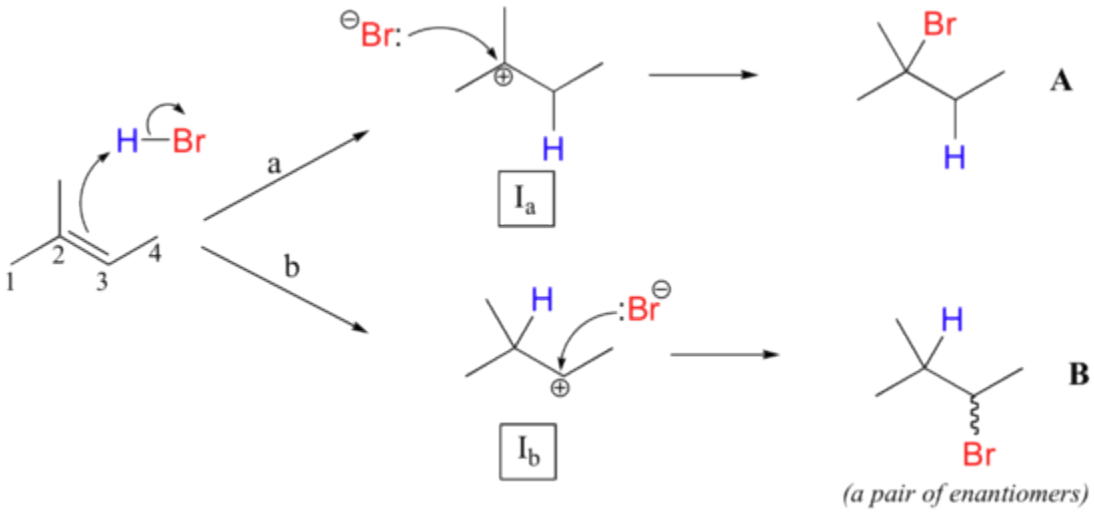


very important regarding electrophilic addition reactions is that if the starting alkene is asymmetrical, there are two possible courses that could be followed, depending on which of the two alkene carbons forms the new sigma bond in the first step.

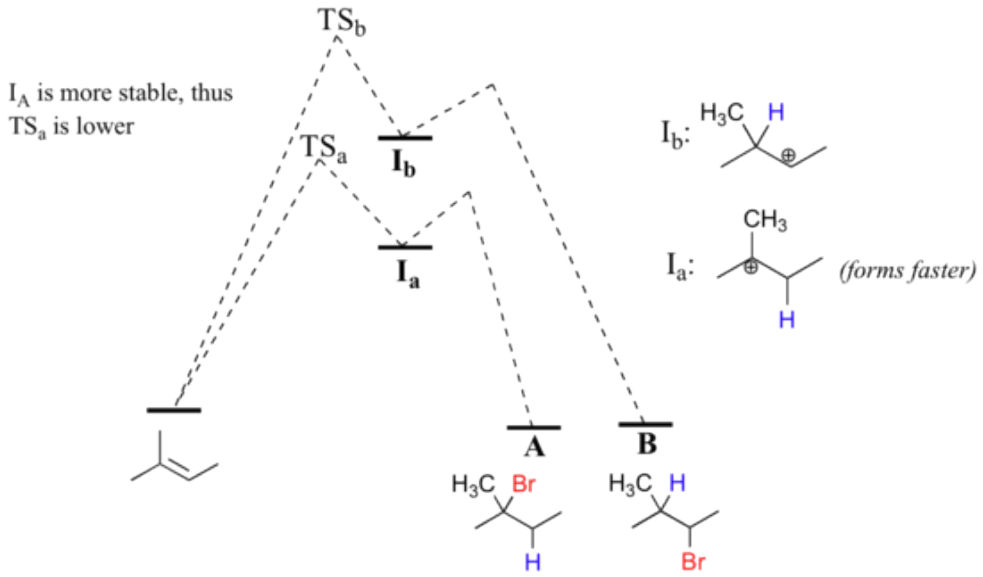


Of course, the two reaction courses involve two different carbocation intermediates, which may have different energy levels. Two different products are possible, and in general *the product which predominates will be the one that is derived from the lower-energy carbocation intermediate*.

This important regiochemical principle is nicely illustrated by a simple electrophilic addition that is commonly carried out in the organic laboratory: the conversion of an alkene to an alkyl bromide by electrophilic addition of HBr to the double bond. Let's look at a hypothetical addition of HBr to 2-methyl-2-butene, pictured below. Two different regiochemical outcomes are possible:

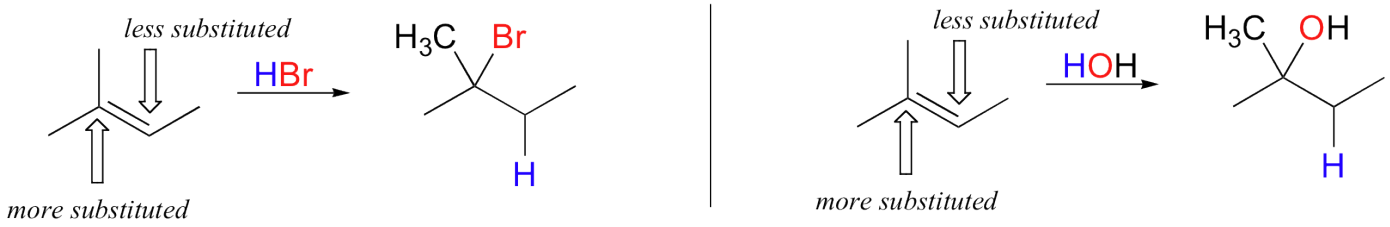


The initial protonation step could follow two different pathways, resulting in two different carbocation intermediates: pathway '**a**' gives a tertiary carbocation intermediate (I_a), while pathway '**b**' gives a secondary carbocation intermediate (I_b) We know already that the tertiary carbocation is more stable (in other words, lower in energy). According to the Hammond postulate, this implies that the activation energy for pathway **a** is lower than in pathway **b**, meaning in turn that I_a forms *faster*.



Because the protonation step is the rate determining step for the reaction, the tertiary alkyl bromide A will form much faster than the secondary alkyl halide B, and thus A will be the predominant product observed in this reaction. This is a good example of a non-enzymatic organic reaction that is highly regiospecific.

In the example above, the difference in carbocation stability can be accounted for by the electron-donating effects of the extra methyl group on one side of the double bond. It is generally observed that, in electrophilic addition of acids (including water) to asymmetrical alkenes, the *more substituted* carbon is the one that ends up bonded to the heteroatom of the acid, while the less substituted carbon is protonated.

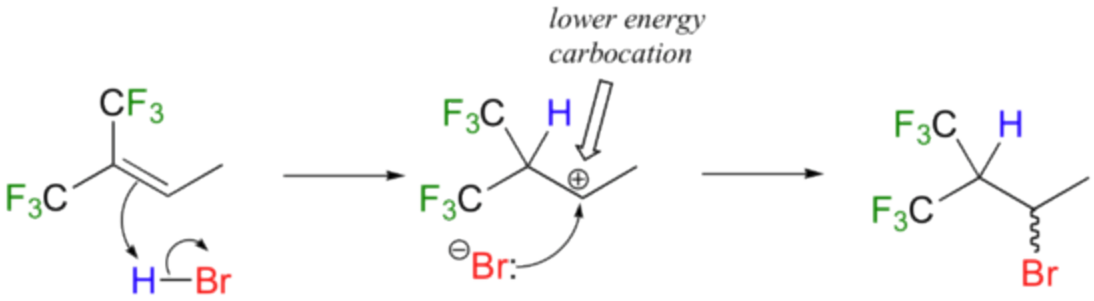


This rule of thumb is known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869.

While it is useful in many cases, Markovikov's rule does not apply to all possible electrophilic additions. It is more accurate to use the more general principle that has already been stated above:

When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

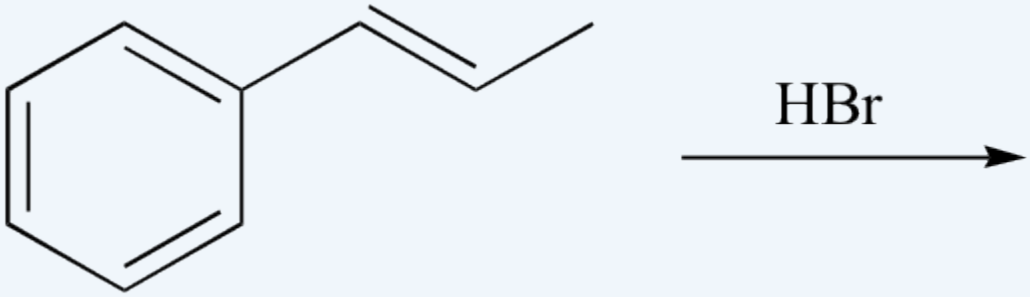
How is this different from Markovnikov's original rule? Consider the following hypothetical reaction, which is similar to the HBr addition shown above except that the six methyl hydrogens on the left side of the double bond have been replaced by highly electron-withdrawing fluorines.



Now when HBr is added, it is the *less* substituted carbocation that forms faster in the rate-determining protonation step, because in this intermediate the carbon bearing the positive charge is located further away from the electron-withdrawing, *cation-destabilizing* fluorines. As a result, the predominant product is the secondary rather than the tertiary bromoalkane. This would be referred to as an 'anti-Markovnikov' addition product, because it 'breaks' Markovnikov's rule.

Example

Predict the product of the following reaction:



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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12.4: Alcohol Synthesis by Electrophilic Hydration: Thermodynamic Control

Electrophilic hydration is the act of adding electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1°, 2°, or 3° alcohol on the alkane.

What Is Electrophilic Hydration?

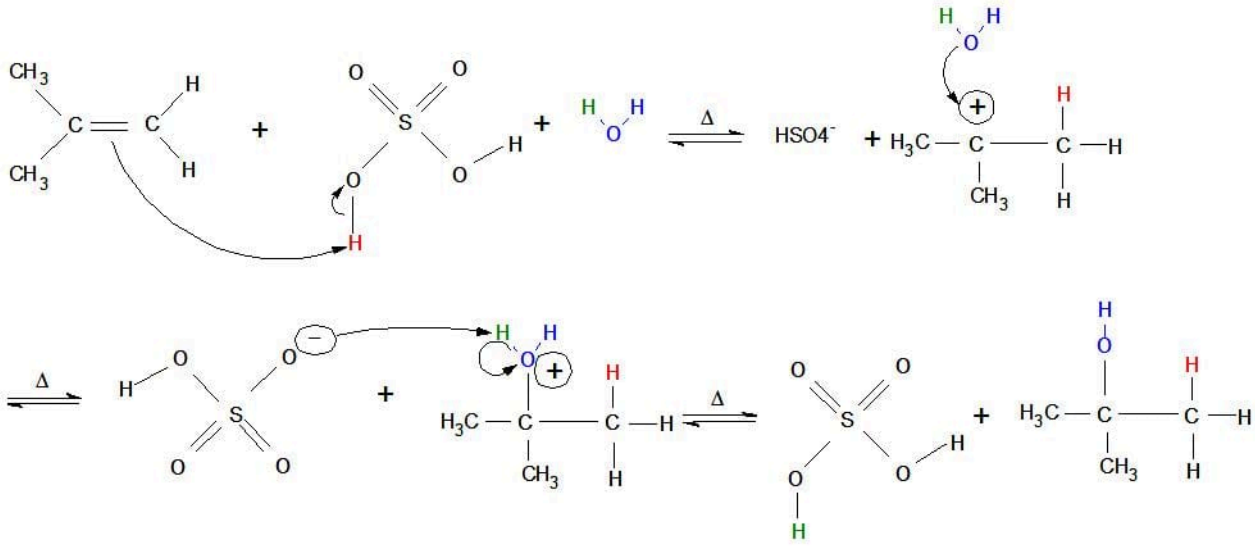
Electrophilic hydration is the reverse dehydration of alcohols and has practical application in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:

Basic Electrophilic Hydration.bmp

The phrase "electrophilic" literally means "electron loving" (whereas "nucleophilic" means "nucleus loving"). Electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electrons. Electrophilic hydrogen is commonly used to help break double bonds or restore catalysts (see S_N2 for more details).

How Does Electrophilic Hydration Work?

Mechanism for 3° Alcohol (1° and 2° mechanisms are similar):



Temperatures for Types of Alcohol Synthesis

Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

- Primary Alcohol: Less than 170°C
- Secondary Alcohol: Less than 100°C
- Tertiary Alcohol: Less than 25°C

But...Why Does Electrophilic Hydration Work?

- An alkene placed in an aqueous non-nucleophilic strong acid immediately "reaches out" with its double bond and attacks one of the acid's hydrogen atoms (meanwhile, the bond between oxygen and hydrogen performs heterolytic cleavage toward the oxygen—in other words, both electrons from the oxygen/hydrogen single bond move onto the oxygen atom).
- A carbocation is formed on the original alkene (now alkane) in the more-substituted position, where the oxygen end of water attacks with its 4 non-bonded valence electrons (oxygen has 6 total valence electrons because it is found in Group 6 on the periodic table and the second row down: two electrons in a 2s-orbital and four in 2p-orbitals. Oxygen donates one valence electron to each bond it forms, leaving four 4 non-bonded valence electrons).
- After the blue oxygen atom forms its third bond with the more-substituted carbon, it develops a positive charge (3 bonds and 2 valence electrons give the blue oxygen atom a formal charge of +1).
- The bond between the green hydrogen and the blue oxygen undergoes heterolytic cleavage, and both the electrons from the bond move onto the blue oxygen. The now negatively-charged strong acid picks up the green electrophilic hydrogen.
- Now that the reaction is complete, the non-nucleophilic strong acid is regenerated as a catalyst and an alcohol forms on the most substituted carbon of the current alkane. At lower temperatures, more alcohol product can be formed.

What is Regiochemistry and How Does It Apply?

Regiochemistry deals with where the substituent bonds on the product. **Zaitsev**'s and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bonds onto the product. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies. See the following for an in-depth explanation of regiochemistry Markovnikov explanation: Radical Additions--Anti-Markovnikov Product Formation

In the mechanism for a 3° alcohol shown above, the red H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3° carbon, causing it to be highly stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, **carbocations form on the most substituted carbon** connected to the double bond. Carbocations are also stabilized by resonance, but resonance is not a large factor in this case because any carbon-carbon double bonds are used to initiate the reaction, and other double bonded molecules can cause a completely different reaction.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.

Hydride Shift.bmp

- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

Alkyl Shift.bmp

The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3° alcohol shown above, water is the nucleophile. When the green H is removed from the water molecule, the alcohol attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

What is Stereochemistry and How Does It Apply?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that **the product is a racemic mixture**.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3° alcohol product could look like either of the following products:

Tert Alcohol Stereochemistry.bmp

Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

Is There a Better Way to Add Water to Synthesize an Alcohol From an Alkene?

A more efficient pathway does exist: see Oxymercuration - Demercuration: A Special Electrophilic Addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (R)-enantiomer and an (S)-enantiomer)
- Using sulfuric or phosphoric acid

Problems

Predict the product of each reaction.

1)

PP1 Q (1).bmp

2) How does the cyclopropane group affect the reaction?

PP2 Q.bmp

3) (Hint: What is different about this problem?)

PP3 Q.bmp

4) (Hint: Consider stereochemistry.)

PP4 Q.bmp

5) Indicate any shifts as well as the major product:

PP5 Q.bmp

Answers to Practice Problems

1) This is a basic electrophilic hydration.

PP1 A.bmp

2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3° carbon will remain as such).

PP2 A.bmp

3) A hydride shift actually occurs from the top of the 1-methylcyclopentane to where the carbocation had formed.

PP3 A (1).bmp

4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.

PP4 A.bmp

5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.

PP5 A.bmp

References

1. Vollhardt and Schore. Organic Chemistry, Structure and Function- Fifth Edition. New York: W. H. Freeman and Company, 2007.
2. Krow, Grant. "Sulfuric Acid." Encyclopedia of Reagents for Organic Synthesis. Philadelphia, Pennsylvania: John Wiley & Sons, 2001.

Outside Links

- http://en.wikipedia.org/wiki/Electrophile
- http://www.youtube.com/watch?v=Z7xskJnGDEM
- For more on Hyperconjugation: http://en.wikipedia.org/wiki/Hyperconjugation
- For more on Markovnikov's Rule: http://en.wikipedia.org/wiki/Markovnikov_rule
- For more on Zaitsev's Rule: http://en.wikipedia.org/wiki/Zaitsev%27s_rule

Contributors

- Lance Peery (UCD)

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12.5: Electrophilic Addition of Halogens to Alkenes

Objectives

After completing this section, you should be able to

- write the equation for the reaction of chlorine or bromine with a given alkene.
- identify the conditions under which an addition reaction occurs between an alkene and chlorine or bromine.
- draw the structure of the product formed when a given alkene undergoes an addition reaction with chlorine or bromine.
- write the mechanism for the addition reaction that occurs between an alkene and chlorine or bromine, and account for the stereochemistry of the product.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- anti stereochemistry
- bromonium ion

Study Notes

In the laboratory you will test a number of compounds for the presence of a carbon-carbon double bond. A common test is the decolourization of a reddish-brown bromine solution by an alkene.

The two-step mechanism shown in the LibreText pages gives you an idea of how the reaction between an alkene and a halogen occurs. Note the formation of the bridged bromonium ion intermediate and the anti stereochemistry of the final product because the two bromine atoms come from opposite faces of the double bond.

Additional evidence in support of the bromonium ion mechanism comes from the results obtained when an alkene (such as cyclopentene) reacts with bromine in the presence of sodium chloride (see Figure 8.2: Reaction of an alkene with bromine in the presence of sodium chloride, below).

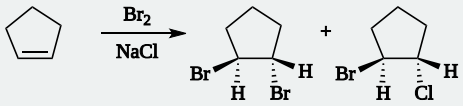


Figure 8.2: *Reaction of an alkene with bromine in the presence of sodium chloride*

Once formed, the bromonium ion is susceptible to attack by two nucleophiles—chloride ion and bromide ion—and, in fact, a mixture of two products (both produced by anti attack) is formed.

Halogens can act as electrophiles to which can be attacked by a pi bond from an alkene. Pi bonds represents a region of electron density and therefore function as a nucleophiles. How is it possible for a halogen to obtain positive charge to be an electrophile?

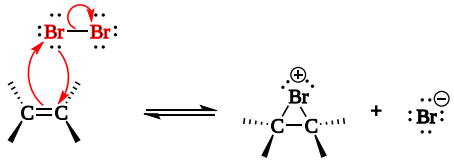
Introduction

A halogen molecule, for example Br_2, approaches a double bond of the alkene, electrons in the double bond repel electrons in the bromine molecule causing polarization of the halogen-halogen bond. This creates a dipole moment in the halogen-halogen bond. Heterolytic bond cleavage occurs and one of the halogens obtains a positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but is stereoselective. Stereochemistry of this addition can be explained by the mechanism of the reaction. In the first step, the electrophilic halogen (with the positive charge) approaches the pi bond and 2p orbitals of the halogen bond with two carbon atoms creating a cyclic ion with a halogen as the intermediate. In the second step, the remaining

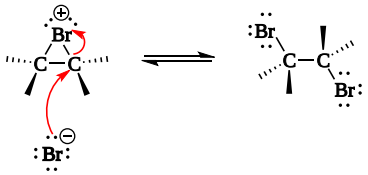
halide ion (halogen with the negative charge) attacks either of the two carbons in the cyclic ion from the back side of the cycle as in the S_N2 reaction. Therefore stereochemistry of the product is anti addition of **vicinal dihalides**.

$$R_2C{=}CR_2 + X_2 \rightarrow R_2CX{-}CR_2X \tag{8.2.1}$$

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a cyclic intermediate with the two carbons from the alkene.



Step 2: In the second step, bromide anion attacks either carbon of the bridged bromonium ion from the back side of the ring. The bromine atom in the bromonium ion acts as a shield in a way, forcing the bromonium anion to attack from the opposite side as it. The result of this is the ring opening up with the two halogens on opposite sides as each other. This is **anti** stereochemistry, which is defined as the two bromine atoms come from opposite faces of the double bond. The product is that the bromines add on trans to each other.



Halogens that are commonly used in this type of the reaction are: Br and Cl. In thermodynamical terms I is too slow for this reaction because of the size of its atom, and F is too vigorous and explosive.

Because the halide ion can attack any carbon from the opposite side of the ring it creates a mixture of steric products. Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

Electrophilic addition mechanism consists of two steps.

Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene.

Nucleophile	**Double bond in alkene**
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

Summary

Halogens can act as electrophiles due to polarizability of their covalent bond. Addition of halogens is stereospecific and produces vicinal dihalides with anti addition.

Exercise 12.5.1

What is the mechanism of adding Cl_2 to the cyclohexene?

Chem2.bmp

Answer available at the end of this section.

Exercise 12.5.2

A reaction of Br_2 molecule in an inert solvent with alkene follows?

a. syn addition
b. anti addition
c. Morkovnikov rule

Answer available at the end of this section.

Exercise 12.5.3

Chem5_Q.bmp

Answer available at the end of this section.

Exercise 12.5.4

Chem_5_Q.bmp

Answer available at the end of this section.

Exercise 12.5.5

Predict the products for 1,2-dimethylcyclopentene reacting with Br_2 with proper stereochemistry.

Answer available at the end of this section.

Exercise 12.5.6

Predict the products for 1,2-dimethylcyclpentene reacting with HCl, give the proper stereochemistry. What is the relationship between the two products?

Answer available at the end of this section.

References

1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function. New York: W.H.Freeman and Company 2007
2. Chemistry-A European Journal 9 (2003) :1036-1044

Answers

Exercise 12.5.1

Choloro__problem_2.bmp

Exercise 12.5.2

b

Exercise 12.5.3

Chem_exampl_4.bmpenantiomer

Exercise 12.5.4

Chemestry_problem_4.bmp

Exercise 12.5.5

8.2.png

Exercise 12.5.6

8.2(2).png

These compounds are enantiomers.

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- 8.2: Halogenation of Alkenes - Addition of X_2 by Dietmar Kennepohl, Lauren Reutenauer, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

12.6: The Generality of Electrophilic Addition

The proton is not the only electrophilic species that initiates addition reactions to the double bond of alkenes. Lewis acids like the halogens, boron hydrides and certain transition metal ions are able to bond to the alkene pi-electrons, and the resulting complexes rearrange or are attacked by nucleophiles to give addition products.The electrophilic character of the halogens is well known. Chlorine (Cl_2) and bromine(Br_2) react selectively with the double bond of alkenes, and these reactions are what we will focus on. Fluorine adds uncontrollably with alkenes,and the addition of iodine is unfavorable, so these are not useful preparative methods.

The addition of chlorine and bromine to alkenes, as shown below, proceeds by an initial electrophilic attack on the pi-electrons of the double bond. Dihalo-compounds in which the halogens are bound to adjacent carbons are called vicinal, from the Latin *vicinalis*, meaning neighboring.

$$R_2C{=}CR_2 + X_2 \longrightarrow R_2CX\text{-}CR_2X$$

Other halogen-containing reagents which add to double bonds include hypohalous acids, HOX, and sulfenyl chlorides, RSCl. These reagents are unsymmetrical, so their addition to unsymmetrical double bonds may in principle take place in two ways. In practice, these addition reactions are regioselective, with one of the two possible constitutionally isomeric products being favored. The electrophilic moiety in both of these reagents is the halogen.

$$(CH_3)_2C{=}CH_2 + HOBr \longrightarrow (CH_3)_2COH\text{-}CH_2Br$$

$$(CH_3)_2C{=}CH_2 + C_6H_5SCl \longrightarrow (CH_3)_2CCl\text{-}CH_2SC_6H_5$$

The regioselectivity of the above reactions may be explained by the same mechanism we used to rationalize the Markovnikov rule. Thus, bonding of an electrophilic species to the double bond of an alkene should result in preferential formation of the more stable (more highly substituted) carbocation, and this intermediate should then combine rapidly with a nucleophilic species to produce the addition product.

To apply this mechanism we need to determine the electrophilic moiety in each of the reagents. By using electronegativity differences we can dissect common addition reagents into electrophilic and nucleophilic moieties, a**s shown on the right**. In the case of hypochlorous and hypobromous acids (HOX), these weak Brønsted acids (pKa's ca. 8) do not react as proton donors; and since oxygen is more electronegative than chlorine or bromine, the electrophile will be a halide cation. The nucleophilic species that bonds to the intermediate carbocation is then hydroxide ion, or more likely water (the usual solvent for these reagents), and the products are called halohydrins. Sulfenyl chlorides add in the opposite manner because the electrophile is a sulfur cation, RS(+), whereas the nucleophilic moiety is chloride anion (chlorine is more electronegative than sulfur).

Below are some examples illustrating the addition of various electrophilic halogen reagents to alkene groups. Notice the specific regiochemistry of the products, as explained above.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.7: Oxymncuration-Demercuration: A Special Elcctrophilic Addition

Objectives

After completing this section, you should be able to

- write an equation for the hydration of an alkene with sulfuric acid.
- write an equation for the formation of an alcohol from an alkene by the oxymercuration-demercuration process.
- identify the alkene, the reagents, or both, that should be used to produce a given alcohol by the oxymercuration-demercuration process.
- write the mechanism for the reaction of an alkene with mercury(II) acetate in aqueous tetrahydrofuran (THF).

Key Terms

Make certain that you can define, and use in context, the key terms below.

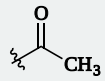
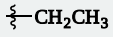
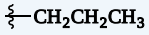
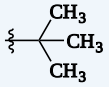
- hydration
- oxymercuration

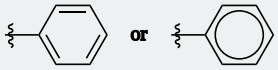
Study Notes

Oxymercuration is the reaction of an alkene with mercury(II) acetate in aqueous THF, followed by reduction with sodium borohydride. The final product is an alcohol.

It is important that you recognize the similarity between the mechanisms of bromination and oxymercuration. Recognizing these similarities helps you to reduce the amount of factual material that you need to remember.

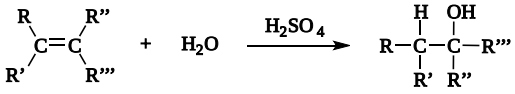
Mercuric acetate, or mercury(II) acetate, to give it the preferred IUPAC name, is written as $Hg(OAc)_2$; by comparing this formula with the formula $Hg(O_2CCH_3)_2$, you can equate Ac with $-COCH_3$. In fact, Ac is an abbreviation used for the acetyl group with the structure shown below as are other similar abbreviations that you will encounter.

Ac (acetyl)	
Me (methyl)	
Et (ethyl)	
Pr^n (*n*-propyl)	
Pr^i (isopropyl)	
Bu^t (*tert*-butyl)	

Ph (phenyl)	

What Is Electrophilic Hydration?

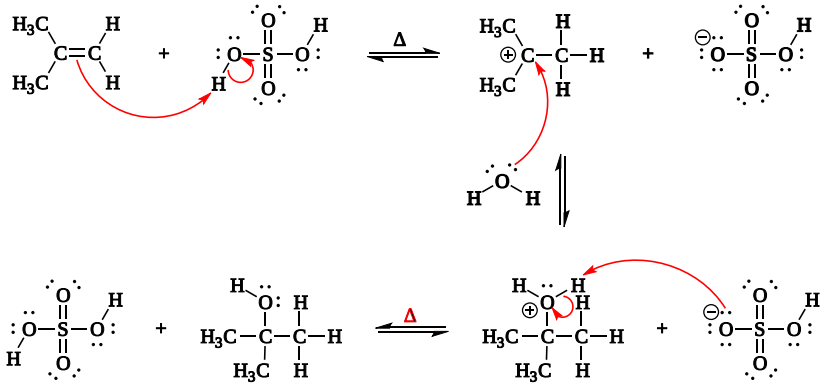
Electrophilic hydration is the act of adding an electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1°, 2°, or 3° alcohol on the alkane. Electrophilic hydration is the reverse dehydration of alcohols and has practical applications in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



An electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electron. An electrophilic hydrogen is commonly used to help break double bonds or restore catalysts (see S_N2 for more details).

Mechanism for the formation of a 3° Alcohol (1° and 2° mechanisms are similar)

Hydration is the process where water is added to an alkene to yield an alcohol. Acid-catalyzed hydration is when a strong acid is used as a catalyst to begin the reaction, but let's look at the mechanism below and break down the steps.



Step 1: A hydrogen atom from the acid is attacked by the nucleophilic Pi-electrons in the double bond. This is similar to the other alkene reactions we have seen so far. In this process, a new C-H bond is formed at the location which creates the more stable carbocation.

Step 2: A nucleophilic water attacks or donates a lone pair to the carbocation intermediate created in the first step. A new C-O bond is formed with the O having a formal charge of +1. The product is a protonated alcohol.

Step 3: To obtain the neutral alcohol product, the final step is to deprotonate the oxygen atom with the +1 formal charge using the conjugate base of the acid catalyst. This final step regenerates the acid catalyst and yields the neutral alcohol product.

> Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

What is Regiochemistry and How Does It Apply?

Regiochemistry deals with where the substituent bonds on the product is formed. **Zaitsev's** and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bond form in the product of an electrophilic additon. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies. See the following for an in-depth explanation of regiochemistry: Markovnikov explanation: Radical Additions--Anti-Markovnikov Product Formation

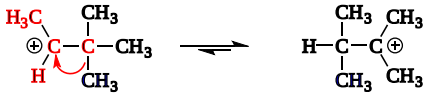
In the mechanism for the formation of a 3° alcohol shown above, the H is added to the least-substituted carbon in the nucleophilic double bond (it has less carbons attached to it). This means that the carbocation forms on the 3° carbon, causing it to be more stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, **carbocations form on the most substituted carbon** in the double bond.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

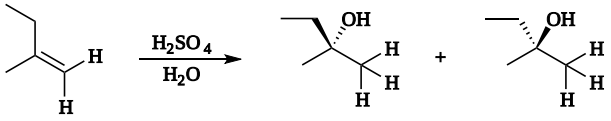


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3° alcohol shown above, water is the nucleophile. After one H atom is removed from the water molecule, the alcohol is attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

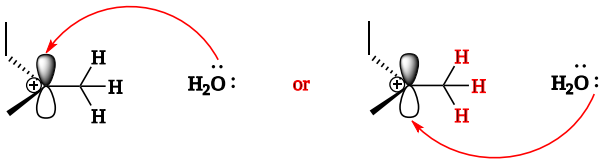
What is Stereochemistry and How Does It Apply?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that **the product is a racemic mixture**.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3° alcohol product of the following reaction could look like either of the following products:



There is no stereochemical control in acid-catalyzed hydration reactions. This is due to the trigonal planar, sp^2 nature of the carbocation intermediate. Water can act as a nucleophile to form a bond to either face of the carbocation, resulting in a mixture of stereochemical outcomes.



Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

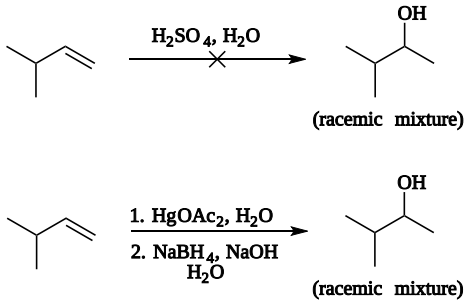
Is There a Better Way to Add Water to Synthesize an Alcohol From an Alkene?

A more efficient pathway does exist: **Oxymercuration - Demercuration**, a special type of electrophilic addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

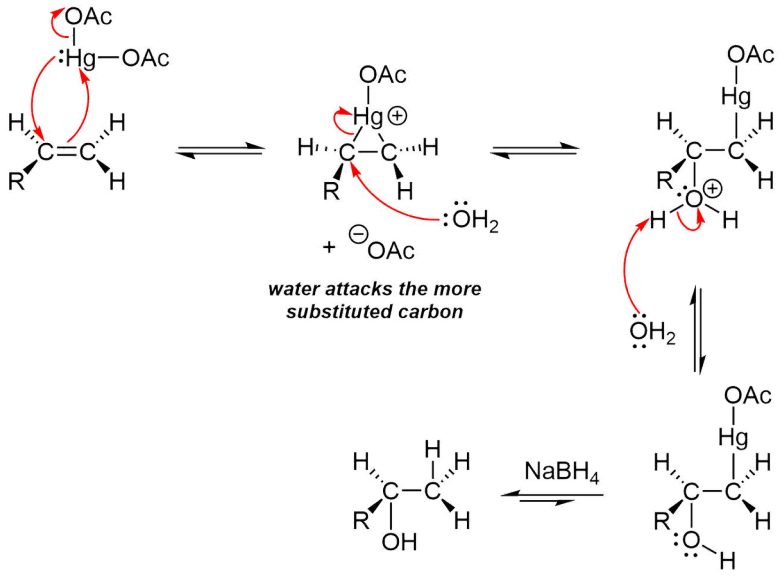
- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (*R*)-enantiomer and an (*S*)-enantiomer)
- Using sulfuric or phosphoric acid

Oxymercuration is a special electrophilic addition. It is anti-stereospecific and regioselective. Regioselectivity is a process in which the substituents choses one direction it prefers to be attached to over all the other possible directions. The good thing about this reaction is that there are no carbocation rearrangement due to stabilization of the reactive intermediate. Similar stabilization is also seen in bromination addition to alkenes.

One of the major advantages to oxymercuration is that carbocation rearrangements cannot occur under these conditions ($Hg(OAc)_2$, H_2O). Carbocation rearrangement is a process in which the carbocation intermediate can undergo a methyl or alkyl shift to form a more stable ion. Due to a possible carbocation rearrangement, the reaction below would not generate the product shown in high yields. In contrast, the oxymercuration reaction would proceed to form the desired product.



This reaction involves a mercury acting as a reagent attacking the alkene double bond to form a *Mercurinium Ion Bridge*. A water molecule will then attack the most substituted carbon to open the mercurium ion bridge, followed by proton transfer to solvent water molecule.



The organomercury intermediate is then reduced by sodium borohydride - the mechanism for this final step is beyond the scope of our discussion here. Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's regioselectivity with the OH group is attached to the most substituted carbon and the H is attach to the least substituted carbon. The reaction is useful, however, because strong acids are not required, and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

It is important to note that for the mechanism shown above, the enantiomer of the product shown is also formed. This is the result of formation of the mercurium ion below the alkene in the first step.

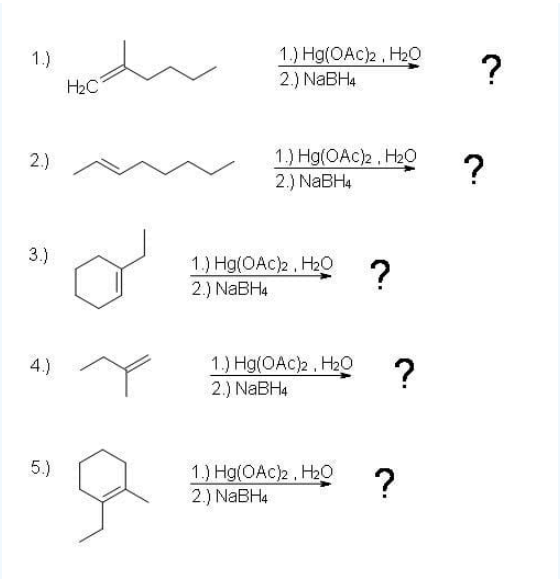
References

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2. Smith, Michael B., and Jerry March. March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure (March's Advanced Organic Chemistry). New York: Wiley-Interscience, 2007 2007.
3. Roderic P. Quirk , Robert E. Lea, Reductive demercuration of hex-5-enyl-1-mercuric bromide by metal hydrides. Rearrangement, isotope effects, and mechanism, *J. Am. Chem. Soc.*, 1976, 98 (19), pp 5973–5978.

Some Practice Problems

Practice problems

What are the end products of these reactants?

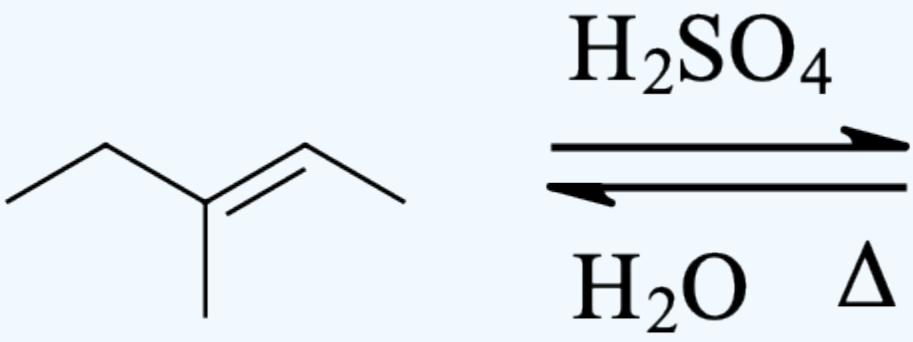


Answer available at the end of this section.

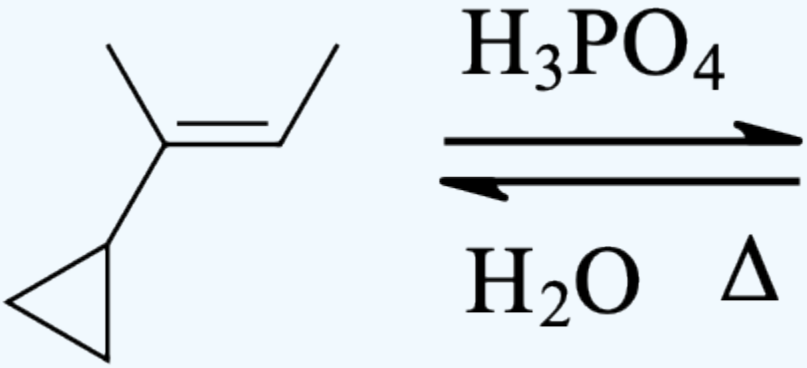
More Problems

Predict the product of each reaction.

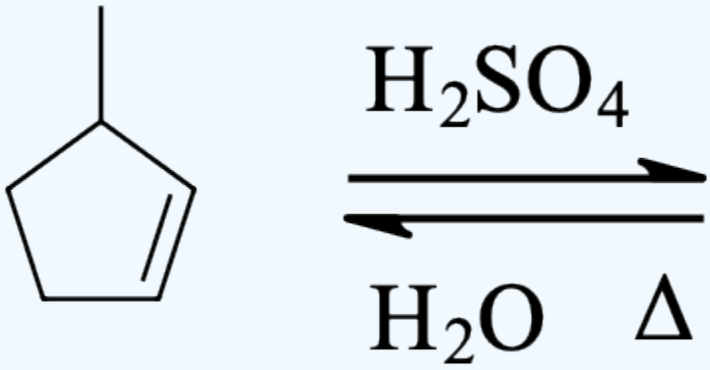
1)



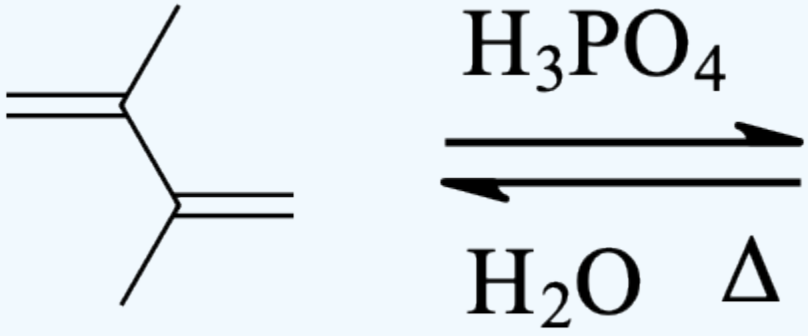
2) How does the cyclopropane group affect the reaction?



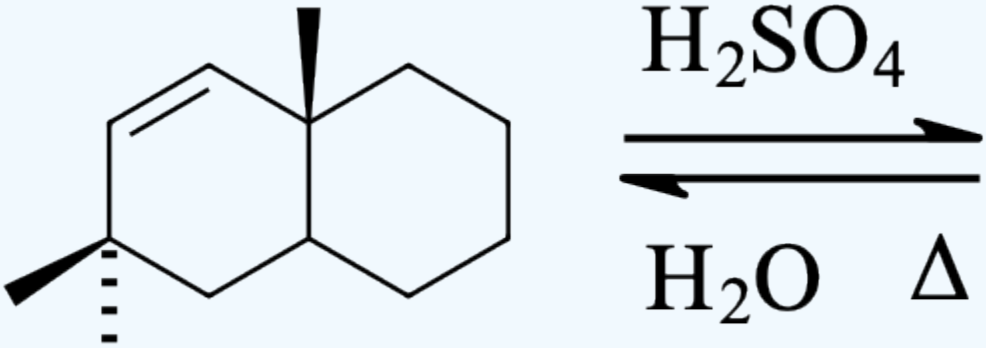
3) (Hint: What is different about this problem?)



4) (Hint: Consider stereochemistry.)



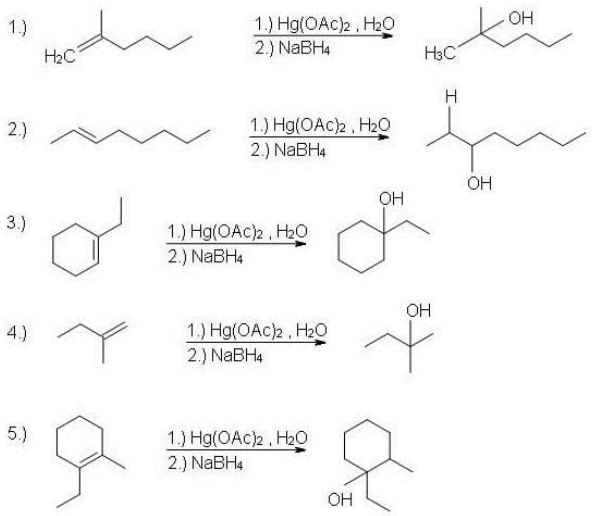
5) Indicate any shifts as well as the major product:



Answer available at the end of this section.

Answers

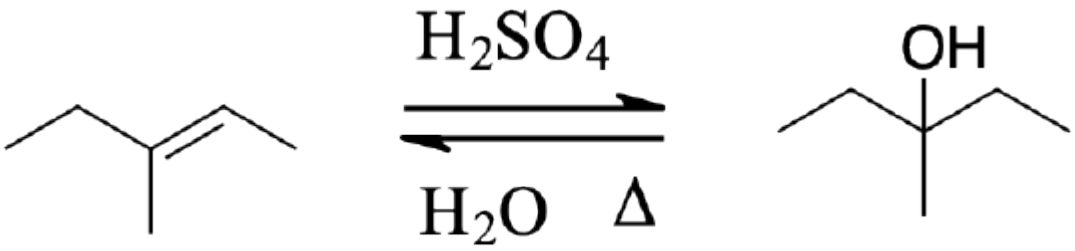
Practice problems



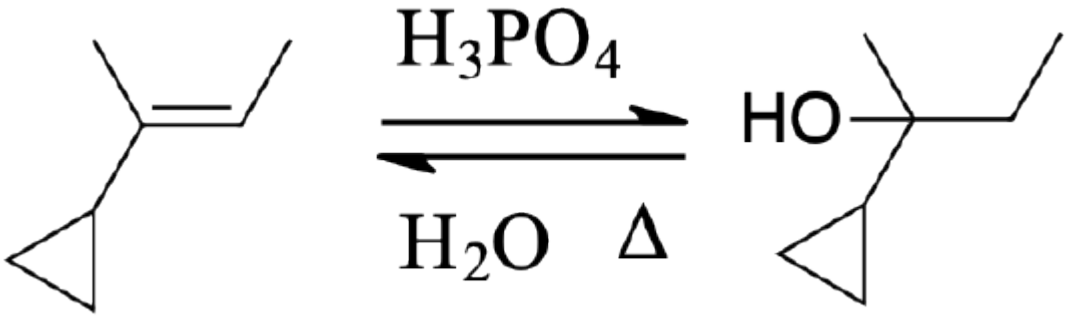
The end product to these practice problems are pretty much very similar. First, you locate where the double bond is on the reactant side. Then, you look at what substituents are attached to each side of the double bond and add the OH group to the more substituent side and the hydrogen on the less substituent side.

More Problems

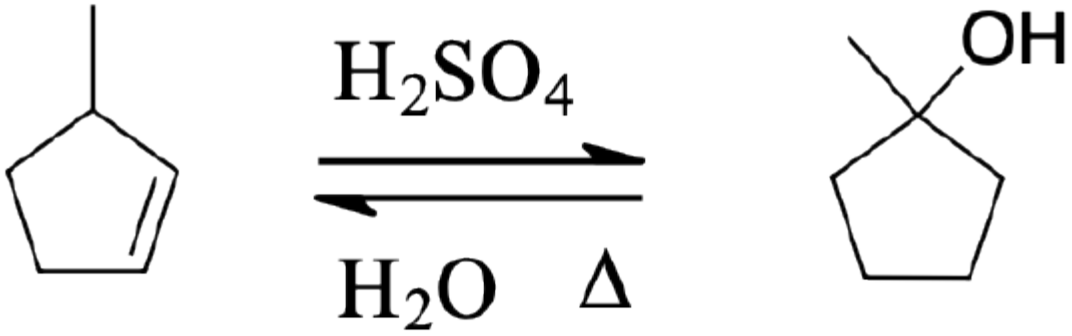
1) This is a simple electrophilic hydration.



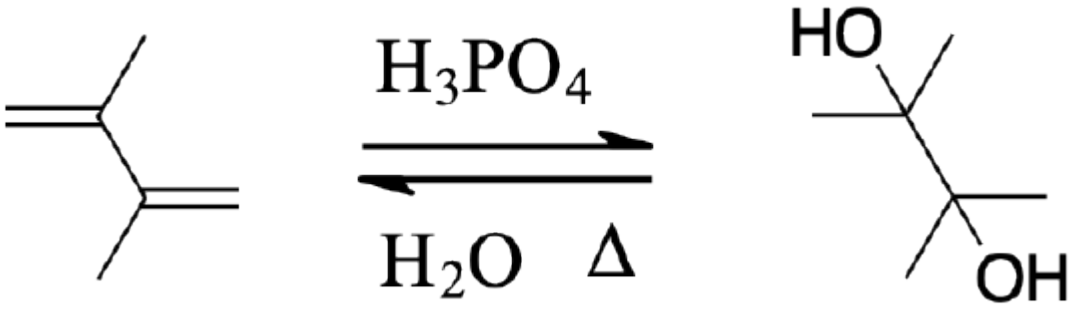
2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3° carbon will remain as such).



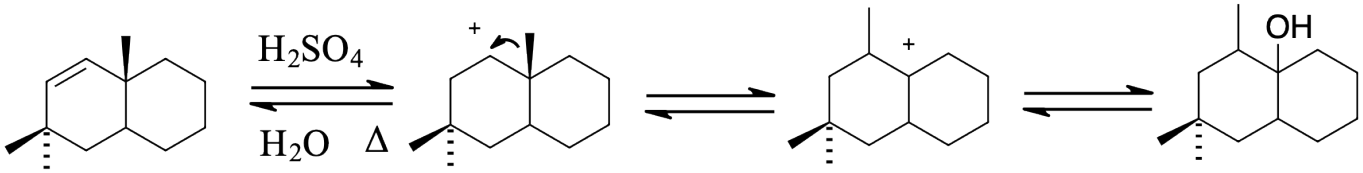
3) A hydride shift actually occurs from the 3 carbon of the 3-methylcyclopentene to where the carbocation had formed.



4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.



5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.



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- 8.4: Hydration of Alkenes - Addition of H_2O by Oxymercuration by Aliza Bother Duke University, Dietmar Kennepohl, Krista Cunningham, Lauren Reutenauer, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

12.8: Hydroboration-Oxidation: A Stereospecific Anti-Markovnikov Hydration

Objectives

After completing this section, you should be able to

- identify hydroboration (followed by oxidation) as a method for bringing about the (apparently) non-Markovnikov addition of water to an alkene.
- write an equation for the formation of a trialkylborane from an alkene and borane.
- write an equation for the oxidation of a trialkylborane to an alcohol.
- draw the structure of the alcohol produced by the hydroboration, and subsequent oxidation, of a given alkene.
- determine whether a given alcohol should be prepared by oxymercuration-demercuration or by hydroboration-oxidation, and identify the alkene and reagents required to carry out such a synthesis.
- write the detailed mechanism for the addition of borane to an alkene, and explain the stereochemistry and regiochemistry of the reaction.

Key Terms

Make certain that you can define, and use in context, the key term below.

- hydroboration

Study Notes

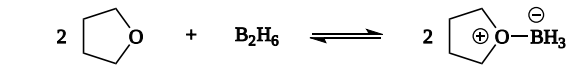
The two most important factors influencing organic reactions are polar (or electronic) effects and steric effects.

Hydroboration-oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. Furthermore, the borane acts as a Lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

Introduction

Hydroboration-oxidation of alkenes has been a very valuable laboratory method for the stereoselectivity and regioselectivity of alkenes. An additional feature of this reaction is that it occurs without rearrangement.

First off it is very important to understand little bit about the structure and the properties of the **borane** molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula B_2H_6 (diborane). Additionally, the dimer B_2H_6 ignites spontaneously in air. Borane is commercially available in ether and tetrahydrofuran (THF), in these solutions the borane can exist as a Lewis acid-base complex, which allows boron to have an electron octet.

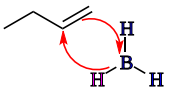


tetrahydrofuran (THF) (BH_3 • THF)

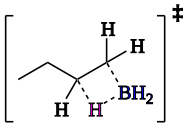
The Mechanism

Step 1

- Part 1: Hydroboration of the alkene. In this first step the addition of the borane to the alkene is initiated and proceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p orbital of the boron electrophile pairing with the electron pair of the pi bond of the nucleophile.

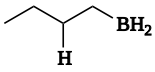


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

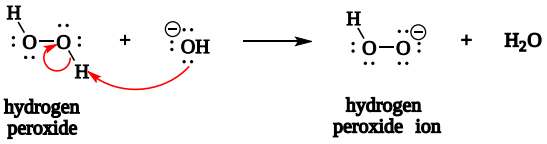
- Part 2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).

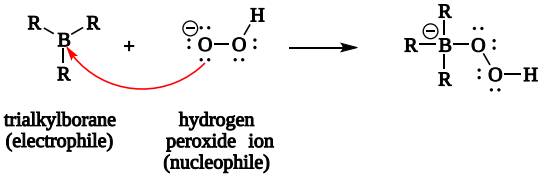


Oxidation of the Trialkylborane by Hydrogen Peroxide

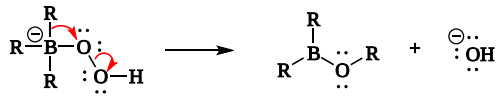
Step 2

- Part 1: The first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. the hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.

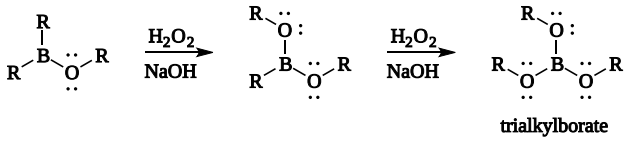




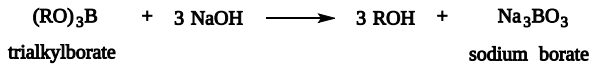
- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



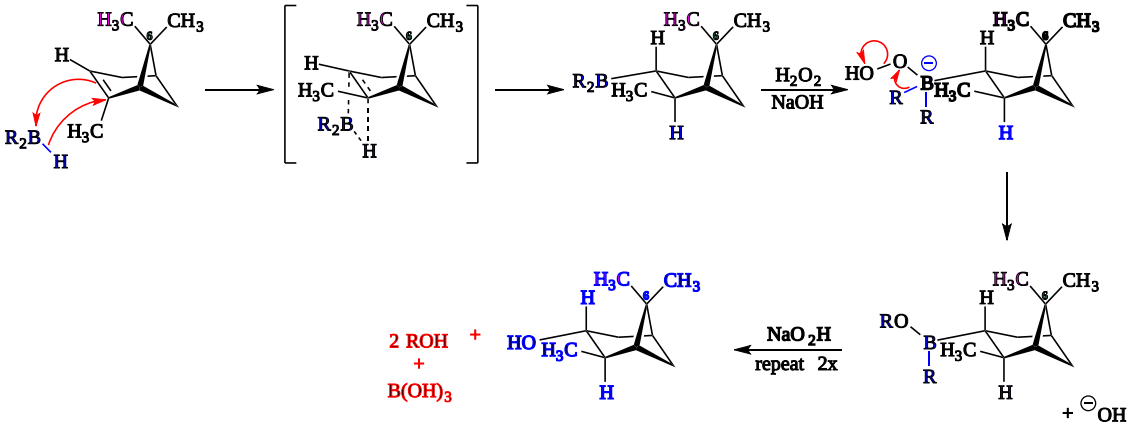
- Part 3: This is the final part of the oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.



If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

Stereochemistry of Hydroboration

The hydroboration reaction is among the few simple addition reactions that proceed cleanly in a *syn* fashion. As noted above, this is a single-step reaction. Since the bonding of the double bond carbons to boron and hydrogen is concerted, it follows that the geometry of this addition must be syn. Furthermore, rearrangements are unlikely inasmuch as a discrete carbocation intermediate is never formed. These features are illustrated for the hydroboration of α-pinene.



Since the hydroboration procedure is most commonly used to hydrate alkenes in an anti-Markovnikov fashion, we also need to know the stereoselectivity of the second oxidation reaction, which substitutes a hydroxyl group for the boron atom. Independent study has shown this reaction takes place with retention of configuration so the overall addition of water is also syn.

The hydroboration of α-pinene also provides a nice example of steric hindrance control in a chemical reaction. In the less complex alkenes used in earlier examples the plane of the double bond was often a plane of symmetry, and addition reagents could approach with equal ease from either side. In this case, one of the methyl groups bonded to C-6 (colored purple in the equation) covers one face of the double bond, blocking any approach from that side. All reagents that add to this double bond must therefore approach from the side opposite this methyl.

Exercise 12.8.1

What are the products of this reactions?

PROBLEM_1.bmp

Answer available at the end of this section.

Exercise 12.8.2

What are the products of this reactions?

PROBLEM_#2.bmp

Answer available at the end of this section.

Exercise 12.8.3

What are the products of this reactions?

PROBELM_#3.bmp

Answer available at the end of this section.

Exercise 12.8.4

Draw the structural formulas for the alcohols that result from hydroboration-oxidation of this alkene.

problem_4.bmp

Answer available at the end of this section.

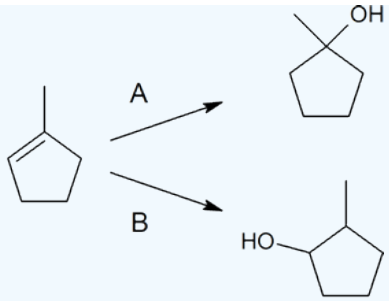
Exercise 12.8.5

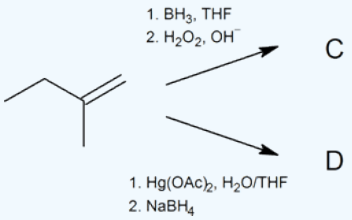
Draw the structural formulas for the alcohols that result from hydroboration-oxidation of (E)-3-methyl-2-pentene. If you need clarification or a reminder on the nomenclature of alkenes refer to the link below on naming the alkenes.

Answer available at the end of this section.

Exercise 12.8.6

Write out the reagents or products (A–D) shown in the following reaction schemes.





Answer available at the end of this section.

References

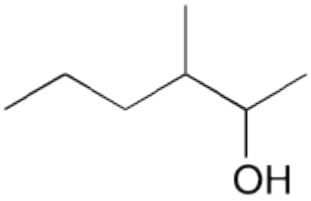
1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
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3. Bruice, Paula Yurkanis. Oragnic Chemistry. 5th. CA. Prentice Hall, 2006.
4. Bergbreiter E. David , and David P. Rainville. Stereochemistry of hydroboration-oxidation of terminal alkenes. *J. Org. Chem.*, 1976, 41 (18), pp 3031–3033
5. Ilich, Predrag-Peter; Rickertsen, Lucas S., and Becker Erienne. Polar Addition to C=C Group: Why Is Anti-Markovnikov Hydroboration-Oxidation of Alkenes Not "Anti-"? Journal of Chemical Education., 2006, v83, n11, pg 1681-1685

Answers

Exercise 12.8.1

answer_#1.bmp

Exercise 12.8.2



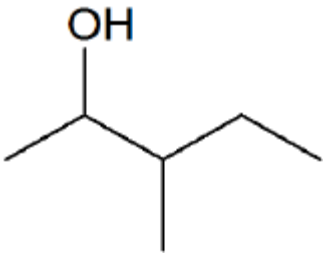
Exercise 12.8.3

Answer_#3.bmp

Exercise 12.8.4

ANSWER_#4.bmp

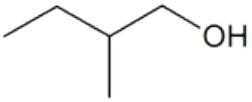
Exercise 12.8.5

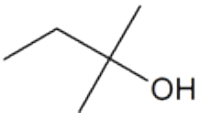


Exercise 12.8.6

A 1. $Hg(OAc)_2$, H_2O/THF
2. $NaBH_4$

B 1. BH_3, THF
2. H_2O_2, OH^-

C 

D 

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12.9: Diazomethane, Carbenes, and Cyclopropane Synthesis

Objectives

After completing this section, you should be able to

- describe, and write the detailed mechanism for, the formation of a carbene, such as dichlorocarbene.
- describe the structure of a carbene in terms of the hybridization of the central carbon atom.
- write an equation for the formation of a substituted cyclopropane from an alkene and a carbene.
- identify the reagents, the alkene, or both, needed to prepare a given substituted cyclopropane by addition of a carbene to a double bond.
- identify the substituted cyclopropane formed from the reaction of a given alkene with the reagents necessary to form a carbene.

Key Terms

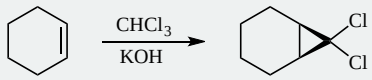
Make certain that you can define, and use in context, the key terms below.

- carbene (R_2C:)
- carbenoid
- Simmons-Smith reaction
- stereospecific

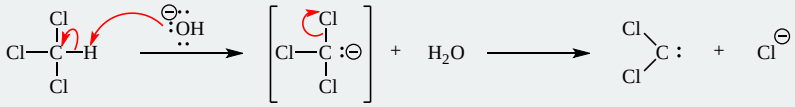
Study Notes

A *carbenoid* is best considered to be a reagent which, while not actually a carbene, behaves as if it were an intermediate of this type.

Dichlorocarbenes can also form cyclopropane structures and are created in situ from reagents such as chloroform and KOH.



The detailed mechanism of the formation of dichlorocarbene is given below. Note that the deprotonation of chloroform generates the trichloromethanide anion, which spontaneously expels the chloride anion.



The highly strained nature of cyclopropane compounds makes them very reactive and interesting synthetic targets. Additionally cyclopropanes are present in numerous biological compounds. One common method of cyclopropane synthesis is the reaction of carbenes with the double bond in alkenes or cycloalkenes. Methylene, H_2C, is simplest carbene, and in general carbenes have the formula R_2C. Other species that will also react with alkenes to form cyclopropanes but do not follow the formula of carbenes are referred to as carbenoids.

Introduction

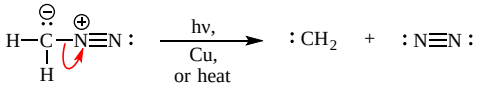
Carbenes were once only thought of as short lived intermediates. The reactions of this section only deal with these short lived

carbenes which are mostly prepared in situ, in conjunction with the main reaction. However, there do exist so called persistent carbenes. These persistent carbenes are stabilized by a variety of methods often including aromatic rings or transition metals. In general a carbene is neutral and has 6 valence electrons, 2 of which are non bonding. These electrons can either occupy the same sp^2 hybridized orbital to form a singlet carbene (with paired electrons), or two different sp^2 orbitals to from a triplet carbene (with unpaired electrons). The chemistry of triplet and singlet carbenes is quite different but can be oversimplified to the statement: singlet carbenes usually retain stereochemistry while triplet carbenes do not. The carbenes discussed in this section are singlet and thus retain stereochemistry.

The reactivity of a singlet carbene is concerted and similar to that of electrophilic or nucleophilic addition wheras, triplet carbenes react like biradicals, explaining why sterochemistry is not retained. The highly reactive nature of carbenes leads to very fast reactions in which the rate determining step is generally carbene formation.

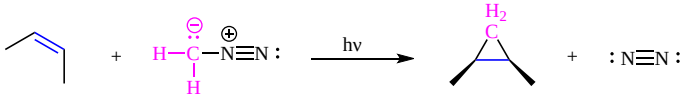
Preparation of methylene

The preparation of methylene starts with the yellow gas diazomethane, CH_2N_2. Diazomethane can be exposed to light, heat or copper to facilitate the loss of nitrogen gas and the formation of the simplest carbene methylene. The process is driven by the formation of the nitrogen gas which is a very stable molecule.

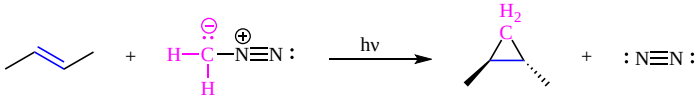


Carbene reaction with alkenes

A carbene such as methlyene will react with an alkene which will break the double bond and result with a cyclopropane. The reaction will usually leave stereochemistry of the double bond unchanged. As stated before, carbenes are generally formed along with the main reaction; hence the starting material is diazomethane not methylene.



In the above case *cis*-2-butene is converted to *cis*-1,2-dimethylcyclopropane. Likewise, below the *trans* configuration is maintained. This shows that the reactions are stereospecific, only a single stereoisomer is obtained as the product.



Additional Types of Carbenes and Carbenoids

In addition to the general carbene with formula R_2C there exist a number of other compounds that behave in much the same way as carbenes in the synthesis of cyclopropane. **Halogenated carbenes** are formed from halomethanes. An example is dicholorcarbene, Cl_2C. The mechanism for the formation of dichlorocarbene is above in the study notes. These halogenated carbenes will form cyclopropanes in the same manner as methylene but with the interesting presence of two halogen atoms in place of the hydrogen atoms.

Carbenoids are substances that form cyclopropanes like carbenes but are not technically carbenes. One common example is the stereospecific Simmon-Smith reaction which utilizes the carbenoid - ICH_2ZnI. The (iodomethyl) zinc iodide is formed in situ via the mixing of Zn-Cu with CH_2I_2. If this ICH_2ZnI is in the presence of an alkene, a CH_2 group is transferred to the double bond to create cyclopropane. Since this reacts as a carbene, the same methods can be applied to determine the product.

Exercise 12.9.1

Knowing that cycloalkenes react much the same as regular alkenes what would be the expected structure of the product of cyclohexene and diazomethane facilitated by copper metal?

Answer available at the end of this section.

Exercise 12.9.2

What would be the result of a Simmons-Smith reaction that used *trans*-2-pentene as a reagent?

Answer available at the end of this section.

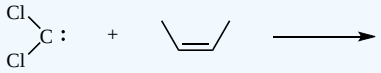
Exercise 12.9.3

What starting material could be used to form *cis*-1,2-diethylcyclopropane?

Answer available at the end of this section.

Exercise 12.9.4

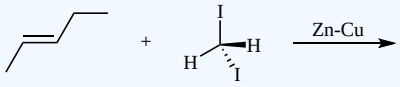
What would the following reaction yield?



Answer available at the end of this section.

Exercise 12.9.5

Draw the product of this reaction. What type of reaction is this?



Answer available at the end of this section.

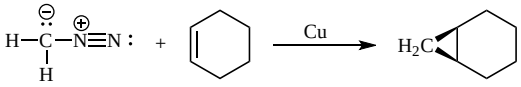
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1. Vollhardt, K. Peter C. and Schore, Neil E. Organic Chemistry: Structure and Function. New York: Bleyer, Brennan, 2007.
2. Abdel-Wahab, Aboel-Magd A. Ahmed, Saleh A. and Dürr, Heinz. "Carbene Formation by Extrusion of Nitrogen" in CRC Handbook of Organic Photochemistry and Photobiology. CRC Press, 2004.

Answers

Exercise 12.9.1

The product will be a bicyclic ring, Bicyclo[4.1.0]heptane.



Exercise 12.9.2

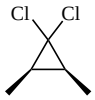
The stereochemistry will be retained making a cyclopropane with trans methyl and ethyl groups. *Trans*-1-ethyl-2-methylcyclopropane

Exercise 12.9.3

The *cis* configuration will be maintained from reagent to product so we would want to start with *cis*-3-hexene. A Simmons Smith reagent, or methylene could be used as the carbene or carbenoid.

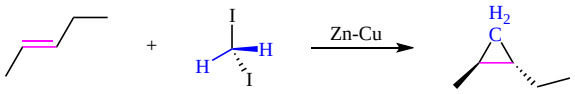
Exercise 12.9.4

The halogenated carbene will react the same as methylene yielding, *cis*-1,1-dichloro-2,3-dimethylcyclopropane.



Exercise 12.9.5

This is a Simmons-Smith reaction which uses the carbenoid formed by the CH_2I_2 and Zu-Cu. The reaction results in the same product as if methylene was used and retains stereospecificity. Iodine metal and the Zn-Cu are not part of the product. The product is *trans*-1,2-ethyl-methylcyclopropane.



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12.10: Oxacyclopropane (Epoxide) Synthesis: Epoxidation by Peroxycarboxylic Acids

Objectives

After completing this section, you should be able to

- write the equation for the epoxidation of an alkene using meta-chloroperoxybenzoic acid.
- identify the alkene, reagents, or both, that must be used to prepare a given epoxide.
- write the equation for the hydroxylation of an alkene using osmium tetroxide, and draw the structure of the cyclic intermediate.
- draw the structure of the diol formed from the reaction of a given alkene with osmium tetroxide.
- identify the alkene, the reagents, or both, that must be used to prepare a given 1,2-diol.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- diol
- glycol
- hydroxylation

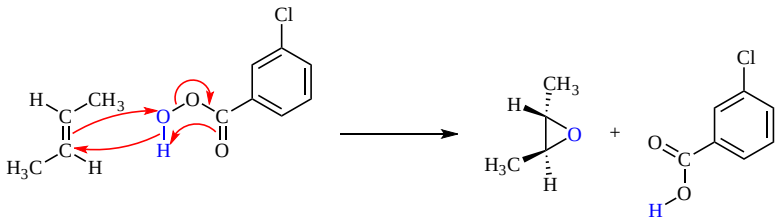
The previous section discussed the reduction of a double bond, so adding hydrogen to the the double bond. This section will discuss oxidation. In organic chemistry, this is a reaction that where the carbon atom loses electron density, which happens when new bond to a more electronegative atom occurs or when a double bond is broken between a carbon and a less electronegative atom. A simplified to say this is in organic chemistry a reduction is more bonds to hydrogen and oxidation is more bonds to oxygen often.

Oxacyclopropane Synthesis by Peroxycarboxylic Acid

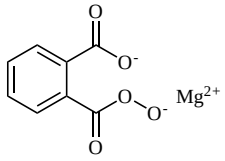
One way to oxidized a double bond is to produce an oxacyclopropane ring. Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid. Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

Mechanism

Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.

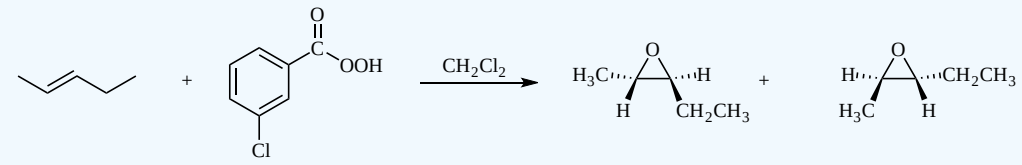


Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.



magnesium monoperoxyphthalate, MMPP

Example 8.7.1



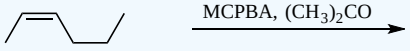
trans-2-pentene MCPBA mixture of enantiomers of *trans*-3-ethyl-2-methyloxacyclopropane

Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen is inserted on top. (See the product of the above reaction.) One way the epoxide ring can be opened is by an acid catalyzed oxidation-hydrolysis. Oxidation-hydrolysis gives a vicinal diol, a molecule with OH groups on neighboring carbons. For this reaction, the dihydroxylation is *anti* since, due to steric hindrance, the ring is attacked from the side opposite the existing oxygen atom. Thus, if the starting alkene is trans, the resulting vicinal diol will have one *(S)* and one (*R*) stereocenter. But, if the starting alkene is cis, the resulting vicinal diol will have a racemic mixture of (S,S) and (*R*,*R*) enantiomers.

Epoxidation exercises

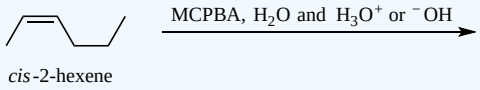
1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

a) in acetone solvent.



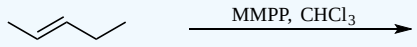
cis-2-hexene

b) in an aqueous medium with acid or base catalyst present.



cis-2-hexene

2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



trans-2-pentene

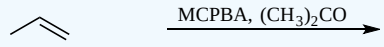
3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.



trans-3-hexene

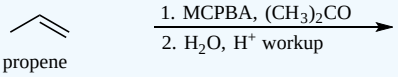
4. Predict the reaction of propene with MCPBA.

a) in acetone solvent



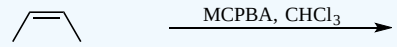
propene

b) after aqueous work-up.



propene

5. Predict the reaction of cis-2-butene in chloroform solvent.

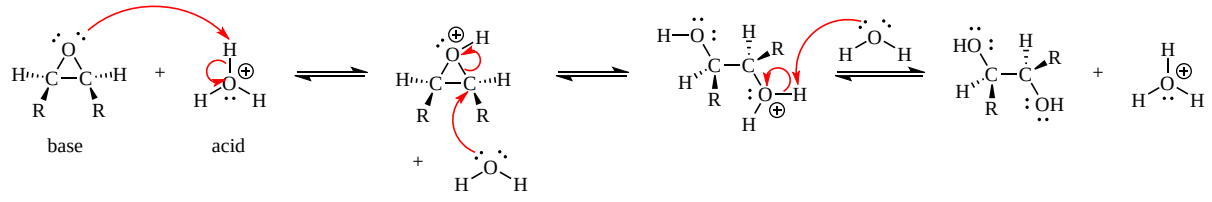


cis-2-butene

Answers available at the end of this section.

Anti Dihydroxylation

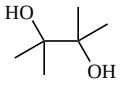
Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



base acid

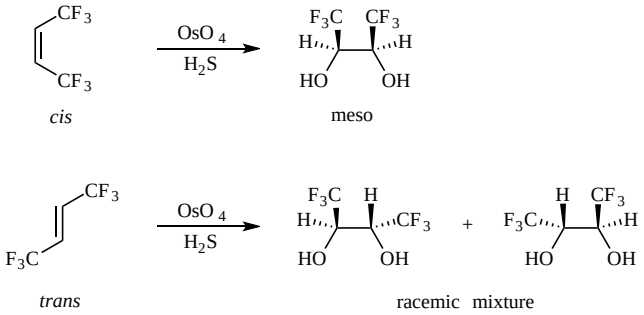
Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



Introduction

The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



OsO_4 is formed slowly when osmium powder reacts with gasoues O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

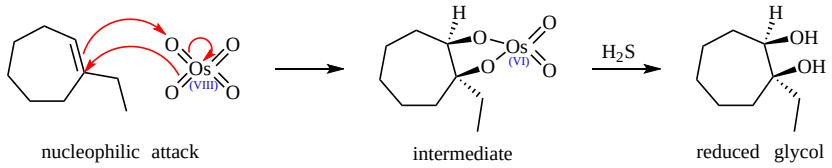
$$\mathrm{Os\,(s) + 2\,O_2\,(g)\ \rightarrow OS_4}$$

Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of $\mathrm{OsO_4}$ and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of $\mathrm{OsO_4}$ was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $\mathrm{KMnO_4}$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of **overoxidation**.

Mechanism

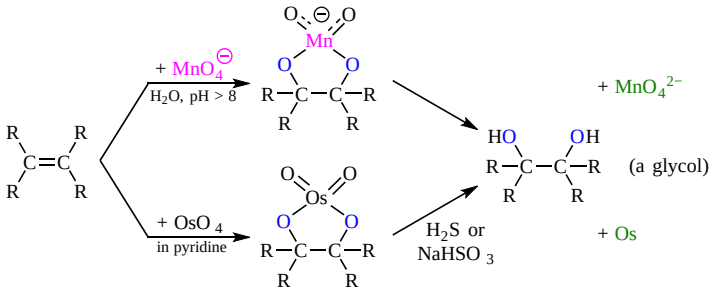
- Electrophilic attack on the alkene
  - Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  - 2 electrons from the double bond flows toward the osmium metal
    - In the process, 3 electron pairs move simultaneously
  - Cyclic ester with Os (VI) is produced
- Reduction
  - H_2S reduces the cyclic ester
    - $NaHSO_4$ with H_2O may be used
  - Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



Hydroxylation of alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.



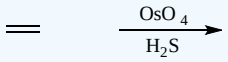
When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown above.

Chemical Highlight

Antitumor drugs have been formed by using dihydroxylation. This method has been applied to the enantioselective synthesis of ovalicin, which is a class of fungal-derived products called antiangiogenesis agents. These antitumor products can cut off the blood supply to solid tumors. A derivative of ovalicin, TNP-470, is chemically stable, nontoxic, and noninflammatory. TNP-470 has been used in research to determine its effectiveness in treating cancer of the breast, brain, cervix, liver, and prostate.

Dihydroxylation Exercises

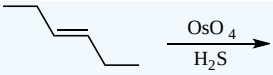
1. Give the major product.



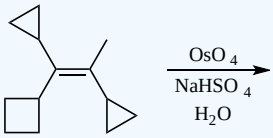
2. What is the product in the dihydroxylation of (Z)-3-hexene?



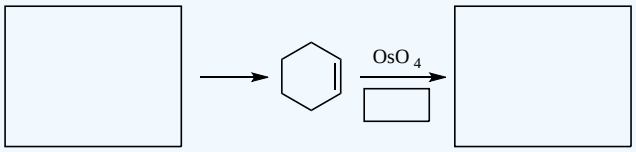
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.



5. Fill in the missing reactants, reagents, and product.



Answers available at the end of this section.

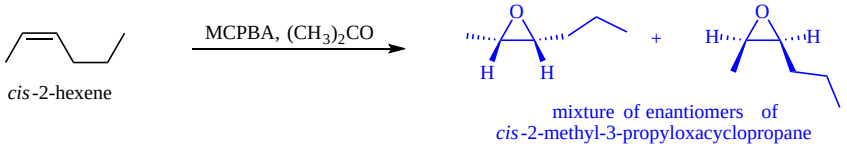
References

1. Dehestani, Ahmad et al. (2005). Ligand-assisted reduction of osmium tetroxide with molecular hydrogen via a [3+2] mechanism. *Journal of the American Chemical Society, 2005, 127 (10),* 3423-3432.
2. Sorrell, Thomas, N. Organic Chemistry. New York: University Science Books, 2006.
3. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

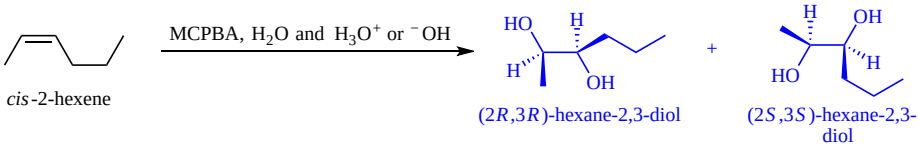
Answers

Epoxidation exercises

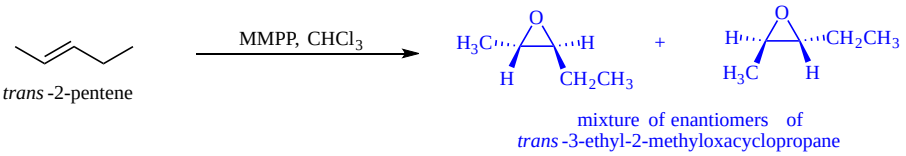
1. a) *Cis*-2-methyl-3-propyloxacyclopropane



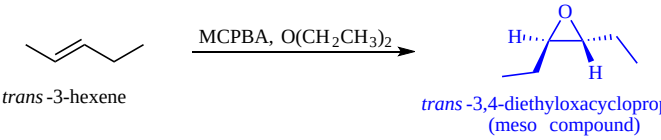
b) Racemic (2*R*,3*R*)-2,3-hexanediol and (2S,3S)-2,3-hexanediol



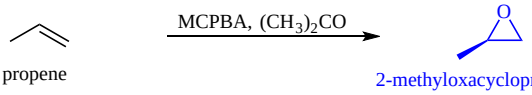
2. *Trans*-3-ethyl-2-methyloxacyclopropane.



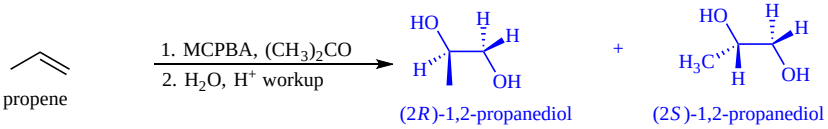
3. *Trans*-3,4-diethyloxacyclopropane.



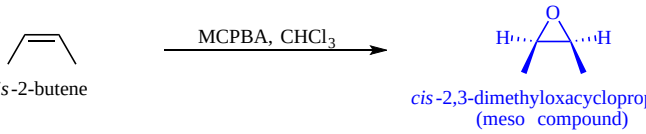
4. a) 2-methyl-oxacyclopropane



b) Racemic (2S)-1,2-propandiol and (2*R*)-1,2-propanediol

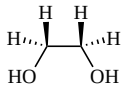


5. *Cis*-2,3-dimethyloxacyclopropane

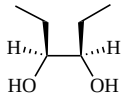


Dihydroxylation Exercises

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

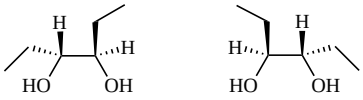


2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.



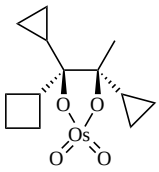
(3*S*,4*R*)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

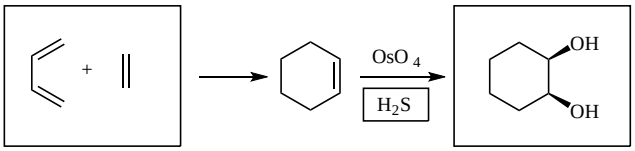


(3*R*,4*R*) (3*S*,4*S*)

4. A cyclic osmic ester is formed.



5. The Diels-Alder cycloaddition reaction is needed in the first box to form the cyclohexene. The second box needs a reagent to reduce the intermediate cyclic ester (not shown). The third box has the product: 1,2-cyclohexanediol.



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12.11: Vicinal SYn Dihydroxylation with Osmium Tetroxide

Objectives

After completing this section, you should be able to

- write the equation for the epoxidation of an alkene using meta-chloroperoxybenzoic acid.
- identify the alkene, reagents, or both, that must be used to prepare a given epoxide.
- write the equation for the hydroxylation of an alkene using osmium tetroxide, and draw the structure of the cyclic intermediate.
- draw the structure of the diol formed from the reaction of a given alkene with osmium tetroxide.
- identify the alkene, the reagents, or both, that must be used to prepare a given 1,2-diol.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- diol
- glycol
- hydroxylation

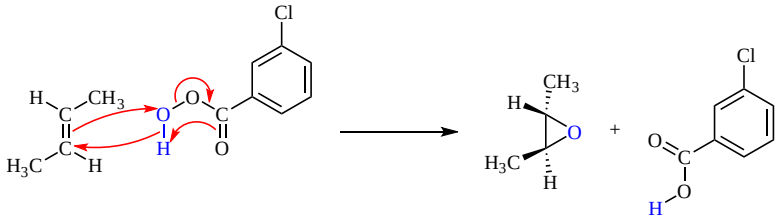
The previous section discussed the reduction of a double bond, so adding hydrogen to the the double bond. This section will discuss oxidation. In organic chemistry, this is a reaction that where the carbon atom loses electron density, which happens when new bond to a more electronegative atom occurs or when a double bond is broken between a carbon and a less electronegative atom. A simplified to say this is in organic chemistry a reduction is more bonds to hydrogen and oxidation is more bonds to oxygen often.

Oxacyclopropane Synthesis by Peroxycarboxylic Acid

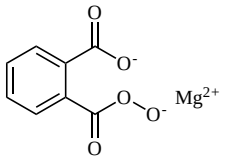
One way to oxidized a double bond is to produce an oxacyclopropane ring. Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid. Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

Mechanism

Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.

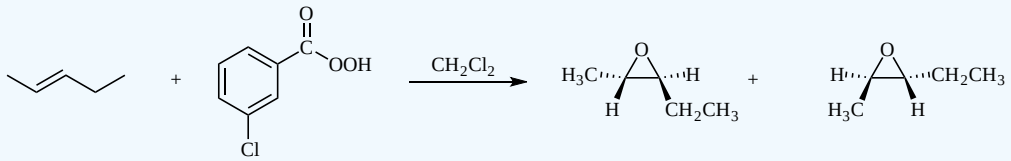


Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.



magnesium monoperoxyphthalate, MMPP

Example 8.7.1



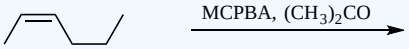
trans-2-pentene MCPBA mixture of enantiomers of *trans*-3-ethyl-2-methyloxacyclopropane

Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen is inserted on top. (See the product of the above reaction.) One way the epoxide ring can be opened is by an acid catalyzed oxidation-hydrolysis. Oxidation-hydrolysis gives a vicinal diol, a molecule with OH groups on neighboring carbons. For this reaction, the dihydroxylation is *anti* since, due to steric hindrance, the ring is attacked from the side opposite the existing oxygen atom. Thus, if the starting alkene is trans, the resulting vicinal diol will have one *(S)* and one (*R*) stereocenter. But, if the starting alkene is cis, the resulting vicinal diol will have a racemic mixture of (S,S) and (*R*,*R*) enantiomers.

Epoxidation exercises

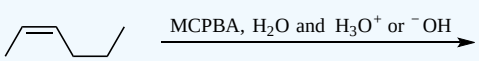
1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

a) in acetone solvent.



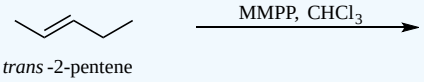
cis-2-hexene

b) in an aqueous medium with acid or base catalyst present.



cis-2-hexene

2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



trans -2-pentene

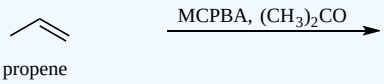
3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.



trans -3-hexene

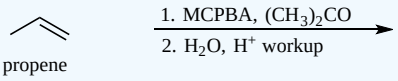
4. Predict the reaction of propene with MCPBA.

a) in acetone solvent



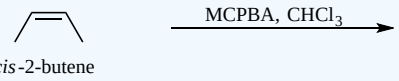
propene

b) after aqueous work-up.



propene

5. Predict the reaction of cis-2-butene in chloroform solvent.

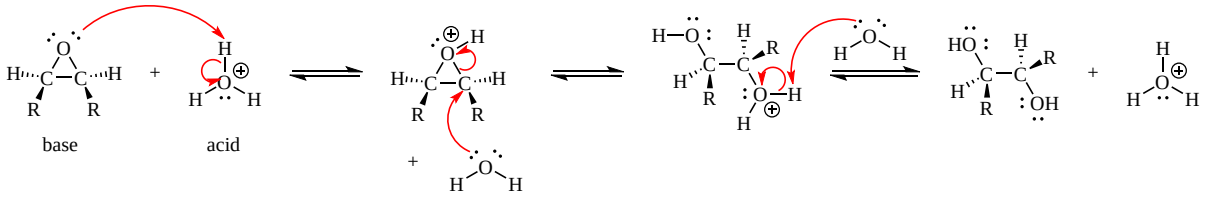


cis -2-butene

Answers available at the end of this section.

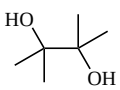
Anti Dihydroxylation

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



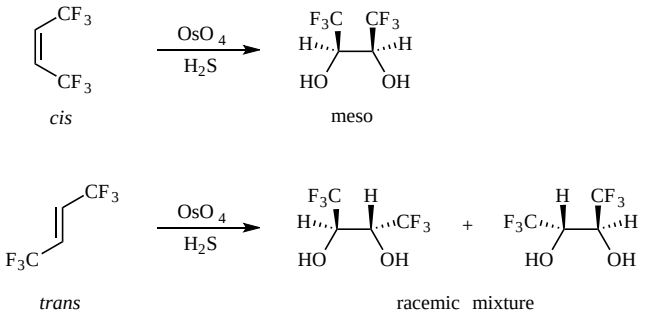
Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



Introduction

The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



OsO_4 is formed slowly when osmium powder reacts with gasoues O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

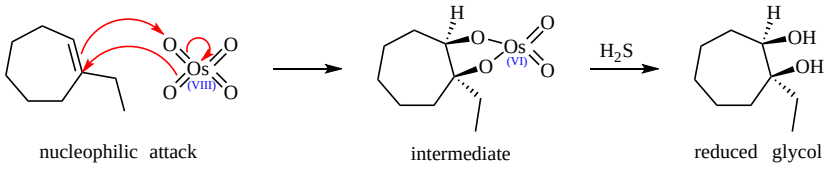
$$\mathrm{Os\,(s) + 2\,O_2\,(g)\ \rightarrow OS_4}$$

Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of $\mathrm{OsO_4}$ and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of $\mathrm{OsO_4}$ was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $\mathrm{KMnO_4}$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of **overoxidation**.

Mechanism

- Electrophilic attack on the alkene
  - Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  - 2 electrons from the double bond flows toward the osmium metal
    - In the process, 3 electron pairs move simultaneously
  - Cyclic ester with Os (VI) is produced
- Reduction
  - H_2S reduces the cyclic ester
    - $NaHSO_4$ with H_2O may be used
  - Forms the syn-1,2-diol (glycol)

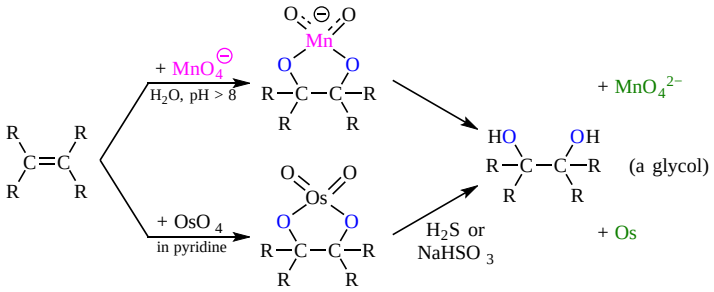
Example: Dihydroxylation of 1-ethyl-1-cycloheptene



Hydroxylation of alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-

stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.



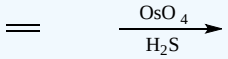
When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown above.

Chemical Highlight

Antitumor drugs have been formed by using dihydroxylation. This method has been applied to the enantioselective synthesis of ovalicin, which is a class of fungal-derived products called antiangiogenesis agents. These antitumor products can cut off the blood supply to solid tumors. A derivative of ovalicin, TNP-470, is chemically stable, nontoxic, and noninflammatory. TNP-470 has been used in research to determine its effectiveness in treating cancer of the breast, brain, cervix, liver, and prostate.

Dihydroxylation Exercises

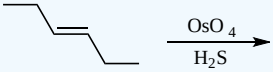
1. Give the major product.



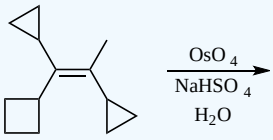
2. What is the product in the dihydroxylation of (Z)-3-hexene?



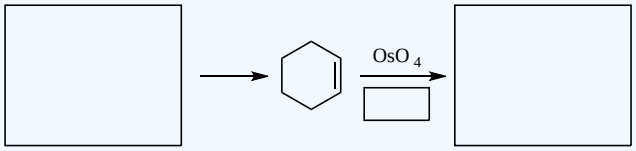
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.



5. Fill in the missing reactants, reagents, and product.



Answers available at the end of this section.

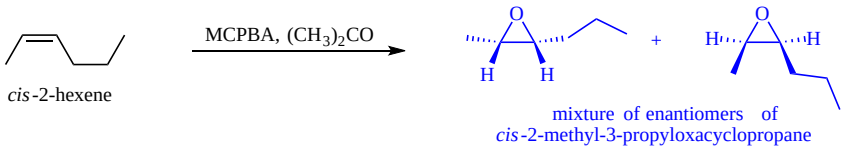
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2. Sorrell, Thomas, N. Organic Chemistry. New York: University Science Books, 2006.
3. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

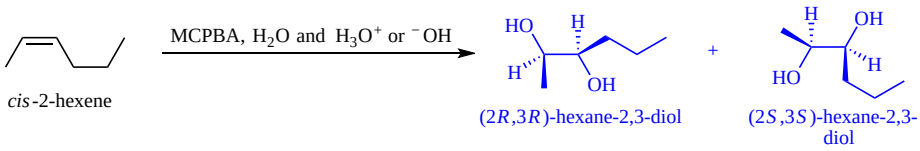
Answers

Epoxidation exercises

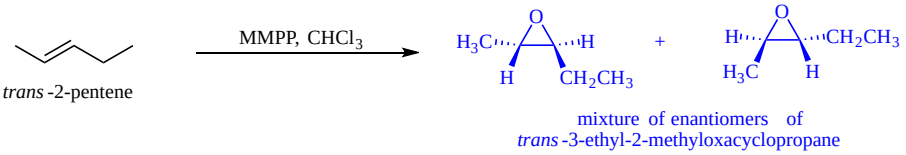
1. a) *Cis*-2-methyl-3-propyloxacyclopropane



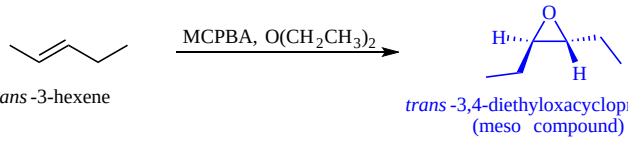
b) Racemic (2*R*,3*R*)-2,3-hexanediol and (2S,3S)-2,3-hexanediol



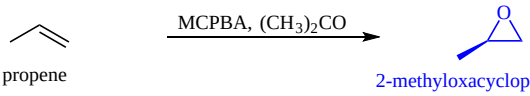
2. *Trans*-3-ethyl-2-methyloxacyclopropane.



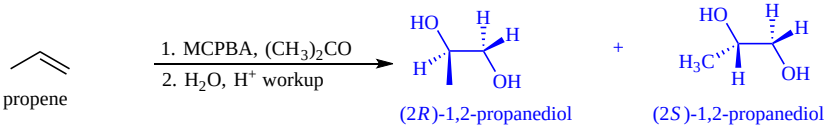
3. *Trans*-3,4-diethyloxacyclopropane.



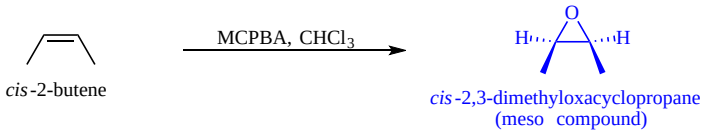
4. a) 2-methyl-oxacyclopropane



b) Racemic (2S)-1,2-propandiol and (2*R*)-1,2-propanediol

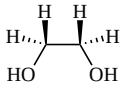


5. *Cis*-2,3-dimethyloxacyclopropane

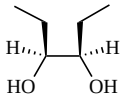


Dihydroxylation Exercises

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

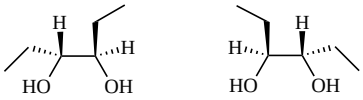


2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.



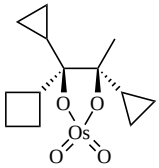
(3*S*,4*R*)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

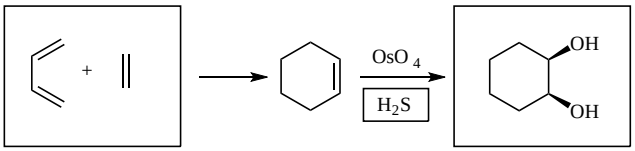


(3*R*,4*R*) (3*S*,4*S*)

4. A cyclic osmic ester is formed.



5. The Diels-Alder cycloaddition reaction is needed in the first box to form the cyclohexene. The second box needs a reagent to reduce the intermediate cyclic ester (not shown). The third box has the product: 1,2-cyclohexanediol.



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- 8.7: Oxidation of Alkenes - Epoxidation and Hydroxylation by Dietmar Kennepohl, Krista Cunningham, Kristen Perano, Lauren Reutenauer, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

12.12: Oxidative Cleavage: Ozonolysis

Objective

After completing this section, you should be able to

- write an equation to describe the cleavage of an alkene by ozone, followed by reduction of the ozonide so formed with either sodium borohydride or zinc and acetic acid.
- predict the products formed from the ozonolysis-reduction of a given alkene.
- write an equation to describe the cleavage of an alkene by potassium permanganate.
- predict the products from the oxidative cleavage of a given alkene by potassium permanganate.
- use the results of ozonolysis-reduction, or cleavage with permanganate, to deduce the structure of an unknown alkene.
- identify the reagents that should be used in the oxidative cleavage of an alkene to obtain a given product or products.
- write the equation for the cleavage of a 1,2-diol by periodic acid, and draw the structure of the probable intermediate.
- predict the product or products that will be formed from the treatment of a given 1,2-diol with periodic acid.
- use the results of hydroxylation/1,2-diol cleavage to deduce the structure of an unknown alkene.

Key Terms

Make certain that you can define, and use in context, the key terms below.

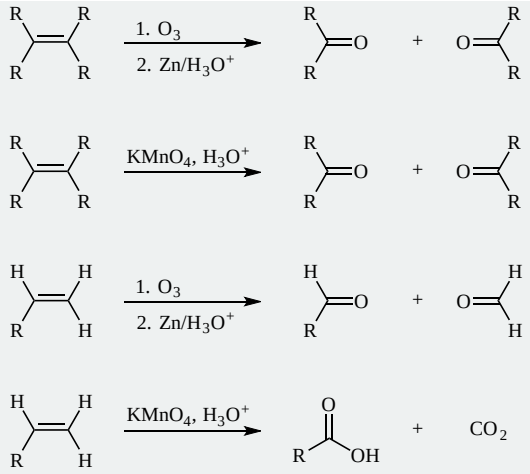
- molozonide
- ozonide
- ozonolysis

Study Notes

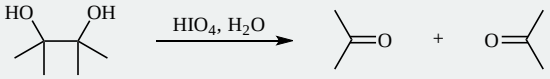
Ozonolysis, or ozonolysis-reduction, refers to the treatment of an alkene with ozone followed by a suitable reducing agent to break down complex double-bond-containing compounds into smaller, more easily identified products. From the identity of the products formed, it may be possible to deduce the structure of the original double-bond-containing substance. Ozonolysis will feature prominently in many of the road-map problems that you will encounter in this course.

A *molozonide* is an unstable, cyclic intermediate that is initially formed when an alkene reacts with ozone.

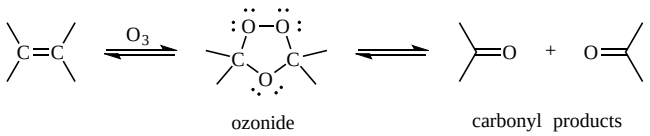
Alkenes can also be cleaved by other oxidizing agents such as potassium permanganate. However, $KMnO_4$ will carry the oxidation further than ozonolysis, so products can be slightly different. Note within the summary of the following reactions that ozonolysis produces aldehydes and ketones, while $KMnO_4$ can oxidize all the way to to carbon dioxide and carboxylic acid.



Diol cleavage is another example of a redox reaction; periodic acid, HIO_4, is reduced to iodic acid, HIO_3.



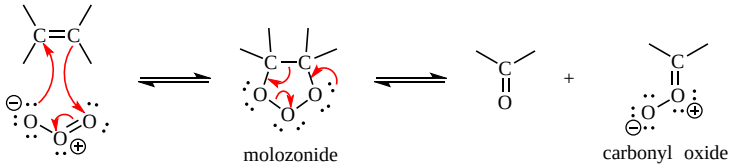
Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes. by breaking them down into smaller, more easily identifiable pieces. Ozonolysis also occurs naturally and would break down repeated units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.



The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the Carbon-Carbon double bond and is replaced by a Carbon-Oxygen double bond instead.

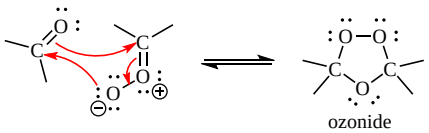
Reaction Mechanism

Step 1:



The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the Carbon-Carbon double bond, which then form the molozonide intermediate. Due to the unstable molozonide molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.

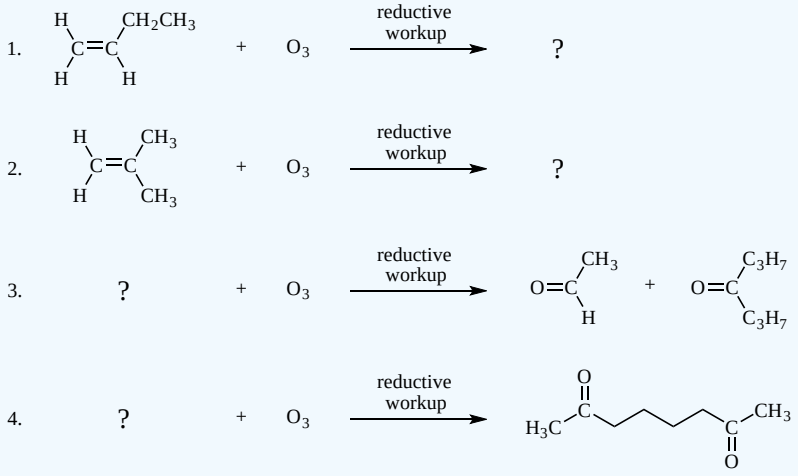
Step 2:



The carbonyl and the carbonyl oxide rearranges itself and reforms to create the stable ozonide intermediate. Since some ozonides are explosive, it is immediately reacted with a reductive workup to then convert the ozonide molecule into the desired carbonyl products. A typical reductive workup is zinc metal in acetic acid. A variety of carbonyl products could result depending on the starting alkene. For example, a tetrasubstituted alkene would yield two ketone products, while a trisubstituted alkene would yield one ketone product and one aldehyde product.

While there are other options for oxidative cleavage of the double bond, this is the most commonly used reaction.

Exercise 12.12.1



Answer available at the end of this section.

Exercise 12.12.2

Draw the structure of the product or products obtained in each of the following reactions:

a. *cis*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

b. *trans*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

c. 2-methylpropene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

d. 2-methyl-1-pentene $\xrightarrow[KMnO_4]{\text{hot, acidic}}$

Answer available at the end of this section.

Exercise 12.12.3

Exercises 1(*a*) and 1(*b*), above, indicate that it is not possible to distinguish between cis and trans isomers of alkenes using oxidative cleavage.

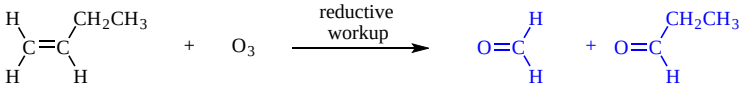
Answer available at the end of this section.

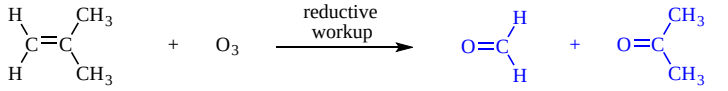
References

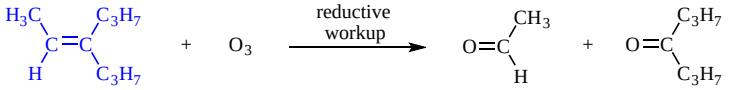
1. Vollhardt, K., Schore, N. Organic Chemistry: Structure and Function. 5th ed. New York, NY: W. H. Freeman and Company, 2007.
2. Shore, N. Study Guide and Solutions Manual for Organic Chemistry. 5th ed. New York, NY: W.H. Freeman and Company, 2007.

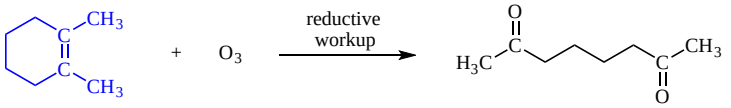
Answers

Exercise 12.12.1

1. 

2. 

3. 

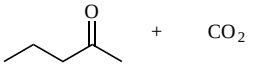
4. 

Exercise 12.12.2

a. 

b. 

c. 

d. 

Exercise 12.12.3

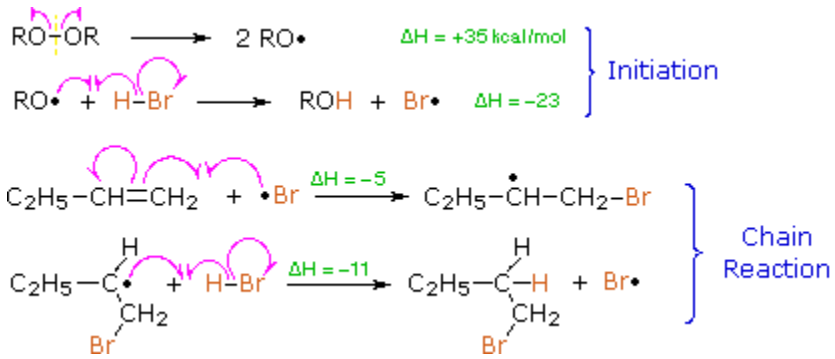
Both isomers give the same product or products.

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12.13: Radical Additions: Anti-Markovnikov Product Formation

Protons and other electrophiles are not the only reactive species that initiate addition reactions to carbon-carbon double bonds. Curiously, this first became evident as a result of conflicting reports concerning the regioselectivity of HBr additions. As noted earlier, the acid-induced addition of HBr to 1-butene gave predominantly 2-bromobutane, the Markovnikov Rule product. However, in some early experiments in which peroxide contaminated reactants were used, 1-bromobutane was the chief product. Further study showed that an alternative radical chain-reaction, initiated by peroxides, was responsible for the anti-Markovnikov product. This is shown by the following equations.



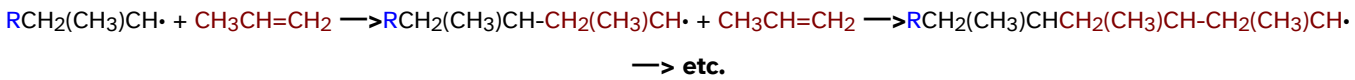
The weak O–O bond of a peroxide initiator is broken homolytically by thermal or hight energy. The resulting alkoxy radical then abstracts a hydrogen atom from HBr in a strongly exothermic reaction. Once a bromine atom is formed it adds to the π-bond of the alkene in the first step of a chain reaction. This addition is regioselective, giving the more stable carbon radical as an intermediate. The second step is carbon radical abstraction of another hydrogen from HBr, generating the anti-Markovnikov alkyl bromide and a new bromine atom. Each of the steps in this chain reaction is exothermic, so once started the process continues until radicals are lost to termination events.

This free radical chain addition competes very favorably with the slower ionic addition of HBr described earlier, especially in non-polar solvents. It is important to note, however, that HBr is unique in this respect. The radical addition process is unfavorable for HCl and HI because one of the chain steps becomes endothermic (the second for HCl & the first for HI).

Other radical addition reactions to alkenes have been observed, one example being the peroxide induced addition of carbon tetrachloride shown in the following equation



The best known and most important use of free radical addition to alkenes is probably polymerization. Since the addition of carbon radicals to double bonds is energetically favorable, concentrated solutions of alkenes are prone to radical-initiated polymerization, as illustrated for propene by the following equation. The blue colored R-group represents an initiating radical species or a growing polymer chain; the propene monomers are colored maroon. The addition always occurs so that the more stable radical intermediate is formed.



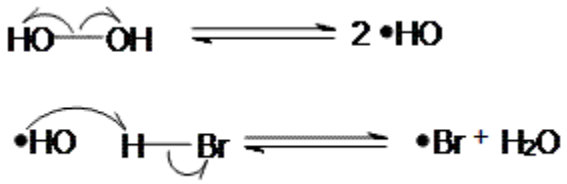
Anti-Markovnikov rule describes the regiochemistry where the substituent is bonded to a less substituted carbon, rather than the more substitued carbon. This process is quite unusual, as carboncations which are commonly formed during alkene, or alkyne reactions tend to favor the more substitued carbon. This is because substituted carbocation allow more hyperconjugation and indution to happen, making the carbocation more stable.

Introduction

This process was first explained by Morris Selig Karasch in his paper: 'The Addition of Hydrogen Bromide to Allyl Bromide' in 1933.[1] Examples of Anti-Markovnikov includes Hydroboration-Oxidation and Radical Addition of HBr. A free radical is any chemical substance with unpaired electron. The more substituents the carbon is connected to, the more substituted is that carbon. For example: Tertiary carbon (most substituted), Secondary carbon (medium substituted), primary carbon (least substituted)

Anti-Markovnikov Radical Addition of Haloalkane can ONLY happen to HBr and there MUST be presence of Hydrogen Peroxide (H_2O_2). Hydrogen Peroxide is essential for this process, as it is the chemical which starts off the chain reaction in the initiation step. **HI and HCl cannot** be used in radical reactions, because in their radical reaction one of the radical reaction steps: Initiation is Endothermic, as recalled from Chem 118A, this means the reaction is unfavorable. To demonstrate the anti-Markovnikov regiochemistry, I will use 2-Methylprop-1-ene as an example below:

Initiation Steps



Hydrogen Peroxide is an unstable molecule, if we heat it, or shine it with sunlight, two free radicals of OH will be formed. These OH radicals will go on and attack HBr, which will take the Hydrogen and create a Bromine radical. Hydrogen radical do not form as they tend to be extremely unstable with only one electron, thus bromine radical which is more stable will be readily formed.

Propagation Steps

dd.bmpThe Bromine Radical will go on and attack the LESS SUBSTITUTED carbon of the alkene. This is because after the bromine radical attacked the alkene a carbon radical will be formed. A carbon radical is more stable when it is at a more substituted carbon due to induction and hyperconjugation. Thus, the radical will be formed at the more substituted carbon, while the bromine is bonded to the less substituted carbon. After a carbon radical is formed, it will go on and attack the hydrogen of a HBr, which a bromine radical will be formed again.

Termination Steps

There are also Termination Steps, but we do not concern about the termination steps as they are just the radicals combining to create waste products. For example two bromine radical combined to give bromine. This radical addition of bromine to alkene by radical addition reaction will go on until all the alkene turns into bromoalkane, and this process will take some time to finish.

References

1. K. Peter C. Vollhardt, Neil E. Schore; Organic Chemistry: Structure and Function Fifth Edition; W. H. Freeman and Campany, 2007
2. Micheal Vokin; Nuffield Advance Chemistry Student's Book Forth Edition; Person Education Limited, 2004

Outside Links

1. http://en.wikipedia.org/wiki/Morris_S._Kharasch

Problems

Please give the product(s) of the reactions below:

1. CH_3-C(CH_3)=CH-CH_3 + HBr + H_2O_2 ==> ?
2. CH_3-C(CH_3)=CH-CH_3 + HI + H_2O_2 ==> ?
3. CH_3-C(CH_3)=CH-CH_3 + HCl + H_2O_2 ==> ?
4. CH_3-CH=CH-CH_3 + HBr + H_2O_2 ==> ?
5. CH_3-C(CH_3)=CH-CH_3 + HBr ==> ?

Answers

1. CH_3-CH(CH_3)-CHBr-CH_3 (Anti-Markovnikov)
2. CH_3-C(CH_3)I-CH_2-CH_3 (Markovnikov)
3. CH_3-C(CH_3)Cl-CH_2-CH_3 (Markovnikov)
4. CH_3-CHBr-CH-CH_3 or CH_3-CH-CHBr-CH_3 (Both molecules are the same)
5. CH_3-C(CH_3)Br-CH_2-CH_3 (Markovnikov)

References

1. http://uncyclopedia.wikia.com/wiki/Organic_chemistry
2. http://uncyclopedia.wikia.com/wiki/Chemistry

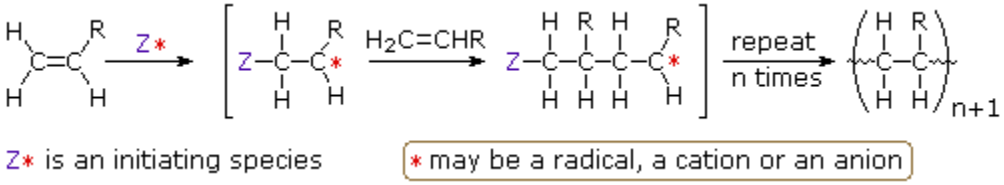
Contributors

- Kelvin Kan (UCD)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.14: Dimerization, Oligomerization. and Polymerization of Alkenes

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

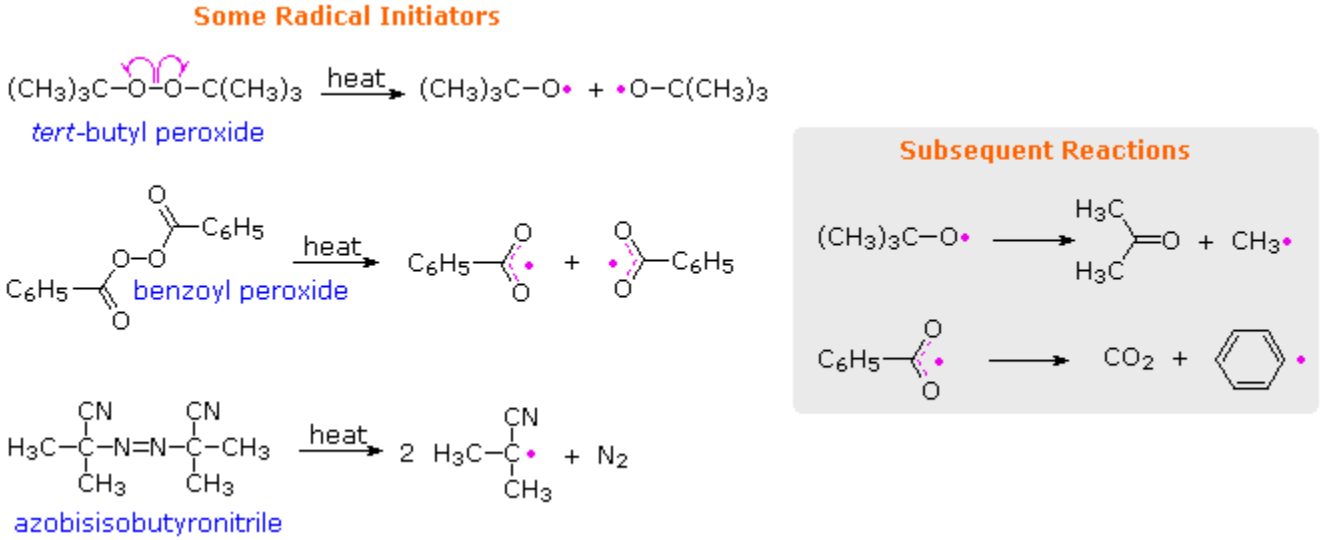


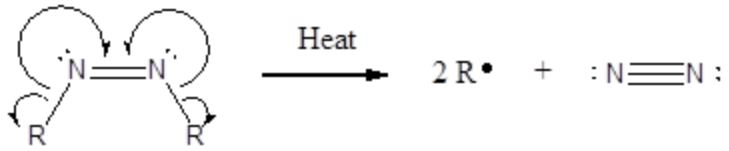
It is useful to distinguish four polymerization procedures fitting this general description.

- Radical Polymerization The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
- Cationic Polymerization The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
- Anionic Polymerization The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
- Coordination Catalytic Polymerization The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

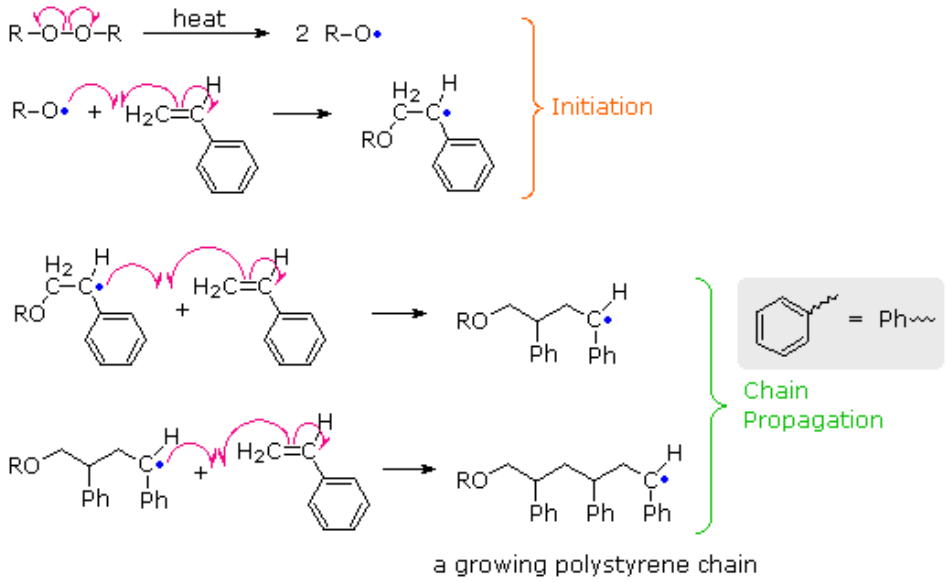
Radical Chain-Growth Polymerization

Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.



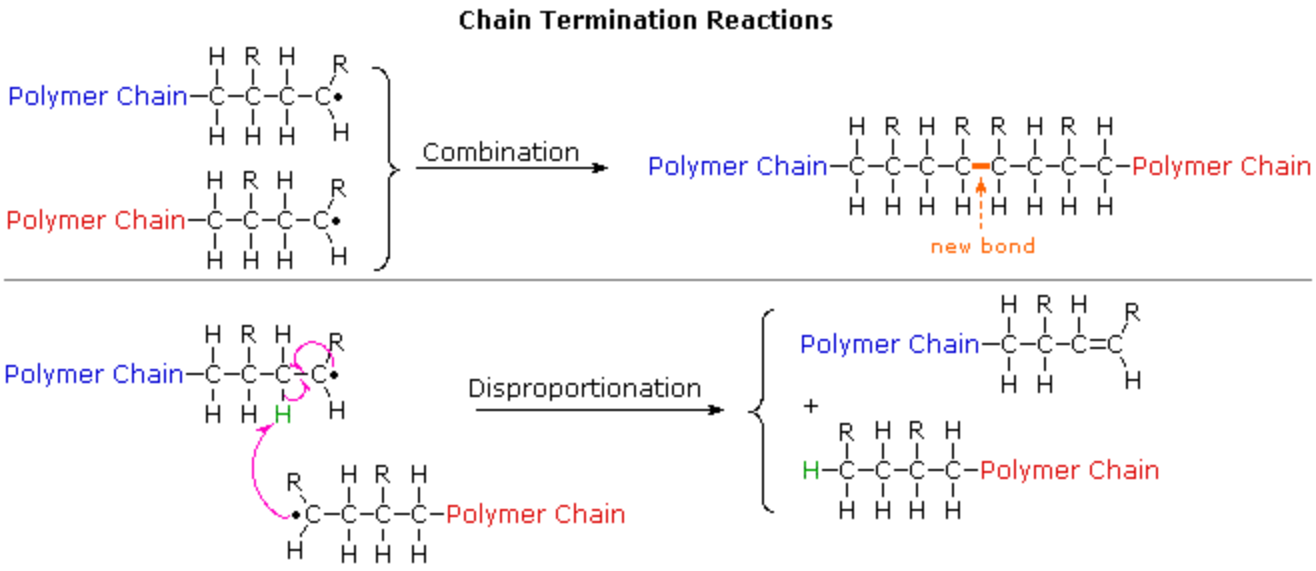


By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.



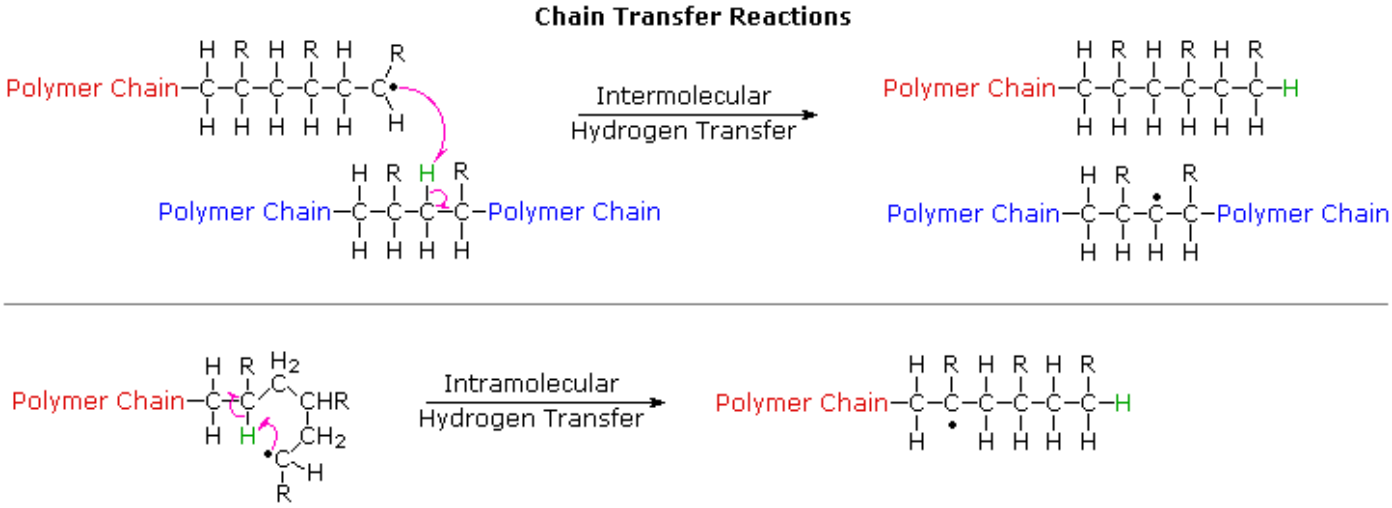
a growing polystyrene chain

In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations



Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1°-radical at the end of a growing chain is converted to a more stable 2°-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

Contributors

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12.15: Synthesis of Polymers

Polymers are long chain giant organic molecules are assembled from many smaller molecules called **monomers**. **Polymers** consist of many repeating monomer units in long chains. A polymer is analogous to a necklace made from many small beads (monomers). Many monomers are alkenes or other molecules with double bonds which react by **addition** to their unsaturated double bonds.

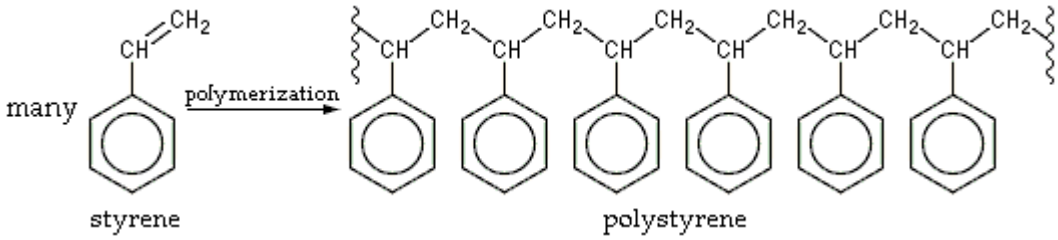
Introduction

The electrons in the double bond are used to bond two monomer molecules together. This is represented by the red arrows moving from one molecule to the space between two molecules where a new bond is to form. The formation of polyethylene from ethylene (ethene) may be illustrated in the graphic on the left as follows. In the complete polymer, all of the double bonds have been turned into single bonds. No atoms have been lost and you can see that the monomers have just been joined in the process of addition. A simple representation is -[A-A-A-A-A]-. Polyethylene is used in plastic bags, bottles, toys, and electrical insulation.

- **LDPE - Low Density Polyethylene:** The first commercial polyethylene process used peroxide catalysts at a temperature of 500 C and 1000 atmospheres of pressure. This yields a transparent polymer with highly branched chains which do not pack together well and is low in density. LDPE makes a flexible plastic. Today most LDPE is used for blow-molding of films for packaging and trash bags and flexible snap-on lids. LDPE is recyclable plastic #4.
- **HDPE - High Density Polyethylene:** An alternate method is to use Ziegler-Natta aluminum titanium catalysts to make HDPE which has very little branching, allows the strands to pack closely, and thus is high density. It is three times stronger than LDPE and more opaque. About 45% of the HDPE is blow molded into milk and disposable consumer bottles. HDPE is also used for crinkly plastic bags to pack groceries at grocery stores. HDPE is recyclable plastic #2.

Other Addition Polymers

- **PVC** (polyvinyl chloride), which is found in plastic wrap, simulated leather, water pipes, and garden hoses, is formed from vinyl chloride (H_2C=CHCl). The reaction is shown in the graphic on the left. Notice how every other carbon must have a chlorine attached.
- **Polypropylene:** The reaction to make polypropylene (H_2C=$CHCH_3$) is illustrated in the middle reaction of the graphic. Notice that the polymer bonds are always through the carbons of the double bond. Carbon #3 already has saturated bonds and cannot participate in any new bonds. A methyl group is on every other carbon.
- **Polystyrene:** The reaction is the same for polystrene where every other carbon has a benzene ring attached. Polystyrene (PS) is recyclable plastic #6. In the following illustrated example, many styrene monomers are polymerized into a long chain polystyrene molecule. The squiggly lines indicate that the polystyrene molecule extends further at both the left and right ends.



- Blowing fine gas bubbles into liquid polystyrene and letting it solidify produces *expanded polystyrene*, called *Styrofoam* by the Dow Chemical Company.
- **Polystyrene with DVB:** Cross-linking between polymer chains can be introduced into polystyrene by copolymerizing with ***p*-divinylbenzene** (**DVB**). DVB has vinyl groups (-CH=CH_2) at each end of its molecule, each of which can be polymerized into a polymer chain like any other vinyl group on a styrene monomer.

Other addition polymers

Table 1: Links to various polymers with Chime molecule - Macrogalleria at U. Southern Mississippi

Monomer	Polymer Name	Trade Name	Uses
$F_2C=CF_2$	polytetrafluoroethylene	Teflon	Non-stick coating for cooking utensils, chemically-resistant specialty plastic parts, Gore-Tex
$H_2C=CCl_2$	polyvinylidene dichloride	Saran	Clinging food wrap
$H_2C=CH(CN)$	polyacrylonitrile	Orlon, Acrilan, Creslan	Fibers for textiles, carpets, upholstery
$H_2C=CH(OCOCH_3)$	polyvinyl acetate		Elmer's glue - Silly Putty Demo
$H_2C=CH(OH)$	polyvinyl alcohol		Ghostbusters Demo
$H_2C=C(CH_3)COOCH_3$	polymethyl methacrylate	Plexiglass, Lucite	Stiff, clear, plastic sheets, blocks, tubing, and other shapes

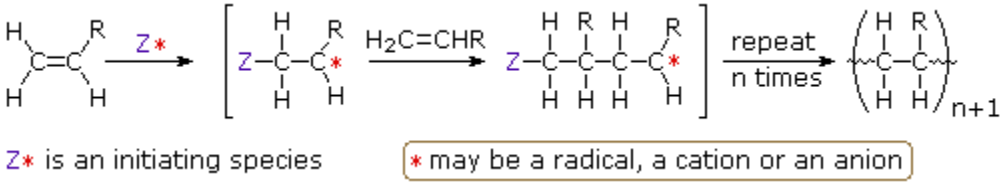
Addition polymers from conjugated dienes

Polymers from conjugated dienes usually give elastomer polymers having rubber-like properties.

Table 2. Addition homopolymers from conjugated dienes

Monomer	Polymer name	Trade name	Uses
$H_2C=CH-C(CH_3)=CH_2$	polyisoprene	natural or some synthetic rubber	applications similar to natural rubber
$H_2C=CH-CH=CH_2$	polybutadiene	polybutadiene synthetic rubber	select synthetic rubber applications
$H_2C=CH-CCl=CH_2$	polychloroprene	Neoprene	chemically-resistant rubber

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

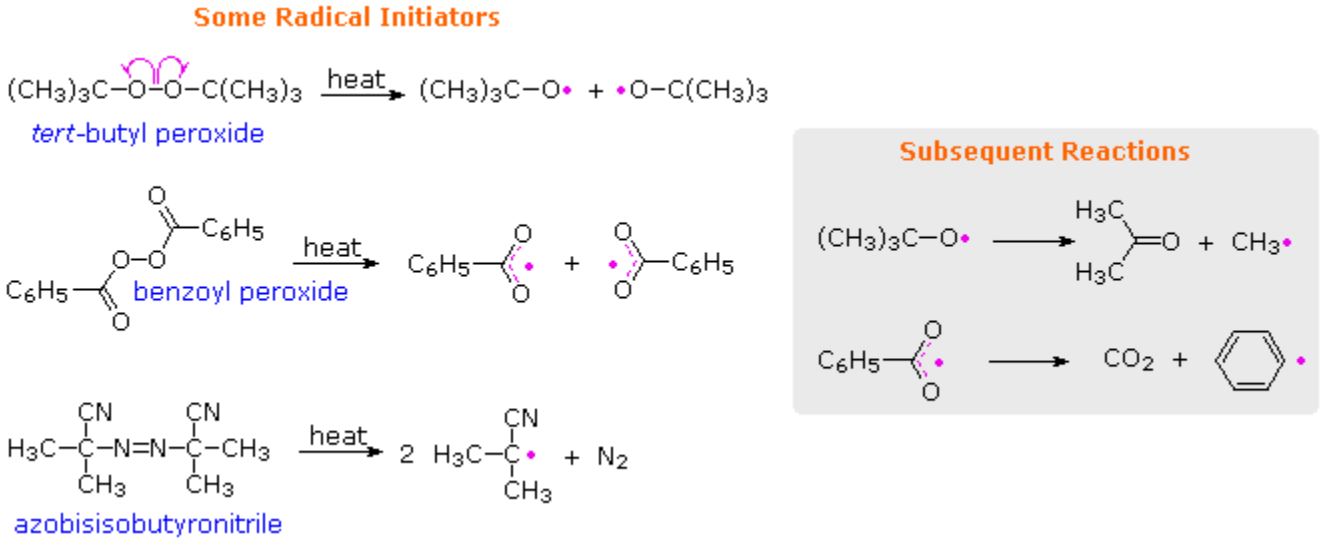


It is useful to distinguish four polymerization procedures fitting this general description.

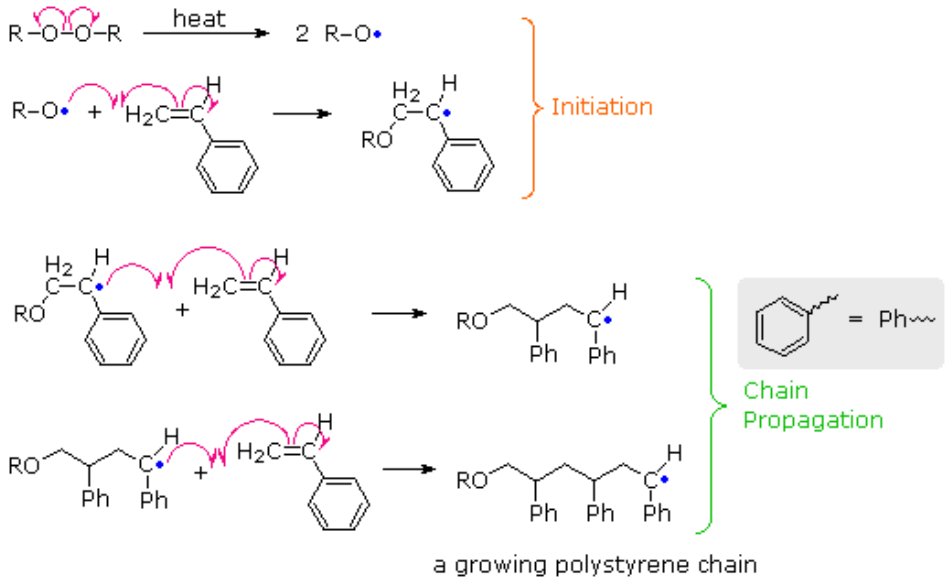
- Radical Polymerization The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
- Cationic Polymerization The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
- Anionic Polymerization The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
- Coordination Catalytic Polymerization The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

Radical Chain-Growth Polymerization

Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.

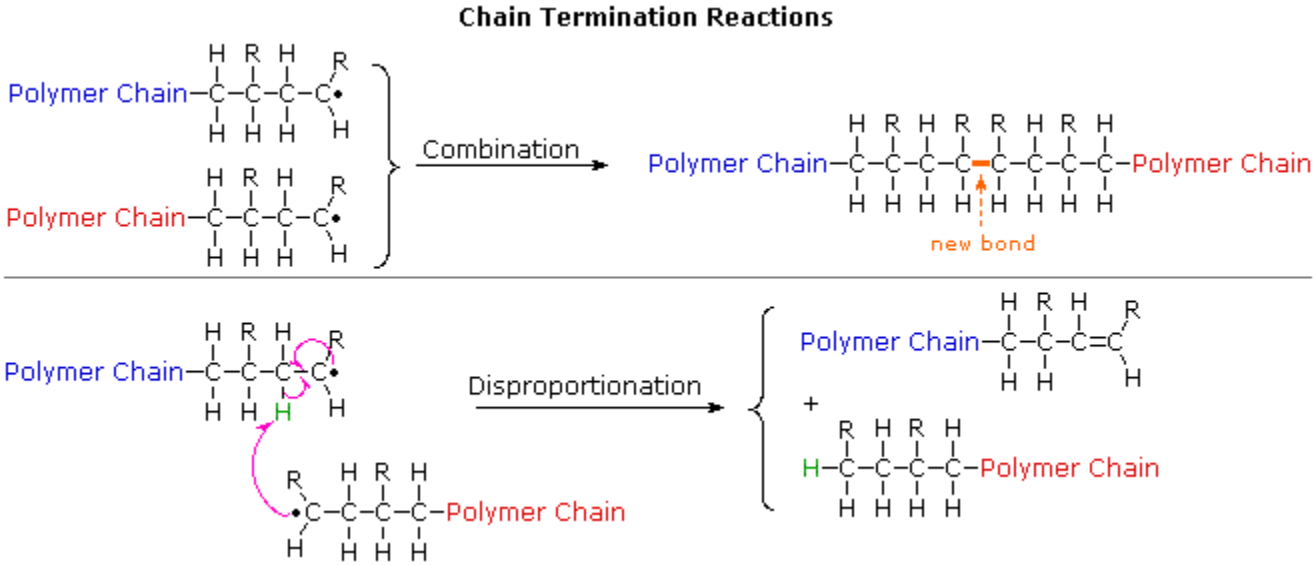


By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.



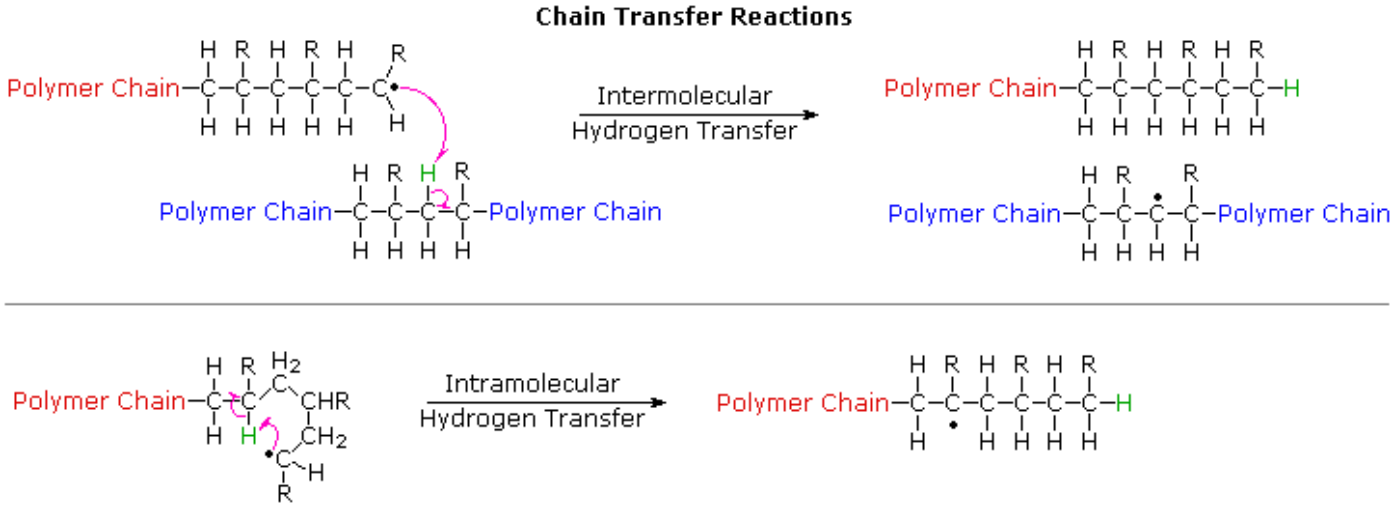
In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom

transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

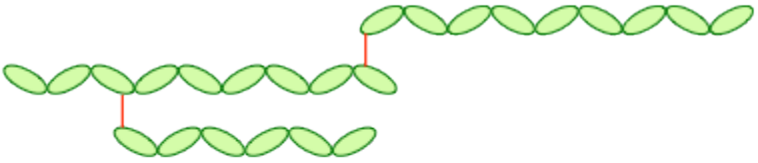
Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations



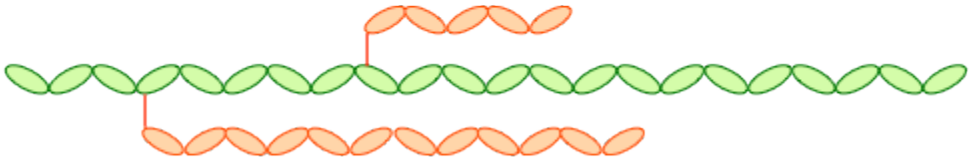
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1°-radical at the end of a growing chain is converted to a more stable 2°-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

Chain topology

Polymers may also be classified as straight-chained or branched, leading to forms such as these:

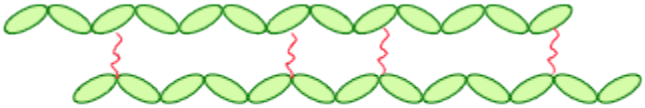


branched homopolymer



graft copolymer

The monomers can be joined end-to-end, and they can also be *cross-linked* to provide a harder material:

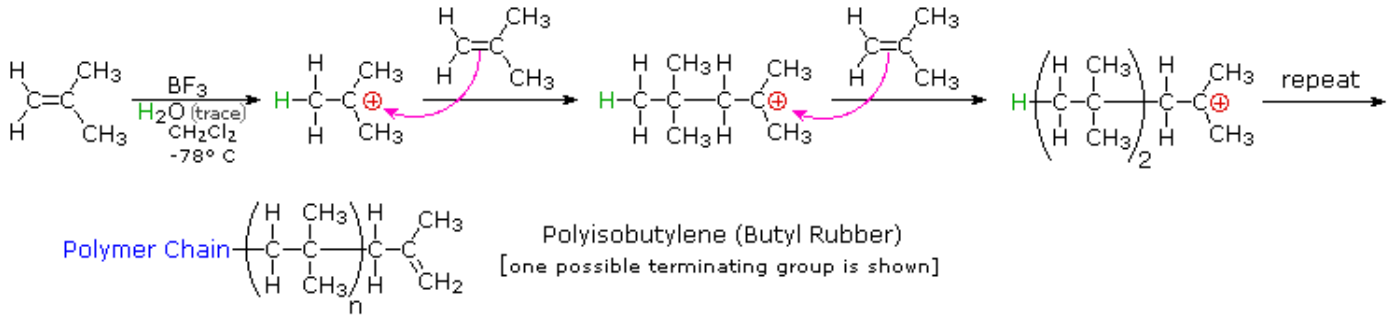


cross-linked homopolymer

If the cross-links are fairly long and flexible, adjacent chains can move with respect to each other, producing an *elastic* polymer or

Cationic Chain-Growth Polymerization

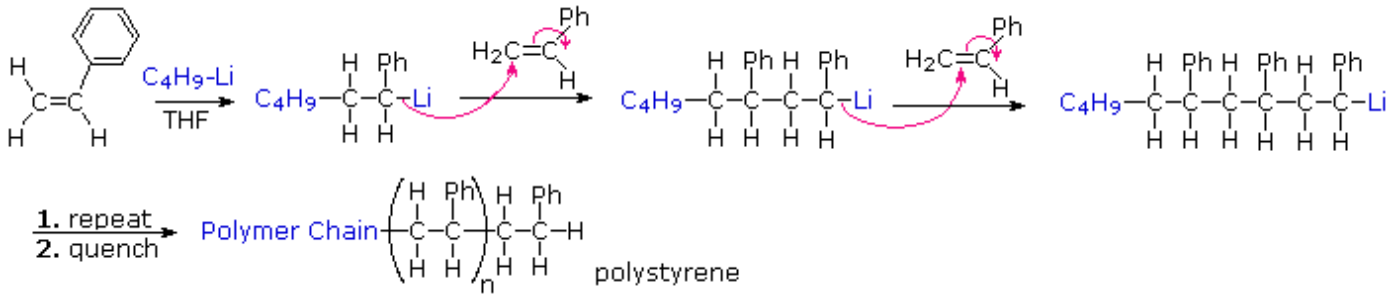
Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The polyisobutylene product is a soft rubbery solid, Tg = _70° C, which is used for inner tubes. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene (as shown here).



Monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes. These are normally initiated at low temperature in methylene chloride solution. Strong acids, such as $HClO_4$, or Lewis acids containing traces of water (as shown above) serve as initiating reagents. At low temperatures, chain transfer reactions are rare in such polymerizations, so the resulting polymers are cleanly linear (unbranched).

Anionic Chain-Growth Polymerization

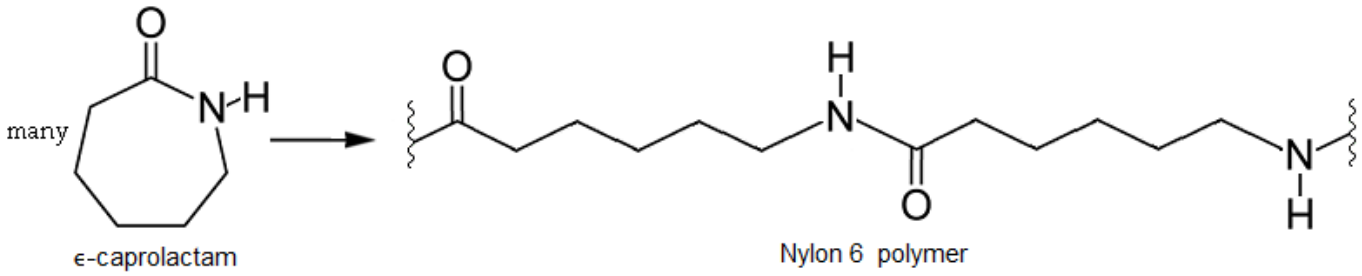
Treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization. This is an example of anionic polymerization, the course of which is described by the following equations. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs. Only monomers having anion stabilizing substituents, such as phenyl, cyano or carbonyl are good substrates for this polymerization technique. Many of the resulting polymers are largely isotactic in configuration, and have high degrees of crystallinity.



Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, CH2=C(CN)CO2CH3. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place.

Ring opening polymerization

In this kind of polymerization, molecular rings are opened in the formation of a polymer. Here epsilon-caprolactam, a 6-carbon cyclic monomer, undergoes ring opening to form a Nylon 6 homopolymer, which is somewhat similar to but not the same as Nylon 6,6 alternating copolymer.



Addition Copolymerization

Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers, or if one monomer is much more reactive a nearly homopolymer of that monomer. The copolymerization of styrene with methyl methacrylate, for example, proceeds differently depending on the mechanism. Radical polymerization gives a statistical copolymer. However, the product of cationic polymerization is largely polystyrene, and anionic polymerization favors formation of poly(methyl methacrylate). In cases where the relative reactivities are different, the copolymer composition can sometimes be controlled by continuous introduction of a biased mixture of monomers into the reaction.

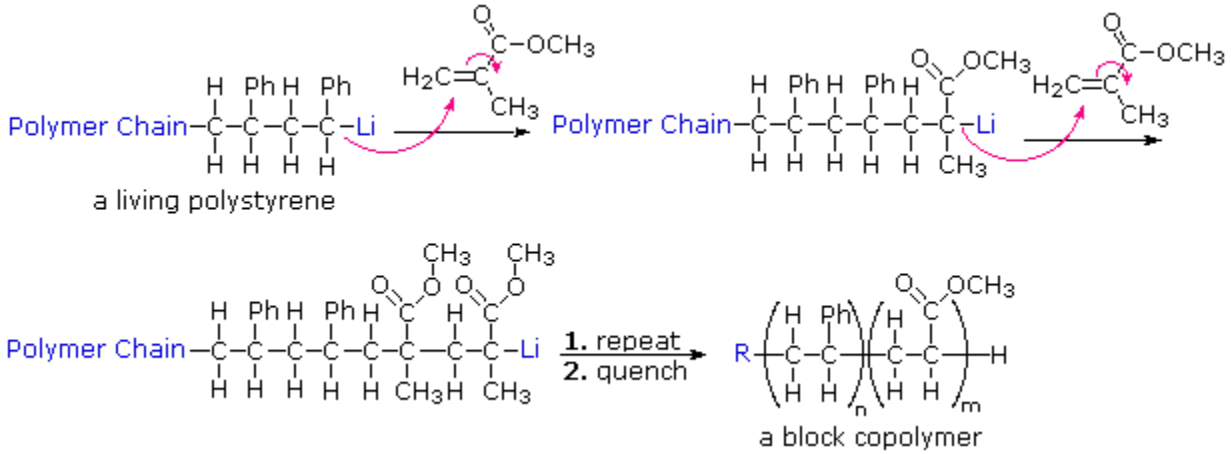
Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals. For example, styrene and acrylonitrile copolymerize in a largely alternating fashion.

Some Useful Copolymers			
Monomer A	**Monomer B**	**Copolymer**	**Uses**
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

A terpolymer of acrylonitrile, butadiene and styrene, called ABS rubber, is used for high-impact containers, pipes and gaskets.

Block Copolymerization

Several different techniques for preparing block copolymers have been developed, many of which use condensation reactions (next section). At this point, our discussion will be limited to an application of anionic polymerization. In the anionic polymerization of styrene described above, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer, and if additional styrene or a different suitable monomer is added a block polymer will form. This is illustrated for methyl methacrylate in the following diagram.

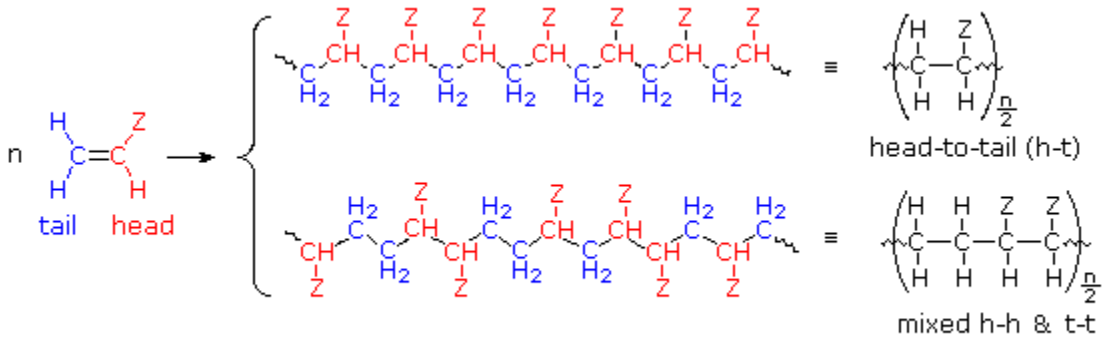


Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

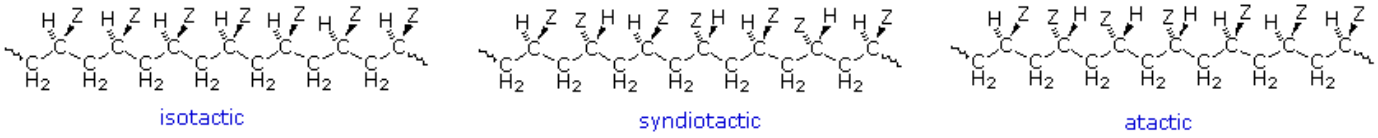
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

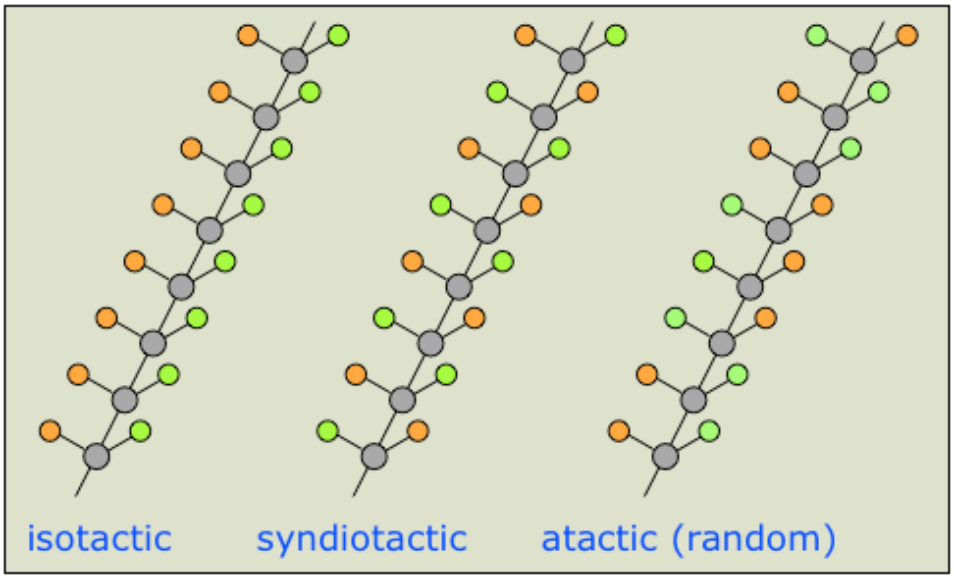
Symmetrical monomers such as ethylene and tetrafluoroethylene can join together in only one way. Monosubstituted monomers, on the other hand, may join together in two organized ways, described in the following diagram, or in a third random manner. Most monomers of this kind, including propylene, vinyl chloride, styrene, acrylonitrile and acrylic esters, prefer to join in a head-to-tail fashion, with some randomness occurring from time to time. The reasons for this regioselectivity will be discussed in the synthetic methods section.



Regioisomeric Polymers from Substituted Monomers

If the polymer chain is drawn in a zig-zag fashion, as shown above, each of the substituent groups (Z) will necessarily be located above or below the plane defined by the carbon chain. Consequently we can identify three configurational isomers of such polymers. If all the substituents lie on one side of the chain the configuration is called isotactic. If the substituents alternate from one side to another in a regular manner the configuration is termed syndiotactic. Finally, a random arrangement of substituent groups is referred to as atactic. Examples of these configurations are shown here.





Many common and useful polymers, such as polystyrene, polyacrylonitrile and poly(vinyl chloride) are atactic as normally prepared. Customized catalysts that effect stereoregular polymerization of polypropylene and some other monomers have been developed, and the improved properties associated with the increased crystallinity of these products has made this an important field of investigation. The following values of Tg have been reported.

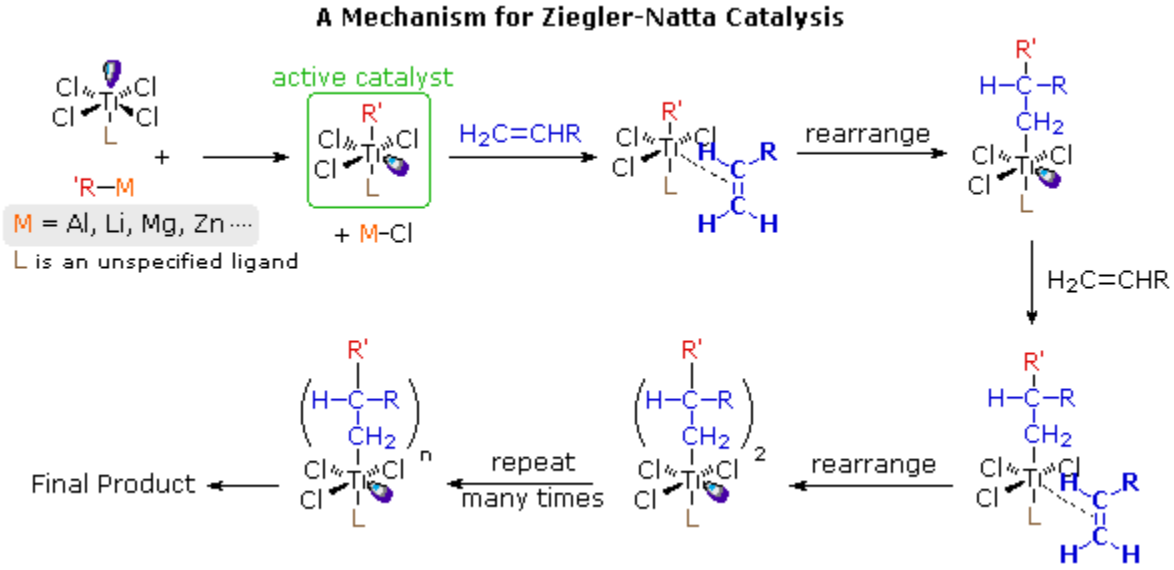
Polymer	T_g atactic	T_g isotactic	T_g syndiotactic
PP	–20 ºC	0 ºC	–8 ºC
PMMA	100 ºC	130 ºC	120 ºC

The properties of a given polymer will vary considerably with its tacticity. Thus, atactic polypropylene is useless as a solid construction material, and is employed mainly as a component of adhesives or as a soft matrix for composite materials. In contrast, isotactic polypropylene is a high-melting solid (ca. 170 °C) which can be molded or machined into structural components.

Ziegler-Natta Catalytic Polymerization

An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. Their findings permitted, for the first time, the synthesis of unbranched, high molecular weight polyethylene (HDPE), laboratory synthesis of natural rubber from isoprene, and configurational control of polymers from terminal alkenes like propene (e.g. pure isotactic and syndiotactic polymers). In the case of ethylene, rapid polymerization occurred at atmospheric pressure and moderate to low temperature, giving a stronger (more crystalline) product (HDPE) than that from radical polymerization (LDPE). For this important discovery these chemists received the 1963 Nobel Prize in chemistry.

Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. The catalyst formed by reaction of triethylaluminum with titanium tetrachloride has been widely studied, but other metals (e.g. V & Zr) have also proven effective. The following diagram presents one mechanism for this useful reaction. Others have been suggested, with changes to accommodate the heterogeneity or homogeneity of the catalyst. Polymerization of propylene through action of the titanium catalyst gives an isotactic product; whereas, a vanadium based catalyst gives a syndiotactic product.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

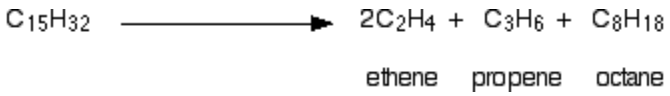
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12.16: Ethene: An Important Industrial Feedstock

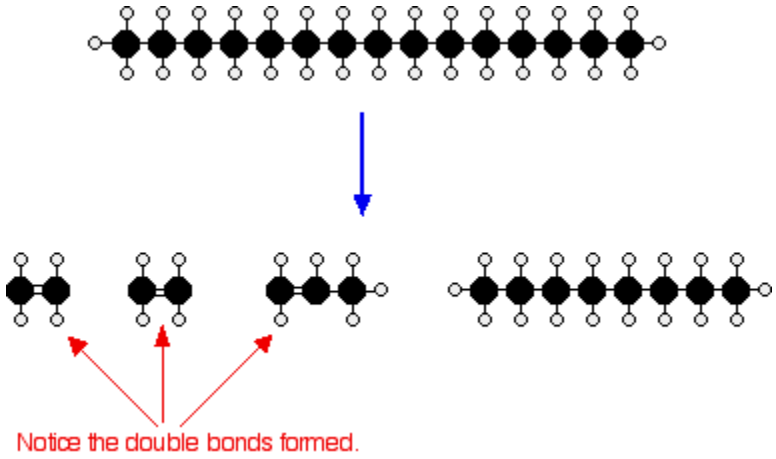
Ethene

Cracking is the name given to breaking up large hydrocarbon molecules into smaller and more useful bits. This is achieved by using high pressures and temperatures without a catalyst, or lower temperatures and pressures in the presence of a catalyst. The source of the large hydrocarbon molecules is often the naphtha fraction or the gas oil fraction from the fractional distillation of crude oil (petroleum). These fractions are obtained from the distillation process as liquids, but are re-vaporized before cracking.

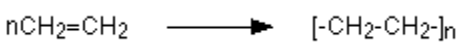
There is not any single unique reaction happening in the cracker. The hydrocarbon molecules are broken up in a fairly random way to produce mixtures of smaller hydrocarbons, some of which have carbon-carbon double bonds. One possible reaction involving the hydrocarbon $C_{15}H_{32}$ might be:



Or, showing more clearly what happens to the various atoms and bonds:

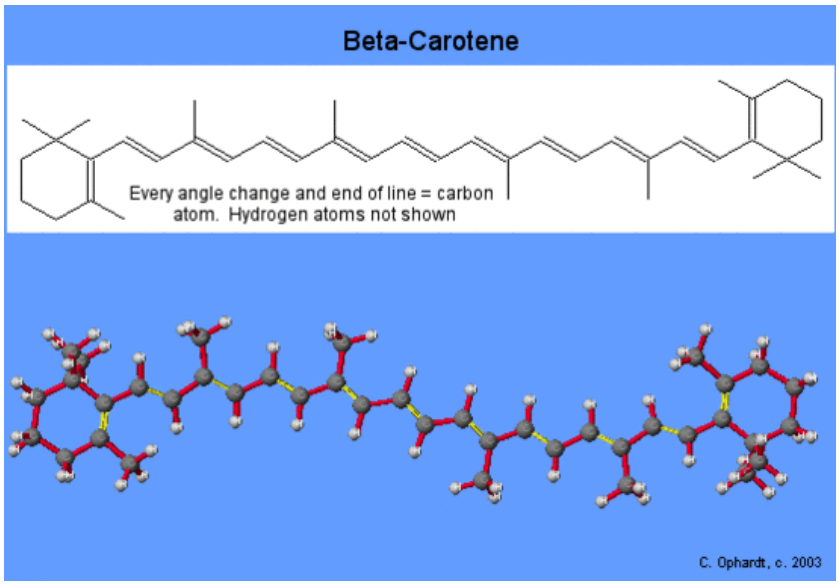


This is only one way in which this particular molecule might break up. The ethene and propene are important materials for making plastics or producing other organic chemicals. You will remember that during the polymeriation of ethene, thousands of ethene molecules join together to make poly(ethene) - commonly called polythene. The reaction is done at high pressures in the presence of a trace of oxygen as an initiator.



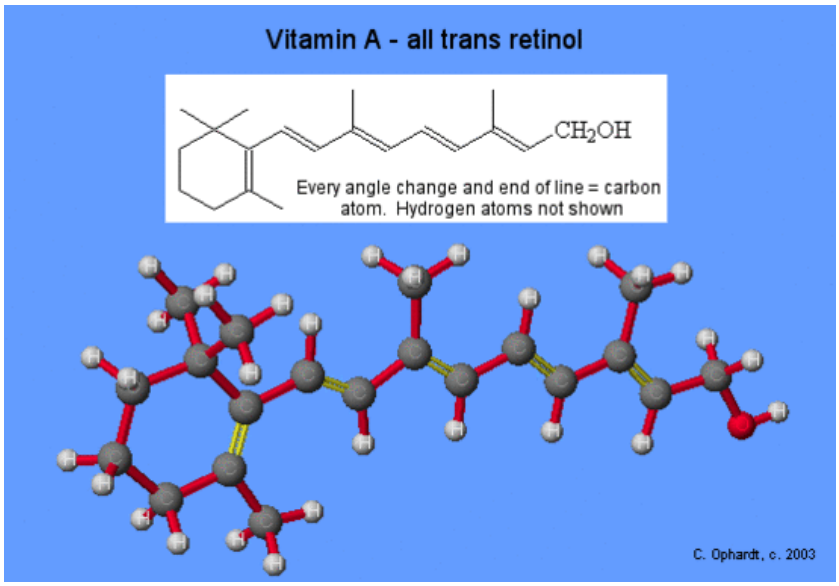
Beta-Carotene

The long chain of alternating double bonds (conjugated) is responsible for the orange color of beta-carotene. The conjugated chain in carotenoids means that they absorb in the visible region - green/blue part of the spectrum. So β-carotene appears orange, because the red/yellow colors are reflected back to us.



Vitamin A

Vitamin A has several functions in the body. The most well known is its role in vision - hence carrots "make you able to see in the dark". The retinol is oxidized to its aldehyde, retinal, which complexes with a molecule in the eye called opsin. When a photon of light hits the complex, the retinal changes from the 11-cis form to the all-trans form, initiating a chain of events which results in the transmission of an impulse up the optic nerve. A more detailed explanation is in Photochemical Events.



Other roles of vitamin A are much less well understood. It is known to be involved in the synthesis of certain glycoproteins, and that deficiency leads to abnormal bone development, disorders of the reproductive system, xerophthalmia (a drying condition of the cornea of the eye) and ultimately death.

Vitamin A is required for healthy skin and mucus membranes, and for night vision. Its absence from diet leads to a loss in weight and failure of growth in young animals, to the eye diseases; xerophthalmia, and night blindness, and to a general susceptibility to infections. It is thought to help prevent the development of cancer. Good sources of carotene, such as green vegetables are good potential sources of vitamin A. Vitamin A is also synthetically manufactured by extraction from fish-liver oil and by synthesis from beta-ionone.

Contributors

- Jim Clark (Chemguide.co.uk)
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

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12.17: Alkenes in Nature - Insect Pheromones

Pheromones are chemicals capable of acting like hormones outside the body of the secreting individual, to impact the behavior of the receiving individuals. Pheromones of certain pest insect species, such as the Japanese beetle, acrobat ant, and the gypsy moth, can be used to trap the respective insect for monitoring purposes, to control the population by creating confusion, to disrupt mating, and to prevent further egg laying.

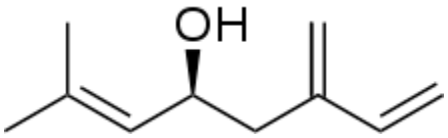


Figure 12.17.1: *(S)-Ipsdienol is a terpene alcohol and is one of the major aggregation pheromones of the bark beetle. It was first identified from Ips confusus, in which it is believed to be a principle sex attractant*

When a female bark beetle produces and secretes a sex pheromone in order to attract a mate, the pheromone can be carried on currents of air to male bark beetles, whose antennae can intercept individual pheromone molecules, completely intact, still in the same form as when they were secreted by the female, no matter how far away she is. The male recognizes the structure of the molecule; it can clearly tell if it has just intercepted the proper pheromone or some subtle imposter that also happens to have the formula $C_{10}H_{16}O$.

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13: ALKYNES: THE CARBON

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

- Topic hierarchy

13.1: Naming the Alkynes
13.2: Properties and Bonding in the Alkynes
13.3: Spectroscopy of the Alkynes
13.4: Preparation of Alkynes by Double Elimination
13.5: Preparation of Alkynes from Alkynyl Anions
13.6: Reduction of Alkynes: The Relative Reactivity of the Two π Bonds
13.7: Electrophilic Addition Reactions of Alkynes
13.8: Anti-Markovnikov Additions to Triple Bonds
13.9: Chemistry of Alkenyl Halides
13.10: Ethyne as an Industrial Starting Material
13.11: Naturally Occurring and Physiologically Active Alkynes

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13.1: Naming the Alkynes

Objectives

After completing this section, you should be able to

- provide the correct IUPAC name of an alkyne, given its Kekulé, condensed or shorthand structure.
- provide the correct IUPAC name of a compound containing both double and triple bonds, given its Kekulé, condensed or shorthand structure.
- draw the structure of a compound containing one or more triple bonds, and possibly one or more double bonds, given its IUPAC name.
- name and draw the structure of simple alkynyl groups, and where appropriate, use these names as part of the IUPAC system of nomenclature.

Study Notes

Simple alkynes are named by the same rules that are used for alkenes (see Section 7.3), except that the ending is *-yne* instead of *-ene*. Alkynes cannot exhibit *E*,*Z* (cis-trans) isomerism; hence, in this sense, their nomenclature is simpler than that of alkenes.

Alkynes are organic molecules made of the functional group carbon-carbon triple bonds and are written in the empirical formula of $\mathrm{C}_n\mathrm{H}_{2n-2}$. They are unsaturated hydrocarbons. Like alkenes have the suffix –ene, alkynes use the ending –yne; this suffix is used when there is only one alkyne in the molecule.

$$\mathrm{HC{\equiv}CH}$$

Introduction

Here are the molecular formulas and names of the first ten carbon straight chain alkynes.

Name	Molecular Formula
Ethyne	C_2H_2
Propyne	C_3H_4
1-Butyne	C_4H_6
1-Pentyne	C_5H_8
1-Hexyne	C_6H_{10}
1-Heptyne	C_7H_{12}
1-Octyne	C_8H_{14}
1-Nonyne	C_9H_{16}
1-Decyne	$C_{10}H_{18}$

The more commonly used name for ethyne is acetylene, which used industrially.

Naming Alkynes

Like previously mentioned, the IUPAC rules are used for the naming of alkynes.

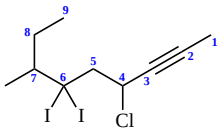
Rule 1

Find the longest carbon chain that includes both carbons of the triple bond.

Rule 2

Number the longest chain starting at the end closest to the triple bond. A 1-alkyne is referred to as a terminal alkyne and alkynes at any other position are called internal alkynes.

For example:

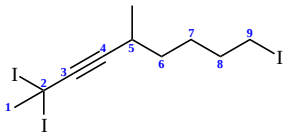


4-chloro-6,6-diiodo-7-methylnon-2-yne

Rule 3

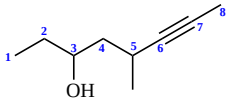
After numbering the longest chain with the lowest number assigned to the alkyne, label each of the substituents at its corresponding carbon. While writing out the name of the molecule, arrange the substituents in alphabetical order. If there are more than one of the same substituent use the prefixes di, tri, and tetra for two, three, and four substituents respectively. These prefixes are not taken into account in the alphabetical order.

For example:



2,2,9-triiodo-5-methylnon-3-yne

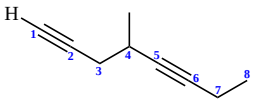
If there is an alcohol present in the molecule, number the longest chain starting at the end closest to it, and follow the same rules. However, the suffix would be –ynol, because the alcohol group takes priority over the triple bond.



5-methyl-6-octyn-3-ol

When there are two triple bonds in the molecule, find the longest carbon chain including both the triple bonds. Number the longest chain starting at the end closest to the triple bond that appears first. The suffix that would be used to name this molecule would be –diyne.

For example:

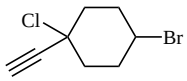


4-methyl-1,5-octadiyne

Rule 4

Substituents containing a triple bond are called alkynyl.

For example:



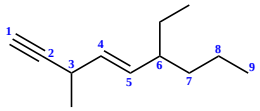
4-bromo-1-chloro-1-ethynylcyclohexane

Here is a table with a few of the alkynyl substituents:

Name	Molecule
Ethynyl	-C≡CH
2- Propynyl	$-CH_2C{\equiv}CH$
2-Butynyl	$-CH_3C{\equiv}CH_2CH_3$

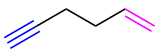
Rule 5

A molecule that contains both double and triple bonds is called an alkenyne. The chain can be numbered starting with the end closest to the functional group that appears first. For example:



(*E*)-6-ethyl-3-methyl-non-4-en-1-yne

If both functional groups are the exact same distance from the ending of the parent chain, the alkene takes precedence in the numbering.

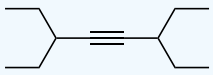


hex- 1-en -5-yne

Exercise 13.1.1

Name the following compounds:

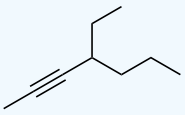
a)



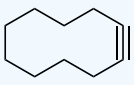
b)



c)



d)



Answer available at the end of this section.

Exercise 13.1.2

How many isomers are possible for C_5H_8? Draw them.

Answer available at the end of this section.

Exercise 13.1.3

Draw the following compounds:

a. 4,4-dimethyl-2-pentyne
b. 3-octyne
c. 3-methyl-1-hexyne
d. *trans* 3-hepten-1-yne

Answer available at the end of this section.

Exercise 13.1.4

Do alkynes show cis-trans isomerism? Explain.

Answer available at the end of this section.

Reference

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Answers

Exercise 13.1.1

a. 3,6-diethyl-4-octyne
b. 3-methylbutyne
c. 4-ethyl-2-heptyne
d. cyclodecyne

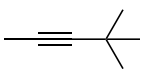
Exercise 13.1.2

2 possible isomers

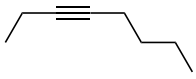


Exercise 13.1.3

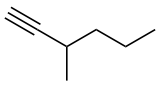
a)



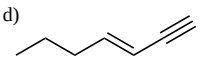
b)



c)



d)



Exercise 13.1.4

No. A triply bonded carbon atom can form only one other bond and has linear electron geometry so there are no "sides". Allkenes have two groups attached to each inyl carbon with a trigonal planar electron geometry that creates the possibility of cis-trans isomerism.

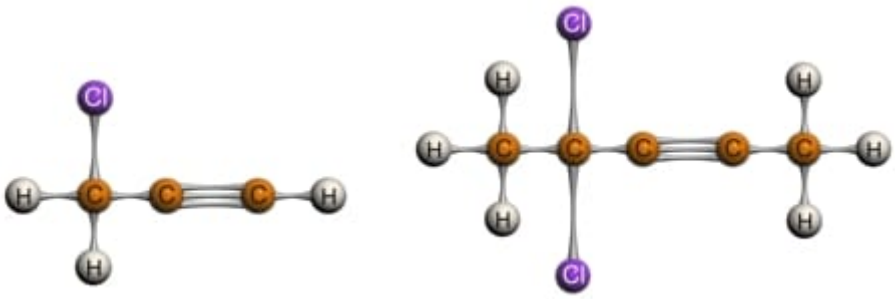
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13.2: Properties and Bonding in the Alkynes

The simplest alkyne—a hydrocarbon with carbon-to-carbon triple bond—has the molecular formula C_2H_2 and is known by its common name—acetylene. Its structure is H–C≡C–H.

Terminal Alkyne: Internal Alkyne:



3-chloro-1-propyne 4,4-dichloro-2-pentyne

Bonding and Hybridization

Bond	Name	Location	Overlap
Bond 1	s (? bond) bond	Formed between 2 sp orbitals of carbon and hydrogen atoms	End-on overlap
Bond 2	S (? bond) bond	Formed between the 2 sp orbital of 2 unsaturated Carbon atoms.	End-on overlap
Bond 3	p-bonds (? bonds)	Formed between the 2 p-orbitals among the carbon atoms	Side-on overlap

Che 11B properties of alkynes image 2.bmp

Che 118B Properties of Alkynes image 1.bmp

Orbital	Name	Location
Orbital 1	sp hybrid orbitals	Formed in the linear structure model of carbon atom
Orbital 2	p-orbitals	Formed on each carbon

Contributors

- Jim Clark (Chemguide.co.uk)

The characteristic of the triple bond helps to explain the properties and bonding in the alkynes.

Importance of Triple Bonds

Che 118B Properties of Alkynes image 3.bmp

Hybridization due to triple bonds allows the uniqueness of alkyne structure. This triple bond contributes to the nonpolar bonding strength, linear, and the acidity of alkynes. Physical Properties include nonpolar due to slight solubility in polar solvents and insoluble in water. This solubility in water and polar solvents is a characteristic feature to alkenes as well. Alkynes dissolve in organic solvents.

Boiling Points

Compared to alkanes and alkenes, alkynes have a slightly higher boiling point. Ethane has a boiling point of -88.6 ?C, while Ethene is -103.7 ?C and Ethyne has a higher boiling point of -84.0 ?C.

Alkynes are High In Energy

Alkynes are involved in a high release of energy because of repulsion of electrons. The content of energy involved in the alkyne molecule contributes to this high amount of energy. The pi-bonds however, do not encompass a great amount of energy even though the concentration is small within the molecule. The combustion of Ethyne is a major contributor from CO_2, water, and the ethyne molecule

Che 118B Properties of alkynes image 4.bmp

??H = -311 kcal/mol

To help understand the relative stabilities of alkyne isomers, heats of hydrogenation must be used. Hydrogenation of the least energy, results in the release of the internal alkyne. With the result of the production of butane, the stability of internal versus terminal alkynes has significant relative stability due to hyperconjugation.

Outside links

- http://www.ucc.ie/academic/chem/dolc...t/alkynes.html
- http://www.cliffsnotes.com/WileyCDA/...eId-22631.html

References

1. Bloch, D.R. Organic chemistry demystified, New York : McGraw-Hill, 2006.
2. Vollhardt. Schore, Organic Chemistry Structure and Function Fifth Edition, New York: W.H. Freeman and Company, 2007.

Problems

1. What is the carbon-carbon, carbon-hydrogen bond length for alkyne? Is it shorter or longer than alkane and alkene?
2. Which is the most acidic and most stable, alkane, alkene, or alkyne? And depends on what?
3. How many pi bonds and sigma bonds are involved in the structure of ethyne?
4. Why is the carbon-hydrogen bond so short?
5. What is the alkyne triple bond characterizes by? How is this contribute to the weakness of the pi bonds?
6. How is heat of hydrogenation effects the stability of the alkyne?

Contributors

- Bao Kha Nguyen, Garrett M. Chin

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13.3: Spectroscopy of the Alkynes

Spectroscopy of the Alkynes

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13.4: Preparation of Alkynes by Double Elimination

Objectives

After completing this section, you should be able to

- write an equation to describe the preparation of an alkyne by the dehydrohalogenation of a vicinal dihalide or vinylic halide.
- identify the alkyne produced from the dehydrohalogenation of a given vicinal dihalide or vinylic halide.
- write a reaction sequence to show how the double bond of an alkene can be transformed into a triple bond.
- identify the vicinal dihalide (or vinylic halide) needed to synthesize a given alkyne by dehydrohalogenation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

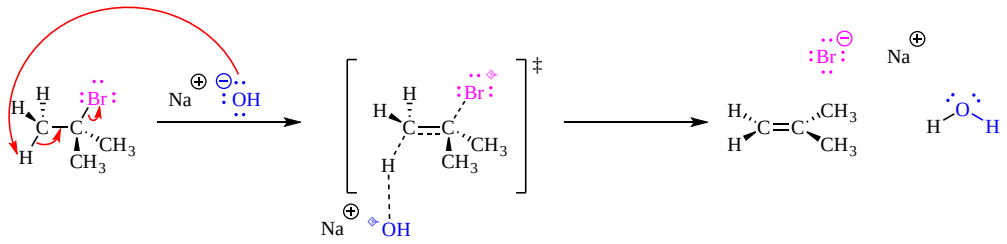
- vicinal dihalide
- vinylic halide

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

E2 Mechanism

Section 8.2 discussed that alkenes can be formed through an elimination reaction. In particular, the synthesis of alkynes will utilize the E2 elimination reaction. During the mechanism of an E2 reaction, a strong base removes a hydrogen adjacent to a halogen. The electrons from the broken C-H bond move to form the C=C double bond. Doing this causes the halogen to be ejected from the compound. Overall, a hydrogen and a halogen are eliminated from the compound to form an alkene. During this mechanism there is a stereoelectronic requirement that the adjacent hydrogen and the halogen be adjacent to each other.

E2 reaction will be discussed in greater detail in **Section 11.10**.

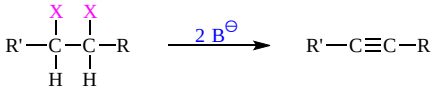


1. The base will deprotonate the haloalkane.
2. The leaving group will depart from the molecule.
3. The deprotonated carbon will rehybridize from sp^3 to sp^2.

Alkyne Formation Through Dihaloalkane Elimination

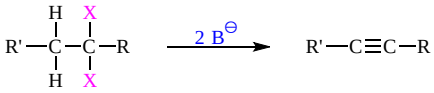
Alkynes are frequently prepared through a double E2 reaction using 2 halides that are vicinal (meaning on adjacent carbons) or geminal (meaning on the same carbon). Because the E2 reaction takes place twice 2 π bonds are formed thus creating an Alkyne. Although hydroxide and alkoxide bases could be used for the strong base required for an E2 reaction, their used opens the possibility of position rearrangement in the alkyne product. Because of this, the stronger base sodium amide in ammonia ($NaNH_2/NH_3$) is commonly used.

General Reaction



Vicinal dihalide converted to an alkyne

or

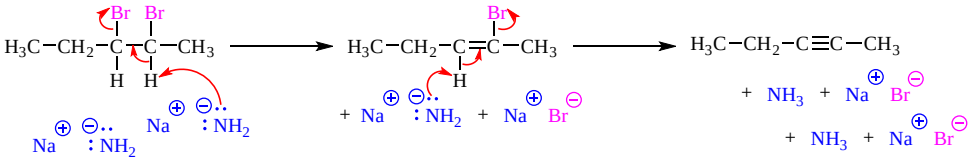


Geminal dihalide converted to an alkyne

Note! If a terminal alkyne is formed during the reaction, 3 equivalents of base are required instead of 2 as discussed below.

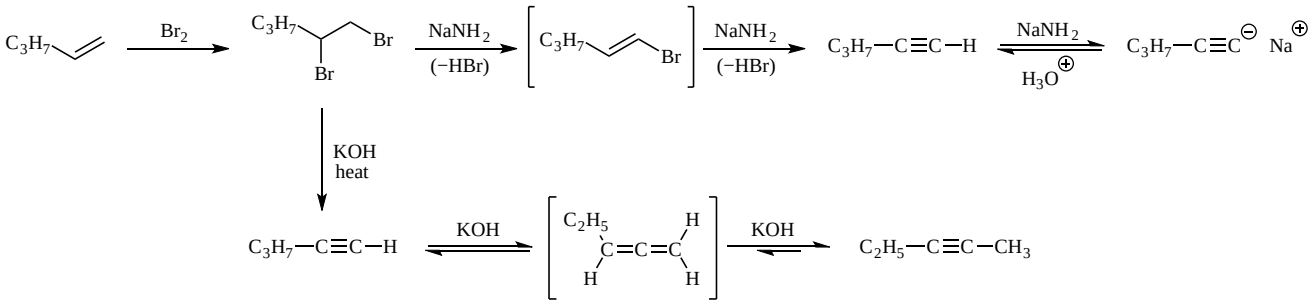
Mechanism

The following mechanism represents the reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia to form pent-2-yne. During this mechanism an intermediate alkene is formed. Notice that in the alkene intermediate, the remaining hydrogen and halogen are anti to each other due to the stereoelectronic requirements of the E2 mechanism. The intermediate alkene is converted to an alkyne by a second E2 elimination of a hydrogen and halogen.



Terminal Alkynes

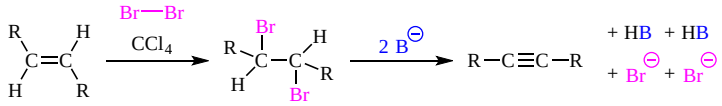
The acidity of terminal alkynes also plays a role in product determination when vicinal (or geminal) dihalides undergo base induced dielimination reactions. The following example illustrates eliminations of this kind starting from 1,2-dibromopentane, prepared from 1-pentene by addition of bromine. The initial elimination presumably forms 1-bromo-1-pentene, since base attack at the more acidic and less hindered 1°-carbon should be favored. The second elimination then produces 1-pentyne. If the very strong base such as sodium amide is used, the terminal alkyne is trapped as its sodium salt, from which it may be released by mild acid treatment. However, if the weaker base KOH with heat is used for the elimination, the terminal alkyne salt is not formed, or is formed reversibly, and the initially generated 1-pentyne rearranges to the more stable 2-pentyne via an allene intermediate. Even though terminal alkynes can be generated using sodium amide as a base, most chemists will prefer to use S_N2 nucleophilic substitution instead of elimination when trying to form a terminal alkyne.



Preparation of Alkynes from Alkenes

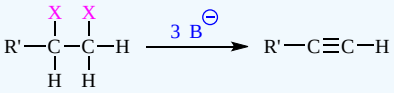
An simple method for the preparation of alkynes utilizes alkenes as starting material. The process begins with the electrophilic addition of a halogen to the alkene bond to form the dihaloalkane. Then the double E2 elimination process is used to form the 2 π bonds of an alkyne.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyne using double elimination, as covered previously on this page.



Exercise 13.4.1

Why would we need three bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?



Answer available at the end of this section.

Exercise 13.4.2

What are the major products of the following reactions:

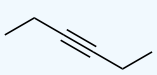
a. 1,2-Dibromopentane with sodium amide in liquid ammonia
b. 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide ($Na^+ {}^-O\text{-}CH_2CH_3$)

Answer available at the end of this section.

Exercise 13.4.3

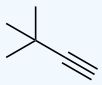
What would be good starting molecules for the synthesis of the following molecules:

a.



from an alkene

b.



from a dihaloalkane

Answer available at the end of this section.

Exercise 13.4.4

Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answer available at the end of this section.

Exercise 13.4.5

Identify the vinyl halide or halides and the vicinal dihalide or dihalides that could be used in the synthesis of:

a. 2,2,5,5-Tetramethyl-3-hexyne.
b. 4-Methyl-2-hexyne.

Answer available at the end of this section.

References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Daley, Richard, and Sally Daley. "13.8 Elimination of Organohalogens." Organic Chemistry. Daley. 5 July 2005. 21 Feb. 2009. <https://studylib.net/doc/8721401/13-elimination-reactions>.

Answers

Exercise 13.4.1

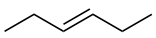
Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Exercise 13.4.2

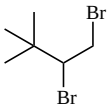
a. 1-Pentyne
b. 1-Pentyne

Exercise 13.4.3

a.

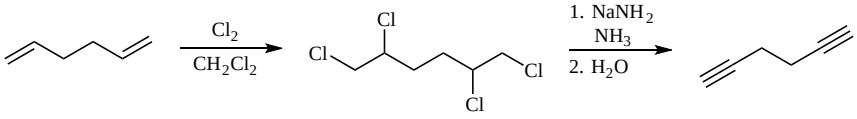


b.



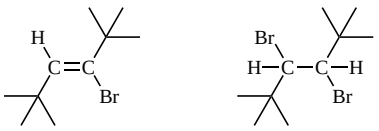
Exercise 13.4.4

Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.

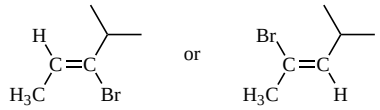


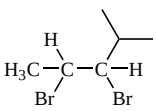
Exercise 13.4.5

a)



b)





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- 9.2: Preparation of Alkynes - Elimination Reactions of Dihalides by Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

13.5: Preparation of Alkynes from Alkynyl Anions

Objectives

After completing this section, you should be able to

1. write an equation for the reaction that occurs between a terminal alkyne and a strong base, such as sodamide, $NaNH_2$.
2. rank a given list of compounds, including water, acetylene and ammonia, in order of increasing or decreasing acidity.
3. rank a given list of hydrocarbons, such as acetylene, ethylene and ethane, in order of increasing or decreasing acidity.
4. describe a general method for determining which of two given compounds is the stronger acid.
5. provide an acceptable explanation of why terminal alkynes are more acidic than alkanes or alkenes.

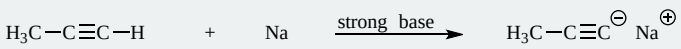
Key Terms

Make certain that you can define, and use in context, the key terms below.

- acetylide anion
- acidity order

Study Notes

An *acetylide anion* is an anion formed by removing the proton from the end carbon of a terminal alkyne:

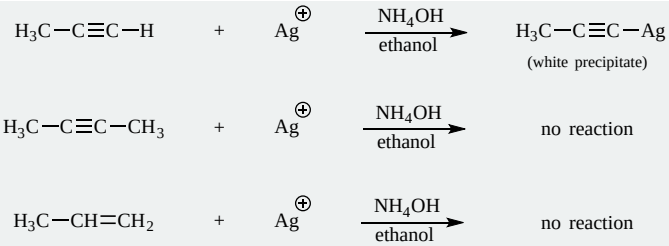


An *acidity order* is a list of compounds arranged in order of increasing or decreasing acidity.

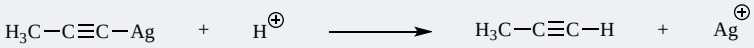
The general ideas discussed in this section should already be familiar to you from your previous exposure to chemistry and from the review in Section 2.8. A slightly different account of why terminal alkynes are stronger acids than are alkenes or alkanes is given below. However, the argument is still based on the differences between *sp*-, sp^2- and sp^3-hybrid orbitals.

The carbons of a triple bond are *sp*-hybridized. An *sp*-hybrid orbital has a 50% *s* character and a 50% *p* character, whereas an sp^2-hybrid orbital is 33% *s* and 67% *p*, and an sp^3-hybrid orbital is 25% *s* and 75% *p*. The greater the *s* character of the orbital, the closer the electrons are to the nucleus. Thus in a C(*sp*)-H bond, the bonding electrons are closer to the carbon nucleus than they are in a C(sp^2)-H bond. In other words, compared to a C(sp^2)-H bond (or a C(sp^3)-H bond), a C(*sp*)-H bond is very slightly polar: $C^{\delta-}$-$H^{\delta+}$. This slight polarity makes it easier for a base to remove a proton from a terminal alkyne than from a less polar or non-polar alkene or alkane.

As you will appreciate, the reaction between sodium amide and a terminal alkyne is an acid-base reaction. The sodium acetylide product is, of course, a salt. Terminal alkynes can also form salts with certain heavy-metal cations, notably silver(I) and copper(I). In the laboratory component of this course, you will use the formation of an insoluble silver acetylide as a method for distinguishing terminal alkynes from alkenes and non-terminal alkynes:

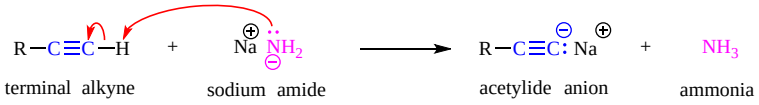


Metal acetylides are explosive when dry. They should be destroyed while still wet by warming with dilute nitric acid:

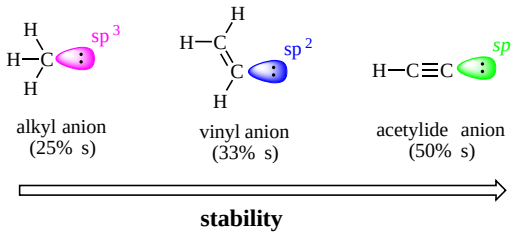


Acidity of Terminal Alkynes: Formation of Acetylide Anions

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the terminal proton leads to the formation of an acetylide anion, RC≡C:$^-$.



As discussed in **Section 2.10**, acidity typically increases with the stability of the corresponding conjugate base. The origin of the enhanced acidity of terminal alkynes can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals increases as the percent s character increases and follows the order sp > sp^2 > sp^3.



This trend indicates the sp hybridized orbitals of the acetylide anion are more electronegative and better able to stabilize a negative charge than sp^2 or sp^3 hybridized orbitals. There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The table below shows how orbital hybridization compares with the identity of the atom when predicting relative acidity. Remember that as the pK_a of a compound decreases its acidity increases.

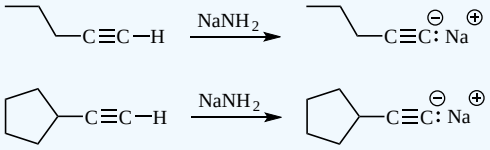
Table 13.5.1*: Akynes*

Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Acetylene, with a pK_a of 25 is shown to be much more acidic than ethylene (pK_a = 44) or ethane (pK_a = 50). Consequently,

acetylide anions can be readily formed by deprotonation of a terminal alkynes with a sufficiently strong base. The amide anion (NH_2^-), in the form of sodium amide ($NaNH_2$) is commonly used for the formation of acetylide anions.

Example 13.5.1



Exercise 13.5.1

Given that the p*K*a of water is 14.00, would you expect hydroxide ion to be capable of removing a proton from each of the substances listed below? Justify your answers, briefly.

a. ethanol (p*K*a = 16)
b. acetic acid (p*K*a = 4.72)
c. acetylene (p*K*a = 25)

Answer available at the end of this section.

Objectives

After completing this section, you should be able to

1. write an equation to describe the reaction of an acetylide ion with an alkyl halide.
2. discuss the importance of the reaction between acetylide ions and alkyl halides as a method of extending a carbon chain.
3. identify the alkyne (and hence the acetylide ion) and the alkyl halide needed to synthesize a given alkyne.
4. determine whether or not the reaction of an acetylide ion with a given alkyl halide will result in substitution or elimination, and draw the structure of the product formed in either case.

Key Terms

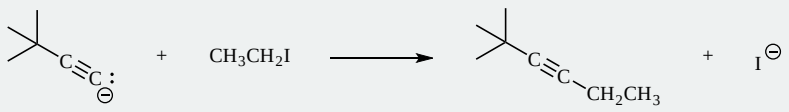
Make certain that you can define, and use in context, the key term below.

- alkylation

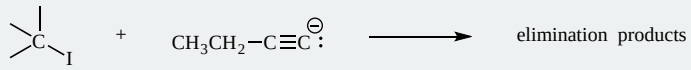
Study Notes

The alkylation of acetylide ions is important in organic synthesis because it is a reaction in which a new carbon-carbon bond is formed; hence, it can be used when an organic chemist is trying to build a complicated molecule from much simpler starting materials.

The alkyl halide used in this reaction must be primary. Thus, if you were asked for a suitable synthesis of 2,2-dimethyl-3-hexyne, you would choose to attack iodoethane with the anion of 3,3- dimethyl-1-butyne



rather than to attack 2-iodo-2-methylpropane with the anion of 1-butyne.



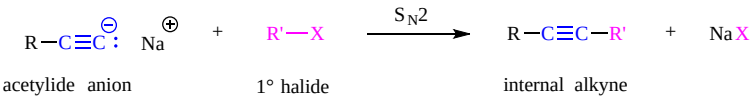
The reasons will be made clear in Chapter 11.

Nucleophilic Substitution Reactions of Acetylides

The presence of lone pair electrons and a negative charge on a carbon, makes acetylide anions are strong bases and strong nucleophiles. Therefore, acetylide anions can attack electrophiles such as alkyl halides to cause a substitution reaction. These substitution reactions will be discussed in detail in **Chapter 11**.

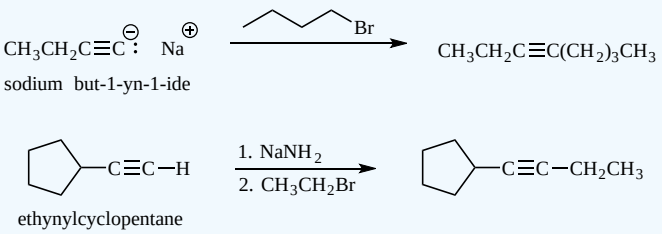
Mechanism

The C-X bonds in 1° alkyl halides are polarized due to the high electronegativity of the halogen. The electrons of the C-X sigma bond are shifted towards the halogen giving it a partial negative charge. This also causes electrons to be shifted away from the carbon giving it a partial positive and making it electrophilic. During this reaction, the lone pair electrons on the acetylide anion attack the electrophilic carbon in the 1° alkyl halide forming a new C-C bond. The formation of this new bond causes the expulsion of the halogen as what is called a leaving group. Overall, this reaction forms a C-C bond and converts a terminal alkyne into a internal alkyne. Because a new alkyl group is added to the alkyne during this reaction, it is commonly called an alkylation.

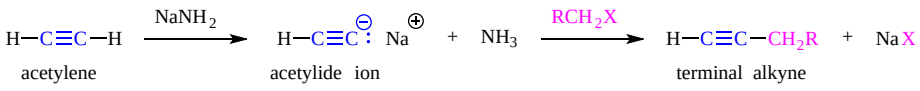


This substitution reaction is often coupled with the acetylide formation, discussed in the previous section, and shown as a single reaction.

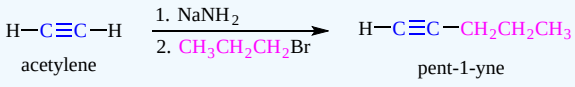
Example 13.5.1



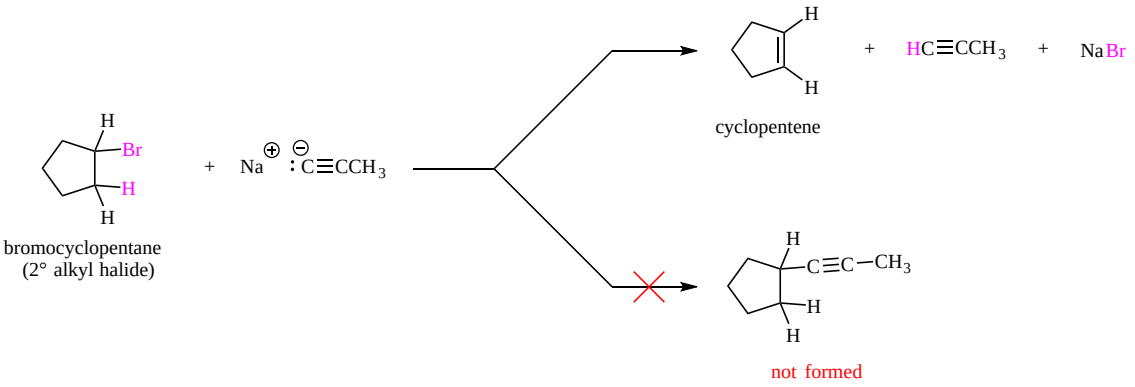
Terminal alkynes can be generated through the reaction of acetylene and a 1° alkyl halide.



Example 13.5.2

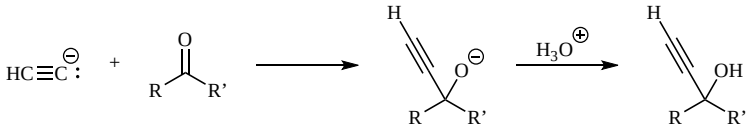


Because the acetylide anion is a very strong base, this substitution reaction is most efficient with methyl or primary halides. Secondary, tertiary, or even bulky primary halogens will give alkenes by the E2 elimination mechanism discussed in **Section 11.10**. An example of this effect is seen in the reaction of bromocyclopentane with a propyne anion. The reaction produces the elimination product cyclopentene rather than the substitution product 1-propynylcyclopentane.



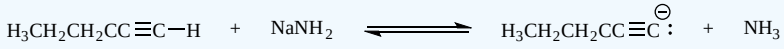
Nucleophilic Addition of Acetylides to Carbonyls

Acetylide anions also add to the electrophilic carbon in aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols. With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers. These types of reaction will be discussed in more detail in **Chapter 19**.



Exercise 13.5.1

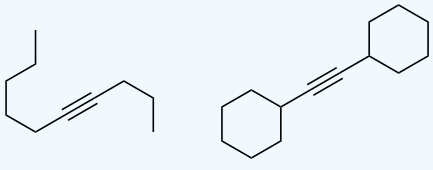
The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by sodium amide, as shown below.



Answer available at the end of this section.

Exercise 13.5.2

Give the possible reactants which could form the following molecules by an alkylation.



Answer available at the end of this section.

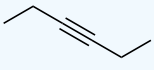
Exercise 13.5.3

Propose a synthetic route to produce 2-pentene from propyne and an alkyl halide.

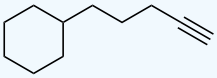
Answer available at the end of this section.

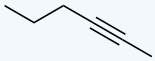
Exercise 13.5.4

Using acetylene as the starting material, show how you would synthesize the following compounds

a) 

b) but-2-yne

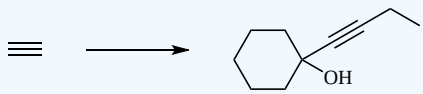
c) 

d) 

Answer available at the end of this section.

Exercise 13.5.5

Show how you would accomplish the following synthetic transformation.

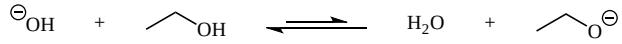


Answer available at the end of this section.

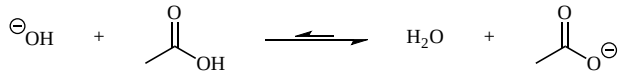
Answers

Exercise 13.5.1

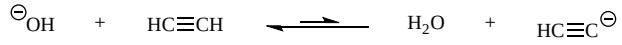
a. No, not very well. The p*K*a of ethanol is greater than that of water, thus the equilibrium lies to the left rather than to the right.Add texts here. Do not delete this text first.



b. Yes, very well. There is a difference of 11 p*K*a units between the p*K*a of water and the p*K*a of acetic acid. The equilibrium lies well to the right.



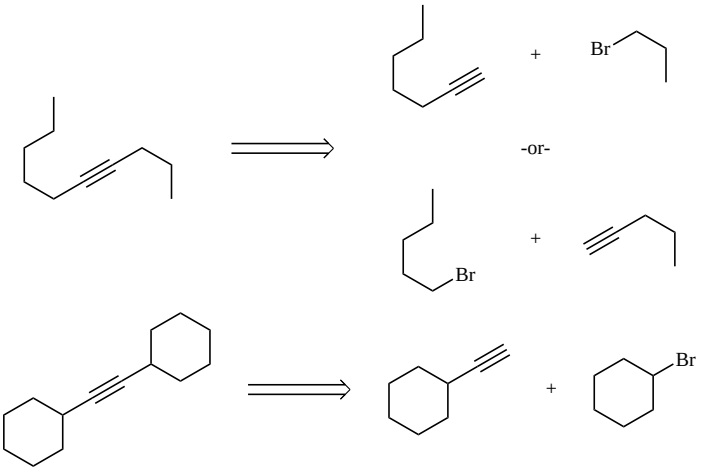
c. No, hardly at all. The hydroxide ion is too weak a base to remove a proton from acetylene. The equilibrium lies well to the left.



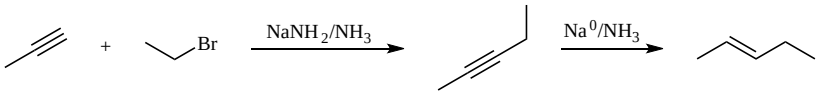
Exercise 13.5.1

Assuming the pK_a of pent-1-yne is about 25, then the difference in pK_as is 10. Since pentyne is more acidic, the formation of the acetylide will be favored at equilibrium, so the equilibrium constant for the reaction is about 10^{10}.

Exercise 13.5.2

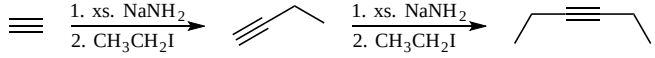


Exercise 13.5.3



Exercise 13.5.4

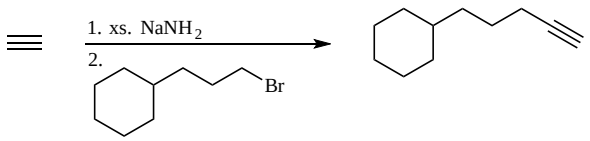
a)



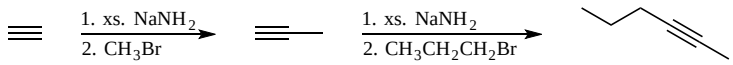
b)



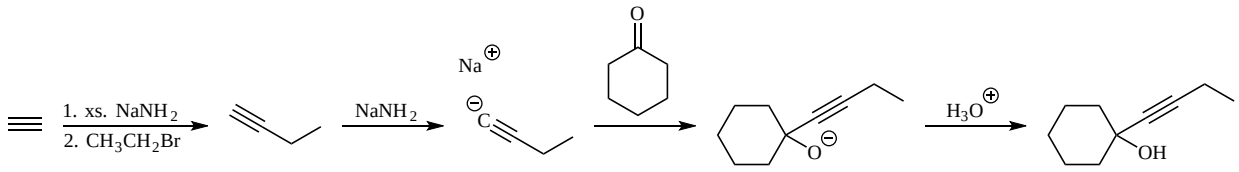
c)



d)



Exercise 13.5.5



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13.6: Reduction of Alkynes: The Relative Reactivity of the Two π Bonds

Objectives

After completing this section, you should be able to

1. write equations for the catalytic hydrogenation of alkynes to alkanes and cis alkenes.
2. identify the reagent and catalyst required to produce a given alkane or *cis* alkene from a given alkyne.
3. identify the product formed from the reaction of a given alkyne with hydrogen and a specified catalyst.
4. identify the alkyne that must be used to produce a given alkane or *cis* alkene by catalytic hydrogenation.
5. write the equation for the reduction of an alkyne with an alkali metal and liquid ammonia.
6. predict the structure of the product formed when a given alkyne is reduced with an alkali metal and liquid ammonia.
7. identify the alkyne that must be used to produce a given alkene by reduction with an alkali metal and ammonia.

Key Terms

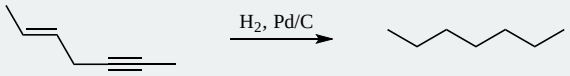
Make certain that you can define, and use in context, the key terms below.

- anion radical
- Lindlar catalyst

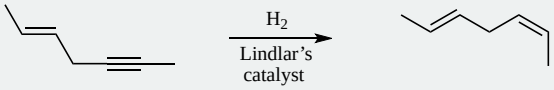
Study Notes

The Lindlar catalyst allows a chemist to reduce a triple bond in the presence of a double bond.

Thus

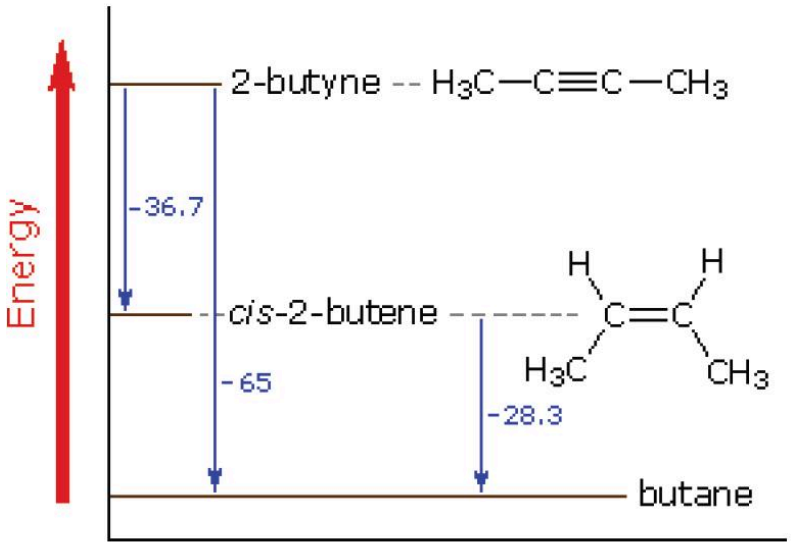


but



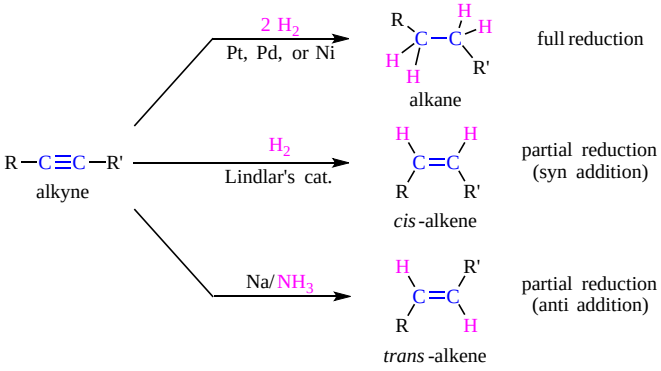
Hydrogenation and the Relative Stability of Hydrocarbons

Like alkenes, alkynes readily undergo catalytic hydrogenation partially to *cis*-alkenes or fully to alkanes depending on the reaction employed.



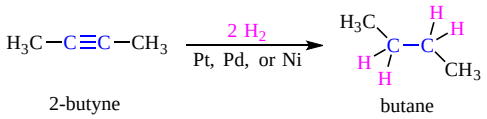
The catalytic addition of hydrogen to 2-butyne provides heat of reaction data that reflect the relative thermodynamic stabilities of these hydrocarbons, as shown above. From the heats of hydrogenation, shown in blue in units of kcal/mole, it would appear that alkynes are thermodynamically less stable than alkenes to a greater degree than alkenes are less stable than alkanes. The standard bond energies for carbon-carbon bonds confirm this conclusion. Thus, a double bond is stronger than a single bond, but not twice as strong. The difference (63 kcal/mole) may be regarded as the strength of the π-bond component. Similarly, a triple bond is stronger than a double bond, but not 50% stronger. Here the difference (54 kcal/mole) may be taken as the strength of the second π-bond. The 9 kcal/mole weakening of this second π-bond is reflected in the heat of hydrogenation numbers (36.7 - 28.3 = 8.4).

Alkynes can undergo reductive hydrogenation reactions similar to alkenes. Due to the presence of two pi bonds within alkynes, reductive hydrogenation reactions can be partial to form an alkene or complete to form an alkane. Since partial reductive hydrogenation of an alkyne produces an alkene, the stereochemistry provided by the reaction's mechanism determines whether a *cis*- or *trans*- alkene is formed. The three most significant alkyne reduction reactions are summarized below:

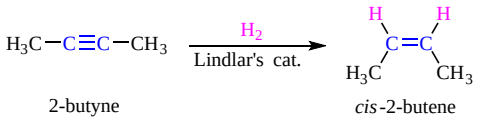


Catalytic Hydrogenation of an Alkyne

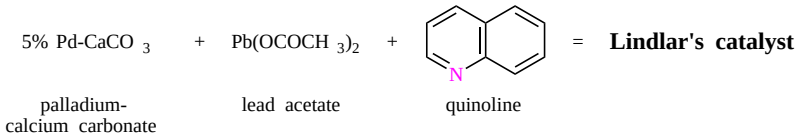
Much like alkenes, alkynes can be fully hydrogenated into alkanes with the help of a platinum, palladium, or nickel catalyst. Because the reaction is catalyzed on the surface of the metal, it is common for these catalysts to be dispersed on carbon (Pd/C) or finely dispersed, such as Raney-Ni. The presence of two pi bonds in the alkyne causes two equivalents of H_2 to be added during the reaction. An alkene intermediate is formed during the reaction but is not isolated.



For catalytic hydrogenation, the Pt, Pd, or Ni catalysts are so effective in promoting the addition of hydrogen to carbon-carbon triple bonds that the alkene intermediate formed cannot be isolated. A less efficient **Lindlar's catalyst**, permits alkynes to be converted to alkenes without further reduction to an alkane. Lindlar's Catalyst transforms an alkyne to a *cis*-alkene because both hydrogen atoms are added to the same side of the alkyne (syn) as shown in the in the previous chapter.

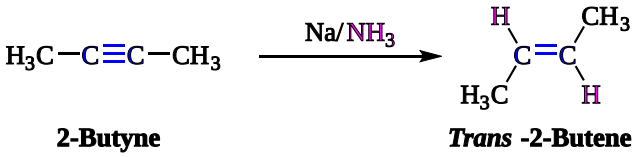


Lindlar's catalyst is prepared by deactivating (or poisoning) a conventional palladium catalyst. Lindlar's catalyst has three components: palladium-calcium carbonate, lead acetate, and quinoline. The quinoline serves to prevent complete hydrogenation of the alkyne to an alkane.



Hydrogenation of an Alkyne to a *Trans*-Alkene

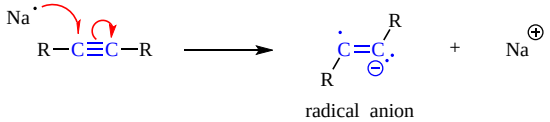
The anti-addition of hydrogen to an alkyne pi bond occurs through reaction with sodium or lithium metal dissolved in ammonia. This reaction, also called a **dissolving metal reduction**, involves a radical mechanism, and produces a *trans*-alkene product.



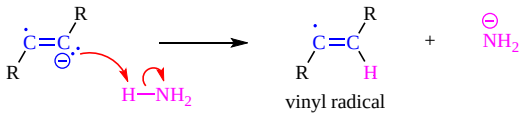
Mechanism

Sodium metal is a powerful reducing agent due to the presence of a $3s^1$ electron in its valence shell. Sodium metal easily gives up this electron to become Na^+. The mechanism start with a sodium atom donating an electron to the alkyne to create an intermediate with a negative charge and an unpaired electron called a radical anion. Next the amine solvent protonates the anion to create a vinyl radical. A second sodium atom then donates an electron to pair the radical to form a vinyl anion. This vinyl anion intermediate rapid interconverts between *cis* and *trans* conformations and determines the stereochemistry of the reaction. The *trans*-vinyl anion is more stable due to reduced steric crowding and is preferentially formed. Finally, the protonation of the *trans*-vinyl anion creates the *trans*-alkene product.

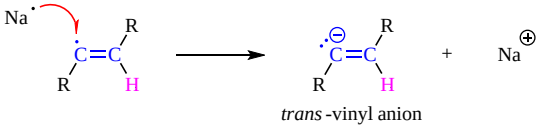
Step 1: Electron Donation



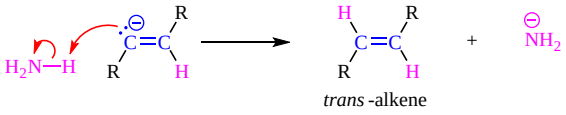
Step 2: Protonation



Step 3: Electron Donation



Step 4: Protonation



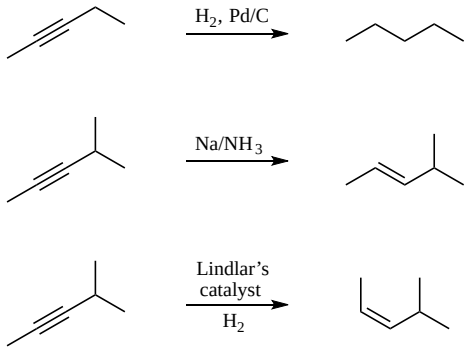
Exercise 13.6.1

Using any alkyne how would you prepare the following compounds: pentane, *trans*-4-methyl-2-pentene, *cis*-4-methyl-2-pentene.

Answer available at the end of this section.

Answers

Exercise 13.6.1



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13.7: Electrophilic Addition Reactions of Alkynes

Contributors and Attributions

•

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Jim Clark (Chemguide.co.uk)

Objectives

After completing this section, you should be able to

- write the equation for the reaction of water with an alkyne in the presence of sulfuric acid and mercury(II) sulfate.
- describe keto-enol tautomerism.
- predict the structure of the ketone formed when a given alkyne reacts with sulfuric acid in the presence of mercury(II) sulfate.
- identify the reagents needed to convert a given alkyne to a given ketone.
- identify the alkyne needed to prepare a given ketone by hydration of the triple bond.
- write an equation for the reaction of an alkyne with borane.
- write the equation for the reaction of a vinylic borane with basic hydrogen peroxide or hot acetic acid.
- identify the reagents, the alkyne, or both, needed to prepare a given ketone or a given cis alkene through a vinylic borane intermediate.
- identify the ketone produced when a given alkyne is reacted with borane followed by basic hydrogen peroxide.
- identify the cis alkene produced when a given alkyne is reacted with borane followed by hot acetic acid.
- explain why it is necessary to use a bulky, sterically hindered borane when preparing vinylic boranes from terminal alkynes.
- predict the product formed when the vinylic borane produced from a terminal alkyne is treated with basic hydrogen peroxide.
- identify the alkyne needed to prepare a given aldehyde by a vinylic borane.

Key Terms

Make certain that you can define, and use in context, the key terms below.

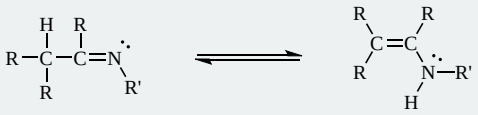
- enol
- keto-enol tautomeric equilibrium
- tautomerism

- tautomers

Study Notes

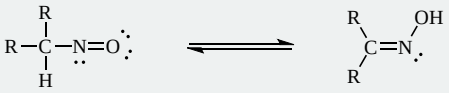
Rapid interconversion between tautomers is called **tautomerism**; however, as the two tautomers are in equilibrium, the term *tautomeric equilibrium* may be used. This section demonstrates the equilibrium between a ketone and an enol; hence, the term *keto-enol tautomeric equilibrium* is appropriate. The term “enol” indicates the presence of a carbon-carbon double bond and a hydroxyl (i.e., alcohol) group. Later in the course, you will see the importance of keto-enol tautomerism in discussions of the reactions of ketones, carbohydrates and nucleic acids.

It is important to note that tautomerism is not restricted to keto-enol systems. Other examples include imine-enamine tautomerism



imine enamine

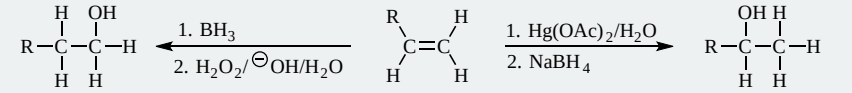
and nitroso-oxime tautomerism



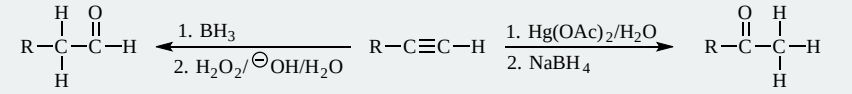
nitroso oxime

However, at the moment you need only concern yourself with keto-enol tautomerism.

Notice how hydroboration complements hydration in the chemistry of both alkenes and alkynes.



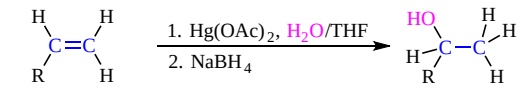
a primary alcohol a terminal alkene a secondary alcohol



an aldehyde a terminal alkyne a ketone

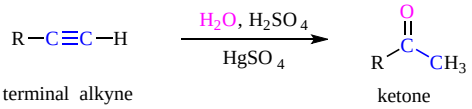
Mercury(II)-Catalyzed Hydration of Alkynes

As with alkenes, hydration (addition of water) of alkynes requires a strong acid, usually sulfuric acid, and is facilitated by the mercuric ion (Hg^{2+}). However, the hydration of alkynes gives ketone products while the hydration of alkenes gives alcohol products. Notice that the addition of oxygen in both reactions follows Markovnikov rule.



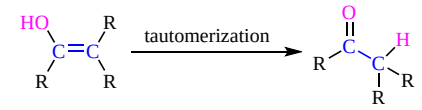
terminal alkene 2° alcohol

During the hydration of an alkyne, the initial product is an enol intermediate (a compound having a hydroxyl substituent attached to a double-bond), which immediately rearranges to the more stable ketone through a process called **enol-keto tautomerization**.



terminal alkyne ketone

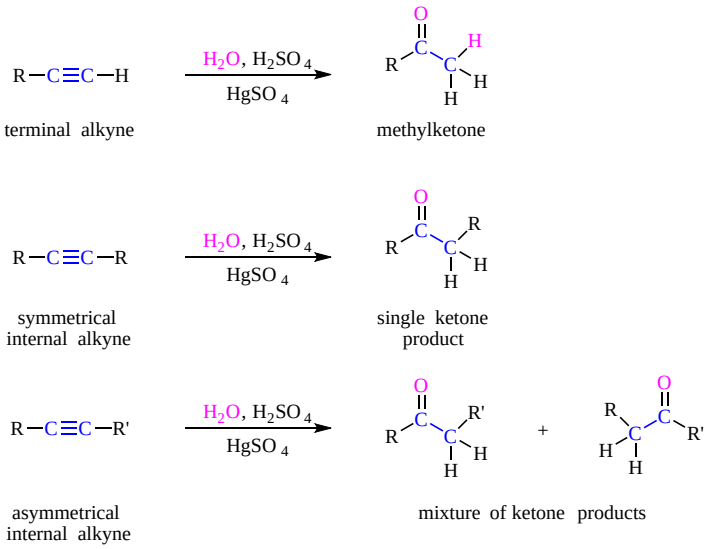
Tautomers are defined as rapidly inter-converted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The keto and enol tautomers are in equilibrium with each other and with few exceptions the keto tautomer is more thermodynamically stable and therefor favored by the equilibrium. This mechanism for tautomerization will be discussed in greater detail in **Section 22-1**.



enol tautomer keto tautomer **(favored)**

General Reaction

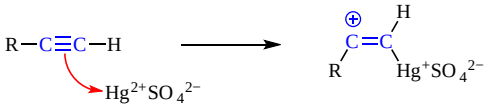
For terminal alkynes, the addition of water follows the Markovnikov rule, and the final product is a methyl ketone. For internal alkynes the addition of water is not regioselective. Hydration of symmetrical internal alkynes produces a single ketone product. However, hydration of asymmetrical alkynes, (i.e. if R & R' are not the same) produces two isomeric ketone products.



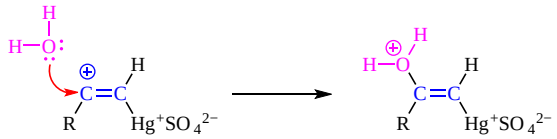
Mechanism

The mechanism starts with the electrophilic addition of the mercuric ion (Hg^{2+}) to the alkyne producing a mercury-containing vinylic carbocation intermediate. Nucleophilic attack of water on the vinylic carbocation forms a C-O bond to produce a protonated enol. Deprotonation of the enol by water then produces a organomercury enol. The mercury is substituted with H^+ to produced a neutral enol and regenerate the Hg^{2+} catalyst. The enol is converted to the ketone product through keto-enol tautomerization the mechanism of which is provided in **Section 22-1**.

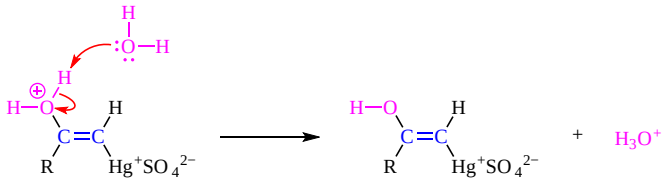
Step 1: Electrophilic addition of Hg^{2+}



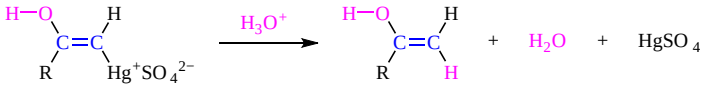
Step 2: Nucleophilic attack by water



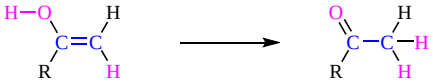
Step 3: Deprotonation



Step 4: Substitution

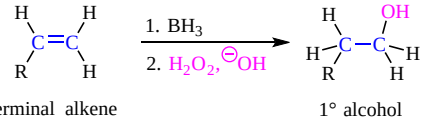


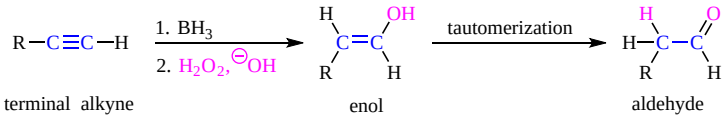
Step 5: Tautomerization



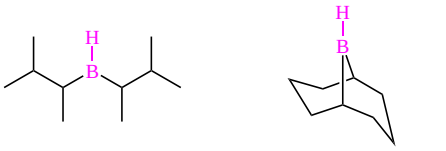
Hydroboration–Oxidation of Alkynes

The hydroboration-oxidation of alkynes is analagous to the reaction with alkenes. However, where alkenes for alcohol products, alkynes for aldehyde or ketone products. In both cases the addition is anti-Markovnikov and an oxygen is placed on the less alkyl substituted carbon. With the hydroboration of an alkyne the presences of a second pi bond allows the initial product to under tautomerization to become the final aldehyde product.





Alkynes have two pi bonds both of which are capable of reacting with borane (BH_3). To limit the reactivity to only one alkyne pi bond, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance which enhances the anti-Markovnikov regioselective of the reaction. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for this hydroboration reaction. The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes.

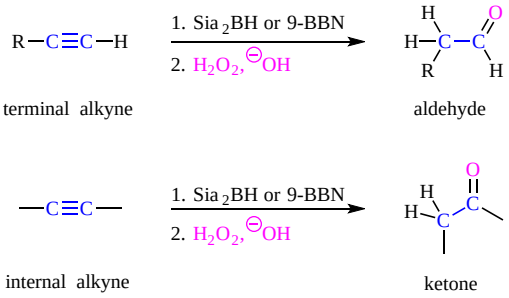


disiamylborane
(Sia_2BH)

9-borabicyclo[3.3.1]nonane
(9-BBN)

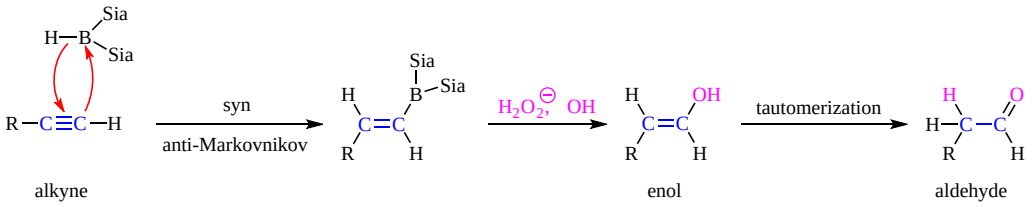
General Reaction

The hydroboration of terminal alkynes produces aldehyde products while internal alkynes produce ketone products. The hydroboration of symmetrical alkynes produces one ketone product and asymmetrical alkynes produce a mixture of product ketones.



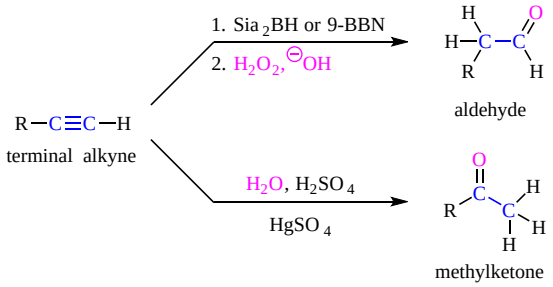
Mechanism

The mechanism starts with the electrophilic addition of the B-H bond of the borane. The hydrogen atom and the borane all on the same side of the alkyne creating a syn addition configuration in the alkene product. Also, the addition is anti-Markovnikov regioselective which means the borane adds to the less substituted carbon of the alkyne and the hydrogen atom adds to the more substituted. The oxidative work-up replaces the borane with a hydroxy group (-OH) creating an enol intermediate. The enol immediately tautomerizes to the product aldehyde for terminal alkynes and the product ketone for internal alkynes.

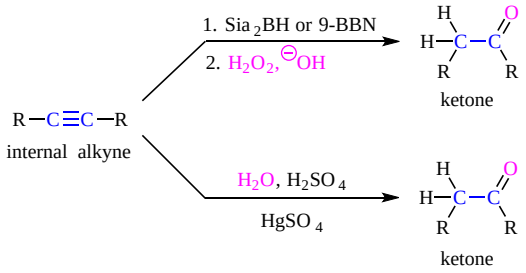


Comparison of Mercury(II)-Catalyzed Hydration and Hydroboration–Oxidation of Alkynes

These two reactions are complementary for the reaction of a terminal alkyne because the produce distinctly different products. The mercury(II) catalyzed hydration of a terminal alkyne produces a methyl ketone, while the hydroboration-oxidation produces an aldehyde.



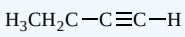
For internal alkynes, the regioslectivity of these reactions are rendered ineffective. The reactions are redundant in that they both produce the same ketone products.



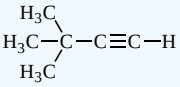
Exercise 13.7.1

Draw the structure of the product formed when each of the substances below is treated with H_2O/H_2SO_4 in the presence of $HgSO_4$.

a)



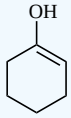
b)



Answer available at the end of this section.

Exercise 13.7.2

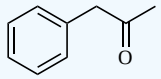
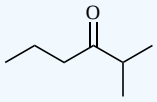
Draw the structure of the keto form of the compound shown below. Which form would you expect to be the most stable?



Answer available at the end of this section.

Exercise 13.7.3

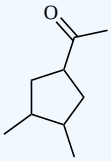
What alkyne would you start with to gain the following products?

a)  b) 

Answer available at the end of this section.

Exercise 13.7.4

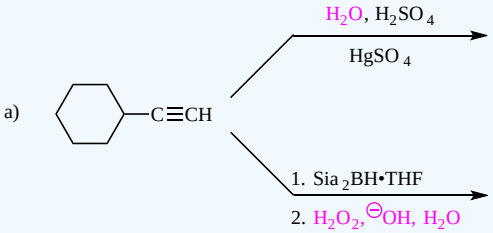
What alkyne would you start with to gain the following product?

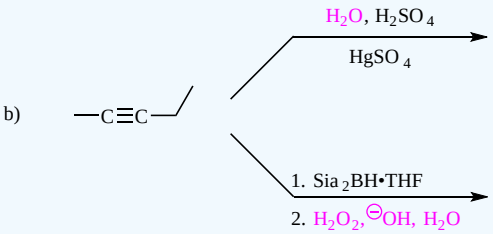


Answer available at the end of this section.

Exercise 13.7.5

Draw the product(s) of the following reactions:

a) 

b) 

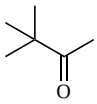
Answer available at the end of this section.

Answers

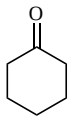
Exercise 13.7.1

a) 

b)

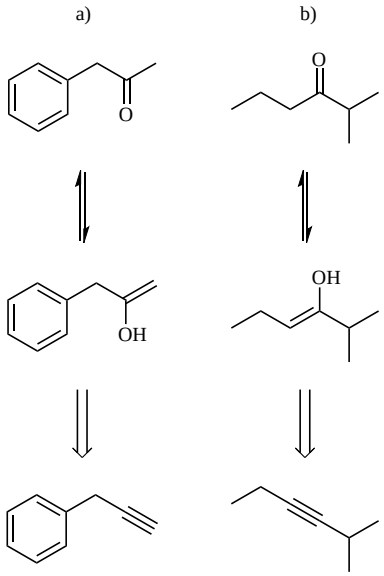


Exercise 13.7.2

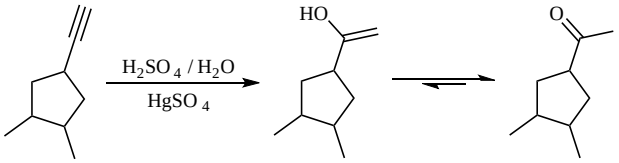


The keto form should be the most stable.

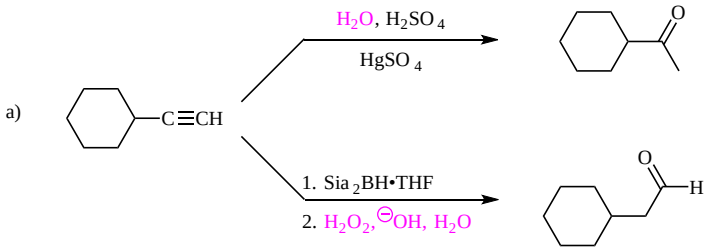
Exercise 13.7.3

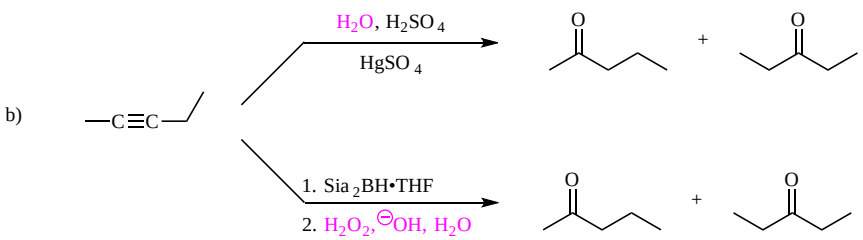


Exercise 13.7.4



Exercise 13.7.5





For internal alkynes, there is no difference in the reaction products.

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13.8: Anti-Markovnikov Additions to Triple Bonds

Objectives

After completing this section, you should be able to

- write the equation for the reaction of water with an alkyne in the presence of sulfuric acid and mercury(II) sulfate.
- describe keto-enol tautomerism.
- predict the structure of the ketone formed when a given alkyne reacts with sulfuric acid in the presence of mercury(II) sulfate.
- identify the reagents needed to convert a given alkyne to a given ketone.
- identify the alkyne needed to prepare a given ketone by hydration of the triple bond.
- write an equation for the reaction of an alkyne with borane.
- write the equation for the reaction of a vinylic borane with basic hydrogen peroxide or hot acetic acid.
- identify the reagents, the alkyne, or both, needed to prepare a given ketone or a given cis alkene through a vinylic borane intermediate.
- identify the ketone produced when a given alkyne is reacted with borane followed by basic hydrogen peroxide.
- identify the cis alkene produced when a given alkyne is reacted with borane followed by hot acetic acid.
- explain why it is necessary to use a bulky, sterically hindered borane when preparing vinylic boranes from terminal alkynes.
- predict the product formed when the vinylic borane produced from a terminal alkyne is treated with basic hydrogen peroxide.
- identify the alkyne needed to prepare a given aldehyde by a vinylic borane.

Key Terms

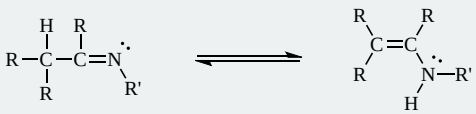
Make certain that you can define, and use in context, the key terms below.

- enol
- keto-enol tautomeric equilibrium
- tautomerism
- tautomers

Study Notes

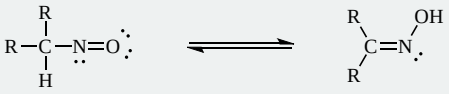
Rapid interconversion between tautomers is called **tautomerism**; however, as the two tautomers are in equilibrium, the term *tautomeric equilibrium* may be used. This section demonstrates the equilibrium between a ketone and an enol; hence, the term *keto-enol tautomeric equilibrium* is appropriate. The term “enol” indicates the presence of a carbon-carbon double bond and a hydroxyl (i.e., alcohol) group. Later in the course, you will see the importance of keto-enol tautomerism in discussions of the reactions of ketones, carbohydrates and nucleic acids.

It is important to note that tautomerism is not restricted to keto-enol systems. Other examples include imine-enamine tautomerism



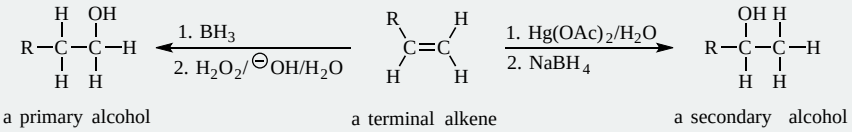
imine enamine

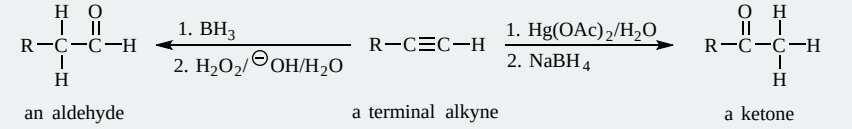
and nitroso-oxime tautomerism



However, at the moment you need only concern yourself with keto-enol tautomerism.

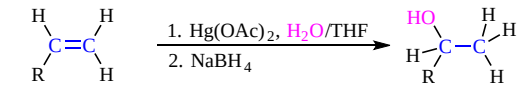
Notice how hydroboration complements hydration in the chemistry of both alkenes and alkynes.



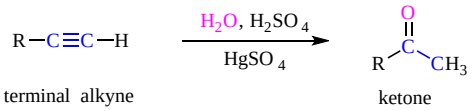


Mercury(II)-Catalyzed Hydration of Alkynes

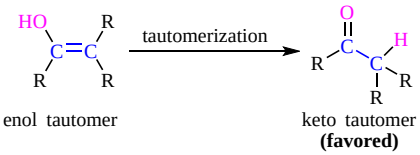
As with alkenes, hydration (addition of water) of alkynes requires a strong acid, usually sulfuric acid, and is facilitated by the mercuric ion (Hg^{2+}). However, the hydration of alkynes gives ketone products while the hydration of alkenes gives alcohol products. Notice that the addition of oxygen in both reactions follows Markovnikov rule.



During the hydration of an alkyne, the initial product is an enol intermediate (a compound having a hydroxyl substituent attached to a double-bond), which immediately rearranges to the more stable ketone through a process called **enol-keto tautomerization**.



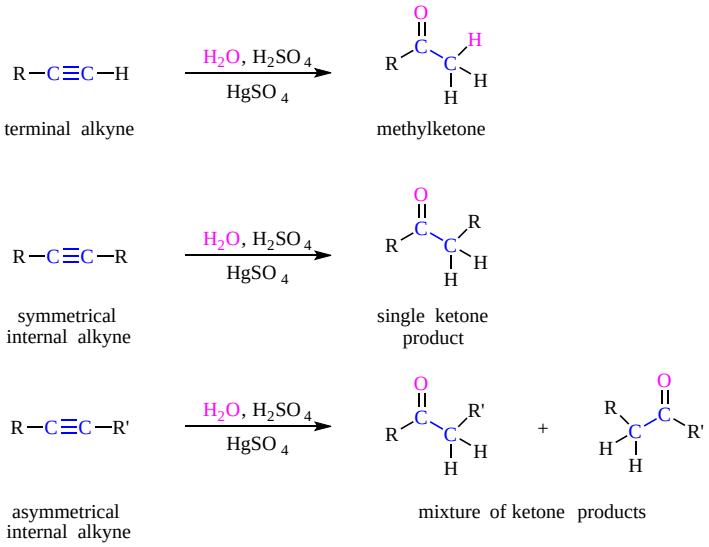
Tautomers are defined as rapidly inter-converted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The keto and enol tautomers are in equilibrium with each other and with few exceptions the keto tautomer is more thermodynamically stable and therefor favored by the equilibrium. This mechanism for tautomerization will be discussed in greater detail in **Section 22-1**.



General Reaction

For terminal alkynes, the addition of water follows the Markovnikov rule, and the final product is a methyl ketone. For internal alkynes the addition of water is not regioselective. Hydration of symmetrical internal alkynes produces a single ketone product.

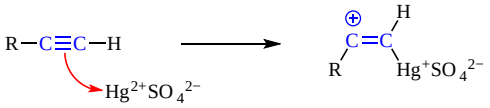
However, hydration of asymmetrical alkynes, (i.e. if R & R' are not the same) produces two isomeric ketone products.



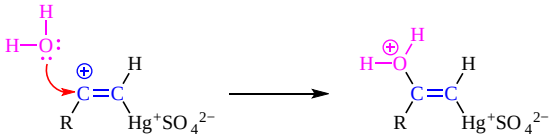
Mechanism

The mechanism starts with the electrophilic addition of the mercuric ion (Hg^{2+}) to the alkyne producing a mercury-containing vinylic carbocation intermediate. Nucleophilic attack of water on the vinylic carbocation forms a C-O bond to produce a protonated enol. Deprotonation of the enol by water then produces a organomercury enol. The mercury is substituted with H^+ to produced a neutral enol and regenerate the Hg^{2+} catalyst. The enol is converted to the ketone product through keto-enol tautomerization the mechanism of which is provided in **Section 22-1**.

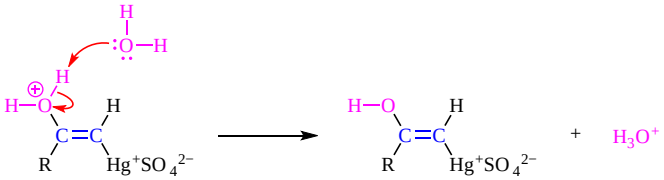
Step 1: Electrophilic addition of Hg^{2+}



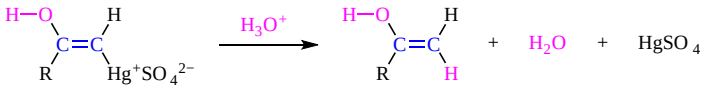
Step 2: Nucleophilic attack by water



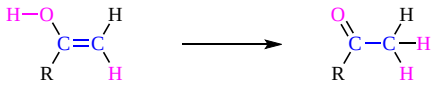
Step 3: Deprotonation



Step 4: Substitution

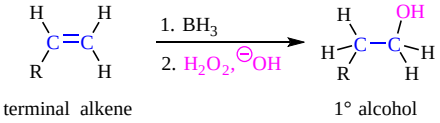


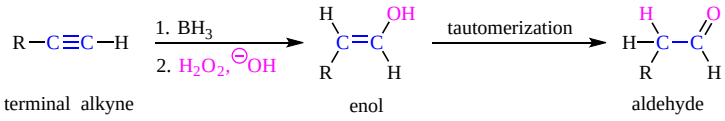
Step 5: Tautomerization



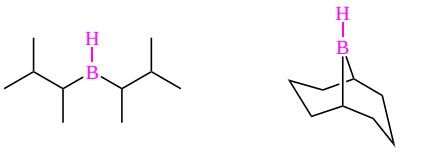
Hydroboration–Oxidation of Alkynes

The hydroboration-oxidation of alkynes is analagous to the reaction with alkenes. However, where alkenes for alcohol products, alkynes for aldehyde or ketone products. In both cases the addition is anti-Markovnikov and an oxygen is placed on the less alkyl substituted carbon. With the hydroboration of an alkyne the presences of a second pi bond allows the initial product to under tautomerization to become the final aldehyde product.



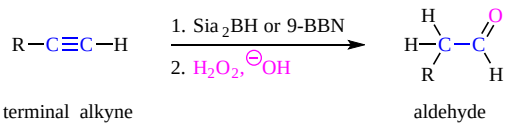


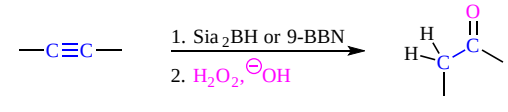
Alkynes have two pi bonds both of which are capable of reacting with borane (BH_3). To limit the reactivity to only one alkyne pi bond, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance which enhances the anti-Markovnikov regioselective of the reaction. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for this hydroboration reaction. The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes.



General Reaction

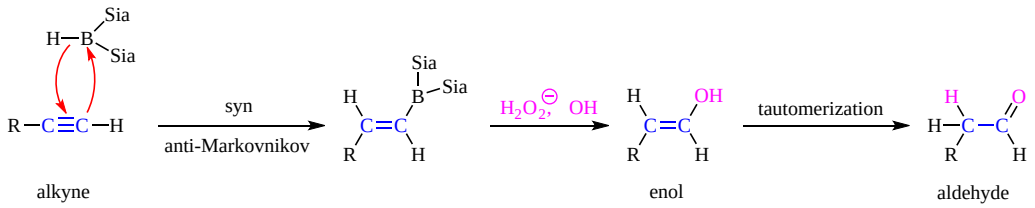
The hydroboration of terminal alkynes produces aldehyde products while internal alkynes produce ketone products. The hydroboration of symmetrical alkynes produces one ketone product and asymmetrical alkynes produce a mixture of product ketones.





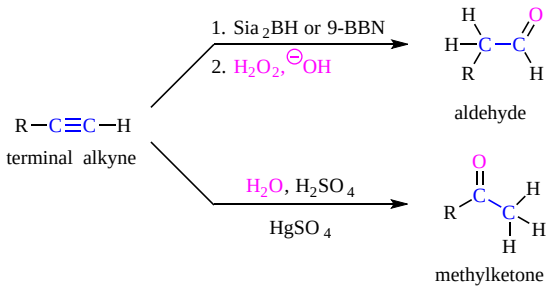
Mechanism

The mechanism starts with the electrophilic addition of the B-H bond of the borane. The hydrogen atom and the borane all on the same side of the alkyne creating a syn addition configuration in the alkene product. Also, the addition is anti-Markovnikov regioselective which means the borane adds to the less substituted carbon of the alkyne and the hydrogen atom adds to the more substituted. The oxidative work-up replaces the borane with a hydroxy group (-OH) creating an enol intermediate. The enol immediately tautomerizes to the product aldehyde for terminal alkynes and the product ketone for internal alkynes.

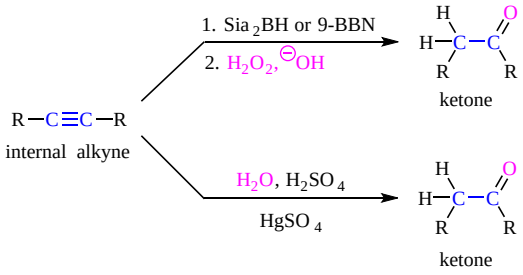


Comparison of Mercury(II)-Catalyzed Hydration and Hydroboration–Oxidation of Alkynes

These two reactions are complementary for the reaction of a terminal alkyne because the produce distinctly different products. The mercury(II) catalyzed hydration of a terminal alkyne produces a methyl ketone, while the hydroboration-oxidation produces an aldehyde.



For internal alkynes, the regioslectivity of these reactions are rendered ineffective. The reactions are redundant in that they both produce the same ketone products.



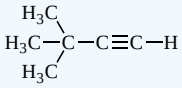
Exercise 13.8.1

Draw the structure of the product formed when each of the substances below is treated with H_2O/H_2SO_4 in the presence of $HgSO_4$.

a)

$$H_3CH_2C—C\equiv C—H$$

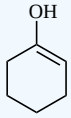
b)



Answer available at the end of this section.

Exercise 13.8.2

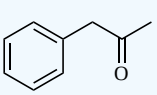
Draw the structure of the keto form of the compound shown below. Which form would you expect to be the most stable?

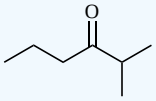


Answer available at the end of this section.

Exercise 13.8.3

What alkyne would you start with to gain the following products?

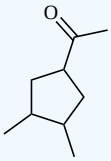
a) 

b) 

Answer available at the end of this section.

Exercise 13.8.4

What alkyne would you start with to gain the following product?

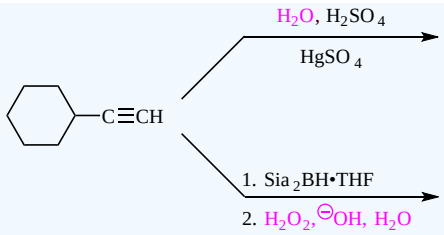


Answer available at the end of this section.

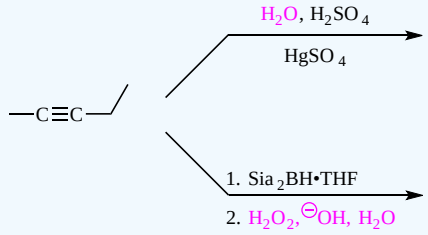
Exercise 13.8.5

Draw the product(s) of the following reactions:

a)



b)



Answer available at the end of this section.

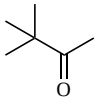
Answers

Exercise 13.8.1

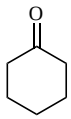
a)



b)

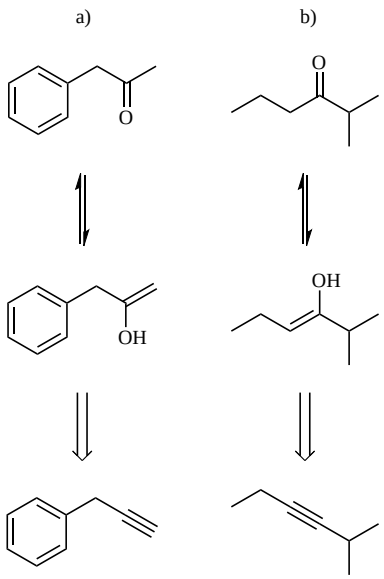


Exercise 13.8.2

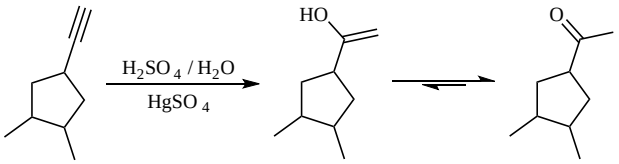


The keto form should be the most stable.

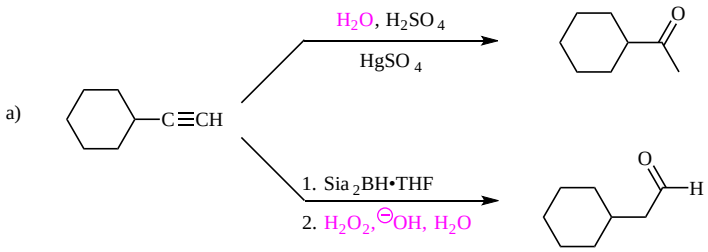
Exercise 13.8.3

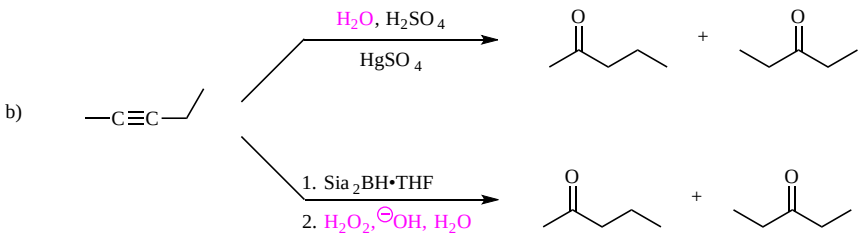


Exercise 13.8.4



Exercise 13.8.5





For internal alkynes, there is no difference in the reaction products.

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13.9: Chemistry of Alkenyl Halides

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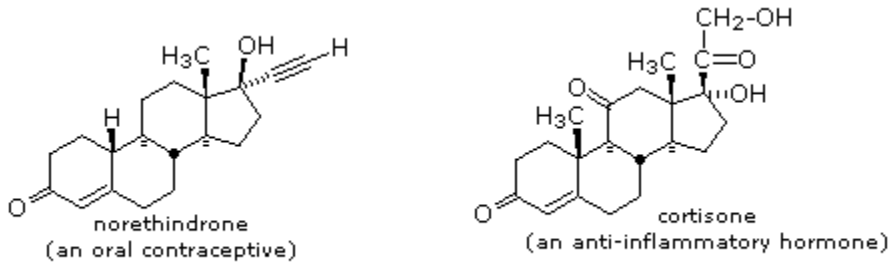
13.10: Ethyne as an Industrial Starting Material

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13.11: Naturally Occurring and Physiologically Active Alkynes

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring.

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.



Medicinally Useful Steroids

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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14: DELOCALIZED PI SYSTEMS: INVESTIGATION BY ULTRAVIOLET AND VISIBLE SPECTROSCOPY

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

14.1: Overlap of Three Adjacent p Orbitals: Electron Delocalization in the 2-Propenyl (Allyl) System

14.2: Radical Allylic Halogenation

14.3: Nucleophilic Substitution of Allylic Halides: SN1 and SN2

14.4: Allylic Organometallic Reagents: Useful Three-Carbon Nucleophiles

14.5: Two Neighboring Double Bonds: Conjugated Dienes

14.6: Electrophilic Attack on Conjugated Dienes: Kinetic and Thermodynamic Control

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14.11: Electronic Spectra: Ultraviolet and Visible Spectroscopy

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14.1: Overlap of Three Adjacent p Orbitals: Electron Delocalization in the 2-Propenyl (Allyl) System

Have you ever wondered why color exists? If you know it is because of molecules, do you know what makes the different colors appear? Most of it can be explained by the presence of the π bonds, and how many there are. When photons hit the atoms and excite the electrons, the bonds that the electrons are in affect the frequency of light that is reflected when the electrons go back to th ground state and is perceived by our eyes.

Introduction

π-Bonds are formed from the overlap of two adjacent parallel *p* orbitals (Fig.1). π bonds are important in the addition reactions. It is vital in synthesising many products like the polymers we use in modern day society. These systems have incredibly unique thermodynamic and photochemical properties. In this section we discover the special properties that three adjacent *p* orbitals (a π double bond and a p orbital) can have on the reactivity of a carbon center. We call a carbon next to a double bonded carbon an allylic carbon. The electrons that are shared between all the atomic centers are commonly said to be **delocalized**.

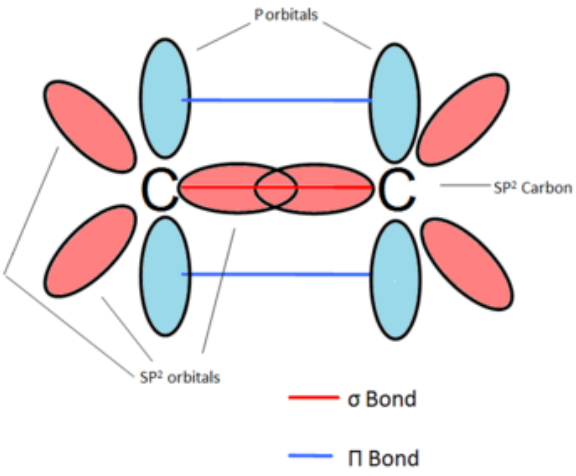


Figure 1 A π Bond is the interaction between the two *p* orbitals of the bonded carbons.

Allylic Carbocations

Lets take a look at the energy required to homolytically cleave (bond enthalpies) a covalent bond fig.2

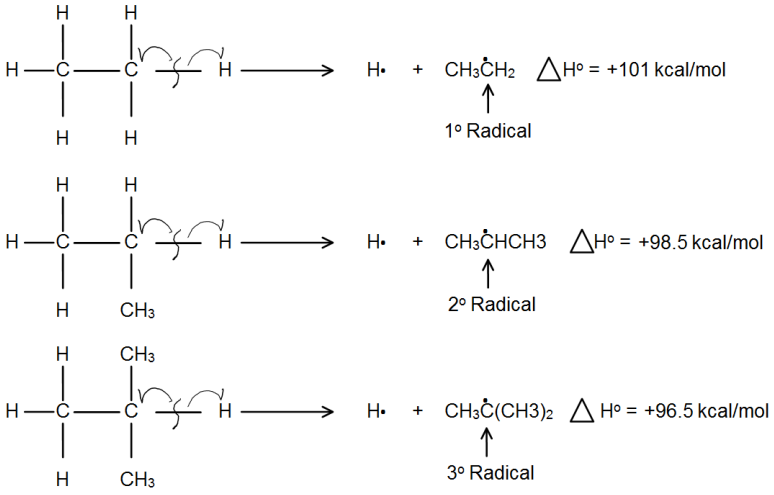


Figure 2: shows the decreasing energy required to a cleave a bond as we add methyl groups (for stabilization)

As you can see, the more stable the carbocation, the easier it is to form. The tertiary carbocation takes less energy to cleave than the primary carbocation. This is due to hyperconjugation which stabilizes the free electron by the slight interaction with nearby bond orbitals in the methyl groups.

Now we look at a propene molecule Figure 3.

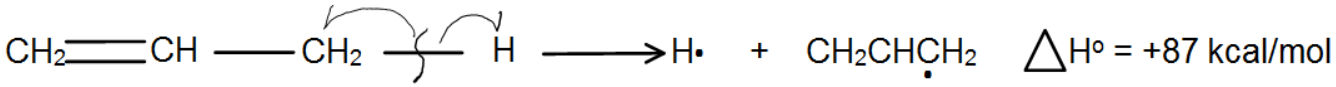


Figure 3: propene radical formation

Even though the carbocation is a primary one, the energy required to cleave the bond is *even lower* than that of a seemingly stable tertiary structure. Also, the pK_a of propene is about 40, compared to propane, which is about 50. This means the propene is much more willing to form the propenyl anion, about ten orders of magnitude more. Let's take a look at why:

Resonance

One way to explain the stability is in terms of resonance, the allylic effect can be shown in all carbon center forms: Cation, Radical, and Anion in figure 4. The double bond's ability to shift in between different carbons gives it extra resonance forms, which lends extra stability.

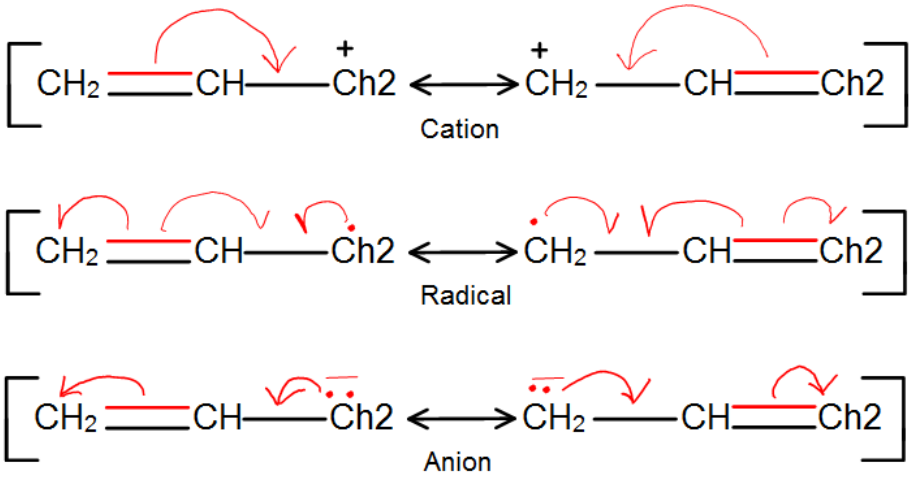


***Figure 4: E**ach type of center is stabilized through resonance because double bond*

Molecular Orbitals

It can also be clearly shown through orbitals in figure 5.

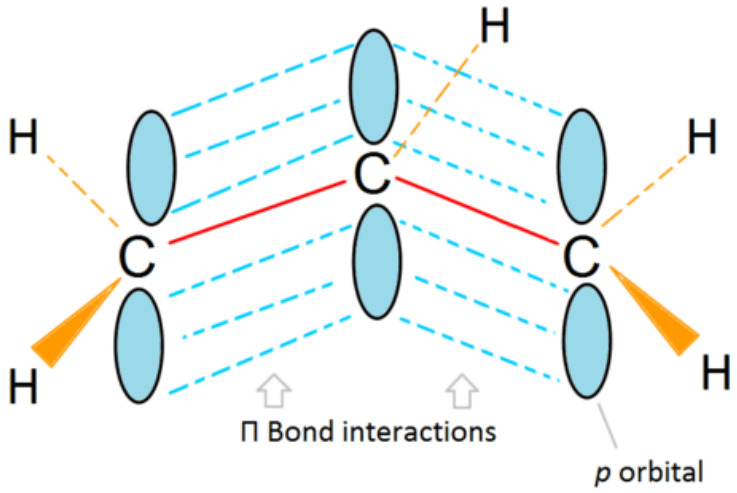


***Figure 5.** A conjugated ? electron system*

The stability of the carbocation of propene is due to a conjugated π electron system. A "double bond" doesn't really exist. Instead, it is a group of 3 adjacent, overlapping, non-hybridized *p* orbitals we call a **conjugated π electron system**. You can clearly see the interactions between all three of the *p* orbitals from the three carbons resulting in a really stable cation. It all comes down to where the location of the electron-deficient carbon is.

Molecular orbital descriptions can explain allylic stability in yet another way using 2-propenyl. Fig.6

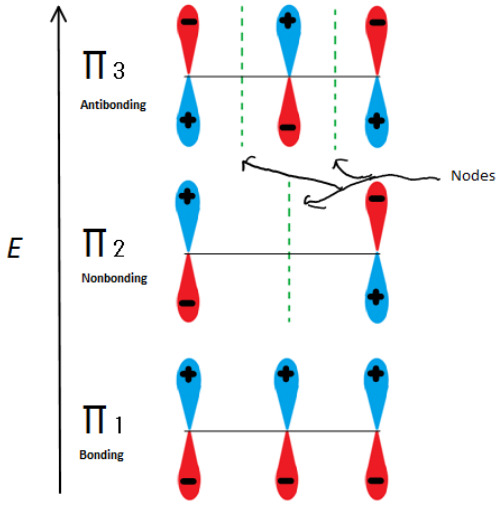


Figure 6: *Shows the 3 possible Molecular orbitals of 2-propenyl*

If we just take the π molecular orbital and not any of the s, we get three of them. π_1 is bonding with no nodes, π_2 is nonbonding (In other words, the same energy as a regular *p*-orbital) with a node, and π_3 is antibonding with 2 nodes (none of the orbitals are interacting). The first two electrons will go into the π_1 molecular orbital, regardless of whether it is a cation, radical, or anion. If it is a radical or anion, the next electron goes into the π_2 molecular orbital. The last anion electron goes into the nonbonding orbital also. So no matter what kind of carbon center exists, no electron will ever go into the antibonding orbital.

The Bonding orbitals are the lowest energy orbitals and are favorable, which is why they are filled first. Even though the nonbonding orbitals can be filled, the overall energy of the system is still lower and more stable due to the filled bonding molecular orbitals.

This figure also shows that π_2 is the only molecular orbital where the electrion differs, and it is also where a single node passes through the middle. Because of this, the charges of the molecule are mainly on the two terminal carbons and not the middle carbon.

This molecular orbital description can also illustrate the stability of allylic carbon centers in figure 7.

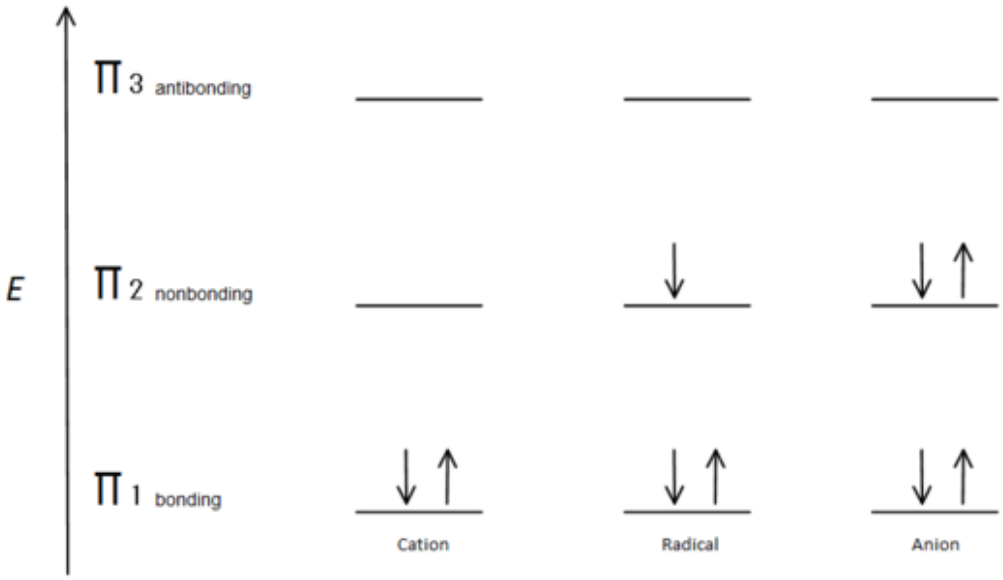


Fig.7 diagram showing how the electrons fill based on the Aufbau principle.

The π bonding orbital is lower in energy than the nonbonding *p* orbital. Since every carbon center shown has two electrons in the lower energy, bonding π orbitals, the energy of each system is lowered overall (and thus more stable), regardless of cation, radical, or anion.

Ultraviolet and Visible Spectroscopy

An electronic spectra can indicate the relative amounts of delocalization in a π electron system. The more conjugated π bonds there are, the longer the wavelength is reflected. Ethene has a maximum wavelength of 171 nm compared to 1,4-Pentadiene, which has a maximum wavelength of 178 nm and 1,3-Butadiene which has a maximum wavelength of 217 nm. The higher wavelength of the 1,3-Butadiene compared to only 178 nm for 1,4-Pentadiene shows the unique difference between a conjugated an non conjugated system.

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3. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.

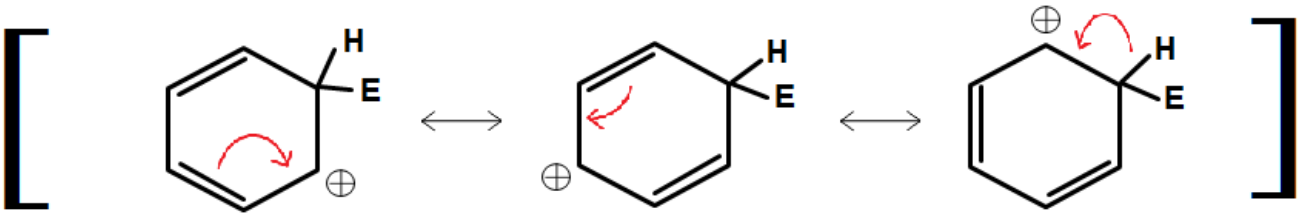
Problems

1. Given 1-bromopropane and water, or 1-bromopropene, which one would react and why?
2. Order these in terms of free radical stability, 1 being most stable: tertiary alkyl, primary alkyl, secondary allylic, tertiary allylic, $^{\bullet}CH_3$, primary allylic, secondary alkyl.
3. Order these molecules in terms of relative wavelength, from longest, to shortest.
4. 1,3-Cyclopentene; 2-Methyl-1,3-Pentadiene; Pyrrole; 2-Methyl-1,4-Pentadiene; *trans*-1,3,5-Hexatriene.
5. Draw out the resonance structures of the arenium ion during a general electrophilic aromatic substitution of a Benzene ring.

Answers

1. 1-bromopropane would have no reaction because water is a poor nucleophile, and a primary carbocation would form. 1-bromopropene is allylic and so stabilizes the carbon attached to the bromine. The water can then successfully react with it through an S_N2 reaction.

2. 1 tertiary allylic, 2 secondary allylic~tertiary alkyl, 3 primary allylic~secondary alkyl, 4 primary alkyl, 5 $^{\bullet}CH3$
3. Long wavelength Pyrrole>1,3-Cyclopentadiene>*trans*-1,3,5-Hexatriene>2-Methyl-1,3-Pentadiene>2-Methyl-1,4-Pentadiene short wavelength
4.



E=Electrophile

Contributors

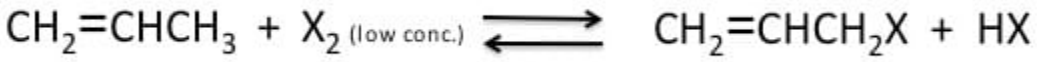
- Jeffrey Hu

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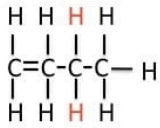
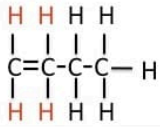
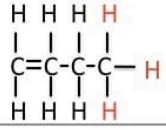
14.2: Radical Allylic Halogenation

When halogens are in the presence of unsaturated molecules such as alkenes, the expected reaction is addition to the double bond carbons resulting in a vicinal dihalide (halogens on adjacent carbons). However, when the halogen concentration is low enough, alkenes containing allylic hydrogens undergo substitution at the allylic position rather than addition at the double bond. The product is an allylic halide (halogen on carbon next to double bond carbons), which is acquired through a radical chain mechanism.



Why Substitution of Allylic Hydrogens?

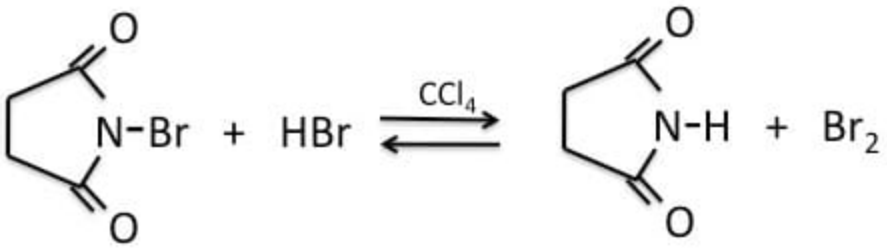
As the table below shows, the dissociation energy for the allylic C-H bond is lower than the dissociation energies for the C-H bonds at the vinylic and alkylic positions. This is because the radical formed when the allylic hydrogen is removed is resonance-stabilized. Hence, given that the halogen concentration is low, substitution at the allylic position is favored over competing reactions. However, when the halogen concentration is high, addition at the double bond is favored because a polar reaction outcompetes the radical chain reaction.

Type of Hydrogen	Dissociation Energy (DH^o)
allylic 	88 kcal/mol
vinylic 	106 kcal/mol
alkylic 	98 kcal/mol

Radical Allylic Bromination (Wohl-Ziegler Reaction)

Preparation of Bromine (low concentration)

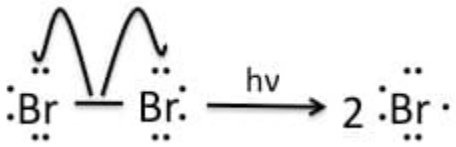
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



Allylic Bromination Mechanism

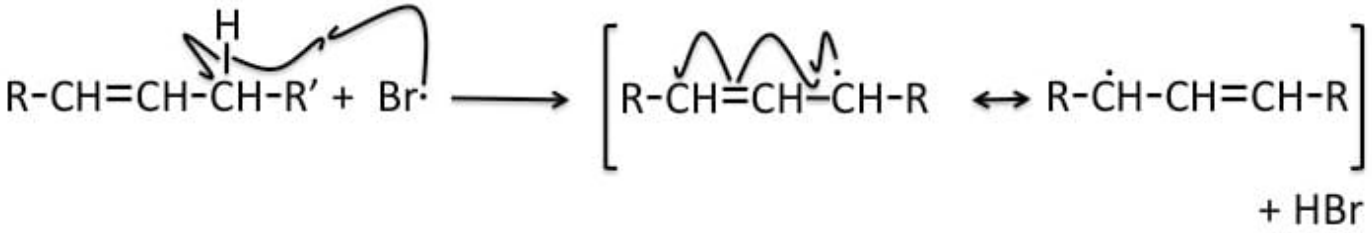
Step 1: Initiation

Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.

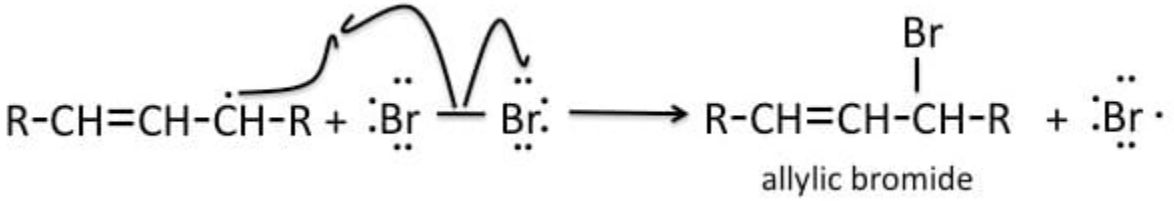


Step 2: Propagation

One bromine radical produced by homolytic cleavage in the initiation step removes an allylic hydrogen of the alkene molecule. A radical intermediate is generated, which is stabilized by resonance. The stability provided by delocalization of the radical in the alkene intermediate is the reason that substitution at the allylic position is favored over competing reactions such as addition at the double bond.

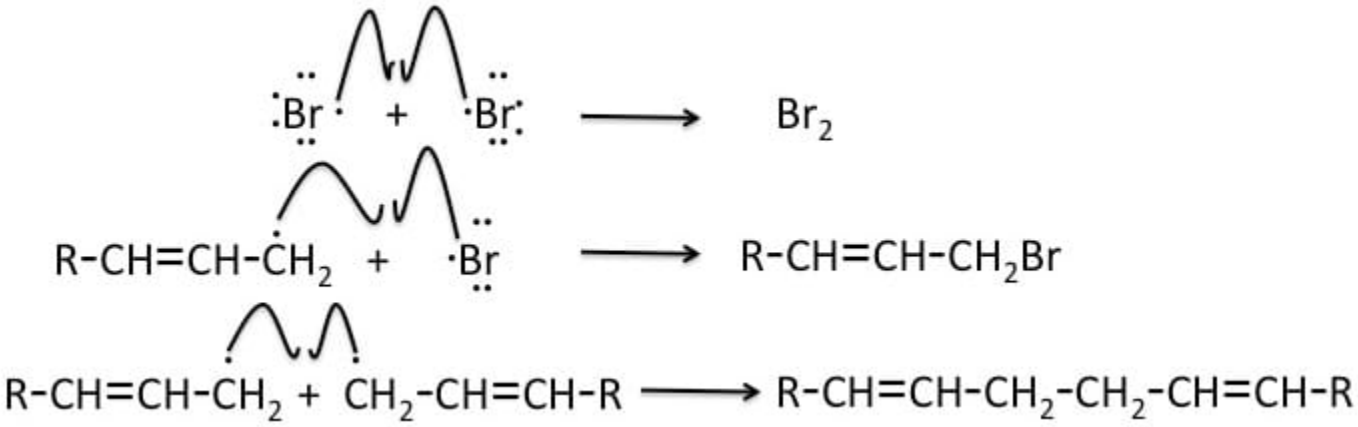


The intermediate radical then reacts with a Br_2 molecule to generate the allylic bromide product and regenerate the bromine radical, which continues the radical chain mechanism. If the alkene reactant is asymmetric, two distinct product isomers are formed.



Step 3: Termination

The radical chain mechanism of allylic bromination can be terminated by any of the possible steps shown below.



Radical Allylic Chlorination

Like bromination, chlorination at the allylic position of an alkene is achieved when low concentrations of Cl_2 are present. The reaction is run at high temperatures to achieve the desired results.

Industrial Uses

Allylic chlorination has important practical applications in industry. Since chlorine is inexpensive, allylic chlorinations of alkenes have been used in the industrial production of valuable products. For example, 3-chloropropene, which is necessary for the synthesis of products such as epoxy resin, is acquired through radical allylic chlorination (shown below).

$$CH_3CH{=}CH_2 + Cl_2 \xrightarrow{400^{\circ}C} ClCH_2CH{=}CH_2 + HCl$$

Problems (Answers are attached as a file)

1. Cyclooctene undergoes radical allylic bromination. Write out the complete mechanism including reactants, intermediates and products.
2. Predict the two products of the allylic chlorination reaction of 1-heptene.
3. What conditions are required for allylic halogenation to occur? Why does this reaction outcompete other possible reactions such as addition when these conditions are met?
4. Predict the product of the allylic bromination reaction of 2-benzylheptane. (Hint: How are benzylic hydrogens similar to allylic hydrogens?)
5. The reactant 5-isopropyl-1-hexene generates the products 3-bromo-5-isopropyl-1-hexene and 1-bromo-5-isopropyl-2-hexene. What reagents were used in this reaction?

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Outside Links

- http://en.wikipedia.org/wiki/N-Bromo...de#Preparation
- http://en.wikipedia.org/wiki/Wohl-Ziegler_reaction
- http://www.mhhe.com/physsci/chemistr...10allylic.html

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14.3: Nucleophilic Substitution of Allylic Halides: SN1 and SN2

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14.4: Allylic Organometallic Reagents: Useful Three-Carbon Nucleophiles

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14.5: Two Neighboring Double Bonds: Conjugated Dienes

Objectives

After completing this section, you should be able to

1. write a reaction sequence to show a convenient method for preparing a given conjugated diene from an alkene, allyl halide, alkyl dihalide or alcohol (diol).
2. identify the reagents needed to prepare a given diene from one of the starting materials listed in Objective 1, above.
3. compare the stabilities of conjugated and non-conjugated dienes, using evidence obtained from hydrogenation experiments.
4. discuss the bonding in a conjugated diene, such as 1,3-butadiene, in terms of the hybridization of the carbon atoms involved.
5. discuss the bonding in 1,3-butadiene in terms of the molecular orbital theory, and draw a molecular orbital for this and similar compounds.

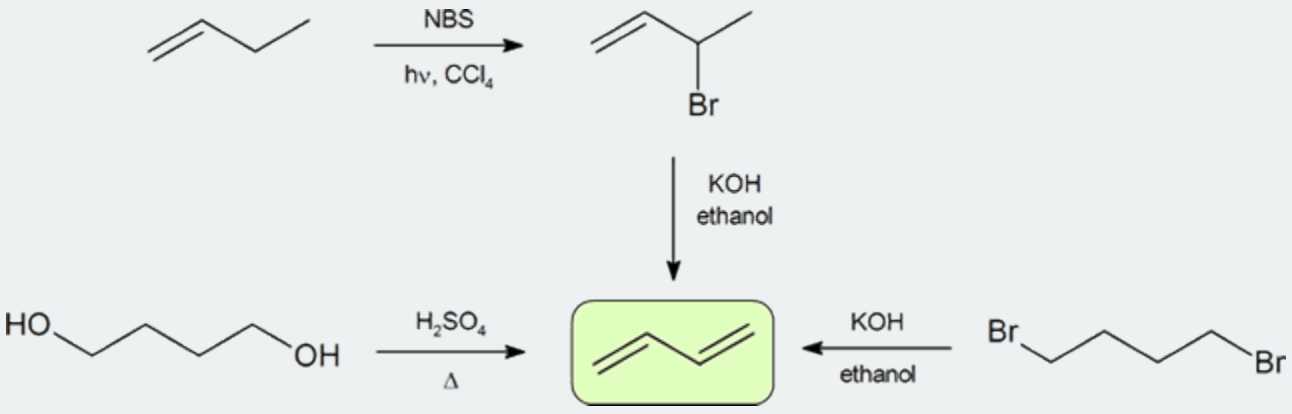
Key Terms

Make certain that you can define, and use in context, the key terms below.

- delocalized electrons
- node

Study Notes

The two most frequent ways to synthesize conjugated dienes are dehydration of alcohols and dehydrohalogenation of organohalides, which were introduced in the preparation of alkenes (Section 8.1). The following scheme illustrates some of the routes to preparing a conjugated diene.



The formation of synthetic polymers from dienes such as 1,3-butadiene and isoprene is discussed in Section 14.6. Synthetic polymers are large molecules made up of smaller repeating units. You are probably somewhat familiar with a number of these polymers; for example, polyethylene, polypropylene, polystyrene and poly(vinyl chloride).

As the hydrogenation of 1,3-butadiene releases less than the predicted amount of energy, the energy content of 1,3-butadiene must be lower than we might have expected. In other words, 1,3-butadiene is more stable than its formula suggests.

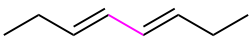
energy diagram for the hydrogenation of 1,3-butadiene

Figure 14.1: Energy diagram for the hydrogenation of 1,3-butadiene (not to scale).

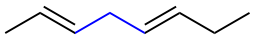
Some university-level general chemistry courses do not introduce the subject of molecular orbitals. If you have taken such a course, or forgotten what is meant by the term “molecular orbital,” combine a review of Section 1.11 with your study of this section.

Conjugated vs. Non-conjugated Dienes

Dienes are compounds which contain two double bonds. These dienes can be non-conjugated (the two double bonds are separated by at least one sp^3 hybridized atom. Conjugated dienes have the two double bonds separated by a single bond. Conjugated dienes have properties and reactivity which are distinctly different than non-conjugated dienes. Determining if double bonds are conjugated represents an important skill in organic chemistry.



3,5-Octadiene
(Conjugated)



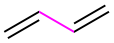
2,5-Octadiene
(Non-Conjugated)



1,3-Cyclohexadiene
(Conjugated)



1,4-Cyclohexadiene
(Non-Conjugated)



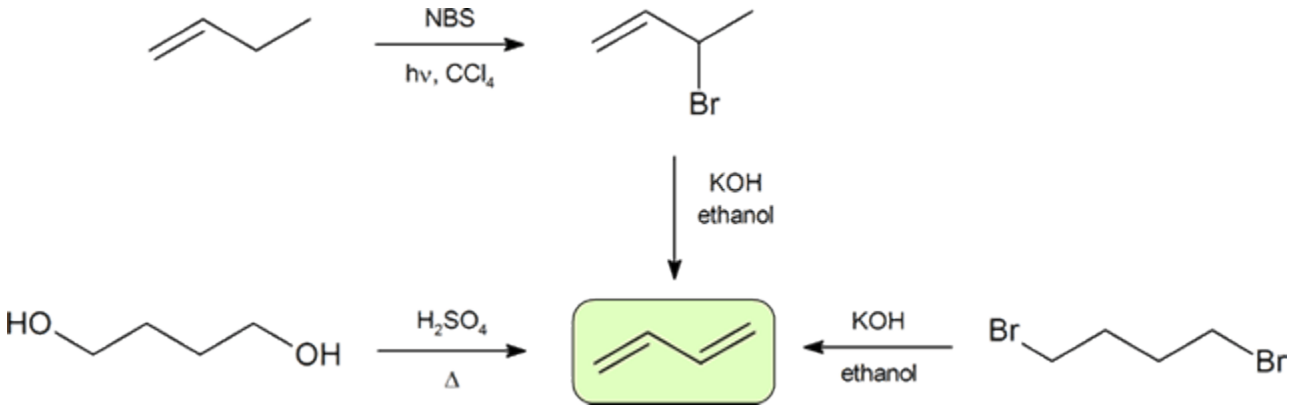
1,3-Butadiene
(Conjugated)



1,4-Pentadiene
(Non-Conjugated)

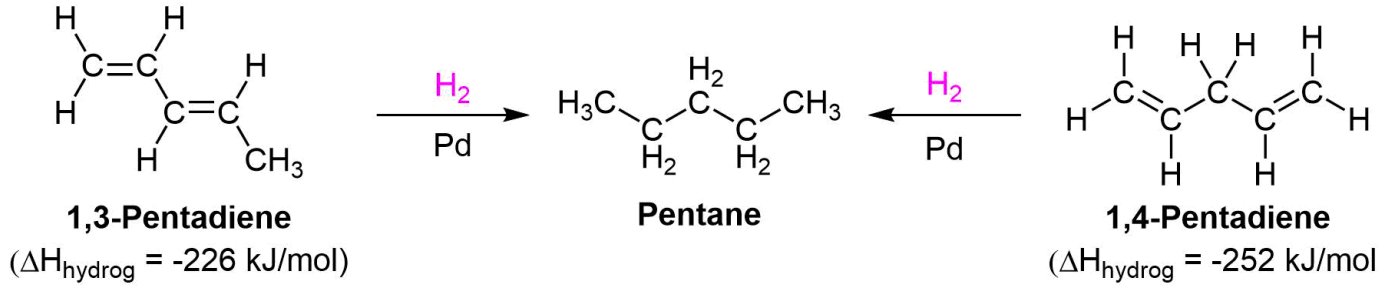
Synthesis of Dienes

Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed (**Sections 11-7, 11-8, 11-9, and 11-10**). A convenient method starts with the free radical halogenation of the allylic carbon of an alkene using NBS. The resulting halide can then be reacted with a strong base to result in E2 elimination and create a diene product. The compound, 1,3-butadiene, is the simplest conjugated diene and has an important use in the synthesis of polymers which will be discussed in **Section 14.6**. Many simple dienes, such as 1,3-butadiene and isoprene, can be prepared industrially by the double dehydration of alcohols and the double dehydrohalogenation of organohalides.



Stability of Conjugated Dienes

Conjugated dienes are known to be more stable than non-conjugated dienes as shown by their experimentally determined heats of hydrogenation. In **Section 7-6**, it was shown that as alkenes become more stable, they contain less energy, and therefore release less heat during hydrogenation. Experiments have shown that conjugated dienes have a lower heat of hydrogenation (-226 kJ/mol) than non-conjugated dienes (-251 kJ/mol). Using the differences in heats of hydrogenation the stabilization energy in conjugated dienes can be estimate to be roughly 25 kJ/mol.



1,3-Pentadiene (ΔH_{hydrog} = -226 kJ/mol)

Pentane

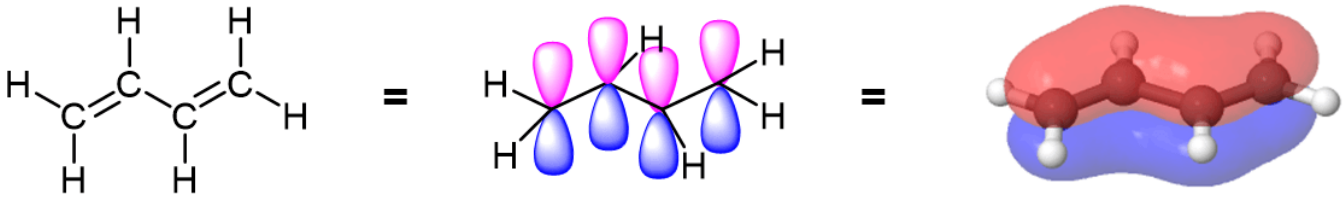
1,4-Pentadiene (ΔH_{hydrog} = -252 kJ/mol)

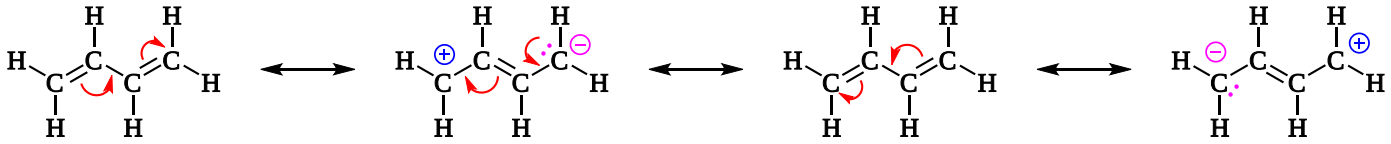
Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

energychart.bmp

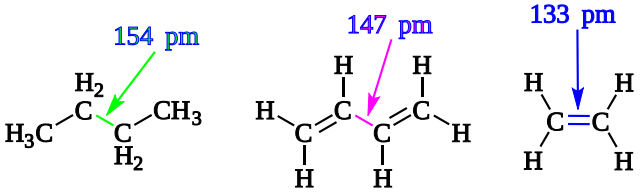
The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

Each alkene carbon in 1,3 dienes are sp^2 hybridized and therefore have one unhybridized *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated diene making them more stable than non-conjugated dienes.

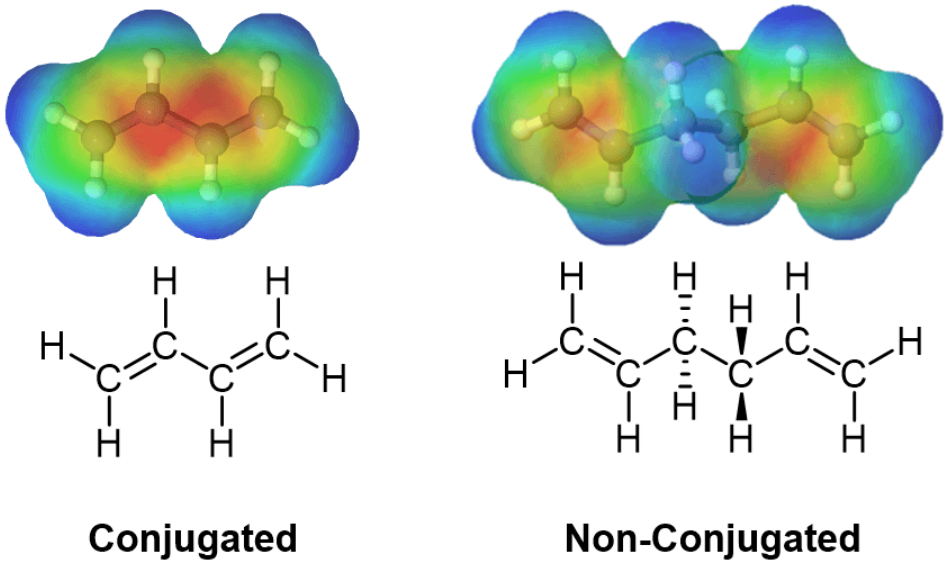




Evidence of conjugation in 1,3 dienes is seen in the single bond being stronger and shorter (147 pm) than an ordinary alkane C-C bond (154 pm). The resonance hybrid of a 1,3-butadiene shows this bond to contain significant double bond character with its bond length being roughly the average of a single and double bond.

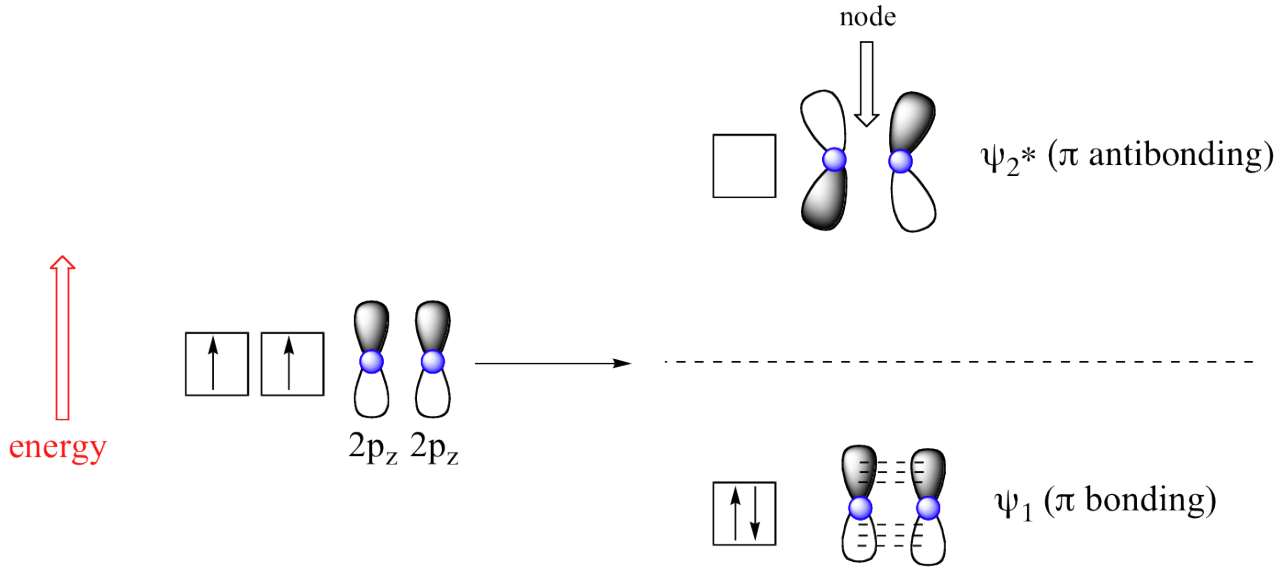


The delocalized electron density of a 1,3 diene can be seen when viewing an electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



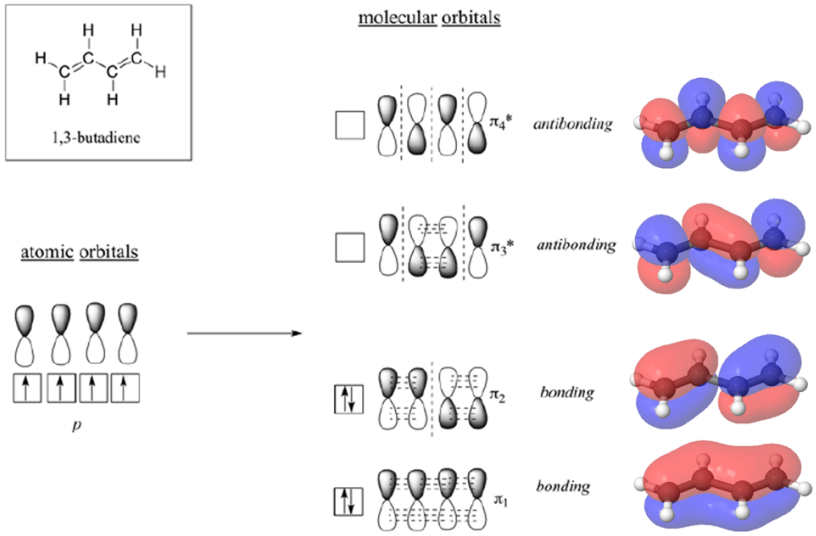
Molecular Orbitals of 1,3 Dienes

According to MO theory discussed in section 1-11, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.



With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two anti-bonding pi* orbitals. The combination of four pi molecular orbitals allow

for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



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14.6: Electrophilic Attack on Conjugated Dienes: Kinetic and Thermodynamic Control

Objectives

After completing this section, you should be able to

1. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
2. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
3. write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
4. explain the stability of allylic carbocations in terms of resonance.
5. draw the resonance contributors for a given allylic carbocation.
6. predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
7. predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
8. use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

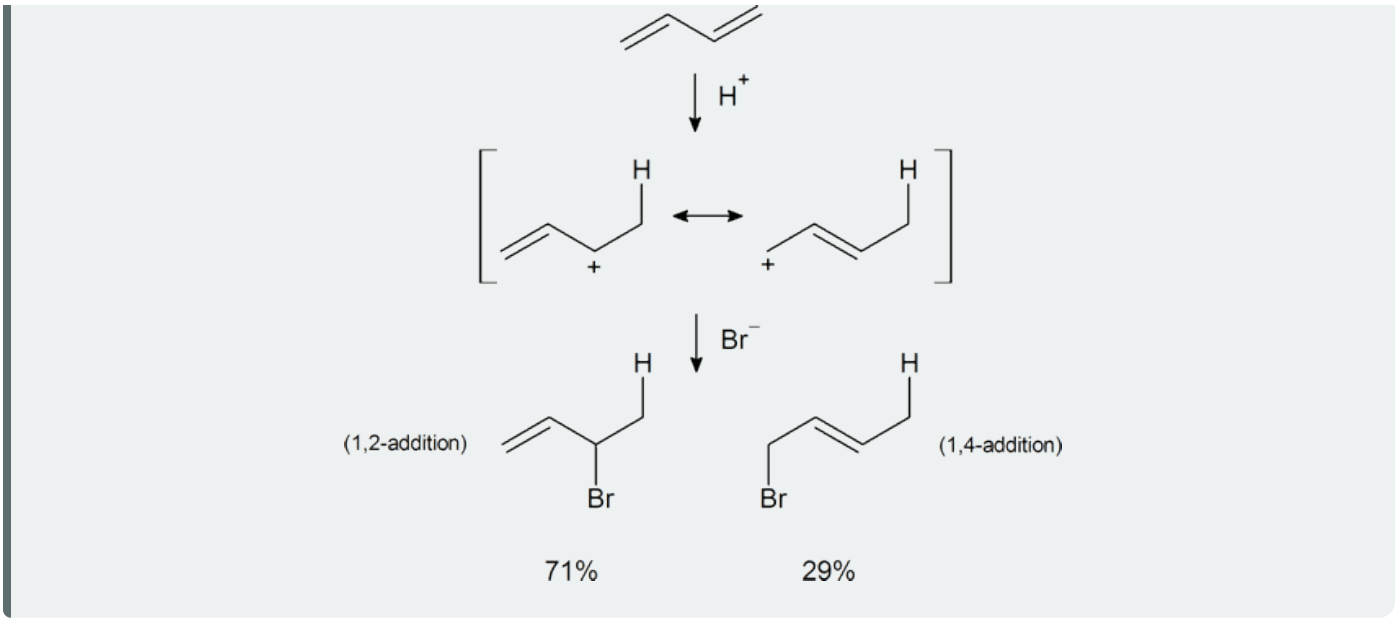
- 1,2-addition
- 1,4-addition

Study Notes

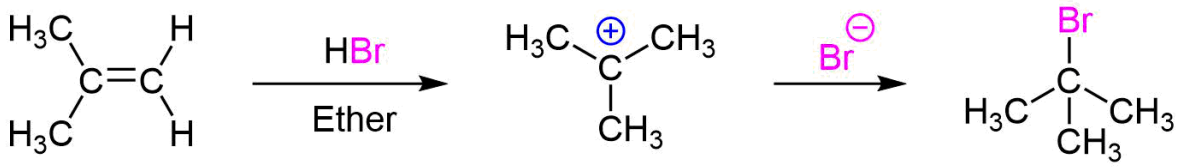
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.

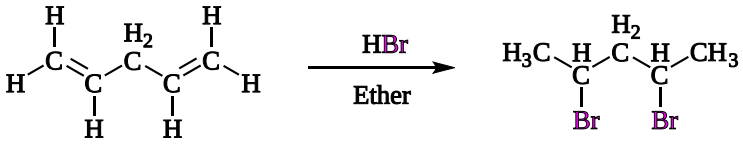


In **Section 7.9** we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents. Because the stability of carbocation intermediates increases as it number of alky groups increases (primary < secondary < tertiary), this regioselectivity is provided by preferably forming a more stable carbocation intermediate during the reaction. During the electrophilic addition of HBr to 2-methylpropene, the more stable tertiary carbocation intermediate is preferably formed which yields the Markovnikov addition product 2-bromo-2-methylpropane. Formation of 1-bromo-2-methylpropane does not occur because it would require the formation of a less stable primary carbocation intermediate.



2-Methylpropene | **Tertiary Carbocation** | **2-Bromo-2-Methylpropane (Markovnikov addition product)**

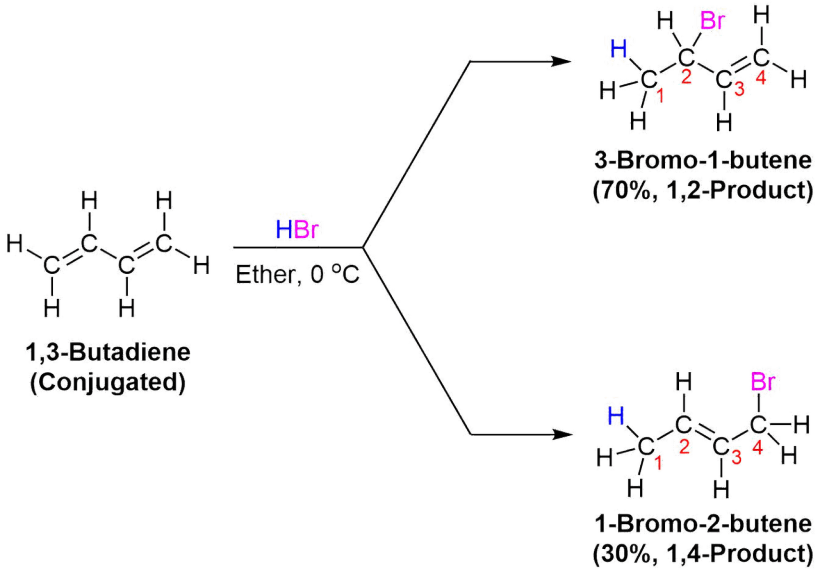
When an electrophilic addition is performed on a non-conjugated diene, the double bonds react in much the same manner as individual alkenes. During the addition of two equivalents of HBr to 1,4-pentadiene, a non-conjugated diene, Markovnikov's rule is still followed producing 2,4-dibromopentane as the product.



1,4-Pentadiene (Non-conjugated) | **2,4-Dibromopentane (Markovnikov addition product)**

Conjugated dienes undergo the usual reactions of alkenes, such as catalytic hydrogenation, radical additions, and electrophilic additions more readily than most alkenes or dienes that have isolated double bonds. During the electrophilic addition of one equivalent of HX to a conjugated diene, the expected Markovnikov addition product is formed during a process called **1,2-addition**. In addition, an unexpected product is formed from **1,4-addition**, i.e. the halogen bonds at the terminal carbon

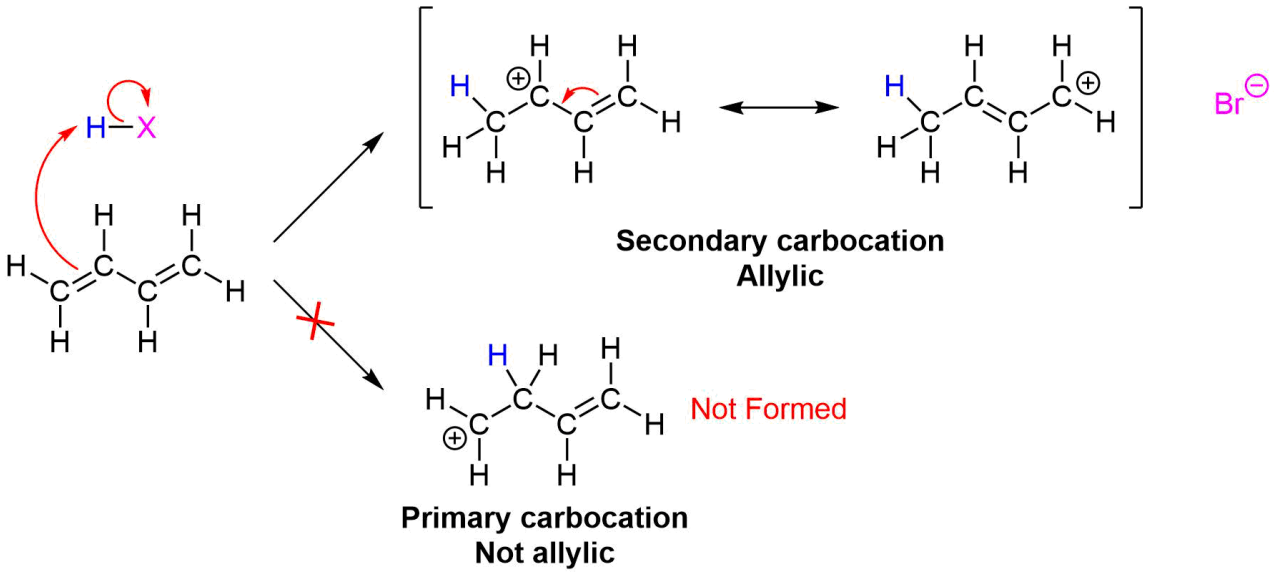
atoms of a conjugated diene and the remaining double bond shifts to the 2,3-location. Note, the numbers (1 and 4) refer to which of the four carbons making up the conjugated diene the H and Br are bonded to in the products and are not used for the compounds IUPAC nomenclature. Although there are various methods for effecting the relative ratio of 1,2 and 1,4 addition products during the electrophilic addition to a conjugated diene, a mixture of these products is almost always produced. When one equivalent HBr undergoes electrophilic addition to 1,3-butadiene, 1,2 addition provides the expected Markovnikov product 3-bromo-1-butene in a 70% yield. This process is called a 1,2 addition because the hydrogen from HBr (labeled blue) bonds to the first carbon of the diene and the bromine from HBr bonds to the second carbon of the diene. The compound 1-bromo-2-butene is also produced in a 30% yield during the reaction as product of 1,4 addition. Here the hydrogen of HBr bonds to the first carbon of the diene and the Br bonds to the fourth carbon of the diene.



The Mechanism for Electrophilic Addition of HBr to a Conjugated Diene

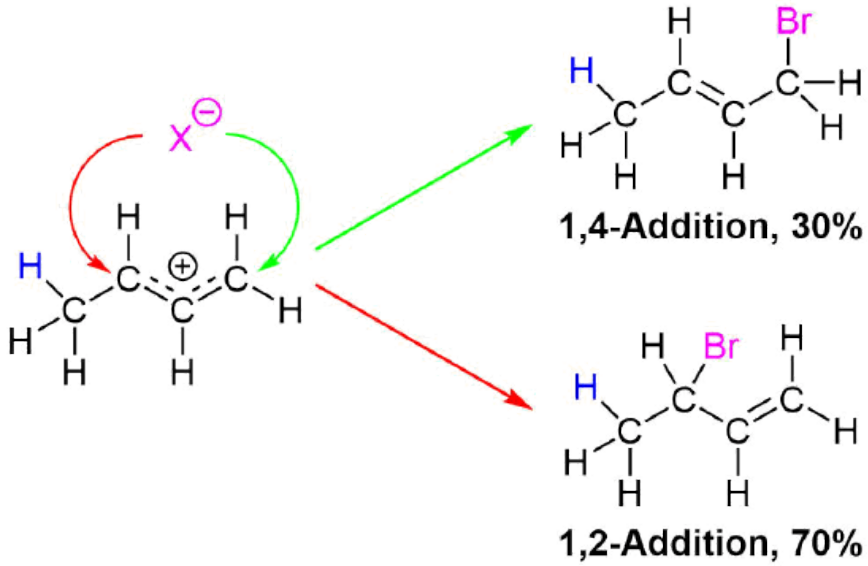
Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated diene, the more stable cation is not only secondary, but also *allylic*, and therefore enjoys the stabilization created from the positive charge being distributed over two carbons by resonance. The resonance hybrid of the allylic carbocation intermediate can be depicted by two resonance forms (shown below) both of which have a full positive charge.

Step 1)



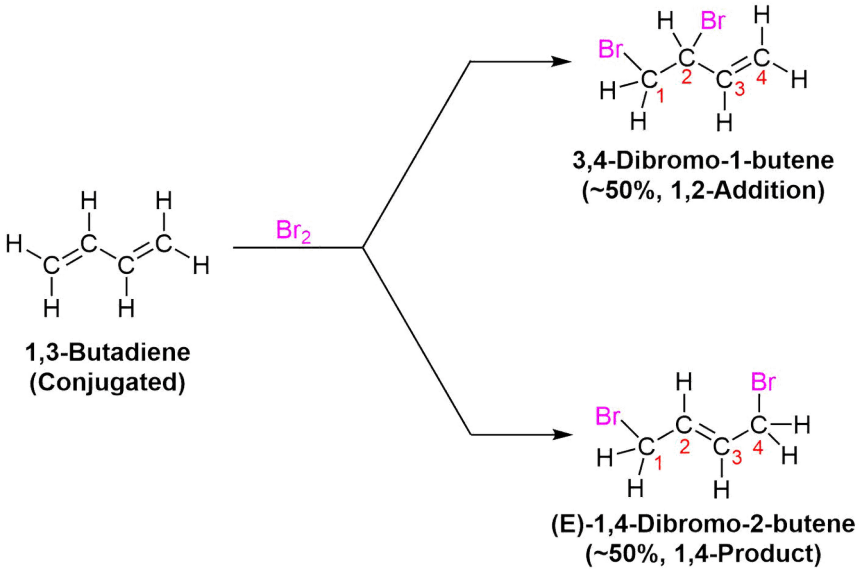
Step 2)

This allylic carbocation, more properly denoted as the resonance hybrid shown below, has two carbons which have significant positive charge. The halide ion can attack either carbon. Attacking the central carbon, adjacent to the site of protonation, leads to the the 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



Other Electrophilic Additions

Formation of both 1,2- and 1,4-addition products occurs not only with hydrogen halides, but also with other electrophiles such as the halogens (X_2). The electrophilic addition of bromine to 1,3-butadiene is an example. As shown below, a roughly 50:50 mixture of 3,4-dibromo-1-butene (the expected 1,2 addition product) and 1,4-dibromo-2-butene (the 1,4 addition product) is obtained. The double bond of the 1,4 addition product is primarily formed as the (E) isomer.



Worked Example 14.6.1

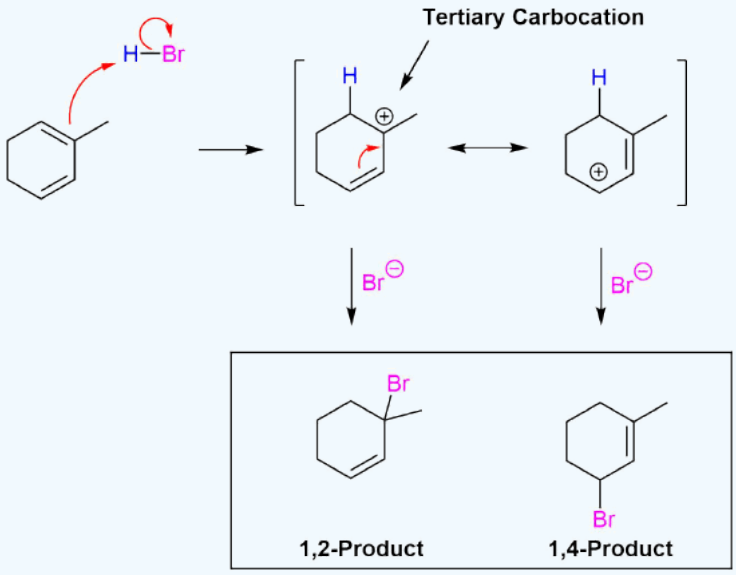
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



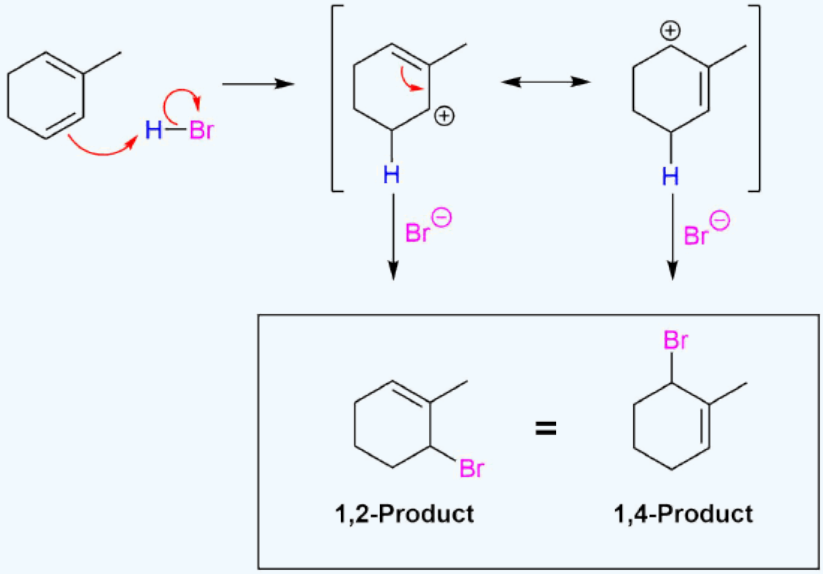
Solution

For this example the two double bonds in the diene are not equivalent and must be considered separately. Each double bond of the reactant has the possibility of forming a 1,2 and a 1,4 addition product so the reaction has the possibility of forming four product. Protonate each double bond separately and draw out the resonance forms of the allylic carbocation intermediate created. Then react each resonance form with Br- to create the two possible products. Repeat this process with the second double bond to create the four possible product. Lastly, look for symmetry in the products to see if any are same molecule. Also, consider the stability of each carbocation created during this process. The most stable carbocation will generally product the favored product of the reaction.

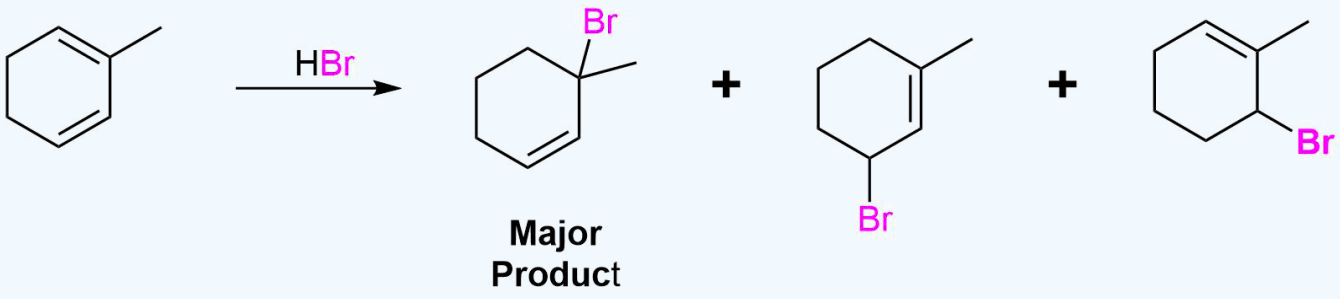
Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



Addition to the second double bond creates a symmetrical compound so only one product is formed.



Over the reaction proposed would be expected to form three products.



Exercise 14.6.1

1. Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.
2. Look at the previous addition reaction of HBr with a diene. Consider the transition states, predict which of them would be the major products and which will be the minor.
3. Write out the products of 1,2 addition and 1,4- addition of HBr to 1,3-cyclohexadiene.
4. What is unusual about the products of 1,2- and 1,4- addition of HX to an unsubstituted cyclic 1,3-diene?
5. Write out the products of 1,2 addition and 1,4- addition of Br2 to 1,3-cyclohexadiene.

Answer available at the end of this section.

Objectives

After completing this section, you should be able to

1. explain the difference between thermodynamic and kinetic control of a chemical reaction; for example, the reaction of a conjugated diene with one equivalent of hydrogen halide.
2. draw a reaction energy diagram for a reaction which can result in both a thermodynamically controlled product and a kinetically controlled product.
3. explain how reaction conditions can determine the product ratio in a reaction in which there is competition between thermodynamic and kinetic control.

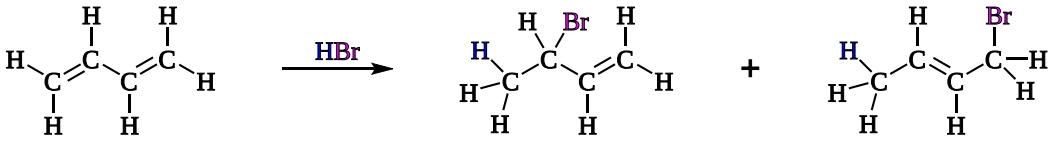
Key Terms

Make certain that you can define, and use in context, the key terms below.

- kinetic control
- thermodynamic control

Like non-conjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated dienes experience relatively greater kinetic reactivity when reacted with electrophiles than non-conjugated dienes do. The reaction mechanism is similar to other electrophilic addition reactions to alkenes (Section 7.9). During the electrophilic addition of HBr to a 1,3-butadiene, However, there are two possible outcomes once the carbocation intermediate is formed. The allyl carbocation is stabilized by resonance structures that vary in the position of the carbocation. This allows the bromide ion to add to either of these carbons resulting in the formation 1,2 and 1,4 addition products. When this reaction is run at a temperature of 0 ^{o}C or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 ^{o}C the 1,4 addition product dominates.

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different product ratios under different reaction conditions and is a classic example of the concept of **thermodynamic** versus **kinetic** control of a reaction.



1,3-Butadiene **1,2-Addition Product** **1,4-Addition Product**

At -80 °C:	80%	20%	**Kinetic Control**
At 0 °C:	70%	30%	**Kinetic Control**
At 40 °C:	15%	85%	**Thermodynamic Control**
At 60 °C:	10%	90%	**Thermodynamic Control**

At lower temperatures the formation of the 1,2 and 1,4 addition products are irreversible and thus do not reach equilibrium. When a reaction is irreversible the major product is determined by the relative reaction rates and not by thermodynamic stability. Of the two products, the formation of the 1,2 addition product has a higher rate of reaction and forms faster making it the major product. The reaction product which forms with a higher rate of reaction is called the **Kinetic Product** and when the kinetic product dominates, the reaction is said to be under **Kinetic Control**.

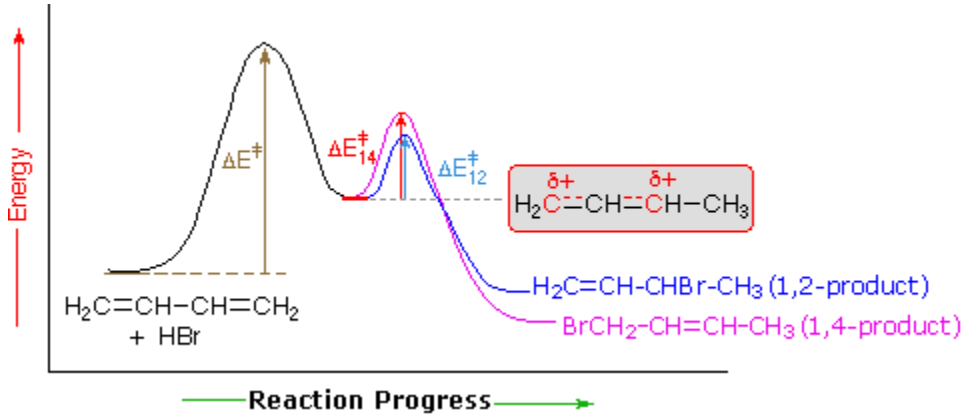
At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. The more stable product is called the **Thermodynamic Product** and when the thermodynamic product dominates, the reaction is said to be under **Thermodynamic Control**.

The 1,4 addition product is more stable because it has an internal, disubstituted double bond, and we know that as a general rule that the thermodynamic stability of an alkene increases with increasing substitution. So, when compared to the terminal, monosubstituted alkene of the 1,2 addition product, the 1,4 addition product is expected to be more stable.

> A simple definition is that the *kinetic product* is the product that is formed *faster*, and the *thermodynamic product* is the product that is more *stable*. This is precisely what is happening here. The kinetic product is 3-bromobut-1-ene, and the thermodynamic product is 1-bromobut-2-ene (specifically, the *trans* isomer).

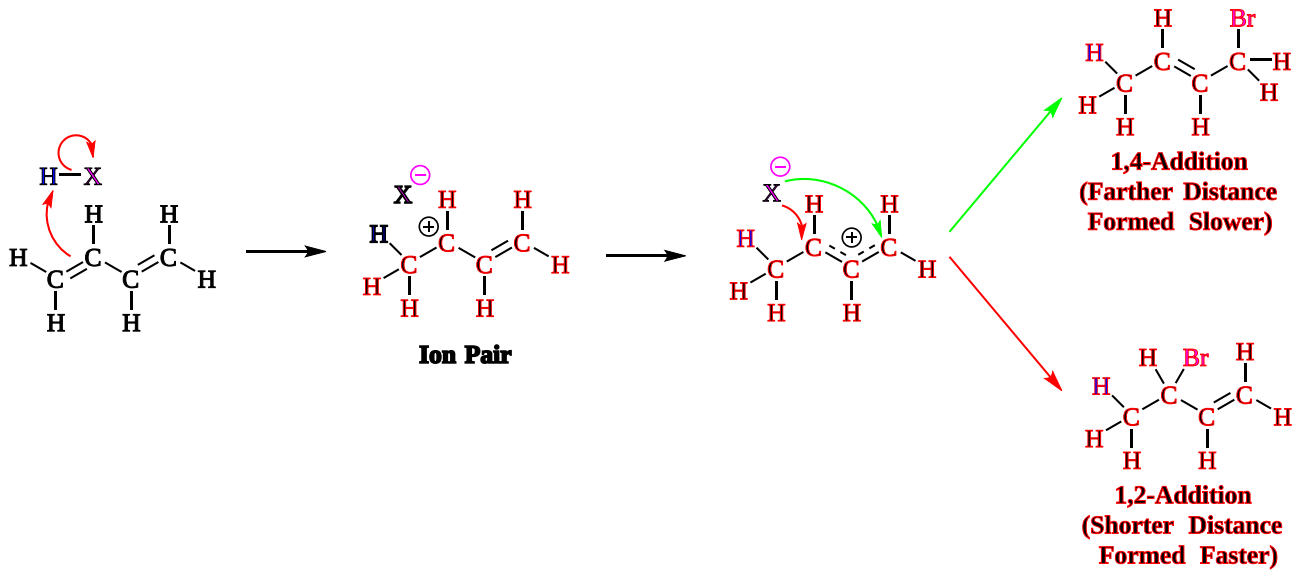
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition).

At elevated temperatures, the products are more likely to have enough energy to overcome the reverse activation barrier for the second step allowing regeneration of the carbocation intermediate. Under these conditions, this step of the mechanism will be reversible and an equilibrium will be established. Since the system is no longer limited by temperature, the system will minimize its Gibbs free energy, which is the thermodynamic criterion for chemical equilibrium. This places the reaction under *thermodynamic control* and the most thermodynamically stable molecule, the 1,4 addition product, will be predominantly formed.



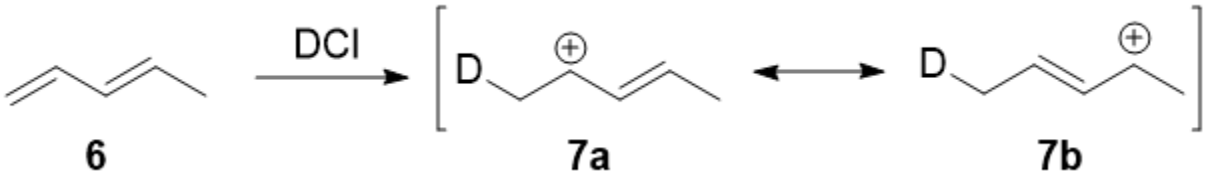
If the reaction temperature is kept sufficiently *low*, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which forms faster, the kinetic product, will predominate.

Of the two reaction pathways, the 1,2-addition has a smaller activation energy and would be expected to have a higher reaction rate than the 1,4-addition. The high reaction rate for 1,2-addition can be attributed to the formation of an ion pair during the reaction mechanism. This means that, after a double bond is protonated, the halide counterion remains in close proximity to the carbocation generated. Immediately following dissociation of HX, the chloride ion is going to be much closer to C–2 than it is to C–4, and therefore attack at C–2 is much faster. This ion pair mechanism is a pre-exponential constant effects that is attributed to the proximity and frequency of collision rather than a activation barrier effect.

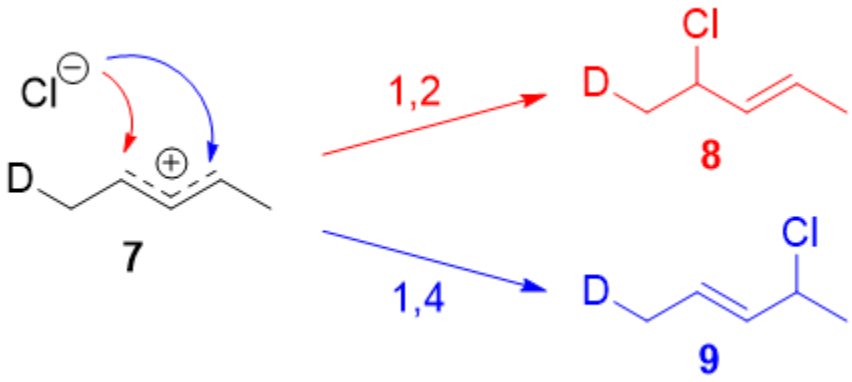


Experimental Evidence for the Ion-Pair Mechanism

In 1979, Nordlander *et al.* carried out a similar investigation on the addition of DCl (deuterated hydrochloric acid) to a different substrate, 1,3-pentadiene. This experiment was ingenious, because it was designed to proceed via an almost symmetrical intermediate:



Resonance forms **7a** and **7b** are both allylic and secondary. There is a very minor difference in their stabilities arising from the different hyperconjugative ability of C-D *vs* C-H bonds, but in any case, it is not very large. Therefore, if we adopt the explanation in the previous section, one would expect there not to be any major *kinetic* pathway, and both 1,2- and 1,4-addition products (**8** and **9**) would theoretically be formed roughly equally.



Instead, it was found that the 1,2-addition product was favored over the 1,4-addition product. For example, at -78°C in the absence of solvent, there was a roughly (75:25) ratio of 1,2- to 1,4-addition products. Clearly, there is a factor that favors 1,2-addition that does not depend on the electrophilicity of the carbon being attacked! The authors attributed this effect to an *ion pair* mechanism.

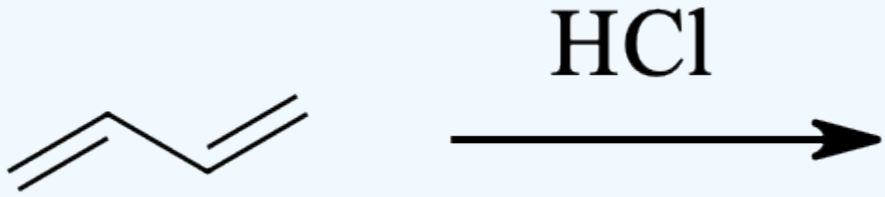
This means that, after the double bond is protonated (deuterated in this case), the chloride counterion remains in close proximity to the carbocation generated. Immediately following dissociation of DCl, the chloride ion is going to be much closer to *C-2* than it is to *C-4*, and therefore attack at *C-2* is much faster. In fact, normal electrophilic addition of HX to conjugated alkenes in polar solvents can also proceed via similar ion pair mechanisms. This is reflected by the greater proportion of *syn* addition products to such substrates.

Exercise 14.6.1

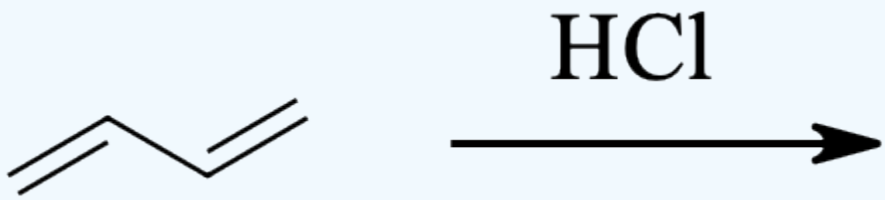
1) Why is the 1,4-addition product the thermodynamically more stable product?

2) Addition of 1 equivalent of bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. What is the structure of that isomer?

3) The kinetically controlled product in the below reaction is:



4) For the reaction above, which product is the result of 1,4-addition?



5) What would be the major product of the addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene under thermodynamic conditions?

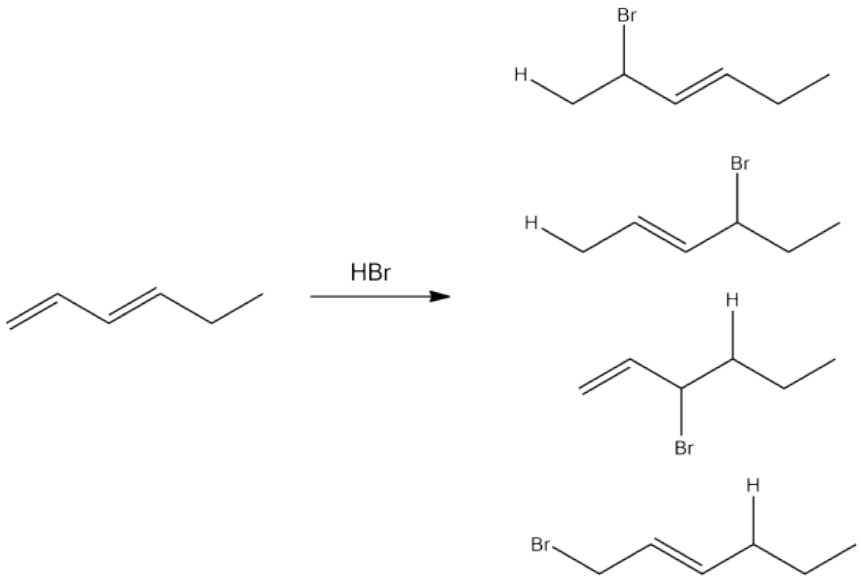
6) Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction. Also, Predict why the 1,4 adduct is the major product in this reaction compared to the 1,2.

Answer available at the end of this section.

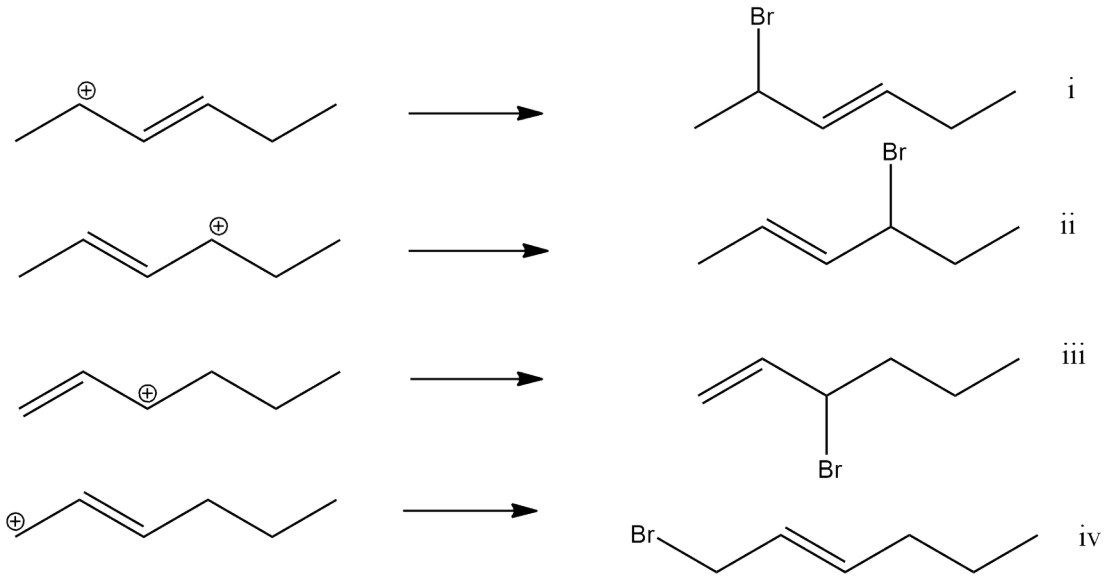
Answers

Exercise 14.6.1

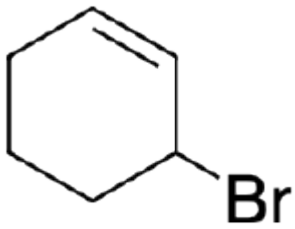
1)



2) The products i-iii all show a secondary cation intermediate which is more stable than primary. Therefore those would be major products and the iv product would be the minor product.

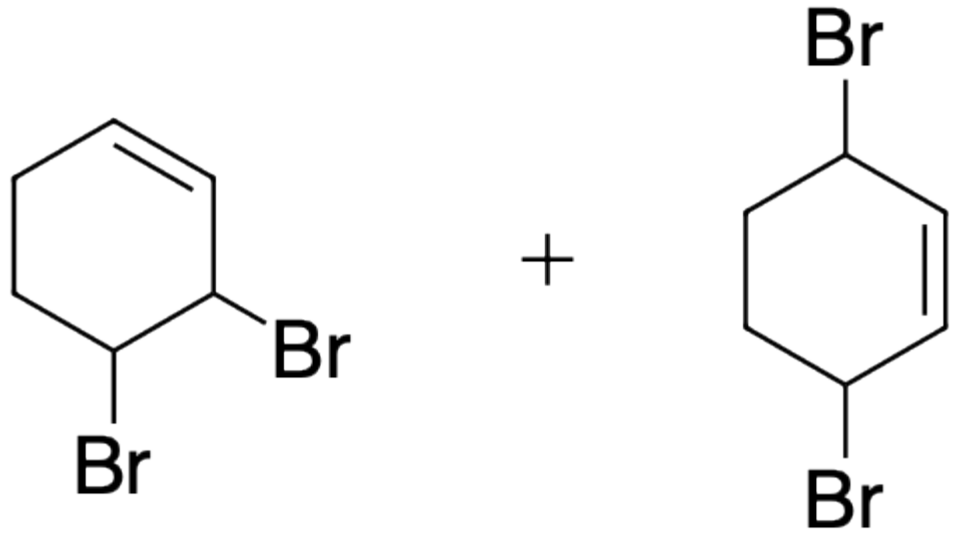


3) The same product will result from 1,2 and 1,4 addition.



4) Addition of the HX to unsubstituted cycloalka-1,3-dienes in either 1,2- or 1,4- manner gives the same product because of symmetry.

5) Both 1,2 and 1,4 products will form.



Exercise 14.6.1

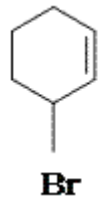
1) The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond and more substituted alkenes are more stable.

2) 2,5-Dibromo-3-hexene

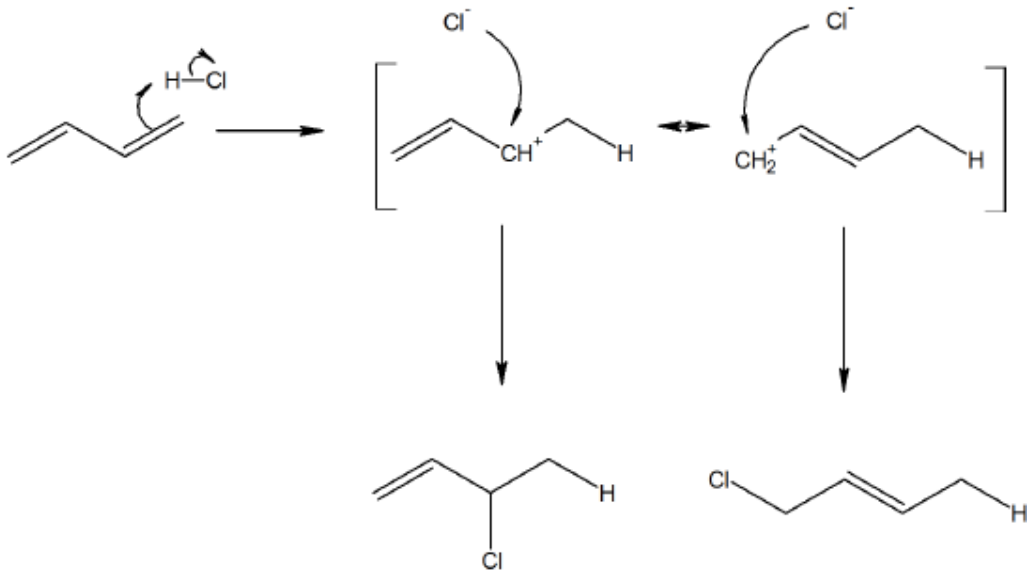
3) 3-Chloro-1-butene

4) 1-Chloro-2-butene

5)



6)



Even though the cation would prefer to be in a secondary position in the transition state, the final product is less stable with a terminal alkene. Therefore the major product will be the 1,4 adduct.

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14.7: Delocalization among More than Two Pi Bonds: Extended Conjugation and Benzene

Among the many distinctive features of benzene, its aromaticity is the major contributor to why it is so unreactive. This section will try to clarify the theory of aromaticity and why aromaticity gives unique qualities that make these conjugated alkenes inert to compounds such as Br_2 and even hydrochloric acid. It will also go into detail about the unusually large resonance energy due to the six conjugated carbons of benzene.

dd.bmp

The delocalization of the p-orbital carbons on the sp^2 hybridized carbons is what gives the aromatic qualities of benzene.



This diagram shows one of the molecular orbitals containing two of the delocalized electrons, which may be found anywhere within the two "doughnuts". The other molecular orbitals are almost never drawn.

- Benzene, C_6H_6, is a planar molecule containing a ring of six carbon atoms, each with a hydrogen atom attached.

  The six carbon atoms form a perfectly regular hexagon. All of the carbon-carbon bonds have exactly the same lengths - somewhere between single and double bonds.

- There are delocalized electrons above and below the plane of the ring.
- The presence of the delocalized electrons makes benzene particularly stable.
- Benzene resists addition reactions because those reactions would involve breaking the delocalization and losing that stability.
- Benzene is represented by this symbol, where the circle represents the delocalized electrons, and each corner of the hexagon has a carbon atom with a hydrogen attached.

Basic Structure of Benzene

Benzene Structure (1).bmp

Because of the aromaticity of benzene, the resulting molecule is planar in shape with each C-C bond being 1.39 Å in length and each bond angle being 120°. You might ask yourselves how it's possible to have all of the bonds to be the same length if the ring is conjugated with both single (1.47 Å) and double (1.34 Å), but it is important to note that there are no distinct single or double bonds within the benzene. Rather, the delocalization of the ring makes each count as one and a half bonds between the carbons which makes sense because experimentally we find that the actual bond length is somewhere in between a single and double bond. Finally, there are a total of six p-orbital electrons that form the stabilizing electron clouds above and below the aromatic ring.

Contributors

Jim Clark (Chemguide.co.uk)

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14.8: A Special Transformation of Conjugated Dienes: Diels-Alder Cycloaddition

Objectives

After completing this section, you should be able to

1. write an equation to represent a typical Diels-Alder reaction.
2. draw the structure of the product formed when a given conjugated diene reacts with a given dienophile in a Diels-Alder reaction.
3. identify the diene and dienophile that must be used to prepare a given compound by a Diels-Alder reaction.
4. explain the general mechanism of the Diels-Alder reaction, without necessarily being able to describe it in detail.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Diels-Alder cycloaddition
- pericyclic reaction

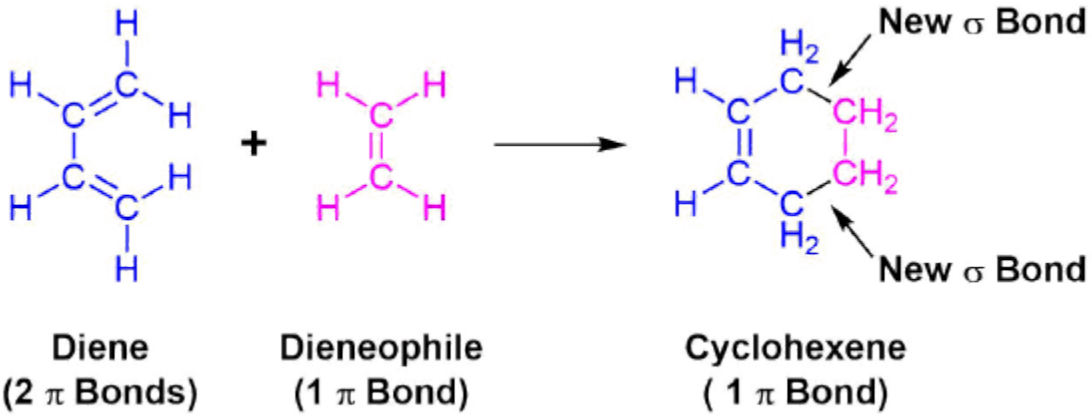
Study Notes

The Diels-Alder reaction is an example of an organic chemical reaction which does not proceed by either a polar or a free radical pathway, but rather a pericyclic reaction.

Although we do not expect you to be able to provide a detailed account of the mechanism of this reaction, you should learn enough about the Diels-Alder reaction to fulfillthe objectives stated above. You will find it useful to contrast the mechanism of the Diels-Alder reaction with the polar and radical mechanisms studied earlier.

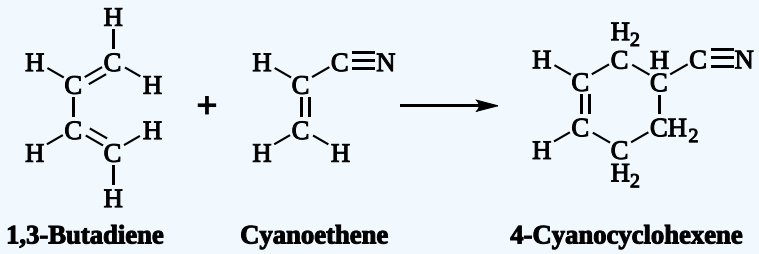
The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. The Diels-Alder reaction is an important and widely used synthetic method for making six-membered rings. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. During the reaction, two pi-bonds are converted to two sigma-bonds. The Diels-Alder cycloaddition is classified as a pericyclic process. Pericyclic reactions involve the redistribution of bonding electrons in a single step mechanism and will be discussed in greater detail in **Chapter 30**. In particular, the Diels-alder reaction is called a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

General Reaction



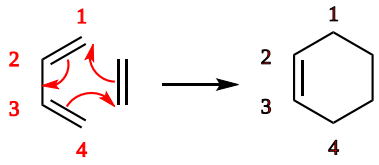
An example of the Diels-Alder reaction is the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) to form 4-cyanocyclohexene.

Example 14.8.1

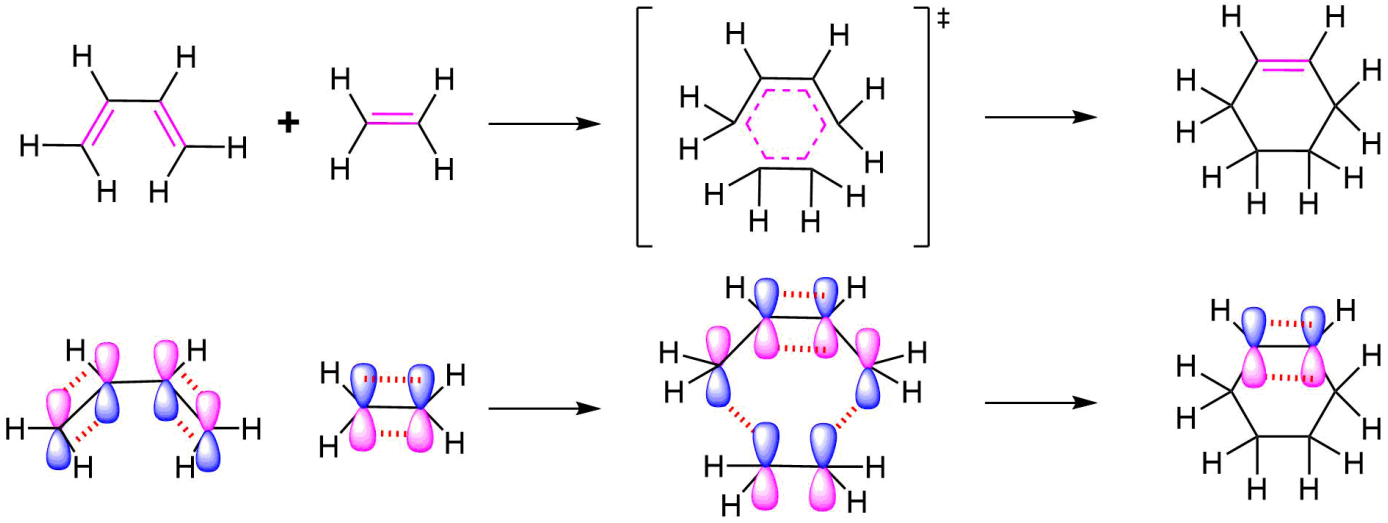


Mechanism

All of the electron rearrangements of the Diels-Alder reaction take place once in a single mechanistic step. During this step carbons 1 and 4 of the diene and both alkene carbons of the dienophile, rehybridize from sp^2 to sp^3 and electrons rearrange to create two new sigma bonds in the cyclic product. Carbons 2 and 3 of the diene remain sp^2 hybridized and form a new pi bond in the product.



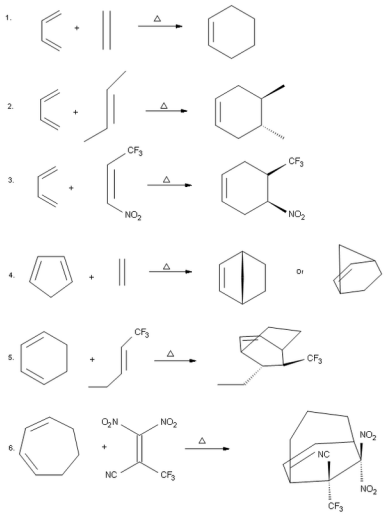
The mechanism occurs through a cyclic transition state in which there is head-on overlap of two p orbitals on carbons 1 and 4 of the diene with the two p orbitals from the alkene of the dienophile to form two new sigma bonds in the cyclohexene product. The remaining two p orbitals from the diene overlap to form the new pi bond.



Problems

Practice_Problems.bmp

Answers



Objectives

After completing this section, you should be able to

1. determine whether or not a given compound would behave as a reactive dienophile in a Diels-Alder reaction.
2. predict the stereochemistry of the product obtained from the reaction of a given diene with a given dienophile.
3. recognize that in order to undergo a Diels-Alder reaction, a diene must be able to assume ans-cis geometry, and determine whether or not a given diene can assume this geometry.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- dienophile
- dimerization

Study Notes

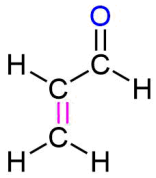
Make sure that you understand that the s-cis and s-trans forms of a diene such as 1,3-butadiene are conformers, not isomers. Note that some textbooks can confuse the issue further by referring to a compound such as (2Z, 4Z)-hexadiene as cis, cis-2,4-hexadiene, and saying that the most stable form of this compound is its s-trans conformer!

In fulfilling Objective 2, above, you must recognize that the Diels-Alder reaction is stereospecific.

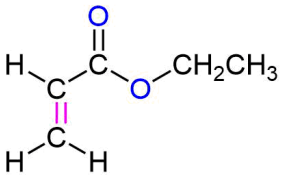
Finally, note reaction **B** in the reading shows 1,3-cyclopentadiene reacting with another molecule of 1,3-cyclopentadiene. When the same compound acts as both diene and dienophile in a Diels-Alder reaction to couple it is a dimerization.

The Dienophile

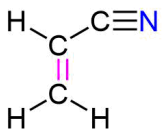
In general, Diels-Alder reactions proceed fastest with electron-withdrawing groups on the dienophile (diene lover). Ethylene reacts slowly while **propenal, ethyl propenoate, and other molecules shown below** are highly reactive in a Diels-Alder reaction.



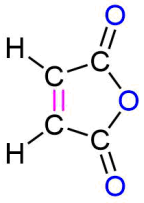
Prepenal (Acrolein)



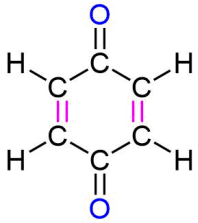
Ethyl propenoate (Ethyl acrylate)



Propenenitrile (Acrylonitrile)

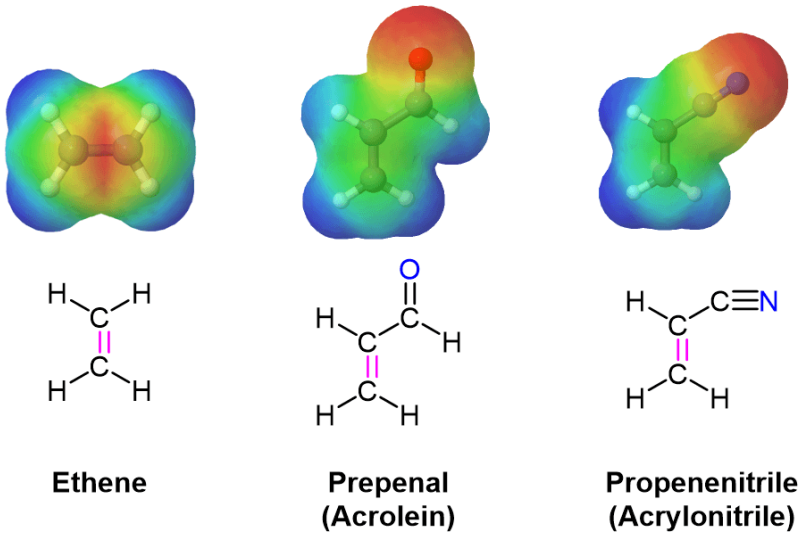


Maleic anhydride



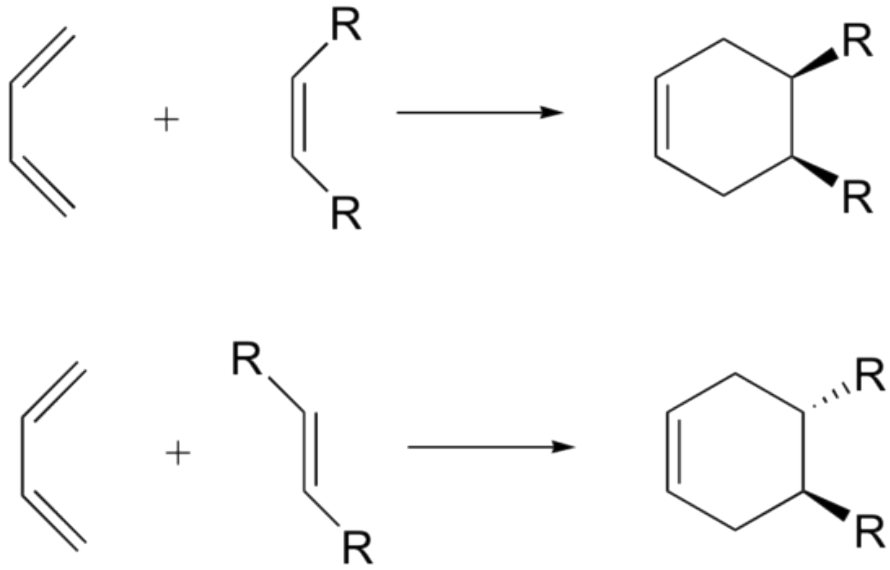
Benzoquinone

In much the same manner as electron-withdrawing substituents on a benzene ring, these are typically a double or triple bond in conjugation with the double bond in the dienophile. A resonance form can be drawn which places a positive charge in the dienophile double bond. This results in the double bond being less electron rich (greater electron density shown in Red/Orange) than ethylene. Electrostatic potential maps show that the electron-withdrawing groups pull electron density away from the double bond.

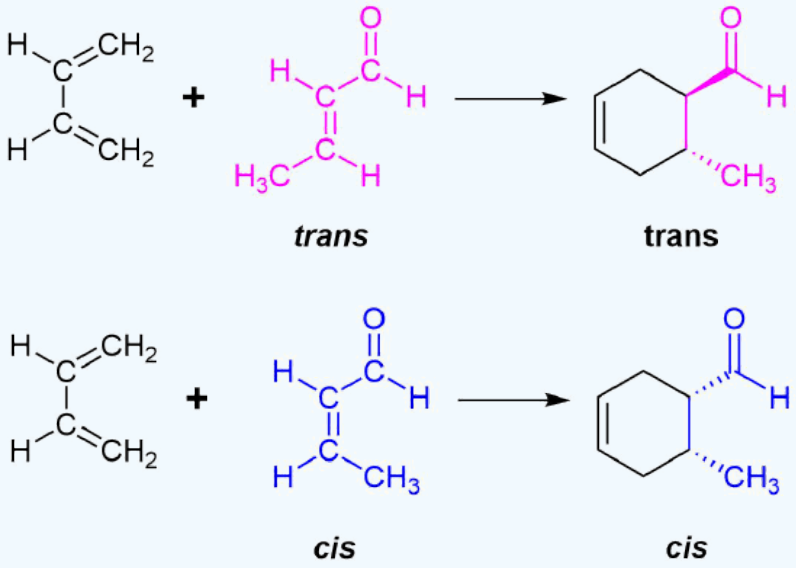


Stereochemistry of Diels-Alder (dienophile)

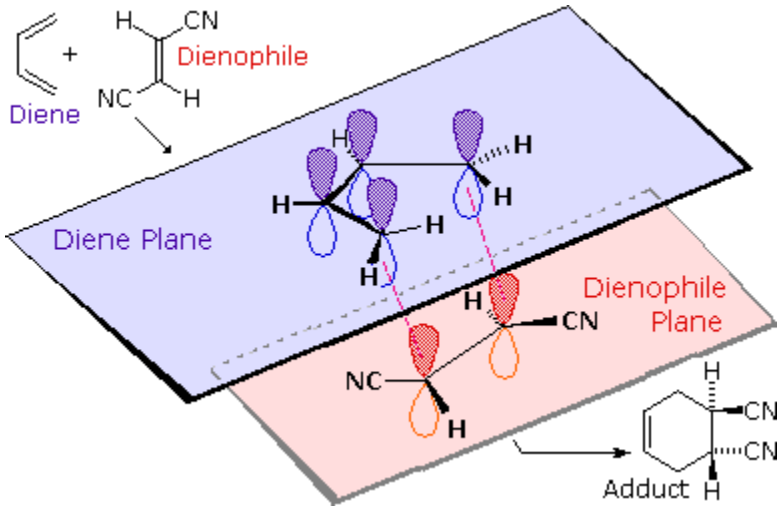
The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases multiple new stereocenters are formed, and the reaction is inherently stereospecific. During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



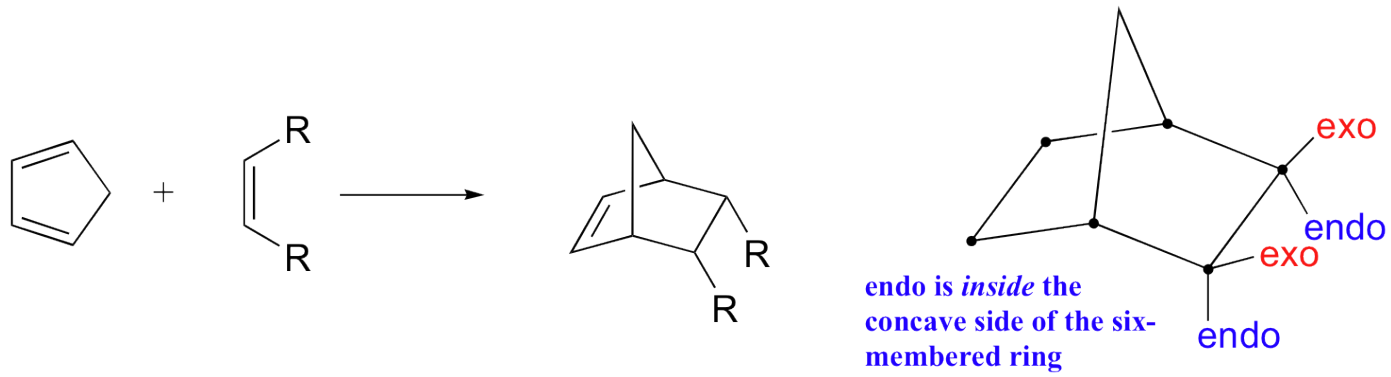
Example 14.8.1



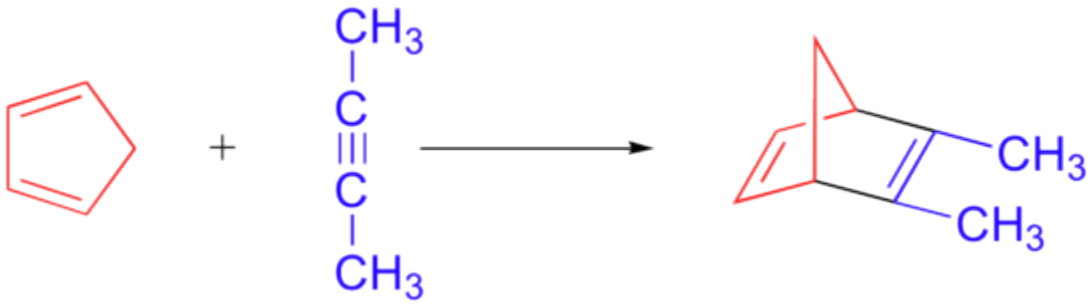
The retention of stereochemistry is due to the planar nature of both reactants and that the forming process is **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the concerted nature of the Diels-Alder mechanism. The drawing below illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct.



Another facet of the stereochemical retention of the dienophile is that only the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes. The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position. Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**. Preference of the endo position is also a facet of the suprafacial nature of the Diels-Alder reaction. The orbital overlap required for the reaction is greater when the dienophile lies directly underneath the diene.

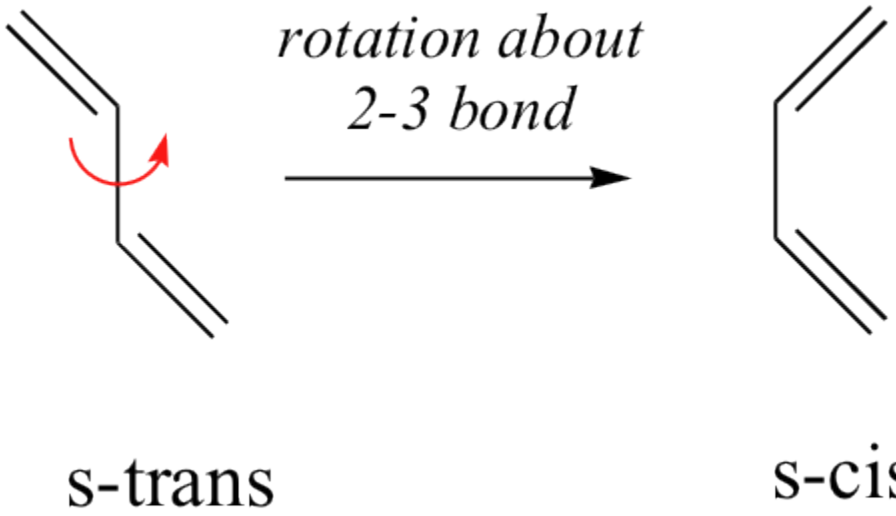


Alkynes can also serve as dienophiles in Diels-Alder reactions:

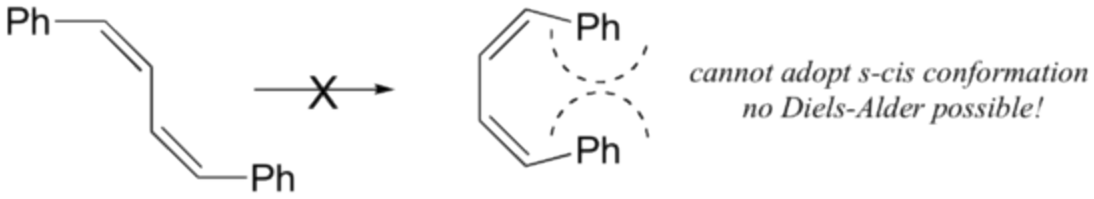


The Diene

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups). The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cis conformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions.



For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.

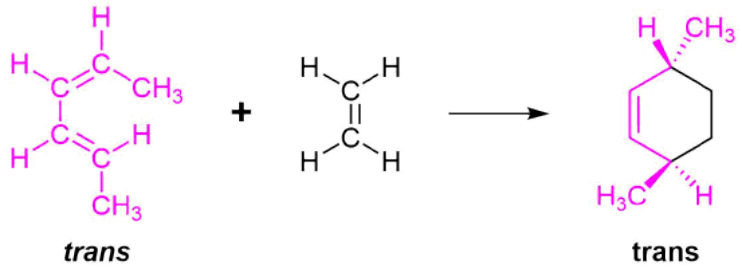


Cyclic dienes, on the other hand, are 'locked' in the s-cis conformation, and are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

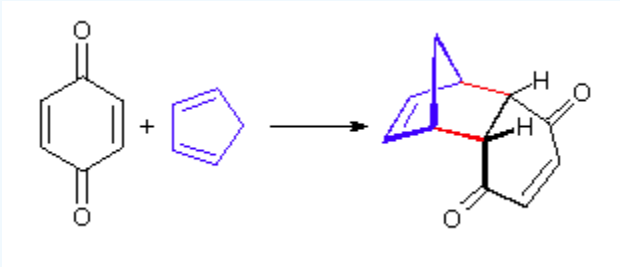


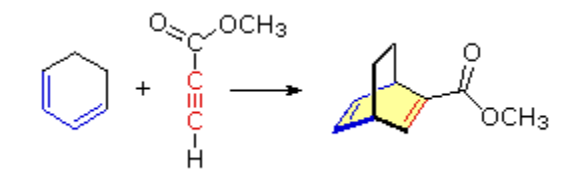
Stereochemistry of Diels-Alder (diene)

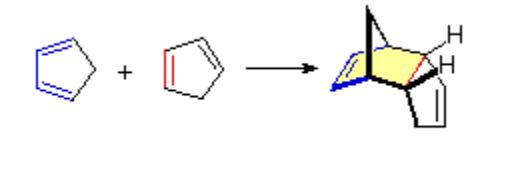
The 1 and 4 Carbons in the diene have the possibility of forming two new stereocenters in the cyclohexene product. Similarly to the effects of dienophile stereochemistry, the positioning of substituents on the 1 and 4 carbons in the diene determine the stereochemistry in the product. The diene substituents can be thought of as being either cis (both facing in or both facing out) or trans and the stereochemistry is retained to form a cis or trans cyclohexene product.

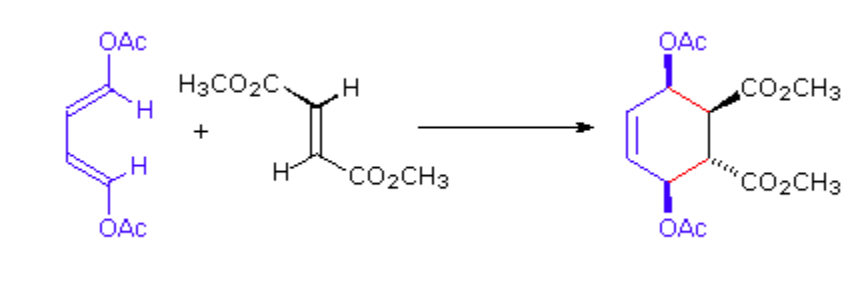


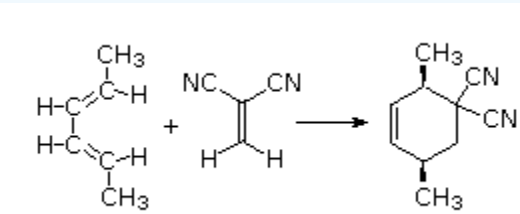
Examples 14.8.1

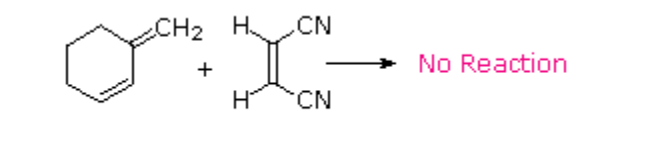










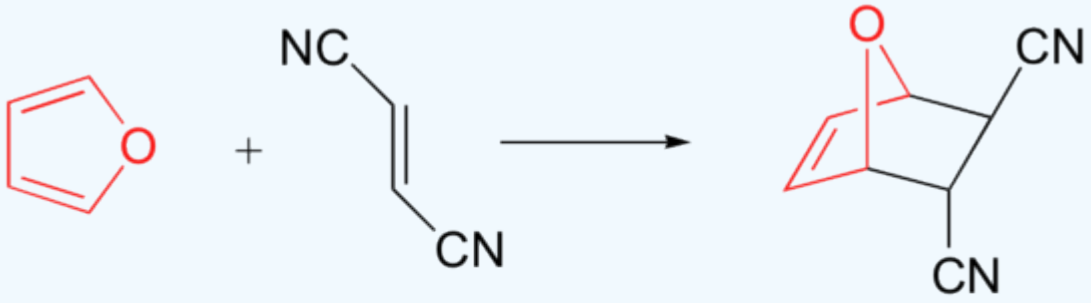


The Essential Characteristics of the Diels-Alder Cycloaddition Reaction:

i. The reaction always creates a new six-membered ring.

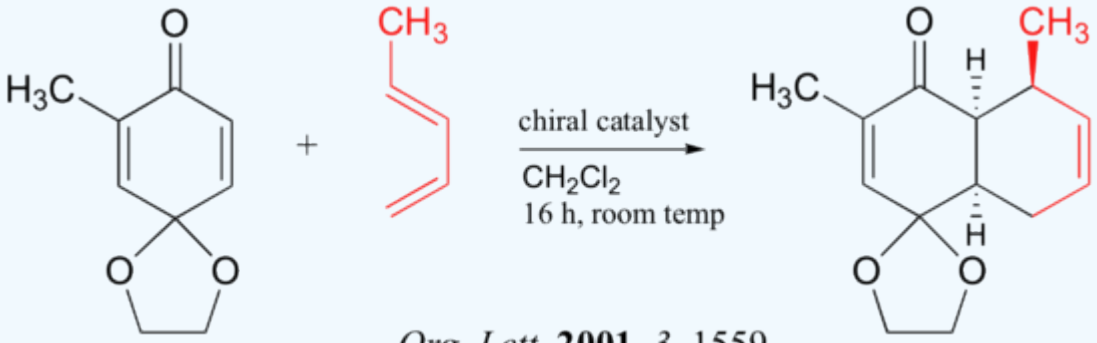
ii. The diene component must be able to assume an s-cis conformation.
iii. Electron withdrawing groups on the dienophile facilitate reaction.
iv. Electron donating groups on the diene facilitate reaction.
v. Steric hindrance at the bonding sites may inhibit or prevent reaction.
vi. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

Examples 14.8.2



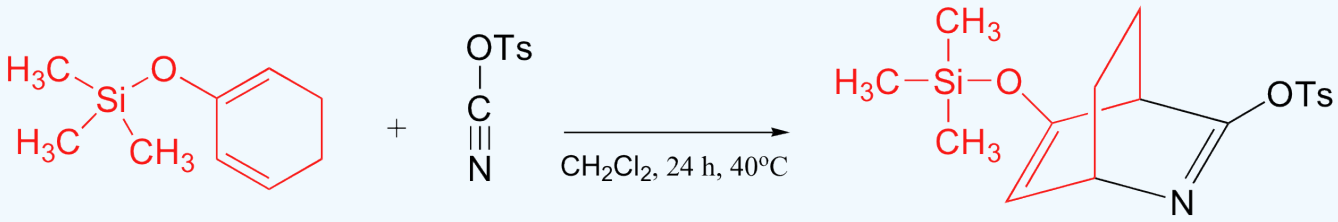
J. Med. Chem. **2008,** *51*, 424

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Org. Lett. **2001,** *3*, 1559

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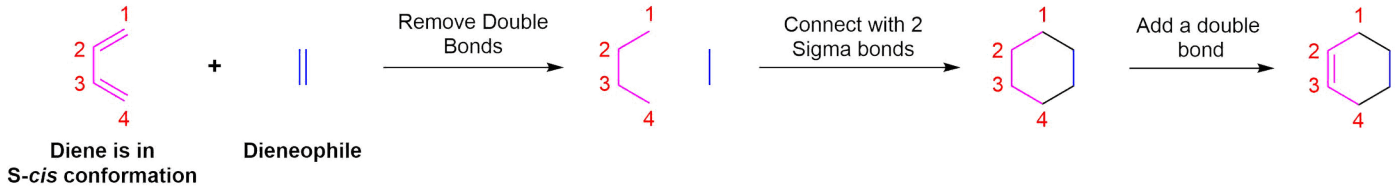


J. Org. Chem. **2003,** *68*, 8256

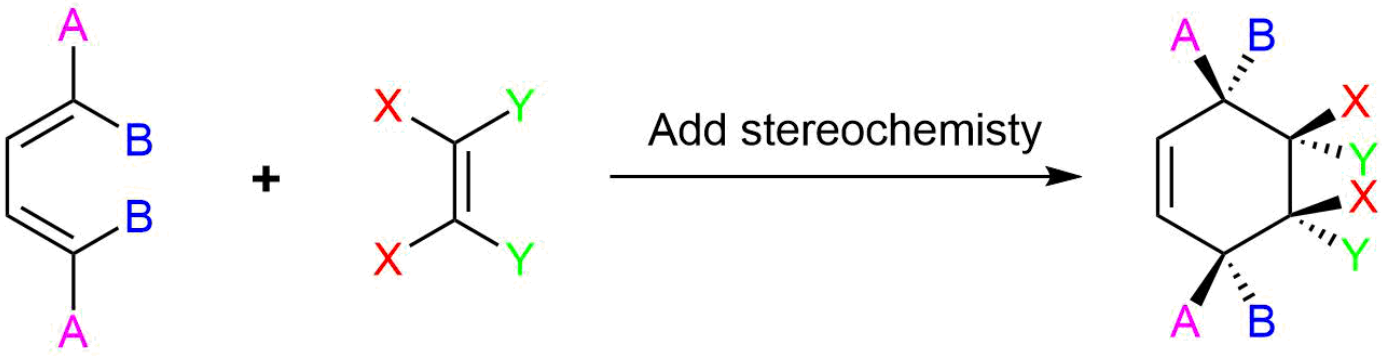
link

Predicting the Product of a Diels-Alder Reaction

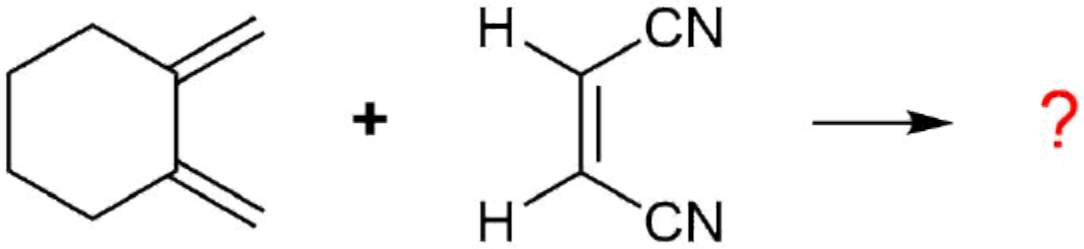
Start by rotating the diene until it is in the s-cis conformation then point it towards the double bond of the dienophile. Remove the double bonds present in the diene and dieneophile. Connect carbons 1 and 4 of the the diene to a carbon in the dienophile double bond using a sigma bond to create a six-membered ring. Create a double bond between carbons 2 and 3 of diene.



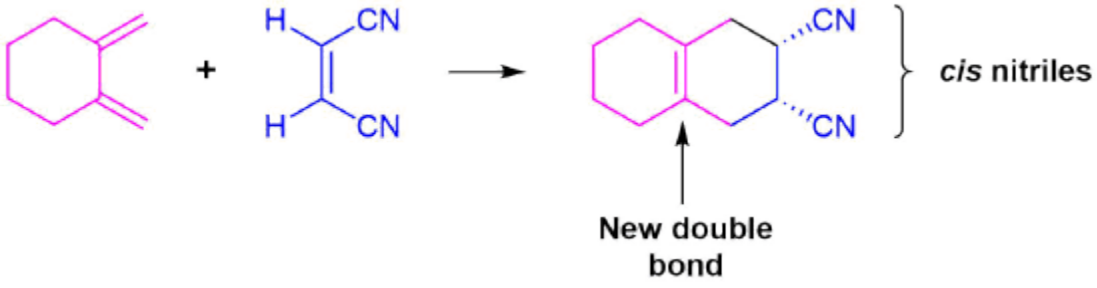
Determine if any substituents attached to either the double bond of the dieneophile or carbons 1 and 4 of the diene have a *cis*/*trans* conformation. If so make sure the substituents have the same configuration in the cycloalkene product.



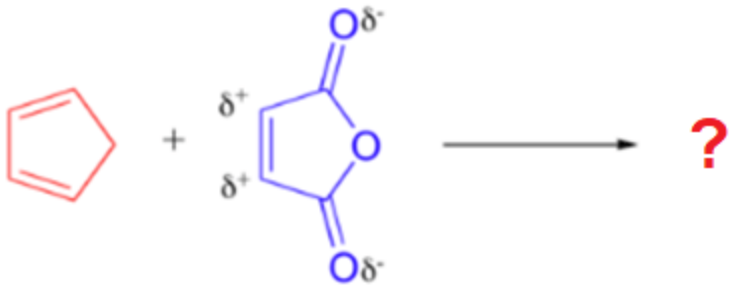
Predict the product of the following reaction:



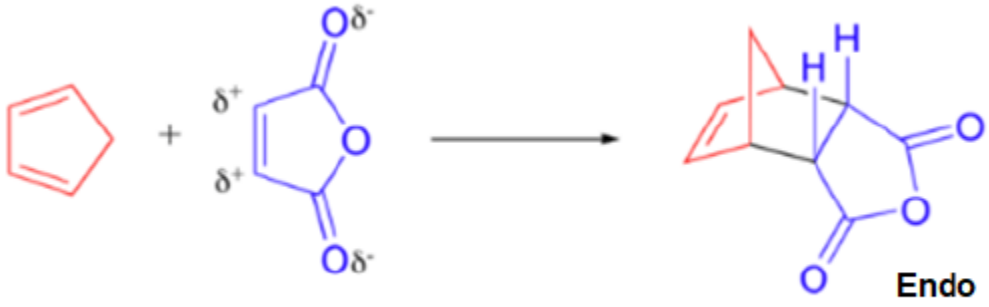
The diene is locked into an s-cis configuration which will promote the reaction. The ring portion of the diene will act as electron donating groups which will also promote the reaction. Because the diene already contained a ring the product will be bicyclic. The dienophile has two nitriles attached to it both of which are electron withdrawing. Since the two nitriles in the dieneophile are *cis* to each other the the two nitriles will be cis to each other in the product.



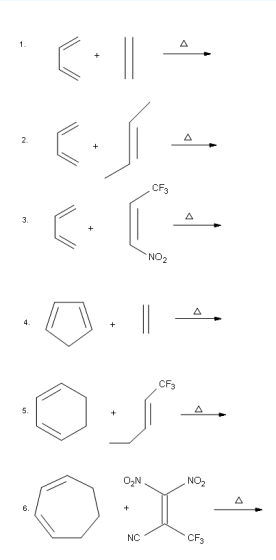
Predict the product of the following reaction:



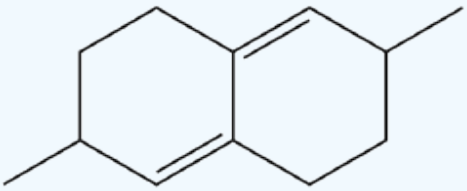
A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride. Cyclopentadiene is held in the required s-cis configuration so it will make a good diene for a Diels-Alder reaction. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for attack by the pi electrons in the diene. Since it is part of a ring, the double bond of maleic anhydride is in a cis configuration so the cyclohexene ring will also have a cis configuration. Lastly, the product will prefer the endo position.

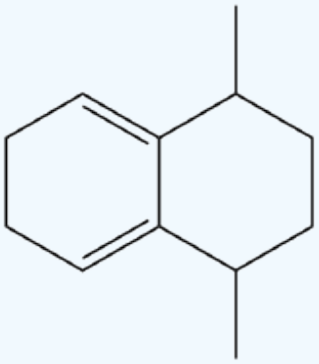


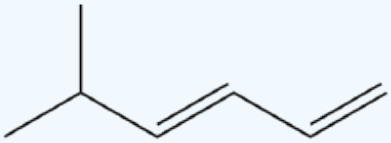
Exercise 14.8.1



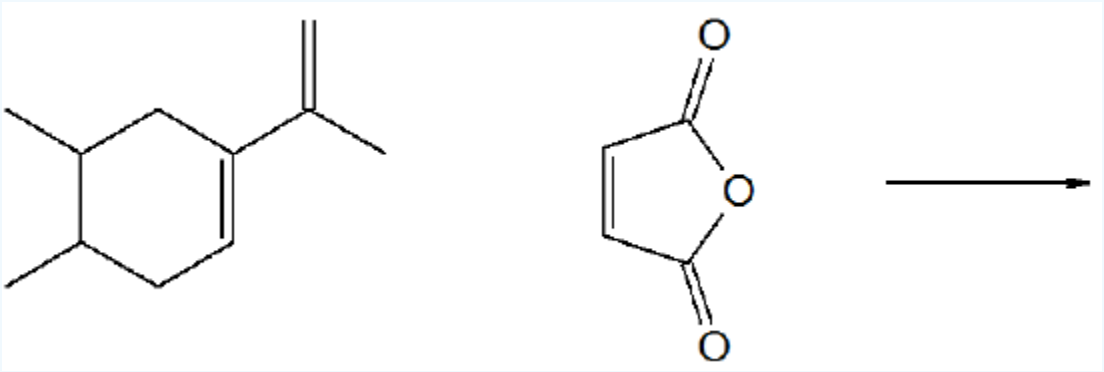
7) Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?

A) 

B) 

C) 

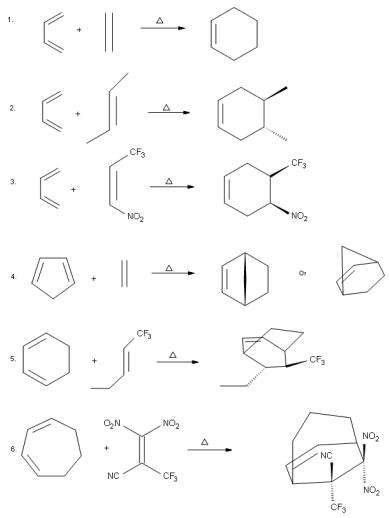
8) Predict the product of the following reaction.



Answer available at the end of this section.

Answers

Exercise 14.8.1



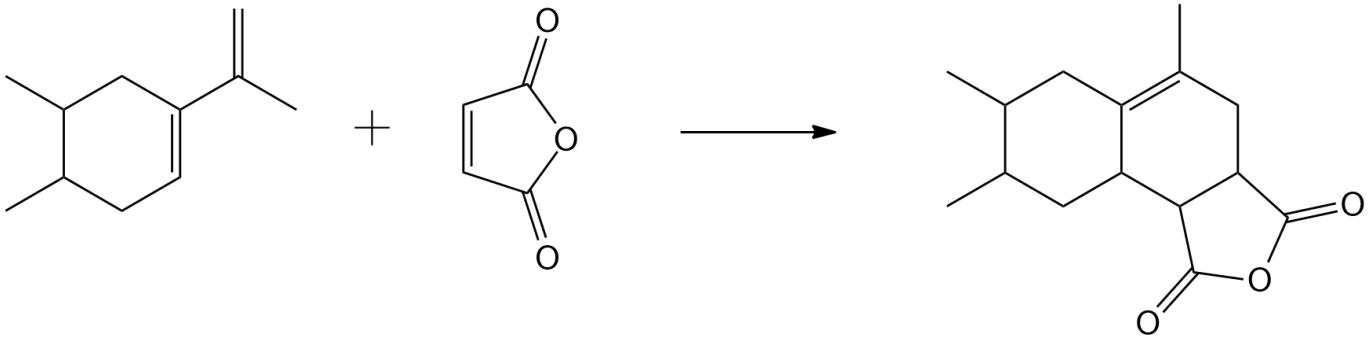
7)

A) s-trans, unable to rotate to become s-cis

B) s-cis

C) s-trans, can rotate to become s-cis.

8)

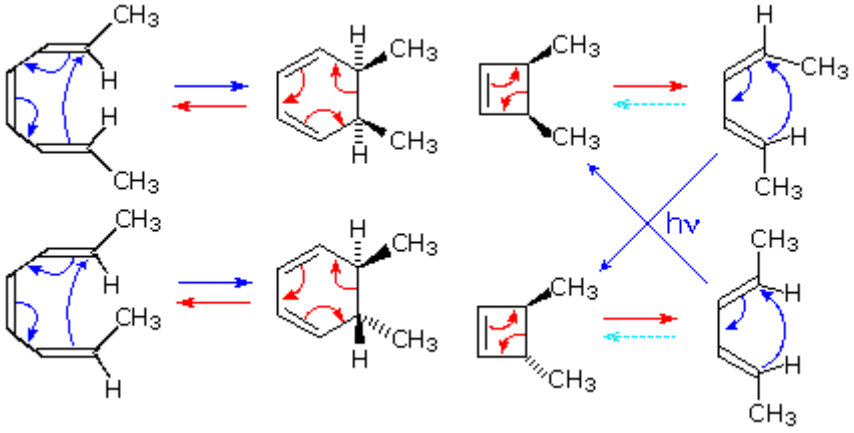


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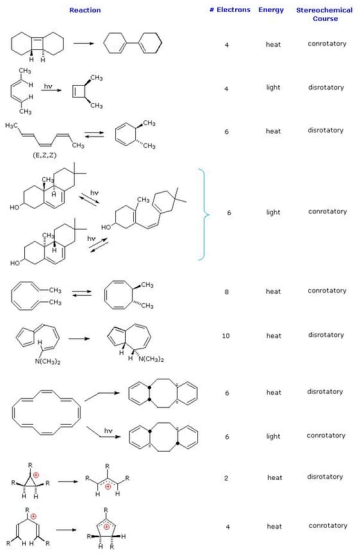
- 14.4: The Diels-Alder Cycloaddition Reaction by Amar Patel, Dietmar Kennepohl, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.
- 14.5: Characteristics of the Diels-Alder Reaction by Dietmar Kennepohl, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

14.9: Electrocyclic Reactions

An electrocyclic reaction is the concerted cyclization of a conjugated π-electron system by converting one π-bond to a ring forming σ-bond. The reverse reaction may be called *electrocyclic ring opening*. Two examples are shown on the right. The electrocyclic ring closure is designated by blue arrows, and the ring opening by red arrows. Once again, the number of curved arrows that describe the bond reorganization is half the total number of electrons involved in the process.



In the first case, *trans,cis,trans*-2,4,6-octatriene undergoes thermal ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene. The sterospecificity of this reaction is demonstrated by closure of the isomeric *trans,cis,cis*-triene to *trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted in the second example.



By clicking on this diagram two examples of thermal electrocyclic opening of cyclobutenes to conjugated butadienes will be displayed. This mode of reaction is favored by relief of ring strain, and the reverse ring closure (light blue arrows) is not normally observed. Photochemical ring closure can be effected, but the stereospecificity is opposite to that of thermal ring opening.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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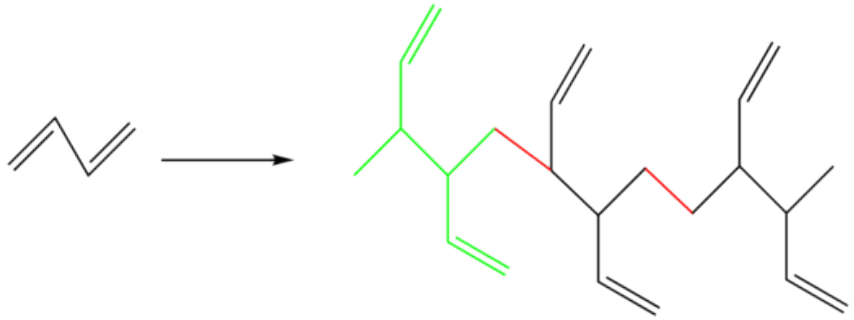
14.10: Polymerization of Conjugated Dienes: Rubber

Conjugated dienes (alkenes with two double bonds and a single bond in between) can be polymerized to form important compounds like rubber. This takes place, in different forms, both in nature and in the laboratory. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound.

Polymerization of 1,3-Butadiene

For rubber compounds to be synthesized, 1,3-butadiene must be polymerized. Below is a simple illustration of how this compound is formed into a chain. The 1,4 polymerization is much more useful to polymerization reactions.

1,2-Polymerization of 1,3- Butadiene



1,4-Polymerization of 1,3- Butadiene

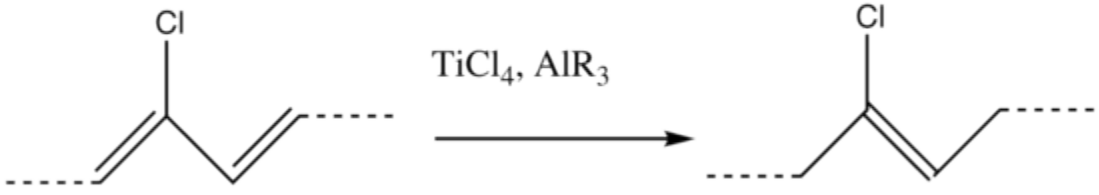


Above, the green structures represent the base units of the polymers that are synthesized and the red represents the bonds between these units which form these polymers. Whether the 1,3 product or the 1,4 product is formed depends on whether the reaction is thermally or kinetically controlled.

Synthetic Rubber

The most important synthetic rubber is Neoprene which is produced by the polymerization of 2-chloro-1,3-butadiene.

Neoprene Synthesis



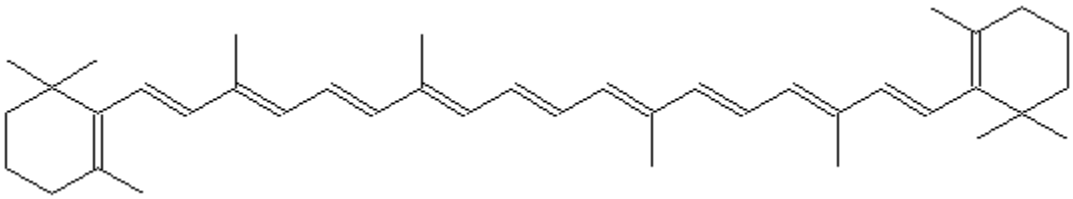
2-Chloro-1,3-butadiene

Neoprene

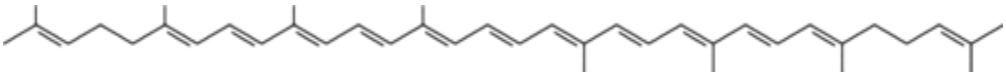
In this illustration, the dashed lines represent repetition of the same base units, so both the products and reactants are polymers. The reaction proceeds with a mechanism similar to the Friedel-Crafts mechanism. Cross-linkage between the chlorine atom of one chain and the double bond of another contributes to the overall elasticity of neoprene. This cross-linkage occurs as the chains lie next to each other at random angles, and the attractions between double bonds prevent them from sliding back and forth.

Colored molecules

The counjugated double bonds in beta-carotene produce the orange color in carrots. The conjugated double bons in lycopene produce the red color in tomatoes.



ß carotene



lycopene

Outside links

- "Dienes," http://en.wikipedia.org/wiki/Diene
- "Rubber," http://en.wikipedia.org/wiki/Rubber
- "Neoprene," http://en.wikipedia.org/wiki/Neoprene

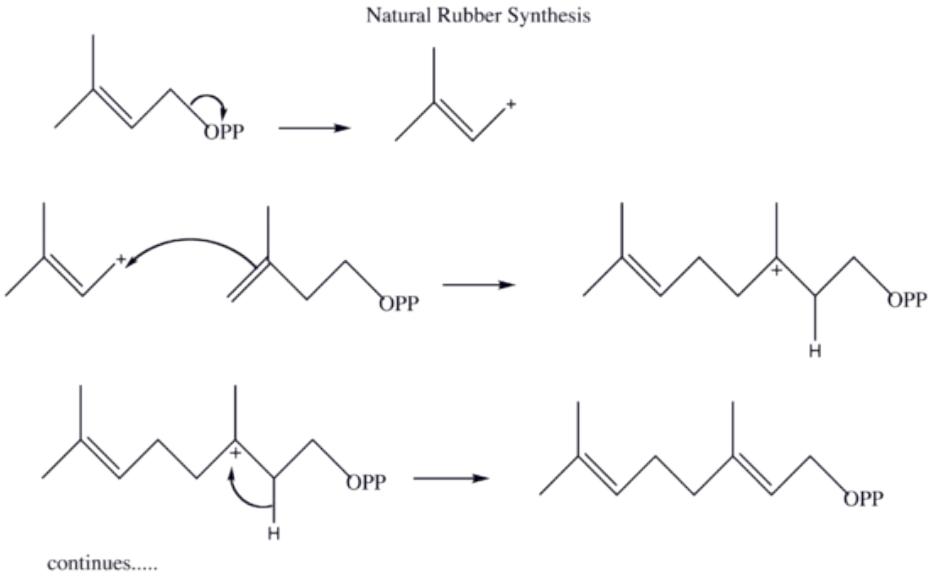
References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W. H. Freeman & Company, 2007.
2. Buehr, Walter. Rubber: Natural and Synthetic. Morrow, 1964.

Problem

Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows.

Answer



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14.11: Electronic Spectra: Ultraviolet and Visible Spectroscopy

Objectives

After completing this section, you should be able to

1. identify the ultraviolet region of the electromagnetic spectrum which is of most use to organic chemists.
2. interpret the ultraviolet spectrum of 1,3-butadiene in terms of the molecular orbitals involved.
3. describe in general terms how the ultraviolet spectrum of a compound differs from its infrared and NMR spectra.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ultraviolet (UV) spectroscopy
- Molar absorptivity

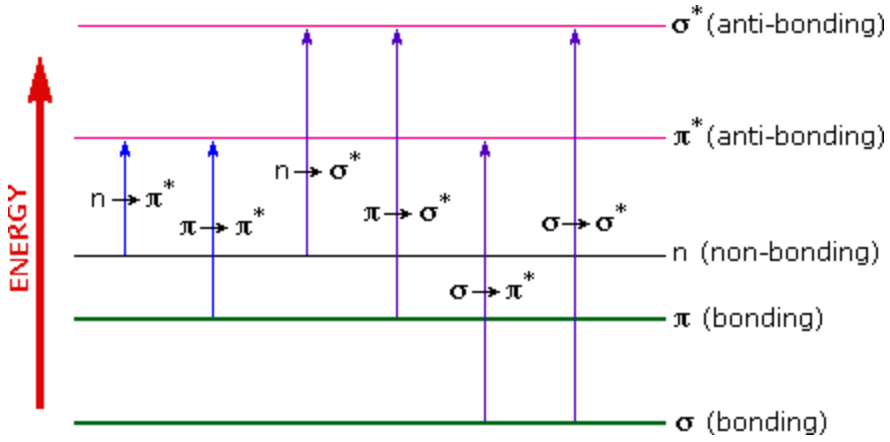
Study Notes

Ultraviolet spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy). Thus, your study of this technique will be restricted to a brief overview. You should, however, note that for an organic chemist, the most useful ultraviolet region of the electromagnetic spectrum is that in which the radiation has a wavelength of between 200 and 400 nm.

UV-Visible Absorption Spectra

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum. Ultraviolet-visible absorption spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy) and mainly provides information about conjugated pi systems. For an organic chemist the most useful ultraviolet region of the electromagnetic spectrum involves radiation with a wavelength between 200 and 400 nm. UV/Vis absorption spectra also involve radiation from the visible region of the electromagnetic spectrum with wavelengths between 400 and 800 nm.

A diagram highlighting the various kinds of electronic excitation that may occur in organic molecules is shown below. Of the six transitions outlined, only the two lowest energy ones, n to pi* and pi to pi* (colored blue) are achieved by the energies available in the 200 to 800 nm range of a UV/VIs spectrum. These energies are sufficient to promote or excite a molecular electron to a higher energy orbital in many conjugated compounds.

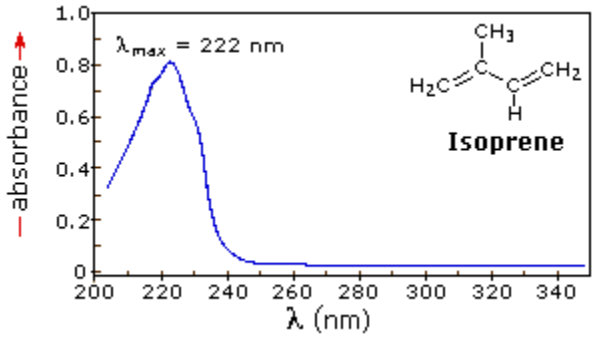


When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. A UV/Vis spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. A**bsorbance**, abbreviated 'A', is a unitless number which contains the same information as the 'percent transmittance' number used in IR spectroscopy. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log\left(\frac{I_0}{I}\right)$$

The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since isoprene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. Notice that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Typically, there are two things that are noted and recorded from a UV-Vis spectrum. The first is **λ_{max}**, which is the wavelength at maximal light absorbance. As you can see, isoprene has **λ_{max}**, = 222 nm. The second valuable piece of data is the absorbance at the **λ_{max}**. In the isoprene spectrum the absorbance at the value **λ_{max}** of 222 nm is about 0.8.



Molar absorptivity

Molar absorptivity ($epsilon$) is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular electron system in the molecule. Molar absorptivities may be very large for strongly absorbing chromophores (>100,000) and very small if absorption is weak (10 to 100). The magnitude of $epsilon$ reflects both the size of the chromophore and the probability that light of a given wavelength will be absorbed when it strikes the chromophore. Molar absorptivity (ϵ) is defined via Beer's law as:

$$\epsilon = \frac{A}{c\,l}$$

where

- A is the sample absorbance
- c is the sample concentration in moles/liter
- l is the length of light path through the sample in cm

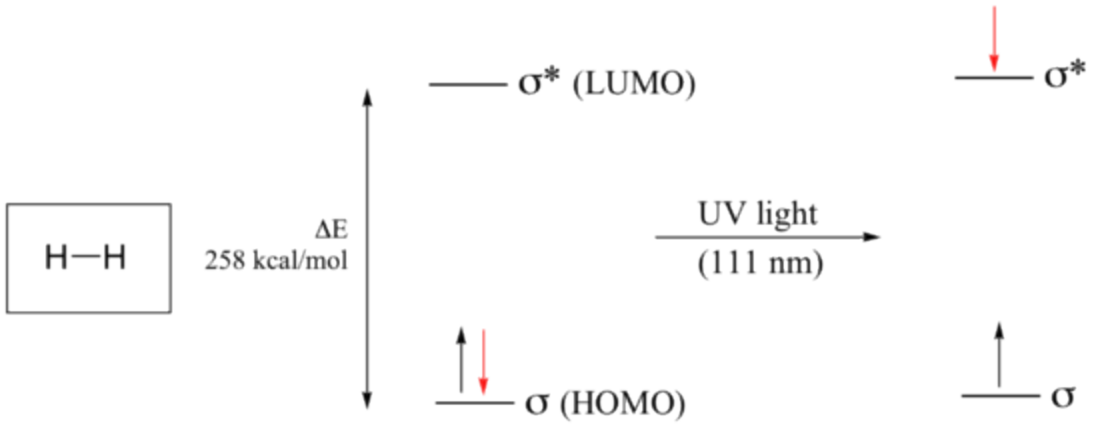
If the isoprene spectrum show above was obtained from a dilute hexane solution (c = 4 * 10^{-5} moles per liter) in a 1 cm sample cuvette, a simple calculation using the above formula indicates a molar absorptivity of 20,000 at the maximum absorption wavelength, symbolized as λ_{max}.

The only molecular moieties likely to absorb light in the 200 to 800 nm region are functional groups that contain pi-electrons and hetero atoms having non-bonding valence-shell electron pairs. Such light absorbing groups are referred to as **chromophores**. A list of some simple chromophores and their light absorption characteristics are provided below. The oxygen non-bonding electrons in alcohols and ethers do not give rise to absorption above 160 nm. Consequently, pure alcohol and ether solvents may be used for spectroscopic studies.

Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=C	Ethene	π → π*	171	15,000	hexane
C≡C	1-Hexyne	π → π*	180	10,000	hexane
C=O	Ethanal	n → π* π → π*	290 180	15 10,000	hexane hexane
N=O	Nitromethane	n → π* π → π*	275 200	17 5,000	ethanol ethanol
C-X X=Br X=I	Methyl bromide Methyl Iodide	n → σ* n → σ*	205 255	200 360	hexane hexane

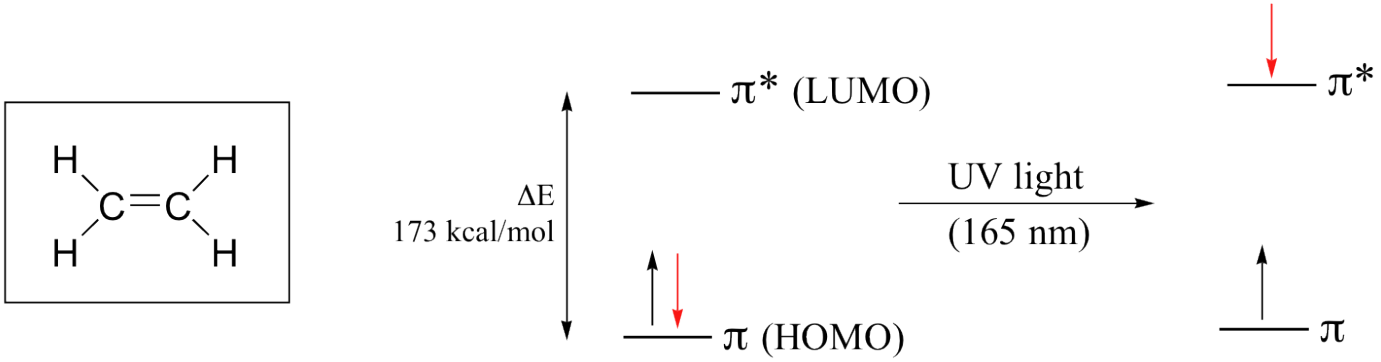
Electronic Transitions (cause of UV-Visible absorption)

As previously noted, electronic transitions in organic molecules lead to UV and visible absorption. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state.** The molecular orbital picture for the hydrogen molecule (H_2) consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).

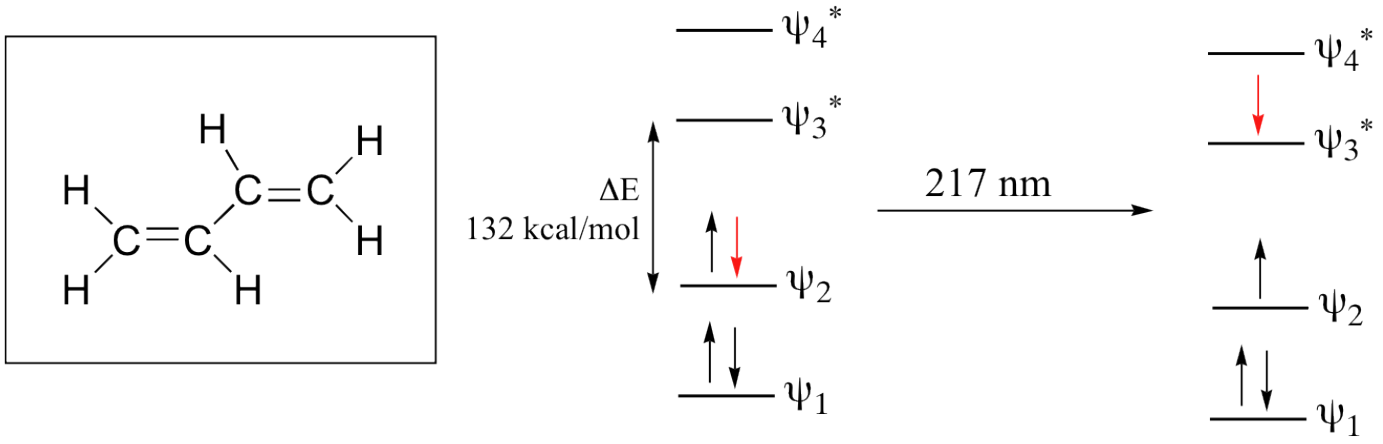


If the molecule is exposed to light of a wavelength with energy equal to ΔE, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. ΔE for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition**. Because π- π* energy gaps are narrower than σ **-** σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.

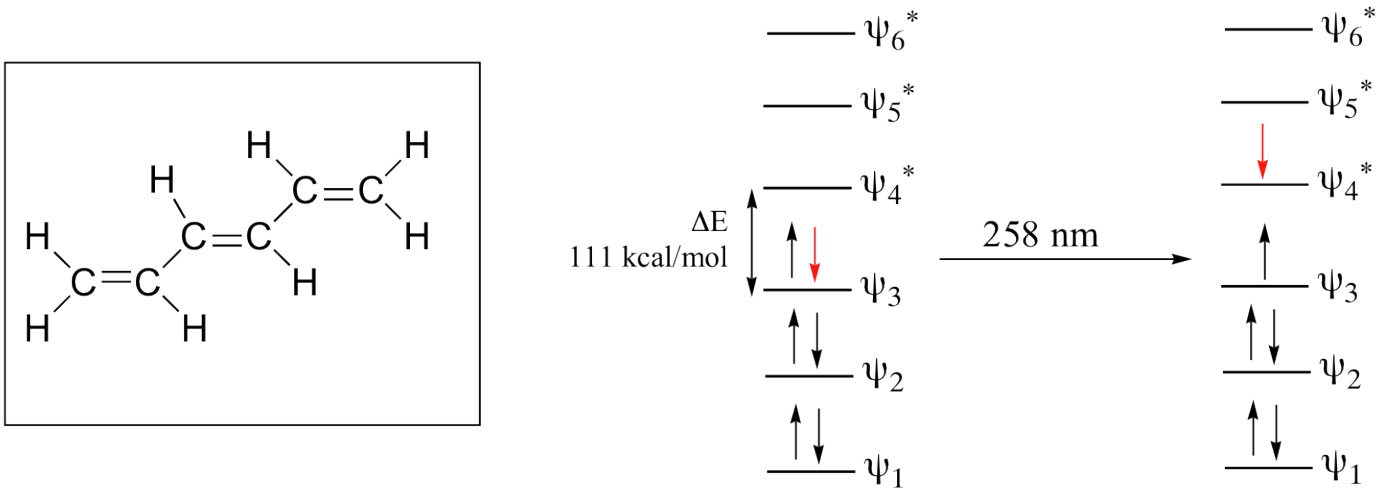


The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded. Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding.

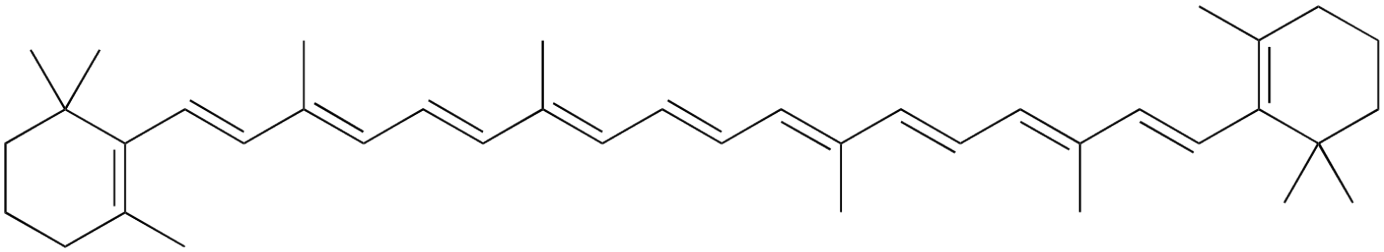


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a ΔE of 111 kcal/mol.

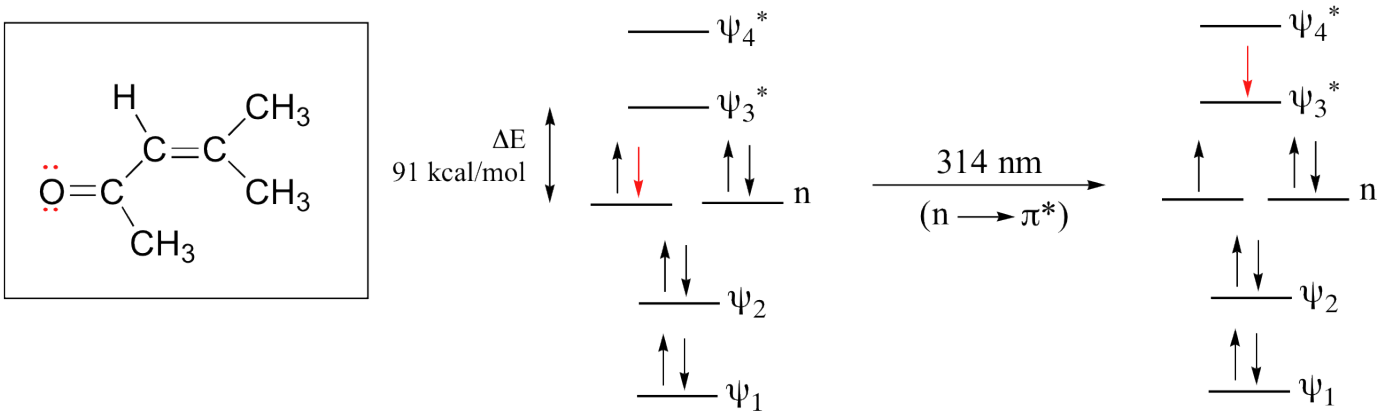


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

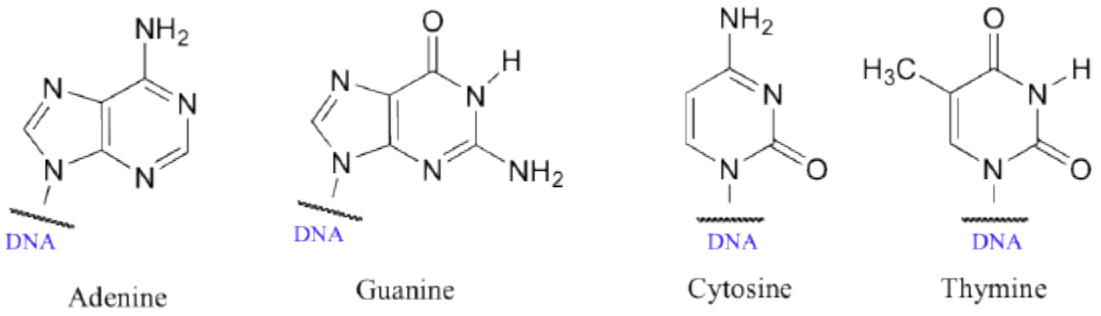
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an $n - \pi^*$ transition. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n - \pi^*$ transition is smaller that that of a $\pi - \pi^*$ transition – and thus the $n - \pi^*$ peak is at a longer wavelength. In general, $n - \pi^*$ transitions are weaker (less light absorbed) than those due to $\pi - \pi^*$ transitions.

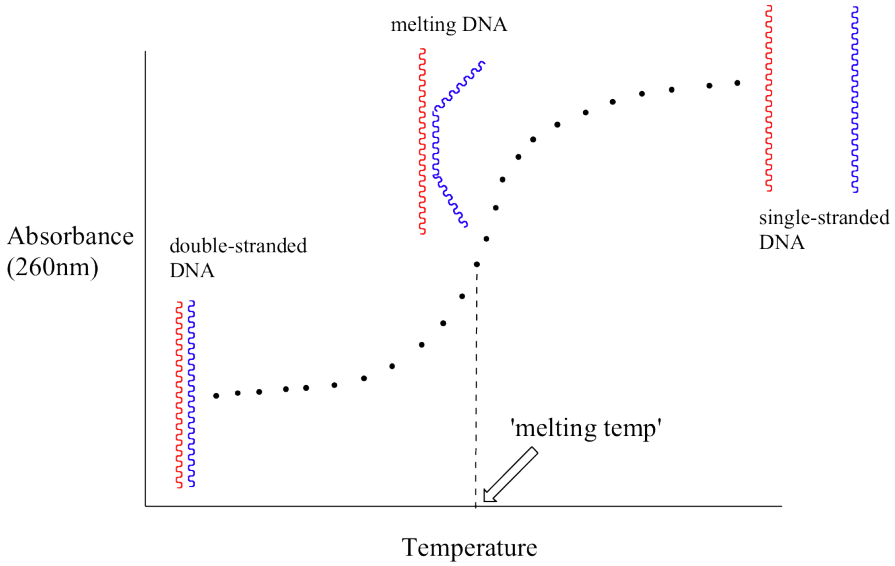
Use of UV/Vis Spectroscopy in Biological Systems

The bases of DNA and RNA are good chromophores:



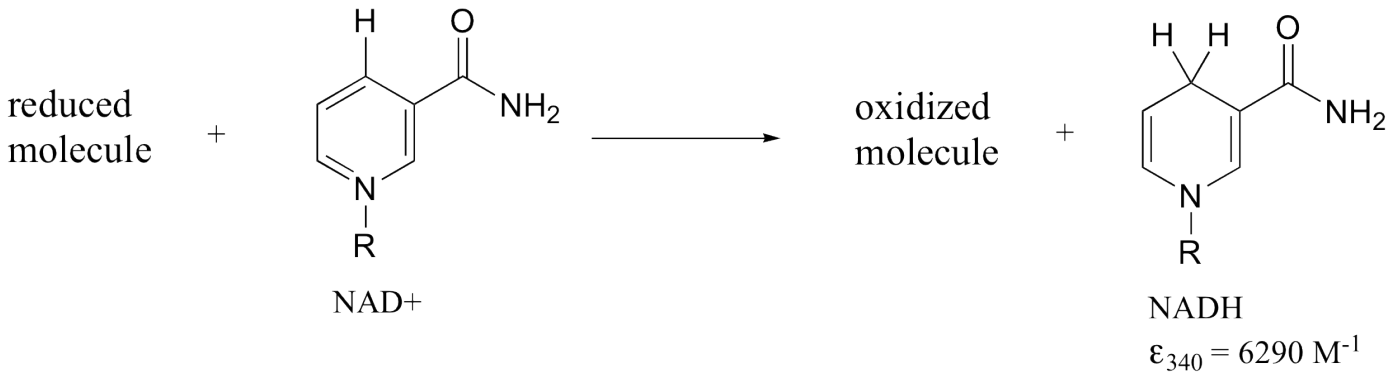
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 $ng^{-1} \times mL$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

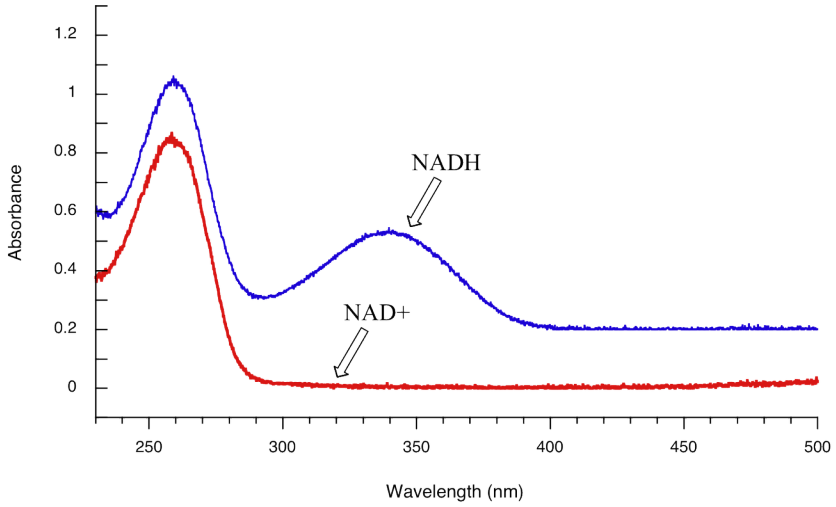


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

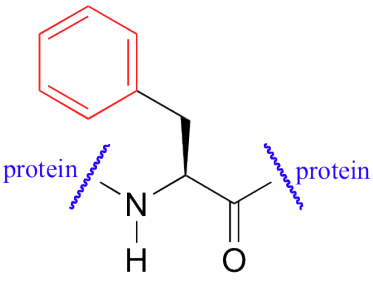


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L*mol^{-1}*cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:

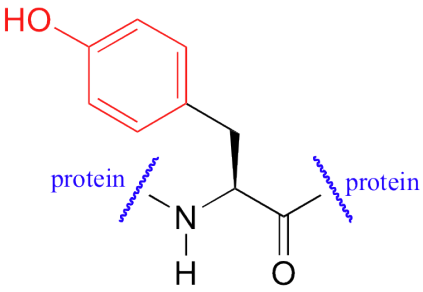


By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

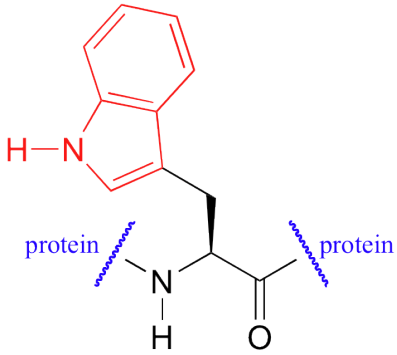
UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



phenylalanine



tyrosine

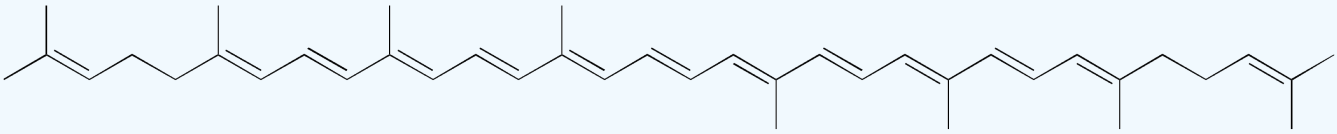


tryptophan

Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

Exercise 14.11.1

1. 50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?
2. What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?
3. Identify all isolated and conjugated pi bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?



lycopene

Answer available at the end of this section.

Objective

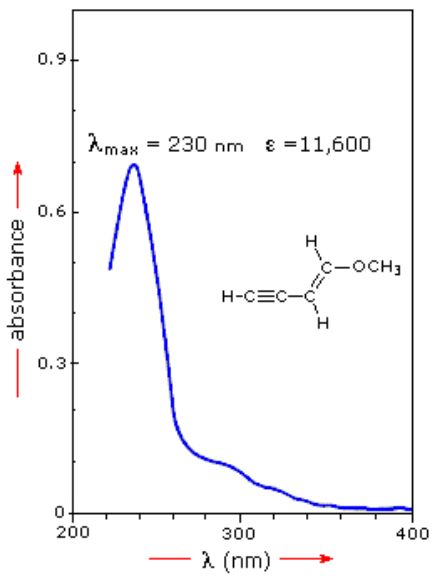
After completing this section, you should be able to use data from ultraviolet spectra to assist in the elucidation of unknown molecular structures.

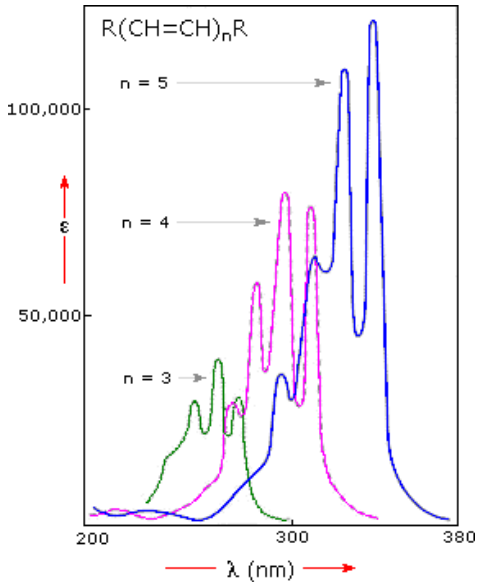
Study Notes

It is important that you recognize that the ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation in the molecule.

The Importance of Conjugation

A comparison of the UV/Vis absorption spectrum of 1-butene, λ_{max} = 176 nm, with that of 1,3-butadiene, λ_{max} = 292 nm, clearly demonstrates that the effect of increasing conjugation is to shift toward longer wavelength (lower frequency, lower energy) absorptions. Further evidence of this effect is shown below. The spectrum on the left illustrates that conjugation of double and triple bonds also shifts the absorption maximum to longer wavelengths. From the polyene spectra displayed in the right it is clear that each additional double bond in the conjugated pi-electron system increases the absorption maximum about 30 nm. Also, the molar absorptivity (ε) roughly doubles with each new conjugated double bond. Spectroscopists use the terms defined in the table below when describing shifts in absorption. Thus, extending conjugation generally results in bathochromic and hyperchromic shifts in absorption.

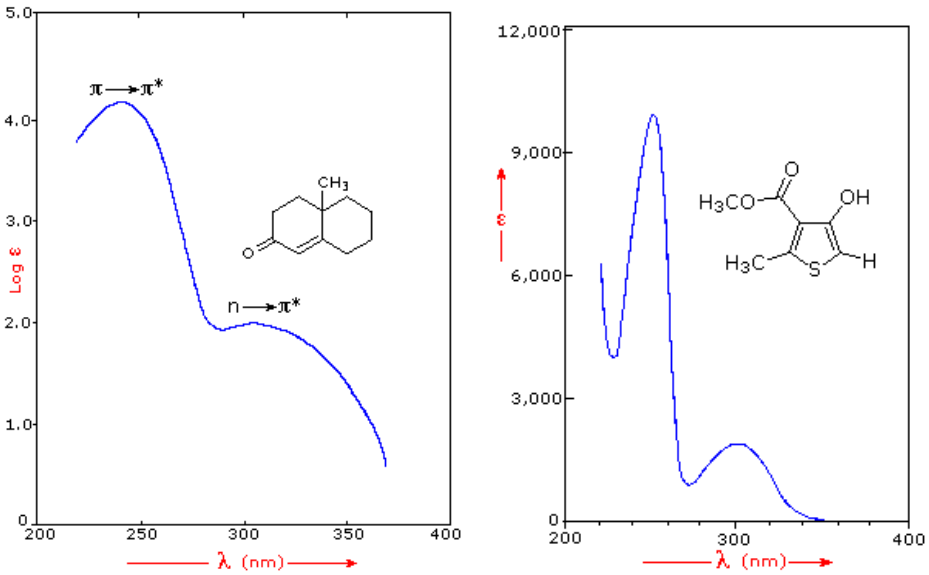




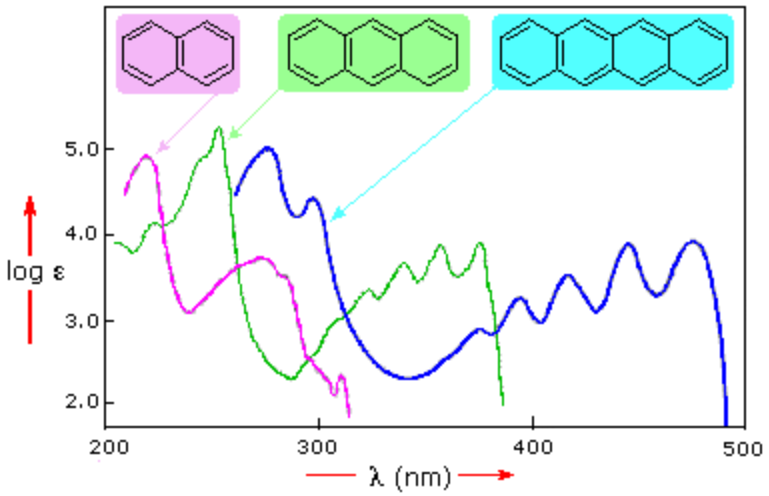
Terminology for Absorption Shifts

Nature of Shift	Descriptive Term
To Longer Wavelength	Bathochromic
To Shorter Wavelength	Hypsochromic
To Greater Absorbance	Hyperchromic
To Lower Absorbance	Hypochromic

Many other kinds of conjugated pi-electron systems act as chromophores and absorb light in the 200 to 800 nm region. These include unsaturated aldehydes and ketones and aromatic ring compounds. A few examples are displayed below. The spectrum of the unsaturated ketone (on the left) illustrates the advantage of a logarithmic display of molar absorptivity. The $\pi \rightarrow \pi^*$ absorption located at 242 nm is very strong, with an ε = 18,000. The weak $n \rightarrow \pi^*$ absorption near 300 nm has an ε = 100.

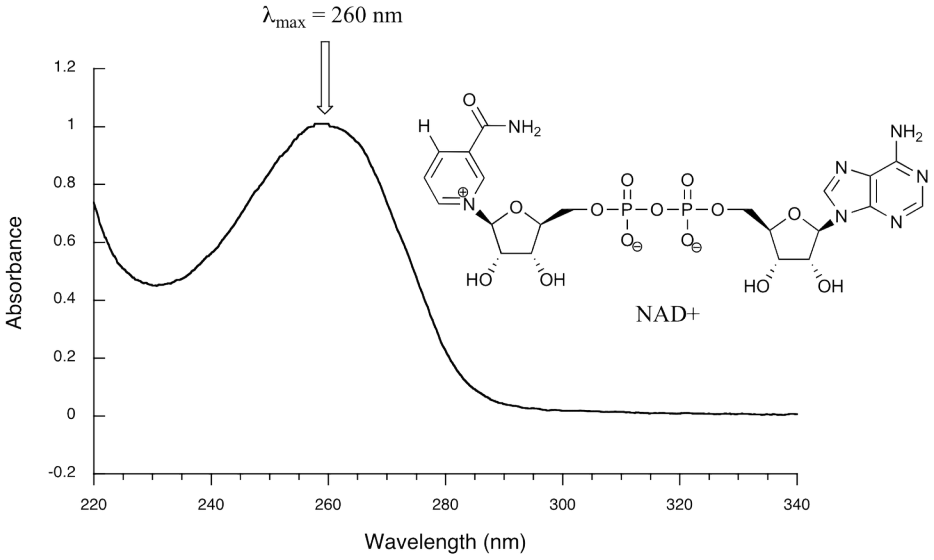


Benzene exhibits very strong light absorption near 180 nm (ε > 65,000) , weaker absorption at 200 nm (ε = 8,000) and a group of much weaker bands at 254 nm (ε = 240). Only the last group of absorptions are completely displayed because of the 200 nm cut-off characteristic of most spectrophotometers. The added conjugation in naphthalene, anthracene and tetracene causes bathochromic shifts of these absorption bands, as displayed in the chart below. All the absorptions do not shift by the same amount, so for anthracene (green shaded box) and tetracene (blue shaded box) the weak absorption is obscured by stronger bands that have experienced a greater red shift. As might be expected from their spectra, naphthalene and anthracene are colorless (with their absorptions in the UV range), but tetracene is orange (since its absorptions move into the visible range).

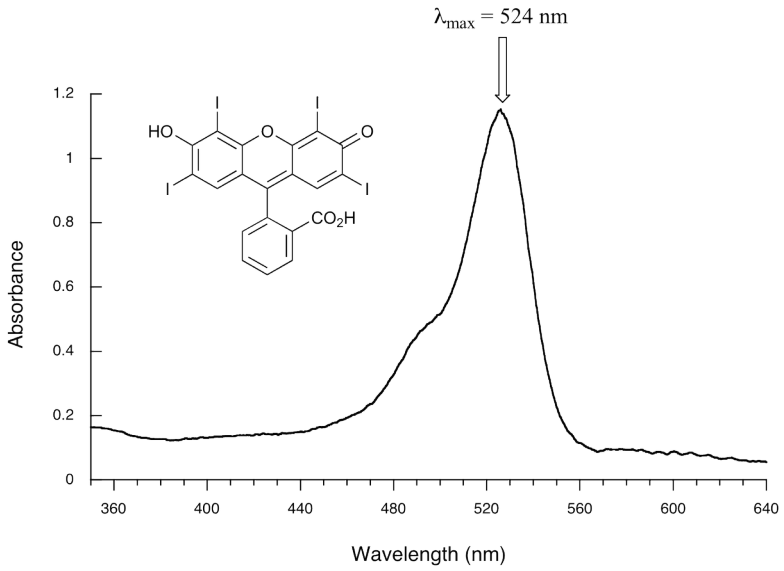


Looking at UV-Vis Spectra

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



Below is the absorbance spectrum of the common food coloring Red #3. The extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes (recalling the color wheel from Section 14.7).



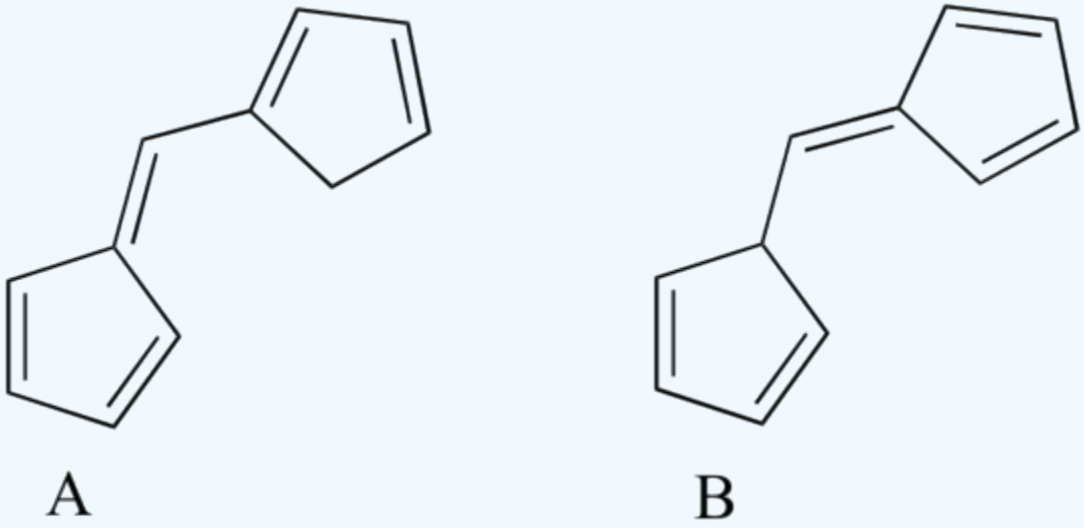
Example 14.8.2

How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

Example 14.8.3

Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



Solution

Exercise 14.11.1

Which of the following would show UV absorptions in the 200-300 nm range?

14.8.png

Answer available at the end of this section.

Answers

Exercise 14.11.1

1) Using ε = A/c, we plug in our values for ε and A and find that c = 3.27 x 10^{-5}M, or 32.7 mM.

2)

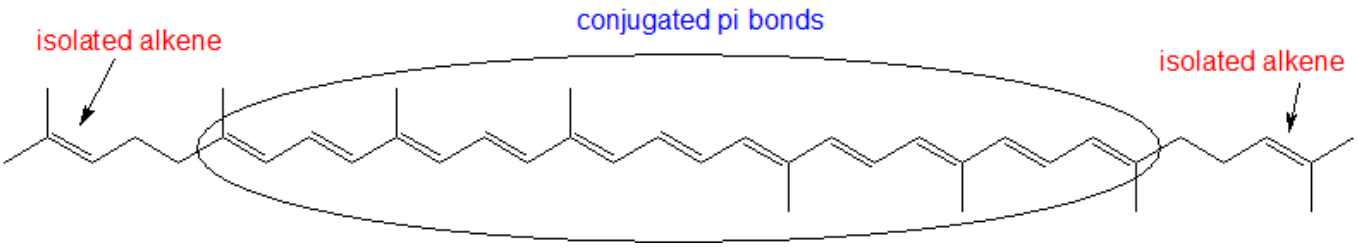
$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972 × 10^{-19} to 6.62 × 10^{-19} joules. This energy range is greater in energy than the in NMR and IR.

3)



Exercise 14.11.1

B and D would be in that range.

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15: BENZENE AND AROMATICITY: ELECTROPHILIC AROMATIC SUBSTITUTION

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

15.1: Naming the Benzenes
15.2: Structure and Resonance Energy of Benzene: A First Look at Aromaticity
15.3: Pi Molecular Orbitals of Benzene
15.4: Spectral Characteristics of the Benzene Ring
15.5: Polycyclic Aromatic Hydrocarbons
15.6: Other Cyclic Polyenes: Huckel 's Rule
15.7: Huckel's Rule and Charged Molecules
15.8: Synthesis of Benzene Derivatives: Electrophilic Aromatic Substitution
15.9: Halogenation of Benzene: The Need for a Catalyst
15.10: Nitration and Sulfonation of Benzene
15.11: Friedel-Crafts Alkylation
15.12: Limitations of Friedel-Crafts Alkylations
15.13: Friedel-Crafts Alkanoylation (Acylation)

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15.1: Naming the Benzenes

Objectives

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 16 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 16, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

Study Notes

You should already know the names and structures of several of the hydrocarbons shown in Figure 15.1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

A phenyl group consists of a benzene ring with one of its hydrogens removed.

phenyl group shown with three double bonds and then with a delocalized ring

Figure 15.1.1: Two ways of representing a phenyl group

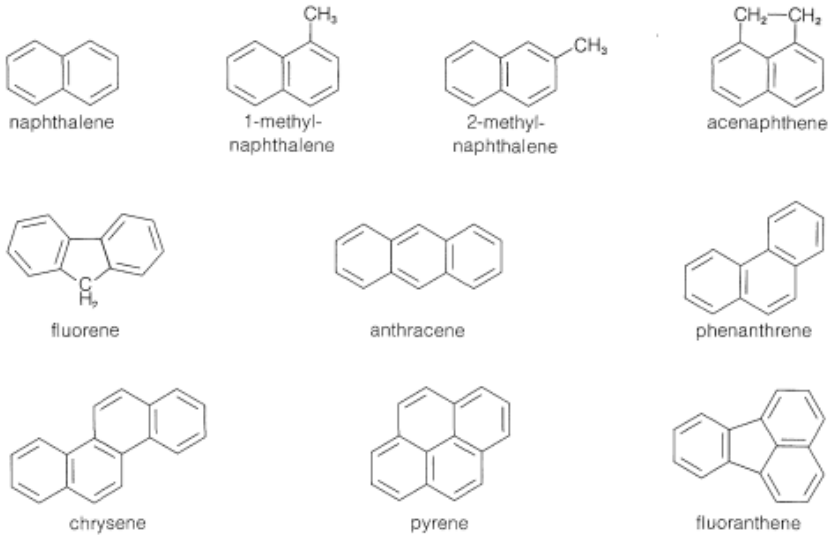
You should memorize the structures and formulas shown in Figure 16. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

Sources of Aromatic Compounds

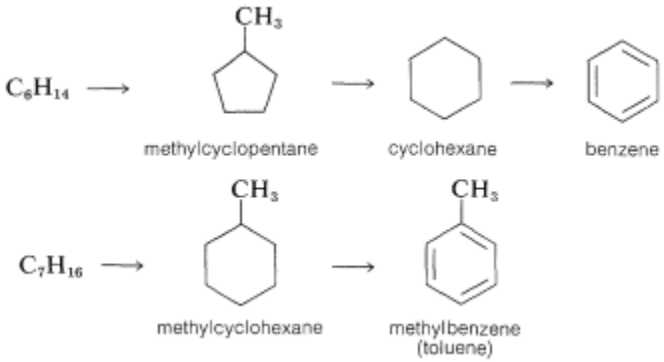
Initially aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ^{o}C in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which

includes nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.



Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



Nomenclature of Mono-Substituted Benzenes

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure 15.1.2 and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

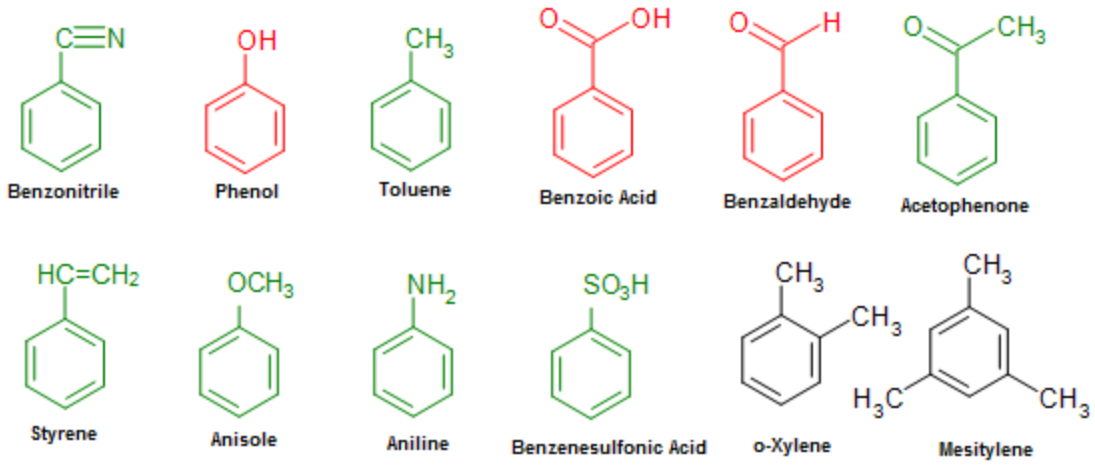
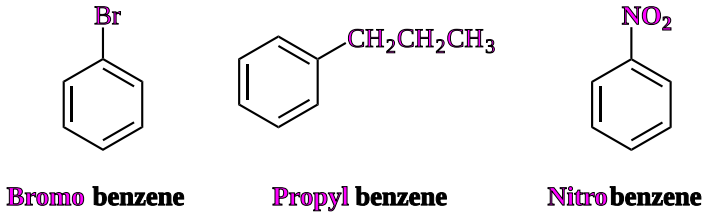


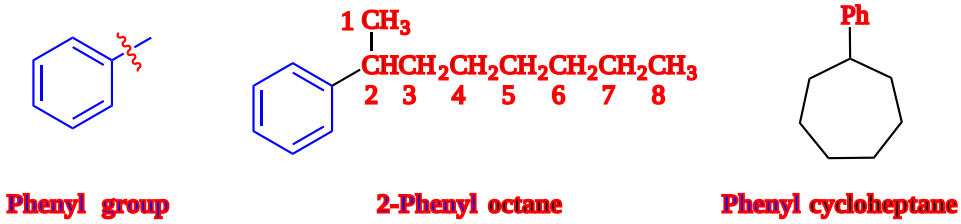
Figure 15.1.2: Common Names for Mono-Substituted Benzenes

Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene*.

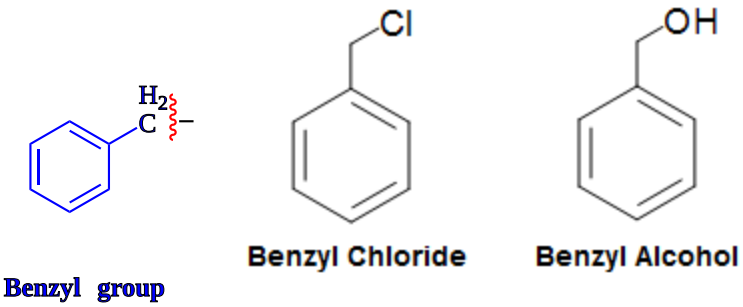


The use of Phenyl and Benzyl in Nomenclature

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



The benzyl group (abbv. Bn), similar to the phenyl group and can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

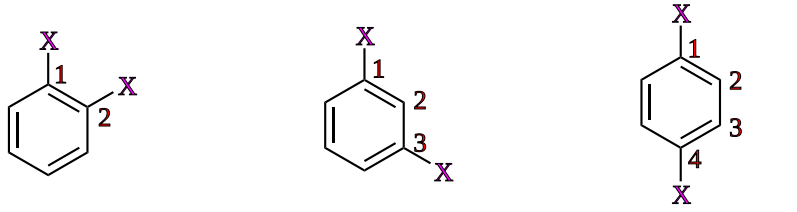


Benzyl group | Benzyl Chloride | Benzyl Alcohol

Nomenclature of Disubstituted Benzenes

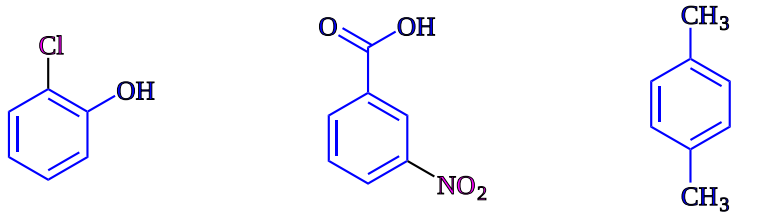
With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two subsituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. They are defined as the following:

- ***ortho- (o-):*** 1,2- (next to each other in a benzene ring)
- ***meta- (m):*** 1,3- (separated by one carbon in a benzene ring)
- ***para- (p):*** 1,4- (across from each other in a benzene ring)



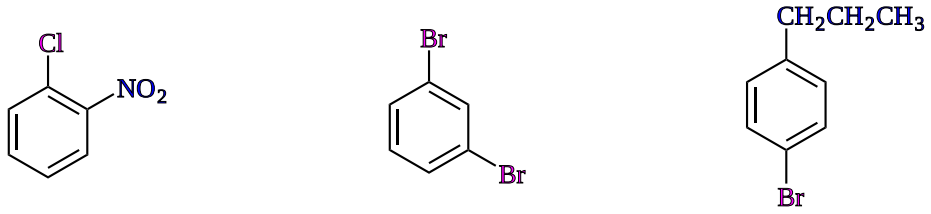
ortho -Disubstituted (1,2) | *meta* -Disubstituted (1,3) | para-Disubstituted (1,4)

Figure 15.1.2. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*



ortho- Chloro phenol | meta- Nitro benzoic acid | para-Xylene

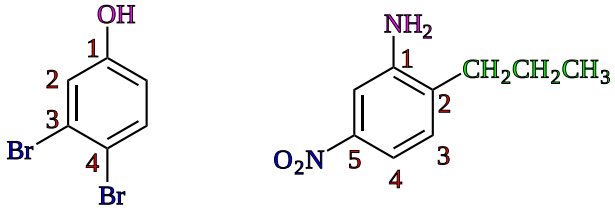
Figure 15.1.2 the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



ortho- Chloro nitro benzene | meta- Dibromo benzene | para- Bromo propyl benzene

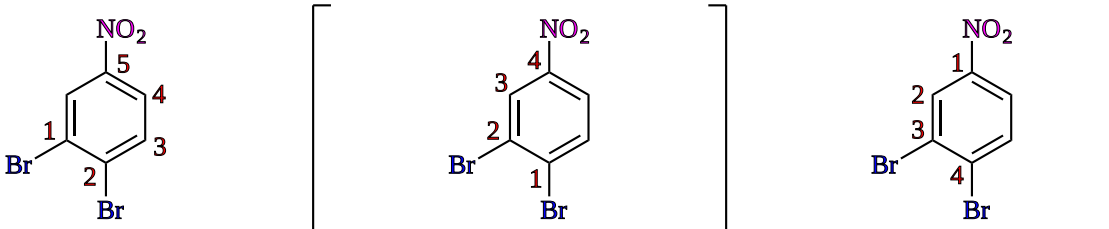
Nomenclature of Benzenes with Three or more Substituents

When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure** 15.1.2 **.** If a substituent from **Figure** 15.1.2 is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the subsituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



3,4-Dibromo phenol **5-Nitro-2-propyl aniline**

Figure 15.1.2, the benzene ring is name in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.



1,2-Dibromo- 5-nitro benzene **1,2-Dibromo- 4-nitro benzene** **3,4-Dibromo- 1-nitro benzene**

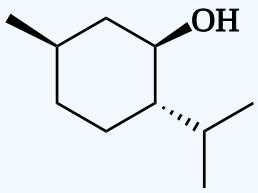
This numbering provides the lowest numbers to the substituents

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Exercises

Exercise 15.1.1



(True/False) The compound above contains a benzene ring and thus is aromatic.

Answer available at the end of this section.

Exercise 15.1.2

Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ___

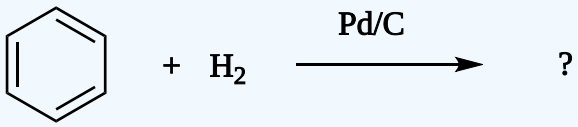
Answer available at the end of this section.

Exercise 15.1.3

Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

Answer available at the end of this section.

Exercise 15.1.4



Answer available at the end of this section.

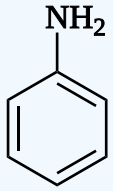
Exercise 15.1.5

At normal conditions, benzene has ___ resonance structures.

Answer available at the end of this section.

Exercise 15.1.6

Which of the following name(s) is/are correct for the following compound?



a. nitrohydride benzene
b. phenylamine
c. phenylamide
d. aniline
e. nitrogenhydrogen benzene
f. All of the above is correct

Answer available at the end of this section.

Exercise 15.1.7

Convert 1,4-dimethylbenzene into its common name.

Answer available at the end of this section.

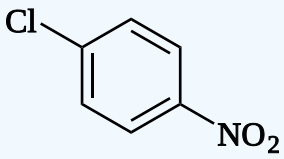
Exercise 15.1.8

TNT's common name is: _____

Answer available at the end of this section.

Exercise 15.1.9

Name the following compound using OMP nomenclature:



Answer available at the end of this section.

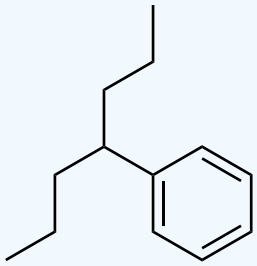
Exercise 15.1.10

Draw the structure of 2,4-dinitrotoluene.

Answer available at the end of this section.

Exercise 15.1.11

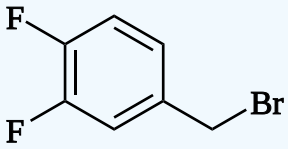
Name the following compound:



Answer available at the end of this section.

Example 15.1.12

Which of the following is the correct name for the following compound?



a. 3,4-difluorobenzyl bromide
b. 1,2-difluorobenzyl bromide
c. 4,5-difluorobenzyl bromide
d. 1,2-difluoroethyl bromide
e. 5,6-difluoroethyl bromide
f. 4,5-difluoroethyl bromide

Solution

a

Exercise 15.1.13

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer available at the end of this section.

Exercise 15.1.14

Benzoic Acid has what R group attached to its phenyl functional group?

Answer available at the end of this section.

Exercise 15.1.15

(True/False) A single aromatic compound can have multiple names indicating its structure.

Answer available at the end of this section.

Exercise 15.1.16

List the corresponding positions for the OMP system (o-, m-, p-).

Answer available at the end of this section.

Exercise 15.1.17

A scientist has conducted an experiment on an unknown compound. He was able to determine that the unknown compound contains a cyclic ring in its structure as well as an alcohol (-OH) group attached to the ring. What is the unknown compound?

a. Cyclohexanol
b. Cyclicheptanol
c. Phenol
d. Methanol
e. Bleach
f. Cannot determine from the above information

Answer available at the end of this section.

Exercise 15.1.18

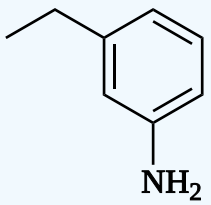
Which of the following statements is **false** for the compound, phenol?

a. Phenol is a benzene derived compound.
b. Phenol can be made by attaching an -OH group to a phenyl group.
c. Phenol is highly toxic to the body even in small doses.
d. Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e. Phenol is used as an antiseptic in minute doses.
f. Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

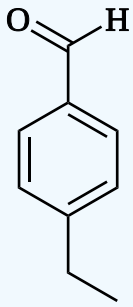
Answer available at the end of this section.

Exercise 15.1.19

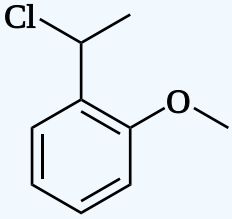
State wither the following is para, meta, or ortho substituted.



A



B

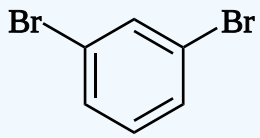


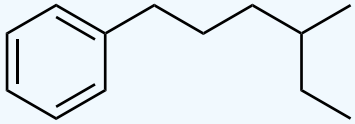
C

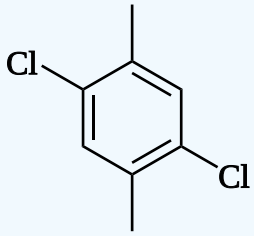
Answer available at the end of this section.

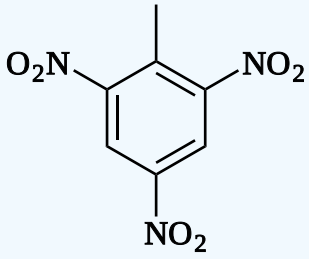
Exercise 15.1.20

Name the following compounds.

A) 

B) 

C) 

D) 

Answer available at the end of this section.

Exercise 15.1.21

Draw the following structures

a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer available at the end of this section.

Answers

Exercise 15.1.1

False, this compound does not contain a benzene ring in its structure.

Exercise 15.1.2

3

Exercise 15.1.3

No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

Exercise 15.1.4

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

Exercise 15.1.5

2

Exercise 15.1.6

b, d

Exercise 15.1.7

p-Xylene

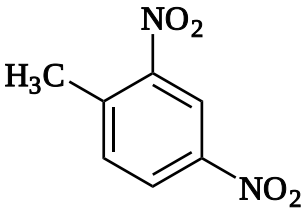
Exercise 15.1.8

2,4,6-trinitrotoluene

Exercise 15.1.9

p-chloronitrobenzene

Exercise 15.1.10



Exercise 15.1.11

4-phenylheptane

Exercise 15.1.13

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

Exercise 15.1.14

COOH

Exercise 15.1.15

True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

Exercise 15.1.16

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

Exercise 15.1.17

The correct answer is f). We cannot determine what structure this is since the question does not tell us what kind of cyclic ring the -OH group is attached on. Just as cyclohexane can be cyclic, benzene and cycloheptane can also be cyclic.

Exercise 15.1.18

d

Exercise 15.1.19

A – meta; B – para; C – ortho

Exercise 15.1.20

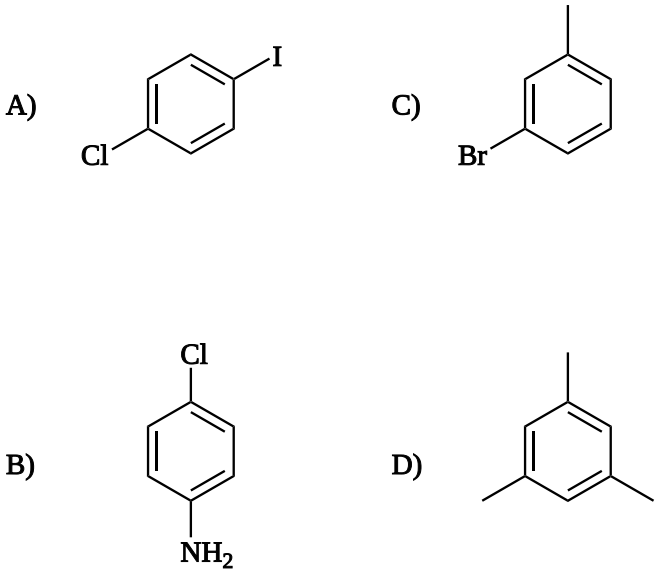
a. 1,3-Dibromobenzene

b. 1-phenyl-4-methylhexane

c. 1,4-Dichloro-2,5-dimethylbenzene

d. 2-methyl-1,3,5-trinitrobenzene. (Also known as trinitrotoluene, or TNT)

Exercise 15.1.21



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15.2: Structure and Resonance Energy of Benzene: A First Look at Aromaticity

Objectives

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

Key Terms

Make certain that you can define, and use in context, the key term below.

- degenerate

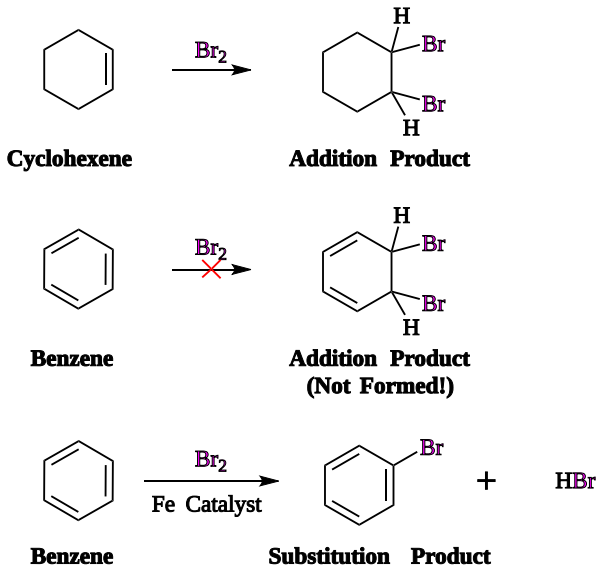
Study Notes

You may wish to review Sections 1.5 and 14.1 before you begin to study this section.

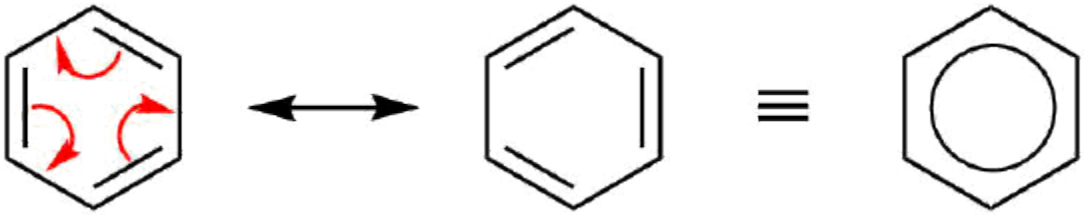
Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and $\pi_5{}^*$) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

Structure of Benzene

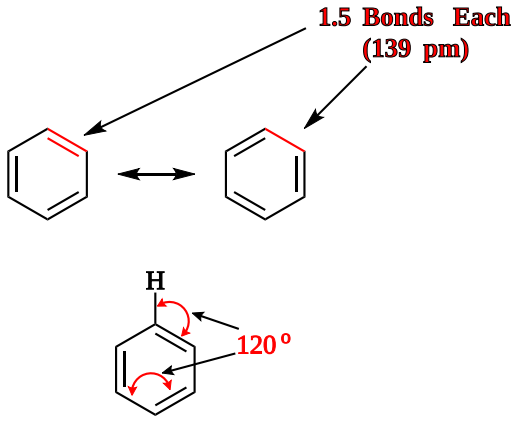
When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.



The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

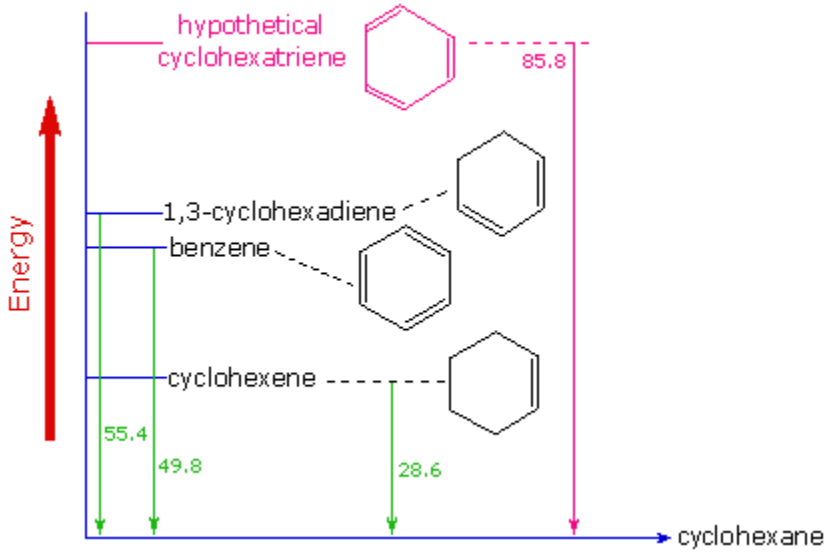


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120^o and makes the overall molecule planar.



The High Stability of Benzene

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole.



These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

Atomic Orbitals of Benzene

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that

extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

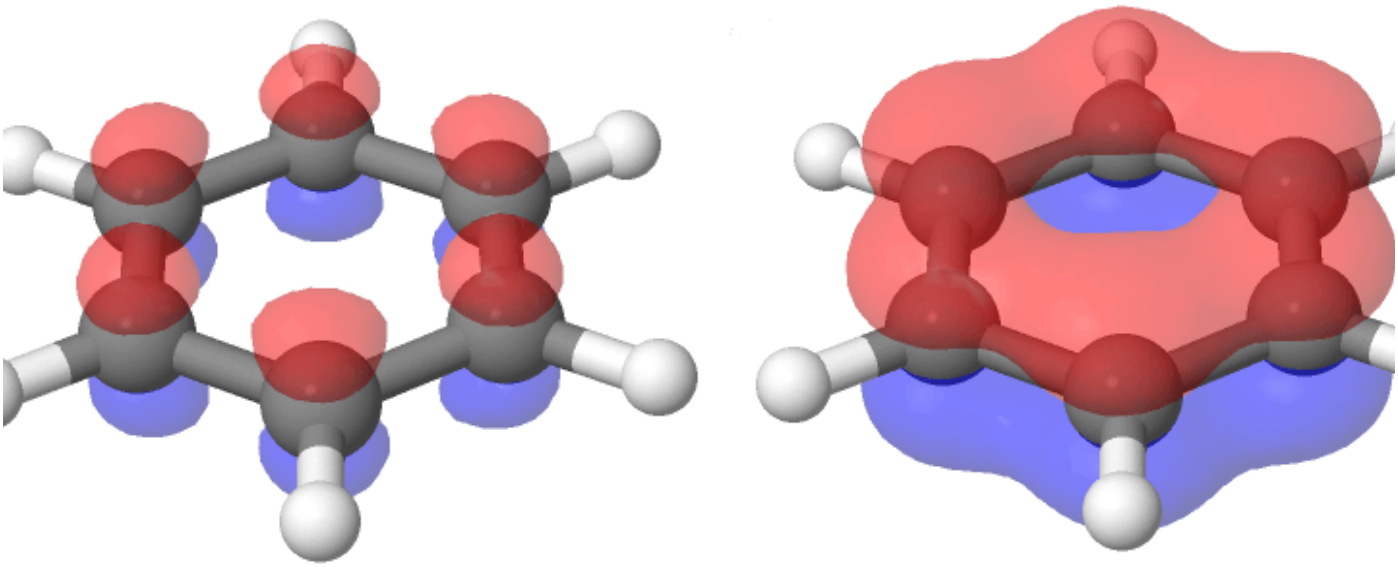


Figure 15.2.1: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

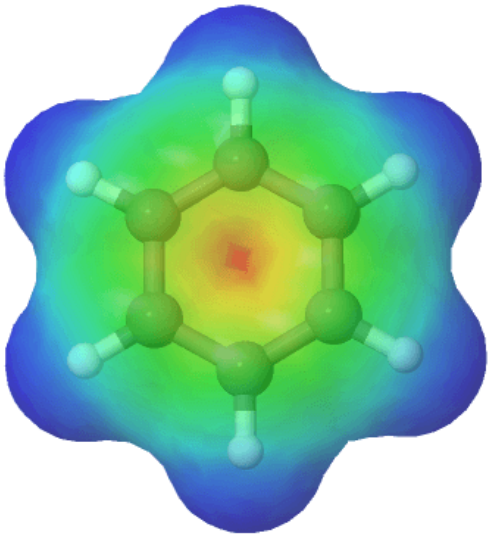
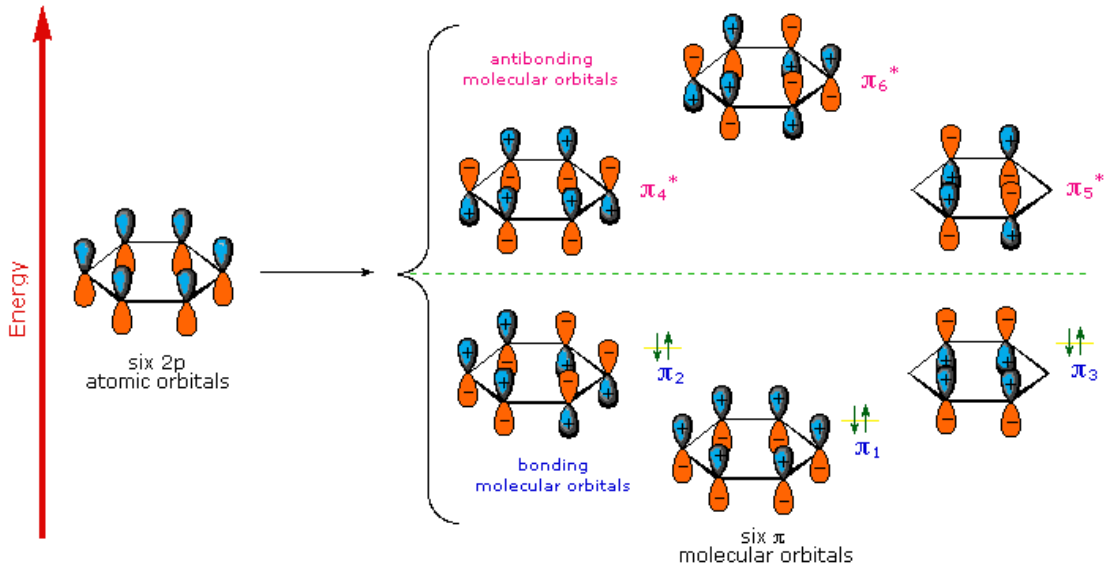


Figure 15.2.2: An electrostatic potential map of benzene

The Molecular Orbitals of Benzene

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals

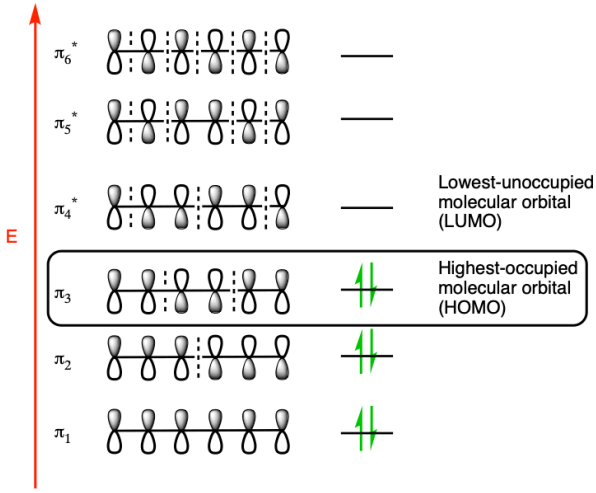
having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.



The Pi Molecular Orbitals Of 1,3,5 Hexatriene



The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding

interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

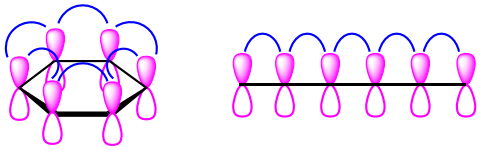
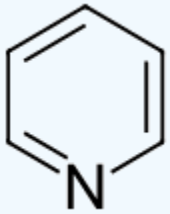


Figure 15.2.3: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

Exercises

Exercise 15.2.1

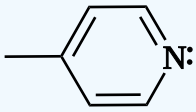
The molecule, pyridine, is planar with bond angles of 120°. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



Answer available at the end of this section.

Exercise 15.2.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer available at the end of this section.

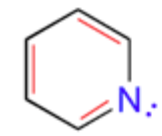
References

https://royalsocietypublishing.org/d...rspa.1964.0092 "A crystallographic study of solid benzene by neutron diffraction" G.E. Bacon, N. A. Curry, and S.A. Wilson, 1964

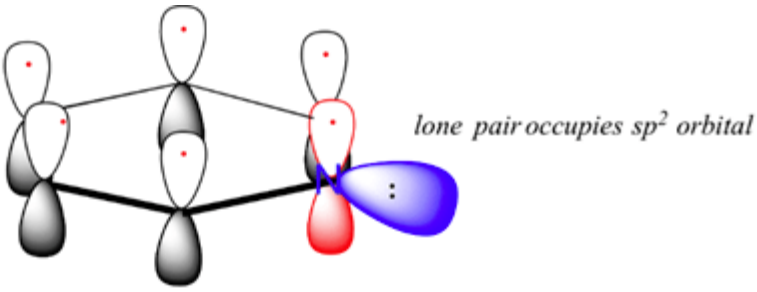
Answers

Exercise 15.2.1

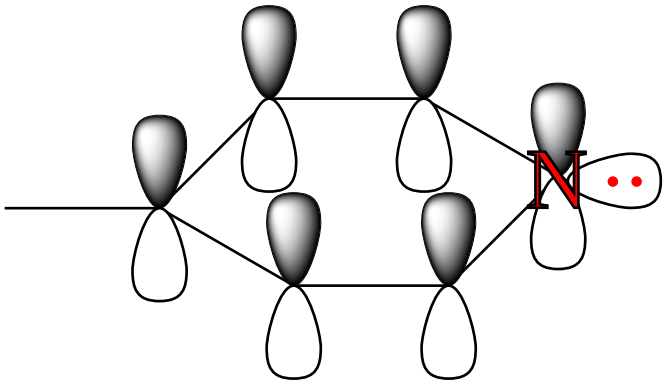
The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120° bond angles.



pyridine
(aromatic)



Exercise 15.2.2



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15.3: Pi Molecular Orbitals of Benzene

Objectives

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

Key Terms

Make certain that you can define, and use in context, the key term below.

- degenerate

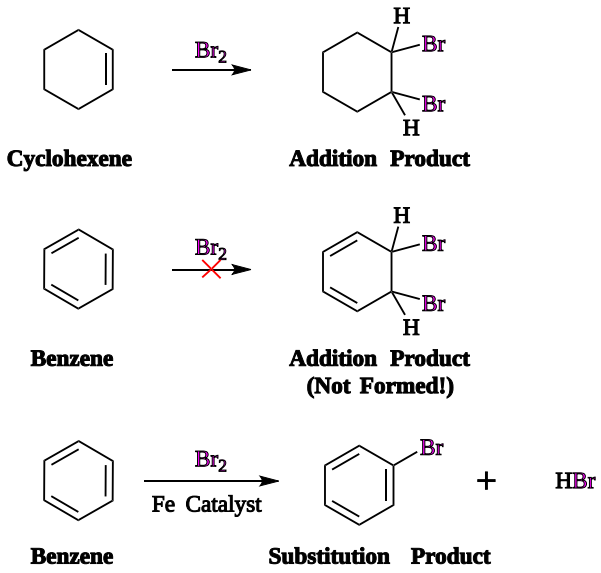
Study Notes

You may wish to review Sections 1.5 and 14.1 before you begin to study this section.

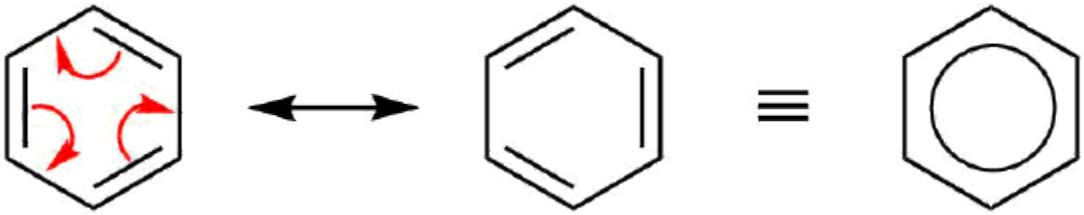
Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and π_5^*) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

Structure of Benzene

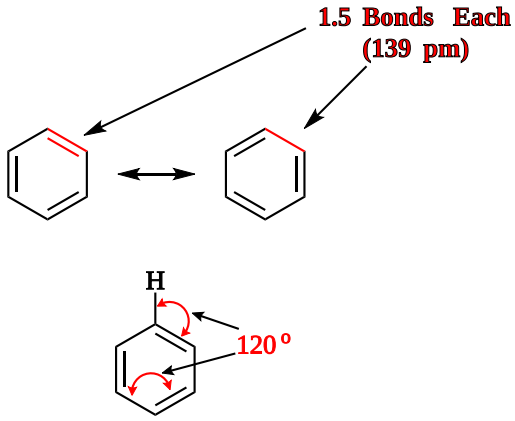
When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.



The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

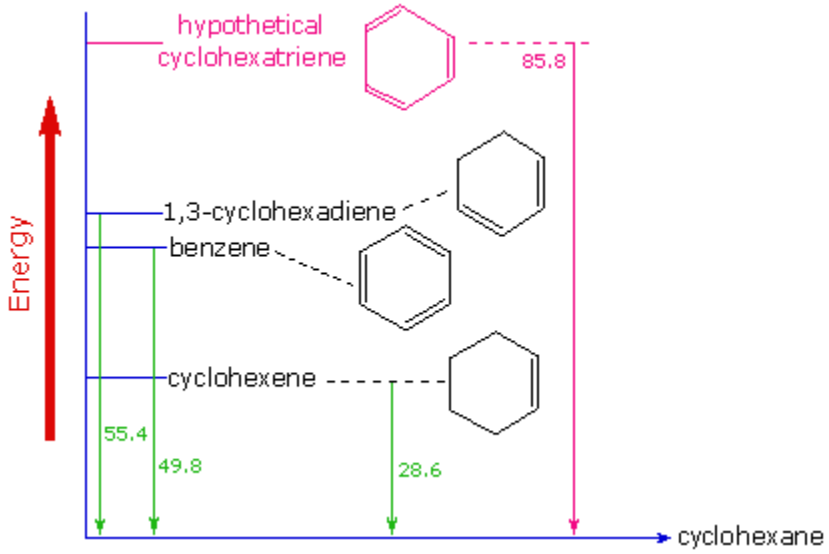


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120^o and makes the overall molecule planar.



The High Stability of Benzene

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole.



These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

Atomic Orbitals of Benzene

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that

extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

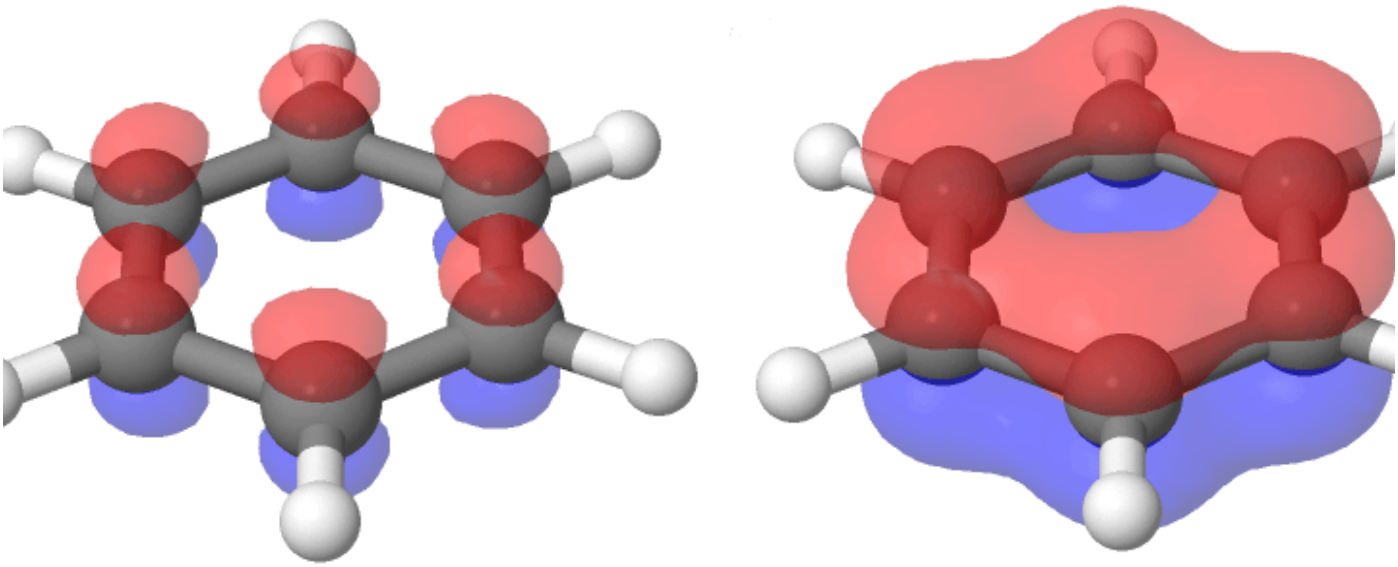


Figure 15.3.1: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

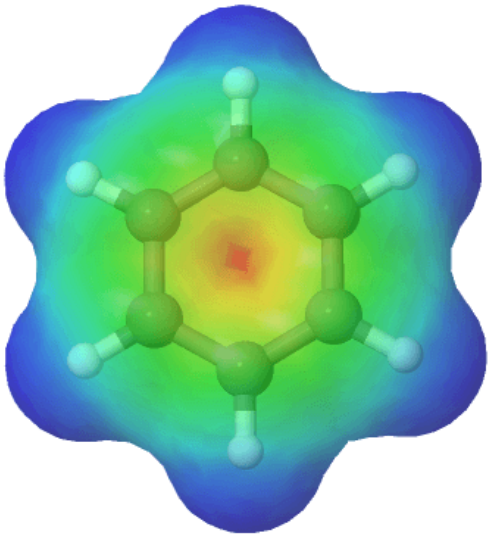
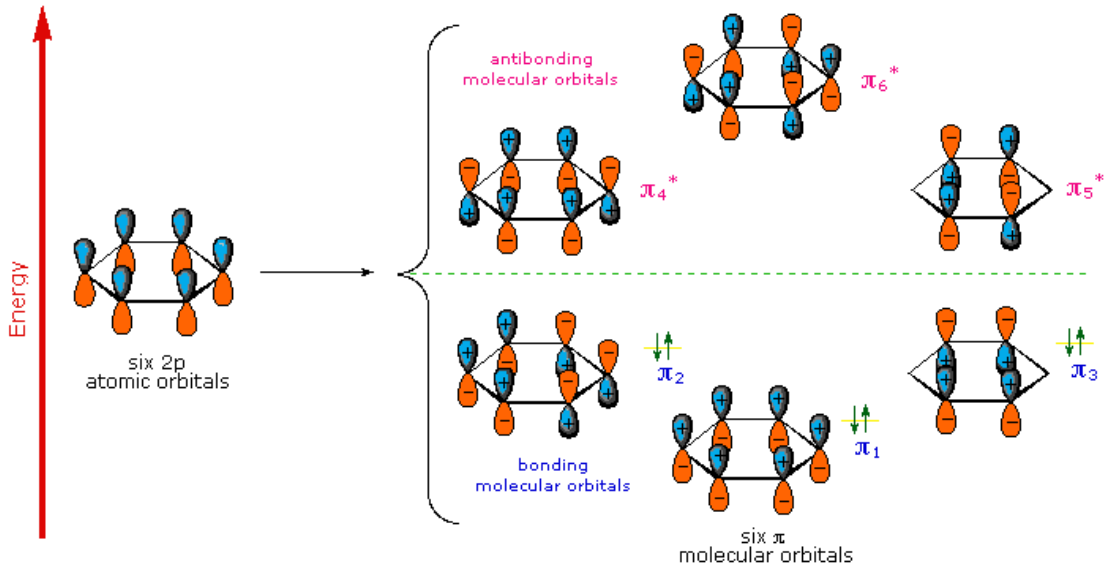


Figure 15.3.2: An electrostatic potential map of benzene

The Molecular Orbitals of Benzene

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals

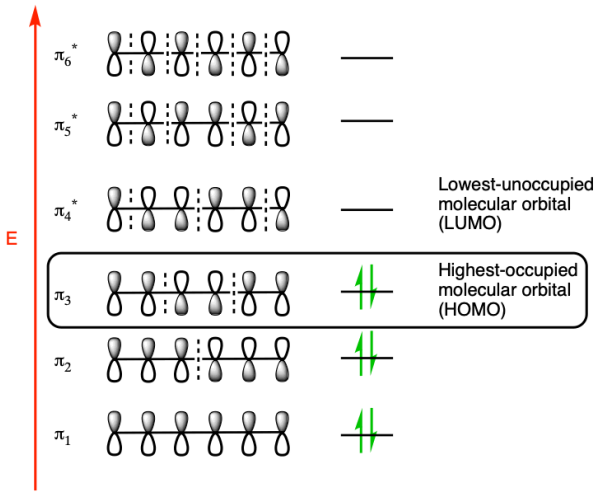
having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.



The Pi Molecular Orbitals Of 1,3,5 Hexatriene



The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding

interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

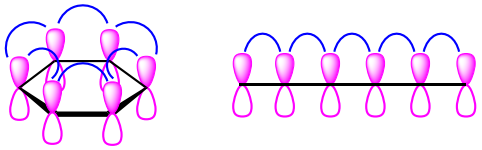
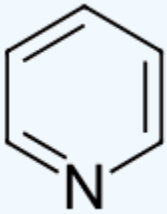


Figure 15.3.3: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

Exercises

Exercise 15.3.1

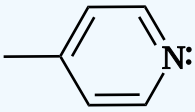
The molecule, pyridine, is planar with bond angles of 120°. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



Answer available at the end of this section.

Exercise 15.3.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer available at the end of this section.

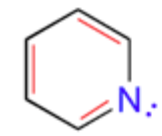
References

https://royalsocietypublishing.org/d...rspa.1964.0092 "A crystallographic study of solid benzene by neutron diffraction" G.E. Bacon, N. A. Curry, and S.A. Wilson, 1964

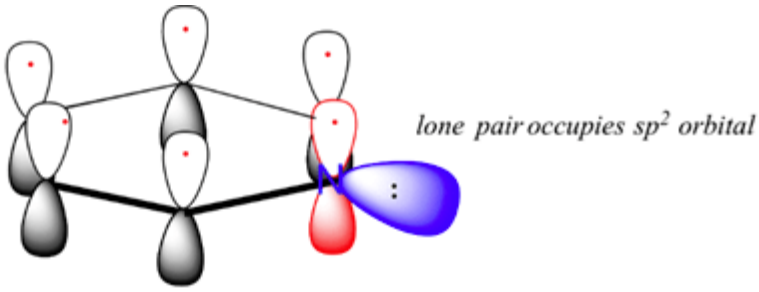
Answers

Exercise 15.3.1

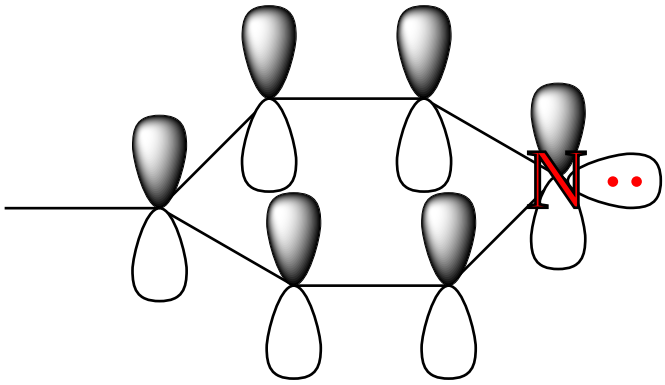
The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120° bond angles.



pyridine
(aromatic)



Exercise 15.3.2



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15.4: Spectral Characteristics of the Benzene Ring

Objectives

After completing this section, you should be able to

1. determine whether an unknown compound contains an aromatic ring by inspection of its infrared spectrum, given a table of characteristic infrared absorptions.
2. state the approximate chemical shift of aryl protons in a proton NMR spectrum.
3. explain why signals resulting from the presence of aryl protons are found downfield from those caused by vinylic protons in a proton NMR spectrum.
4. propose possible structures for an unknown aromatic compound, given its proton NMR spectrum, other spectroscopic data (such as a ^{13}C NMR or infrared spectrum), or both.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ring current

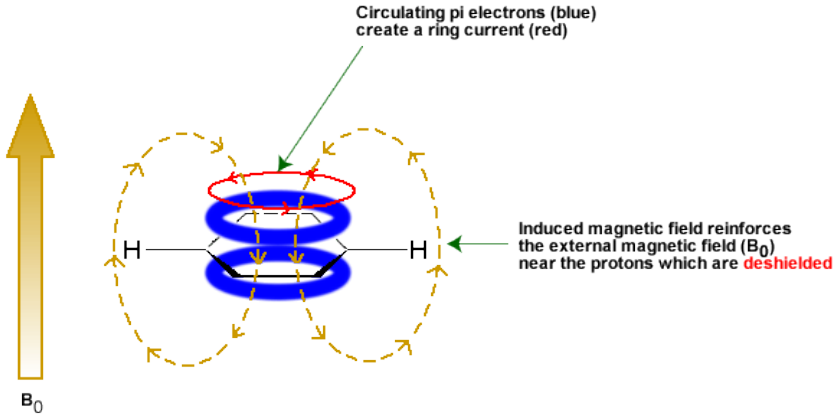
Study Notes

It is not necessary that you memorize detailed spectroscopic data. In the laboratory, on assignments and when writing examinations, you will be provided with a table of characteristic infrared absorptions to assist you in interpreting infrared spectra.

The important points to note about the proton NMR of aromatic compounds are the approximate chemical shifts of such protons and the complex splitting pattern that is sometimes observed. You are advised not to spend too long trying to understand why the signal for an aryl proton is found downfield from the signal for a vinylic proton. In general, we want you to be able to interpret NMR spectra, and leave the underlying theory for subsequent chemistry courses.

The chemical shifts of aromatic protons

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.



We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a **ring current**, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the p electrons does not shield the benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.

If we are outside the ring in the figure above, we feel a magnetic field pointing in a northerly direction. If we are inside the ring, however, we feel a field pointing to the south.

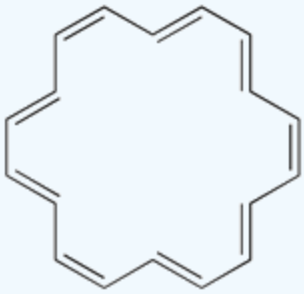
In the induced field generated by the aromatic ring current, the benzylic protons are outside the ring – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the electrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly de-shielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

The presence of anisotropy effects is often used to indicate aromaticity in a molecule. An example is the nonaromatic 8 pi electron cyclooctatetraene. In order to avoid anti-aromatic destabilization, the molecule takes a non-planar conformation which prevents conjugation and ring currents. Consequently, the molecule's protons absorbed at 5.8 ppm which is within the alkene region of ^{1}H NMR.

Exercise 15.4.1

The ^{1}H-NMR spectrum of [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.

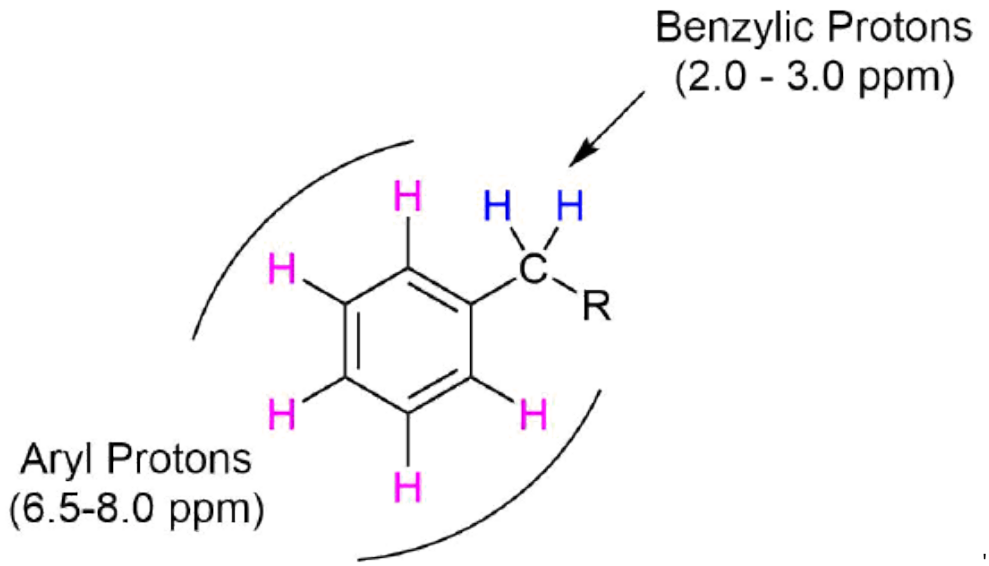


[18] annulene

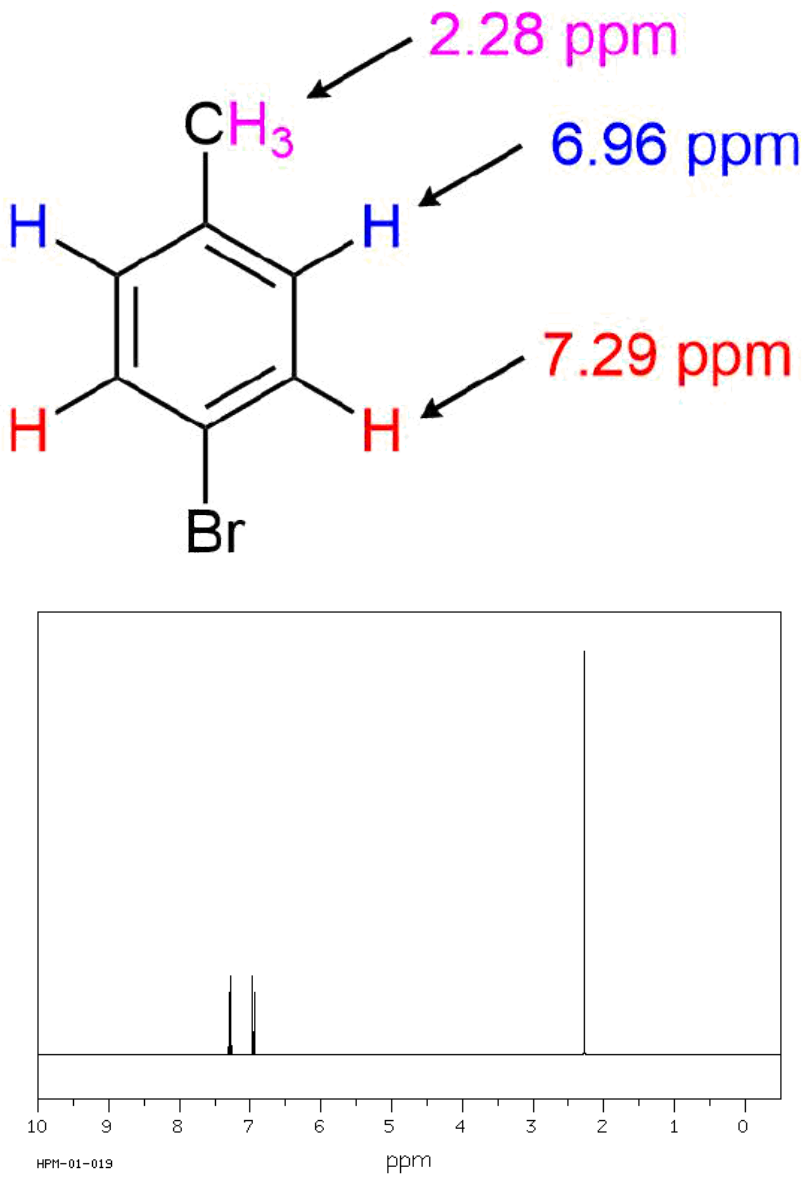
Answer available at the end of this section.

Characteristic ^{1}H NMR Absorptions of Aromatic Compounds

Protons directly attached to an aromatic ring, commonly called aryl protons, show up about 6.5-8.0 PPM. This range is typically called the aromatic region of an ^{1}H NMR spectrum. Protons on carbons directly bonded to an aromatic ring, called benzylic protons, show up about 2.0-3.0 PPM.



For the ^{1}H NMR spectrum of p-bromotoluene, the absorption for the benzylic protons appears as a strong singlet at 2.28 ppm. Due to the molecule's symmetry, the aryl protons appear as two doublets at 6.96 & 7.29 ppm.



Characteristic ^{13}C NMR Absorptions of Aromatic Compounds

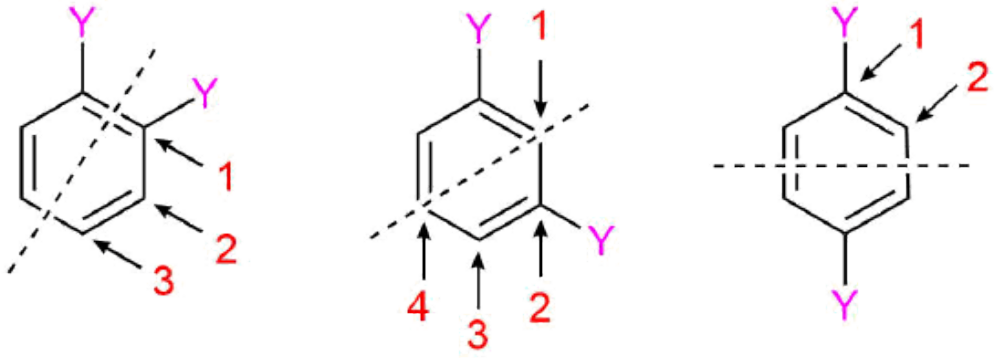
Carbons in an aromatic ring absorb in the range of 120-150 ppm in a ^{13}C NMR spectrum. This is virtually the same range as nonaromatic alkenes (110-150 ppm) so peaks in this region are not definitive proof of a molecule's aromaticity.

Due to the decoupling in ^{13}C NMR, the number of absorptions due to aromatic carbons can easily be observed. This can be used to determine the relative positions (*ortho*, *meta*, or *para*) for di-substituted benzenes. Peak assignments can be simplified by noting that ^{13}C peaks tend to be larger if two carbons contribute to the absorption.

Symmetrical Di-substituted Benzenes

Benzenes substituted with two identical groups have a relatively high amount of symmetry. In all three configurations, there is a plane of symmetry which reduces the number of distinct aryl carbon absorptions to less than six. The *ortho* configuration has a plane of symmetry which mirrors each carbon in the benzene ring causing only three ^{13}C aryl absorptions to occur. The *meta* configuration's plane of symmetry mirrors two carbons of the benzene ring allowing for four aryl absorptions to occur. The *para*

configuration actually has two planes of symmetry (one vertical and one horizontal on the structure below) through the benzene ring, which only allows two distinct aryl absorptions to occur.



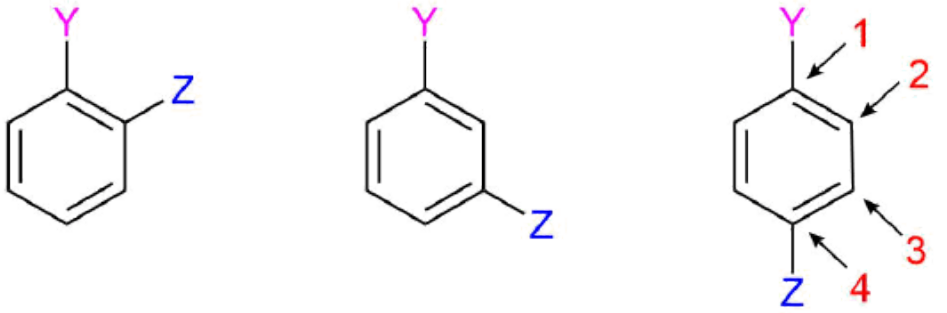
Ortho
Three ^{13}C
Arene Peaks

Meta
Four ^{13}C
Arene Peaks

Para
Two ^{13}C
Arene Peaks

Asymmetrical Di-substituted Benzenes

The lack of a plane of symmetry in asymmetrical di-substituted benzenes makes each carbon in the *ortho* and *meta* configuration unique. Consequently, their ^{13}C NMR spectra show six arene absorptions. However, the *para* configuration has a plane of symmetry drawn through the two substituents which mirrors two carbons of the benzene ring causing only 4 arene absorptions to appear.

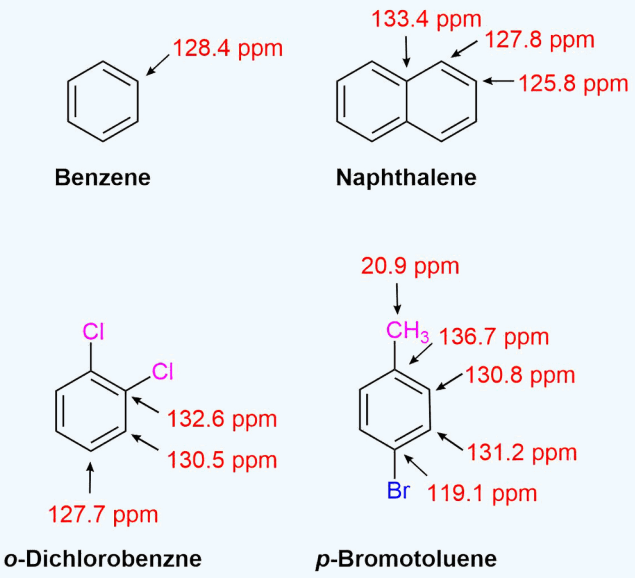


Ortho
No Symmetry
Six ^{13}C
Arene Peaks

Meta
No Symmetry
Six ^{13}C
Arene Peaks

Para
Four ^{13}C
Arene Peaks

Example 15.4.1



Charateristic IR Absorption of Benzene Derivatives

Arenes have absorption bands in the 650-900 cm^{-1} region due to bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

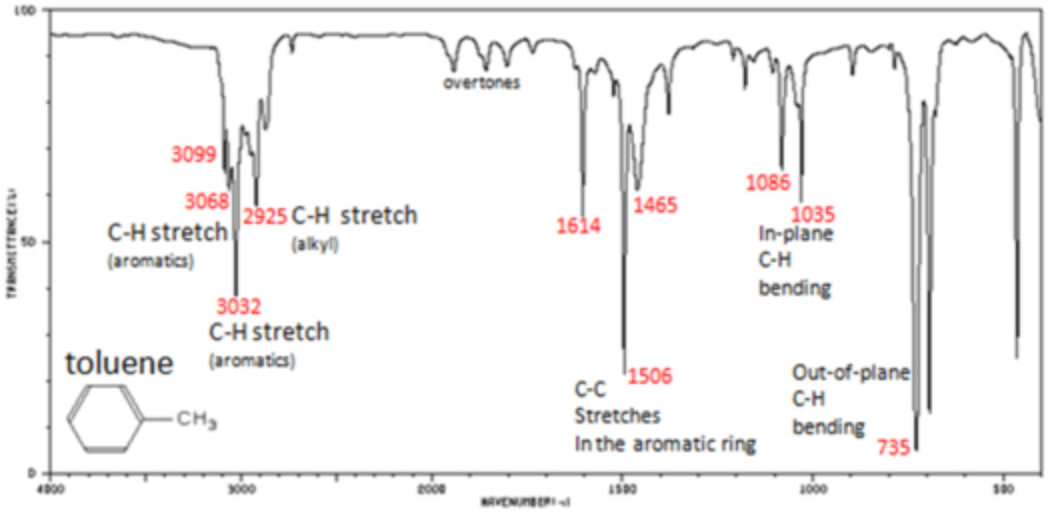
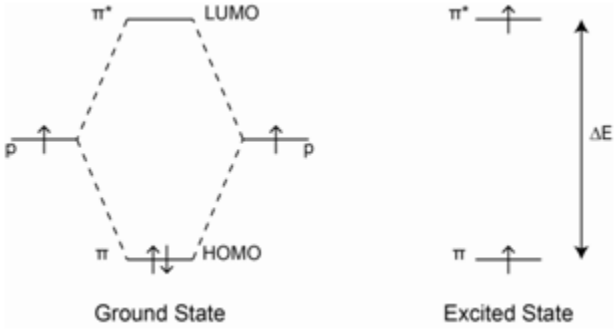


Figure 6. Infrared Spectrum of Toluene

Ultraviolet Spectroscopy

The presence of conjugated π bonds makes aromatic rings detectable in a UV/Vis spectrum. Benzene primarily absorbs through a be a π-π* transition over the range from 160-208 nm with a λ_{max} value of about 178 nm.



Benzene shows a less intense absorption in 230-276 nm range. These absorptions are due to vibrational fine structure often displayed by rigid molecules such as benzene and other aromatic compounds.

Answers

Exercise 15.4.1

The molecule contains two groups of equivalent protons: the twelve pointing to the outside of the ring, and the six pointing into the center of the ring. The molecule is aromatic, as evidenced by the chemical shift of the 'outside' protons' (and the fact that there are 18 p electrons - a Hückel number). The inside protons are *shielded* by the induced field of the aromatic ring current, because *inside the ring this field points in the opposite direction of* B_0. This is the source of the unusually low (negative relative to TMS) chemical shift for these protons.

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15.5: Polycyclic Aromatic Hydrocarbons

Objectives

After completing this section, you should be able to draw the resonance contributors for polycyclic aromatic compounds, such as naphthalene, anthracene, etc.

Key Terms

Make certain that you can define, and use in context, the key term below.

- polycyclic aromatic compounds

Study Notes

As their name indicates, *polycyclic aromatic hydrocarbons* are aromatic hydrocarbons which contain more than one benzenoid (i.e., benzene-like) ring. This section deals only with those compounds in which the benzenoid rings are fused together; in other words, compounds in which at least one carbon-carbon bond is common to two aromatic rings. Another type of polycyclic aromatic hydrocarbon contains two or more benzenoid rings joined by a carbon-carbon single bond. The simplest compound of this type is biphenyl, the compound from which PCBs (polychlorinated biphenyls) are derived.

biphenyl and 2,4,2',5'-tetrachlorobiphenyl

Figure 15.3: Structures of biphenyl and a typical PCB

Polycyclic Aromatic Compounds

Hückel's 4n +2 rule for aromaticity does not only apply to mono-cyclic compounds. Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons. The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms (in the structure below, note that the top right and center right rings are not attached to one another). This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

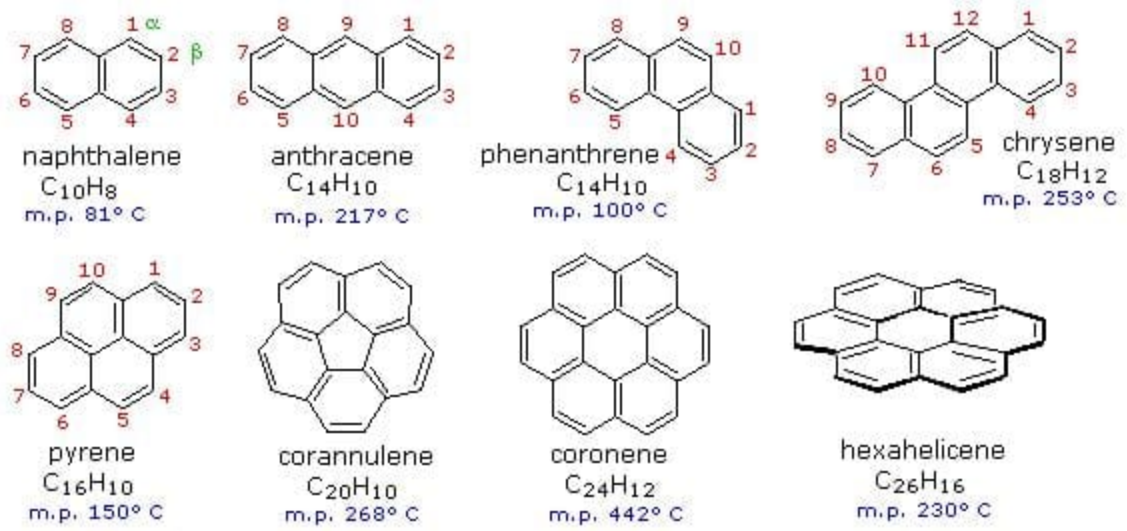
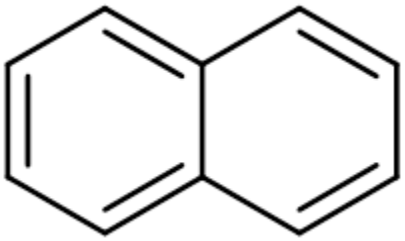
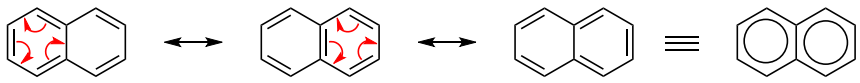


***Figure 2**: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).*

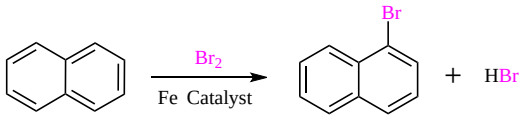
Probably the most well know polycyclic aromatic compound which only contains carbon is naphthalene ($C_{10}H_8$). Naphthalene shares many of the same characteristic as benzene. Naphthalene is cyclic and known to be flat. Each carbon in naphthalene is sp^2 hybridized so it is completely conjugated. The true structure of naphthalene is a combination of three resonance hybrids.



Naphthalene

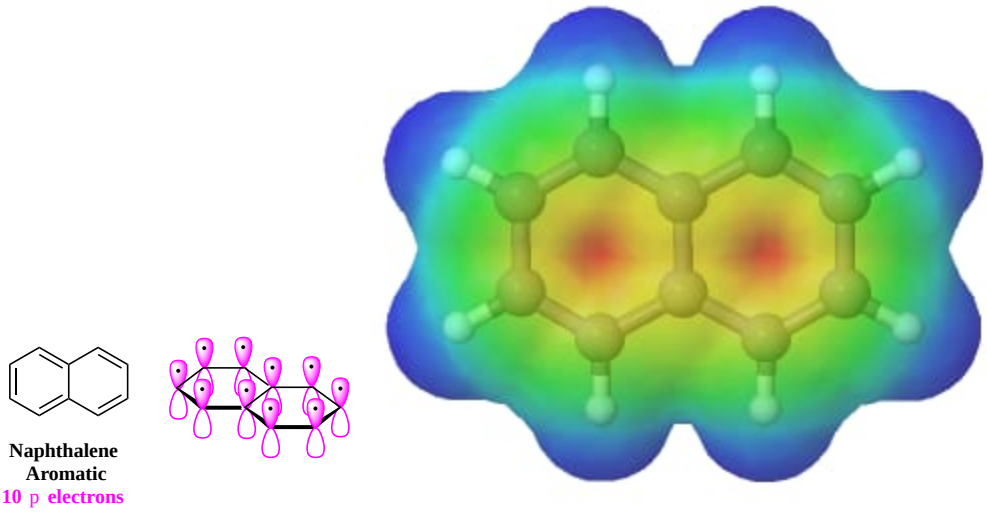


Heat of hydrogenation experiments with naphthalene shows an unusual "aromatic" stabilization energy. Also, naphthalene prefers to react with electrophiles to give substitution products rather than the typical double bond addition products.



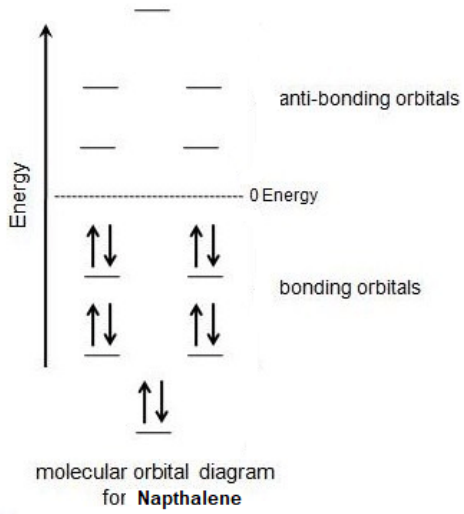
Naphthalene **1-Bromonaphthalene**
Substitution Product

Every carbon in naphthalene is sp^2 hybridized so there is conjugated p orbital overlap over the entire ring system. The electrostatic potential map shows that pi electrons in naphthalene are evenly distributed making each carbon equivalent.



Naphthalene
Aromatic
10 p electrons

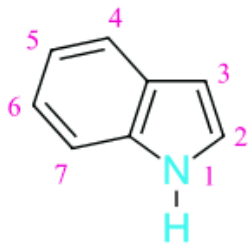
Lastly, naphthalene has 10 pi electrons which fulfills Hückel's rule. The importance of the 4n + 2 rule can be seen when considering the molecular orbital diagram of naphthalene. Naphthalene has 10 p orbitals which is 4 more than benzene. In the molecular orbital diagram of naphthalene, the 4 additional p orbitals become 2 bonding orbitals and two anti-bonding orbitals. The two additional bonding orbitals require 4 additional pi electrons to be filled so naphthalene needs 10 pi electrons in total to fill all of the bonding molecular orbitals.



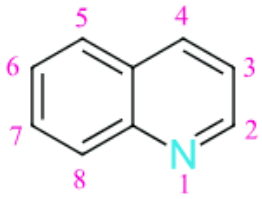
molecular orbital diagram
for **Napthalene**

Polycyclic Aromatic Heterocycles

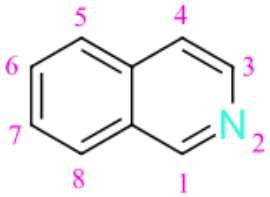
There is a wide variety of polycyclic aromatic heterocycles, many of which contain nitrogen, oxygen, or sulfur. Some of the biologically important structures, are the nitrogen containing polycyclic aromatic heterocycles indole, quinoline, isoquinoline, and purine which are all polycyclic aromatic heterocycles commonly found in nature. Notice that these compound all have 10 pi electrons.



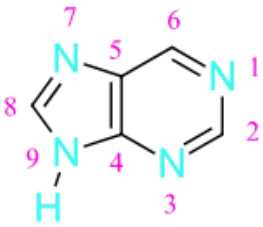
Indole



Quinoline

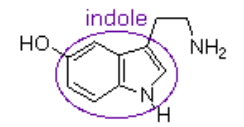


Isoquinoline

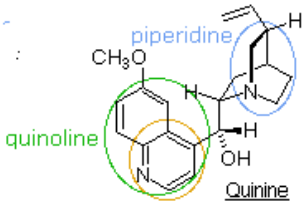


Purine

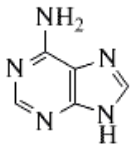
Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.



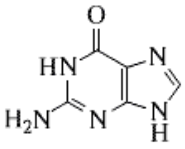
Serotonin
an important neurochemical



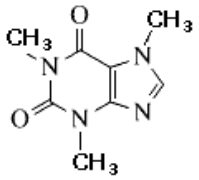
pyridine Quinine
antimalarial



adenine



guanine

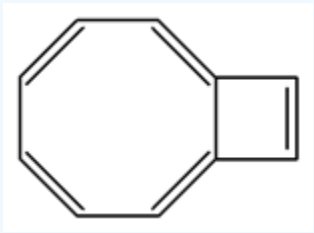


caffeine

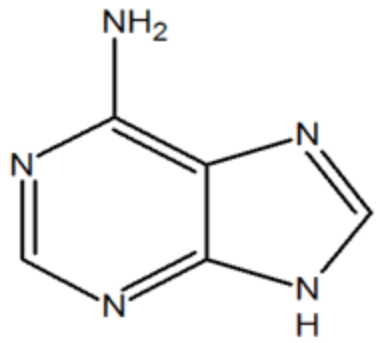
Exercises

Exercise 15.5.1

1) The following molecule is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



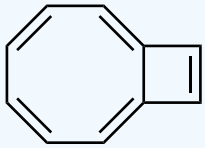
2) The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?



Answer available at the end of this section.

Exercise 15.5.2

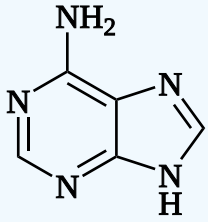
This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



Answer available at the end of this section.

Exercise 15.5.3

The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?



Answer available at the end of this section.

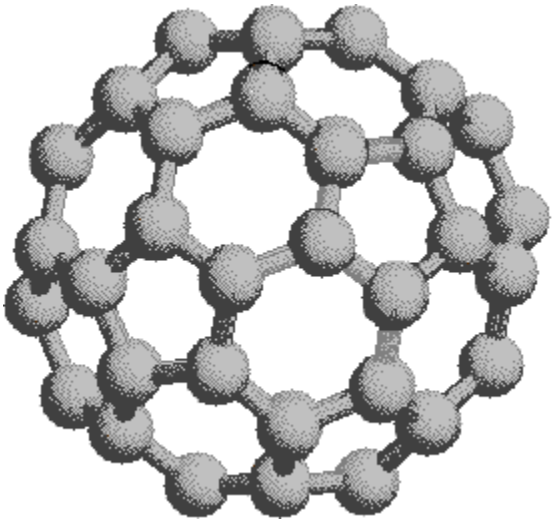
If we extend the structure of corannulene by adding similar cycles of five benzene rings, the curvature of the resulting molecule should increase, and eventually close into a sphere of carbon atoms. The archetypical compound of this kind (C_{60}) has been named **buckminsterfullerene** because of its resemblance to the geodesic structures created by Buckminster Fuller. It is a member of a family of similar carbon structures that are called **fullerenes**. These materials represent a third class of carbon allotropes. Alternating views of the C_{60} fullerene structure are shown on the right, together with a soccer ball-like representation of the 12 five and 20 six-membered rings composing its surface. Precise measurement by Atomic Force Microscopy (AFM) has shown that the C-C bond lengths of the six-membered rings are not all equal, and depend on whether the ring is fused to a five or six-membered beighbor. By clicking on this graphic, a model of C_{60} will be displayed.

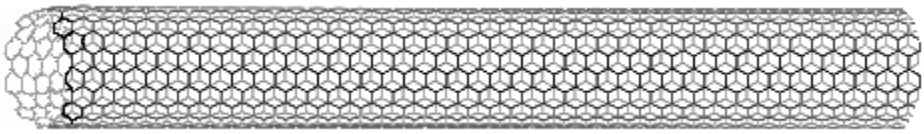
Although C_{60} is composed of fused benzene rings its chemical reactivity resembles that of the cycloalkenes more than benzene. Indeed, exposure to light and oxygen slowly degrade fullerenes to cage opened products. Most of the reactions thus far reported for C_{60} involve addition to, rather than substitution of, the core structure. These reactions include hydrogenation, bromination

and hydroxylation. Strain introduced by the curvature of the surface may be responsible for the enhanced reactivity of C_{60}.

. Larger fullerenes, such as C_{70}, C_{76}, C_{82} & C_{84}have ellipsoidal or distorted spherical structures, and fullerene-like assemblies up to C_{240} have been detected. A fascinating aspect of these structures is that the space within the carbon cage may hold atoms, ions or small molecules. Such species are called **endohedral fullerenes**. The cavity of C_{60} is relatively small, but encapsulated helium, lithium and atomic nitrogen compounds have been observed. Larger fullerenes are found to encapsulate lanthanide metal atoms.

Interest in the fullerenes has led to the discovery of a related group of carbon structures referred to as nanotubes. As shown in the following illustration, nanotubes may be viewed as rolled up segments of graphite. The chief structural components are six-membered rings, but changes in tube diameter, branching into side tubes and the capping of tube ends is accomplished by fusion with five and seven-membered rings. Many interesting applications of these unusual structures have been proposed.

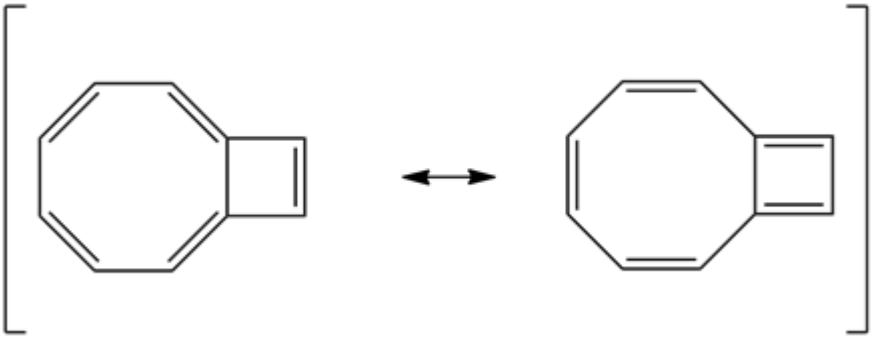




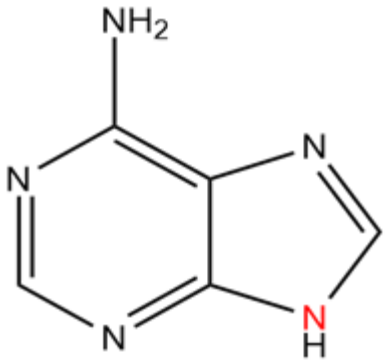
Answers

Exercise 15.5.1

1) It has 10 pi electrons which follows the 4n+2 rule making it aromatic.

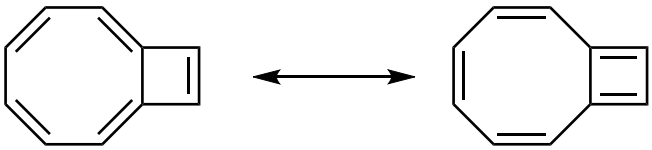


2) There is only one nitrogen of the core that contributes a set of lone pair electrons as 2 pi electrons (in red). All of the other nitrogens are sp2 hybrized and contribute 1 pi electron each. In total, the core is aromatic with 10 electrons in the pi-system.



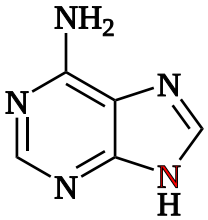
Exercise 15.5.2

Yes, it is aromatic. 4n+2 pi-electrons.



Exercise 15.5.3

There is only one nitrogen of the core that contributes to the pi-system (in red). With this one lone pair the core is aromatic with 10 electrons in the pi-system.



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15.6: Other Cyclic Polyenes: Huckel 's Rule

Objectives

After completing this section, you should be able to

1. define aromaticity in terms of the Hückel $4n + 2$ rule.
2. use the Hückel $4n + 2$ rule to determine whether or not a given polyunsaturated cyclic hydrocarbon should exhibit aromatic properties.
3. describe the difference in properties between an aromatic hydrocarbon, such as benzene, and a non-aromatic polyunsaturated cyclic hydrocarbon, such as cyclobutadiene or cyclooctatetraene.
4. draw molecular orbital diagrams for aromatic species, such as benzene, the cyclopentadienyl anion and pyridine, and compare these diagrams with those obtained for non-aromatic species, such as cyclobutadiene and the cyclopentadienyl cation.

Study Notes

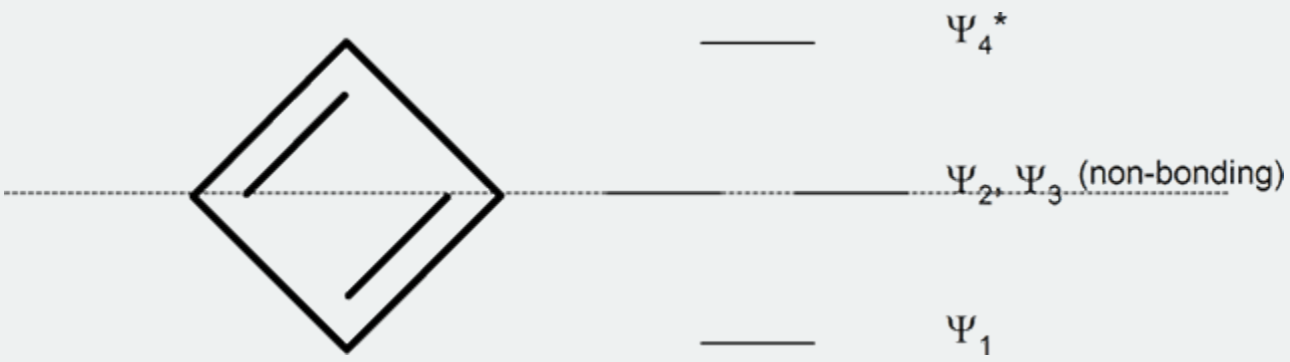
The following mnemonic device will help you establish the approximate energy levels for the molecular orbitals of various organic ring systems.

Whatever the size of the ring, place one point of the ring down to the bottom. The corners of the ring, where the carbons are located, will roughly approximate the location and pattern of the molecular orbital energy levels. Cut the ring exactly in half. The energy levels in the top half will be anti-bonding (Ψ^*) orbitals and those in the bottom will be bonding (Ψ) orbitals. If the carbons fall directly in the centre of the ring (e.g., four-membered rings) the energy levels there are non-bonding.

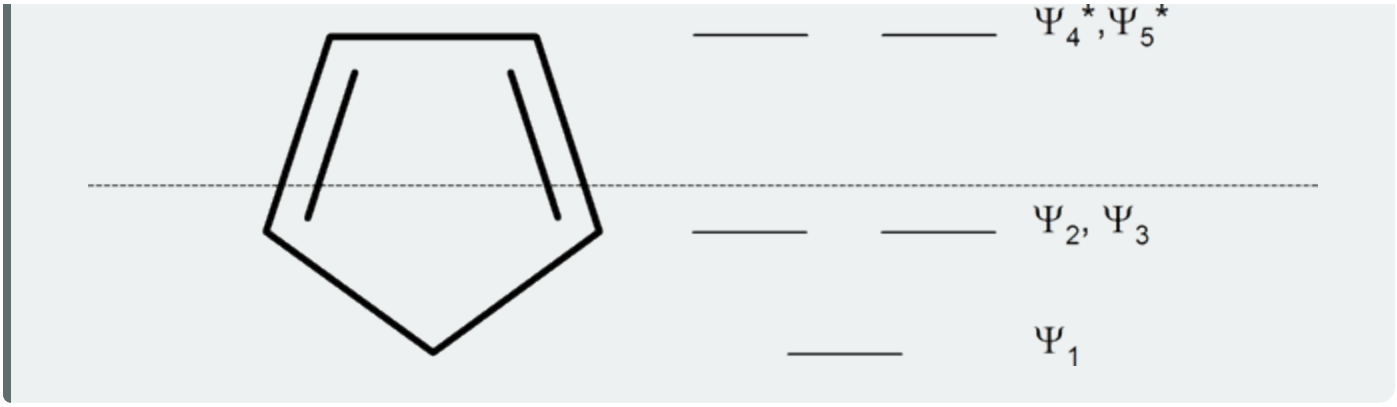
cyclopropenyl ring (three-membered ring)



cyclobutadienyl ring (four-membered ring)



cyclopentadienyl ring (five-membered ring)



In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has $4n + 2$ π electrons, it is considered aromatic. This rule would come to be known as **Hückel's Rule**.

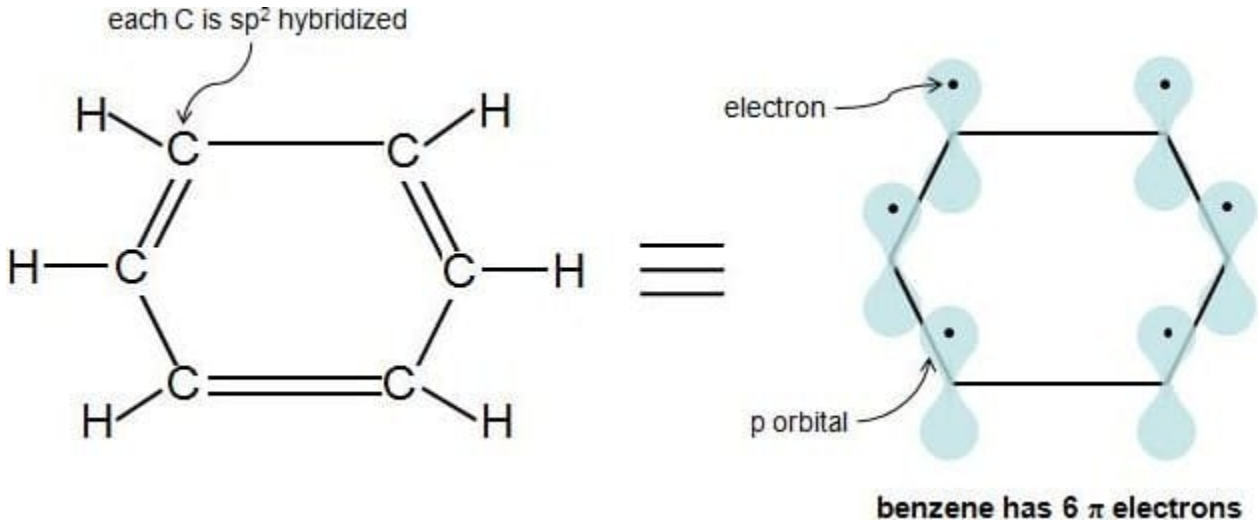
Four Criteria for Aromaticity

When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has 4n+2 π electrons (n=0 or any positive integer)

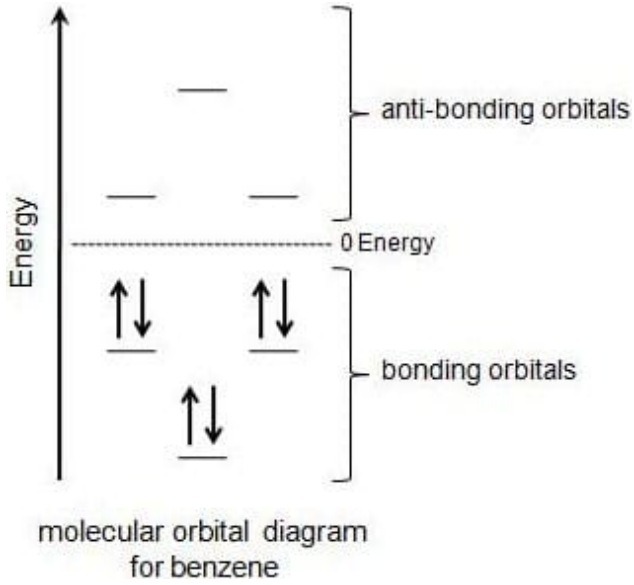
Counting π Electrons?

Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. Pi electrons lie in the p orbitals and sp^2 hybridized atoms have 1 of these p orbitals each. When looking at a C=C double bond we know that there is one sigma bond and one pi bond. The pi bond is formed by the overlap of 1 p orbital from each carbon in the double bond. Each p orbital contains one electron so when the two p orbitals overlap the two electrons become a pi bond and are thus called pi electrons. Because aromaticity deals directly with double bonds and conjugation it is simpler to just count the number pi electrons in a compound. Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.



Why 4n+2 π Electrons?

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram for benzene

To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

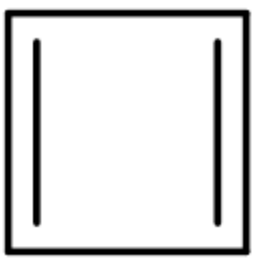
$$4n + 2 = 6 \tag{15.6.1}$$
$$4n = 4 \tag{15.6.2}$$
$$n = 1 \tag{15.6.3}$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

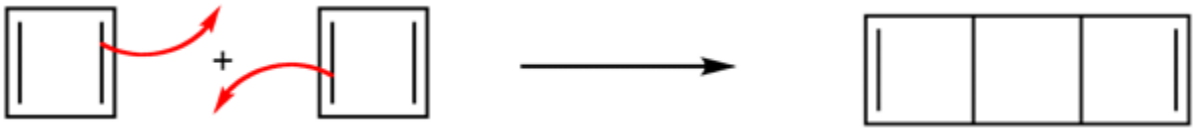
With Hückel's theory we can assume that if a molecule meets the other criteria for aromaticity and also has 2, 6, 10, 14, 18 ect. pi electrons it will most likely be aromatic.

Antiaromaticity

More than 100 years ago, chemists recognized the possible existence of other conjugated cyclic polyalkenes, which at least superficially would be expected to have properties like benzene. The most interesting of these are cyclobutadiene, whose shape and alignment of p orbitals suggested it should have substantial electron-delocalization energies.

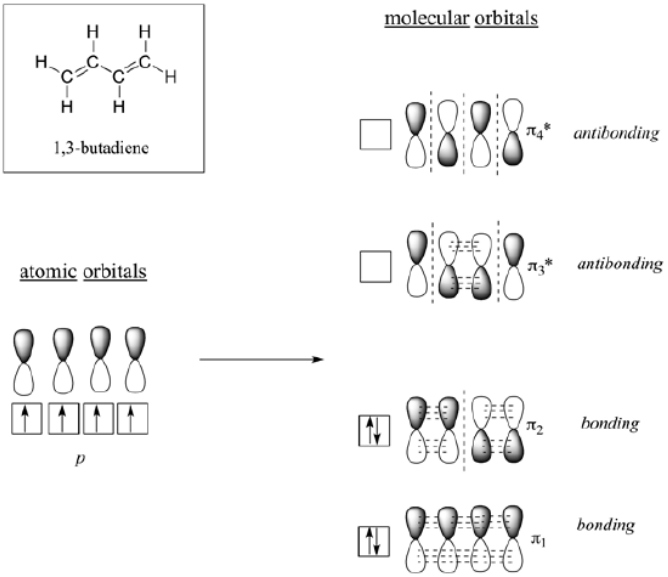


However, cyclobutadiene was found to be an extremely unstable molecules. In fact, cyclobutadiene is even more reactive than most alkenes. The synthesis of cyclobutadiene eluded chemists for almost 100 years. As more work was done, it became increasingly clear that the molecule, when formed in reactions, was immediately converted to something else. Finally, cyclobutadiene was captured in an essentially rigid matrix of argon at 8K. On warming to even 35K , it dimerizes through a Diels Alder reaction to yield a tricyclicdiene.



Due to the square ring, cyclobutadiene was expected to have some degree of destabilization associated with ring strain. However, estimations of the strain energies, though substantial, did not account for cyclobutadiene's high degree of instability. Also, why was it not being stabilized through cyclic conjugation in the same way as benzene. The answer can be seen in the molecular orbitals.

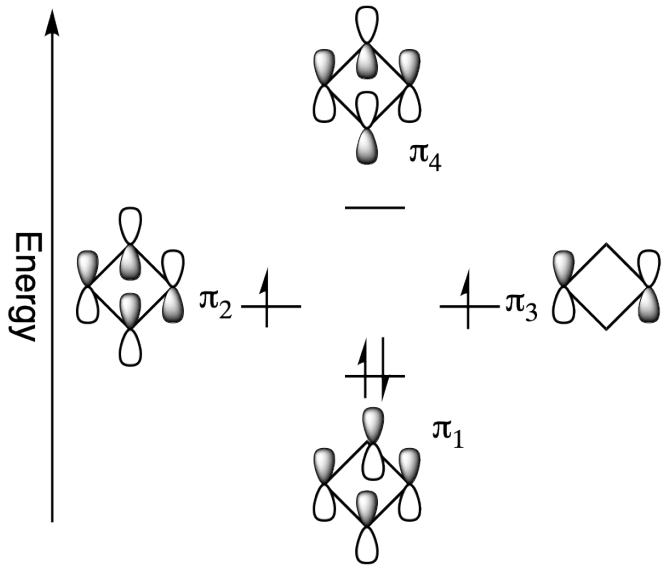
We considering the molecular orbitals diagram of the analogous 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



However, when placed into a ring the molecular orbitals undergo a significant change. The four p orbitals of cyclobutadiene combine to form the following 4 molecular orbitals:

- a bonding molecular orbital which is lower in energy than the atomic orbitals
- two degenerate non-bonding molecular orbitals which are of equivalent energy to the atomic orbitals
- one antibonding molecular orbital which is higher in energy

The non-bonding orbitals represent that there is no direct interaction between adjacent atoms. When adding cyclobutadiene's 4 pi electrons to the molecular orbital diagram, the bonding orbital is filled and both non-bonding orbitals are singly occupied. If cyclobutadiene's double bonds were delocalized, all the pi electrons would be in low energy bonding orbitals. However, only two of the pi electrons are in bonding orbitals; the other two are non-bonding. In addition, the molecular orbital diagram shows that two of the electrons are unpaired, a situation called a triplet state, which usually makes organic molecules very reactive. For cyclobutadiene cyclic conjugation has made the molecule less stable. This unexpected instability in 4n π-electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.



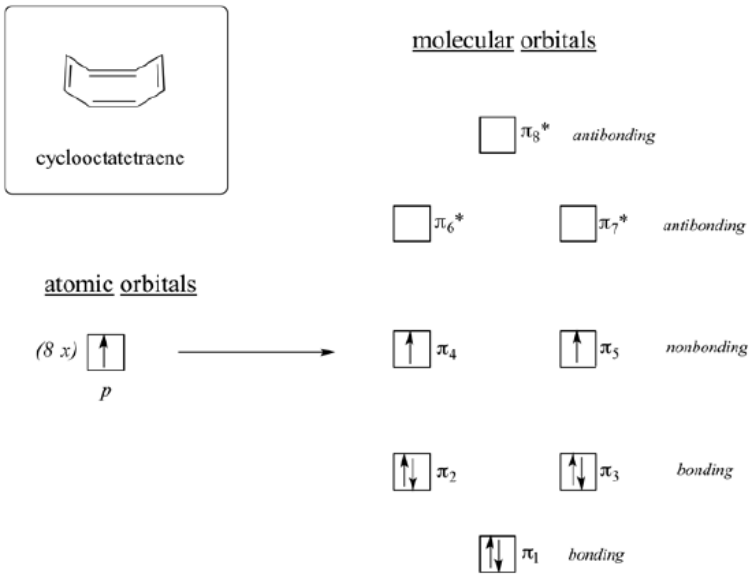
Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, and shape would be square. In fact, cyclobutadiene's double bonds are not conjugated but locked into position.

Just like 4n + 2 rule with aromaticity, compounds which are flat, cyclic, have a p orbital at every member of the ring, and 4n pi electrons should be antiaromatic. Another potentially antiaromatic molecule is 1,3,5,7-cyclooctatetraene.

Cyclooctatetraene was first synthesized in 1911 by a German chemist, R. Willstatter (Nobel Prize 1915), who reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. However, during the Second World War, the German chemist W. Reppe found that cyclooctatetraene can be made in reasonable yields by the tetramerization of ethyne under the influence of a nickel cyanide catalyst:



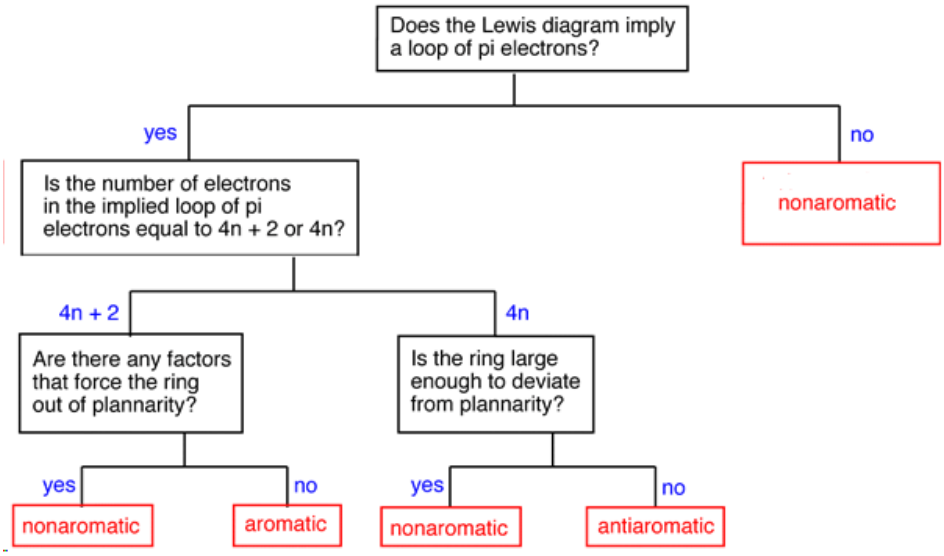
If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the molecular orbitals are fill with cyclooctatetraene's 8 pi electrons the last two electrons are unpaired in the two nonbonding orbitals creating a triplet state. Based off the molecular orbital diagram cyclooctatetraene should be antiaromatic.



However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbtials between double bond are out of alignment for overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its its pi bonds react like 'normal' alkenes. Because cyclooctatetraene is not flat nor conjugated it is properly defined as non-aromatic. In general, if an antiaromatic compound has the ability to form a non-planar shape it will do so to avoid destabilization by becoming non-aromatic.

Determining if a Compound is Aromatic, Antiaromatic, or Nonaromatic

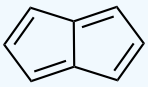
To make this determination it is important to first as if the compound has the possibility of cyclic conjugation. This requires that the compound be cyclic and have a p orbital at every atom in the ring. If the compound does not have both of these criteria it cannot be aromatic or antiaromatic and must therefore be nonaromatic. Next the number of pi electrons in the ring is determined to see if it follows the count of aromaticity (4n + 2) or antiaromaticity (4n). Before making the final determination, it is vital to know the actual geometry of the molecule. Despite the number of pi electrons, a compound cannot be aromatic or antiaromatic if its geometry is not planar to allow for p orbital overlap.



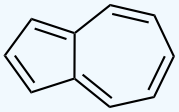
Example 15.6.1



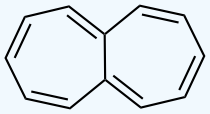
Cyclopentadiene (planar)
4 p Electrons
Nonaromatic



Pentalene (planar)
8 p Electrons
Antiaromatic



Azulene (planar)
10 p Electrons
Aromatic



Heptalene (planar)
12 p Electrons
Antiaromatic

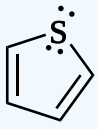
A Common Misconception

A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

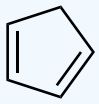
The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel 4n+2 aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so Hückel rule is applicable and furan is aromatic.

Exercise 15.6.1

Using the criteria for aromaticity, determine if the following molecules are aromatic:



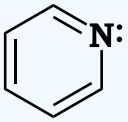
a)



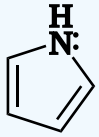
b)



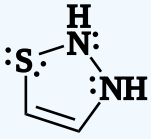
c)



d)



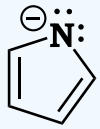
e)



f)



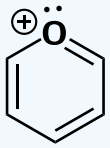
g)



h)



i)

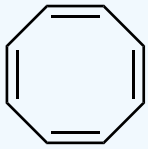


j)

Answer available at the end of this section.

Exercise 15.6.2

To be aromatic, a molecule must be planar conjugated, and obey the 4n+2 rule. The following is the following molecule aromatic?



Answer available at the end of this section.

References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman & Company, 2007.
2. Berson, Jerome. Chemical Creativity: Ideas from the Work of Woodward, Hückel, Meerwein, and Others. New York: Wiley-VCH, 1999.
3. Badger, G.M. Aromatic Character and Aromaticity. London, England: Cambridge University Press, 1969.
4. Lewis, David and David Peters. Facts and Theories of Aromaticity. London, England: Macmillan Press, 1975.

Answers

Exercise 15.6.1

a) Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1

b) Not aromatic - not fully conjugated, top C is sp^3 hybridized

c) Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2

d) Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

e) Aromatic - there are 6 π electrons, n=1

f) Not aromatic - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5

g) Not aromatic - there are 4 π electrons, n=1/2

h) Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1

i) Not aromatic - not fully conjugated, top C is sp^3 hybridized

j) Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

Exercise 15.6.2

No, it is not. It does not obey the 4n+2 rule. Also it is not planar.

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15.7: Huckel's Rule and Charged Molecules

Objectives

After completing this section, you should be able to

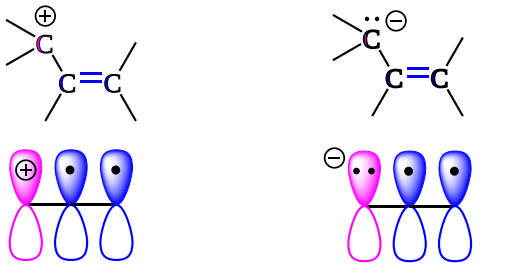
1. use the Hückel 4*n* + 2 rule to explain the stability of the cyclopentadienyl anion, the cycloheptatrienyl cation and similar species.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given unsaturated cyclic hydrocarbon anion or cation is aromatic.
3. draw the resonance contributors for the cyclopentadienyl anion, cation and radical, and similar species.

Aromatic Ions

As previously, noted a ring must be fully conjugated to have the potential to be aromatic. This means that every atom in the ring must have a *p* orbital which can overlap with adjacent *p* orbitals. Until now the atoms providing the *p* orbitals have been neutral sp^2 hybridized carbons, however it is also possible for sp^2 hybridized carbons to have a charge. There are several examples of cationic and anionic compounds with unexpected stabilities that suggest that they are aromatic. It is important to understand how charged carbons in these compounds will affect the determination of aromaticity.

There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized *p* orbital holds the carbocation's positive charge and is vacant of pi electrons. Although a carbocation is capable of extending conjugation it does not add to the compound's pi electron count.

A carbanion carbon is surrounded by four electron groups and would normally be sp^3 hybridized. However, to obtain the stabilizing effects of conjugation, carbanion carbons can becomes sp^2 hybridized putting the set of lone pair electrons into the unhybridized *p* orbital. Because the carbanion's *p* orbital contains two electrons in the form of a set of lone pair electrons, it increases a compound's pi electron count by 2.



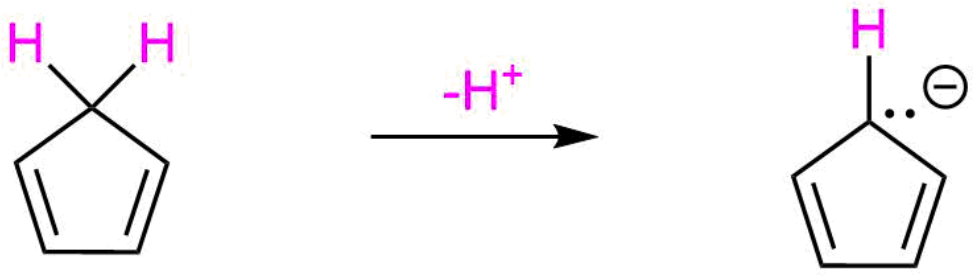
2 p Electrons Total
The carbocation adds
0 p Electrons

4 p Electrons Total
The carbanion adds
2 p Electrons

Cyclopentadiene Ion

One of the most well know examples of an aromatic ion is the 1,3-cyclopentadiene ion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized -CH_2- carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's 4n + 2 rule. However, if a proton is removed form the CH_2 group to form the cyclopentadienyl anion, the carbon atom becomes sp^2 hybridized and the two electrons of the resulting lone pair occupy the newly produced *p* orbital. This increases the number of pi electrons in the cyclopentadienyl anion to 6 which

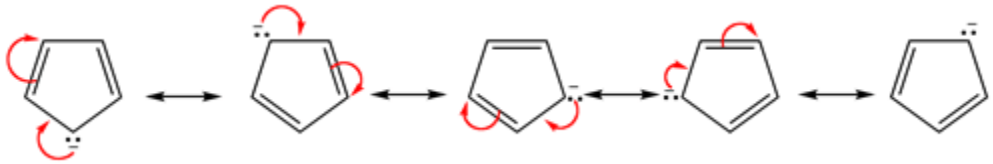
follows the 4n +2 rule. Moreover, this new *p* orbital overlaps with the *p* orbitals already present allowing for cyclic delocalization of pi electrons about the entire ring.

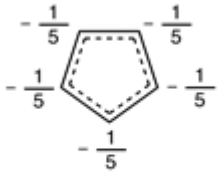


1,3-Cyclopentadiene
Nonaromatic
4 π electrons

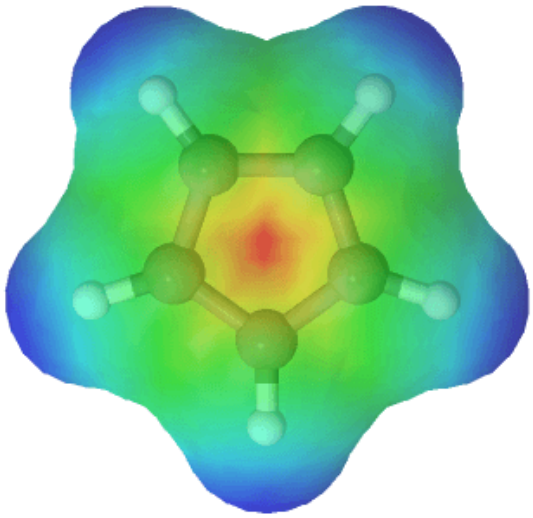
Cyclopentadienyl Anion
Aromatic
6 π electrons

The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance form. Also, the electrostatic potential map of the cyclopentadienyl anion show the negative charge, seen in red/yellow is distributed over the entire ring. The fact that the red/yellow color is held in the center of the ring indicates that the extra electrons of the ion are involved in the aromatic p-electron system.

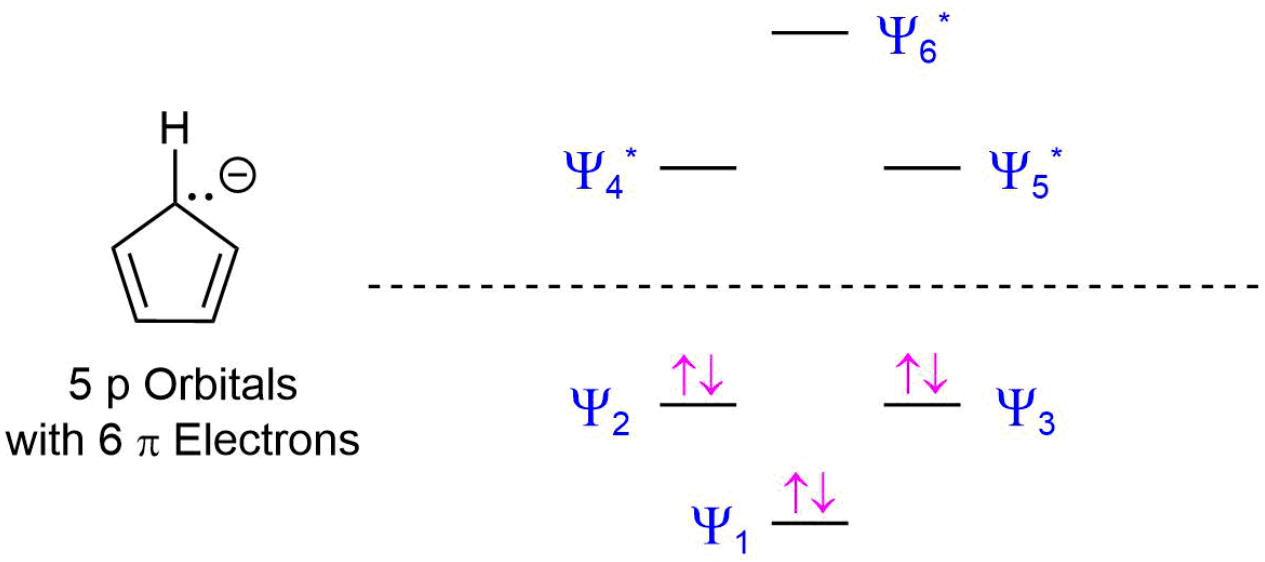




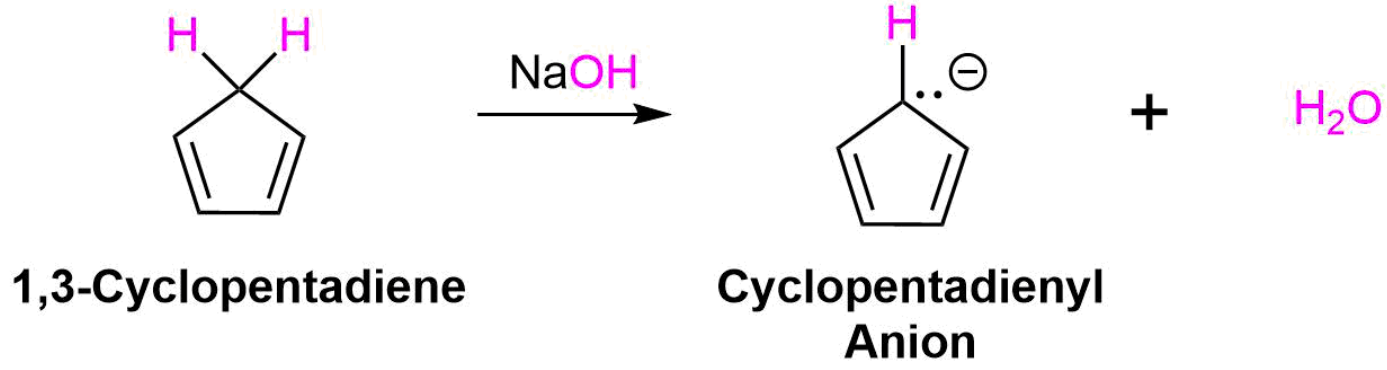
hybrid



The reason why the 4n +2 rule still works for a 5 p orbital ring system can be seen by looking the molecular orbital diagram of the cyclopentadienyl anion. As discussed in **Section 15.3**, the molecular orbital diagram of a 5 p orbital system is made up of 3 bonding MO's and 2 antibonding MO's. The 6 pi electrons gained by forming an anion is enough to completely fill the bonding MO's in the diagram giving the cyclopentadienyl anion aromaticity.



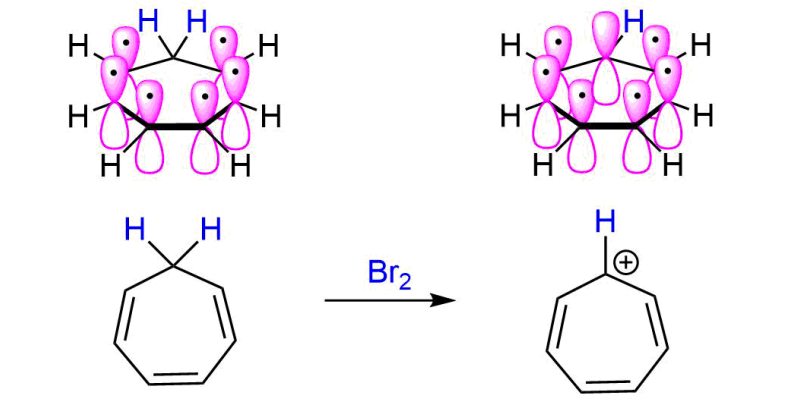
One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl anion, is stabilized through aromaticity. This makes 1,3-cyclopentadiene one of the most acidic hydrocarbons known with a pK_a of 16. This is almost 10^{30} times more acidic than cyclopentane. Because of its acidity, cyclopentadiene can be deprotonated by moderately strong bases such as NaOH.



Tropylium ion

The molecule 1,3,5-cycloheptatriene has six pi electrons but is nonaromatic due the presence of an sp^3 hybridized -CH_2- group which prevents cyclic delocalization. When 1,3,5-cycloheptatriene is reacted with a reagent that can remove a hydride ion ($H:^-$), the 1,3,5-cycloheptatrienyl cation, which is commonly known as the tropylium cation, is formed with unexpected ease. Despite the presence of an electron deficient carbocation, the tropylium cation, is unusually stable and can be isolated as a salt.

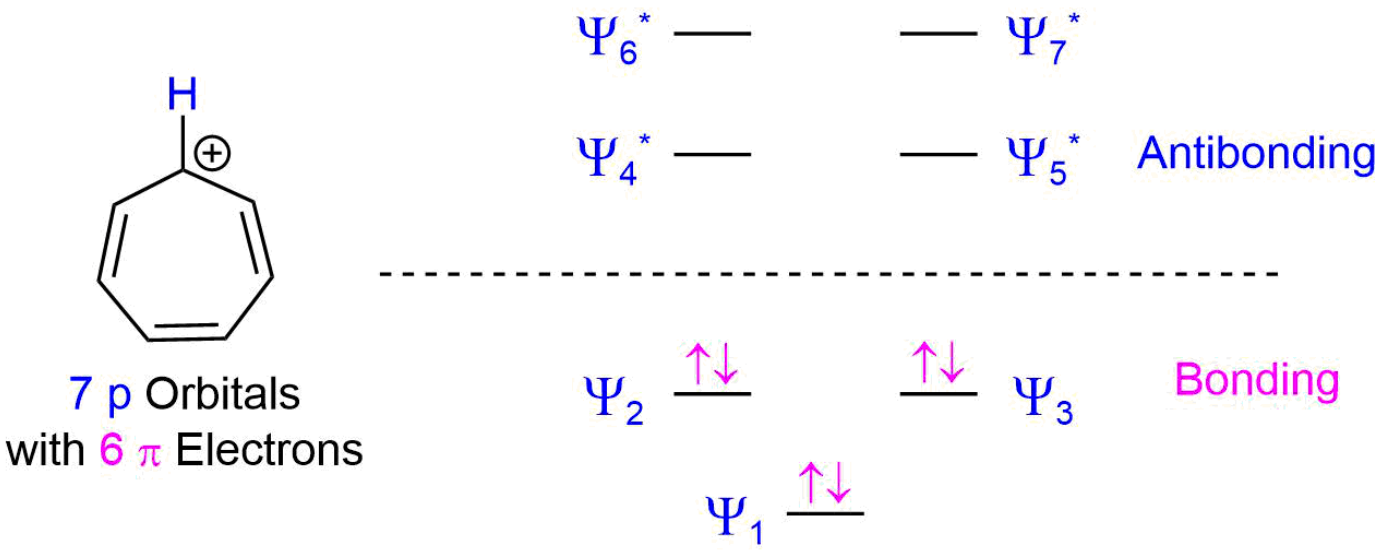
Removal of a hydride from the -CH_2- group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant *p* orbital. The new *p* orbital allows for cyclic conjugation to occur among the seven *p* orbitals in the tropylium cation. The vacant *p* orbital does not change the pi electron count so the tropylium cation has 6 pi electrons which obeys the 4n + 2 rule for aromaticity.



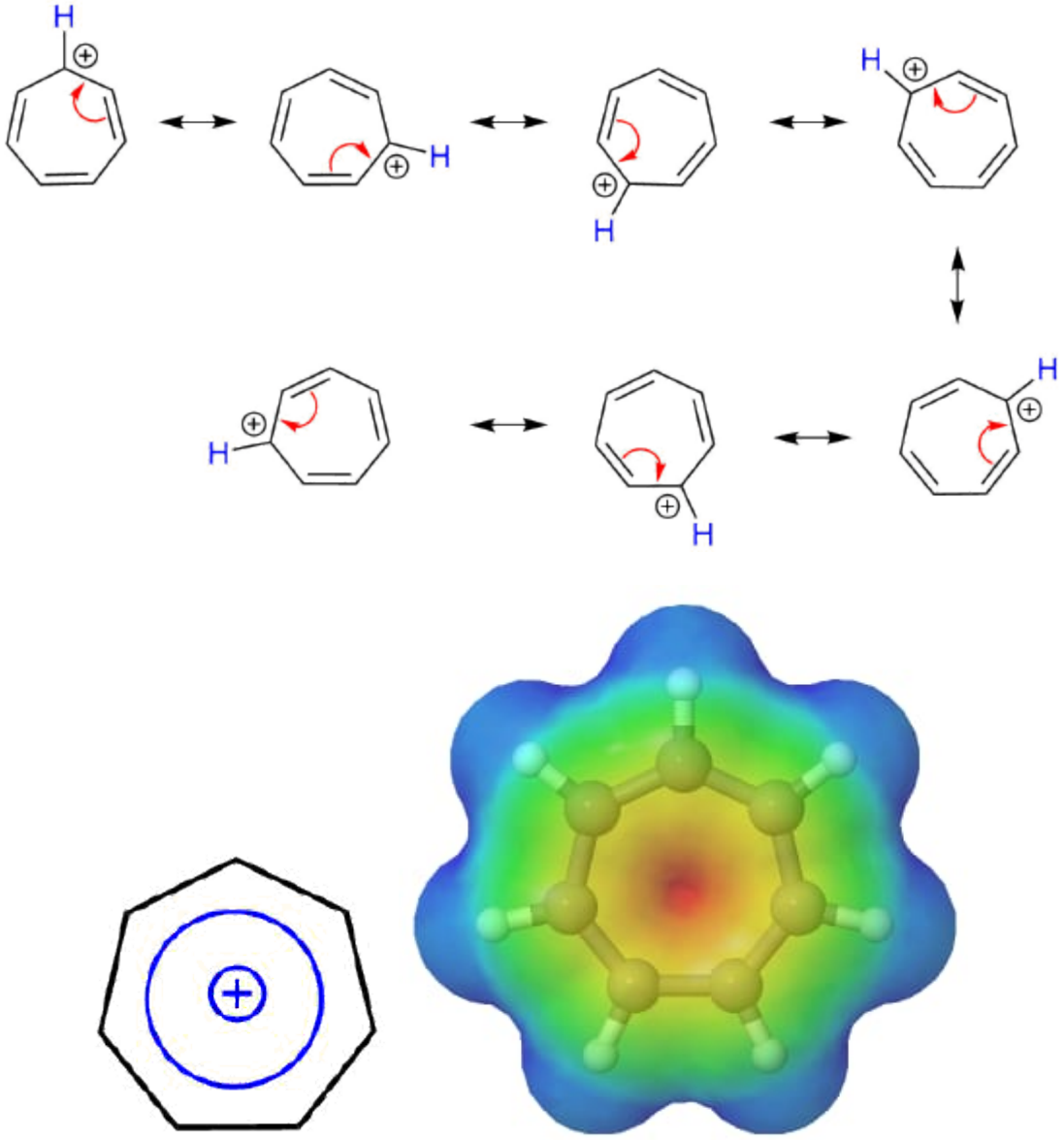
1,3,5-Cycloheptatriene
Nonaromatic
6 π electrons

Cycloheptatrienyl Cation
Tropylium cation
Aromatic
6 π electrons

The molecular orbital diagram for the 7 *p* orbitals in the tropylium cation has three bonding MO's and 4 antibonding MO's. The tropylium cation's 6 pi electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.

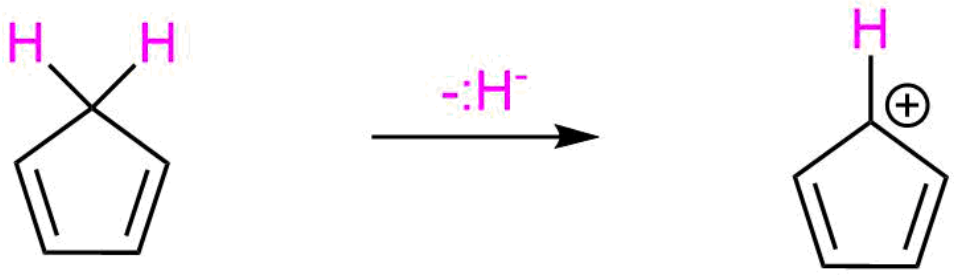


As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon +1/7 charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge is evenly distributed over the entire ring. The equivalency of the carbons in the seven membered ring is experimentally supported by an ^{1}H NMR spectrum of the tropylium cation which contains one peak showing that all seven protons are equivalent.



Antiaromatic Ions

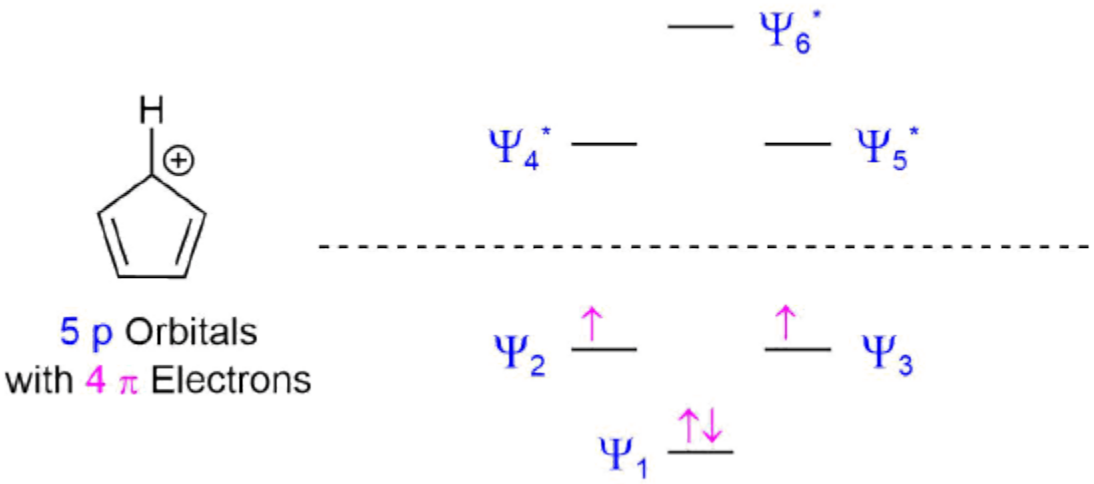
In a similar fashion, cyclically conjugated ions with 4n pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic, however, the formation of a carbocation produces a different result. Although the vacant *p* orbital provided by the carbocation allows for cyclic conjugation to occur the compound only has 4 pi electrons.



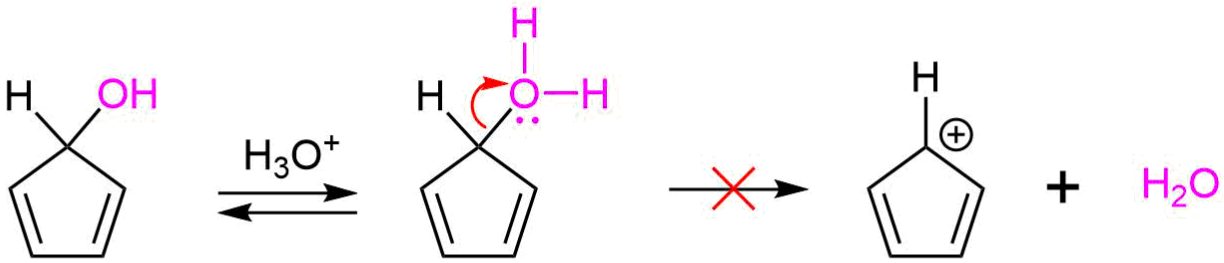
1,3-Cyclopentadiene
Nonaromatic
4 π electrons

Cyclopentadienyl Cation
Antiromatic
4 π electrons

After placing these 4 pi electrons into the molecular orbital for a cyclic 5 *p* orbital species the bonding molecular orbitals remain unfilled. Two of the pi electrons are unpaired in degenerate molecular orbitals creating the highly unstable triplet state. As predicted by Hückel's Rule, the cyclopentadienyl cation has 4n pi electrons and should be anitaromatic and very unstable.



Although there is some discussion as to whether the cyclopentadienyl cation is truly antiaromatic, there is experimental evidence which shows it is usually unstable. In particular, the compound 2,4-cyclopentadien-1-ol is usually resistant to S_N1 reactions with acid halides. The carbocation intermediate created during the mechanism of this reaction would be expected to easily form due to the resonance stabilization provided by the two double bonds. Because the carbocation intermediate is antiaromatic it does not form so the reaction does not occur.



2,4-Cyclopentadien-1-ol

4 π Electrons
Antiaromatic
Not Formed

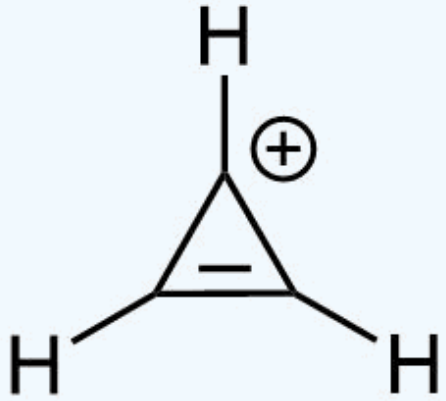
Exercise 15.7.1

1) Are all bonds equivalent cyclopentadienyl anion? How many lines (signals) would you expect to see in a H^1 and C^{13} NMR spectrum?

2) The following reaction occurs readily. Propose a reason why this occurs?

15.4(2).png

3) Is the cyclopropenium ion aromatic? Use the 4n + 2 rule and the MO diagram for a 3 p orbital ring system to explain your answer.



Cyclopropenium Ion

Answer available at the end of this section.

Exercises

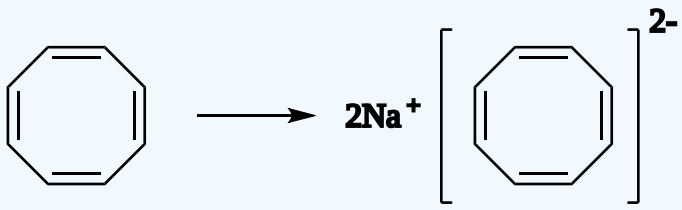
Exercise 15.7.2

Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^1 NMR? C^{13} NMR?

Answer available at the end of this section.

Exercise 15.7.3

The following reaction occurs readily. Propose a reason why this occurs?



Answer available at the end of this section.

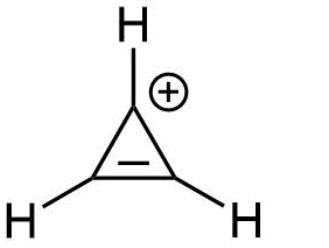
Answers

Exercise 15.7.1

1) Due to the cyclopentadienyl anion being fully conjugated a protons and carbons are equivalent. Both the ^1H and ^{13}C NMR spectrum would only have one signal.

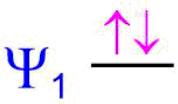
2) The addition of two electrons gives the ring system 10 pi electrons which follows the 4n+2 rule making the dianion aromatic. When looking at the MO diagram for an 8 p orbital ring system, 10 pi electrons completely fills the three bonding MO's and the two nonbonding MO's allowing for aromaticity.

3) The cyclopropenium ion has 2 pi electrons which follows the 4n + 2 rule when n = 0. When considering the molecular orbital diagram for a 3 p orbital ring system the is one bonding MO and two antibonding MO's. The two pi electrons completely fill the bonding MO allowing for aromaticity.



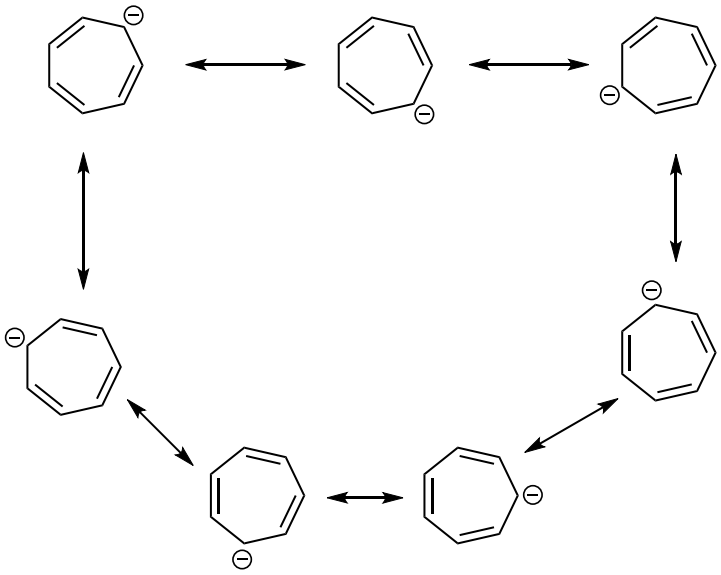
3 p Orbitals
with 2 π Electrons





Exercise 15.7.2

All protons and carbons are the same, so therefore each spectrum will only have one signal each in the proton NMR and carbon NMR.



Exercise 15.7.3

The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

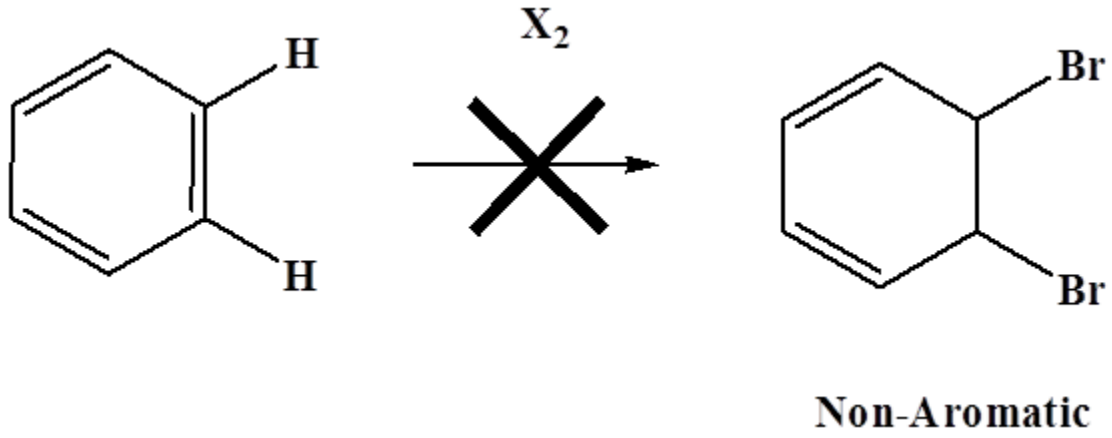
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- 15.4: Aromatic Ions by Dietmar Kennepohl, James Kabrhel, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

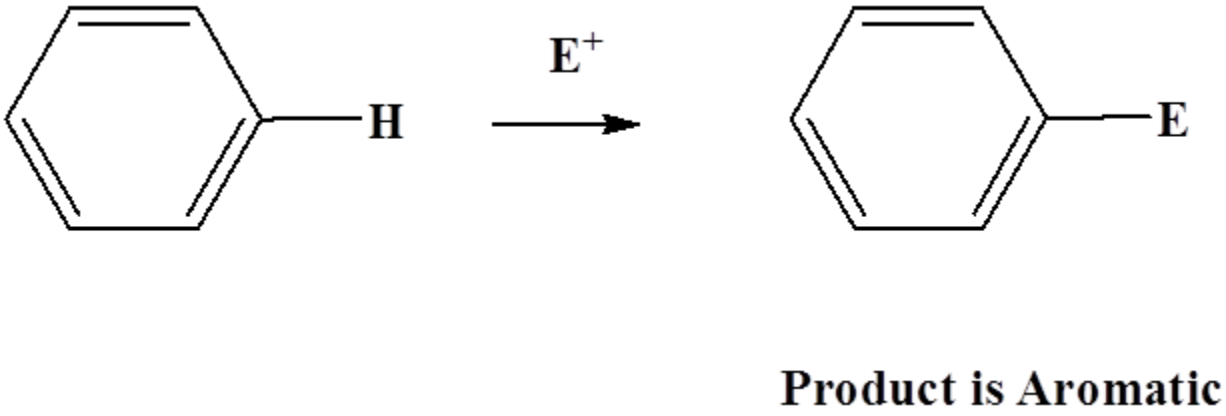
15.8: Synthesis of Benzene Derivatives: Electrophilic Aromatic Substitution

Bensene contains six pi electrons which are delocalized in six p orbitals above and below the plane of the benzene ring.

The six pi electrons obey Huckel's rule so benzene is especially stable. This means that the aromatic ring want to be retained during reactions. Because of this benzene does not undergo addition like other unsaturated hydrocarbons.



Benzene can undergo electrophilic aromatic substitution because aromaticity is maintained.

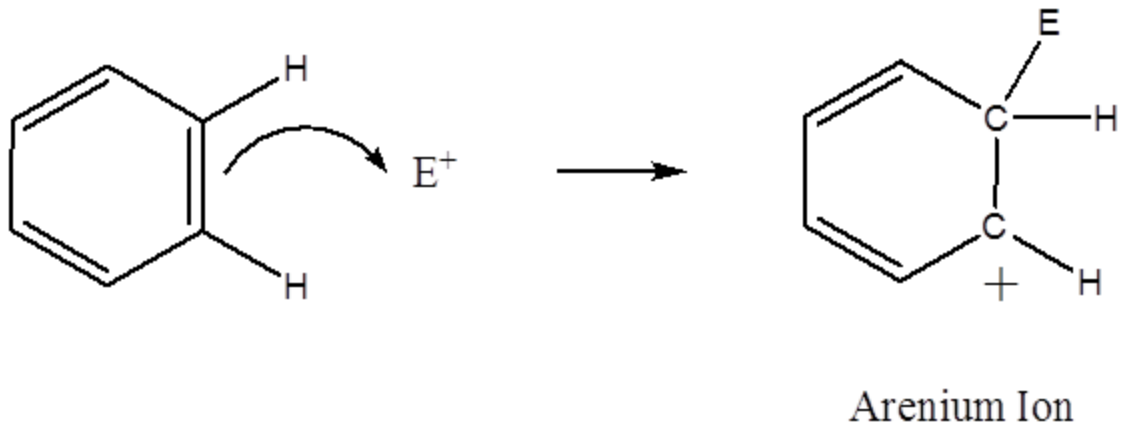


Contributors

- Prof. Steven Farmer (Sonoma State University)

The General Mechanism

Step 1 (Slow)



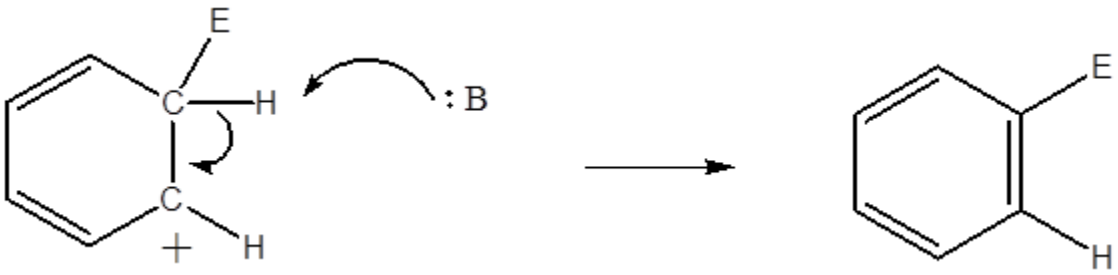
Arenium Ion

The e- in the pi bond attacks the electrophile

One carbon gets a positive charge the other forms a C-E bond

This forms the arenium ion.
The arenium ion is conjugated but not aromatic.

Step 2 (Fast)

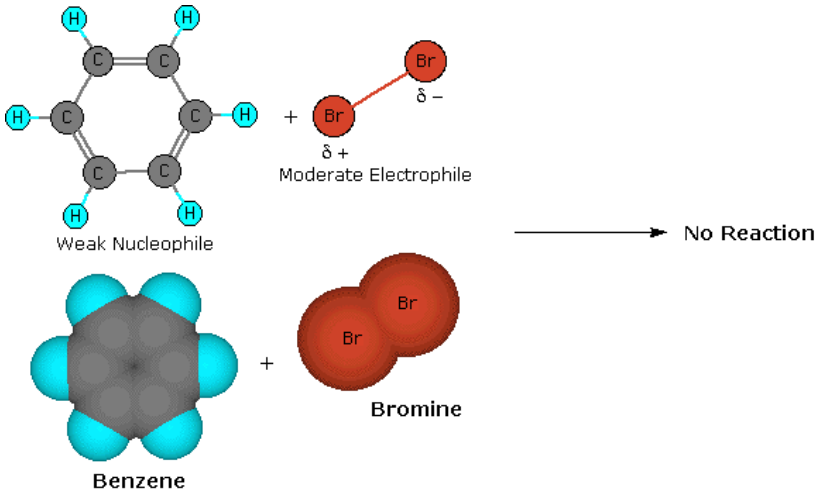


The LPE on a base attacks the hydrogen.

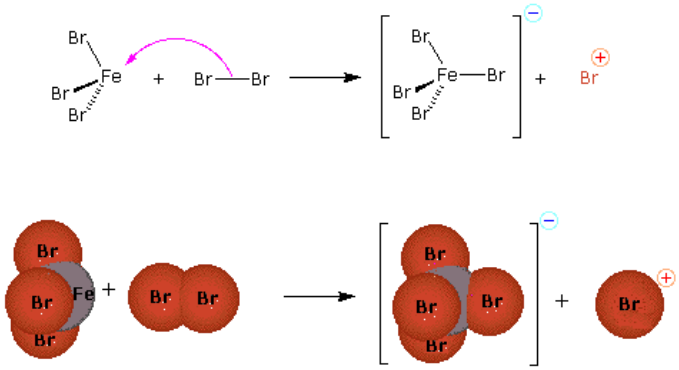
This causes the e- in the C-H bond to form a C-C double bond and aromaticity is reformed

A Detailed discussion of the Mechanism for Electrophilic Substitution Reactions of Benzene

A two-step mechanism has been proposed for these electrophilic substitution reactions. In the first, slow or rate-determining, step the electrophile forms a sigma-bond to the benzene ring, generating a positively charged **benzenonium intermediate**. In the second, fast step, a proton is removed from this intermediate, yielding a substituted benzene ring. The following four-part illustration shows this mechanism for the bromination reaction. Also, an animated diagram may be viewed.

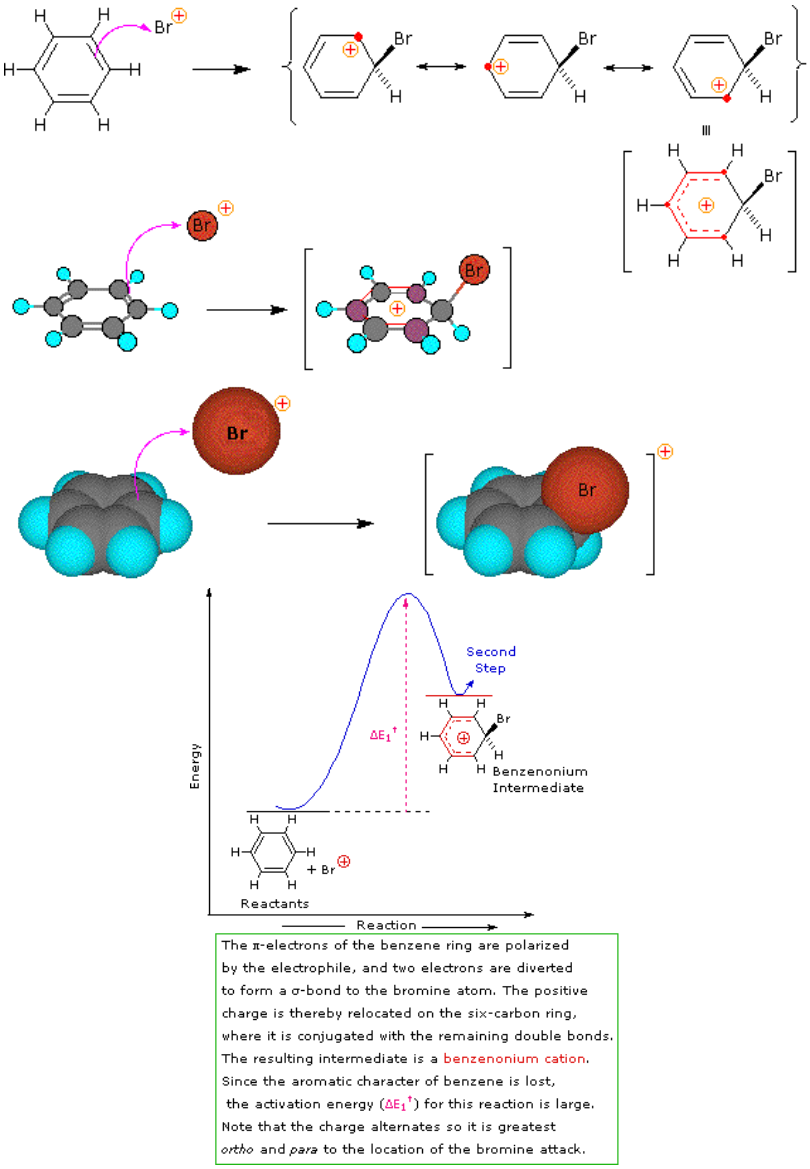


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π-electron system of benzene.

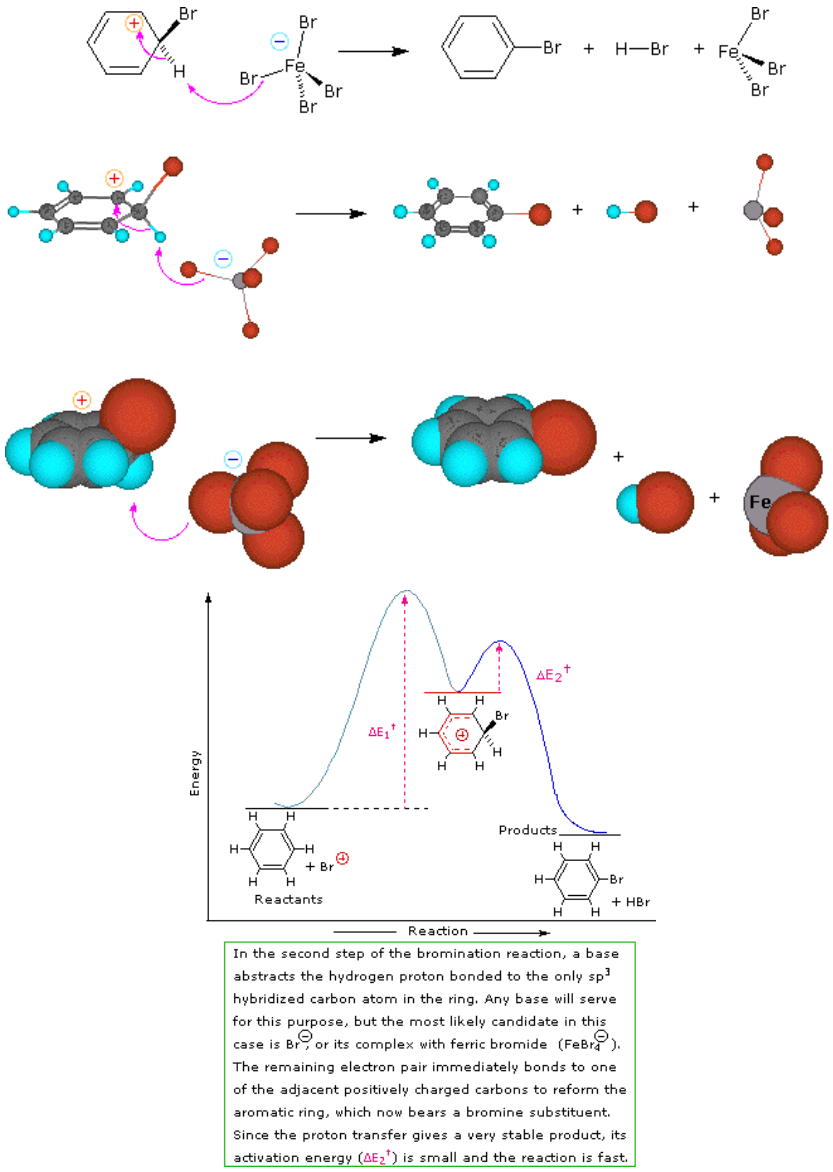


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

Preliminary step: Formation of the strongly electrophilic bromine cation



Step 1: The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate



In the second step of the bromination reaction, a base abstracts the hydrogen proton bonded to the only sp^3 hybridized carbon atom in the ring. Any base will serve for this purpose, but the most likely candidate in this case is $Br^{\ominus}$, or its complex with ferric bromide ($FeBr_4^{\ominus}$). The remaining electron pair immediately bonds to one of the adjacent positively charged carbons to reform the aromatic ring, which now bears a bromine substituent. Since the proton transfer gives a very stable product, its activation energy ($\Delta E_2^{\ddagger}$) is small and the reaction is fast.

Step 2: A proton is removed from this intermediate, yielding a substituted benzene ring

This mechanism for electrophilic aromatic substitution should be considered in context with other mechanisms involving carbocation intermediates. These include S_N1 and E1 reactions of alkyl halides, and Brønsted acid addition reactions of alkenes.

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

S_N1 and E1 reactions are respective examples of the first two modes of reaction. The second step of alkene addition reactions proceeds by the first mode, and any of these three reactions may exhibit molecular rearrangement if an initial unstable carbocation is formed. The carbocation intermediate in electrophilic aromatic substitution (the benzenonium ion) is stabilized by charge delocalization (resonance) so it is not subject to rearrangement. In principle it could react by either mode 1 or 2, but the energetic advantage of reforming an aromatic ring leads to exclusive reaction by mode 2 (*ie.* proton loss).

Other Examples of Electophilic Aromatic Substitution

Many other substitution reactions of benzene have been observed, the five most useful are listed below (chlorination and bromination are the most common halogenation reactions). Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents serve to generate the strong electrophilic species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	——>	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	——>	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	——>	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	——>	C_6H_5-R + HCl An Arene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	——>	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

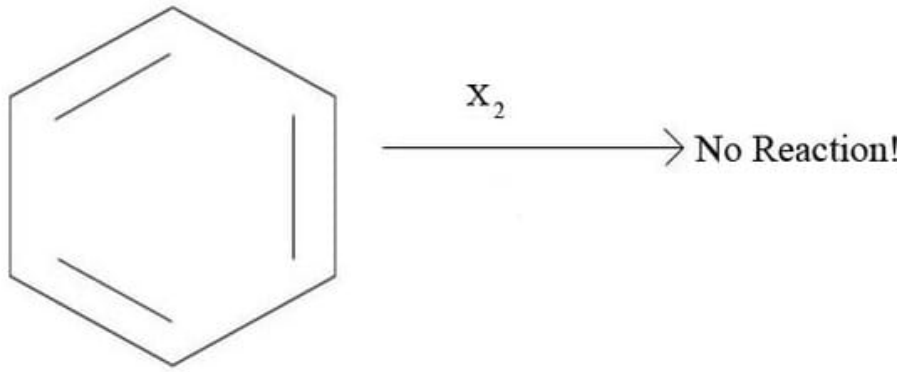
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15.9: Halogenation of Benzene: The Need for a Catalyst

Halogenation is an example of electrophillic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substition of hydrogens. However, halogens are not electrophillic enough to break the aromaticity of benzenes, which require a catalyst to activate.

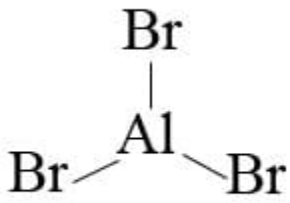
Activation of Halogen

(where X= Br or Cl, we will discuss further in detail later why other members of the halogen family Flourine and Iodine are not used in halogenation of benzenes)

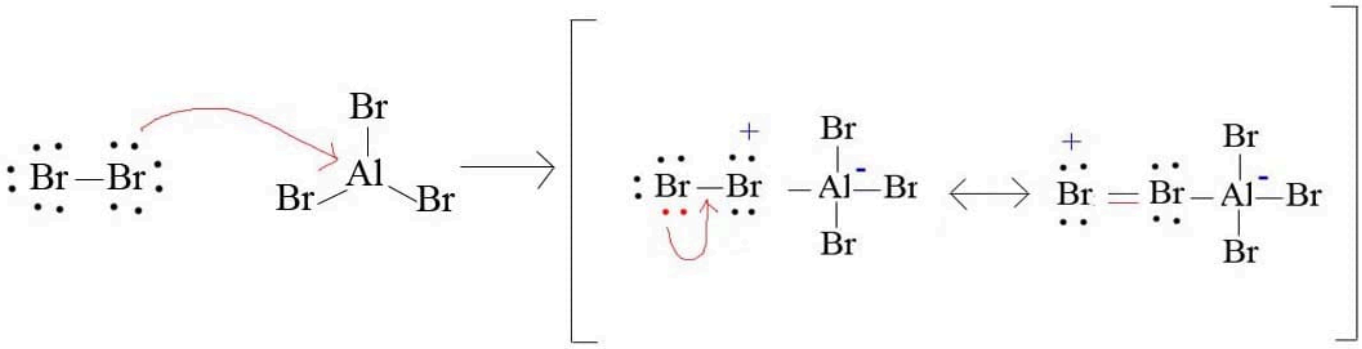


Hence, Halogen needs the help and aid of Lewis Acidic Catalysts to activate it to become a very strong electrophile. Examples of these activated halogens are Ferric Hallides (FeX_3) Aluminum Halides (AlX_3) where X= Br or Cl. In the following examples, the halogen we will look at is Bromine.

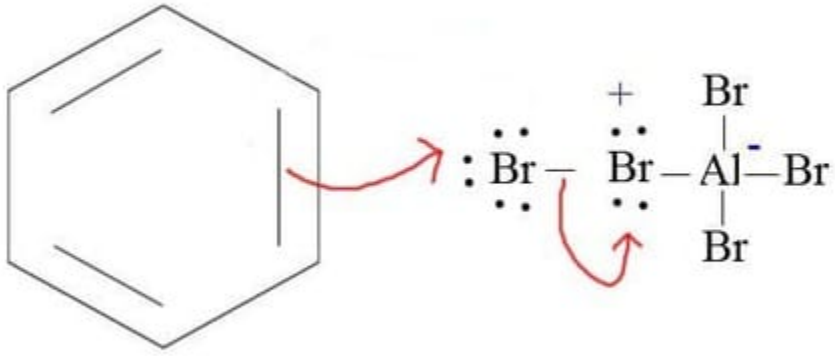
In the example of bromine, in order to make bromine electrophillic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.

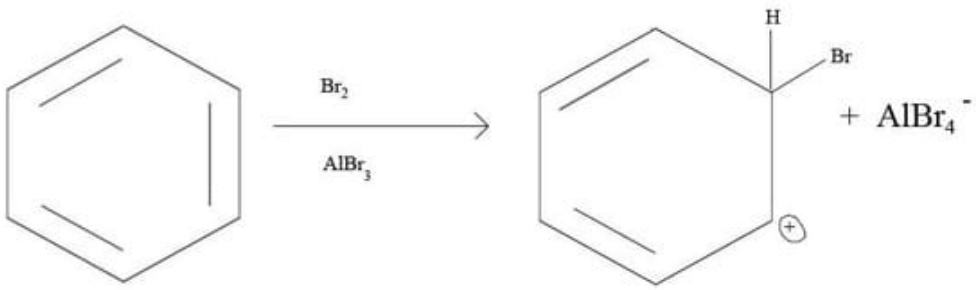


With aluminum bromide as a Lewis acid, we can mix Br_2 with $AlBr_3$ to give us Br^+. The presence of Br^+ is a much better electrophile than Br_2 alone. Bromination is acheived with the help of $AlBr_3$ (Lewis acid catalysts) as it polarizes the Br-Br bond. The polarization causes polarization causes the bromine atoms within the Br-Br bond to become more electrophillic. The presence of Br^+ compared to Br_2 alone is a much better electrophille that can then react with benzene.

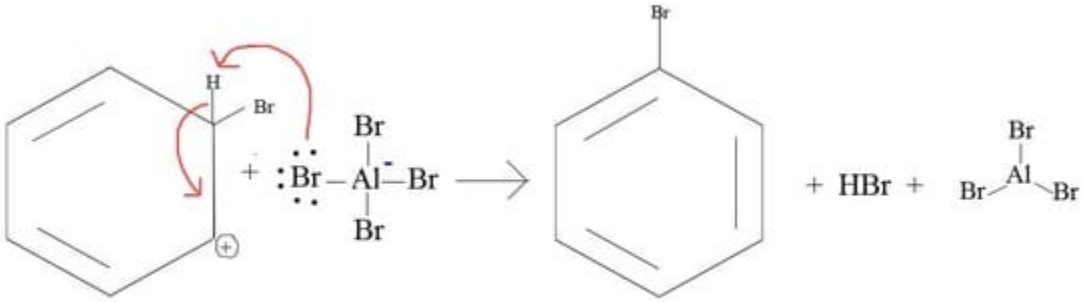


As the bromine has now become more electrophillic after activation of a catalyst, an electrophillic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. This allows the other bromine atom to leave with the $AlBr_3$ as a good leaving group, $AlBr_4$-.





After the electrophilic attack of bromide to the benzene, the hydrogen on the same carbon as bromine substitutes the carbocation in which resulted from the attack. Hence it being an electrophilic aromatic SUBSTITUTION. Since the by-product aluminum tetrabromide is a strong nucleophile, it pulls of a proton from the Hydrogen on the same carbon as bromine.



In the end, $AlBr_3$was not consumed by the reaction and is regenerated. It serves as our catalyst in the halogenation of benzenes.

Dissociation Energies of Halogens and its Effect on Halogenation of Benzenes

The electrophillic bromination of benzenes is an exothermic reaction. Considering the exothermic rates of aromatic halogenation decreasing down the periodic table in the Halogen family, Flourination is the most exothermic and Iodination would be the least. Being so exothermic, a reaction of flourine with benzene is explosive! For iodine, electrophillic iodination is generally endothermic, hence a reaction is often not possible. Similar to bromide, chlorination would require the aid of an activating presence such as Alumnium Chloride or Ferric Chloride. The mechanism of this reaction is the same as with Bromination of benzene.

Outside linksEdit section

- http://www.chemguide.co.uk/mechanism...ogenation.html
- http://en.wikipedia.org/wiki/Electro...c_halogenation

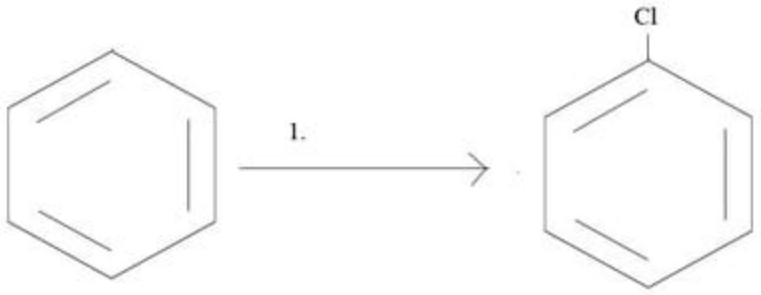
References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th Edition. New York: W.H. Freeman and Company, 2007.

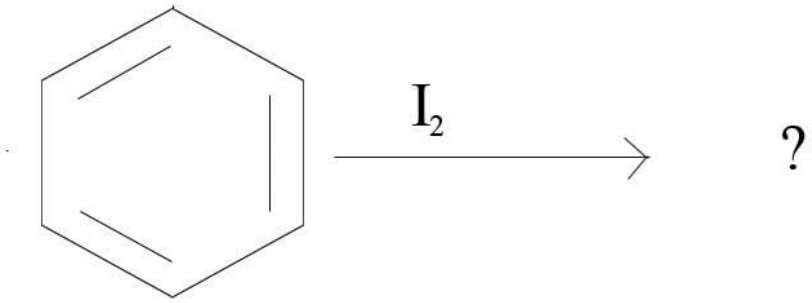
Problems

1. What reagents would you need to get the given product?

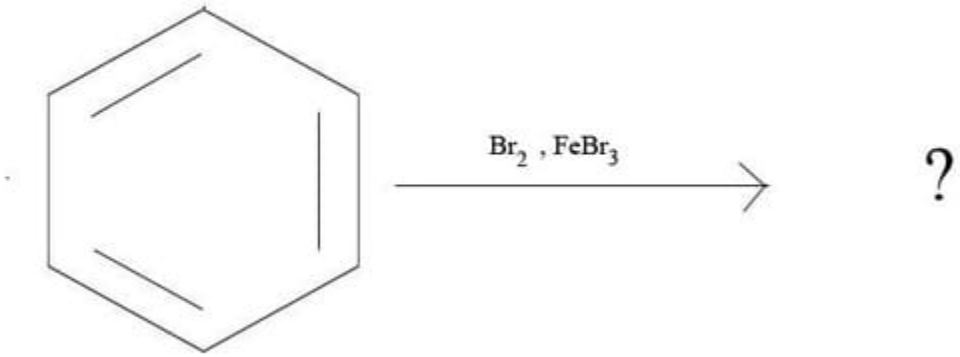
Edit sectionWhat reagents would you need to gete given product



2. What product would result from the given reagents?



3. What is the major product given the reagents below?



4. Draw the formatin of Cl^+ from $AlCl_3$ and Cl_2

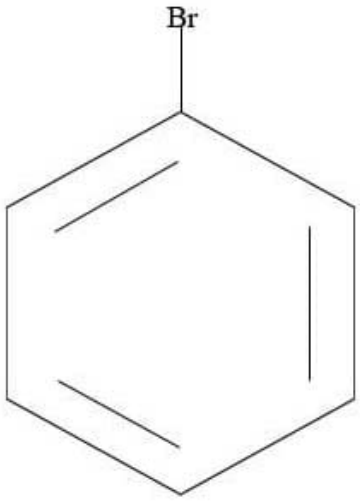
5. Draw the mechanism of the reaction between Cl^+ and a benzene.

Solutions

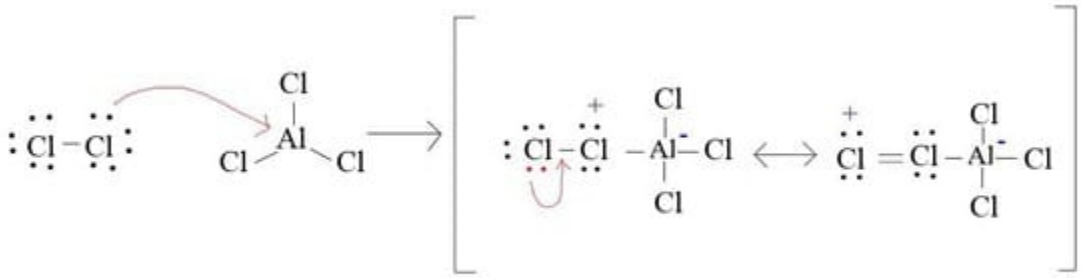
1. Cl_2 and AlCl3 or Cl_2 and $FeCl_3$

2. No Reaction

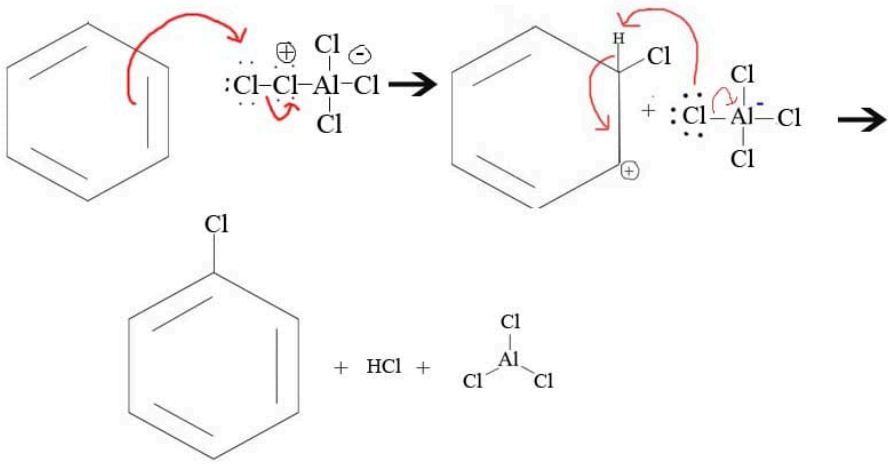
3.



4.



5.



ContributorsEdit section

- Catherine Nguyen

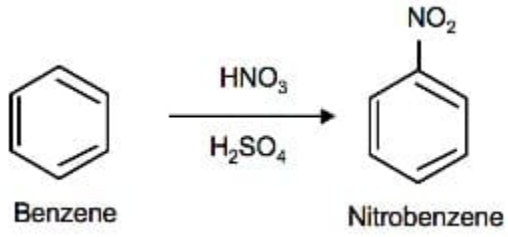
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15.10: Nitration and Sulfonation of Benzene

Nitration and sulfonation of benzene are two examples of electrophilic aromatic substitution. The nitronium ion (NO_2^+) and sulfur trioxide (SO_3) are the electrophiles and individually react with benzene to give nitrobenzene and benzenesulfonic acid respectively.

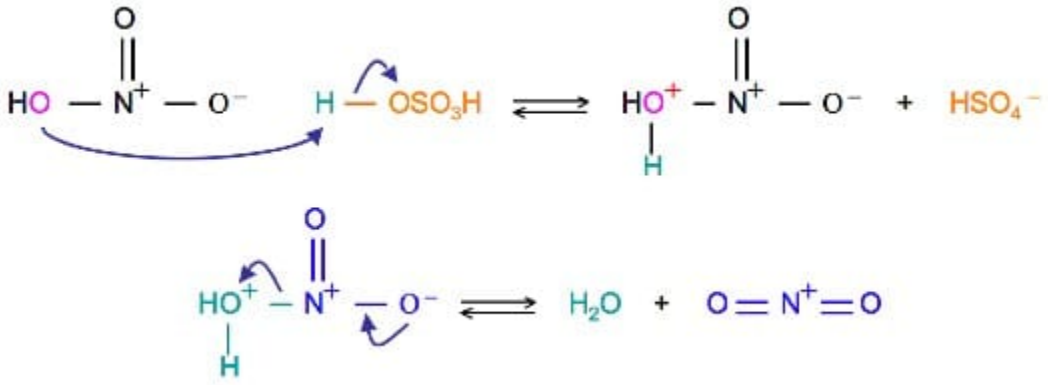
Nitration of Benzene

The source of the nitronium ion is through the protonation of nitric acid by sulfuric acid, which causes the loss of a water molecule and formation of a nitronium ion.



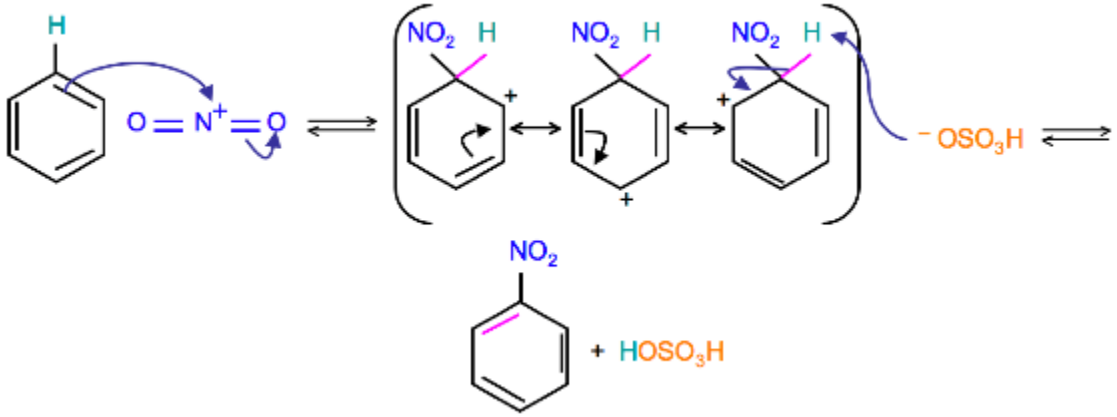
Sulfuric Acid Activation of Nitric Acid

The first step in the nitration of benzene is to activate $HNO_3$with sulfuric acid to produce a stronger electrophile, the nitronium ion.



Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

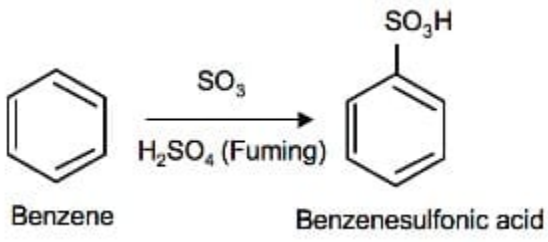
Mechanism



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

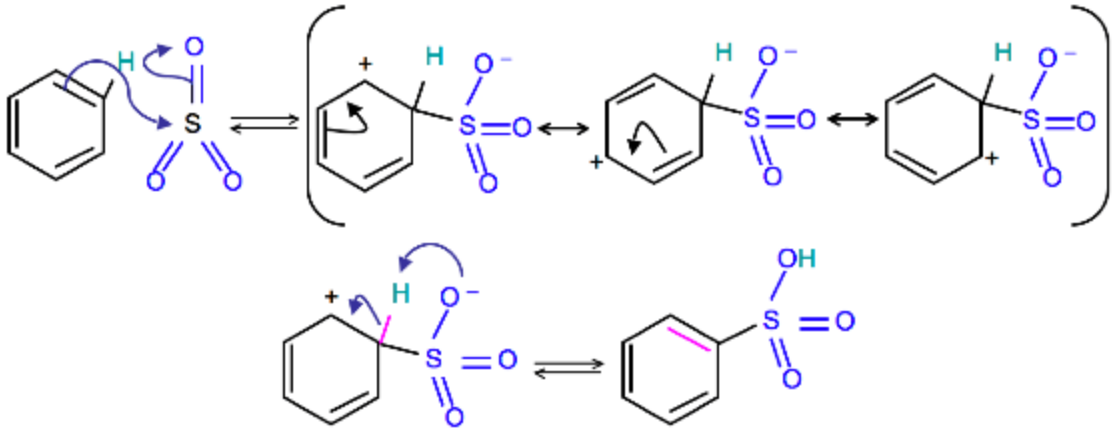
Sulfonation of Benzene

Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



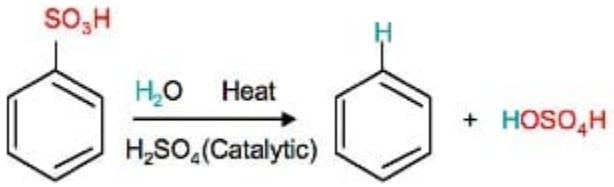
Mechanism

To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also refered to as *oleum*, is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is electrophilic because the oxygens pull electrons away from it because oxygen is very electronegative. The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.



Reverse Sulfonation

Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



Further Applications of Nitration and Sulfonation

Nitration is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic nitrations are very important intermediates in industrial chemistry.

Because sulfonation is a reversible reaction, it can also be used in further substitution reactions in the form of a directing blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is completed it can be removed by reverse sulfonation. Benzenesulfonic acids are also used in the synthesis of detergents, dyes, and sulfa drugs. Bezenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

Outside Links

Aromatic Sulfonation

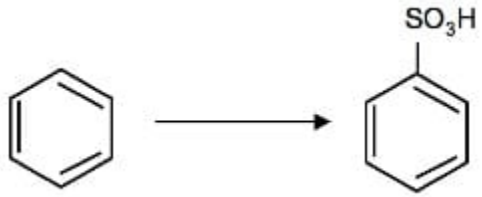
- Wikipedia: http://en.wikipedia.org/wiki/Aromatic_sulfonation
- Video: http://www.youtube.com/watch?v=s1qJ1...eature=related
- Interactive 3D Reaction: http://www.chemtube3d.com/Electrophi...20benzene.html

Aromatic Nitration

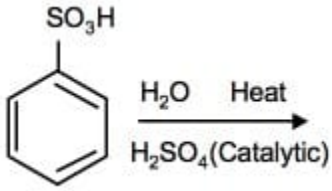
- Wikipedia: http://en.wikipedia.org/wiki/Nitration
- Video: http://www.youtube.com/watch?v=i7ucl...eature=related
- Interactive 3D Reaction: http://www.chemtube3d.com/Electrophi...20benzene.html

Problems

1. What is/are the required reagent(s)for the following reaction:



2. What is the product of the following reaction:



3. Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

4. Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

5. Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states. (For questions 1 and 2 see Electrophilic Aromatic Substitution for hints)

For other problems involving Electrophilic Aromatic Substitution and similar reactions see:

- Electrophilic Aromatic Substitution
- Activating and Deactivating Benzene Rings
- Electrophilic Attack on Disubstituted Benzenes

Solutions

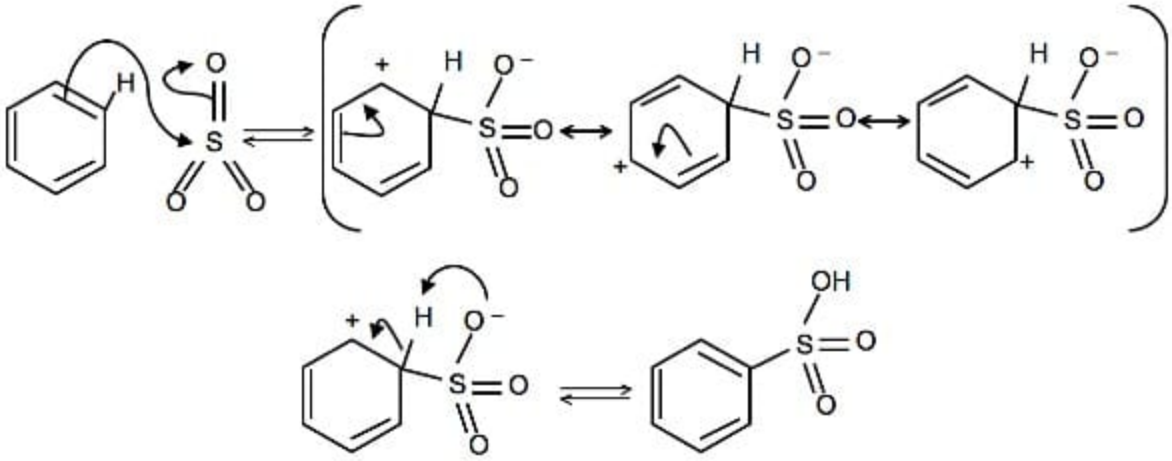
1. SO_3 and H_2SO_4 (fuming)

2.

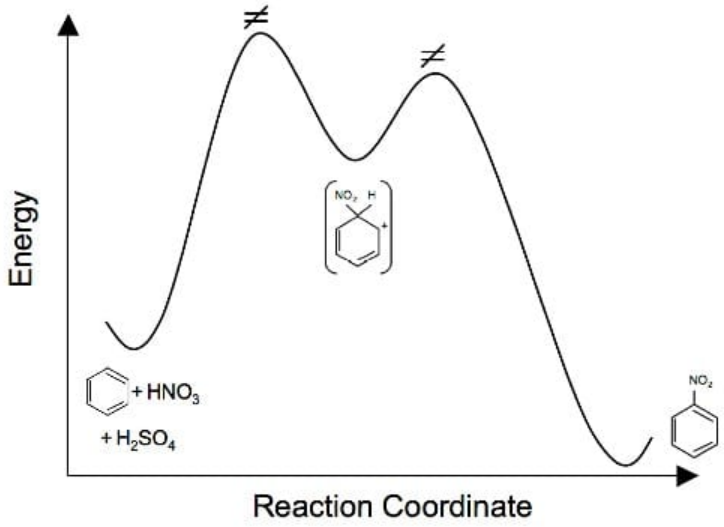


3. Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

4.



5.



References

1. Laali, Kenneth K., and Volkar J. Gettwert. “Electrophilic Nitration of Aromatics in Ionic Liquid Solvents.” The Journal of Organic Chemistry 66 (Dec. 2000): 35-40. American Chemical Society.
2. Malhotra, Ripudaman, Subhash C. Narang, and George A. Olah. Nitration: Methods and Mechanisms. New York: VCH Publishers, Inc., 1989.
3. Sauls, Thomas W., Walter H. Rueggeberg, and Samuel L. Norwood. “On the Mechanism of Sulfonation of the Aromatic Nucleus and Sulfone Formation.” The Journal of Organic Chemistry 66 (1955): 455-465. American Chemical Society.
4. Vollhardt, Peter. Organic Chemistry : Structure and Function. 5th ed. Boston: W. H. Freeman & Company, 2007.

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15.11: Friedel-Crafts Alkylation

Friedel-Crafts Alkylation

Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877. This reaction allowed for the formation of alkyl benzenes from alkyl halides, but was plagued with unwanted supplemental activity that reduced its efficiency.

Alkylation.bmp

The mechanism takes place as follows:

Step one:

mechpart1_(1)1.bmp

The first step creates a cabocation that acts as the electrophile in the reaction. This step activates the haloalkane. Secondary and teriary halides only form the free cabocation in the step.

Step two

mechpart2 2.bmp

The second step has an electrophilic attack on the benzene that results in multiple resonance forms. The halogen reactions with the intermediate and picks up the hydrogen to eliminate the positive charge.

Finish

mechpart2 3.bmp

The final step shown above is the results of the end of step and shows the final products.

The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

Some limitations of Friedel-Crafts Alkylation

There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. For a look at substituents that activating or deactivating Benzene Rings.

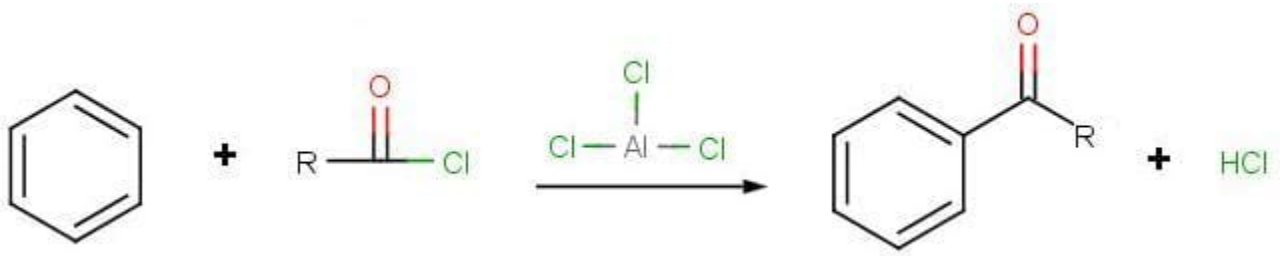
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3. **Polyalkylation** - Products of Friedel-Crafts are even more reactive than starting material. Alkyl groups produced in Friedel-Crafts Alkylation are electron-donating substituents meaning that the products are more susceptible to electrophilic attack than what we began with. For synthetic purposes, this is a big dissapointment.

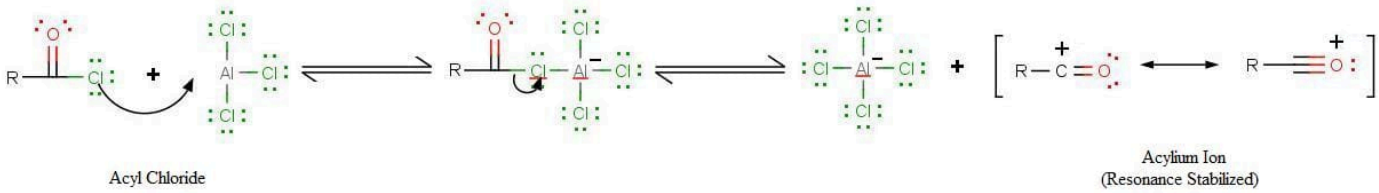
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Friedel-Crafts Acylation

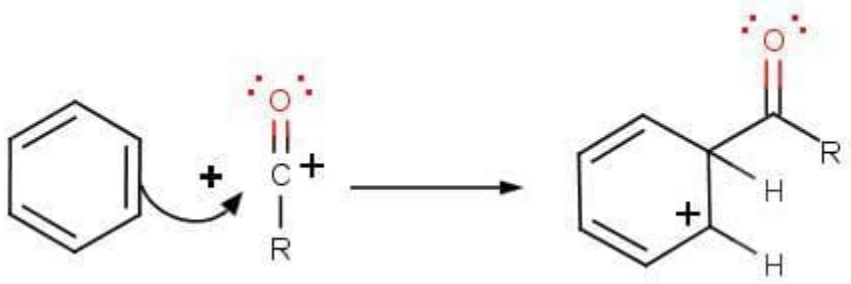
The goal of the reaction is the following:



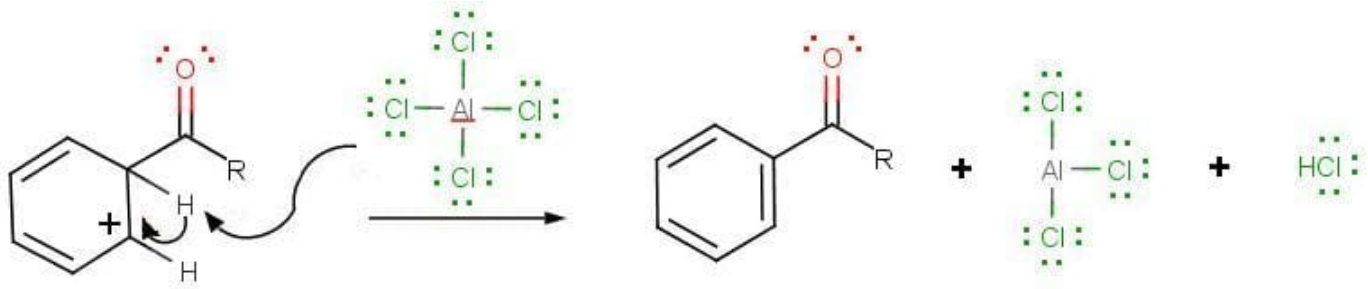
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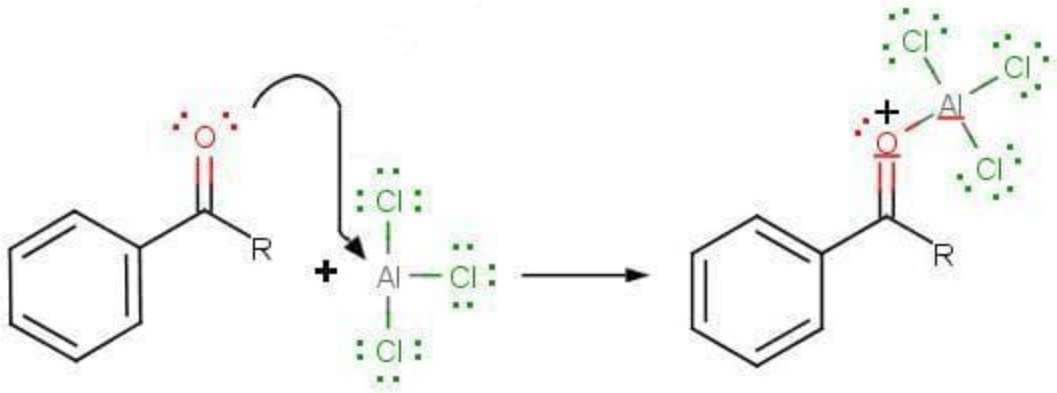
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



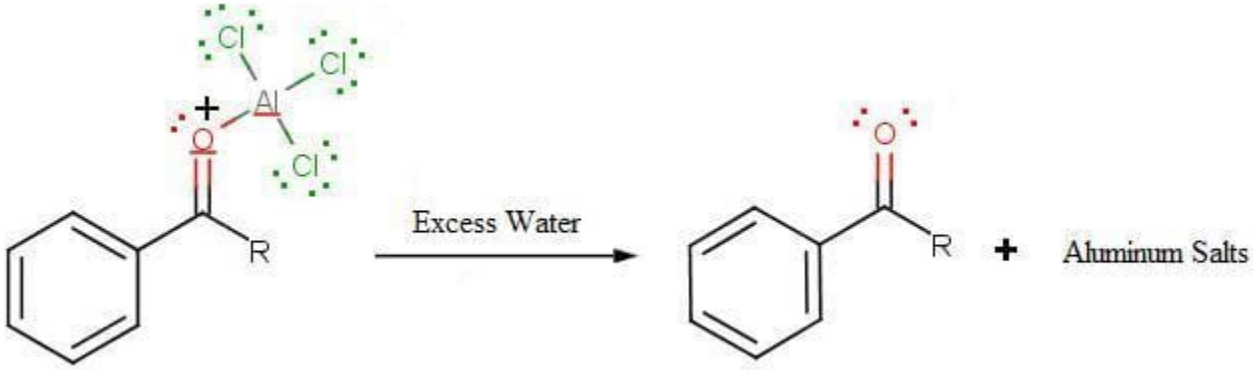
The third step involves the departure of the proton in order for aromaticity to return to benzene:



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the first part of the final product of the reaction, which is a ketone. Thie first part of the product is the complex with aluminum chloride as shown:



The final step involves the addition of water to liberate the final product as the acylbenzene:



Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (Limitation 1). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

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15.12: Limitations of Friedel-Crafts Alkylations

Friedel-Crafts Alkylation

Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877. This reaction allowed for the formation of alkyl benzenes from alkyl halides, but was plagued with unwanted supplemental activity that reduced its efficiency.

Alkylation.bmp

The mechanism takes place as follows:

Step one:

mechpart1_(1)1.bmp

The first step creates a cabocation that acts as the electrophile in the reaction. This step activates the haloalkane. Secondary and teriary halides only form the free cabocation in the step.

Step two

mechpart2 2.bmp

The second step has an electrophilic attack on the benzene that results in multiple resonance forms. The halogen reactions with the intermediate and picks up the hydrogen to eliminate the positive charge.

Finish

mechpart2 3.bmp

The final step shown above is the results of the end of step and shows the final products.

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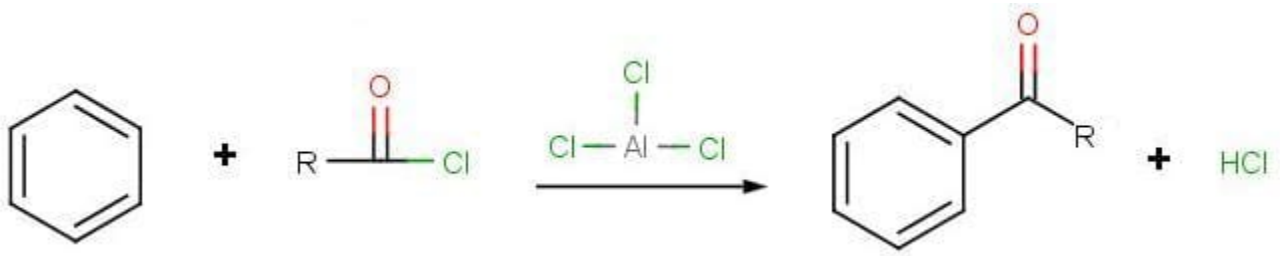
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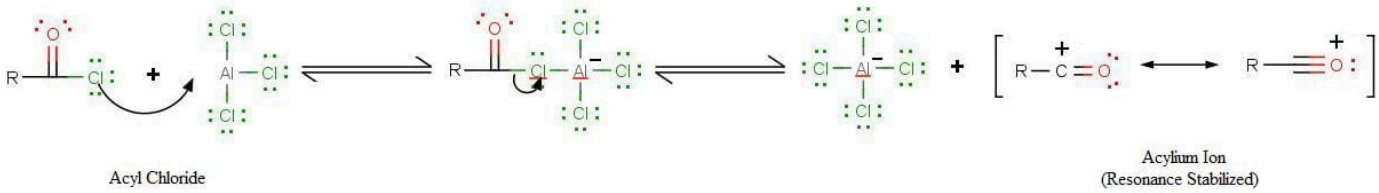
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Friedel-Crafts Acylation

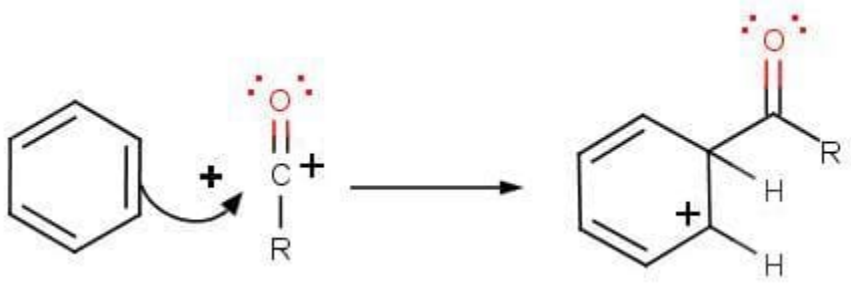
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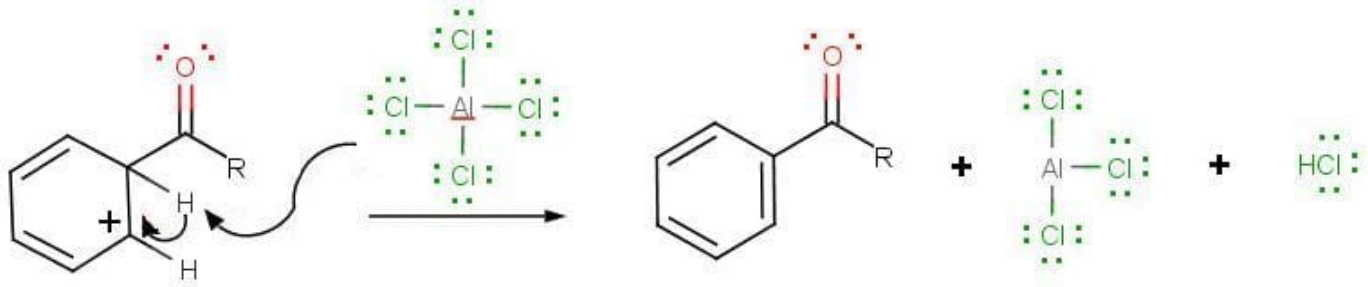
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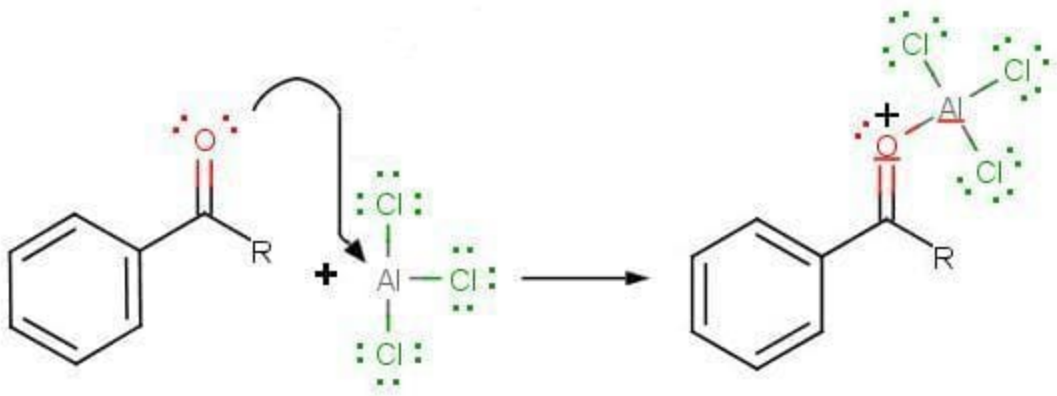
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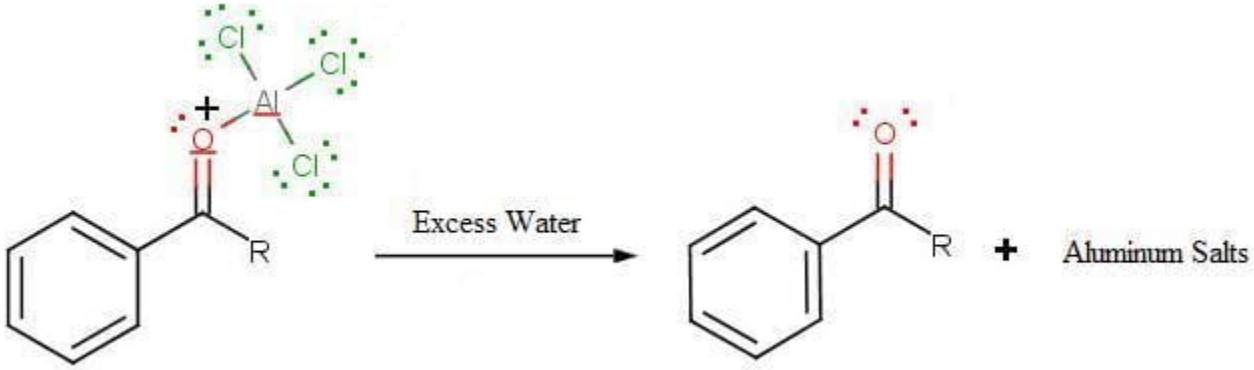
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15.13: Friedel-Crafts Alkanoylation (Acylation)

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Alkylation.bmp

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mechpart1_(1)1.bmp

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mechpart2 2.bmp

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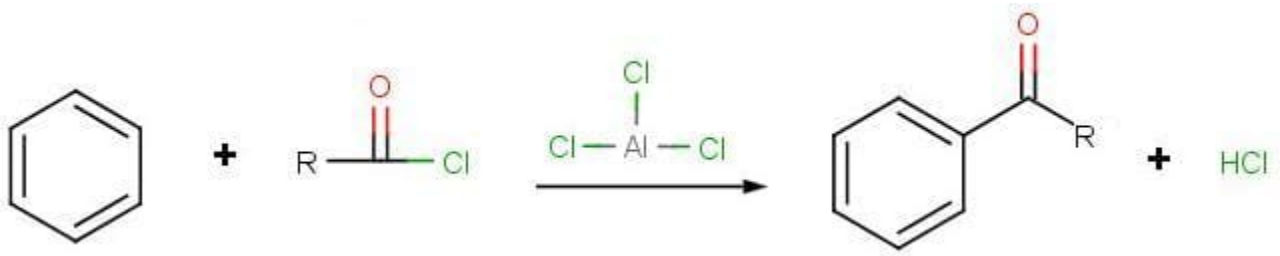
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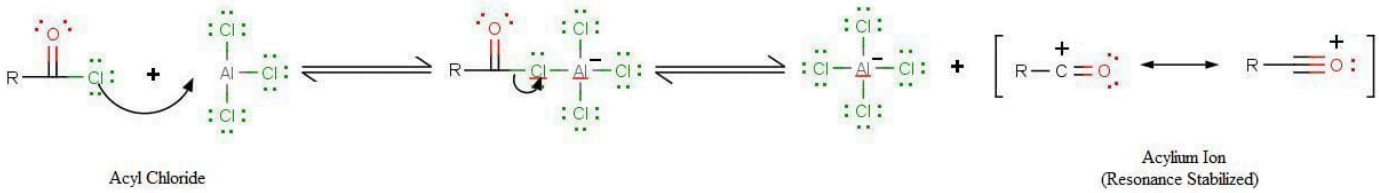
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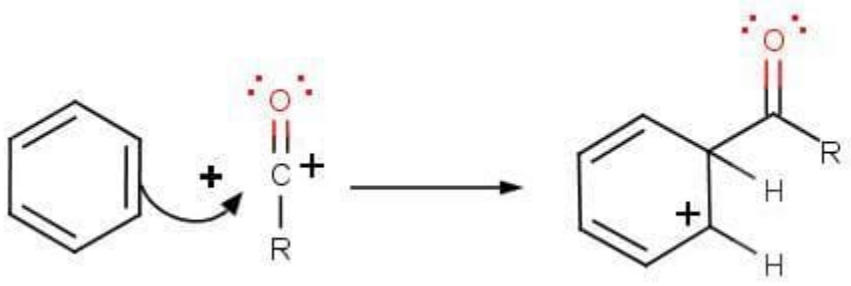
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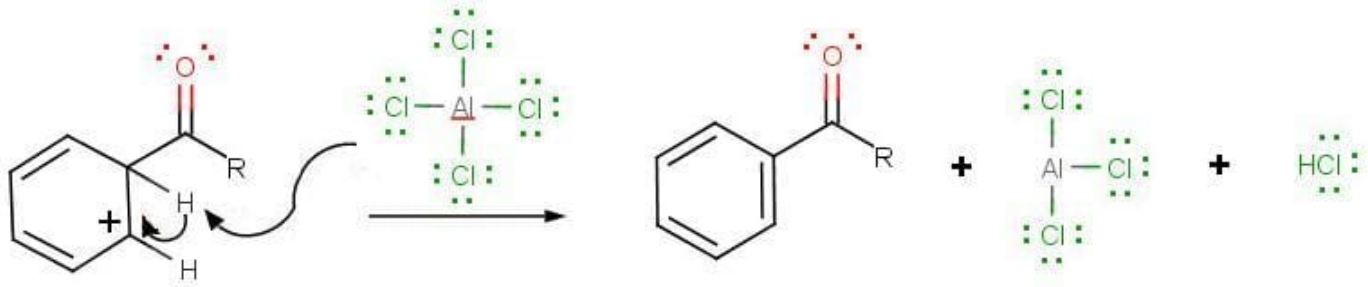
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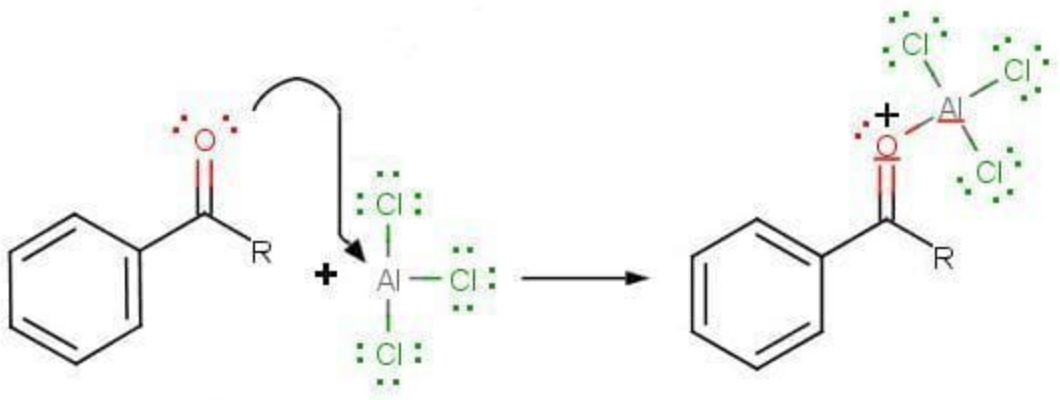
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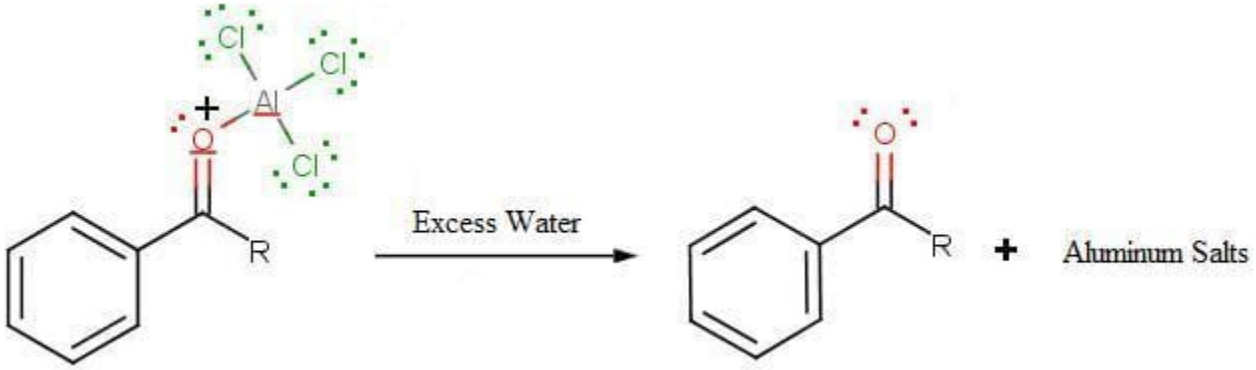
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16: ELECTROPHILIC ATTACK ON DERIVATIVES OF BENZENE: SUBSTITUENTS CONTROL REGIOSELECTIVITY

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

16.1: Activation or Deactivation by Substituents on a Benzene Ring
16.2: Directing Inductive Effects of Alkyl Groups
16.3: Directing Effects of Substituents in Conjugation with the Benzene Ring
16.4: Electrophilic Attack on Disubstituted Benzenes
16.5: Synthetic Strategies Toward Substituted Benzenes
16.6: Reactivity of Polycyclic Benzenoid Hydrocarbons
16.7: Polycyclic Aromatic Hydrocarbons and Cancer

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16.1: Activation or Deactivation by Substituents on a Benzene Ring

Objectives

After completing this section, you should be able to

1. describe the two ways in which a substituent influences the electrophilic substitution of a monosubstituted aromatic compound.
2. classify each of the following substituents as being either activating or deactivating with respect to electrophilic aromatic substitution: —NH2, —OH, —NHR, —NR2, —OR, —NHCOR, alkyl (R), phenyl, R3N+, —NO2, —CN, —COR, —CO2H, —CO2R, —CHO, halogens.
3. list a given series of substituents (selected from those given in Objective 2) in order of increasing or decreasing ability to activate or deactivate an aromatic ring with respect to electrophilic substitution.
4. explain, in general terms, the factors that determine whether a given substituent will activate or deactivate an aromatic ring with respect to electrophilic substitution.
5. list a given series of aromatic compounds in order of increasing or decreasing reactivity with respect to electrophilic substitution.
6. explain the inductive effects displayed by substituents such as nitro, carboxyl, alkyl and the halogens during electrophilic aromatic substitution reactions.
7. explain the resonance effects displayed by substituents such as nitro, carbonyl-containing, hydroxy, alkoxy and amino groups during electrophilic aromatic substitution reactions.

Key Terms

Make certain that you can define, and use in context, the key terms below.

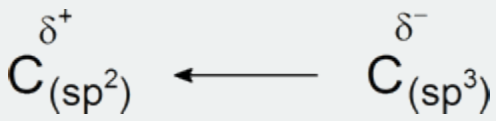
- inductive effect
- resonance effect

Study Notes

On reading Objective 2 students may exclaim “How am I ever going to memorize all of this!”—or words to that effect. The answer is that if you are trying to memorize such things, you are taking the wrong approach to organic chemistry. What you should be doing is trying to understand the factors that determine whether a given substituent will activate or deactivate a benzene ring with respect to electrophilic substitution.

You may wish to review earlier material on to the inductive effect. If so, refer to Sections 2.1, 7.9 (paying particular attention to the “Study Notes”) and 14.5.

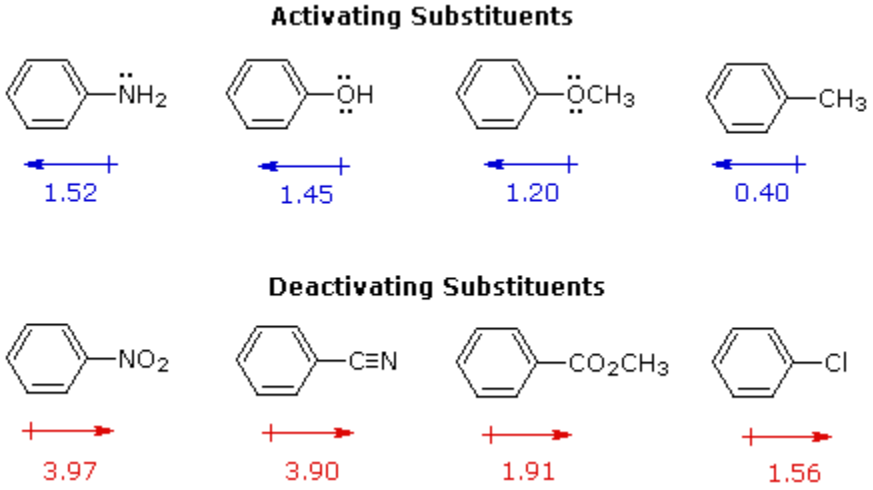
Note that one argument sometimes used to explain the ability of alkyl groups to donate electrons inductively to an aromatic ring is that sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms. Thus, a sigma bond between sp^2- and sp^3-carbon is slightly polarized, as follows:



When substituted benzene compounds undergo electrophilic substitution reactions of the kind discussed above, **two related**

features must be considered:

I. The first is the relative reactivity of the compound compared with benzene itself. Experiments have shown that substituents on a benzene ring can influence reactivity in a profound manner. For example, a hydroxy or methoxy substituent increases the rate of electrophilic substitution about ten thousand fold, as illustrated by the case of anisole in the virtual demonstration (above). In contrast, a nitro substituent decreases the ring's reactivity by roughly a million. This **activation** or **deactivation** of the benzene ring toward electrophilic substitution may be correlated with the electron donating or electron withdrawing influence of the substituents, as measured by molecular dipole moments. In the following diagram we see that electron donating substituents (blue dipoles) activate the benzene ring toward electrophilic attack, and electron withdrawing substituents (red dipoles) deactivate the ring (make it less reactive to electrophilic attack).

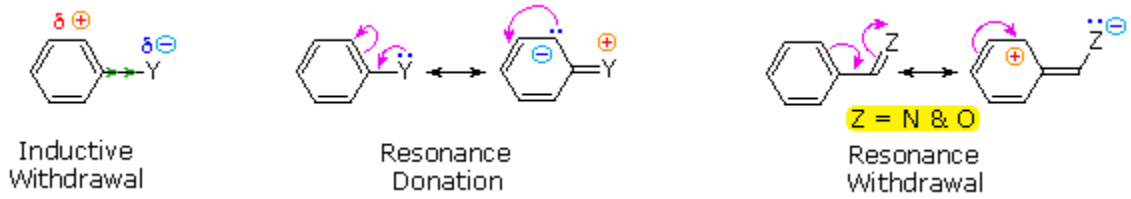


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

The first is the **inductive effect** of the substituent. Most elements other than metals and carbon have a significantly greater electronegativity than hydrogen. Consequently, substituents in which nitrogen, oxygen and halogen atoms form sigma-bonds to the aromatic ring exert an inductive electron withdrawal, which deactivates the ring (left-hand diagram below).

The second effect is the result of **conjugation** of a substituent function with the aromatic ring. This conjugative interaction facilitates electron pair donation or withdrawal, to or from the benzene ring, in a manner different from the inductive shift. If the atom bonded to the ring has one or more non-bonding valence shell electron pairs, as do nitrogen, oxygen and the halogens, electrons may flow into the aromatic ring by p-π conjugation (resonance), as in the middle diagram. Finally, polar double and triple bonds conjugated with the benzene ring may withdraw electrons, as in the right-hand diagram. Note that in the resonance examples all the contributors are not shown. In both cases the charge distribution in the benzene ring is greatest at sites ortho and para to the substituent.

In the case of the nitrogen and oxygen activating groups displayed in the top row of the previous diagram, electron donation by resonance dominates the inductive effect and these compounds show exceptional reactivity in electrophilic substitution reactions. Although halogen atoms have non-bonding valence electron pairs that participate in p-π conjugation, their strong inductive effect predominates, and compounds such as chlorobenzene are less reactive than benzene. The three examples on the left of the bottom row (in the same diagram) are examples of electron withdrawal by conjugation to polar double or triple bonds, and in these cases the inductive effect further enhances the deactivation of the benzene ring. Alkyl substituents such as methyl increase the nucleophilicity of aromatic rings in the same fashion as they act on double bonds.



Exercises

Exercise 16.1.1

Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

Answer available at the end of this section.

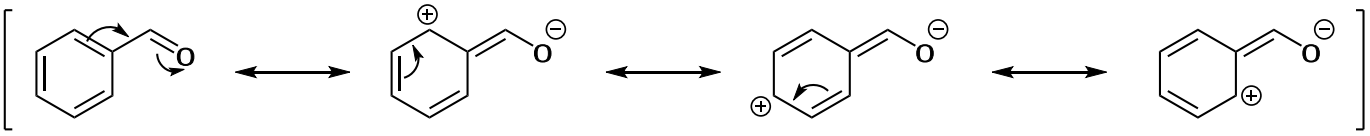
Exercise 16.1.2

Draw the resonance structures for methoxybenzene to show the electron-donating group.

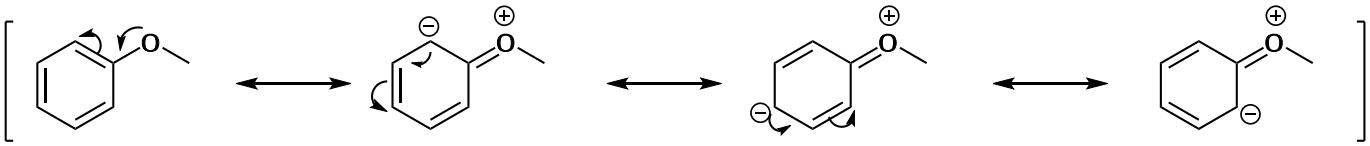
Answer available at the end of this section.

Answers

Exercise 16.1.1



Exercise 16.1.2



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- 16.4: Substituent Effects in Substituted Aromatic Rings by Dietmar Kennepohl, James Kabrhel, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

16.2: Directing Inductive Effects of Alkyl Groups

Objectives

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify each of the substituents listed in Objective 2 of Section 16.4 as being either meta or ortho/para directing.
3. classify each of the substituents listed in Objective 2 of Section 16.4 as being ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.
11. use the principles developed in this chapter to predict in which of the three categories listed in Objective 3, above, a previously unencountered substituent should be placed.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- steric effect
- steric hindrance

Study Notes

As you saw in Section 16.4, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta director or an ortho/para director. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom (see Figure below).

ortho and para sites identified on a toluene ring

Figure 16.2.1: Proportions of *o*-nitrotoluene and *p*-nitrotoluene produced by the nitration of toluene

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

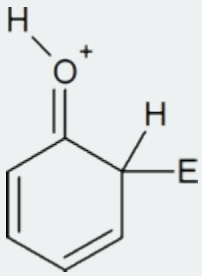
Substrate	% ortho	% para	ortho/para ratio
toluene	58	37	1.57:1
ethylbenzene	45	49	0.92:1
isopropylbenzene	30	62	0.48:1
tert-butylbenzene	16	73	0.22:1

[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 16.2.1**:** Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important, because in such structures each atom possesses a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.

Introduction

Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

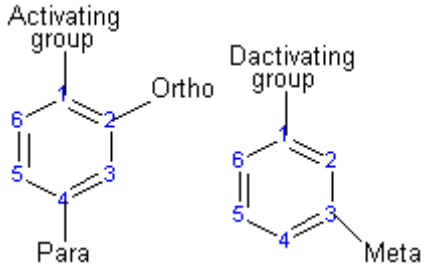
The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

$$F > Cl > Br > I$$

The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity. The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegative halogen is the least reactive ring (more deactivating substituent), when we compare rings with halogen substituents. Also the size of the halogen effects the reactivity of the benzene ring that the halogen is attached to. As the size of the halogen increase, the reactivity of the ring decreases.

The direction of the reaction

The activating group directs the reaction to the ortho or para position, which means the electrophile substitutes for the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen that is on carbon 3 with the exception of the halogens which are deactivating groups but direct the ortho or para substitution.

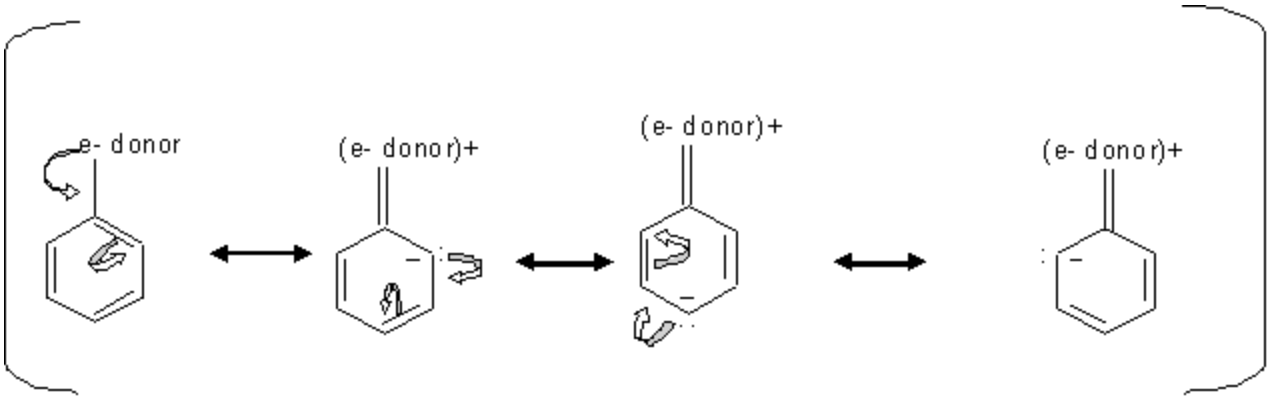


Substituents determine the reaction direction by resonance or inductive effect

Resonance effect is the conjugation between the ring and the substituent, which means the delocalizing of the π electrons between the ring and the substituent. Inductive effect is the withdraw of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

Activating groups (ortho or para directors)

When substituents such as -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

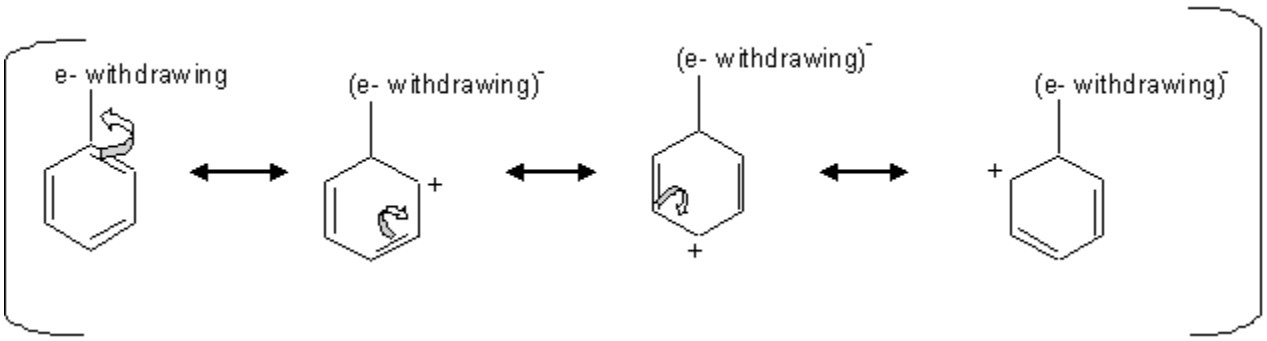


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

Deactivating group (meta directors)

The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws electron density away from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, that leaves the carbons at the ortho, para positions with a parital positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

Halogens are an exception of the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

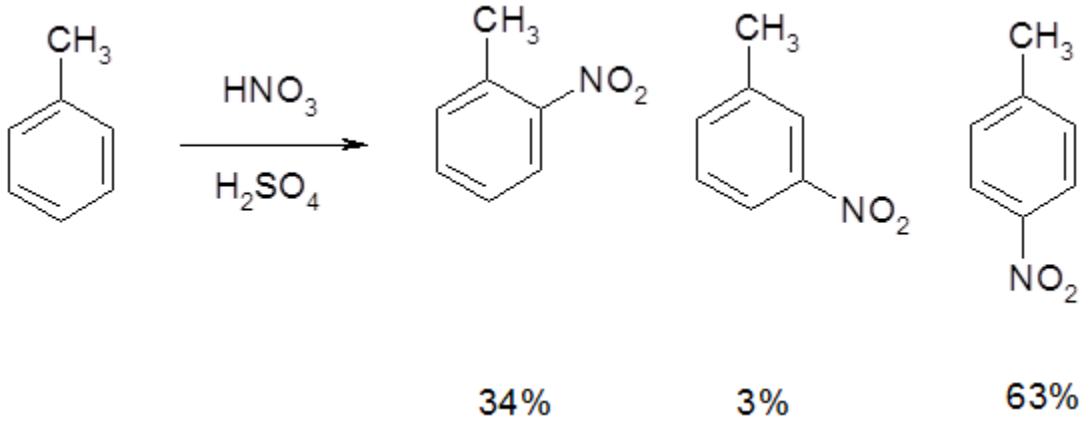
Substituents determine the reactivity of rings

The reaction of a substituted ring with an activating group is faster than the same reaction wtih benzene. On the other hand, a

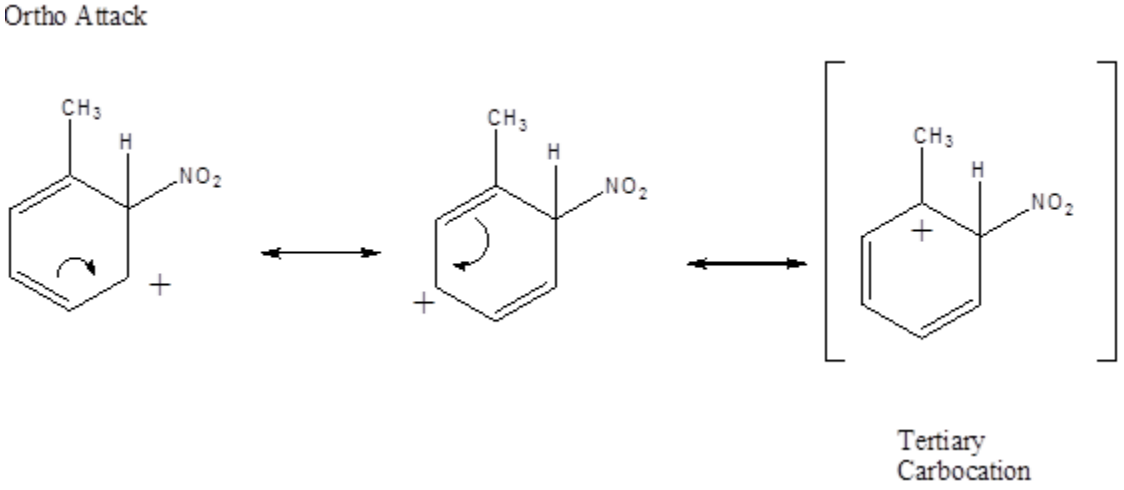
substituted ring with a deactivated group reacts slower than benzene.

Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the intermediate carbocation, which decreases the activation energy for the reaction. On the other hand, deactivating groups withdraw electron density away from the carbocation formed in the intermediate step, increasing the activation energy, which slows down the reaction.

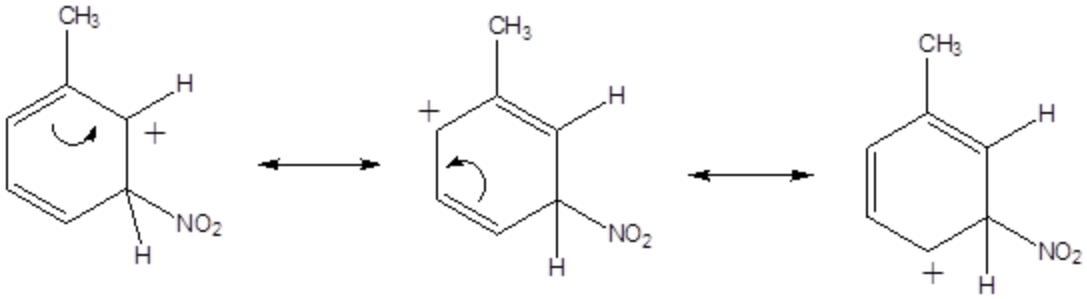
The CH_3 Group is an ortho, para director



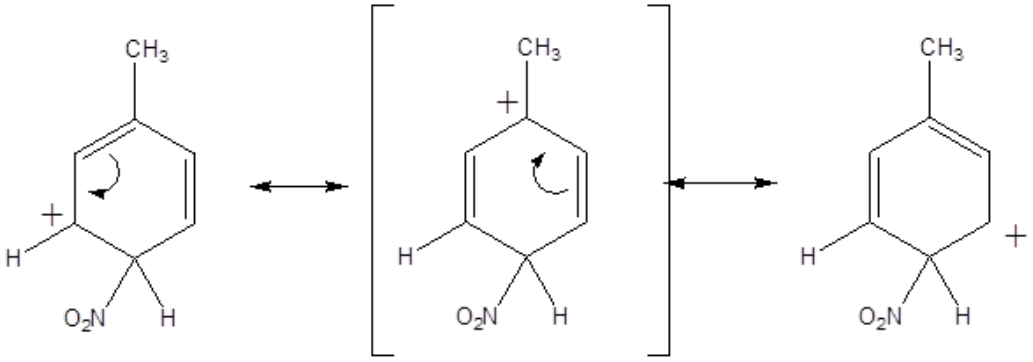
Alkyl groups are inductively donating, therefore are activators. This resulsts in o/p attack to form a tertiary arenium carbocation which speeds up the reaction.



Meta Attack

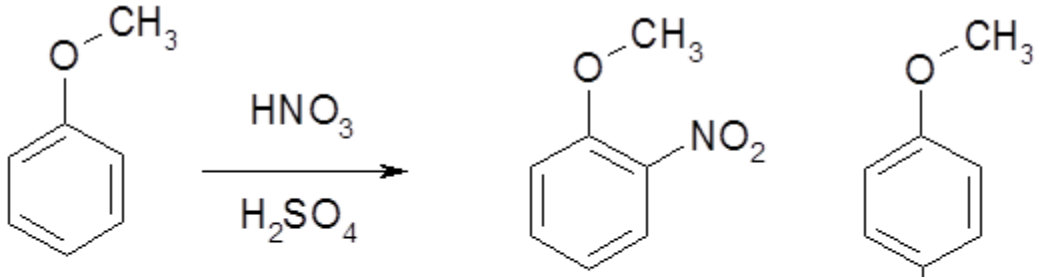


Para Attack



Tertiary
Carbocation

The O-CH_3 Group is an ortho, para director



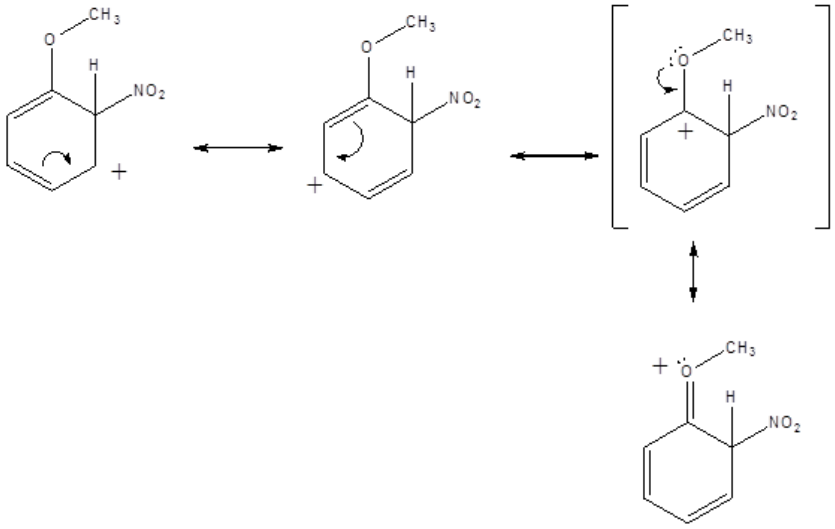
40%

60%

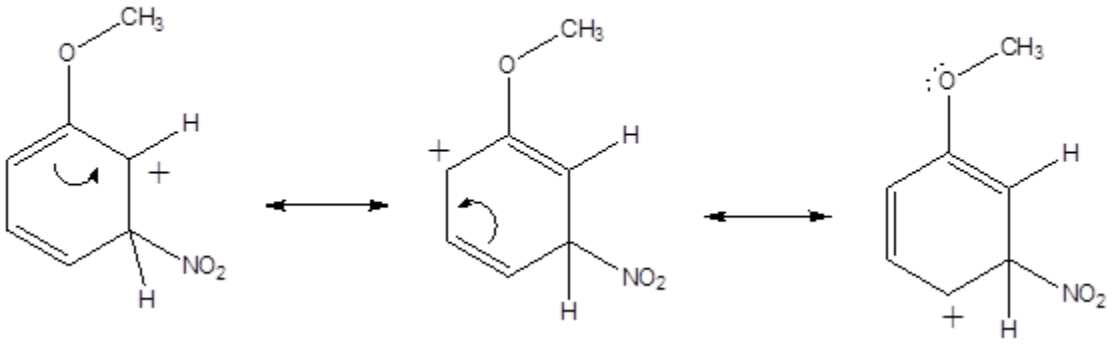
The methoxy group is an example of groups that are ortho, para directors by having and oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with an oxygen or nitrogen attached to the aromatic ring are ortho and para directors since the O or N can push electrons into the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes the ortho and para products to form faster than meta. Generally, the para product is preferred because of steric effects.

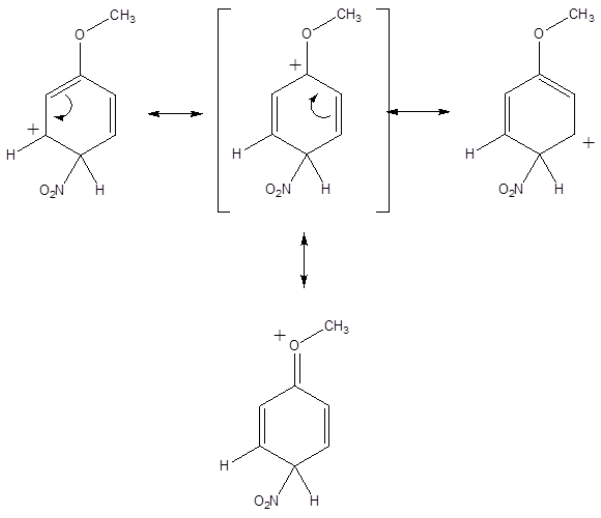
Ortho Attack



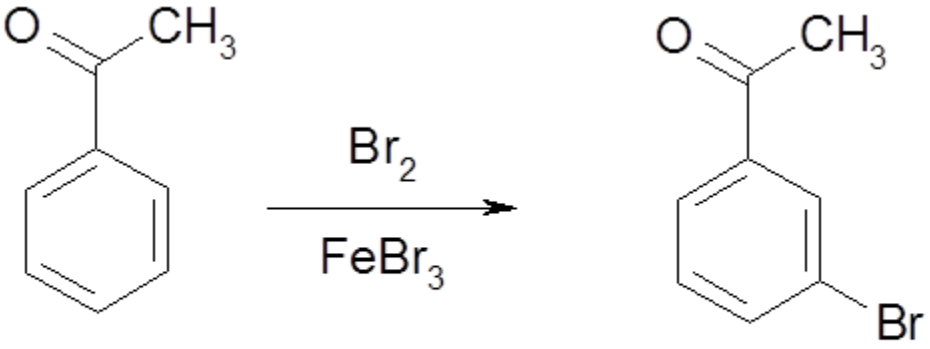
Meta Attack



Para Attack



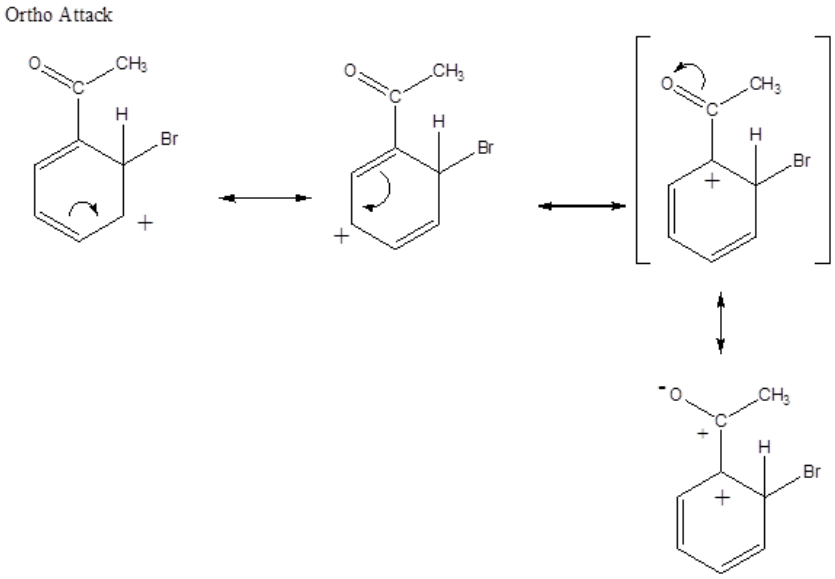
Acyl groups are meta directors



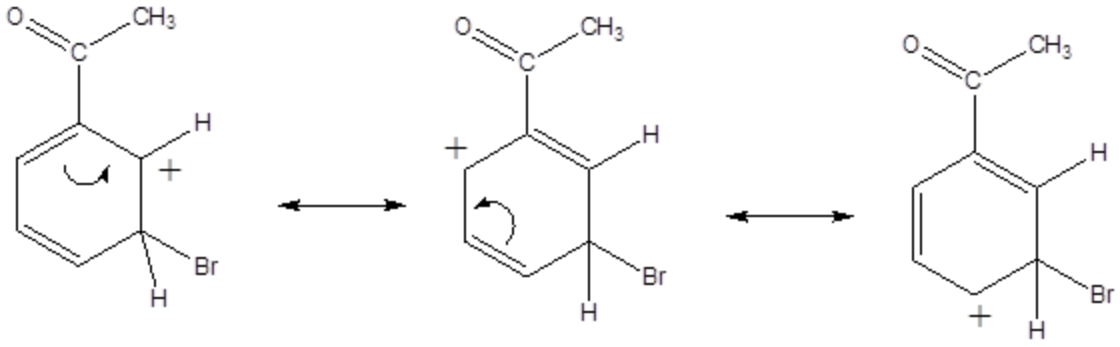
72%

Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

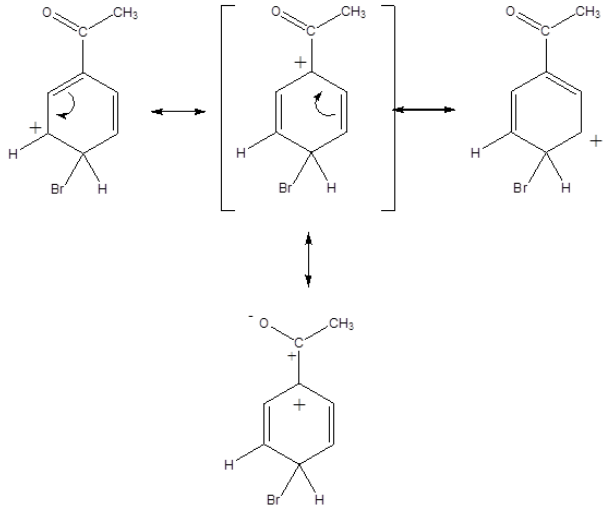
Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to an additional cation. This destabilizes the arenium cation and slows down ortho and para reaction. By default the meta product forms faster because it lacks this destabilizing resonance structure.



Meta Attack



Para Attack



Halogens

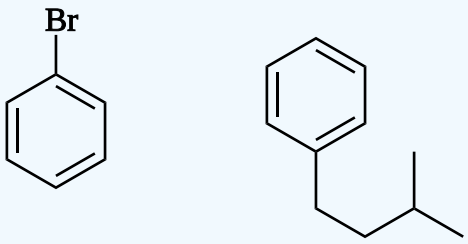
Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

References

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function,* 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry,* 9th ed.Danvers,MA: Wiley.

Exercise 16.2.1

Predict the pattern of the electrophilic substitution on these rings:



Answer available at the end of this section.

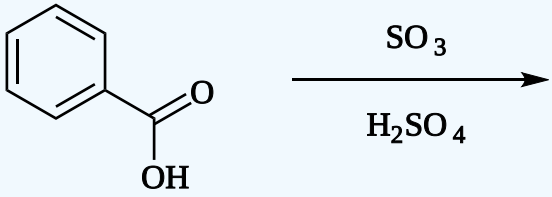
Exercise 16.2.2

Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer available at the end of this section.

Exercise 16.2.3

Predict the product of the following sulfonation reaction:



Answer available at the end of this section.

Exercise 16.2.4

Classify these two groups as activating or deactivating groups:

A. alcohol

B. ester

Answer available at the end of this section.

Exercise 16.2.5

Does a chloride substituent activate or deactivate an aromatic ring?

Answer available at the end of this section.

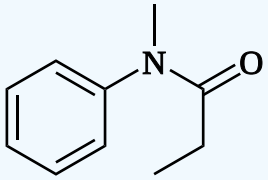
Exercise 16.2.6

(Trichloromethyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Answer available at the end of this section.

Exercise 16.2.7

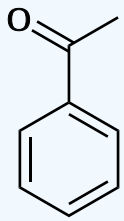
The following compound is less reactive towards electrophilic substitution than aniline? Explain.



Answer available at the end of this section.

Exercise 16.2.8

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer available at the end of this section.

Answers

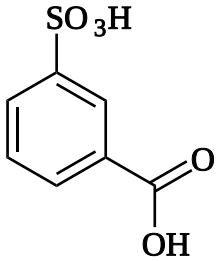
Exercise 16.2.1

The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substitution is going to be ortho and/or para substitution also since we have an alkyl substituent.

Exercise 16.2.2

The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

Exercise 16.2.3



Exercise 16.2.4

A. alcohol is an activating group.

B. Esters can be either. If the oxygen atom is next to the ring, esters are activating. However if the carbonyl is next to the ring, the ester is a deactivating group.

Exercise 16.2.5

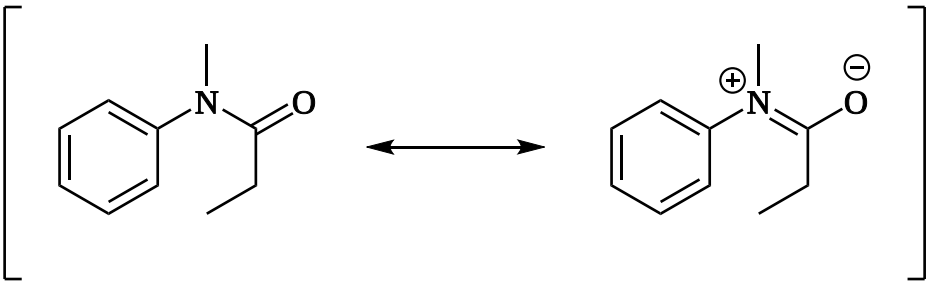
Chloride deactivate an aromatic ring due to the inductive effect.

Exercise 16.2.6

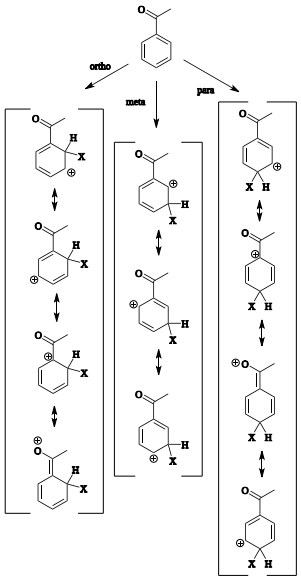
The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

Exercise 16.2.7

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



Exercise 16.2.8



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16.3: Directing Effects of Substituents in Conjugation with the Benzene Ring

Objectives

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify each of the substituents listed in Objective 2 of Section 16.4 as being either meta or ortho/para directing.
3. classify each of the substituents listed in Objective 2 of Section 16.4 as being ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.
11. use the principles developed in this chapter to predict in which of the three categories listed in Objective 3, above, a previously unencountered substituent should be placed.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- steric effect
- steric hindrance

Study Notes

As you saw in Section 16.4, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta director or an ortho/para director. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom (see Figure below).

ortho and para sites identified on a toluene ring

Figure 16.3.1: Proportions of *o*-nitrotoluene and *p*-nitrotoluene produced by the nitration of toluene

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

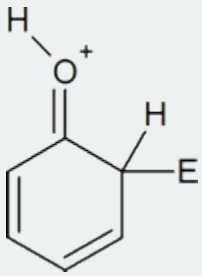
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[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 16.3.1**:** Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important, because in such structures each atom possesses a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.

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Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

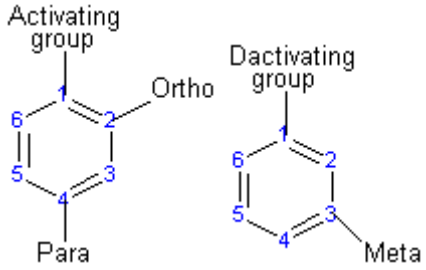
The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

$$F > Cl > Br > I$$

The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity. The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegative halogen is the least reactive ring (more deactivating substituent), when we compare rings with halogen substituents. Also the size of the halogen effects the reactivity of the benzene ring that the halogen is attached to. As the size of the halogen increase, the reactivity of the ring decreases.

The direction of the reaction

The activating group directs the reaction to the ortho or para position, which means the electrophile substitutes for the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen that is on carbon 3 with the exception of the halogens which are deactivating groups but direct the ortho or para substitution.

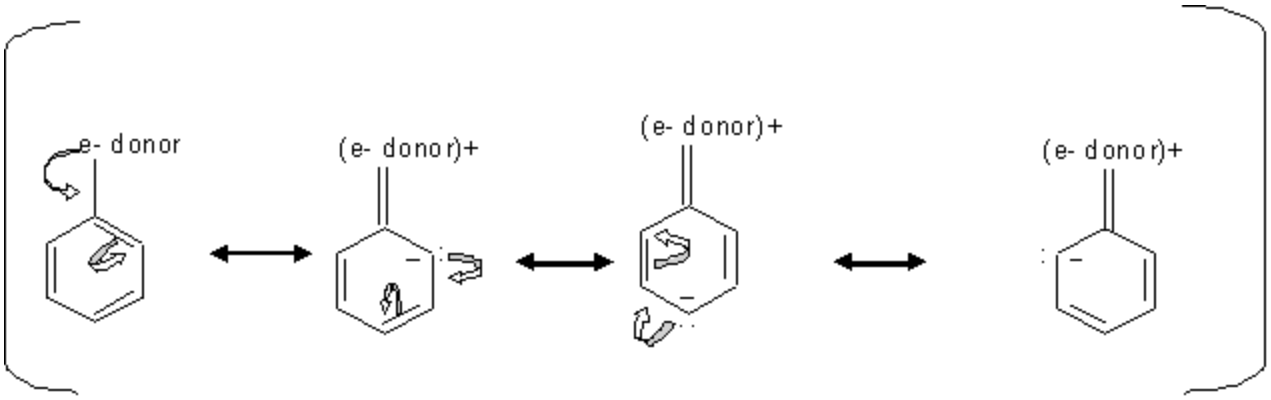


Substituents determine the reaction direction by resonance or inductive effect

Resonance effect is the conjugation between the ring and the substituent, which means the delocalizing of the π electrons between the ring and the substituent. Inductive effect is the withdraw of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

Activating groups (ortho or para directors)

When substituents such as -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

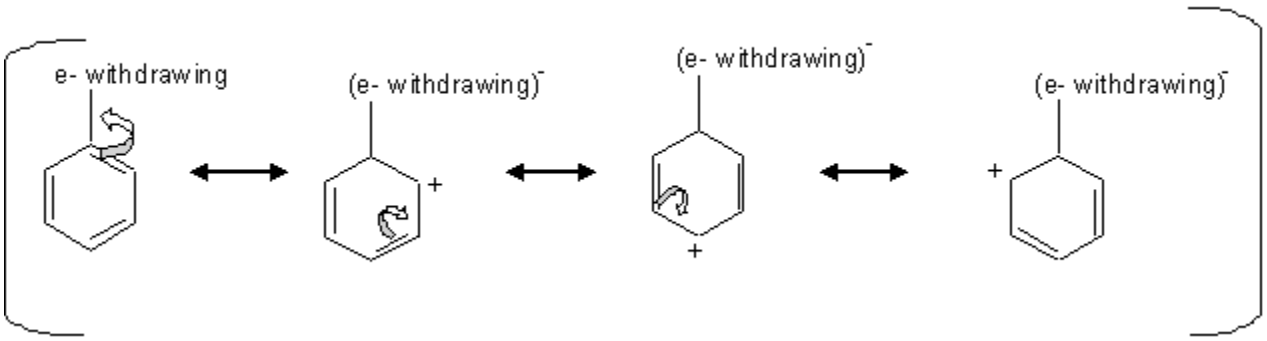


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

Deactivating group (meta directors)

The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws electron density away from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, that leaves the carbons at the ortho, para positions with a parital positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

Halogens are an exception of the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

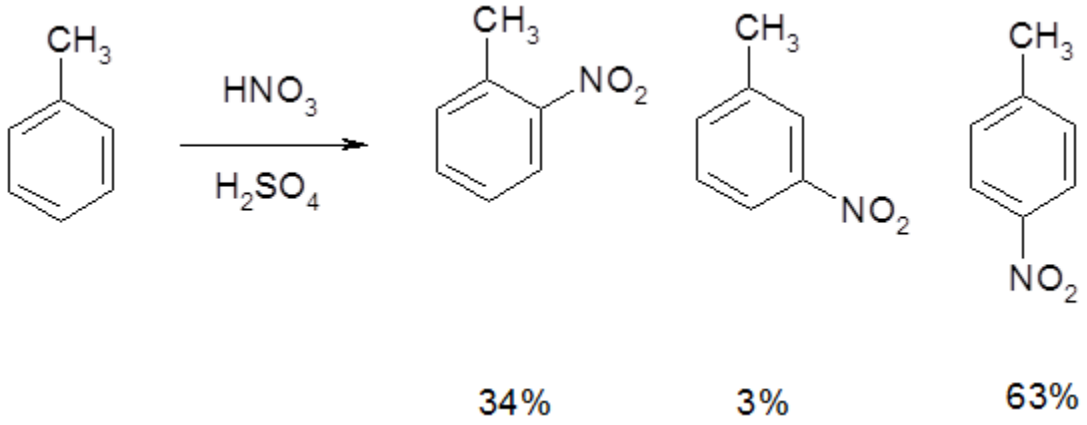
Substituents determine the reactivity of rings

The reaction of a substituted ring with an activating group is faster than the same reaction wtih benzene. On the other hand, a

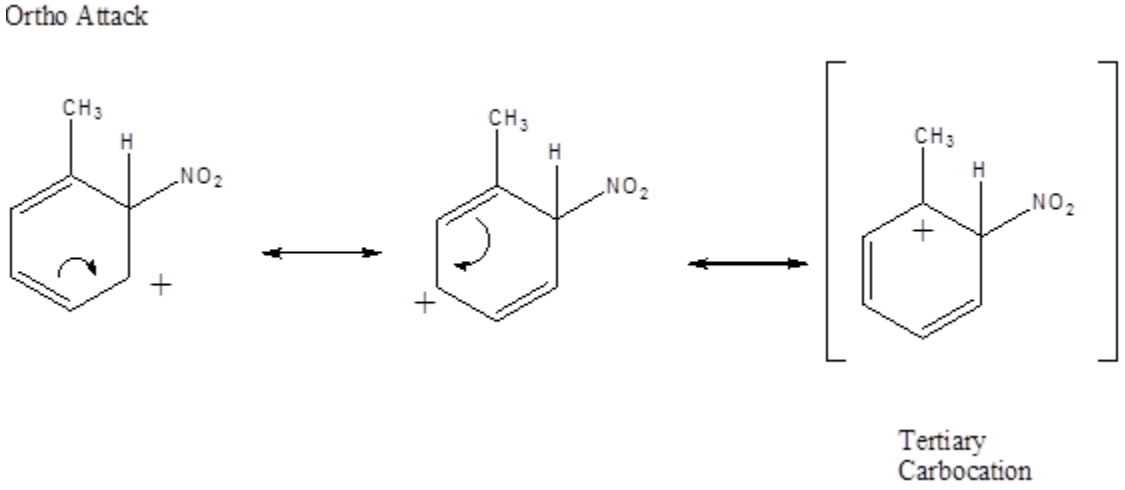
substituted ring with a deactivated group reacts slower than benzene.

Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the intermediate carbocation, which decreases the activation energy for the reaction. On the other hand, deactivating groups withdraw electron density away from the carbocation formed in the intermediate step, increasing the activation energy, which slows down the reaction.

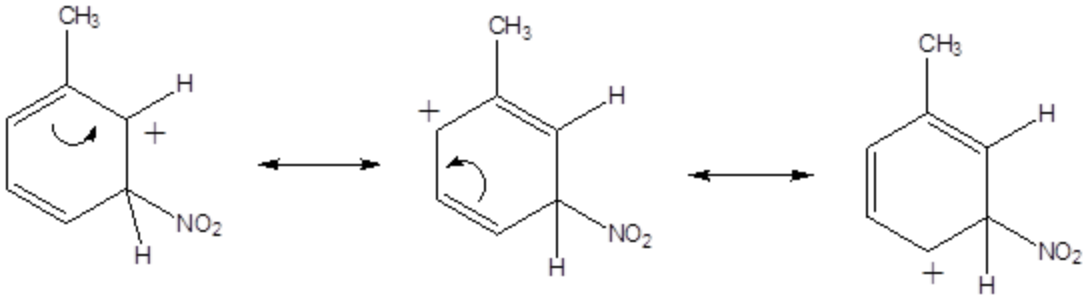
The CH_3 Group is an ortho, para director



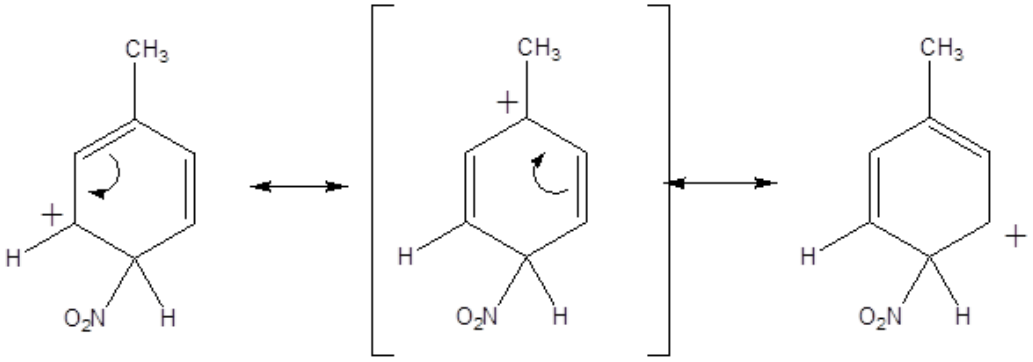
Alkyl groups are inductively donating, therefore are activators. This resulsts in o/p attack to form a tertiary arenium carbocation which speeds up the reaction.



Meta Attack

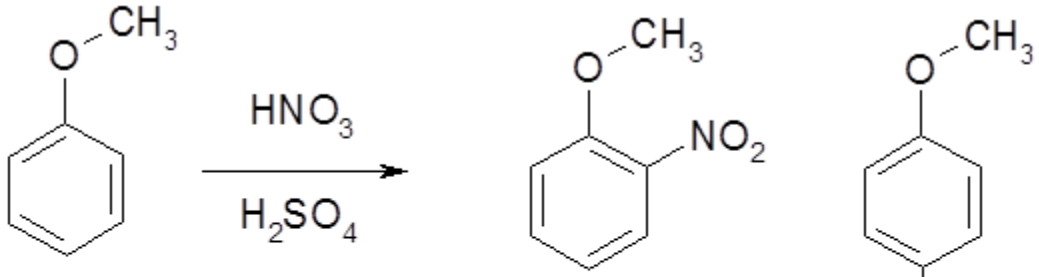


Para Attack



Tertiary
Carbocation

The O-CH_3 Group is an ortho, para director



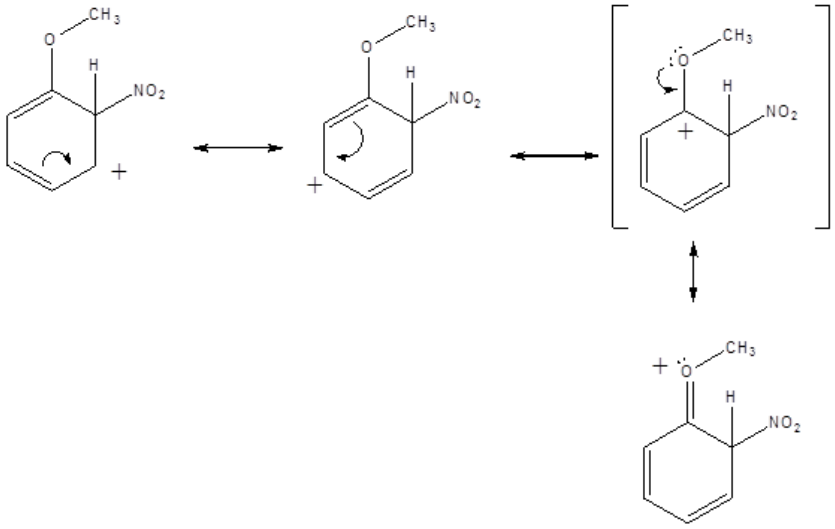
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60%

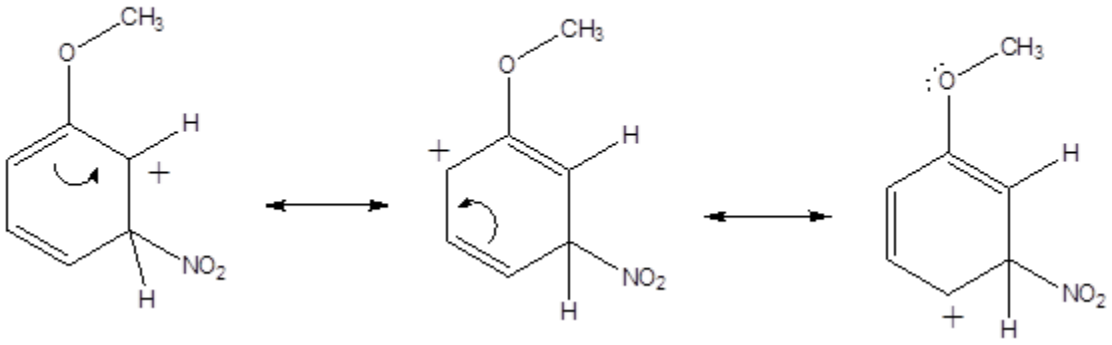
The methoxy group is an example of groups that are ortho, para directors by having and oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with an oxygen or nitrogen attached to the aromatic ring are ortho and para directors since the O or N can push electrons into the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes the ortho and para products to form faster than meta. Generally, the para product is preferred because of steric effects.

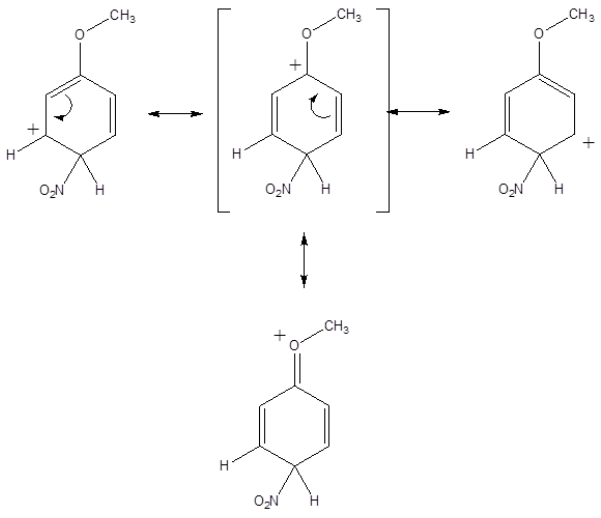
Ortho Attack



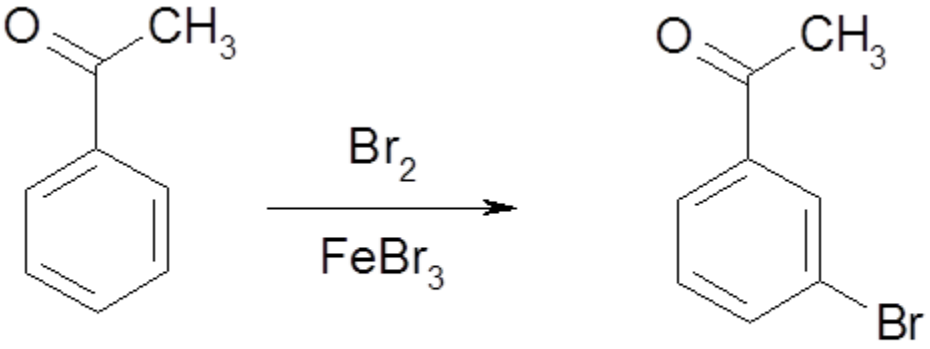
Meta Attack



Para Attack



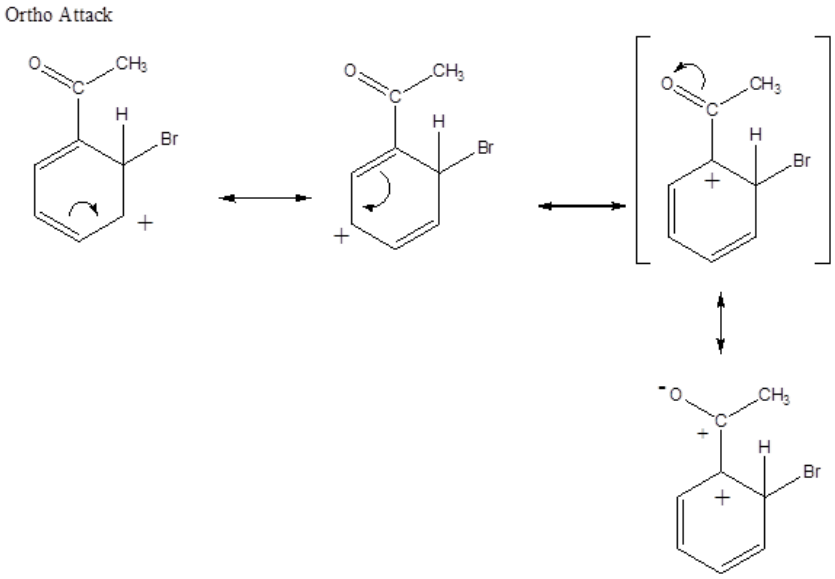
Acyl groups are meta directors



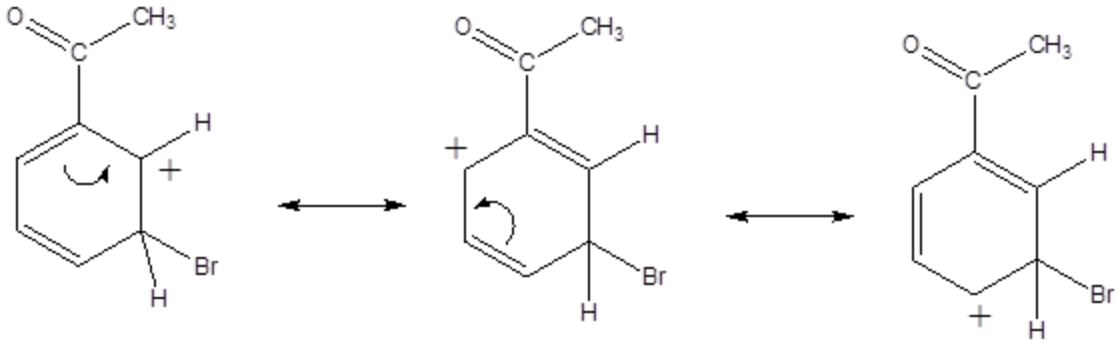
72%

Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

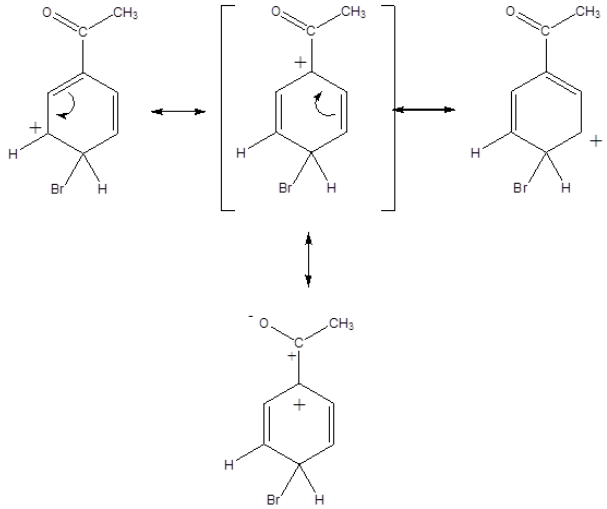
Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to an additional cation. This destabilizes the arenium cation and slows down ortho and para reaction. By default the meta product forms faster because it lacks this destabilizing resonance structure.



Meta Attack



Para Attack



Halogens

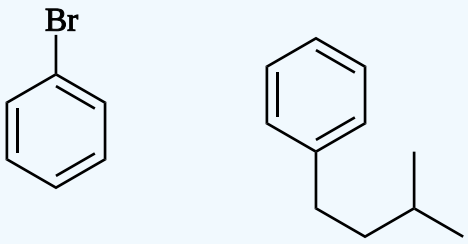
Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

References

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function,* 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry,* 9th ed.Danvers,MA: Wiley.

Exercise 16.3.1

Predict the pattern of the electrophilic substitution on these rings:



Answer available at the end of this section.

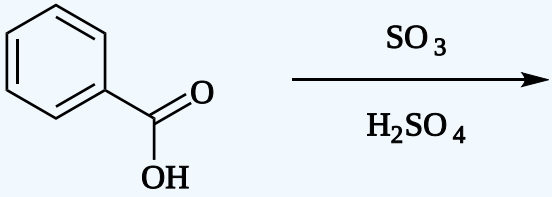
Exercise 16.3.2

Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer available at the end of this section.

Exercise 16.3.3

Predict the product of the following sulfonation reaction:



Answer available at the end of this section.

Exercise 16.3.4

Classify these two groups as activating or deactivating groups:

A. alcohol

B. ester

Answer available at the end of this section.

Exercise 16.3.5

Does a chloride substituent activate or deactivate an aromatic ring?

Answer available at the end of this section.

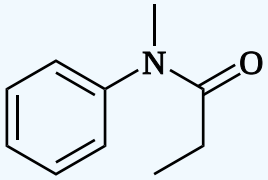
Exercise 16.3.6

(Trichloromethyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Answer available at the end of this section.

Exercise 16.3.7

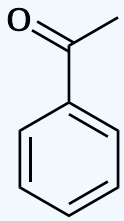
The following compound is less reactive towards electrophilic substitution than aniline? Explain.



Answer available at the end of this section.

Exercise 16.3.8

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer available at the end of this section.

Answers

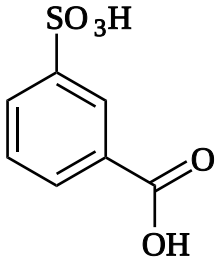
Exercise 16.3.1

The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substitution is going to be ortho and/or para substitution also since we have an alkyl substituent.

Exercise 16.3.2

The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

Exercise 16.3.3



Exercise 16.3.4

A. alcohol is an activating group.

B. Esters can be either. If the oxygen atom is next to the ring, esters are activating. However if the carbonyl is next to the ring, the ester is a deactivating group.

Exercise 16.3.5

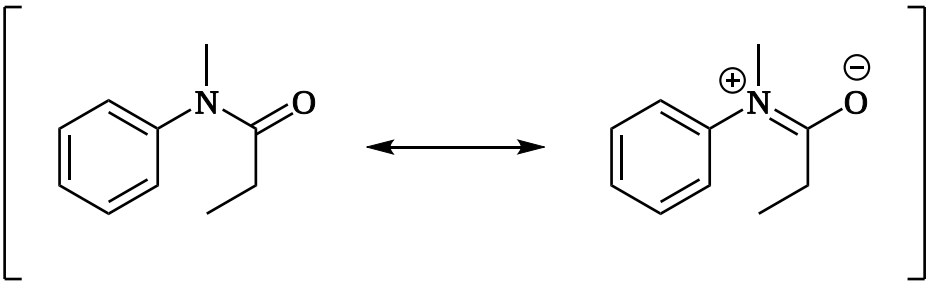
Chloride deactivate an aromatic ring due to the inductive effect.

Exercise 16.3.6

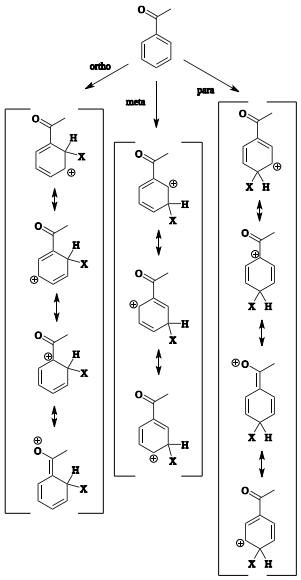
The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

Exercise 16.3.7

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



Exercise 16.3.8



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16.4: Electrophilic Attack on Disubstituted Benzenes

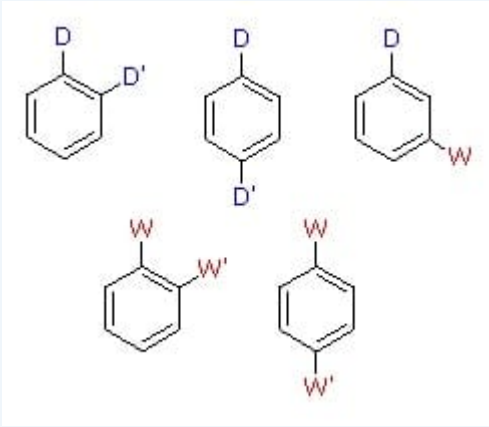
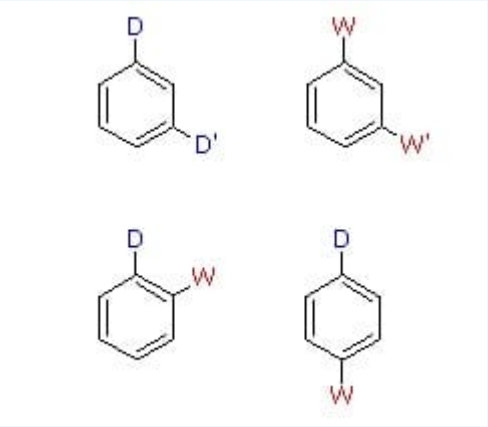
Objectives

After completing this section, you should be able to

1. predict the position or positions at which electrophilic substitution will occur when a third substituent is introduced into a disubstituted benzene ring.
2. explain the observed substitution pattern when a third substituent is introduced into a disubstituted benzene ring.

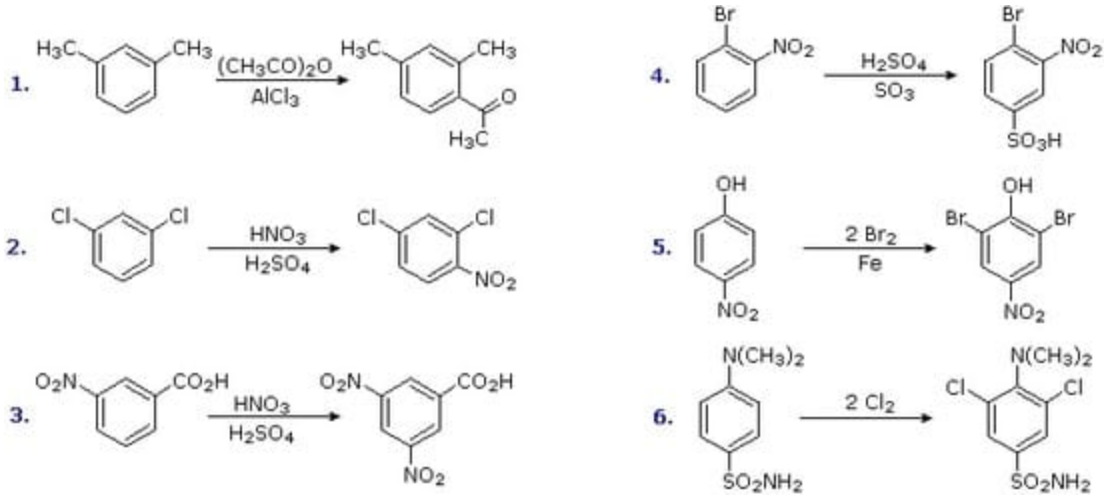
Orientational Interaction of Substituents

When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	**Reinforcing or Cooperative**
	
D = Electron Donating Group (ortho/para-directing) W = Electron Withdrawing Group (meta-directing)	

Reinforcing or Cooperative Substitutions

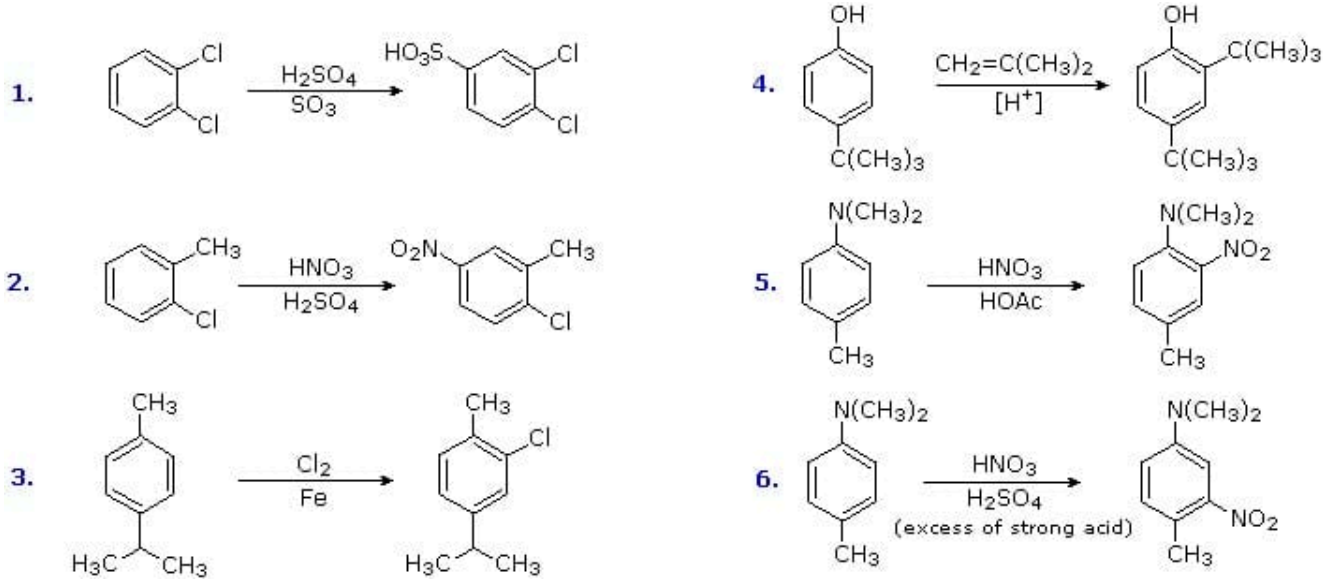
The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.



The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and 6.

Antagonistic or Non-Cooperative Substitutions

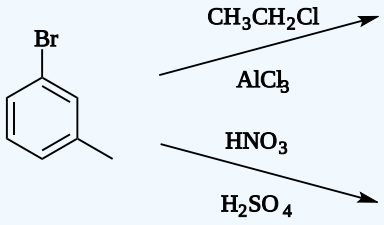
Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [$–NH(CH_3)_2^{(+)}$] in a strong acid environment.

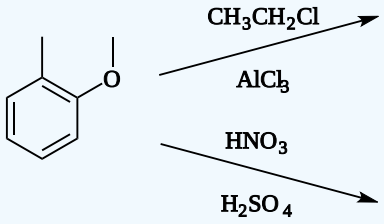


Exercises

Exercise 16.4.1

Predict the products of the following reactions:

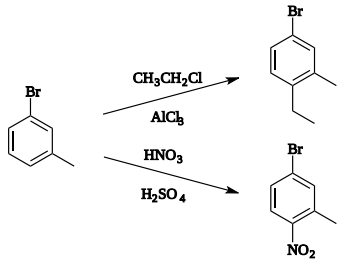


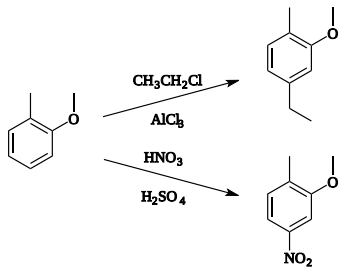


Answer available at the end of this section.

Answers

Exercise 16.4.1





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16.5: Synthetic Strategies Toward Substituted Benzenes

Objectives

After completing this section, you should be able to

- Design a multistep synthesis which may involve reactions in the alkyl side chain of an alkylbenzene and the electrophilic substitution reactions discussed in this chapter. You should pay particular attention to
  - carrying out the reactions in the correct order.
  - using the most appropriate reagents and conditions.
  - the limitations of certain types of reactions.
- Analyze a proposed multistep synthesis involving aromatic substitution to determine its feasibility, point out any errors in the proposal and identify possible problem areas.

Study Notes

As you can see, designing a multistep synthesis requires an analytical mind and an ability to think logically, as well as a knowledge of organic reactions. The best way to become an expert in designing such syntheses is to get lots of practice by doing plenty of problems.

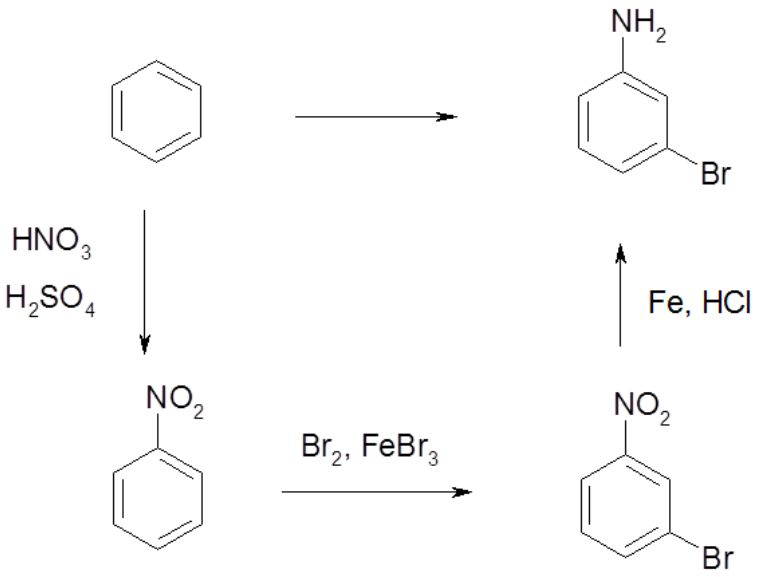
The ability to plan a successful multi step synthesis of complex molecules is one of the goals of organic chemists. It requires a working knowledge of the uses and limitations of many organic reactions - not only which reactions to use, but when. A few examples follow:

From benzene make *m*-bromoaniline

In this reaction three reactions are required.

1. A nitration
2. A conversion from the nitro group to an amine
3. A bromination

Because the end product is meta a meta directing group must be utilized. Of the nitro, bromine, and amine group, only the nitro group is meta direction. This means that the first step need to be the nitration and not the bromination. Also, the conversion of the nitro group to an amine must occur last because the amine group is ortho/para direction.

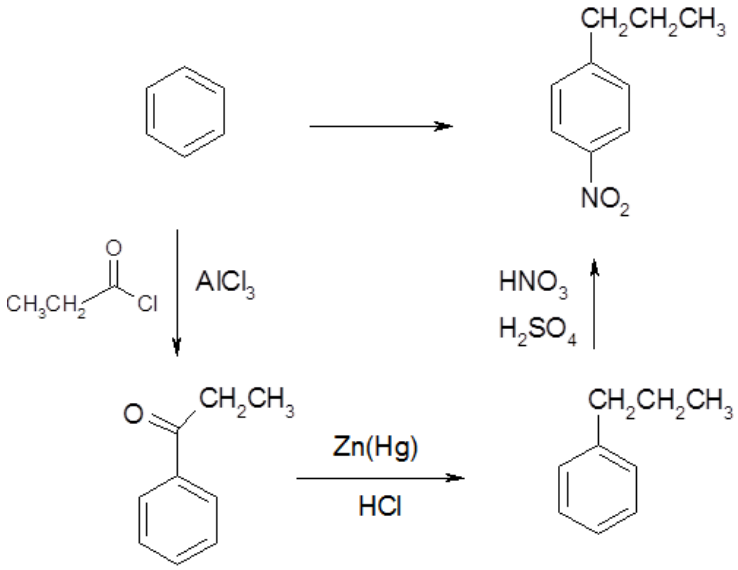


From benzene make *p*-nitropropylbenzene :

In this reaction three reactions are required.

1. A Friedel Crafts acylation
2. A conversion from the acyl group to an alkane
3. A nitration

Because the propyl group has more than two carbons, it must be added in two steps. A Friedel Crafts acylation followed by a Clemmensen Reduction. Remember that Friedel Crafts reactions are hindered if the benzene ring is strongly deactivated. This means that the acyl group must go on first. Because the end product is para a para directing group must be utilized. Of the nitro, acyl, and alkane group, only the alkane group is meta direction. This means that the acyl group must be converted to an alkane prior to the nitration step.



Exercise 16.5.1

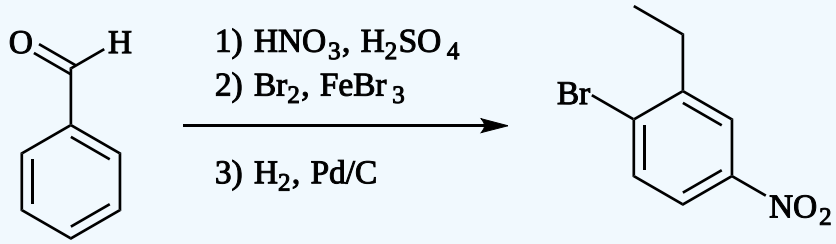
How would make the following compounds from benzene?

a. *m*-bromonitrobenzene
b. *m*-bromoethylbenzene

Answer available at the end of this section.

Exercise 16.5.2

There is something wrong with the following reaction, what is it?



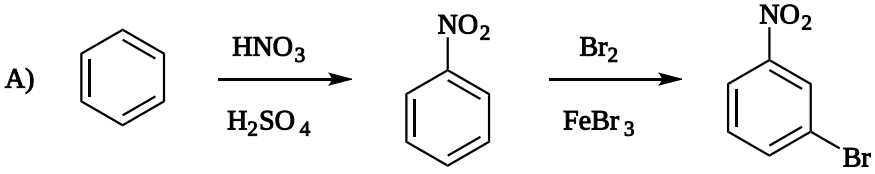
Answer available at the end of this section.

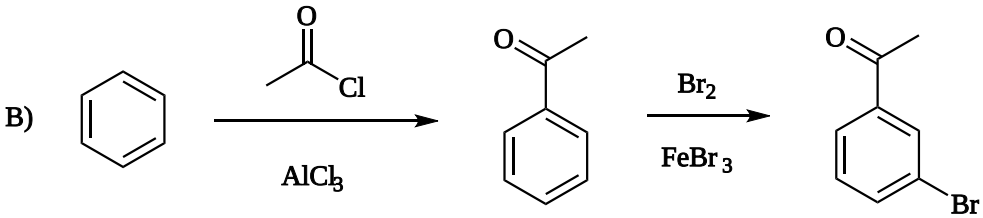
- Topic hierarchy

Answers

Exercise 16.5.1

Only one possible synthesis is shown for each compound. There are multiple possibilities.





Exercise 16.5.2

The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.

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16.6: Reactivity of Polycyclic Benzenoid Hydrocarbons

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16.7: Polycyclic Aromatic Hydrocarbons and Cancer

To Your Health: Polycyclic Aromatic Hydrocarbons and Cancer

The intense heating required for distilling coal tar results in the formation of PAHs. For many years, it has been known that workers in coal-tar refineries are susceptible to a type of skin cancer known as tar cancer. Investigations have shown that a number of PAHs are carcinogens. One of the most active carcinogenic compounds, benzopyrene, occurs in coal tar and has also been isolated from cigarette smoke, automobile exhaust gases, and charcoal-broiled steaks. It is estimated that more than 1,000 t of benzopyrene are emitted into the air over the United States each year. Only a few milligrams of benzopyrene per kilogram of body weight are required to induce cancer in experimental animals.

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17: ALDEHYDES AND KETONES - THE CARBONYL GROUP

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

17.1: Naming the Aldehydes and Ketones
17.2: Structure of the Carbonyl Group
17.3: Spectroscopic Properties of Aldehydes and Ketones
17.4: Preparation of Aldehydes and Ketones
17.5: Reactivity of the Carbonyl Group: Mechanisms of Addition
17.6: Addition of Water to Form Hydrates
17.7: Addition of Alcohols to Form Hemiacetals and Acetals
17.8: Acetals as Protecting Groups
17.9: Nucleophilic Addition of Ammonia and Its Derivatives
17.10: Deoxygenation of the Carbonyl Group
17.11: Addition of Hydrogen Cyanide to Give Cyanohydrins
17.12: Addition of Phosphorus Ylides: The Wittig Reaction
17.13: Oxidation by Peroxycarboxylic Acids: The Baeyer- Villiger Oxidation
17.14: Oxidative Chemical Tests for Aldehydes

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17.1: Naming the Aldehydes and Ketones

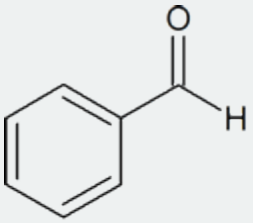
Objectives

After completing this section, you should be able to

1. provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed or shorthand structure.
2. draw the structure of an aldehyde or ketone, given its IUPAC name.
3. draw the structure of the following aldehydes and ketones, given their trivial names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

Study Notes

We only use those trivial names listed under Objective 3, above. We use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the trivial name of benzaldehyde.



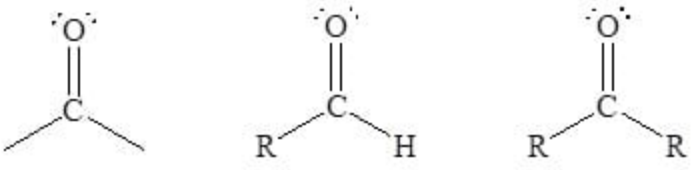
benzenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehydr*ation of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

Introduction

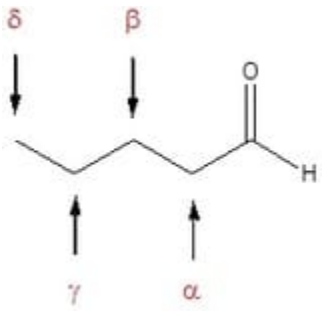
Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

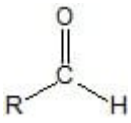


Naming Aldehydes

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C{=}O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



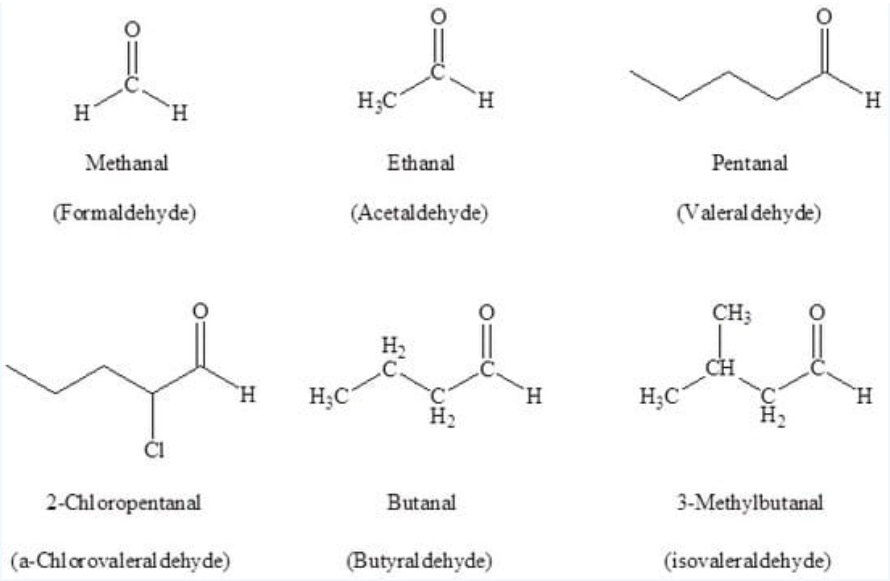
If the aldehyde moiety  (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this moiety will get the #1 location number in naming the ring.

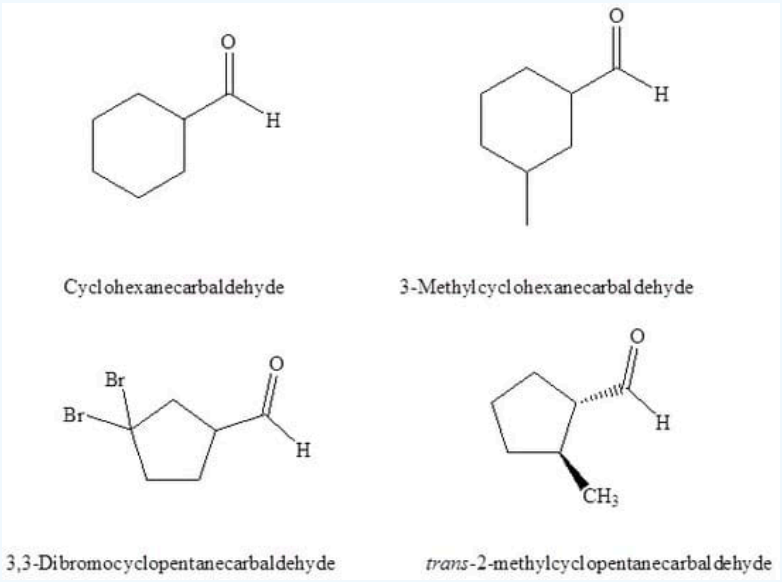
Summary of Aldehyde Nomenclature rules

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

Example 19.1.1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.





Naming Ketones

The IUPAC system of nomenclature assigns a characteristic suffix of -**one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

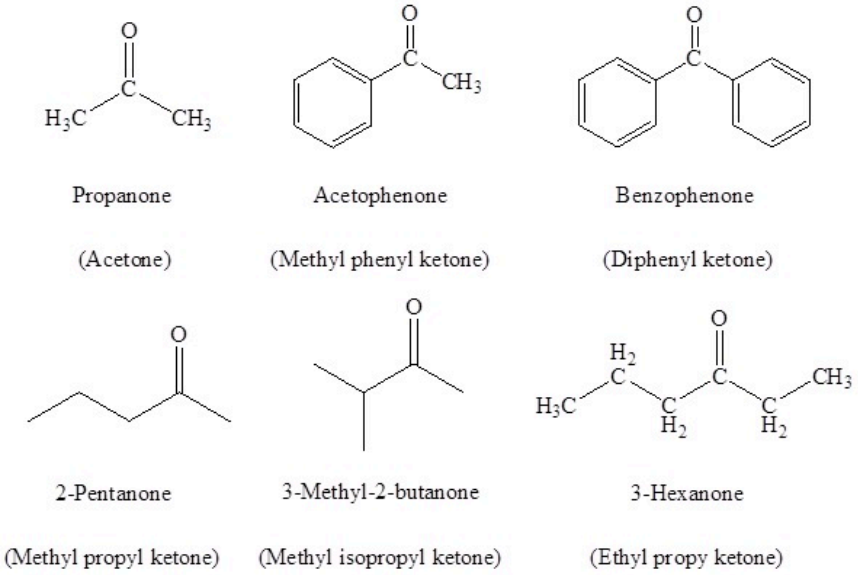
The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix -**ketone**. The attached alkyl groups are arranged in the name alphabetically.

Summary of Ketone Nomenclature rules

1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some common ketones are known by their generic names. Such as the fact that *propanone* is commonly referred to as *acetone*.

Example 19.1.2

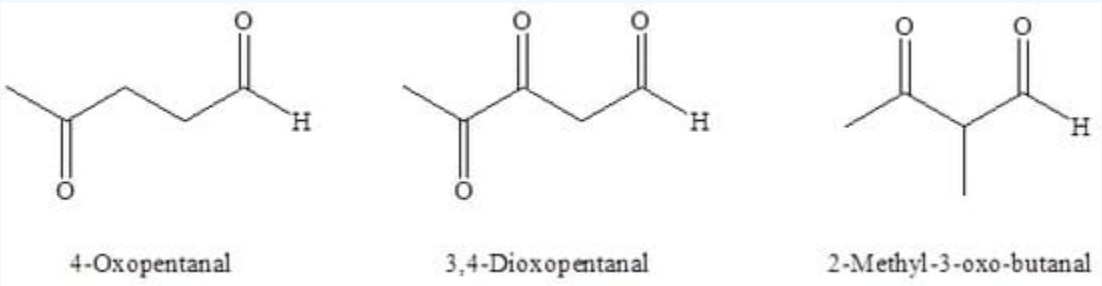
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



Naming Aldehydes and Ketones in the Same Molecule

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

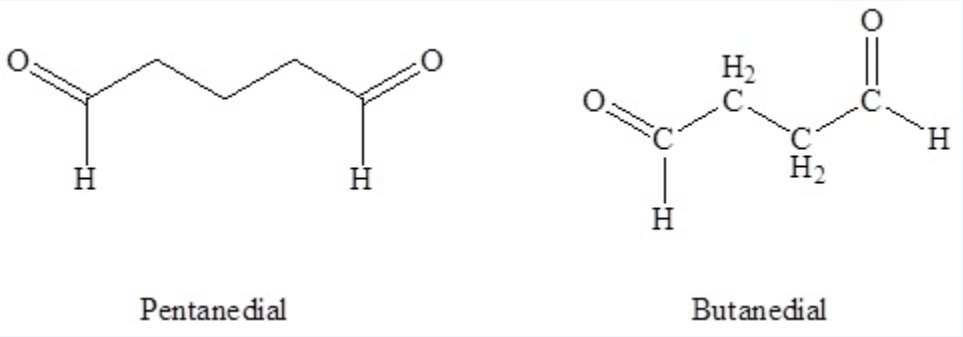
Example 19.1.3



Naming Dialdehydes and Diketones

For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

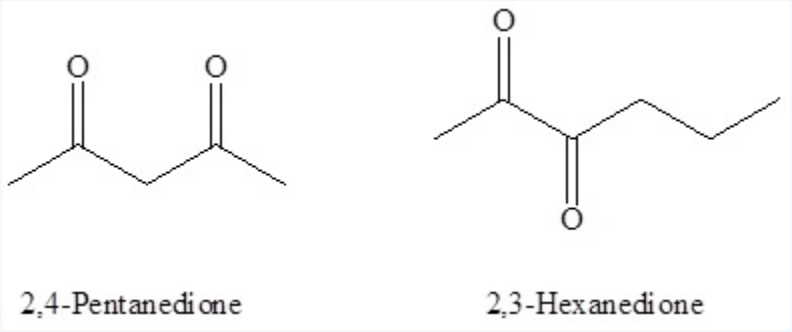
Example 19.1.4



Pentanedial Butanedial

For diketones both carbonyls require a location number. The ending **-dione** or **-dial** is added to the end of the parent chain.

Example 19.1.5



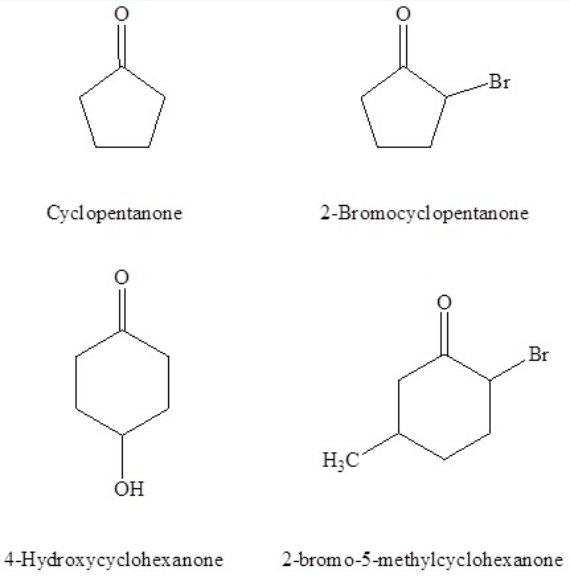
2,4-Pentanedione 2,3-Hexanedione

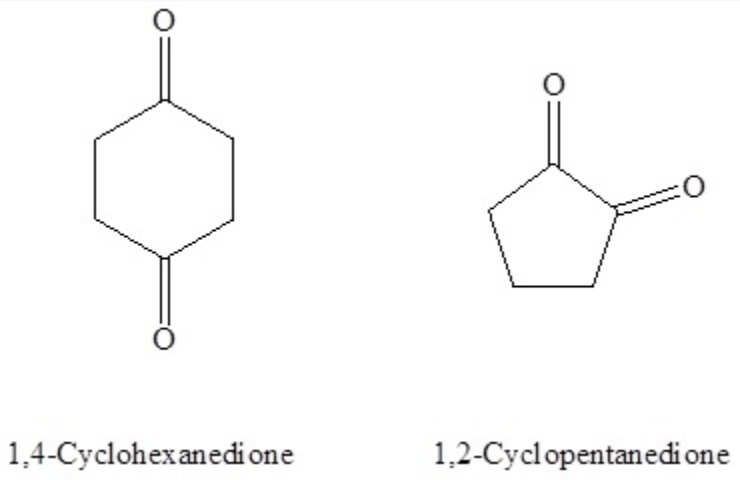
Naming Cyclic Ketones and Diketones

In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

Example 19.1.6

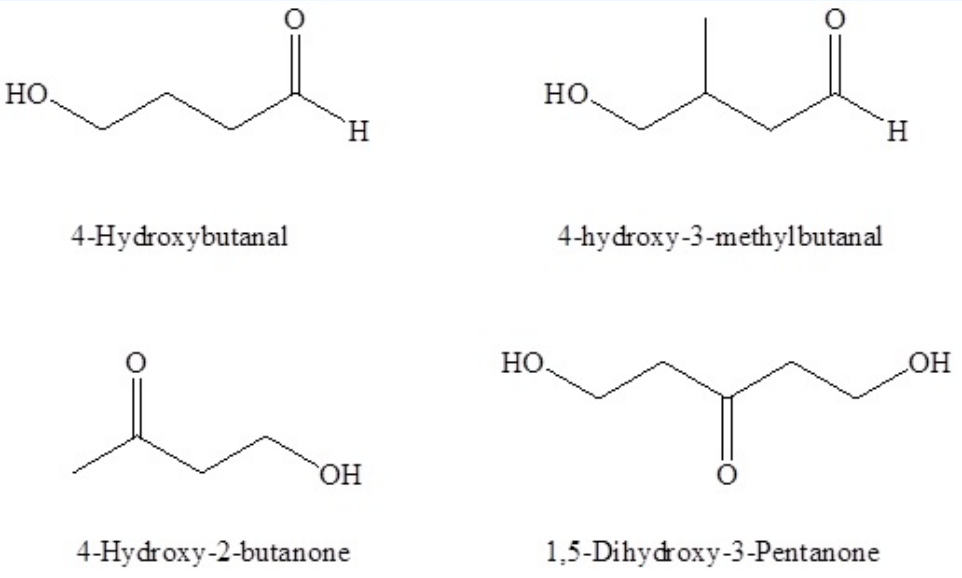




Naming Carbonyls and Hydroxyls in the Same Molecule

When and aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

Example 19.1.7



Naming Carbonyls and **Alkenes** in the Same Molecule

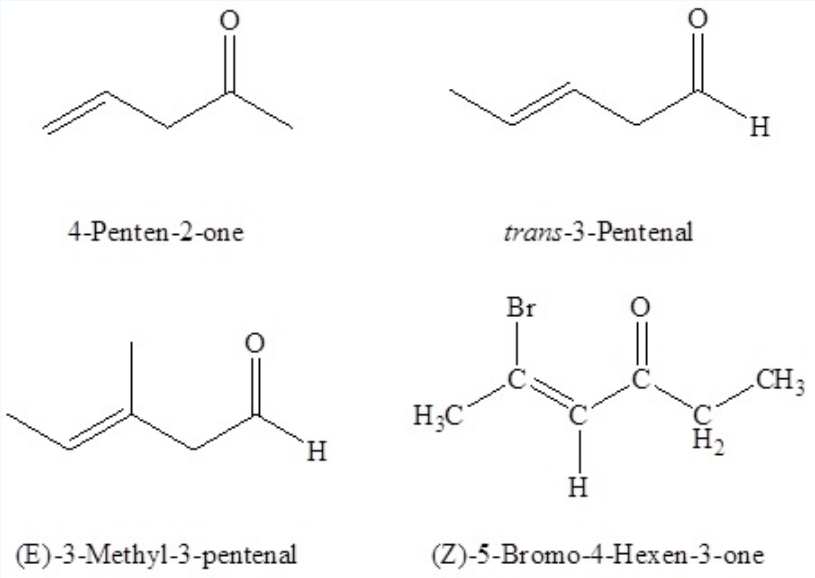
When and aldehyde or ketone is present in a molecule which also contains analkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

When carbonyls are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

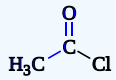
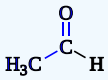
Example 19.1.8



Aldehydes and Ketones as Fragments

- *Alkanoyl* is the common name of the fragment, though the older naming, *acyl*, is still widely used.
- *Formyl* is the common name of the fragment.
- *Acety* is the common name of the CH_3-C=O- fragment.

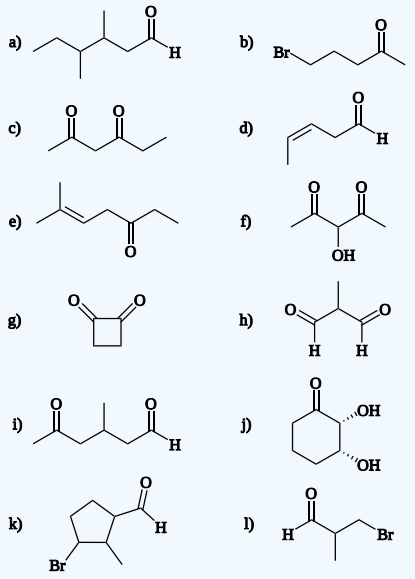
Example 19.1.9

 acetyl chloride	 acetylaldehyde	 formyl fluoride

Exercises

Exercise 19.1.1

Give the IUPAC name for each compound:



Answer available at the end of this section.

Exercise 19.1.2

Give the structure corresponding to each IUPAC name:

A) butanal

B) 2-hydroxycyclopentanone

C) 2,3-pentanedione

D) 1,3-cyclohexanedione

E) 3,4-dihydoxy-2-butanone

F) (E) 3-methyl-2-hepten-4-one

G) 3-oxobutanal

H) *cis*-3-bromocyclohexanecarboaldehyde

I) butanedial

J) *trans*-2-methyl-3-hexenal

Answer available at the end of this section.

References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

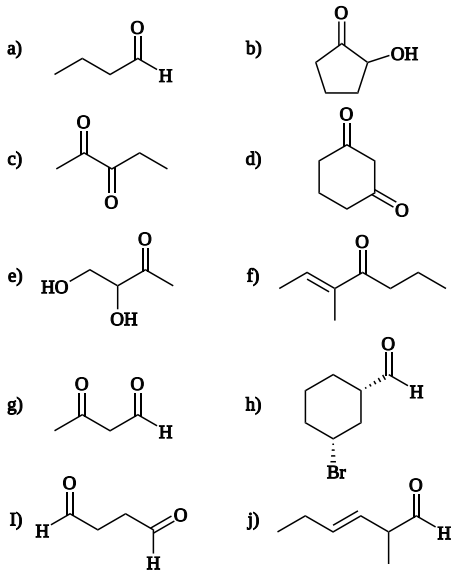
Answers

Exercise 19.1.1

Add texts here. Do not delete this text first.

A) 3,4-dimethylhexanal
B) 5-bromo-2-pentanone
C) 2,4-hexanedione
D) *cis*-3-pentenal
E) 6-methyl-5-hepten-3-one
F) 3-hydroxy-2,4-pentanedione
G) 1,2-cyclobutanedione
H) 2-methyl-propanedial
I) 3-methyl-5-oxo-hexanal
J) *cis*-2,3-dihydroxycyclohexanone
K) 3-bromo-2-methylcyclopentanecarboaldehyde
L) 3-bromo-2-methylpropanal

Exercise 19.1.2



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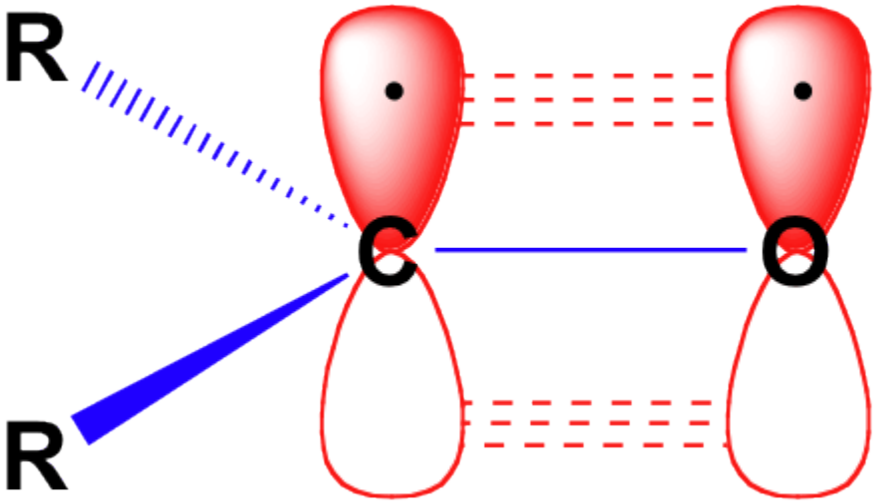
17.2: Structure of the Carbonyl Group

A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

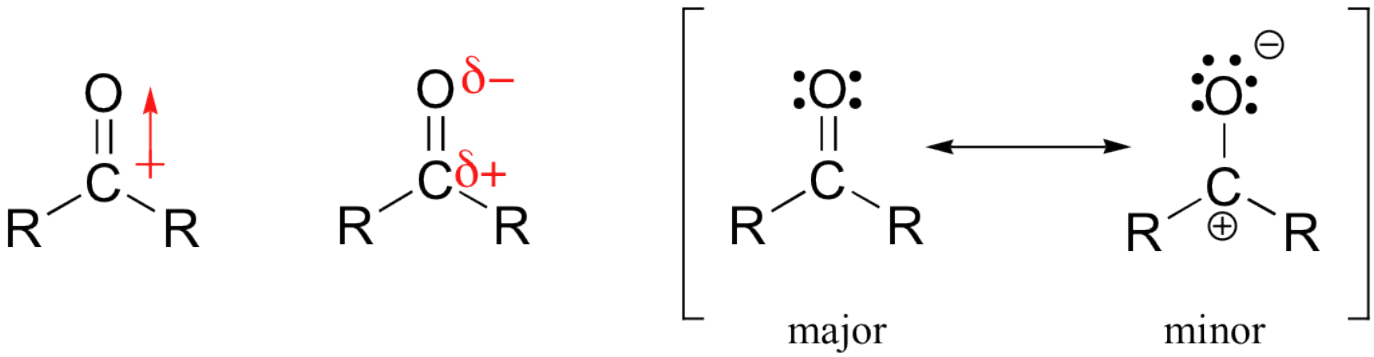
The Carbonyl Group

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming soverlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a ‘side-by-side’ pbond with a 2p orbital on the oxygen.

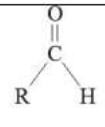
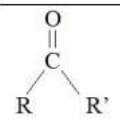
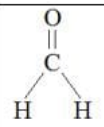
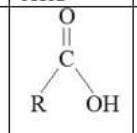
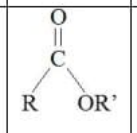
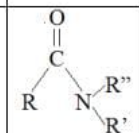
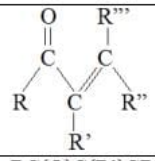
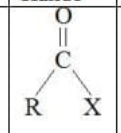
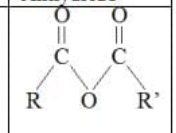


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

Some Carbonyl Compounds

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH2O	RCOOH	RCOOR'	RCONR'R"	RC(O)C(R')CR"R"'	RCOX	(RCO)2O

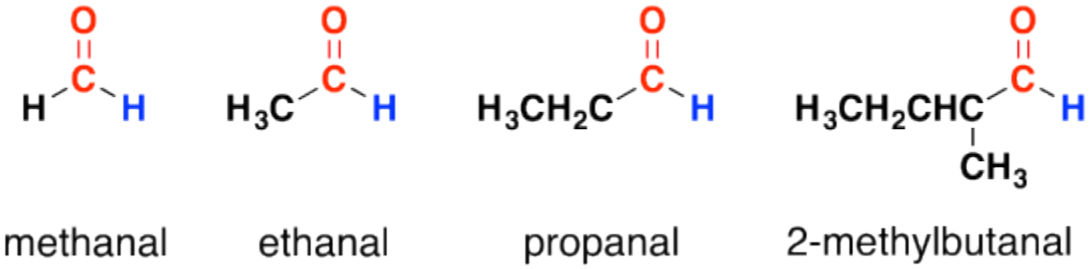
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

This page explains what aldehydes and ketones are, and looks at the way their bonding affects their reactivity. It also considers their simple physical properties such as solubility and boiling points. Aldehydes and ketones are simple compounds which contain a carbonyl group - a carbon-oxygen double bond. They are simple in the sense that they don't have other reactive groups like -OH or -Cl attached directly to the carbon atom in the carbonyl group - as you might find, for example, in carboxylic acids containing -COOH.

Aldehydes

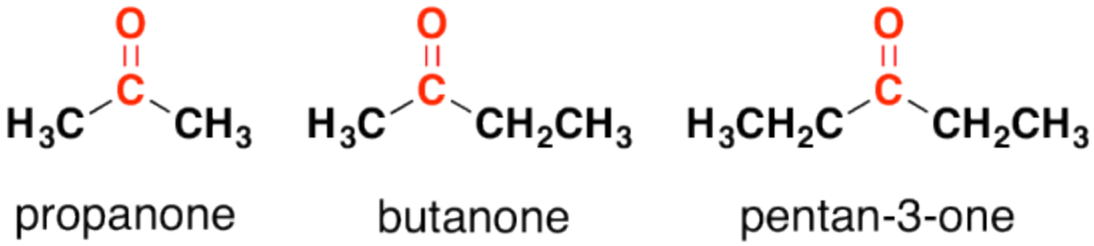
In aldehydes, the carbonyl group has a hydrogen atom attached to it together with either a second hydrogen atom or, more commonly, a hydrocarbon group which might be an alkyl group or one containing a benzene ring. For the purposes of this section, we shall ignore those containing benzene rings.



Notice that these all have exactly the same end to the molecule. All that differs is the complexity of the other group attached. When you are writing formulae for these, the aldehyde group (the carbonyl group with the hydrogen atom attached) is always written as -CHO - never as COH. That could easily be confused with an alcohol. Ethanal, for example, is written as CH_3CHO; methanal as HCHO. The name counts the total number of carbon atoms in the longest chain - including the one in the carbonyl group. If you have side groups attached to the chain, notice that you always count from the carbon atom in the carbonyl group as being number 1.

Ketones

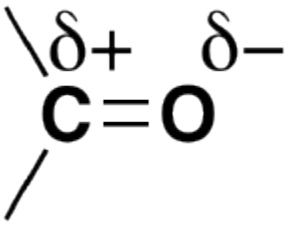
In ketones, the carbonyl group has two hydrocarbon groups attached. Again, these can be either alkyl groups or ones containing benzene rings. Again, we'll concentrated on those containing alkyl groups just to keep things simple. Notice that ketones never have a hydrogen atom attached to the carbonyl group.



Propanone is normally written CH_3COCH_3. Notice the need for numbering in the longer ketones. In pentanone, the carbonyl group could be in the middle of the chain or next to the end - giving either pentan-3-one or pentan-2-one.

Bonding and reactivity

Oxygen is far more electronegative than carbon and so has a strong tendency to pull electrons in a carbon-oxygen bond towards itself. One of the two pairs of electrons that make up a carbon-oxygen double bond is even more easily pulled towards the oxygen. That makes the carbon-oxygen double bond very highly polar.



The slightly positive carbon atom in the carbonyl group can be attacked by nucleophiles. A nucleophile is a negatively charged ion (for example, a cyanide ion, CN^-), or a slightly negatively charged part of a molecule (for example, the lone pair on a nitrogen atom in ammonia, NH_3).

During the reaction, the carbon-oxygen double bond gets broken. The net effect of all this is that the carbonyl group undergoes addition reactions, often followed by the loss of a water molecule. This gives a reaction known as addition-elimination or condensation. You will find examples of simple addition reactions and addition-elimination if you explore the aldehydes and ketones menu (link at the bottom of the page). Both aldehydes and ketones contain a carbonyl group. That means that their reactions are very similar in this respect.

Where aldehydes and ketones differ

An aldehyde differs from a ketone by having a hydrogen atom attached to the carbonyl group. This makes the aldehydes very easy to oxidise. For example, ethanal, CH_3CHO, is very easily oxidised to either ethanoic acid, CH_3COOH, or ethanoate ions, CH_3COO^-.

Ketones don't have that hydrogen atom and are resistant to oxidation. They are only oxidised by powerful oxidising agents which have the ability to break carbon-carbon bonds. You will find the oxidation of aldehydes and ketones discussed if you follow a link from the aldehydes and ketones menu (see the bottom of this page).

Boiling Points

Methanal is a gas (boiling point -21°C), and ethanal has a boiling point of +21°C. That means that ethanal boils at close to room temperature. The other aldehydes and the ketones are liquids, with boiling points rising as the molecules get bigger. The size of the boiling point is governed by the strengths of the intermolecular forces.

- **Van der Waals dispersion forces**: These attractions get stronger as the molecules get longer and have more electrons. That

increases the sizes of the temporary dipoles that are set up. This is why the boiling points increase as the number of carbon atoms in the chains increases - irrespective of whether you are talking about aldehydes or ketones.

- **van der Waals dipole-dipole attractions**: Both aldehydes and ketones are polar molecules because of the presence of the carbon-oxygen double bond. As well as the dispersion forces, there will also be attractions between the permanent dipoles on nearby molecules. That means that the boiling points will be higher than those of similarly sized hydrocarbons - which only have dispersion forces. It is interesting to compare three similarly sized molecules. They have similar lengths, and similar (although not identical) numbers of electrons.

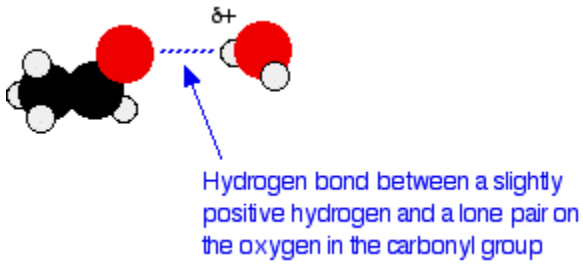
molecule	type	boiling point (°C)
$CH_3CH_2CH_3$	alkane	-42
CH_3CHO	aldehyde	+21
CH_3CH_2OH	alcohol	+78

Notice that the aldehyde (with dipole-dipole attractions as well as dispersion forces) has a boiling point higher than the similarly sized alkane which only has dispersion forces. However, the aldehyde's boiling point isn't as high as the alcohol's. In the alcohol, there is hydrogen bonding as well as the other two kinds of intermolecular attraction.

> Although the aldehydes and ketones are highly polar molecules, they don't have any hydrogen atoms attached directly to the oxygen, and so they can't hydrogen bond with each other.

Solubility in water

The small aldehydes and ketones are freely soluble in water but solubility falls with chain length. For example, methanal, ethanal and propanone - the common small aldehydes and ketones - are miscible with water in all proportions.The reason for the solubility is that although aldehydes and ketones can't hydrogen bond with themselves, they can hydrogen bond with water molecules. One of the slightly positive hydrogen atoms in a water molecule can be sufficiently attracted to one of the lone pairs on the oxygen atom of an aldehyde or ketone for a hydrogen bond to be formed.



There will also, of course, be dispersion forces and dipole-dipole attractions between the aldehyde or ketone and the water molecules. Forming these attractions releases energy which helps to supply the energy needed to separate the water molecules and aldehyde or ketone molecules from each other before they can mix together.

As chain lengths increase, the hydrocarbon "tails" of the molecules (all the hydrocarbon bits apart from the carbonyl group) start to get in the way. By forcing themselves between water molecules, they break the relatively strong hydrogen bonds between water molecules without replacing them by anything as good. This makes the process energetically less profitable, and so solubility decreases.

Contributors

- Jim Clark (Chemguide.co.uk)

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17.3: Spectroscopic Properties of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which the carbonyl absorption of aldehydes and ketones is found.
2. identify the region of the infrared spectrum in which the two characteristic C$\ce{-}$H absorptions of aldehydes are found.
3. use a table of characteristic absorption frequencies to assist in the determination of the structure of an unknown aldehyde or ketone, given its infrared spectrum and other spectral or experimental data.
4. identify the region of a proton NMR spectrum in which absorptions caused by the presence of aldehydic protons and protons attached to the α-carbon atoms of aldehydes and ketones occur.
5. identify two important fragmentations that occur when aliphatic aldehydes and ketones are subjected to analysis by mass spectrometry.

Key Terms

Make certain that you can define, and use in context, the key term below.

- McLafferty rearrangement

Study Notes

The appearance of a strong absorption at 1660–1770 cm^{-1} in the infrared spectrum of a compound is a clear indication of the presence of a carbonyl group. Although you need not remember the detailed absorptions it is important that you realize that the precise wavenumber of the infrared absorption can often provide some quite specific information about the environment of the carbonyl group in a compound. Notice how conjugation between a carbonyl group and a double bond (α, β-unsaturated aldehyde or ketone or aromatic ring) lowers the absorption by about 25–30 cm^{-1}.

You may wish to review the McLafferty rearrangement and the alpha cleavage in Section 12.3.

IR Spectra

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

C=O stretch

- aliphatic ketones 1715 cm^{-1}
- alpha, beta-unsaturated ketones 1685-1666 cm^{-1}

Figure 8. shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

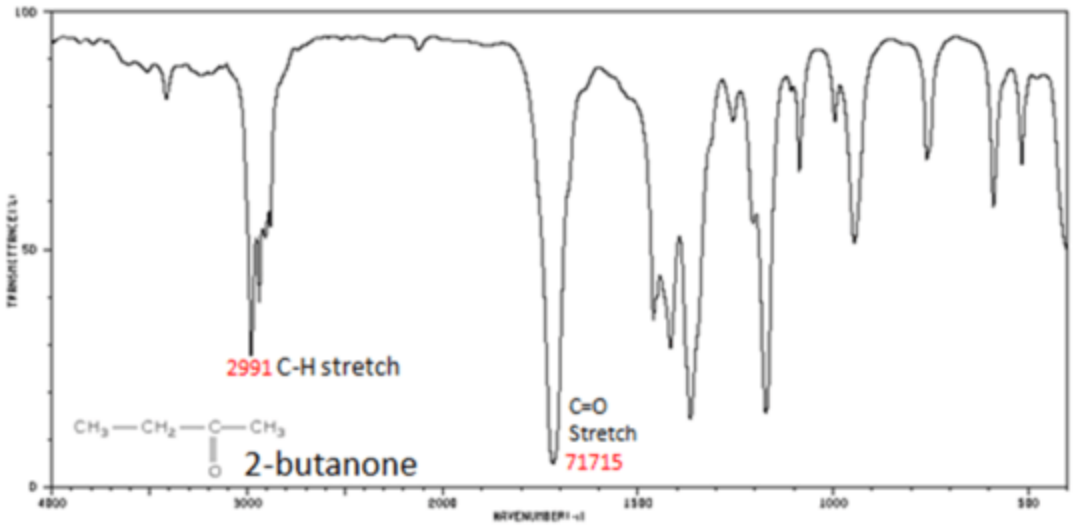


Figure 8. Infrared Spectrum of 2-Butanone

If a compound is suspected to be an aldehyde, a peak always appears around 2720 cm^{-1} which often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

H–C=O stretch 2830-2695 cm^{-1}

C=O stretch

- aliphatic aldehydes 1740-1720 cm^{-1}
- alpha, beta-unsaturated aldehydes 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

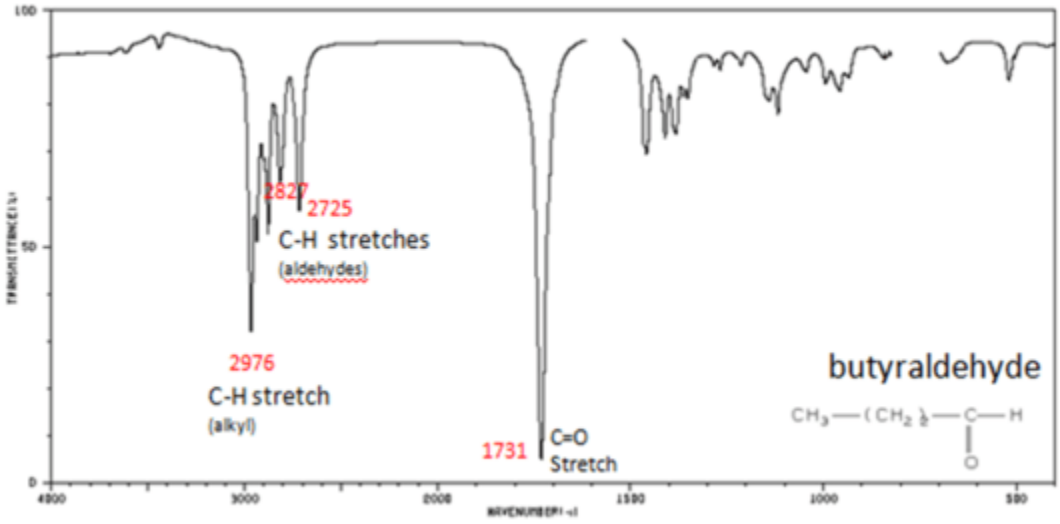
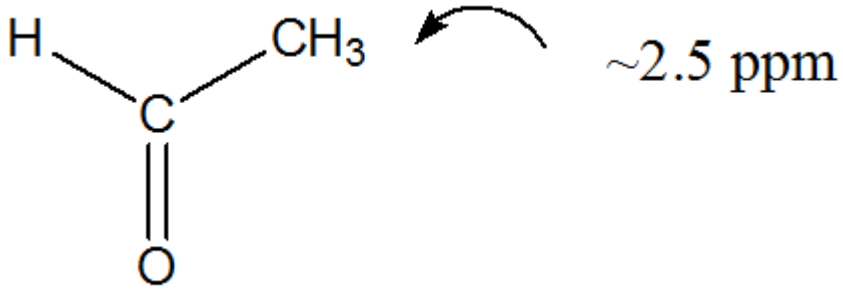


Figure 9. *Infrared Spectrum of Butyraldehyde*

NMR Spectra

Hydrogens attached to carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones usually show up 2.0-2.5 ppm.



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Aldehyde hydrogens are highly deshielded and appear far downfield as 9-10 ppm.

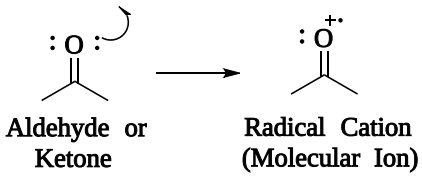
Chemical shift of each protons is predicted by ^{1}H chemical shift ranges (H_a): chemical shift of methyl groups (1.1 ppm). (H_b) The chemical shift of the -CH- group move downfield due to effect an adjacent aldehyde group: (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm).

4) Splitting pattern is determined by (N+1) rule: Ha is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak.(Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)

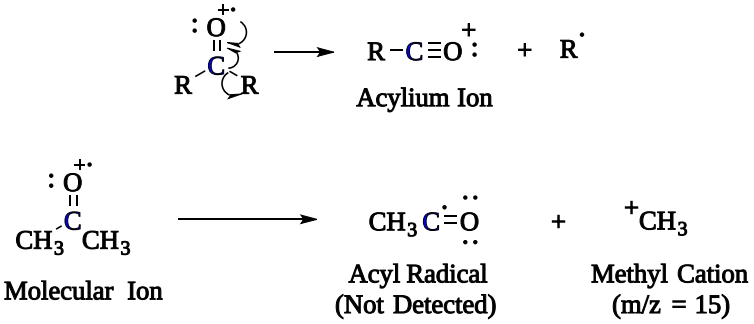
Mass Spectra

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, M^+. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

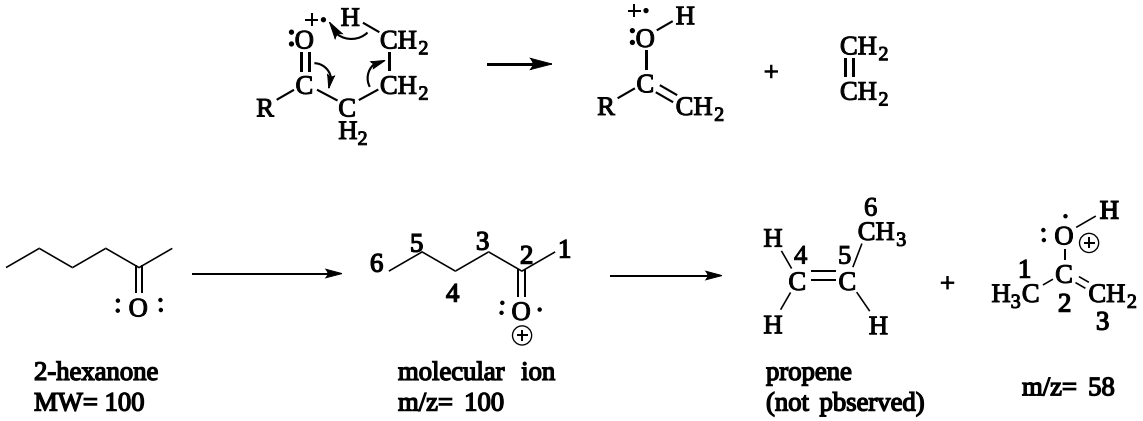
- Formation of the molecular ion:



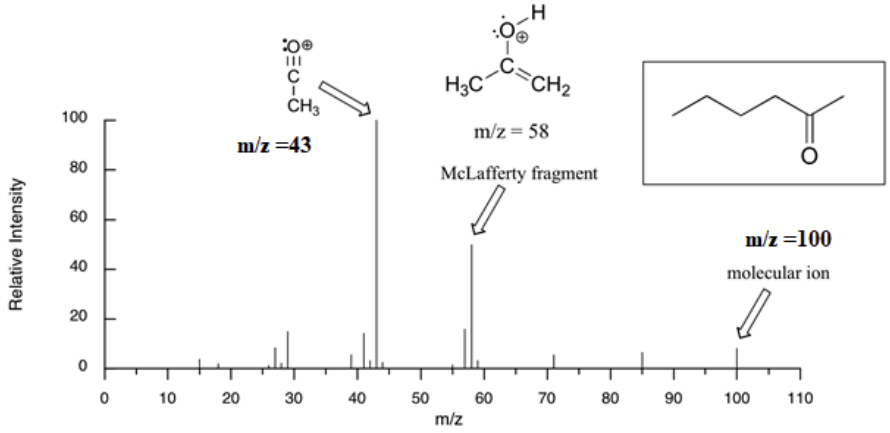
- *α cleavage to form an acylium ion. This is usually the base peak in the mass spectra.*



- *A common fragmentation pattern for larger carbonyl compounds is a transfer of γ hydrogen with β cleavage* called the **McLafferty rearrangement:**



The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is an acylium ion formed after alpha cleavage is at m/z = 43. The molecular ion peak is at m/z =100.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.5: Typical Carbonyl-Addition Reactions

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17.4: Preparation of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

Study Notes

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

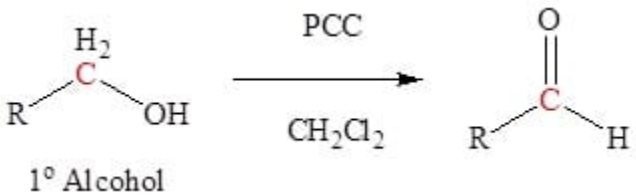
There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.4.

The “new” method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.7, which you might now wish to review.

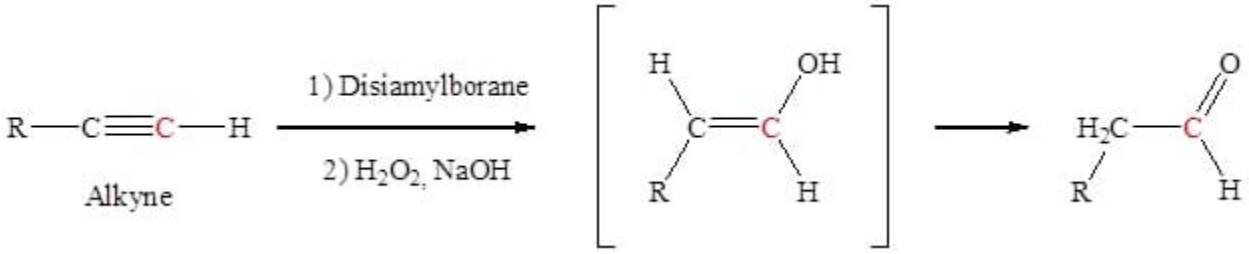
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

Oxidation of 1° alcohols with PCC to form aldehydes

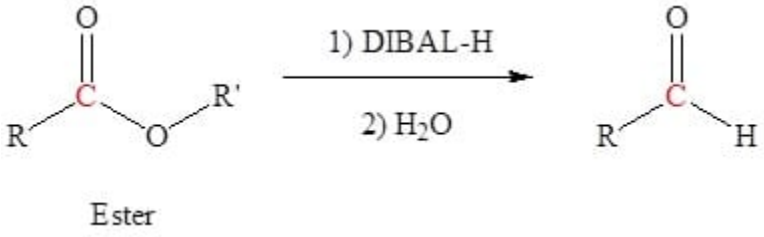


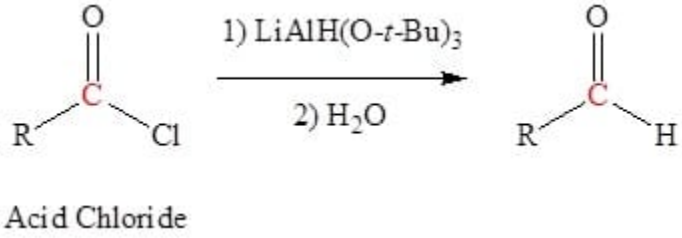
Hydration of an alkyne to form aldehydes

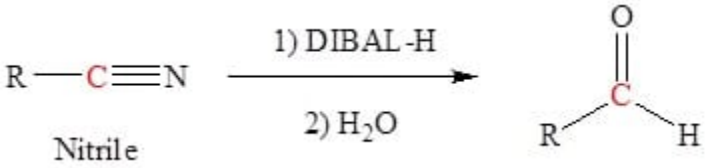
Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl.



Reduction of an ester, acid chloride or nitrile to form aldehydes

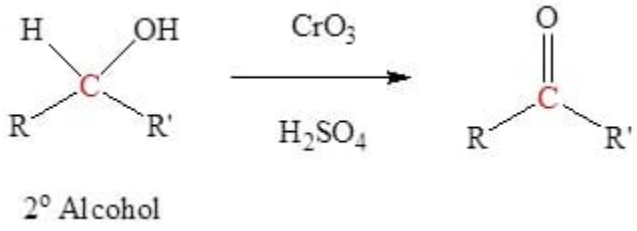






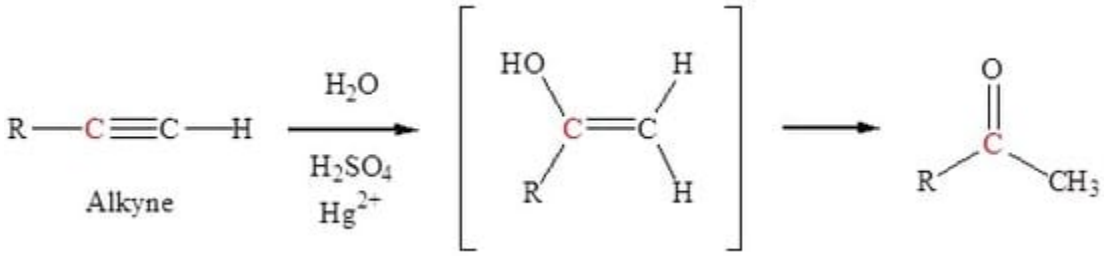
Oxidation of 2° alcohols to form ketones

Typically uses Jones reagent (CrO_3 in H_2SO_4) but many other reagents can be used

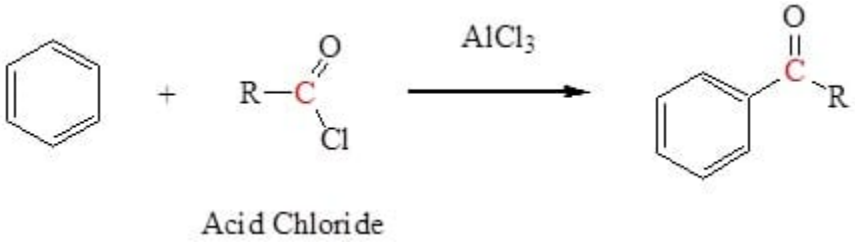


Hydration of an alkyne to form ketones

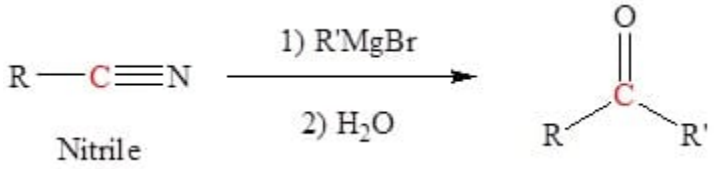
The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.



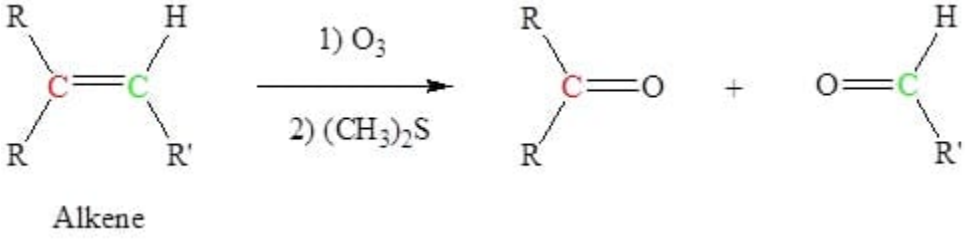
Friedel-Crafts acylation to form a ketone



Reaction of Grignard reagents with nitriles to form ketones

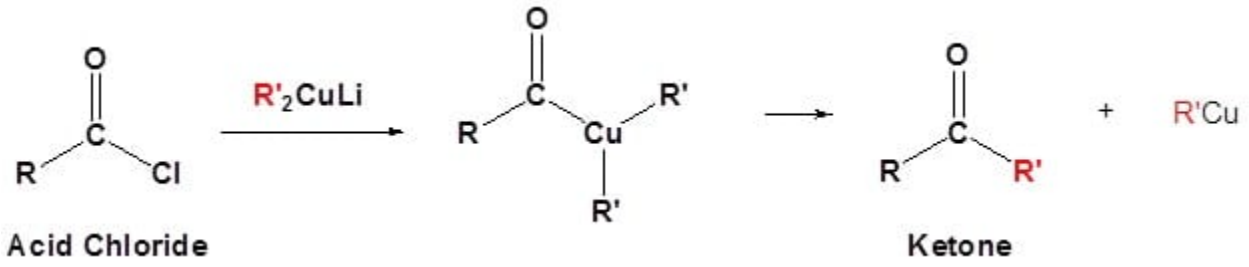


Alkenes can be cleaved using ozone (O_3) to form aldehydes and/or ketones

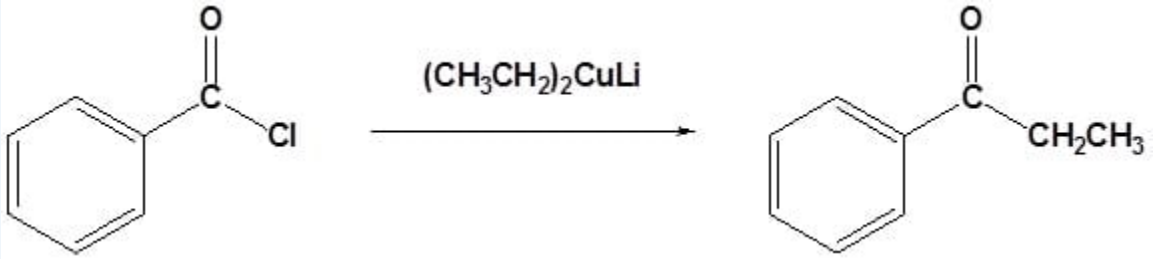


This is an example of a Ozonolysis reaction.

Organocuprate reagents convert acid chlorides to ketones



Example 1:



Exercise

Exercise 19.2.1

What reagents would be required to prepare hexanal from the following starting materials?

(a) $CH_3CH_2CH_2CH_2CH_2CH_2OH$

(b) $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$

(c) $CH_3CH_2CH_2CH_2CO_2CH_3$

(d) $CH_3CH_2CH_2CH{=}CH_2$

Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 19.2.1

(a) Dess–Martin periodinane or PCC in CH_2Cl_2

(b) 1. O_3, 2. Zn/H_3O^+

(c) 1. DIBAH 2. H_2O

(d) 1. BH_3 2. H_2O_2/NaOH; 2. Dess–Martin periodinane or PCC

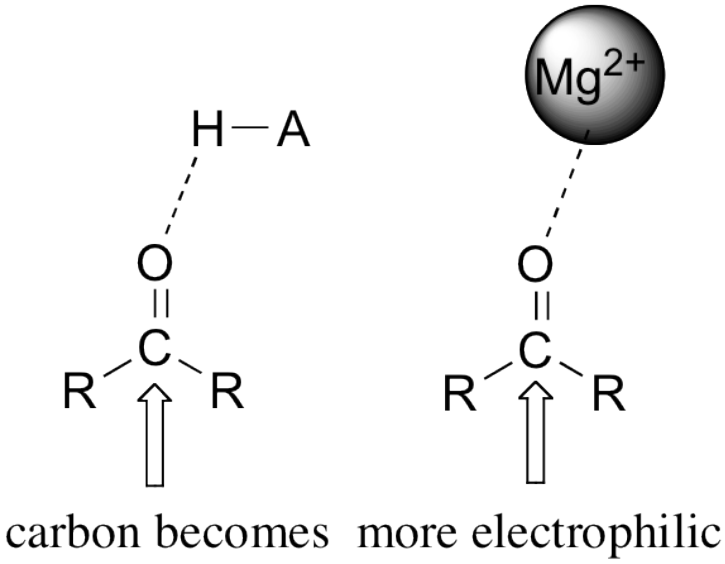
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17.5: Reactivity of the Carbonyl Group: Mechanisms of Addition

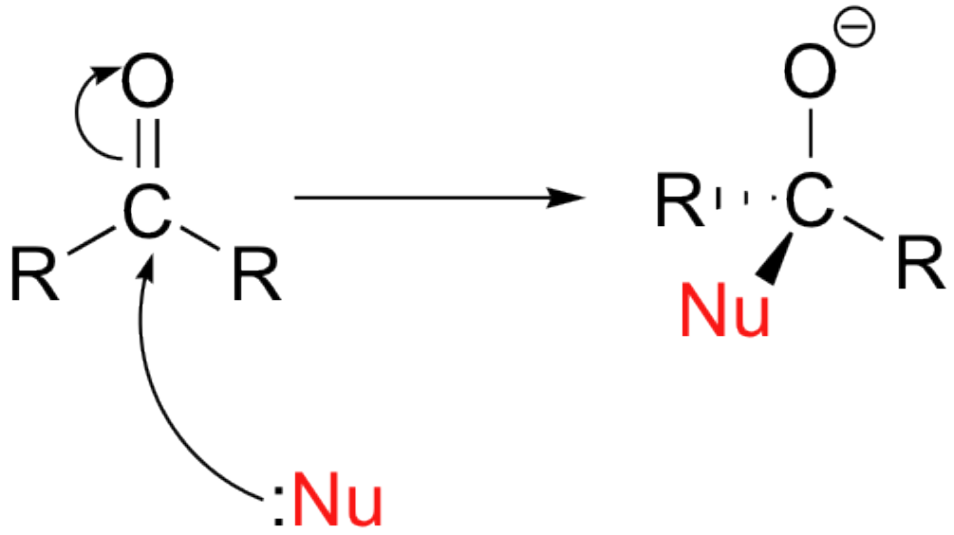
Nucleophilic Addition to Aldehydes and Ketones

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

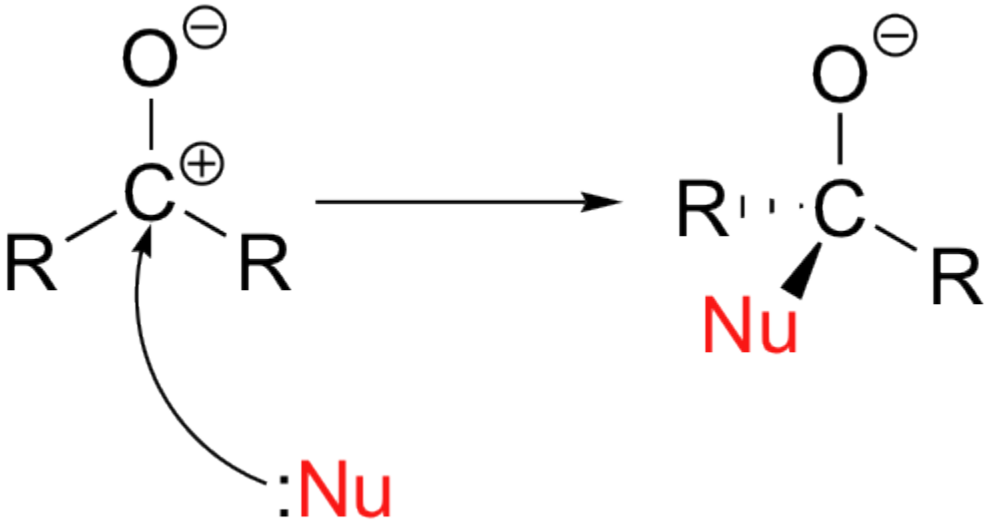


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

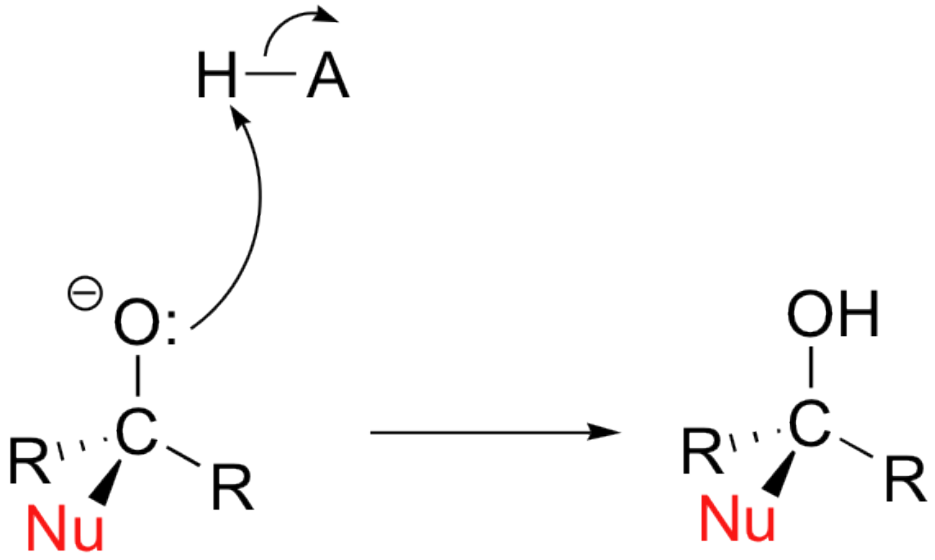
Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



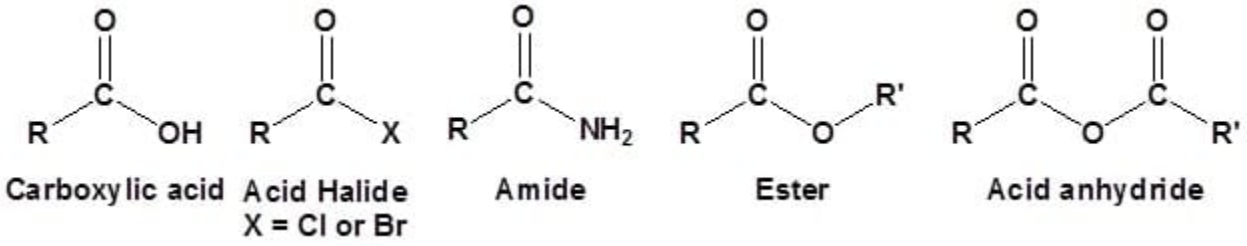
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



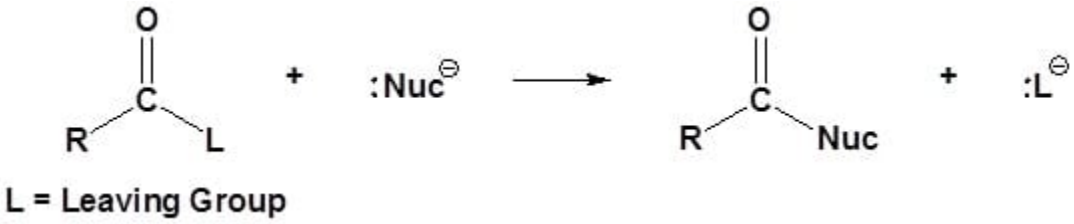
This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction (which we will learn about in section 13.3) the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

Nucleophilic Substitution of RCOZ (Z = Leaving Group)

Carbonyl compounds with leaving groups have reactions similar to aldehydes and ketones. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

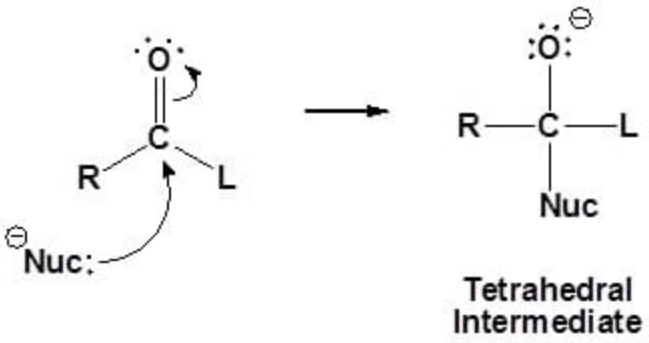


General reaction

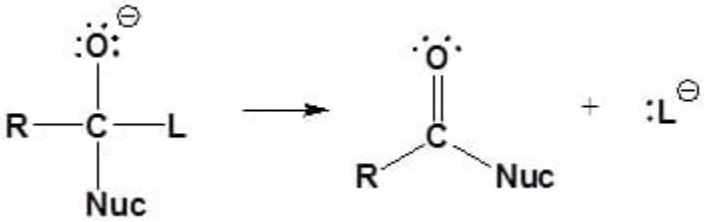


General mechanism

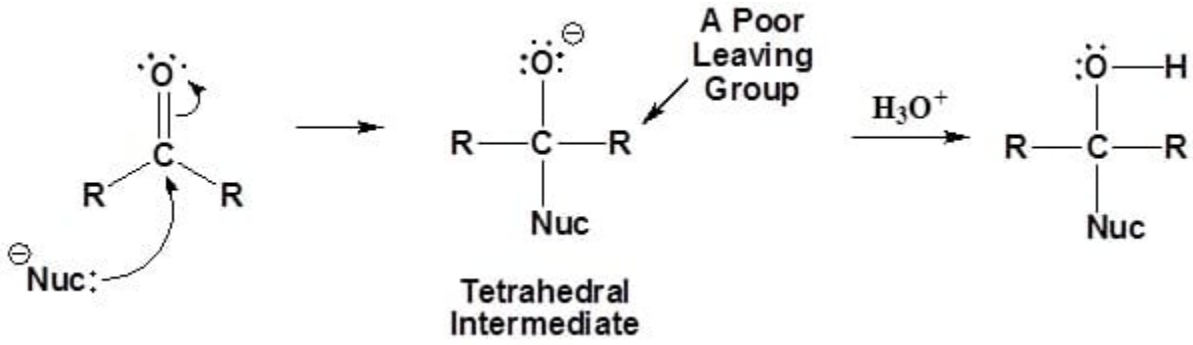
1) Nucleophilic attack on the carbonyl



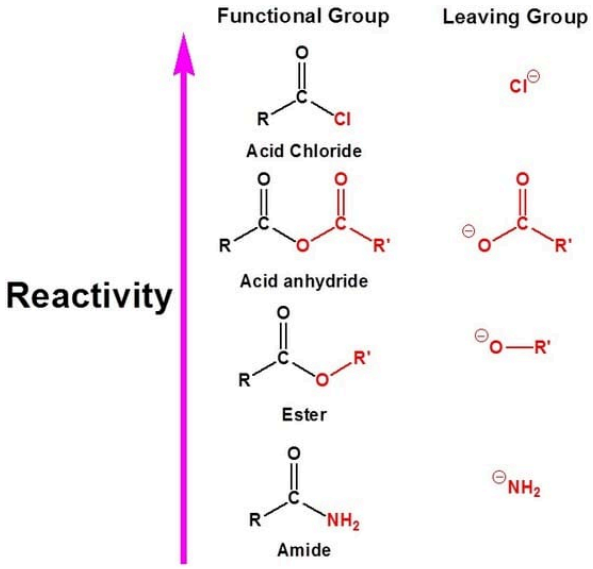
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.



Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Prof. Steven Farmer (Sonoma State University)

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17.6: Addition of Water to Form Hydrates

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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17.7: Addition of Alcohols to Form Hemiacetals and Acetals

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of acetals.
2. identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
3. identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
4. write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
5. explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
6. illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- acetal
- hemiacetal

Study Notes

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

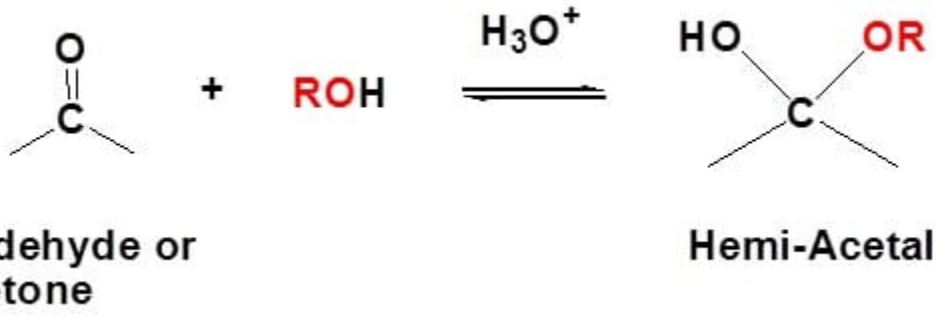
In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. Carbonyl groups are characterized by a carbon-oxygen double bond. The two main functional groups that consist of this carbon-oxygen double bond are Aldehydes and Ketones.

Introduction

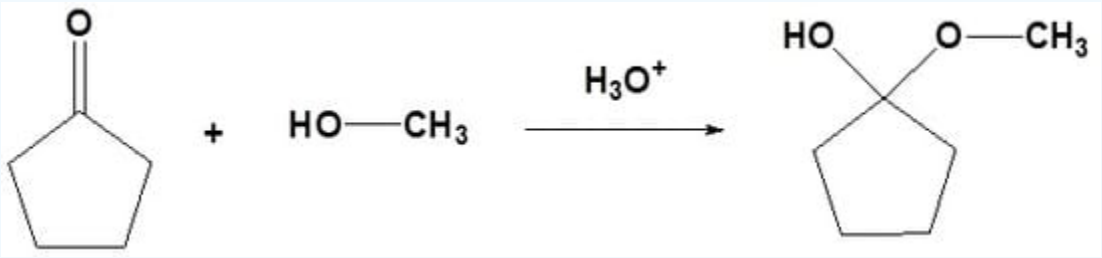
It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diol. In a similar reaction alcohols add reversibly to aldehydes and ketones to form hemiacetals (h*emi,* Greek, half). This reaction can continue by adding another alcohol to form an acetal. Hemiacetals and acetals are important functional groups because they appear in sugars.

To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark trap**. The latter is important, since acetal formation is reversible. Indeed, once pure hemiacetal or acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

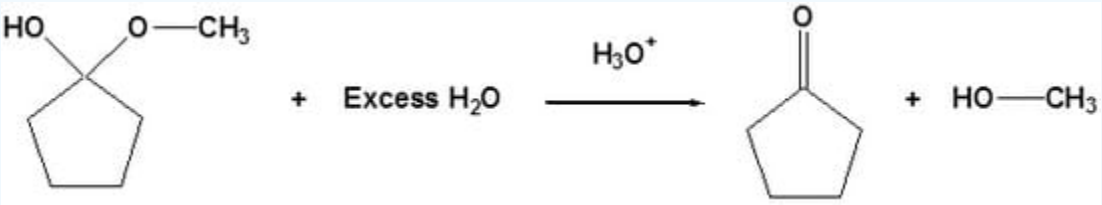
Formation of Hemiacetals



Example 19.10.1: Formation of Hemiacetals

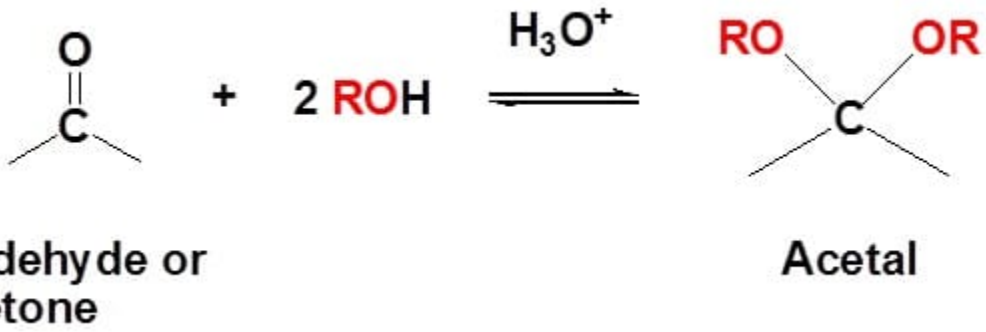


Example 19.10.2: Hemiacetal Reversibility

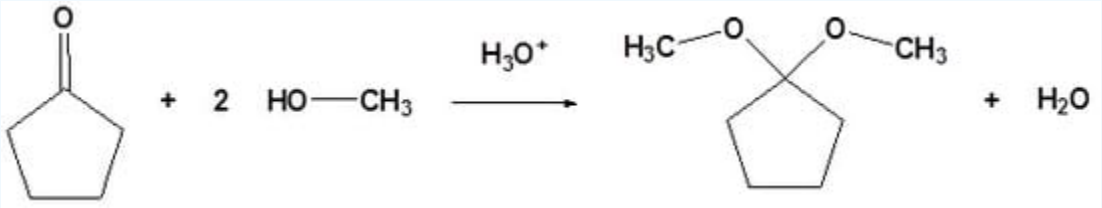


Formation of Acetals

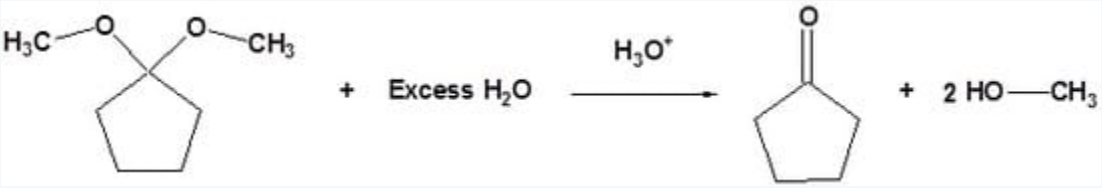
Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.



Example 19.10.3: Formation of Acetals



Example 19.10.4: Acetal Reversibility



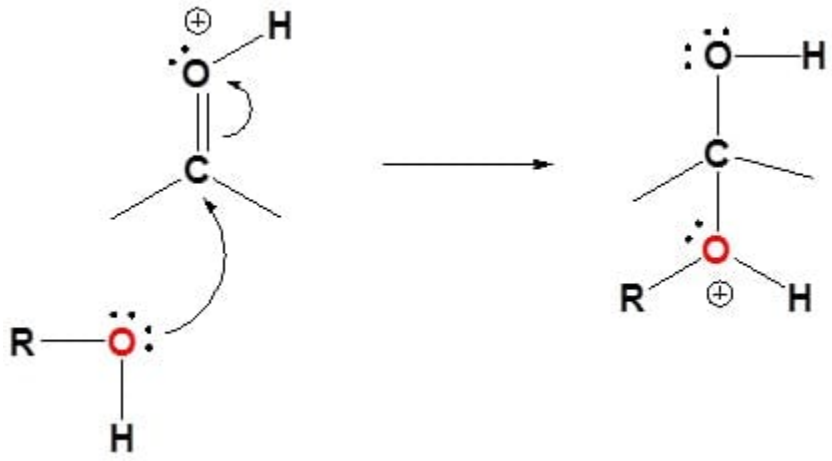
Mechanism for Hemiacetal and Acetal Formation

The mechanism shown here applies to both acetal and hemiacetal formation

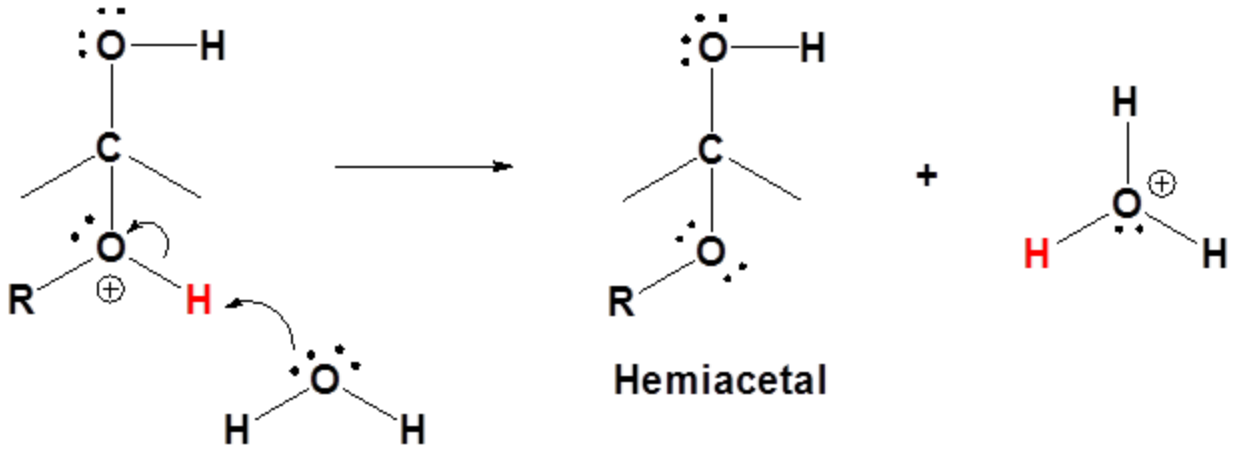
1) Protonation of the carbonyl



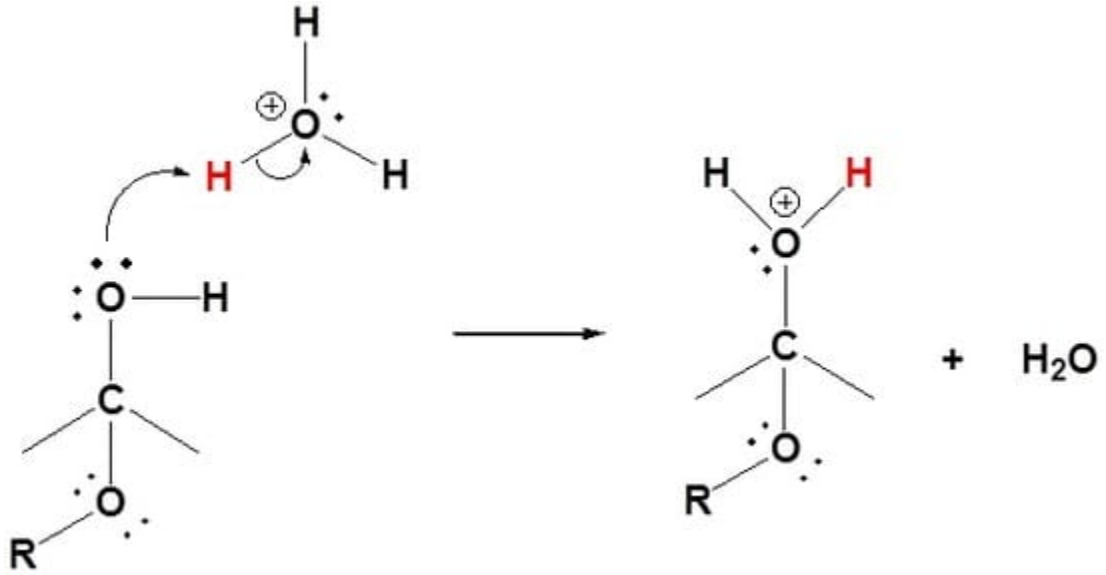
2) Nucleophilic attack by the alcohol



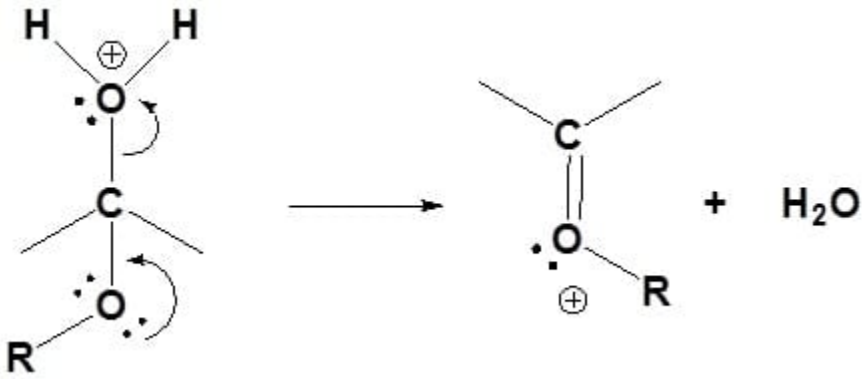
3) Deprotonation to form a hemiacetal



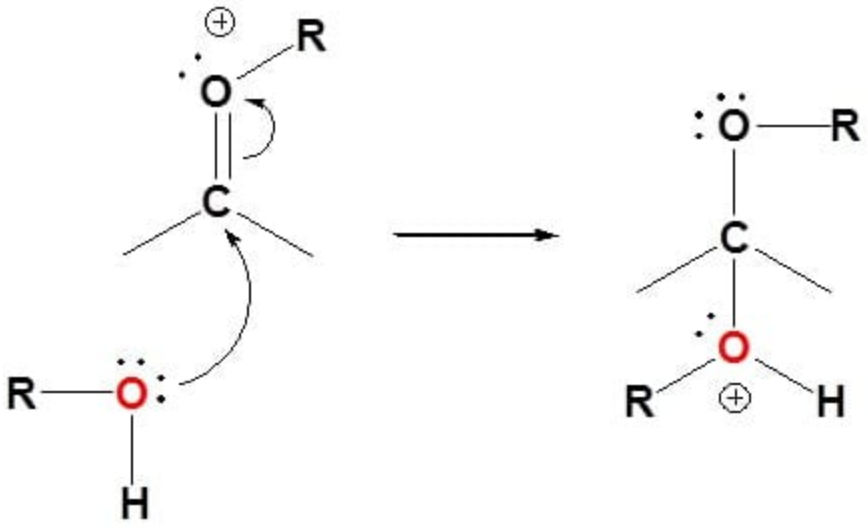
4) Protonation of the alcohol



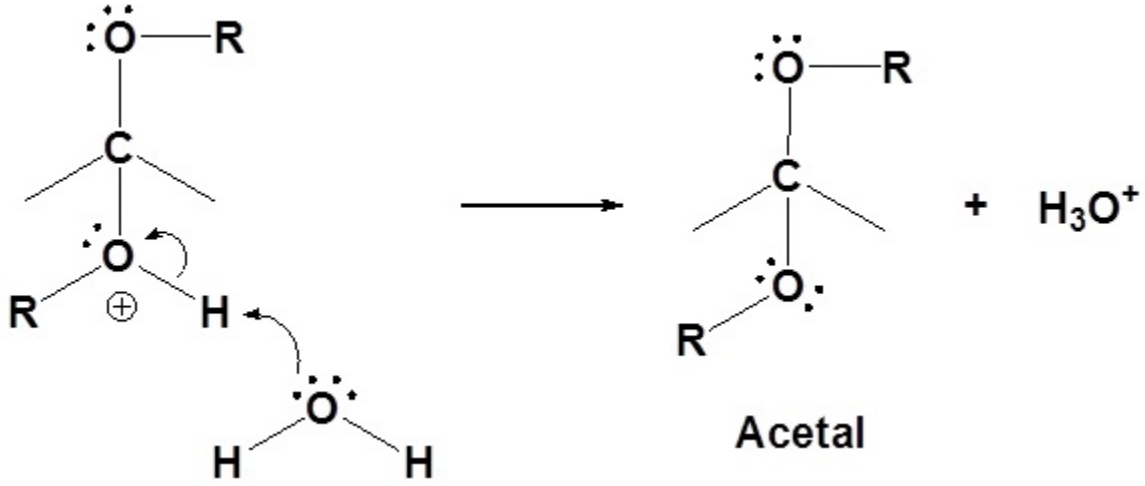
5) Removal of water



6) Nucleophilic attack by the alcohol



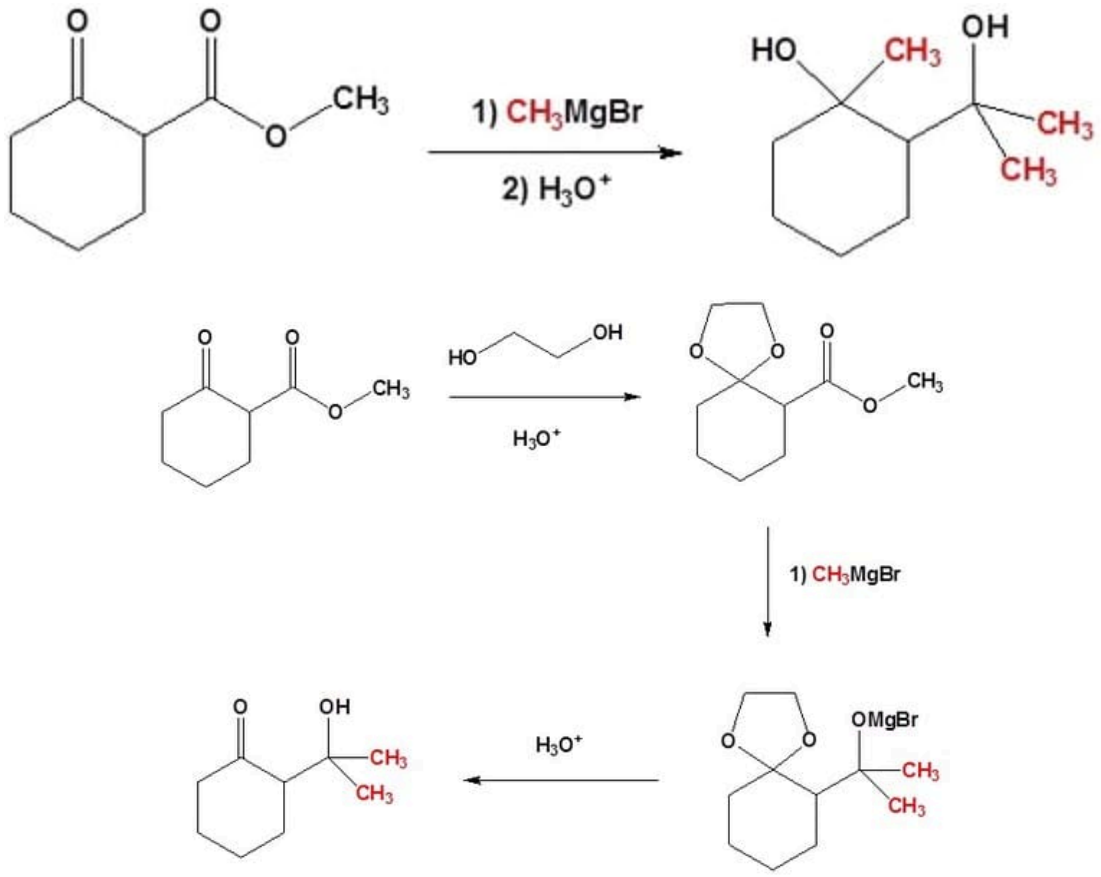
7) Deprotonation by water



Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

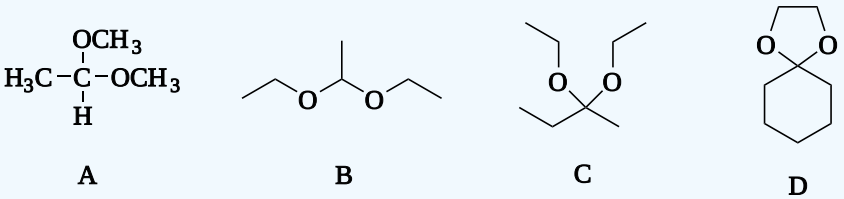
In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



Exercises

Exercise 19.10.1

For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.

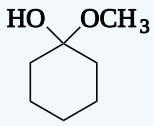


A B C D

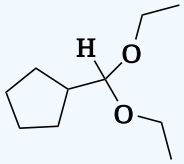
Answer available at the end of this section.

Exercise 19.10.2

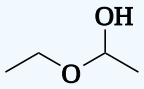
Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



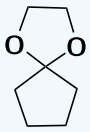
A



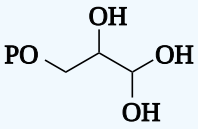
B



C



D



E

Answer available at the end of this section.

Exercise 19.10.3

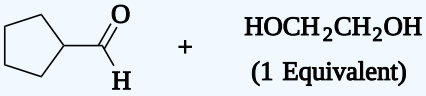
Specify the acetal that would form from a reaction between the given starting compounds.

a.



(2 Equivalents)

b.



(1 Equivalent)

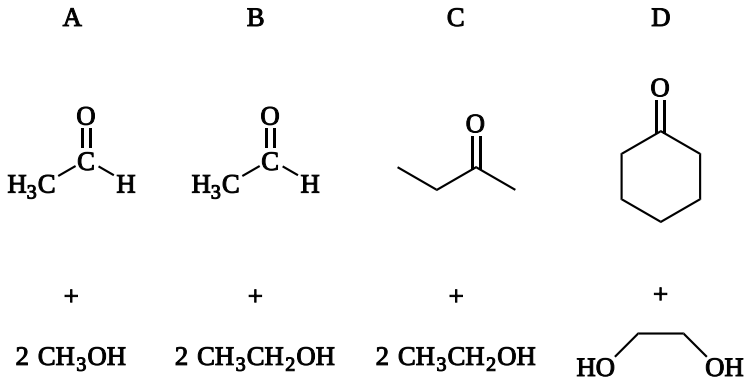
Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 19.10.1

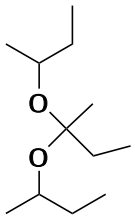


Exercise 19.10.2

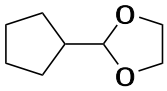
A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

Exercise 19.10.3

a)



b)



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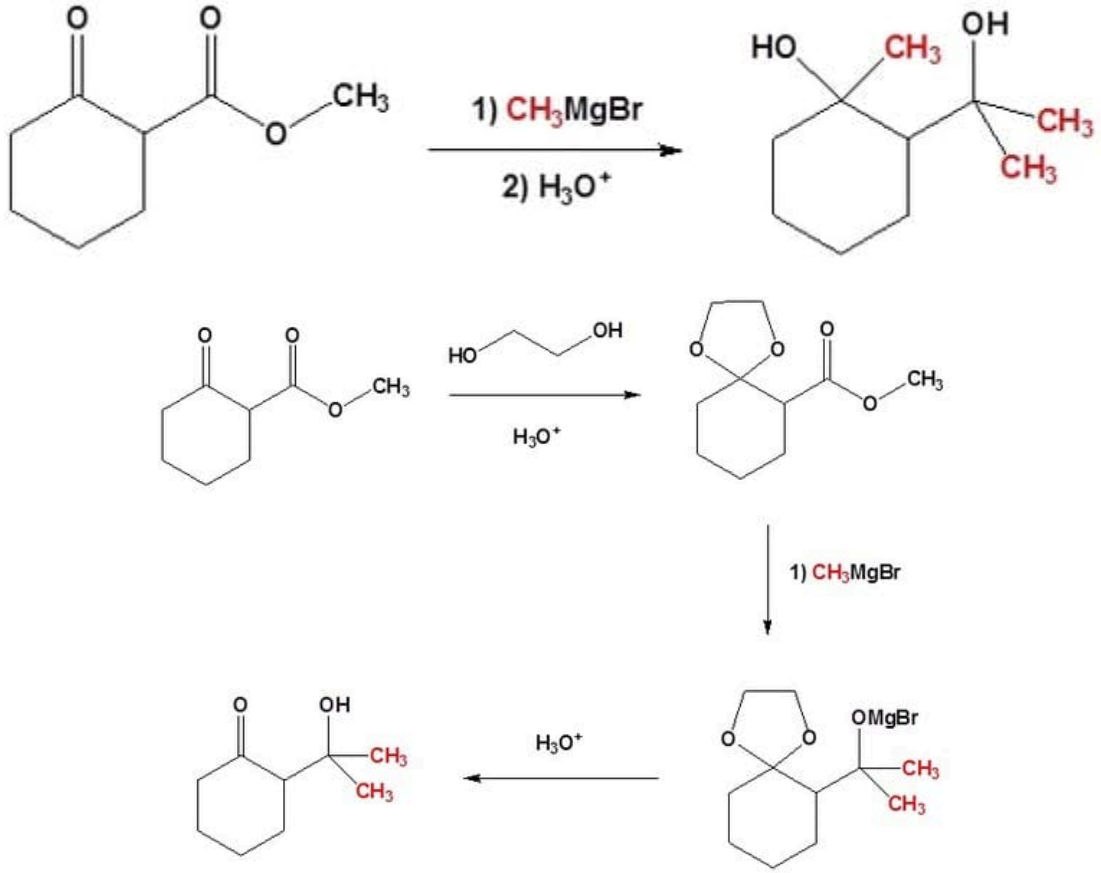
- 19.10: Nucleophilic Addition of Alcohols - Acetal Formation by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

17.8: Acetals as Protecting Groups

Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



Contributors

- Prof. Steven Farmer (Sonoma State University)

Compound **1.4.1.4A** illustrates several important points in Protection / Deprotection protocol. Both the functional groups could react with a Grignard Reagent. Carboxylic acid group would first react with one mole of the Grignard Reagent to give a carboxylate anion salt. This anion does not react any further with the reagent. When two moles of Grignard Reagent are added to the reaction mixture, the second mole attacks the ketone to give a tertiary alcohol. On aqueous work-up, the acid group is regenerated. Thus, the first mole of the reagent provides a selective transient protection for the –COOH group. Once the acid group is esterified, such selectivity towards this reagent is lost. The reagent attacks at both sites. If reaction is desired only at the ester site, the keto-

group should be selectively protected as an acetal. In the next step, the grignard reaction is carried out. Now the reagent has only one group available for reaction. On treatment with acid, the ketal protection in the intermediate compound is also hydrolyzed to regenerated the keto- group.

Fig 1.4.1.4

Protection of Aldehydes and Ketones

Since alcohols, aldehydes and ketones are the most frequently manipulated functional groups in organic synthesis, a great deal of work has appeared in their protection / deprotection strategies. In this discussion let us focus on the classes of protecting groups rather than an exhaustive treatment of all the protections.

Acetals

There are two general methods for the introduction of this protection. Transketalation is the method of choice when acetals (ketals) with methanol are desired. Acetone is the by-product, which has to be removed to shift the equilibrium to the right hand side. This is achieved by refluxing with a large excess of the acetonide reagent. Acetone formed is constantly distilled. In the case of cyclic diols, the water formed is continuously removed using a Dean-Stork condenser **(Fig 1.4.1.6)**.

1.4.1.6...png

Fig 1.4.1.6

The rate of formation of ketals from ketones and 1,2-ethanediol (ethylene glycol), 1,3-propanediol and 2,2-dimethyl-1,3-propanediol are different. So is the deketalation reaction. This has enabled chemists to selectively work at one center. The following examples from steroid chemistry illustrate these points **(Fig 1.4.1.7)**.

1.4.1.7...png

Fig 1.4.1.7

The demand for **Green Chemistry processes** has prompted search for new green procedures. Some examples from recent literature are given here **(Fig 1.4.1.8)**.

1.4.1.8...png

Fig 1.4.1.8

Thioketals

Compared with their oxygen analogues, thioketals markedly differ in their chemistry. The formation as well as deprotection is promoted by suitable Lewis acids. The thioacetals are markedly stable under deketalation conditions, thus paving way for selective operations at two different centers. When conjugated ketones are involved, the ketal formation (as well as deprotection) proceeds with double bond migration. On the other hand, thioketals are formed and deketalated without double bond migration **(Fig 1.4.1.9)**.

Fig 1.4.1.9

Silyl Ethers (R – OSiR_3)

The oxygen – silicon sigma bond is stable to lithium and Grignard reagents, nucleophiles and hydride reagents but very unstable to water and mild aqueous acid and base conditions. A silyl ether of secondary alcohol is less reactive than that of a primary

alcohol. The O – trimethylsilyl (O – SiMe3) was first protection of this class. **(Fig 1.4.1.24)**.

Fig 1.4.1.24

Replacement of methyl group with other alkyl and aryl groups gives a large variety of silyl ether with varying degrees of stability towards hydrolysis **(Fig 1.4.1.25)**.

Fig 1.4.1.25

The following examples illustrate the selectivity in formation and hydrolysis of this group **(Fig 1.4.1.26)**.

Fig 1.4.1.26

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

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17.9: Nucleophilic Addition of Ammonia and Its Derivatives

Objectives

After completing this section, you should be able to

1. write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
2. identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
3. identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
4. write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
5. write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
6. explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

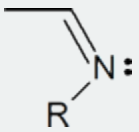
Key Terms

Make certain that you can define, and use in context, the key terms below.

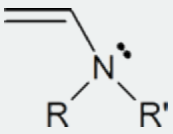
- 2,4-dinitrophenylhydrozone
- enamine
- imine

Study Notes

An imine is a compound that contains the structural unit



An enamine is a compound that contains the structural unit



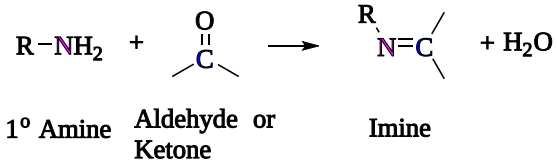
Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colourful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

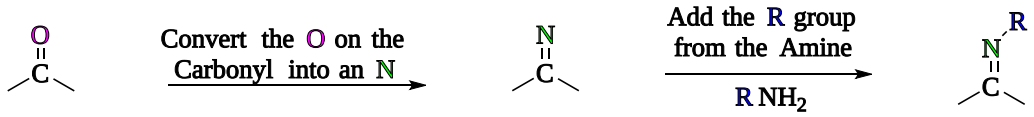
Reaction with Primary Amines to form Imines

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

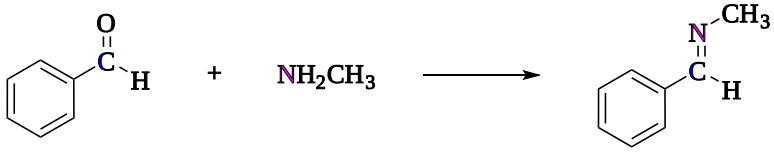


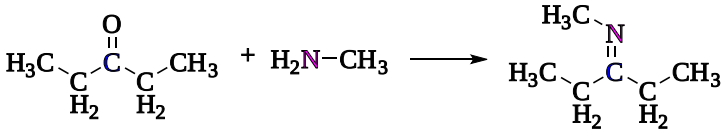
Predicting the Products of an Imine Forming Reaction

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



Examples of Imine Forming Reactions

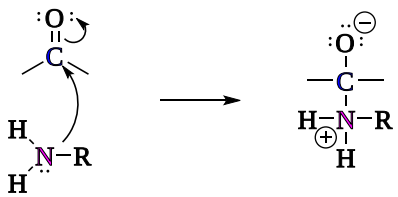




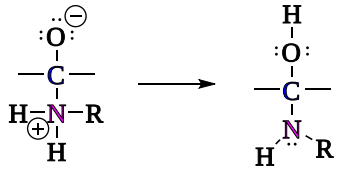
Mechanism of Imine Formation

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

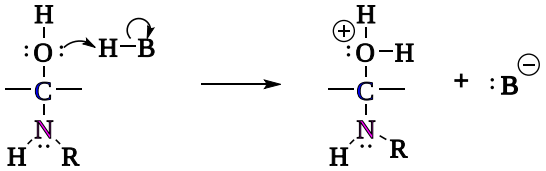
1) Nucleophilic addition



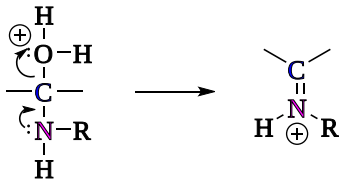
2) Protron transfer



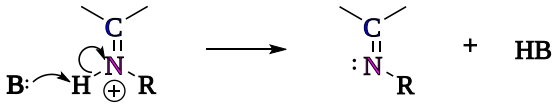
3) Protonation



4) Water is eliminated to form an iminium ion.

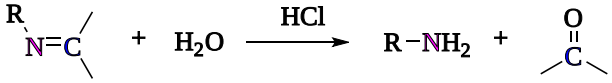


5) Deprotonation



Reversibility of Imine Forming Reactions

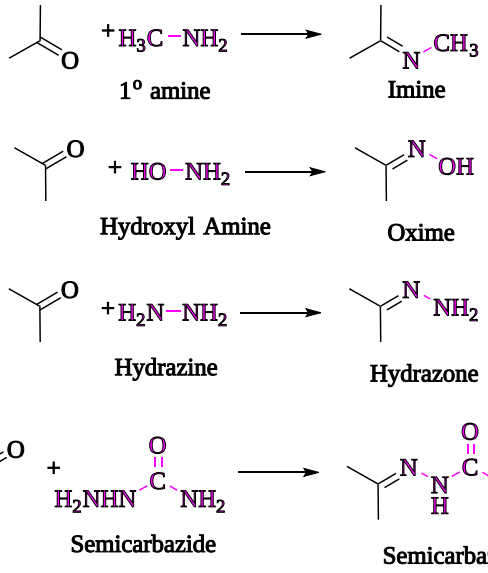
Imines can be hydrolyzed back to the corresponding 1^{o} amine under acidic conditions.



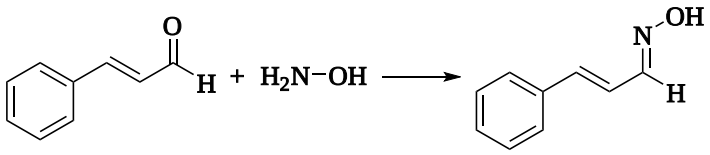
Reactions Involving other Reagents of the type Y-NH_2

A wide variety of substances with $-NH_2$ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y-NH_2 have been studied, and found to give stable products ($R_2C{=}N{-}Y$) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed below, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in Section 19.9.

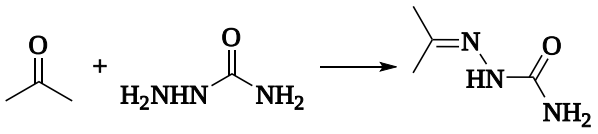
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups ($-NH_2$) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.



Example



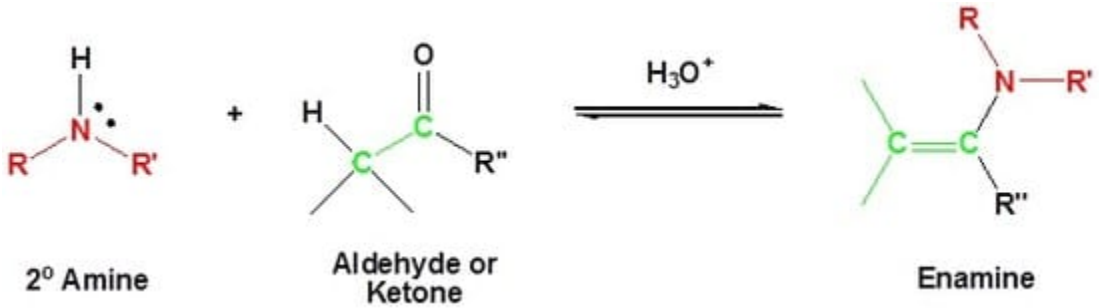
Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime

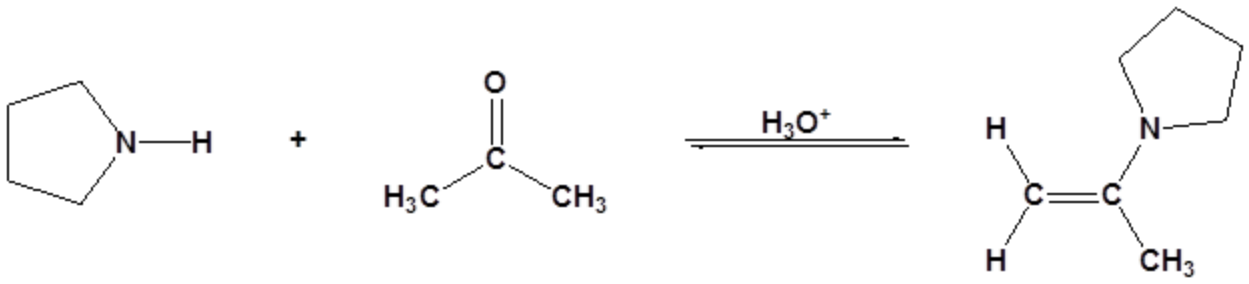


Acetone reacting with semicarbazide to form acetone semicarbazide

Reaction with Secondary Amines to form Enamines

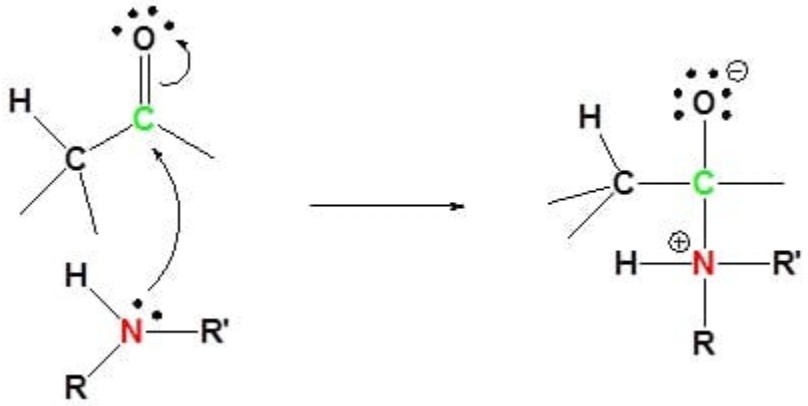
Most aldehydes and ketones react with 2°-amines to give products known as **enamines**. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.



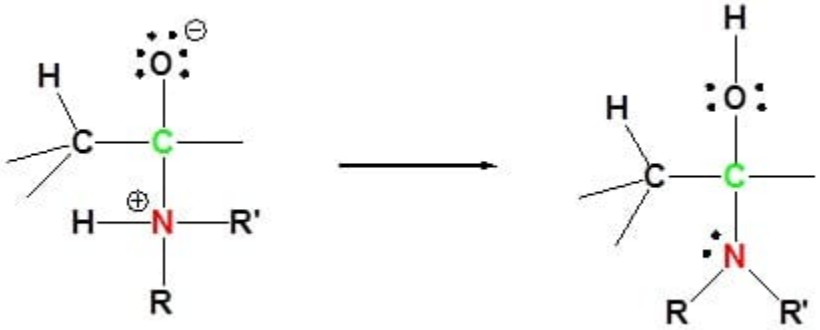


Mechanism

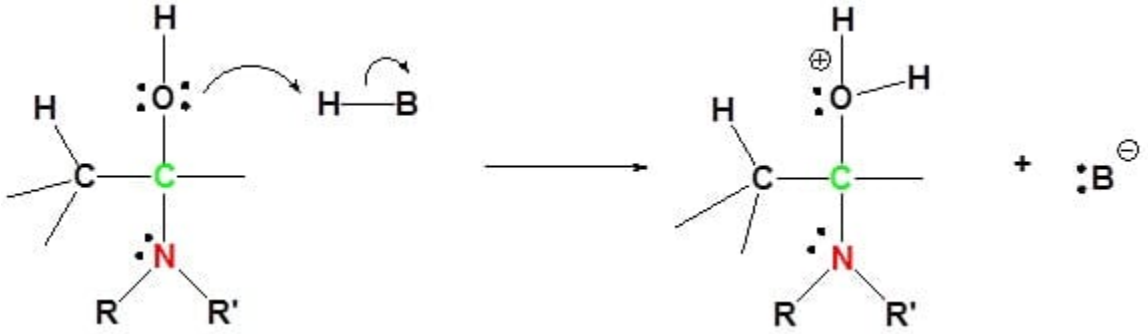
1) Nuleophilic attack



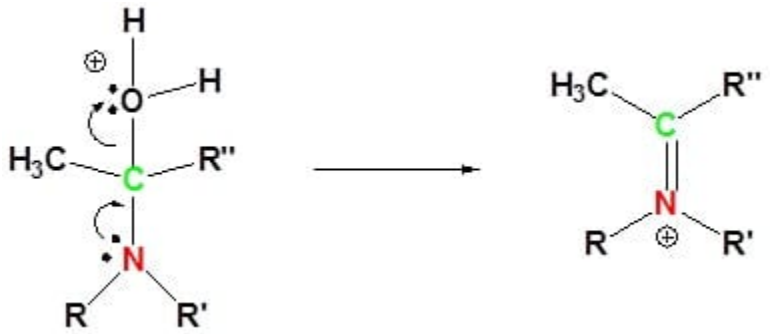
2) Proton transfer



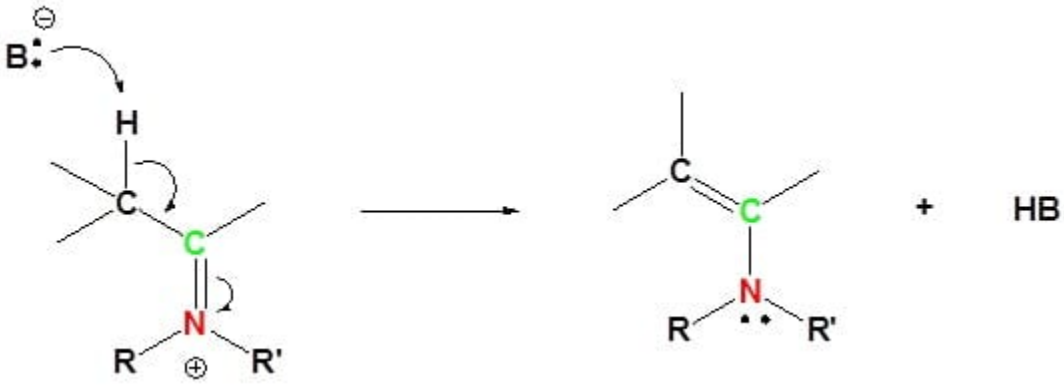
3) Protonation of OH



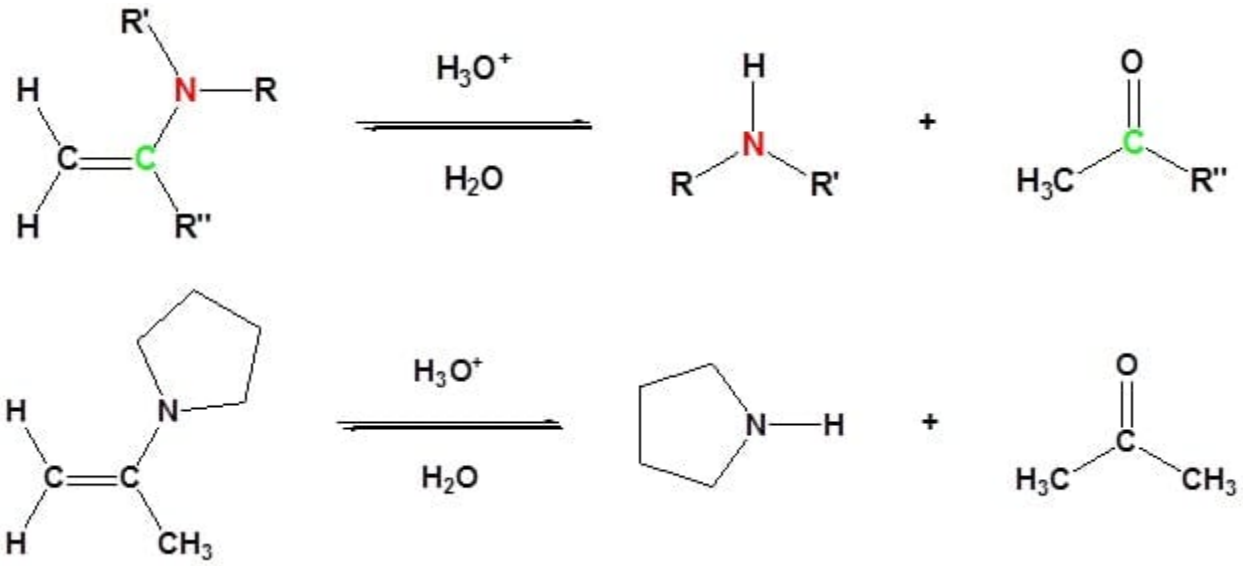
4) Removal of water



5) Deprotonation



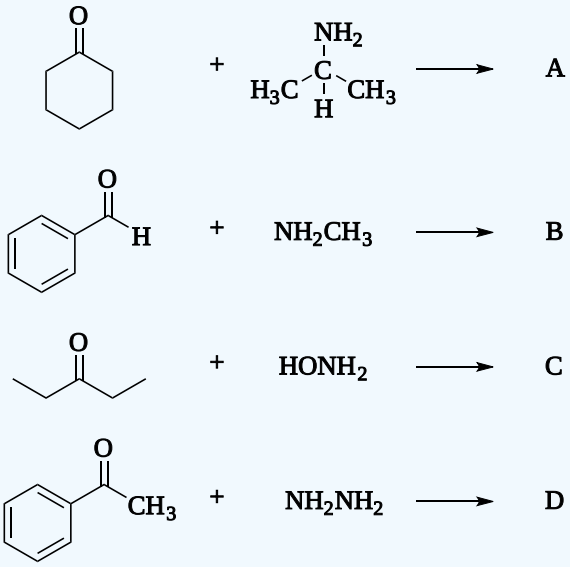
Reversibility of Enamines



Exercises

Exercise 19.8.1

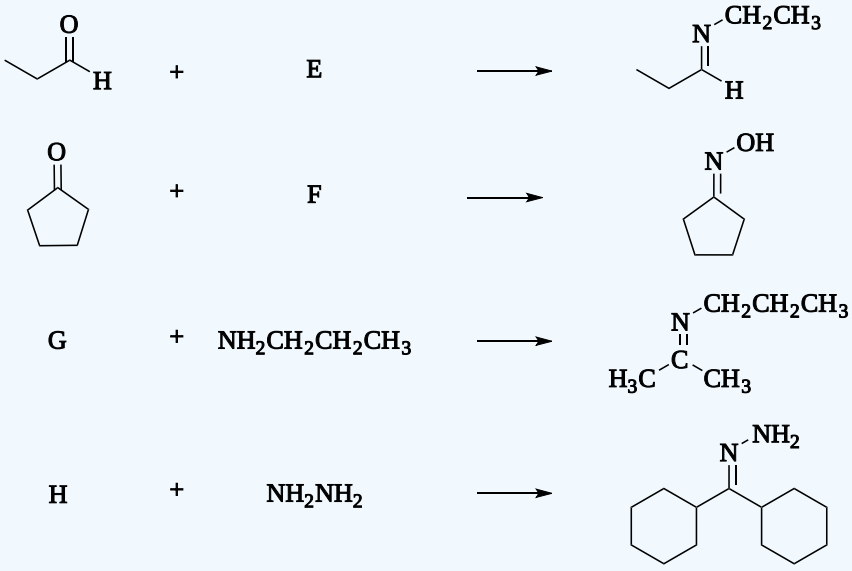
Please draw the products of the following reactions.



Answer available at the end of this section.

Exercise 19.8.2

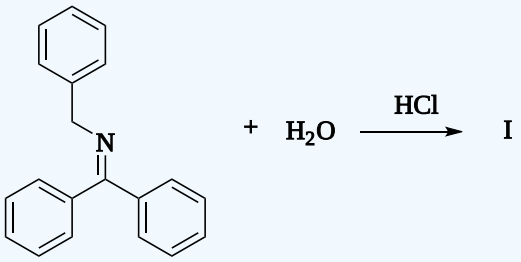
Please draw the structure of the reactant needed to produce the indicated product.



Answer available at the end of this section.

Exercise 19.8.3

Please draw the products of the following reaction.



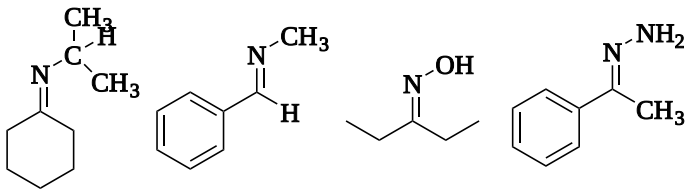
Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

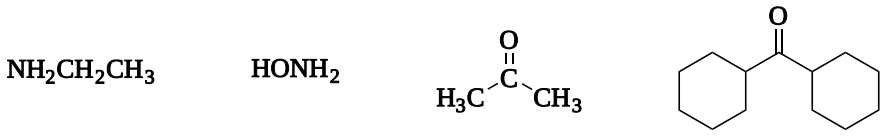
Answers

Exercise 19.8.1



A B C D

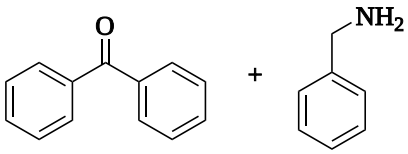
Exercise 19.8.2



E F G H

Exercise 19.8.3

I



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17.10: Deoxygenation of the Carbonyl Group

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Wolff-Kishner reduction of an aldehyde or ketone.
2. identify the product formed from the Wolff-Kishner reduction of a given aldehyde or ketone.

Key Terms

Make certain that you can define, and use in context, the key term below.

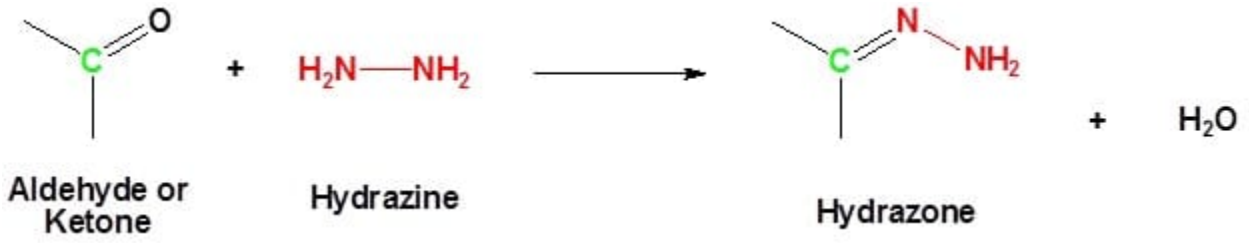
- Wolff-Kishner reduction

Study Notes

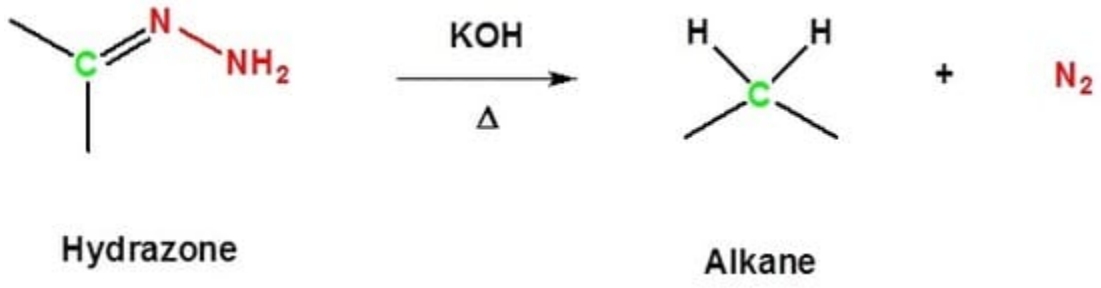
After studying this section, you can add yet another method of reducing organic compounds to your growing list of reduction reactions.

Aldehydes and ketones can be converted to a hydrazine derivative by reaction with hydrazine. These "hydrazones" can be further converted to the corresponding alkane by reaction with base and heat. These two steps can be combined into one reaction called the Wolff-Kishner Reduction which represents a general method for converting aldehydes and ketones into alkanes. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. Note! Nitrogen gas is produced as part of this reaction.

Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone



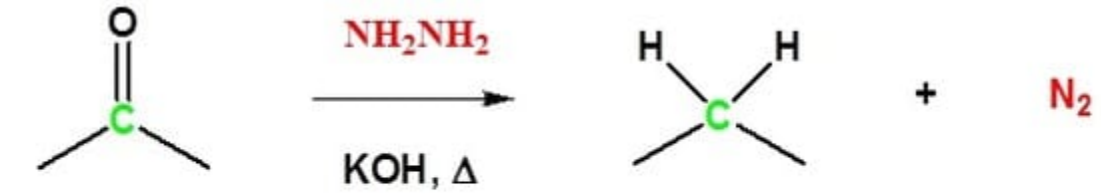
Reaction with a Base and Heat Converts a Hydrazone to an Alkane



Hydrazone

Alkane

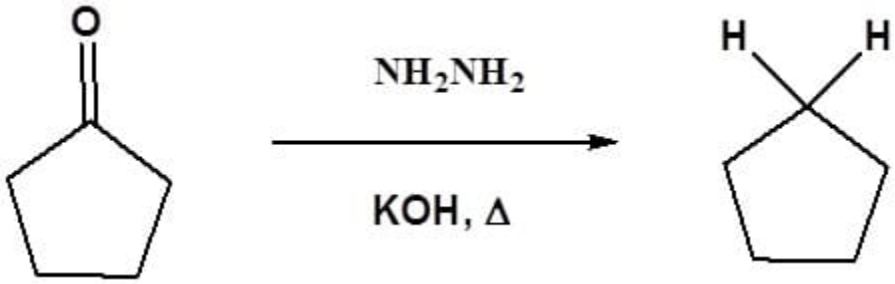
Both Reactions Together Produces the Wolff-Kishner Reduction



Aldehyde or Ketone

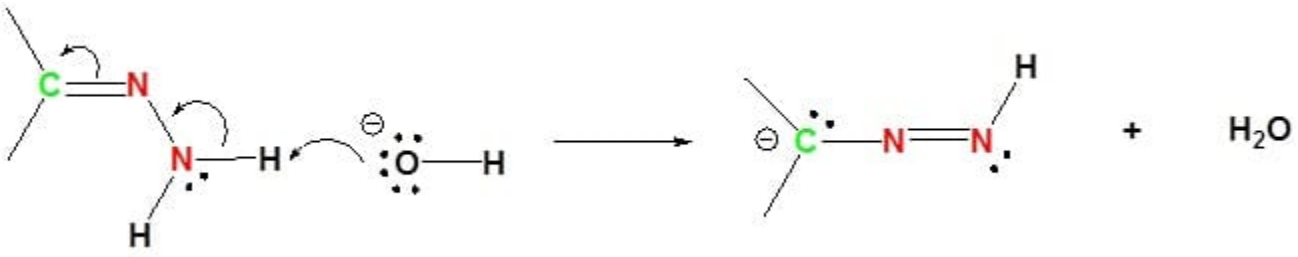
Alkane

Example

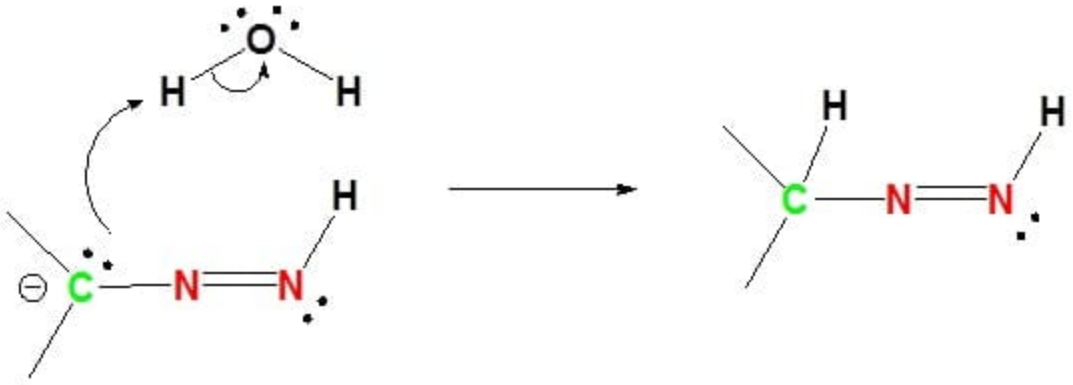


Mechanism of the Wolff-Kishner Reduction

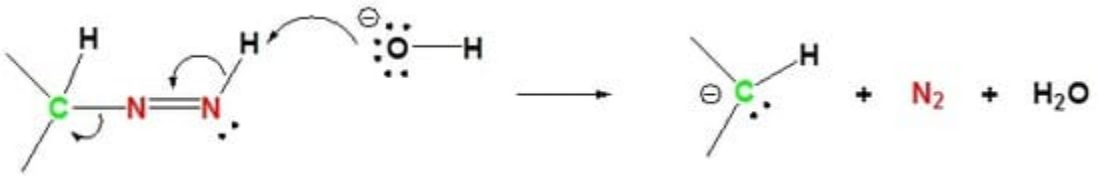
1) Deprotonation of Nitrogen



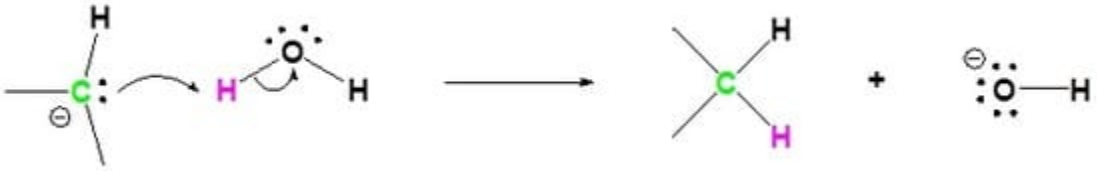
2) Protonation of the Carbon



3) Deprotonation of Nitrogen



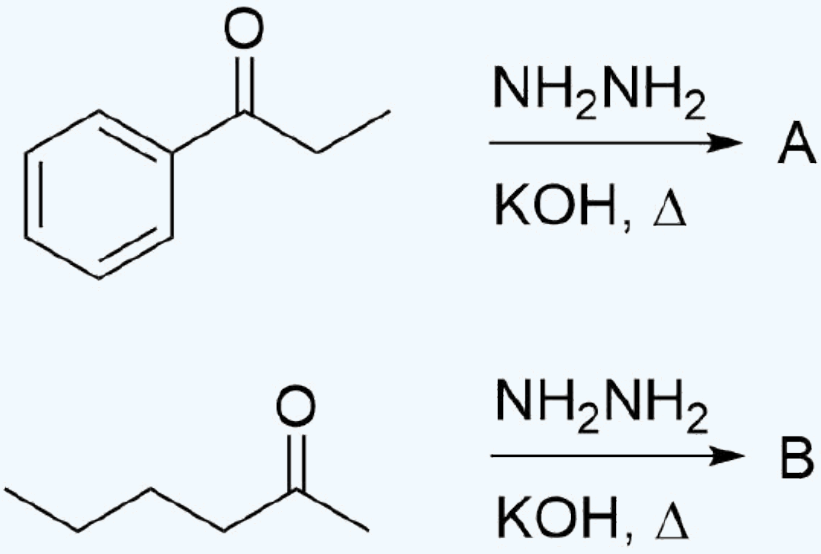
4) Protonation of Carbon



Exercise

Exercise 19.9.1

Please draw the products of the following reactions.



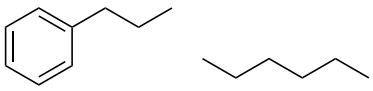
Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 19.9.1



A

B

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- 19.9: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

17.11: Addition of Hydrogen Cyanide to Give Cyanohydrins

Objectives

After completing this section, you should be able to

1. write an equation to describe the formation of a cyanohydrin from an aldehyde or ketone.
2. identify the cyanohydrin formed from the reaction of a given aldehyde or ketone with hydrogen cyanide.
3. identify the aldehyde or ketone, the reagents, or both, needed to prepare a given cyanohydrin.
4. write the detailed mechanism for the addition of hydrogen cyanide to an aldehyde or ketone.
5. write equations to represent the conversion of cyanohydrins to hydroxyamines and hydroxycarboxylic acids, and hence recognize the importance of cyanohydrin formation in organic synthesis.

a. identify the product formed when a given cyanohydrin is either reduced with lithium aluminum hydride or hydrolyzed with mineral acid.

b. identify the aldehyde or ketone, and other reagents needed to prepare a given α-hydroxyamine or α-hydroxycarboxylic acid.

Key Terms

Make certain that you can define, and use in context, the key term below.

- cyanohydrin

Study Notes

For successful cyanohydrin formation it is important to have free cyanide ions available to react with the ketone or aldehyde. This can be achieved by using a salt (e.g. KCN or NaCN) or a silylated (e.g. Me_3SiCN) form of cyanide under acidic conditions or by using HCN with some base added to produce the needed CN^- nucleophile.

Cyanohydrins have the structural formula of $R_2C(OH)CN$. The “R” on the formula represents an alkyl, aryl, or hydrogen. To form a cyanohydrin, a hydrogen cyanide adds reversibly to the carbonyl group of an organic compound thus forming a hydroxyalkanenitrile adducts (commonly known and called as cyanohydrins).

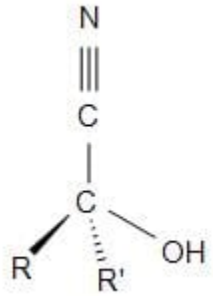
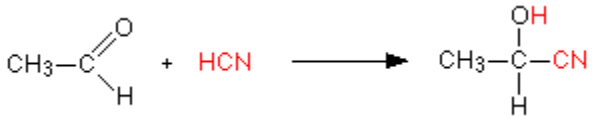


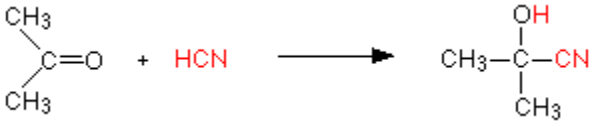
***Figure 19.6.1**: General structure of a cyanohydrin*

Hydrogen cyanide adds across the carbon-oxygen double bond in aldehydes and ketones to produce compounds known as

hydroxynitriles. For example, with ethanal (an aldehyde) you get 2-hydroxypropanenitrile:



With propanone (a ketone) you get 2-hydroxy-2-methylpropanenitrile:

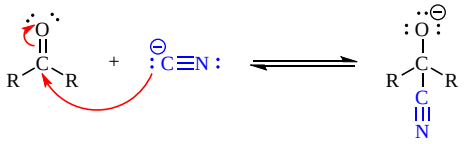


The reaction isn't normally done using hydrogen cyanide itself, because this is an extremely poisonous gas. Instead, the aldehyde or ketone is mixed with a solution of sodium or potassium cyanide in water to which a little sulphuric acid has been added. The pH of the solution is adjusted to about 4 - 5, because this gives the fastest reaction. The solution will contain hydrogen cyanide (from the reaction between the sodium or potassium cyanide and the sulphuric acid), but still contains some free cyanide ions. This is important for the mechanism.

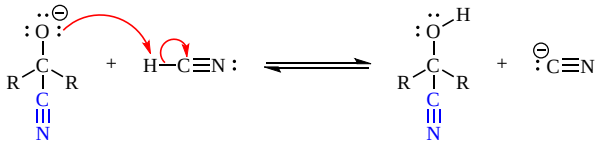
Mechanism of Cyanohydrin Formation

In the first step of the mechanism, the cyanide ion acts as a nucleophile and forms a C-C bond with the electrophillic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion intermediate. In the second step, the alkoxide ion is protonated by HCN which regenerates the cyanide ion.

Step 1: Nucleophilic attack



Step 2: Protonation



Acetone Cyanohydrins

Acetone cyanohydrins (ACH) have the structural formula of $(CH_3)_2C(OH)CN$. It is an organic compound serves in the production of methyl methacrylate (also known as acrylic).

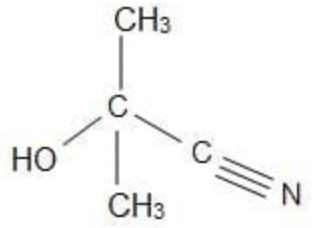


Figure 19.6.2: *Acetone cyanohydrins*

It is classified as an extremely hazardous substance, since it rapidly decomposes when it's in contact with water. In ACH, sulfuric acid is treated to give the sulfate ester of the methacrylamid. Preparations of other cyanohydrins are also used from ACH: for HACN to Michael acceptors and for the formylation of arenas. The treatment with lithium hydride affords anhydrous lithium cyanide.

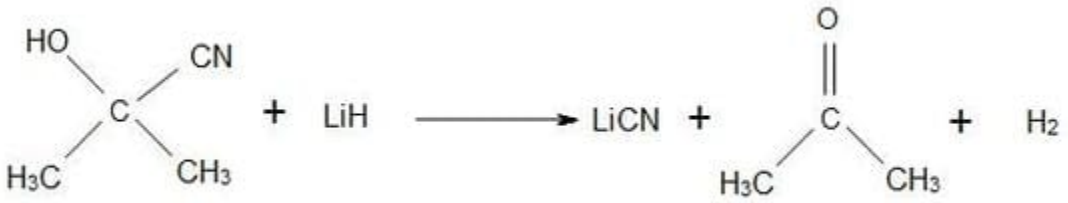
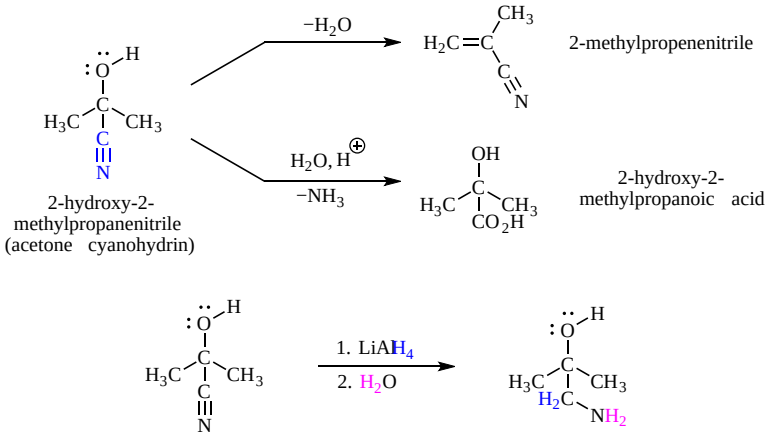


Figure 19.6.3: *Reduction of* Acetone cyanohydrins

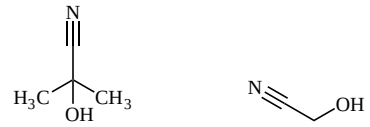
Further Chemistry of Cyanohydrins

Cyanohydrin functional groups often prove useful because of the further chemistry that can be carried out due to the presence of a hydroxyl and a nitrile functionality. In particular, dehydration can convert the hydroxyl group into an alkene (Section 17.6). The nitrile can be converted into a carboxylic acid function group through reaction with a hot acidic aqueous solution (Section 20.7). Also, the nitrile can be reduced by the addition of $LiAlH_4$ to form a primary amine.



Other Cyanohydrins

Other interesting cyanohydrins are: **acetone cyanohydrin**, and **glycolonitrile**.



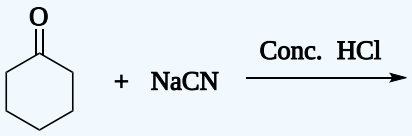
acetone cyanohydrin glycolonitrile

Acetone cyanohydrin has the structure, $(CH_3)_2C(OH)CN$, and is used in the production of methyl methacrylate (also known as acrylic). Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

Exercise

Exercise 19.6.1

What product is formed in this reaction?



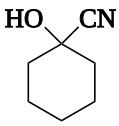
Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

Answers

Exercise 19.6.1



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17.12: Addition of Phosphorus Ylides: The Wittig Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of an ylide (phosphorane).
2. write an equation to illustrate the reaction that takes place between an ylide and an aldehyde or ketone.
3. identify the alkene which results from the reaction of a given ylide with a given aldehyde or ketone.
4. identify the aldehyde or ketone, the ylide, or both, needed to prepare a given alkene by a Wittig reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- betaine
- Wittig reaction
- ylide (phosphorane)

Study Notes

The name triphenylphosphine is derived as follows: the compound PH_3 is called phosphine; replacing the three hydrogen atoms with phenyl groups therefore gives us triphenylphosphine.

Note the following series of IUPAC-accepted trivial names:

NH_3—ammonia

PH_3—phosphine

AsH_3—arsine

Organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

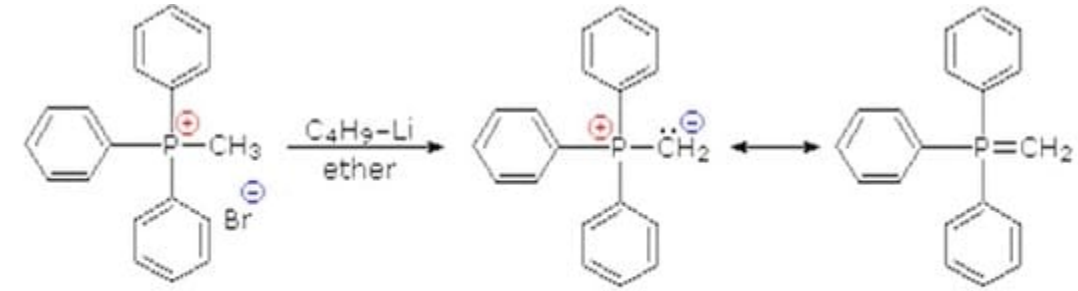
Preparation of Phosphorus Ylides

It has been noted that dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers, and the zwitterionic conjugate bases derived from such cations are known as ylides. An **ylide** is defined as a compound with opposite charges on adjacent atoms both of which have complete octets. For the Wittig reaction discussed below an organophosphorus ylide, also called Wittig reagents, will be used. The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure.



An Ylide

The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.



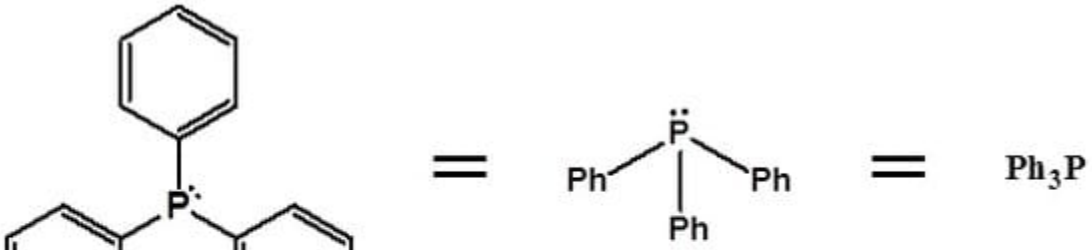
methyltriphenylphosphonium bromide

methylenetriphenylphosphorane
a phosphorous ylide

The ylides shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols, and are sensitive to oxygen. Water decomposes phosphorous ylides to hydrocarbons and phosphine oxides, as shown.

$$R_3P{=}CR'_2 \;+\; H_2O \longrightarrow R_3P{=}O \;+\; R'_2CH_2$$

Although many ylides are commercially available it is often necessary to create them synthetically. Ylides can be synthesized from an alkyl halide and a trialkyl phosphine. Typically triphenyl phosphine is used to synthesize ylides. Because a S_N2 reaction is used in the ylide synthesis methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthesis which involves a synthesized Wittig reagent.

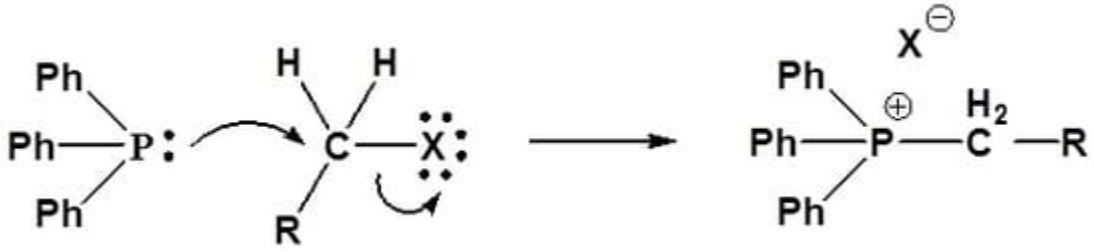


Triphenyl Phosphine

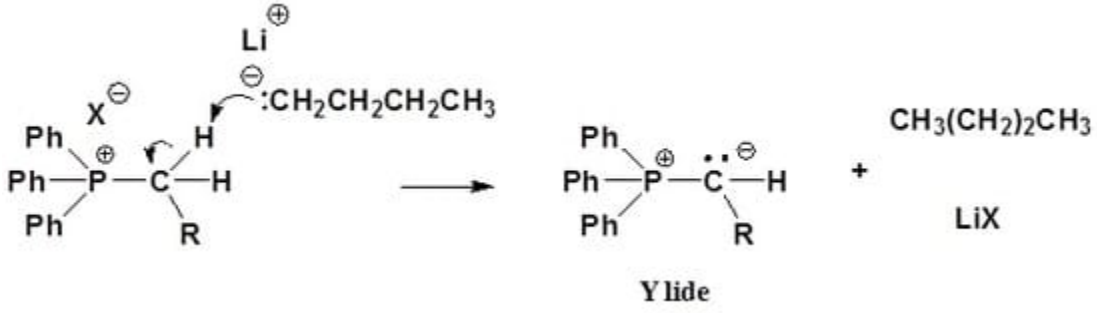
Ph =

Mechanism of ylide formation

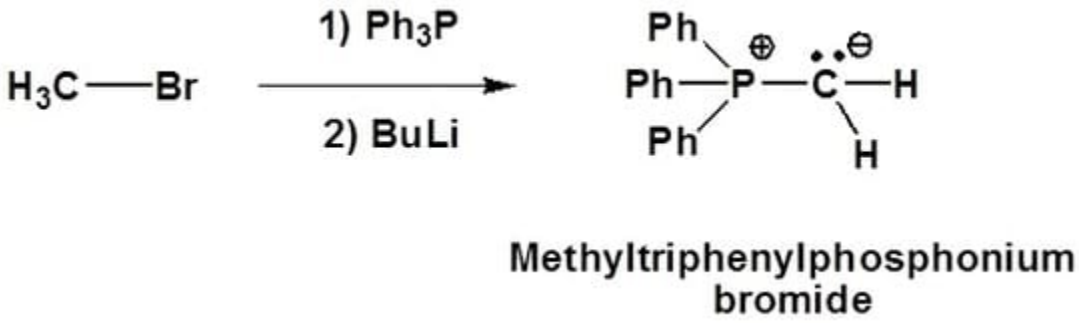
1) S_N2 reaction



2) Deprotonation

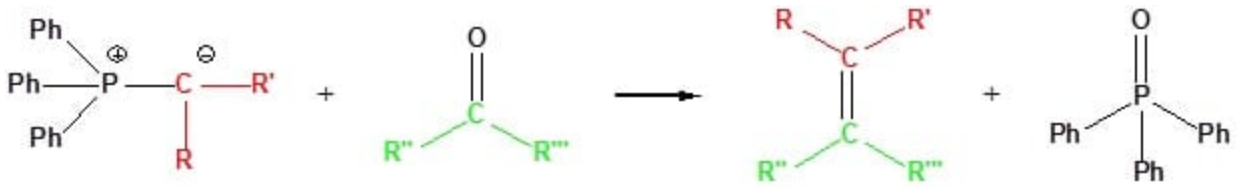


Examples of ylide formation

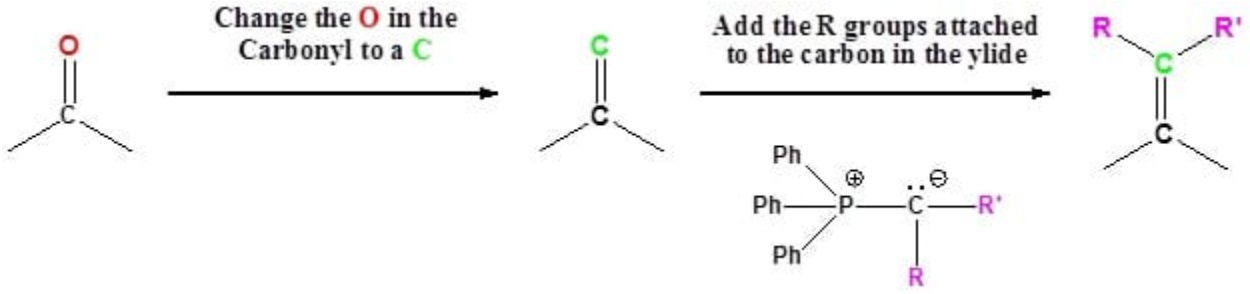


The Wittig Reaction

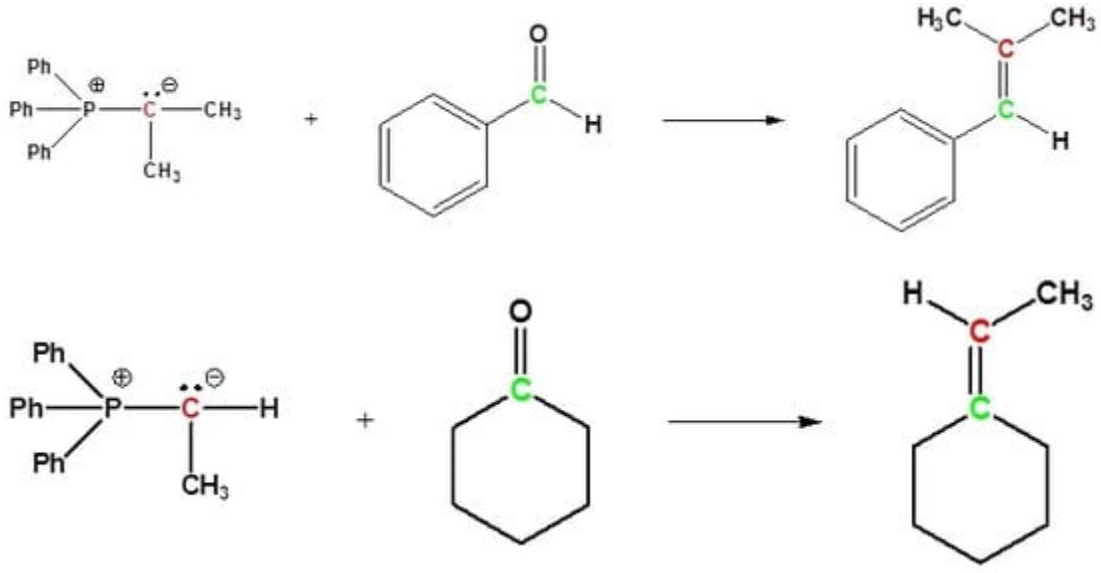
The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon. Ylides react to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.



Going from reactants to products simplified



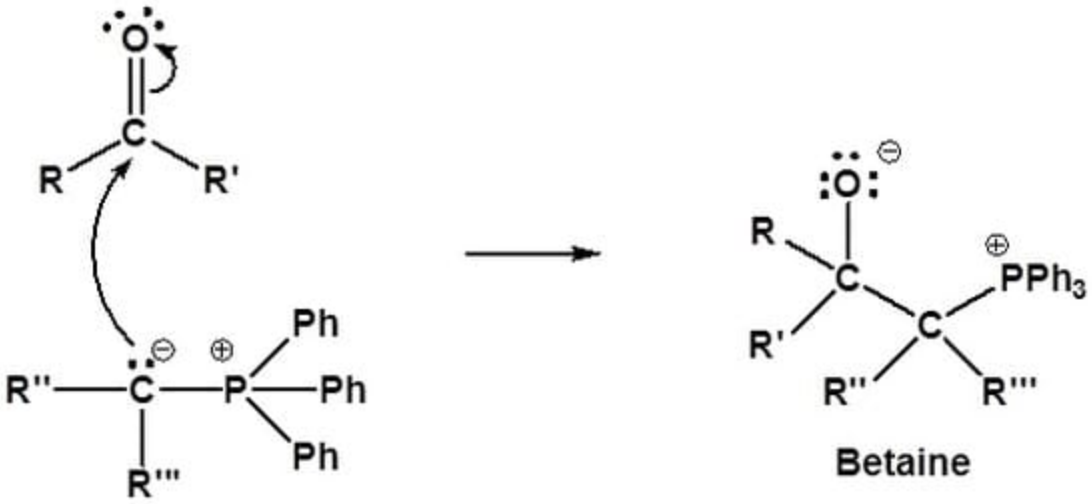
Examples of the Wittig reaction



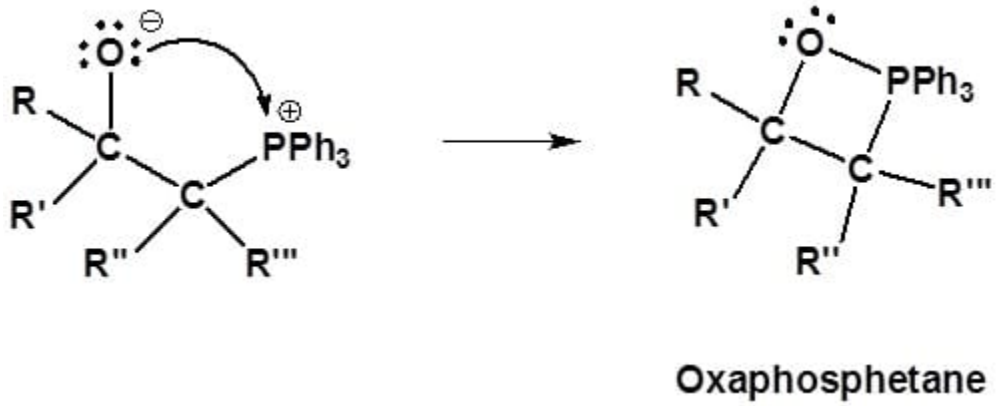
Mechanism of the Wittig reaction

Following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

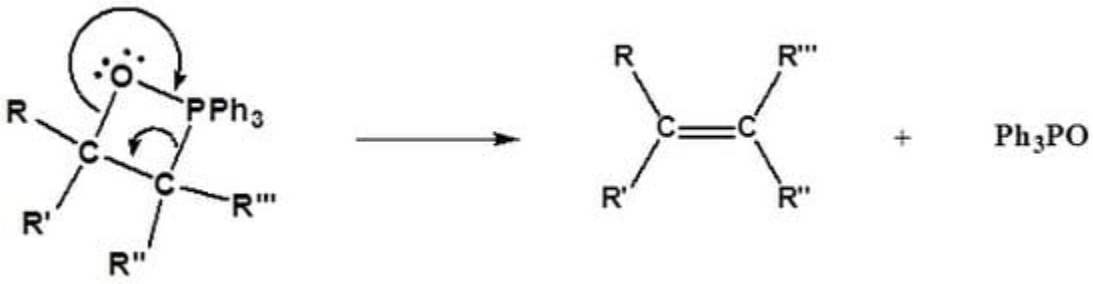
1) Nucleophillic attack on the carbonyl



2) Formation of a 4 membered ring

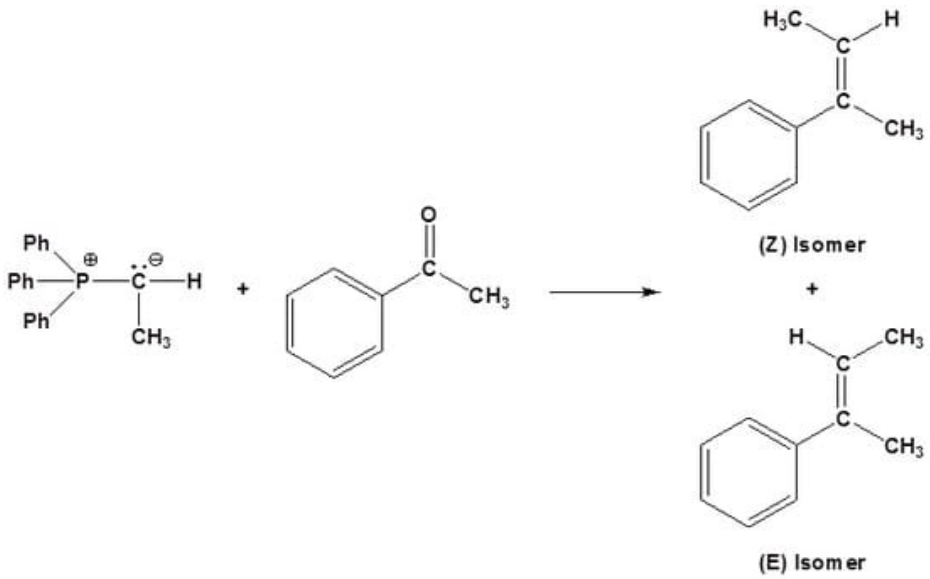


3) Formation of the alkene



Limitation of the Wittig reaction

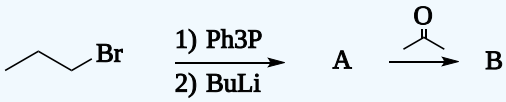
If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

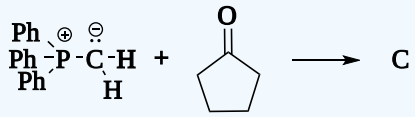


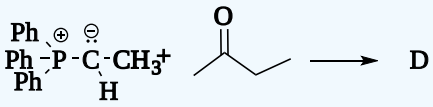
Exercises

Exercise 19.11.1

Draw the product of the following reactions.







Answer available at the end of this section.

Exercise 19.11.2

Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

Answer available at the end of this section.

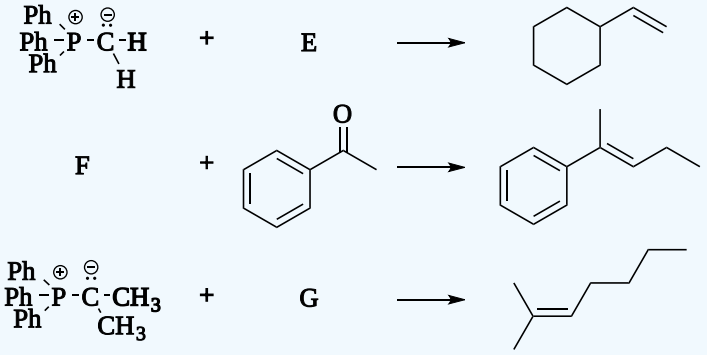
Exercise 19.11.3

Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

Answer available at the end of this section.

Exercise 19.11.4

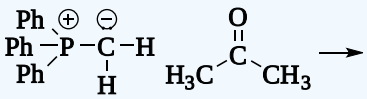
Indicate the starting material required to produce the product in each reaction.



Answer available at the end of this section.

Exercise 19.11.5

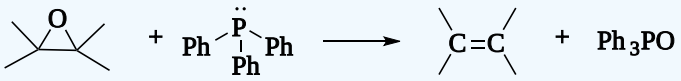
Give a detailed mechanism and the final product of this reaction.



Answer available at the end of this section.

Exercise 19.11.6

It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Please propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.



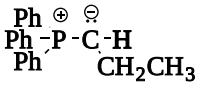
Answer available at the end of this section.

Contributors and Attributions

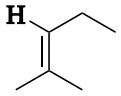
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

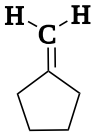
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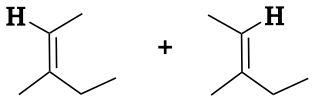
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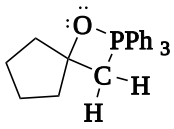


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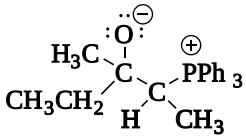


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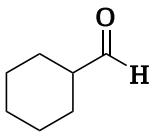
Exercise 19.11.2



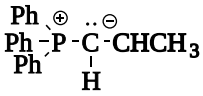
Exercise 19.11.3



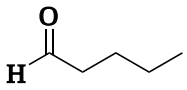
Exercise 19.11.4



E



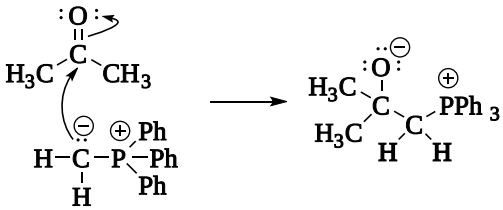
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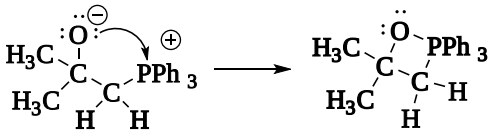
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Exercise 19.11.5

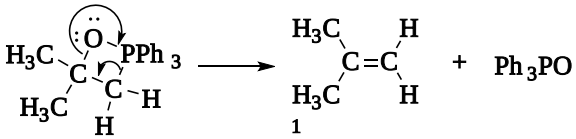
Nucleophillic attack on the carbonyl



Formation of a 4 membered ring



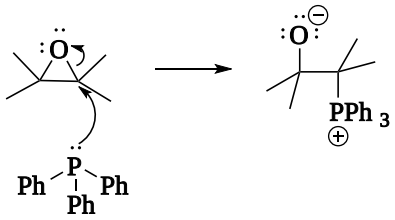
Formation of the alkene



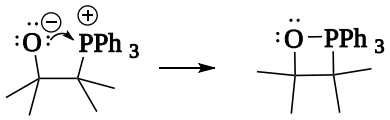
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Exercise 19.11.6

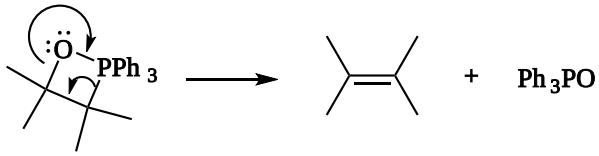
Nucleophillic attack on the epoxide



Formation of a 4 membered ring



Formation of the alkene

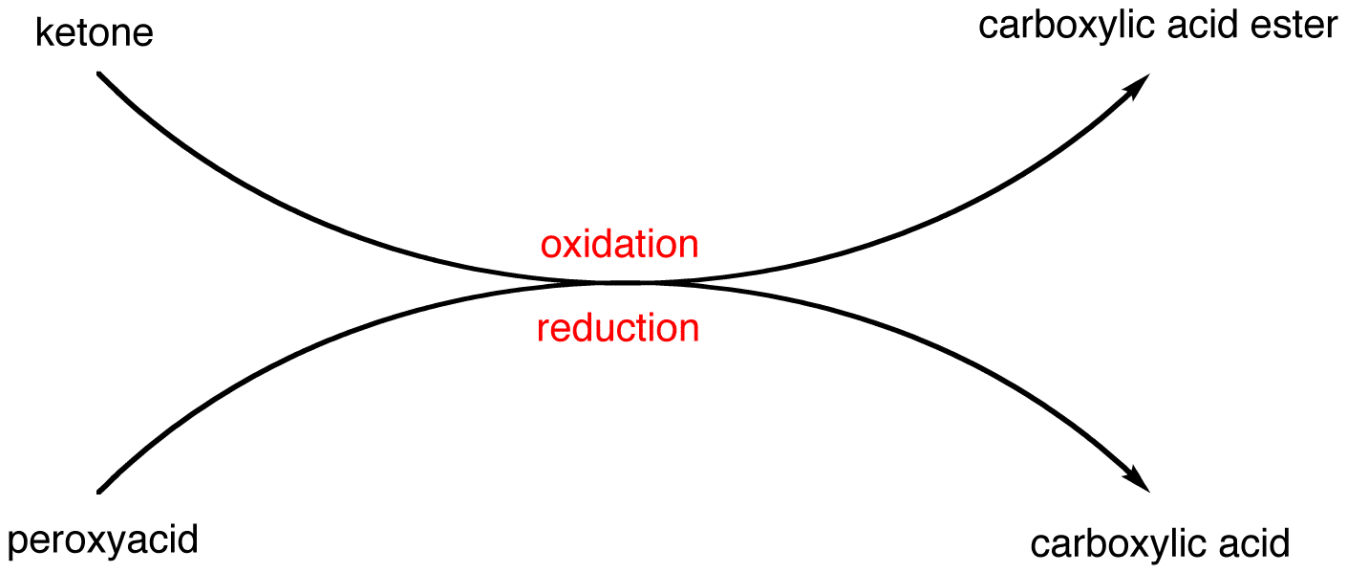


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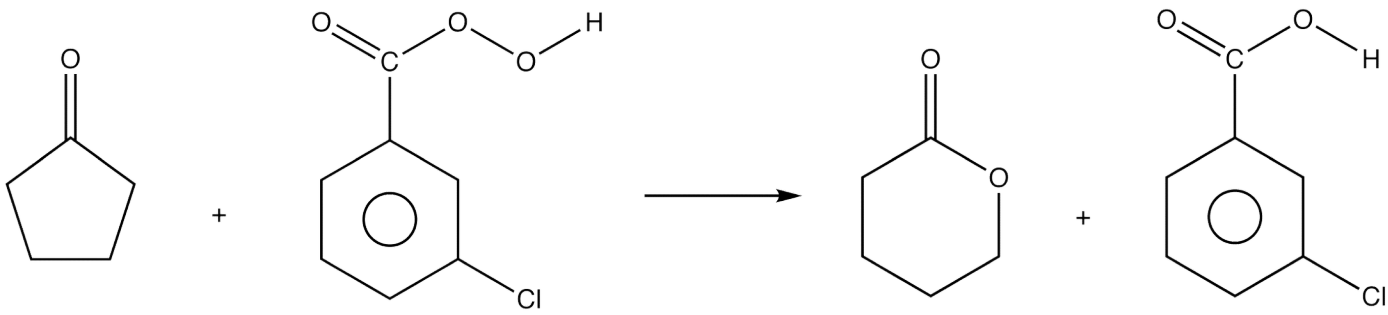
- 19.11: Nucleophilic Addition of Phosphorus Ylides - The Wittig Reaction by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

17.13: Oxidation by Peroxycarboxylic Acids: The Baeyer-Villiger Oxidation

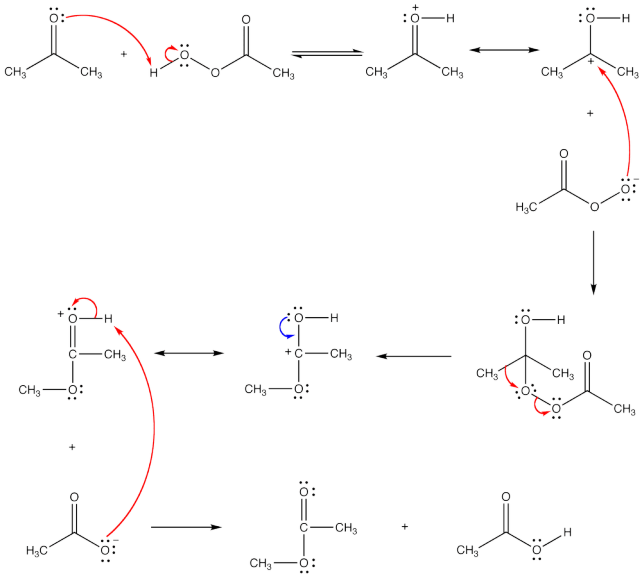
Baeyer-Villiger oxidation is the oxidation of a ketone to a carboxylic acid ester using a peroxyacid as the oxidizing agent. eg. 1:



eg. 2:



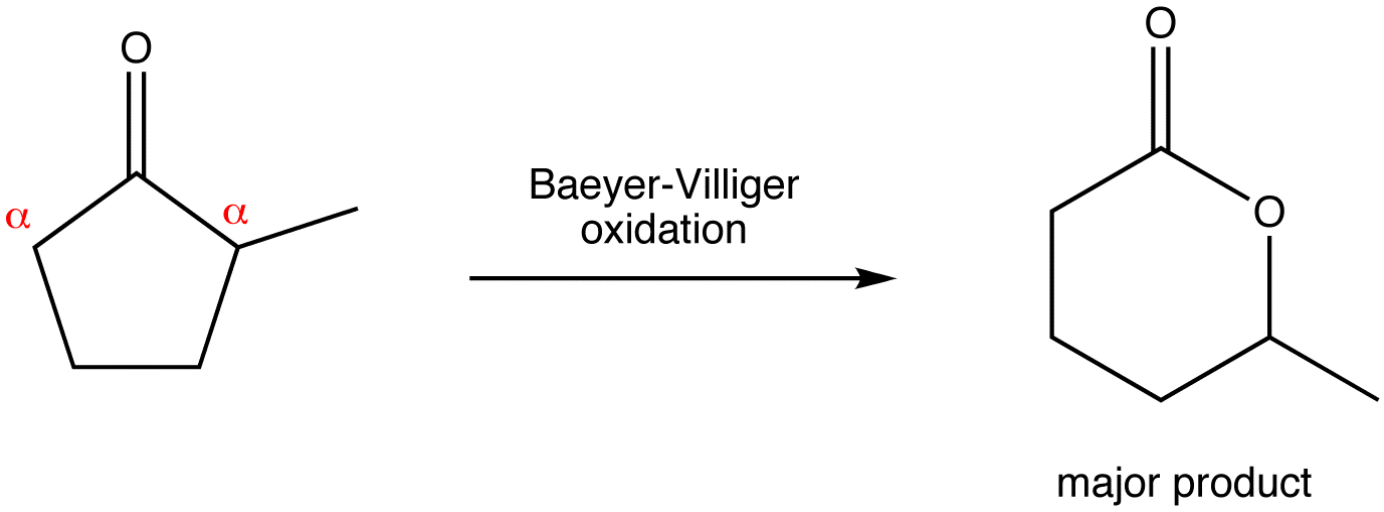
Mechanism



When the two ligands on the carbonyl carbon in the ketone are different, Baeyer-Villiger oxidation is regioselective. Of the two alpha carbons in the ketone, the one that can stabilize a positive charge more effectively, which is the more highly substituted one, migrates from carbon to oxygen preferentially.

eg. 1:

eg. 2:



References

1. ◦ Gamini Gunawardena from the OChemPal site (Utah Valley University)

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17.14: Oxidative Chemical Tests for Aldehydes

Objectives

After completing this section, you should be able to

1. write an equation for the oxidation of an aldehyde using
   a. CrO_3/sulfuric acid.
   b. Tollens reagent.
2. explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
3. identify the carboxylic acid produced when a given aldehyde is oxidized.
4. identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

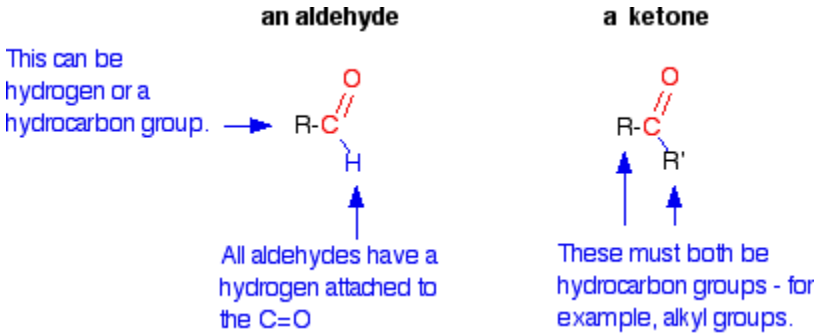
Study Notes

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

This page looks at ways of distinguishing between aldehydes and ketones using oxidizing agents such as acidified potassium dichromate(VI) solution, Tollens' reagent, Fehling's solution and Benedict's solution.

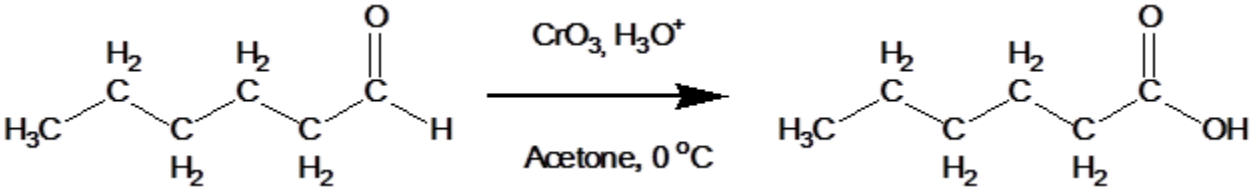
Why do aldehydes and ketones behave differently?

You will remember that the difference between an aldehyde and a ketone is the presence of a hydrogen atom attached to the carbon-oxygen double bond in the aldehyde. Ketones don't have that hydrogen.

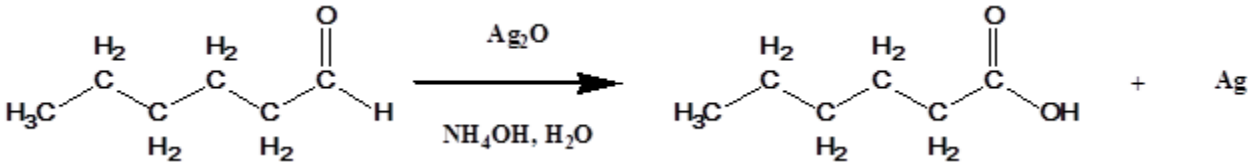


Oxidation of Aldehydes

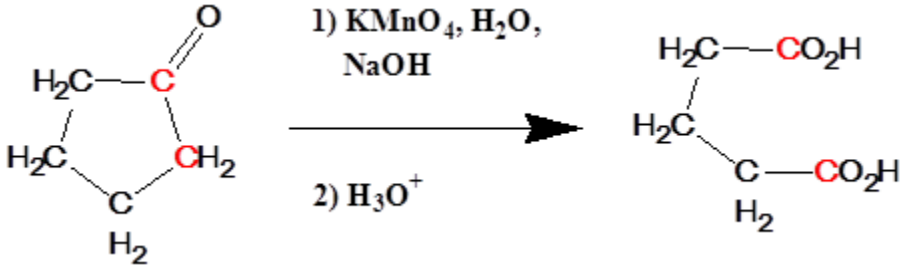
The presence of that hydrogen atom makes aldehydes very easy to oxidize. Or, put another way, they are strong reducing agents. The most common reagent for this conversion is CrO_3 in aqueous acid. This reaction generally gives good yields at room temperature.



Unfortunately, the acid condition for the previous reaction can cause unwanted side reaction. If this problem occurs it can be rectified by using a solution of sliver oxide, Ag_2O, in aqueous ammonia, also called Tollens' reagent.



Because ketones do not have that particular hydrogen atom, they are resistant to oxidation, and only very strong oxidizing agents like potassium manganate(VII) solution (potassium permanganate solution) oxidize ketones. However, they do it in a destructive way, breaking carbon-carbon bonds and forming two carboxylic acids.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

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18: ENOLS, ENOLATES, AND THE ALDOL CONDENSATION: A,B-UNSATURATED ALDEHYDES AND KETONES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

18.1: Acidity of Aldehydes and Ketones: Enolate Ions

18.2: Keto-Enol Equilibria

18.3: Halogenation of Aldehydes and Ketones

18.4: Alkylation of Aldehydes and Ketones

18.5: Attack by Enolates on the Carbonyl Function: Aldol Condensation

18.6: Crossed Aldol Condensation

18.7: Keys to Success: Competitive Rection Pathways and the Intramolecular Aldol Condensation

18.8: Properties of a,b-Unsaturated Aldehydes and Ketones

18.9: Conjugate Additions to a,b-Unsaturated Aldehydes and Ketones

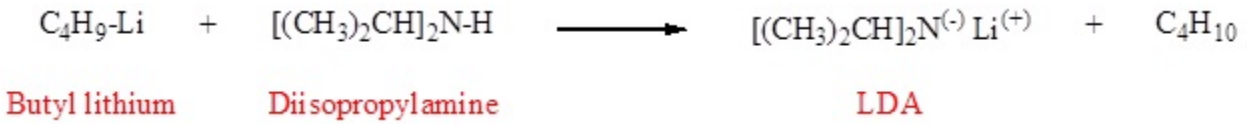
18.10: 1,2- and 1,4-Additions of Organometallic Reagents

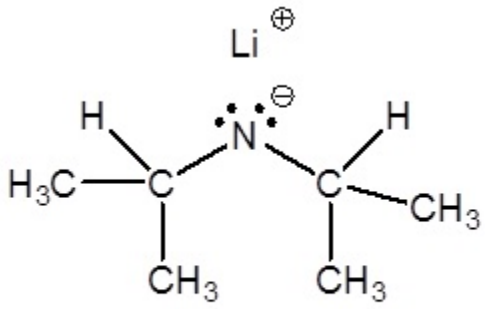
18.11: Conjugate Additions of Enolate Ions: Michael Addition and Robinson Annulation

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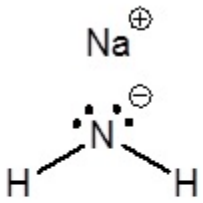
18.1: Acidity of Aldehydes and Ketones: Enolate Ions

For alkylation reactions of enolate anions to be useful, these intermediates must be generated in high concentration in the absence of other strong nucleophiles and bases. The aqueous base conditions used for the aldol condensation are not suitable because the enolate anions of simple carbonyl compounds are formed in very low concentration, and hydroxide or alkoxide bases induce competing S_N2 and E2 reactions of alkyl halides. It is necessary, therefore, to achieve complete conversion of aldehyde or ketone reactants to their enolate conjugate bases by treatment with a very strong base (pK_a > 25) in a non-hydroxylic solvent before any alkyl halides are added to the reaction system. Some bases that have been used for enolate anion formation are: NaH (sodium hydride, pK_a > 45), $NaNH_2$ (sodium amide, pK_a = 34), and $LiN[CH(CH_3)_2]_2$ (lithium diisopropylamide, LDA, pK_a 36). Ether solvents like tetrahydrofuran (THF) are commonly used for enolate anion formation. With the exception of sodium hydride and sodium amide, most of these bases are soluble in THF. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to carbonyl groups. Nevertheless, these very strong bases are useful in making soluble amide bases. In the preparation of lithium diisopropylamide (LDA), for example, the only other product is the gaseous alkane butane.





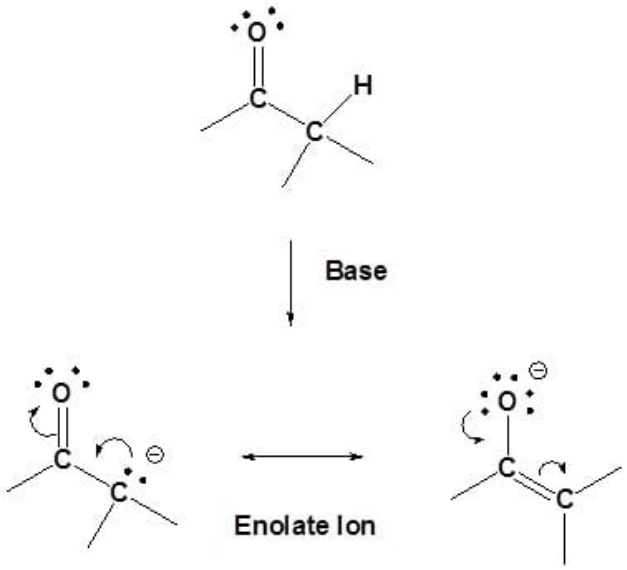
LDA



Sodium Amide

Because of its solubility in THF, LDA is a widely used base for enolate anion formation. In this application, one equivalent of diisopropylamine is produced along with the lithium enolate, but this normally does not interfere with the enolate reactions and is easily removed from the products by washing with aqueous acid. Although the reaction of carbonyl compounds with sodium hydride is heterogeneous and slow, sodium enolates are formed with the loss of hydrogen, and no other organic compounds are produced.

The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).

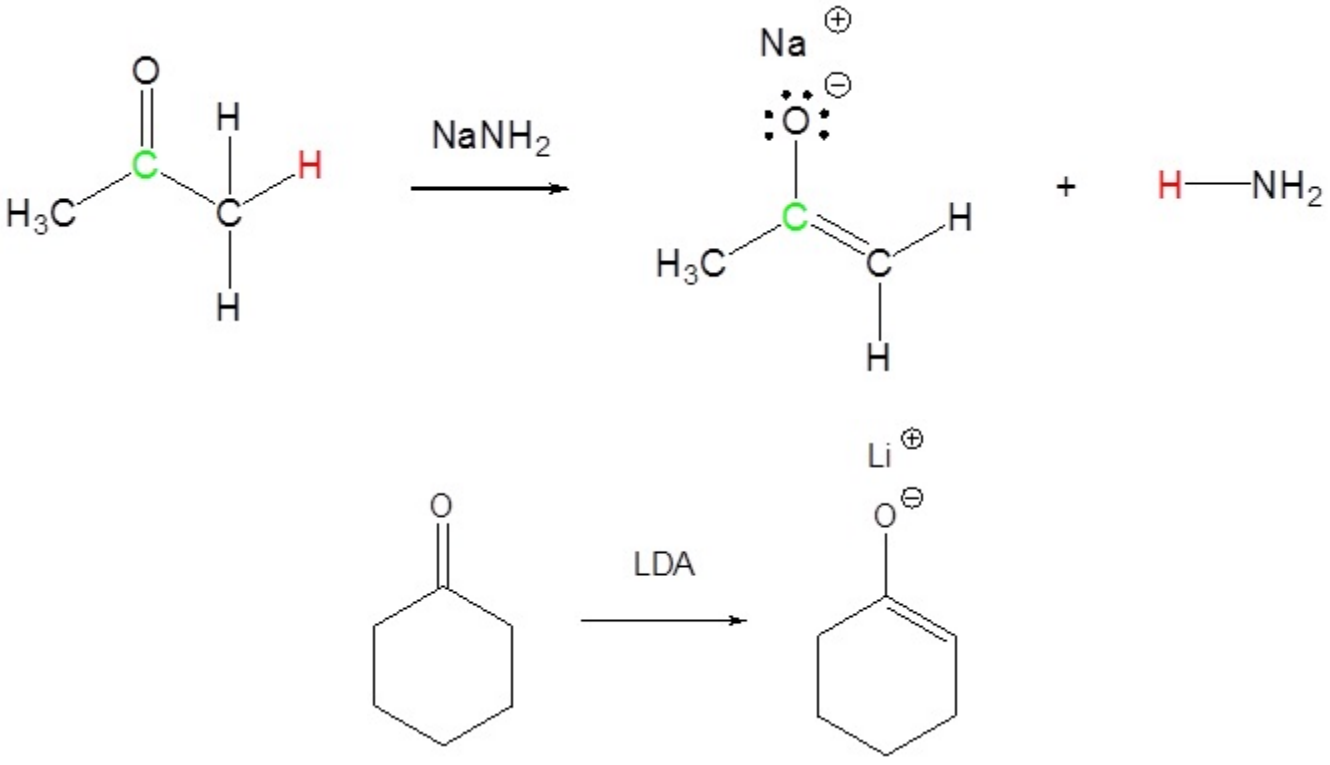


Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

Acidity of α-Hydrogens in Some Activated Compounds

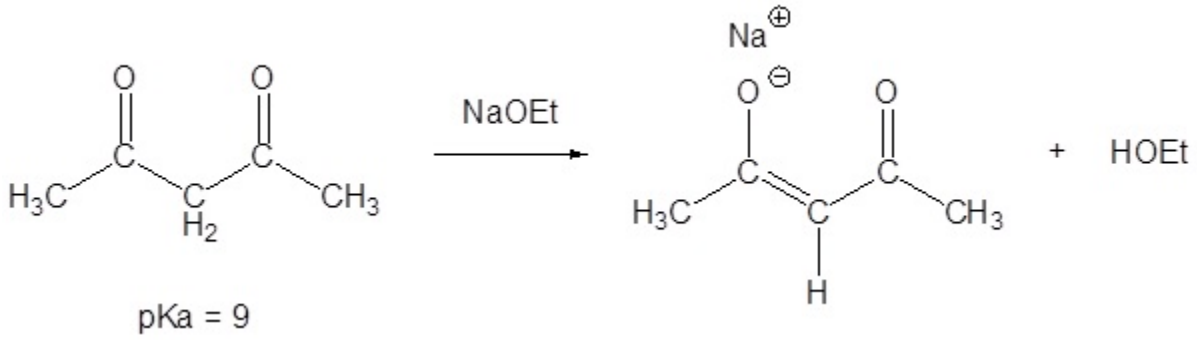
Compound	RCH_2-NO_2	RCH_2-COR	$RCH_2-C\equiv N$	RCH_2-SO_2R
pK_a	9	20	25	25

Examples



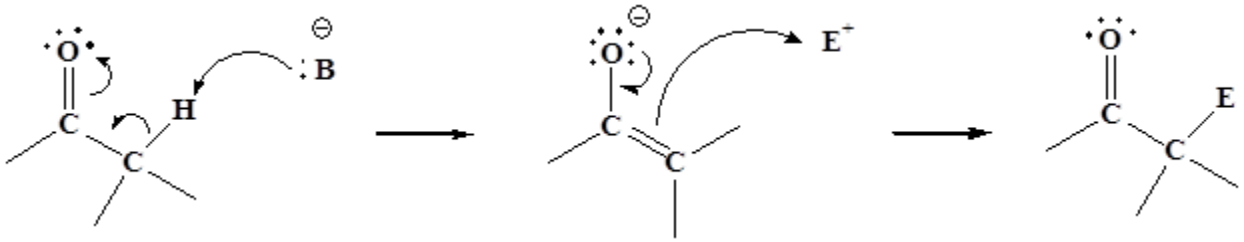
If the formed enolate is stabilized by more than one carbonyl it is possible to use a weaker base such as sodium ethoxide.

$NaOCH_2CH_3 = Na^+ \ ^-OCH_2CH_3 = NaOEt$



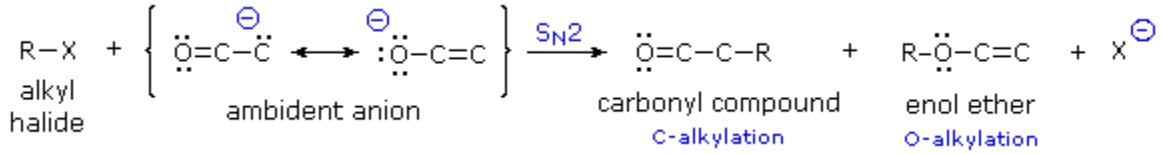
Because of the acidity of α hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.

General Reaction of Enolates



The Ambident Character of Enolate Anions

Since the negative charge of an enolate anion is delocalized over the alpha-carbon and the oxygen, as shown earlier, electrophiles may bond to either atom. Reactants having two or more reactive sites are called **ambident**, so this term is properly applied to enolate anions. Modestly electrophilic reactants such as alkyl halides are not sufficiently reactive to combine with neutral enol tautomers, but the increased nucleophilicity of the enolate anion conjugate base permits such reactions to take place. Because alkylations are usually irreversible, their products should reflect the inherent (kinetic) reactivity of the different nucleophilic sites.



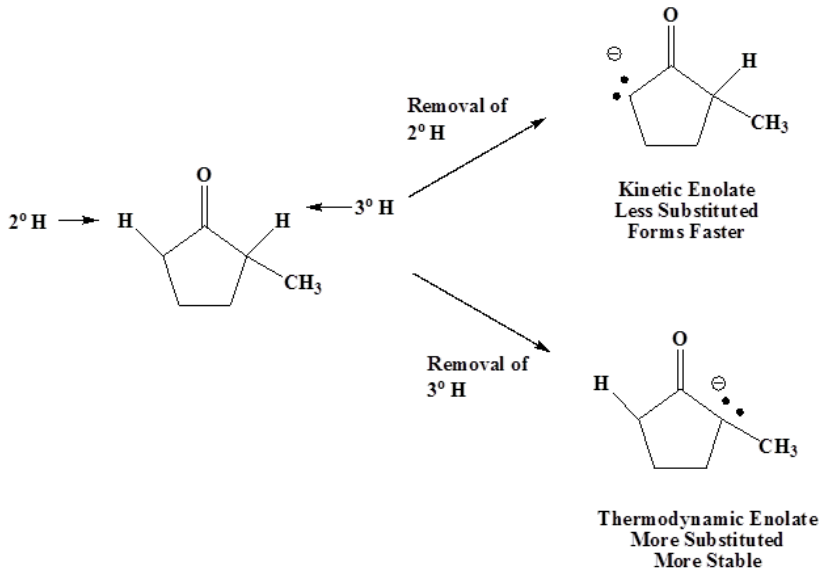
If an alkyl halide undergoes an S_N2 reaction at the carbon atom of an enolate anion the product is an alkylated aldehyde or ketone. On the other hand, if the S_N2 reaction occurs at oxygen the product is an ether derivative of the enol tautomer; such compounds are stable in the absence of acid and may be isolated and characterized. These alkylations (shown above) are irreversible under the conditions normally used for S_N2 reactions, so the product composition should provide a measure of the relative rates of substitution at carbon versus oxygen. It has been found that this competition is sensitive to a number of factors, including negative charge density, solvation, cation coordination and product stability.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

Enolate of Unsymmetrical Carbonyl Compounds

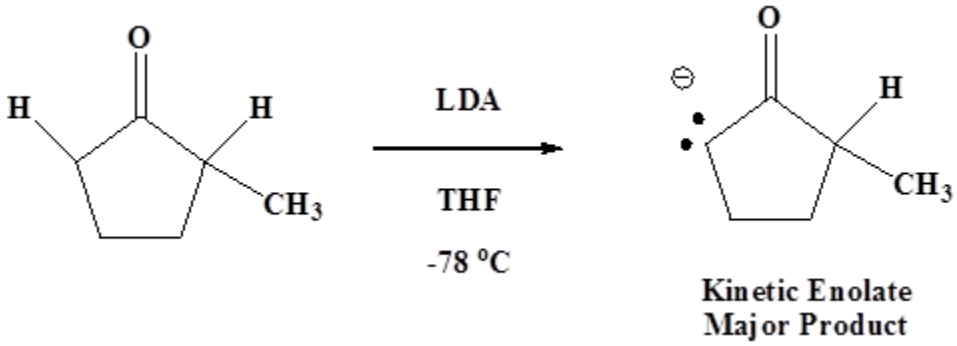
Now let's consider what happens when an unsymmetrical carbonyl is treated with a base. In the case displayed below there are two possible enolates which can form. The removal of the 2o hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3o hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



Kinetic Enolates

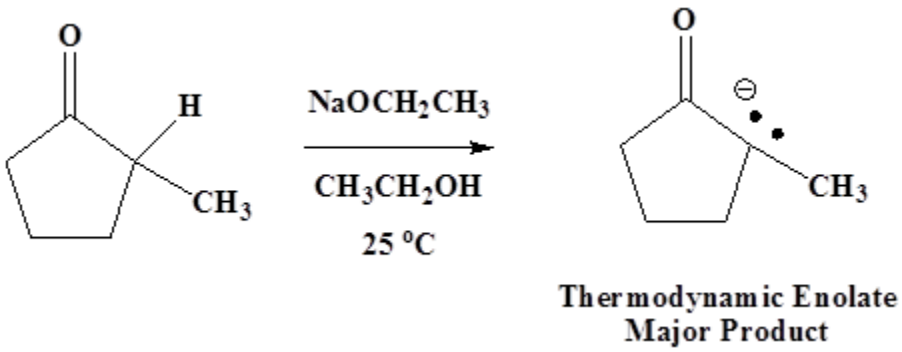
Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2o hydrogen less sterically hindered and preferable removes it.

Low temperature are typically used when forming the kinetic enolate to prevent equilibration to the more stable thermodynamic enolate. Typically a temperature of -78 oC is used.



Thermodynamic Enolates

The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.



Thermodynamic Enolate
Major Product

Contributors

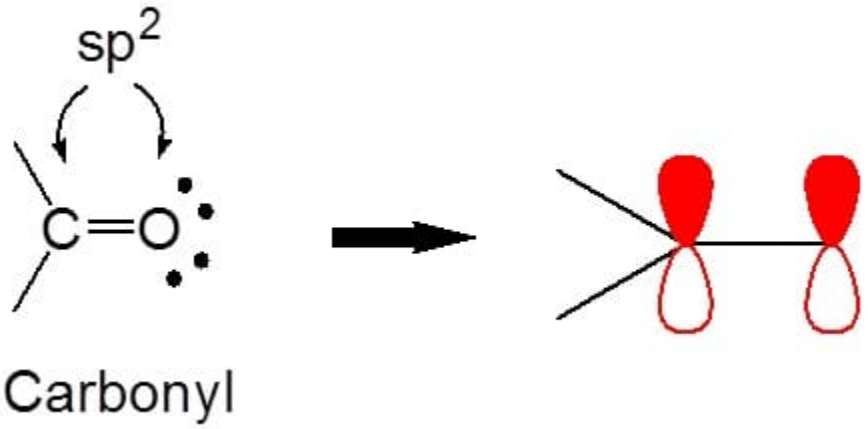
- Prof. Steven Farmer (Sonoma State University)

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18.2: Keto-Enol Equilibria

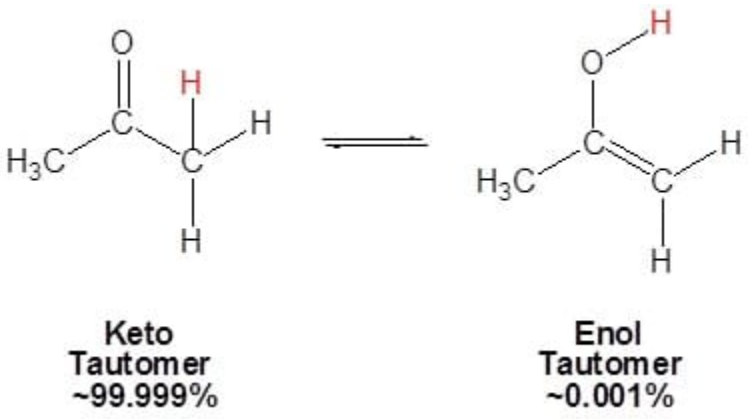
Acidity of Alpha Hydrogens

Functional groups, such as aldehydes, ketones and esters, contain a carbonyl group which is made up of a sp^2 hybridized carbon and oxygen. Because they are sp^2 hybridized the carbon and oxygen both have unhybridized p orbitals which can overlap to form the C=O π bond.



Keto-enol Tautomerism

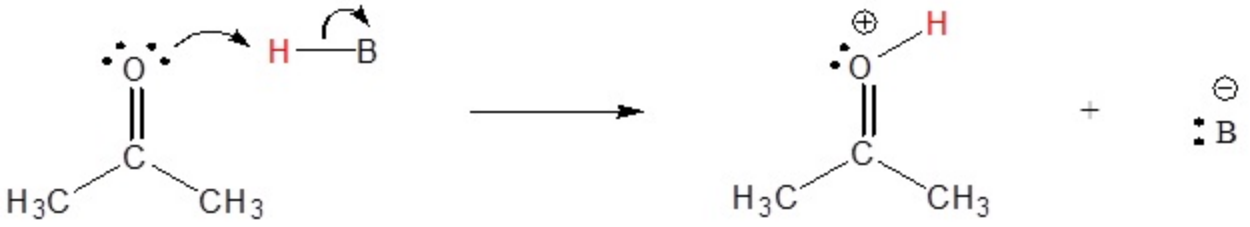
Because of the acidity of α hydrogens carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



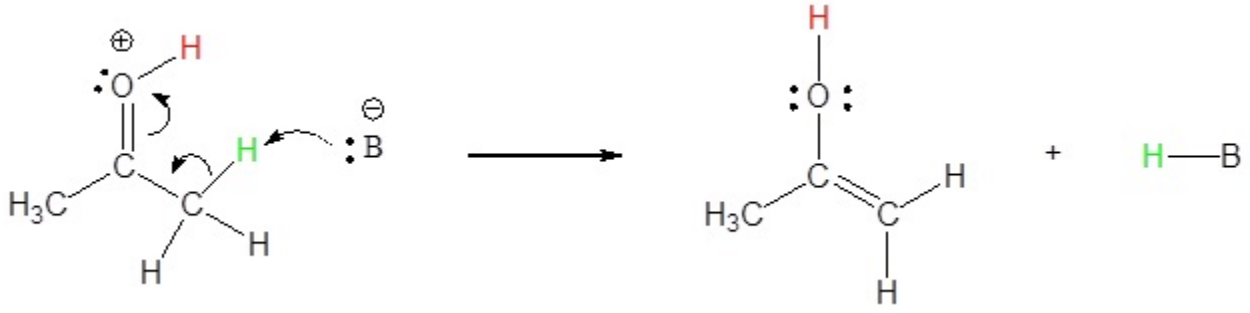
Mechanism for Enol Formation

Acid conditions

1) Protonation of the Carbonyl

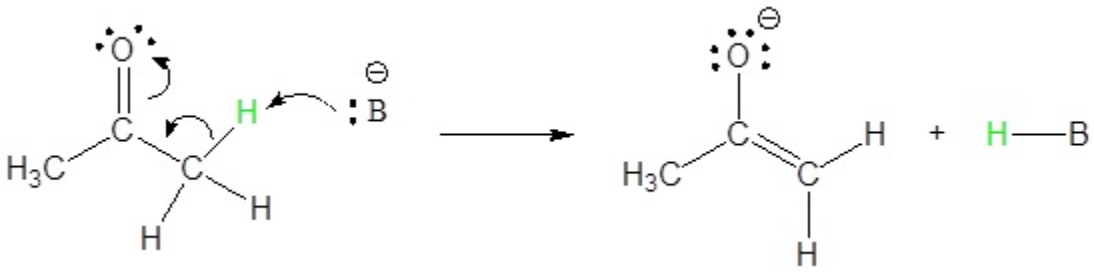


2) Enol formation

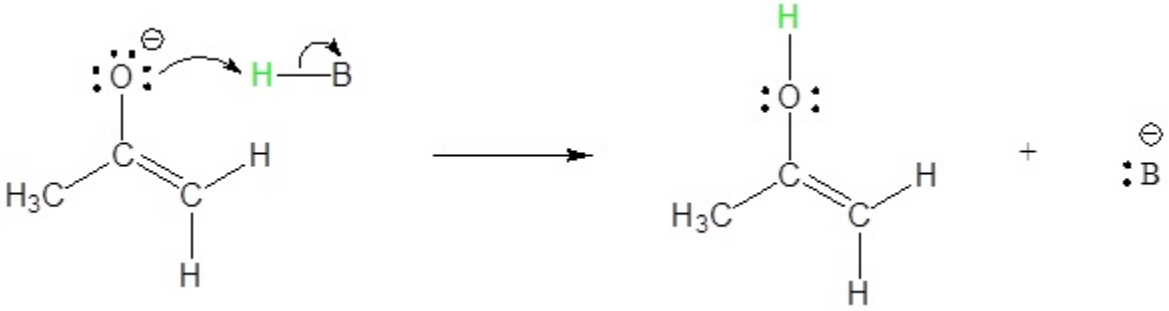


Basic conditions

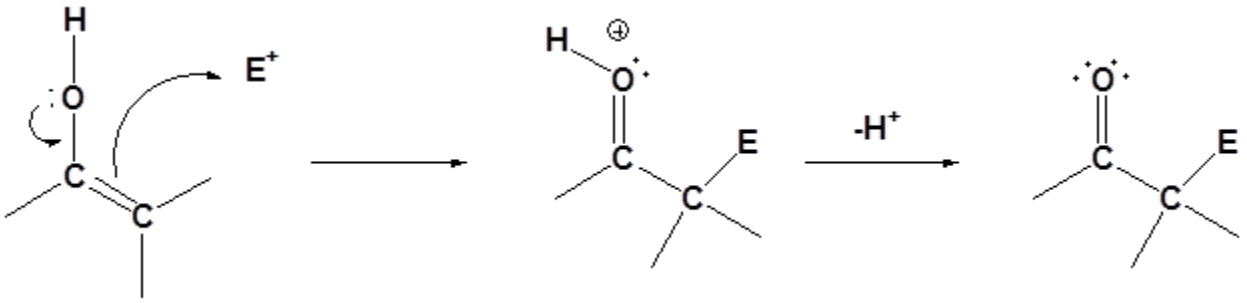
1) Enolate formation



2) Protonation



How Enols React

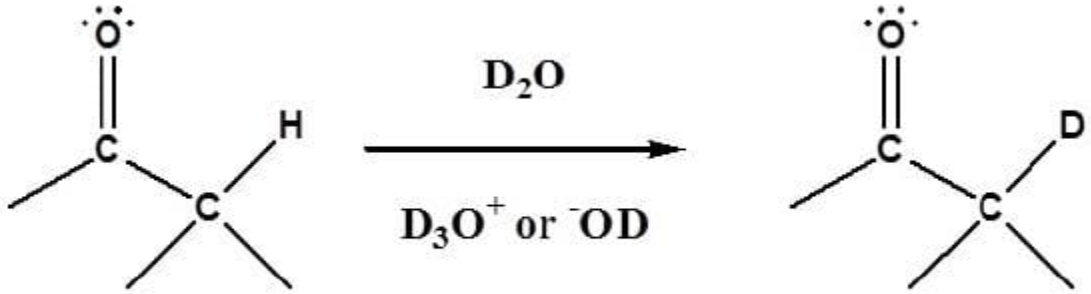


Contributors

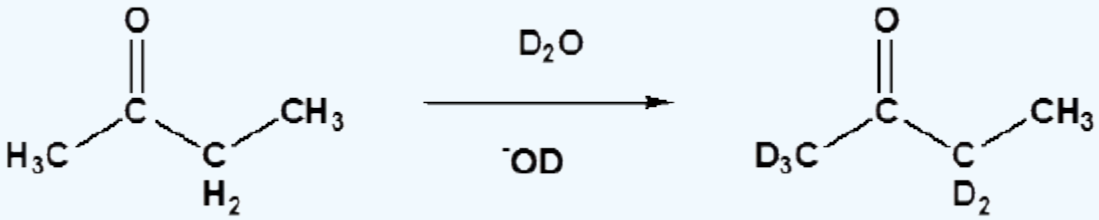
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with D_2O (heavy water). The process is accelerated by the addition of an acid or base; an excess of D_2O is required. The end result is the complete exchange of all α hydrogens with deuterium.

General reaction

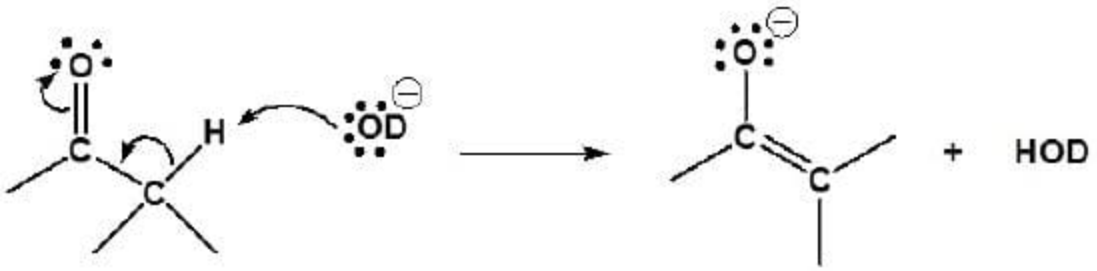


Example 1: Deuterium Exchange

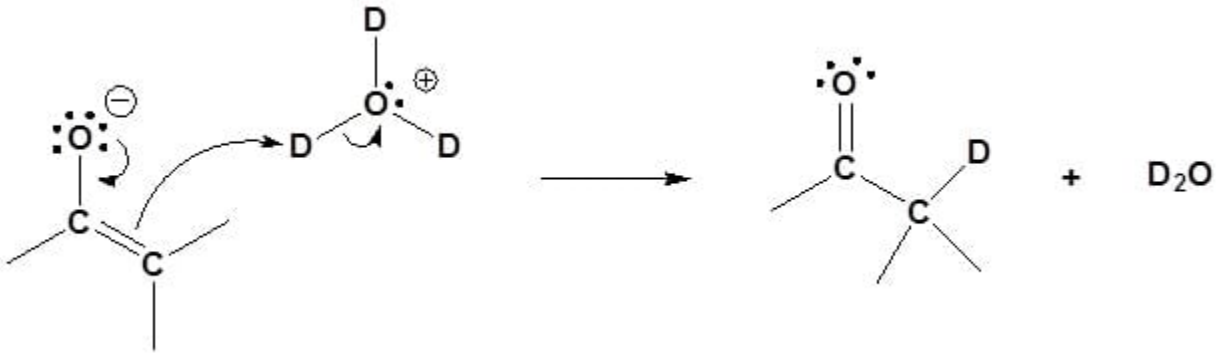


Mechanism in basic conditions

Step 1: Enolate Formation

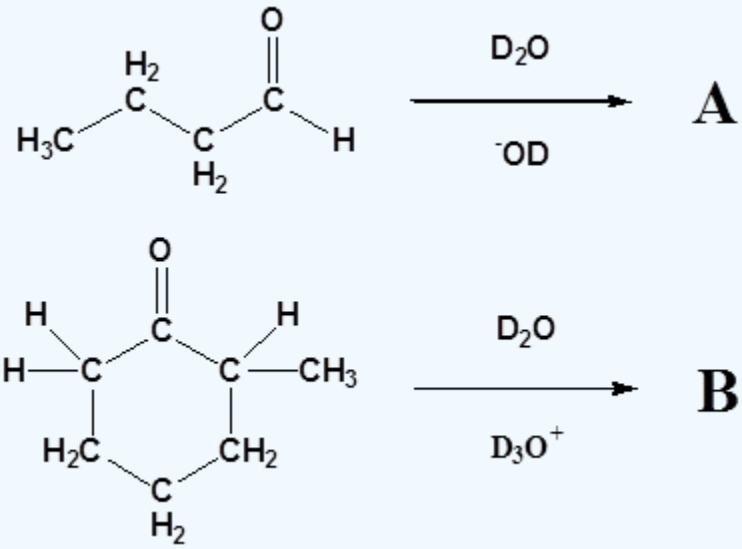


Step 2: Deuteration



Exercise 18.2.1

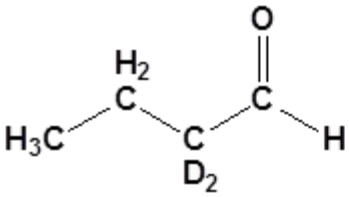
Please draw the product for the following reactions.



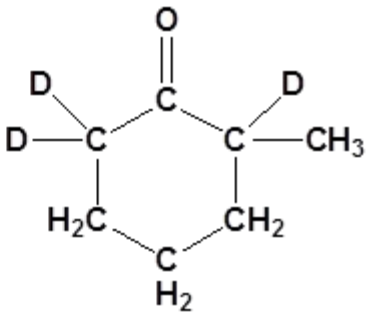
Answer available at the end of this section.

Answers

Exercise 18.2.1



A



B

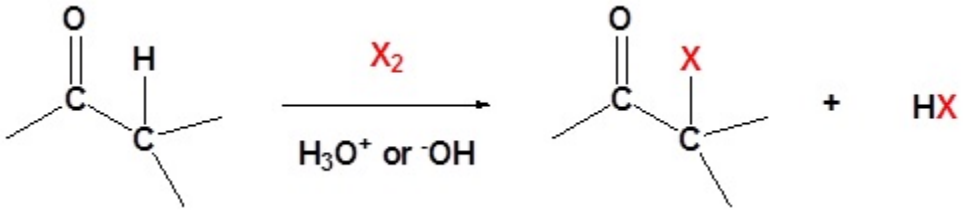
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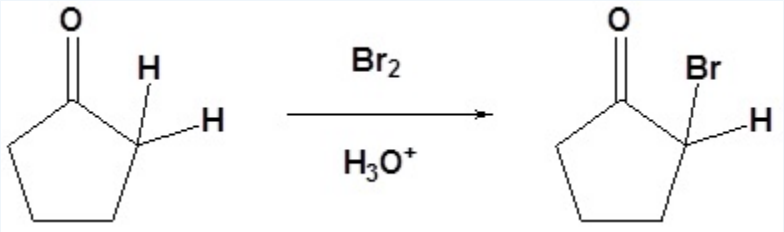
18.3: Halogenation of Aldehydes and Ketones

A carbonyl containing compound with α hydrogens can undergo a substitution reaction with halogens. This reaction comes about because of the tendency of carbonyl compounds to form enolates in basic condition and enols in acidic condition. In these cases even weak bases, such as the hydroxide anion, is sufficient enough to cause the reaction to occur because it is not necessary for a complete conversion to the enolate. For this reaction Cl_2, Br_2 or I_2 can be used as the halogens.

General reaction



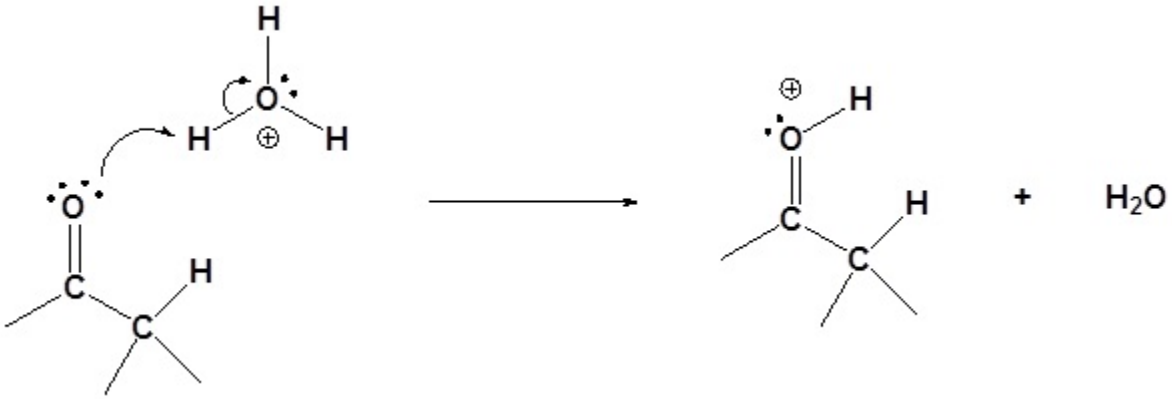
Example



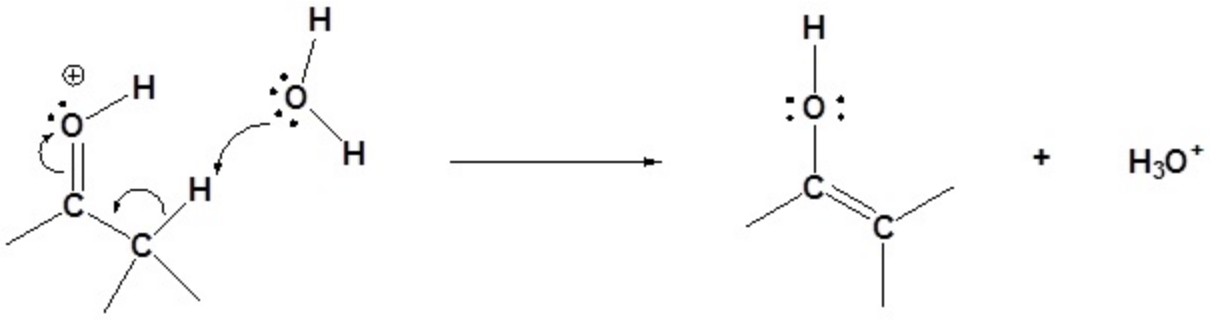
Acid Catalyzed Mechanism

Under acidic conditions the reaction occurs thought the formation of an enol which then reacts with the halogen.

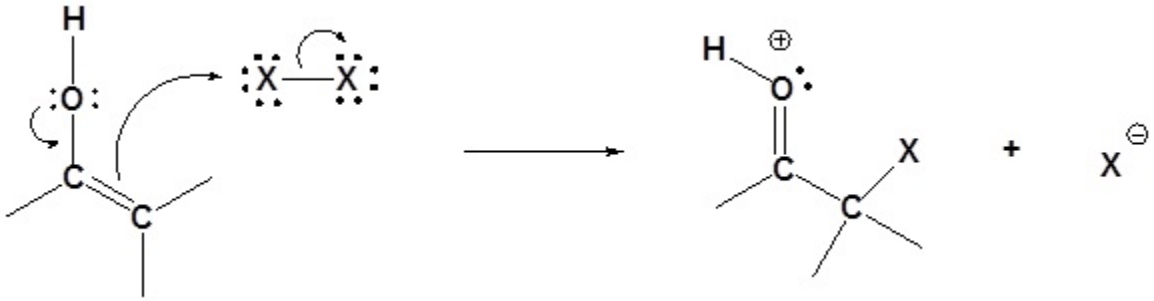
1) Protonation of the carbonyl



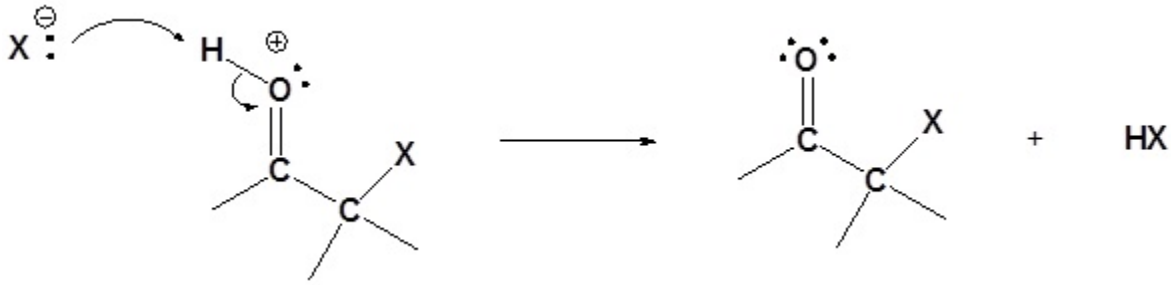
2) Enol formation



3) S_N2 attack



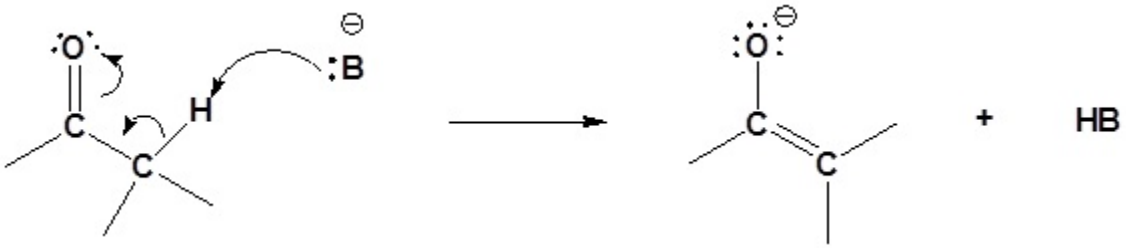
4) Deprotonation



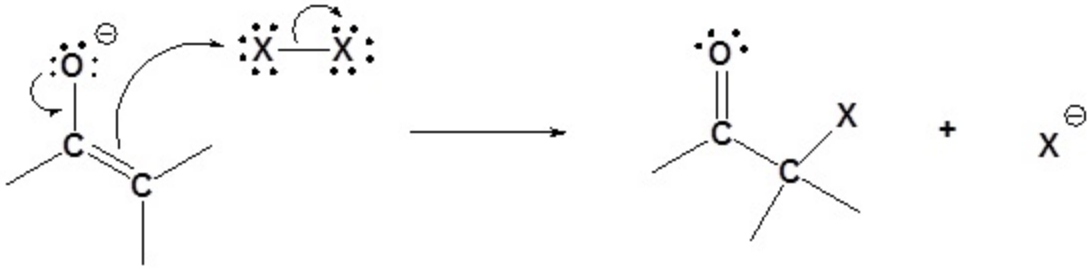
Base Catalyzed Mechanism

Under basic conditions the enolate forms and then reacts with the halogen. Note! This is base promoted and not base catalyzed because an entire equivalent of base is required.

1) Enolate formation

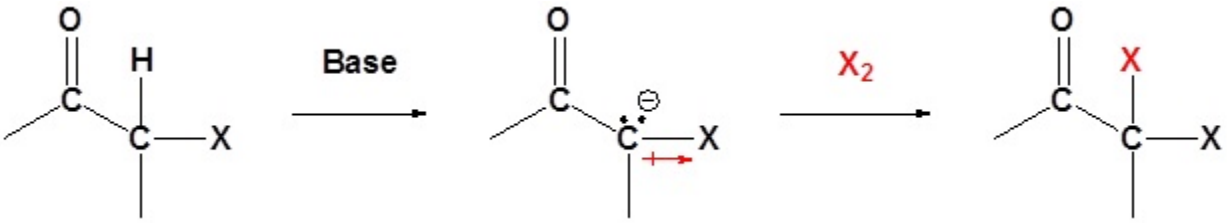


2) S_N2 attack



Overreaction during base promoted α halogenation

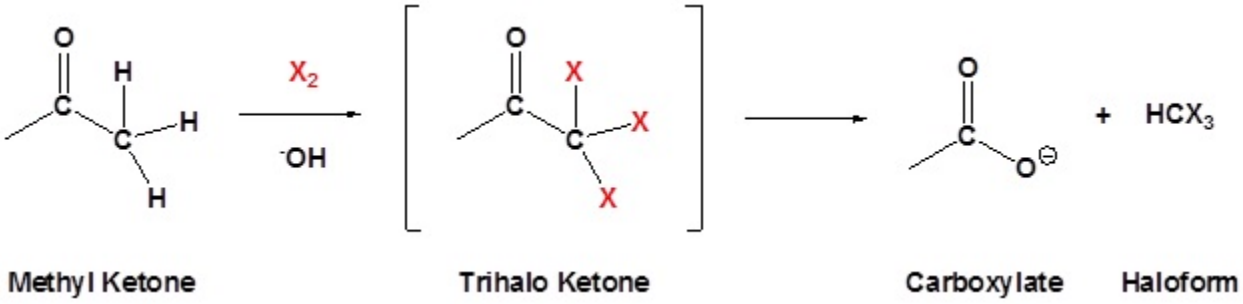
The fact that an electronegative halogen is placed on an α carbon means that the product of a base promoted α halogenation is actually more reactive than the starting material. The electron withdrawing effect of the halogen makes the α carbon even more acidic and therefor promotes further reaction. Because of this multiple halogenations can occur. This effect is exploited in the haloform reaction discussed later. If a monohalo product is required then acidic conditions are usually used.



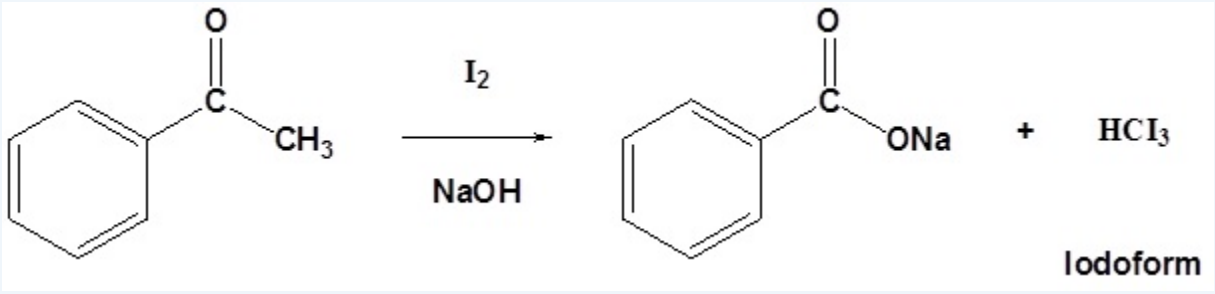
The Haloform Reaction

Methyl ketones typically undergo halogenation three times to give a trihalo ketone due to the increased reactivity of the halogenated product as discussed above. This trihalomethyl group is an effective leaving group due to the three electron withdrawing halogens and can be cleaved by a hydroxide anion to effect the haloform reaction. The product of this reaction is a carboxylate and a haloform molecule ($CHCl_3$, $CHBr_3$, CHI_3). Overall the haloform reaction represents an effective method for the conversion of methyl ketones to carboxylic acids. Typically, this reaction is performed using iodine because the subsequent iodoform (CHI_3) is a bright yellow solid which is easily filtered off.

General reaction

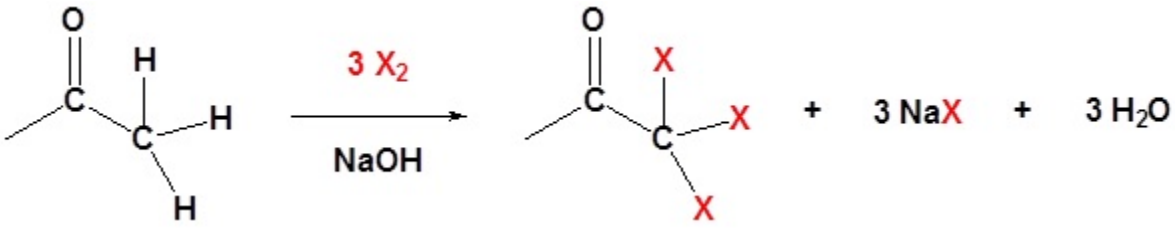


Example: The Haloform Reaction

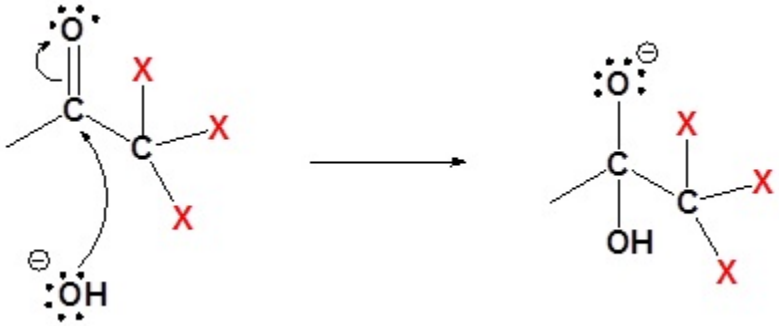


Mechanism

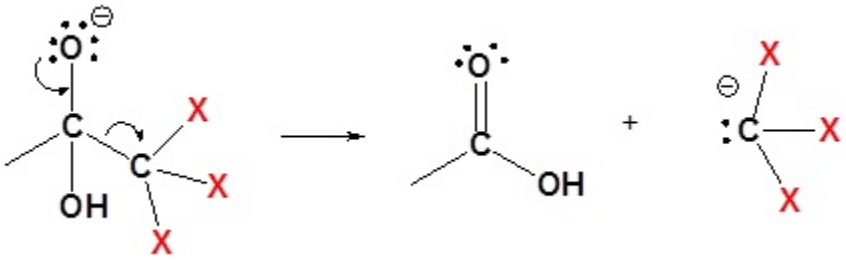
1) Formation of the trihalo species



2) Nulceophilic attack on the carbonyl carbon



3) Removal of the leaving group

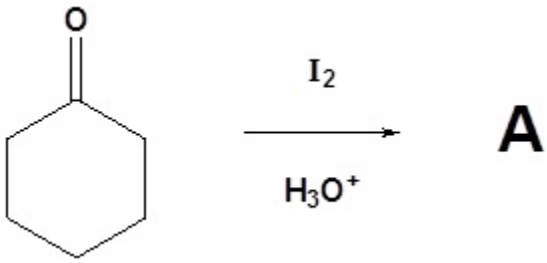


4) Deprotonation



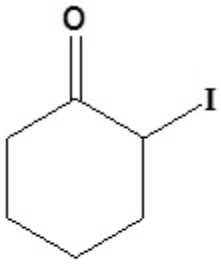
Problems

1) Please draw the products of the following reactions



Answers

1)



A

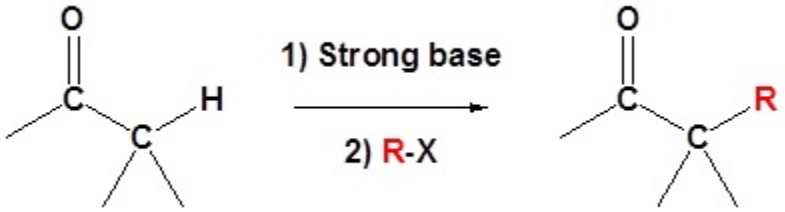
Contributors

- Prof. Steven Farmer (Sonoma State University)

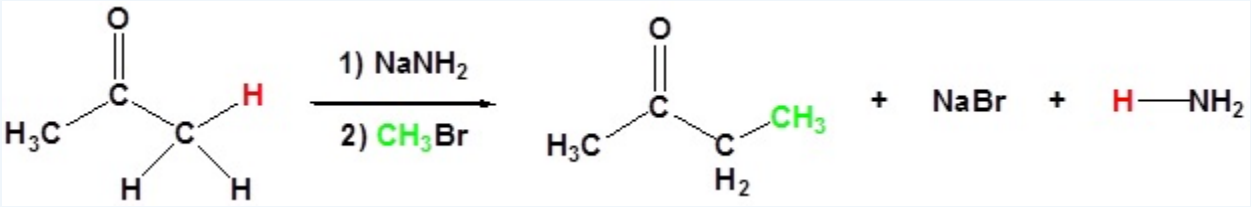
This page titled 18.3: Halogenation of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

18.4: Alkylation of Aldehydes and Ketones

Enolates can act as a nucleophile in S_N2 type reactions. Overall an α hydrogen is replaced with an alkyl group. This reaction is one of the more important for enolates because a carbon-carbon bond is formed. These alkylations are affected by the same limitations as S_N2 reactions previously discussed. A good leaving group, Chloride, Bromide, Iodide, Tosylate, should be used. Also, secondary and tertiary leaving groups should not be used because of poor reactivity and possible competition with elimination reactions. Lastly, it is important to use a strong base, such as LDA or sodium amide, for this reaction. Using a weaker base such as hydroxide or an alkoxide leaves the possibility of multiple alkylation's occurring.

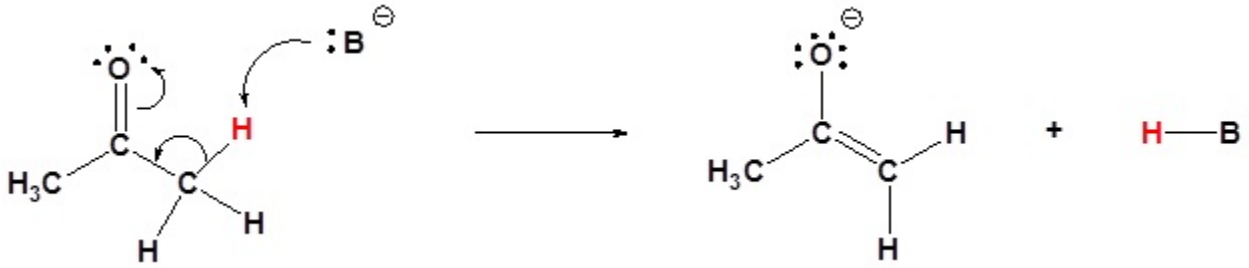


Example 1: Alpha Alkylation

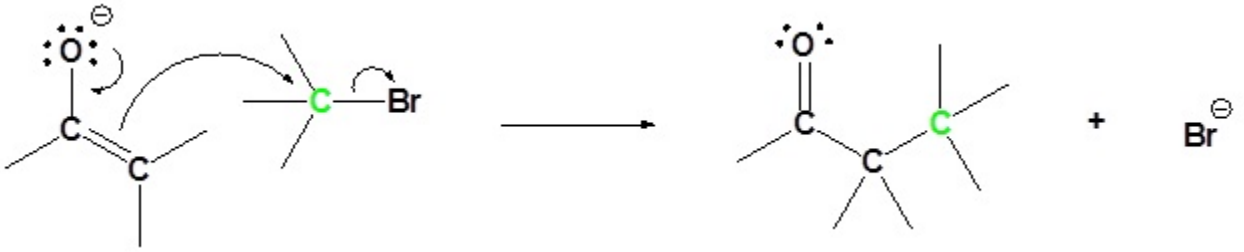


Mechanism

1) Enolate formation



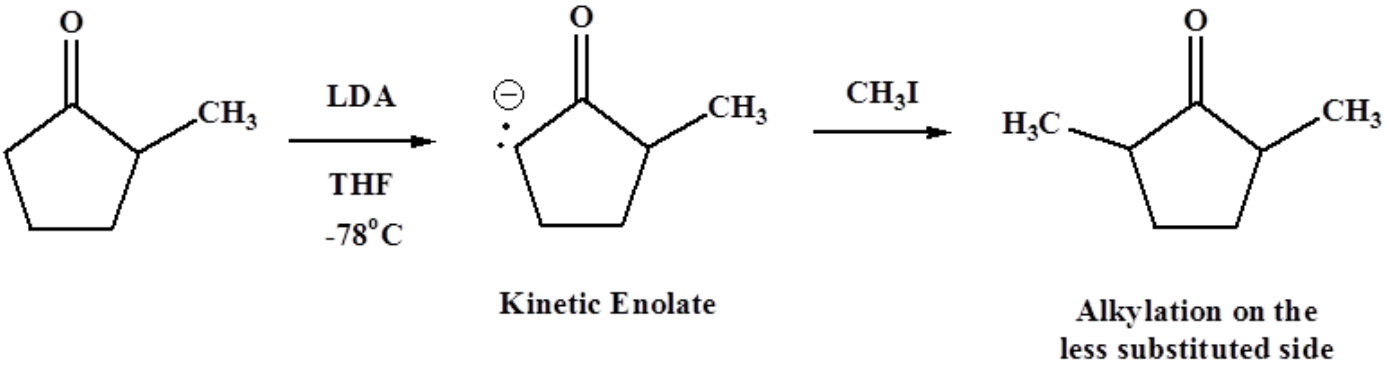
2) S_n2 attack



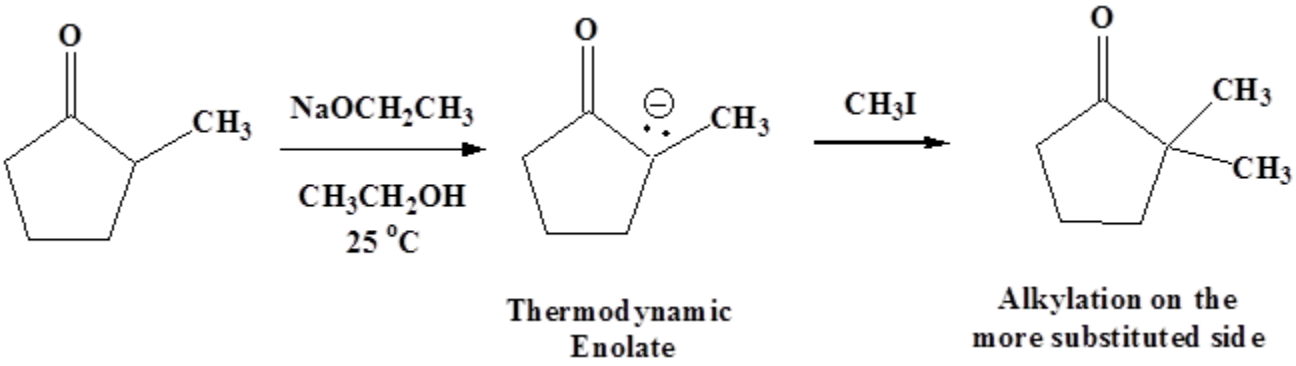
Alkylation of Unsymmetrical Ketones

Unsymmetrical ketones can be regioselctively alkylated to form one major product depending on the reagents.

Treatment with LDA in THF at -78°C tends to form the less substituted kinetic enolate.

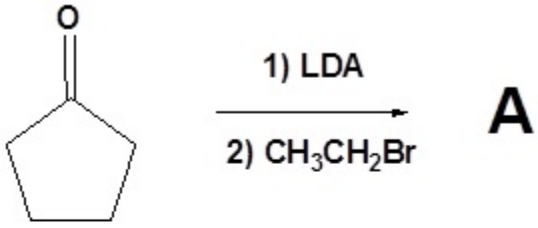


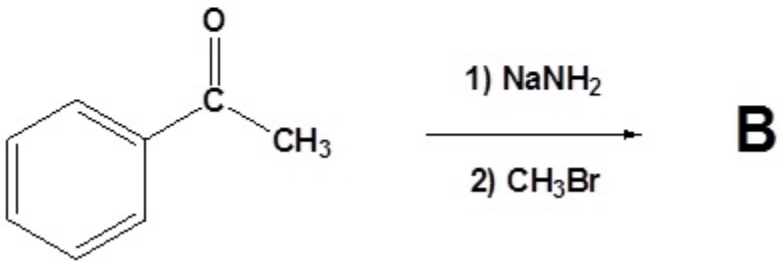
Using sodium ethoxide in ethanol at room temperature forms the more substituted thermodynamic enolate.



Problems

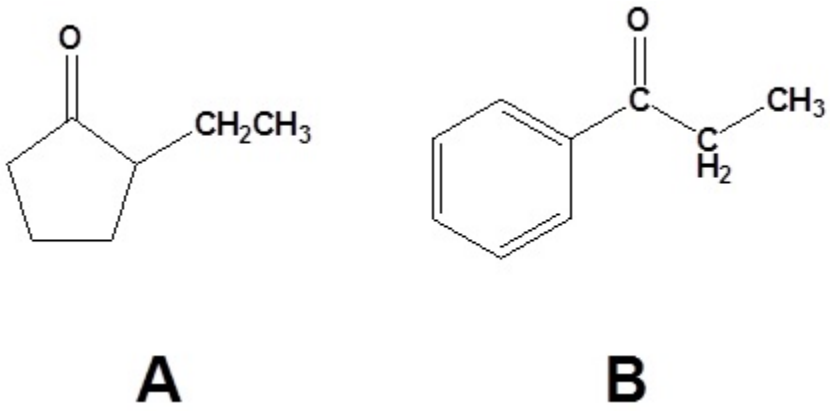
1) Please write the structure of the product for the following reactions.





Answers

1)



A B

Contributors

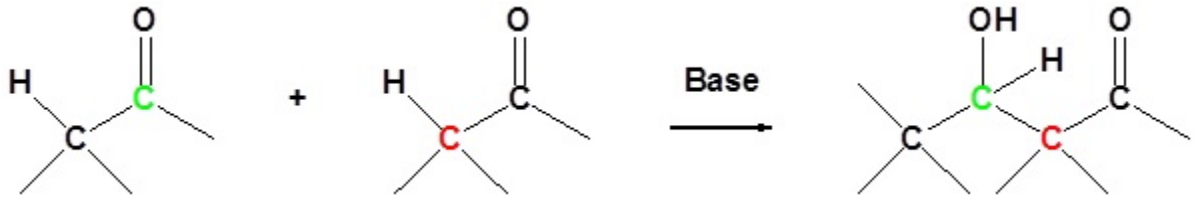
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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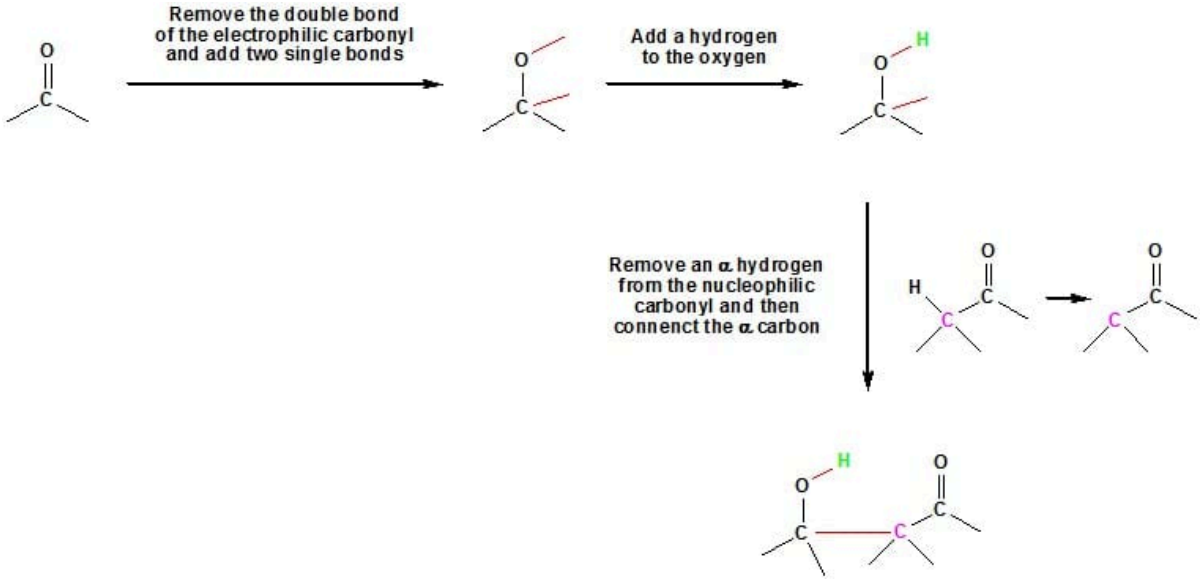
18.5: Attack by Enolates on the Carbonyl Function: Aldol Condensation

A useful carbon-carbon bond-forming reaction known as the **Aldol Reaction** is yet another example of electrophilic substitution at the alpha carbon in enolate anions. The fundamental transformation in this reaction is a dimerization of an aldehyde (or ketone) to a beta-hydroxy aldehyde (or ketone) by alpha C–H addition of one reactant molecule to the carbonyl group of a second reactant molecule. Due to the carbanion like nature of enolates they can add to carbonyls in a similar manner as Grignard reagents. For this reaction to occur at least one of the reactants must have α hydrogens.

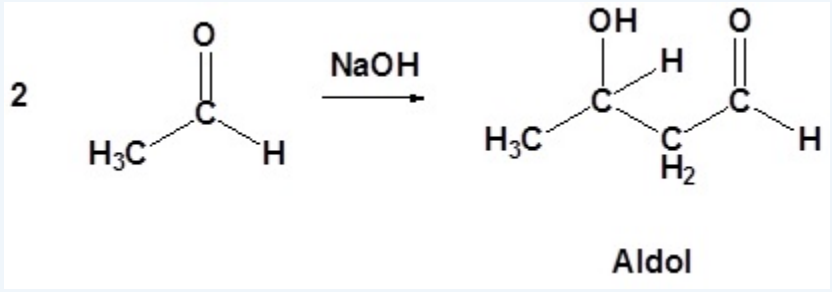
General Aldol reaction

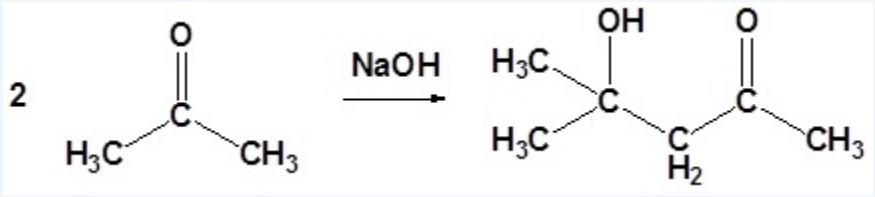


Going from reactants to products simply



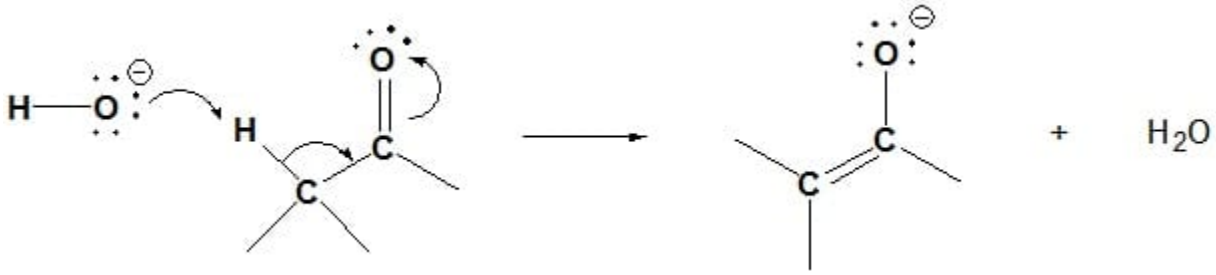
Example 1: Aldol Reactions



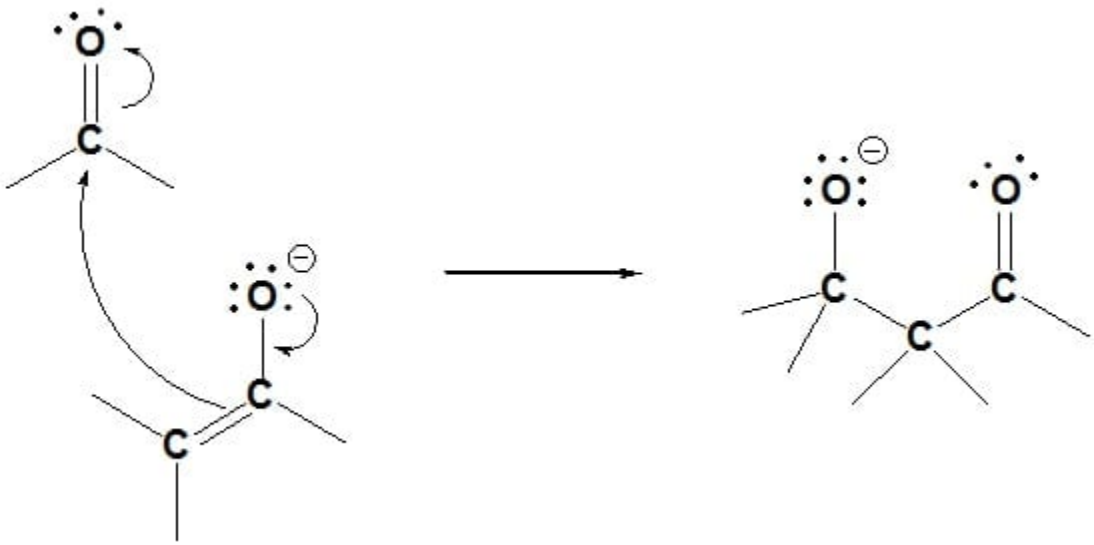


Aldol Reaction Mechanism

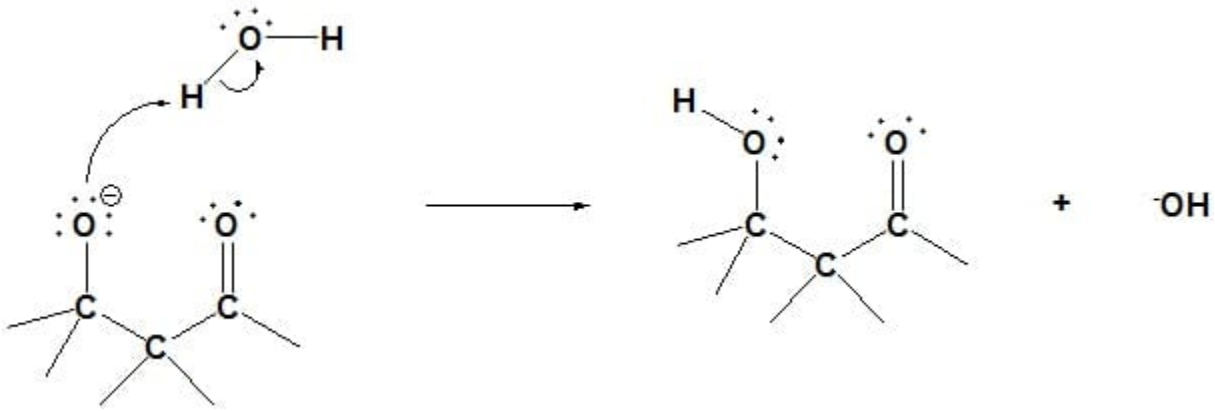
Step 1: Enolate formation



Step 2: Nucleophilic attack by the enolate



Step 3: Protonation



Aldol Condensation: the dehydration of Aldol products to synthesize α, β unsaturated carbonyl (enones)

The products of aldol reactions often undergo a subsequent elimination of water, made up of an alpha-hydrogen and the beta-hydroxyl group. The product of this β**-elimination** reaction is an α,β-unsaturated aldehyde or ketone. Base-catalyzed elimination occurs with heating. The additional stability provided by the conjugated carbonyl system of the product makes some aldol reactions thermodynamically and mixtures of stereoisomers (E & Z) are obtained from some reactions. Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water, are termed **Condensations**. Hence, the following examples are properly referred to as **aldol condensations**. Overall the general reaction involves a dehydration of an aldol product to form an alkene:

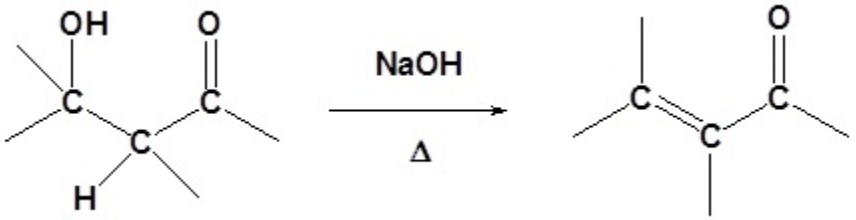


***Figure**: General reaction for an aldol condensation*

Going from reactants to products simply

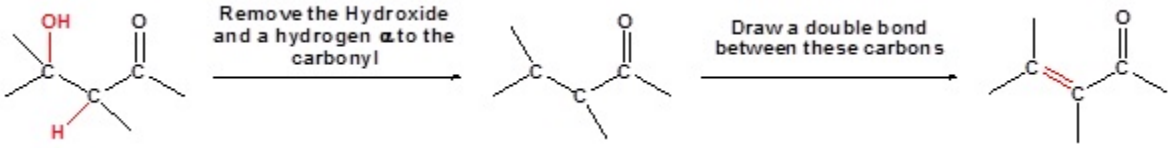
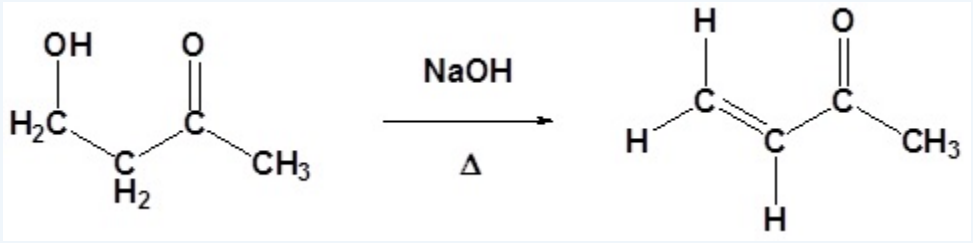


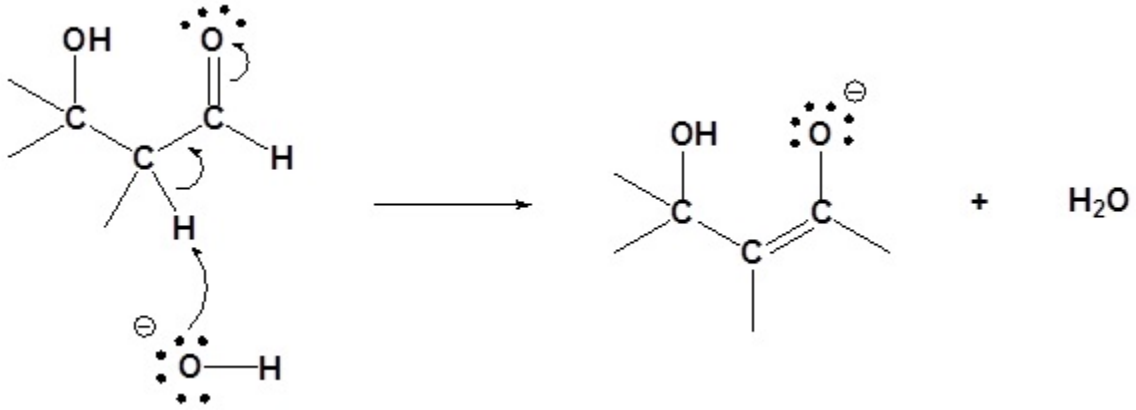
***Figure**: The aldol condensatio* example

Example 2: Aldol Condensation

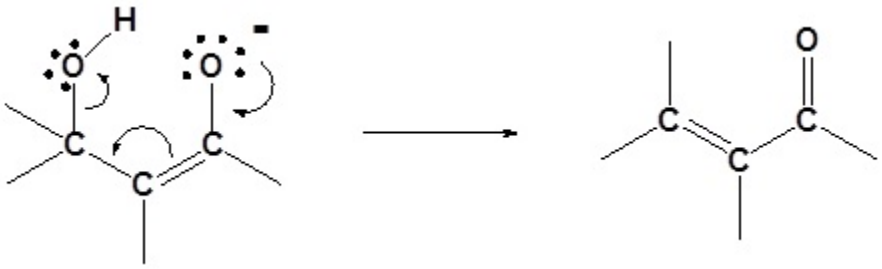


Aldol Condensation Mechanism

1) Form enolate

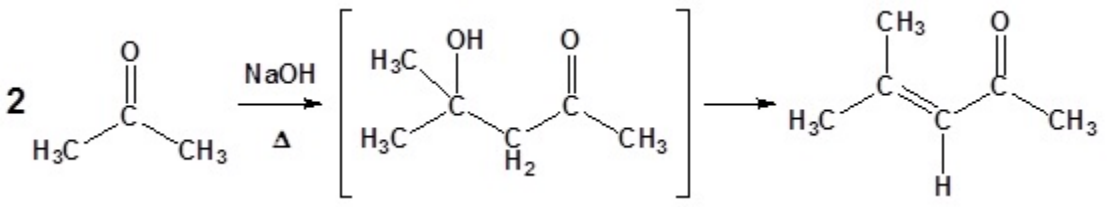


2) Form enone



When performing both reactions together always consider the aldol product first then convert to the enone. Note! The double bond always forms in conjugation with the carbonyl.

Example



Contributors

- Prof. Steven Farmer (Sonoma State University)

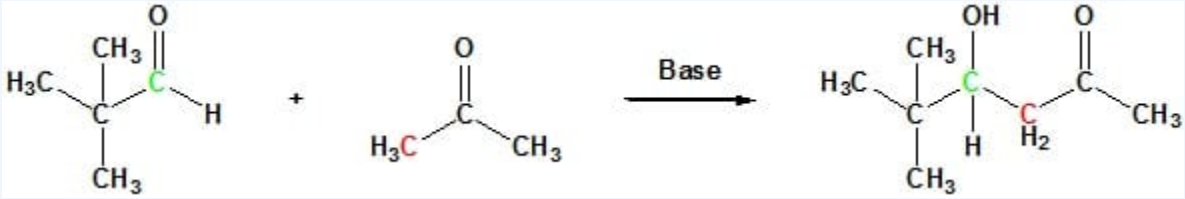
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18.6: Crossed Aldol Condensation

Mixed Aldol Reaction and Condensations

The previous examples of aldol reactions and condensations used a common reactant as both the enolic donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called **crossed** or **mixed** reactions, and under certain conditions such crossed aldol condensations can be effective.

Example 3: Mixed Aldol Reaction



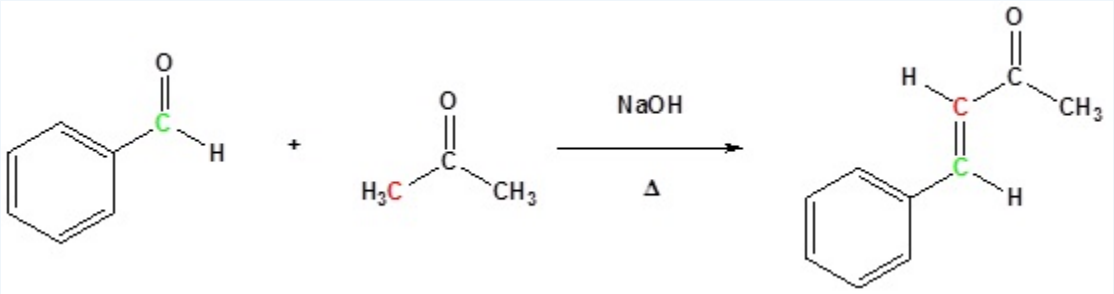
The success of these mixed aldol reactions is due to two factors. First, aldehydes are more reactive acceptor electrophiles than ketones, and formaldehyde is more reactive than other aldehydes. Second, aldehydes lacking alpha-hydrogens can only function as acceptor reactants, and this reduces the number of possible products by half. Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this most mixed aldol reactions are usually not performed unless one reactant has no alpha hydrogens.

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.

$$\mathbf{A}\mathbf{A}CH_2CHO + \mathbf{B}CH_2CHO + NaOH \rightarrow A\text{–}A + B\text{–}B + A\text{–}B + B\text{–}A$$

The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the **Claisen-Schmidt** reaction.

Example 4: Claisen-Schmidt Reaction



Contributors

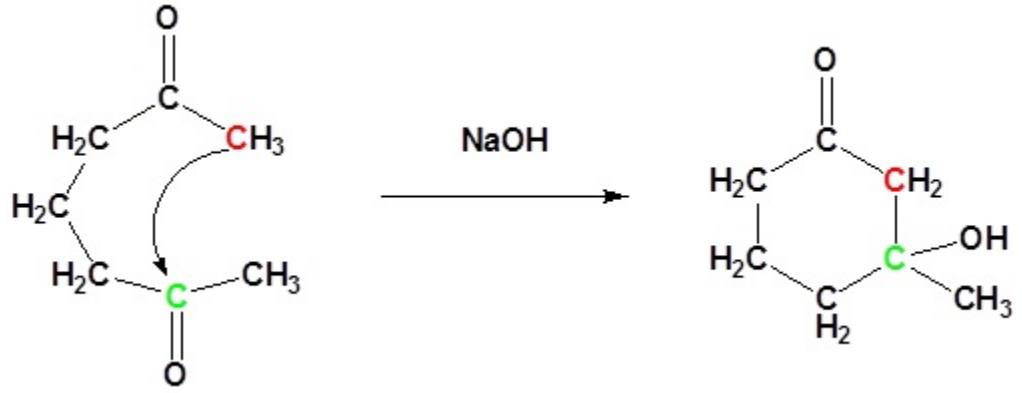
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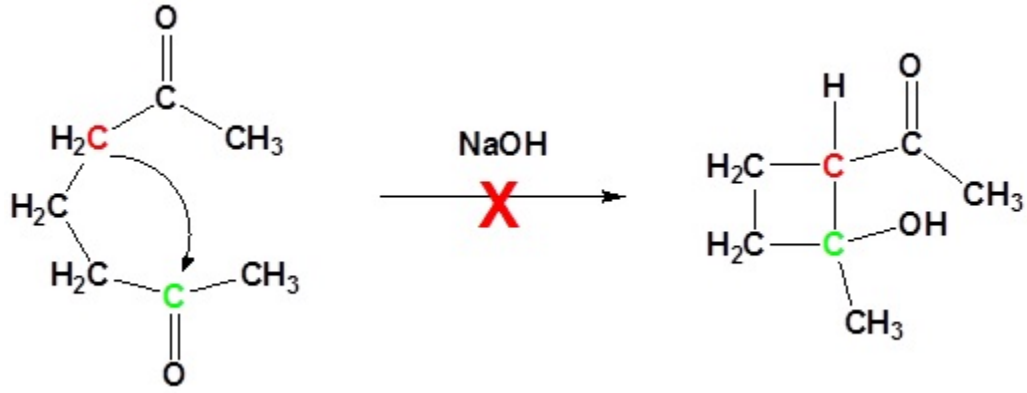
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18.7: Keys to Success: Competitive Rection Pathways and the Intramolecular Aldol Condensation

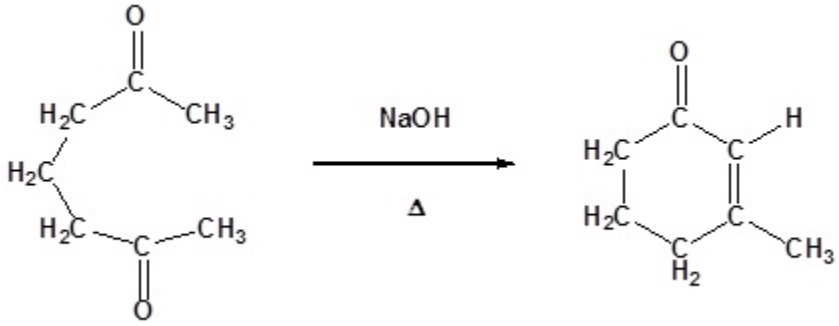
Intramolecular aldol reaction

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. In most cases two sets of α hydrogens need to be considered. As with most ring forming reaction five and six membered rings are preferred.





As with other aldol reaction the addition of heat causes an aldol condensation to occur.



Contributors

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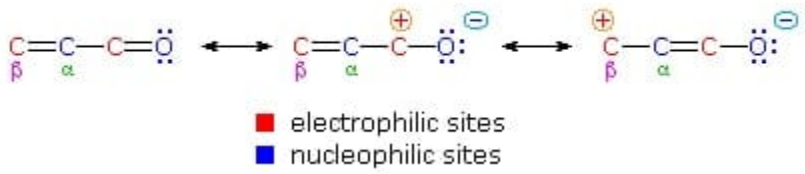
18.8: Properties of a,b-Unsaturated Aldehydes and Ketones

23.10 Conjugate Carbonyl Additions: The Michael Reaction

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18.9: Conjugate Additions to a,b-Unsaturated Aldehydes and Ketones

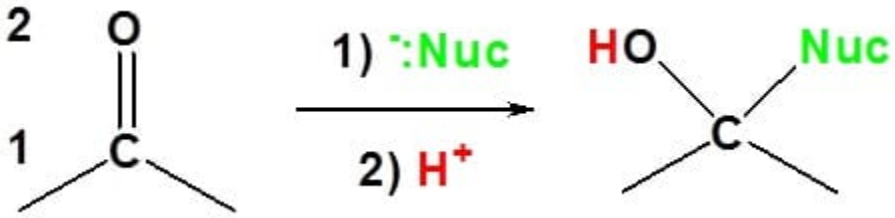
One of the largest and most diverse classes of reactions is composed of nucleophilic additions to a carbonyl group. Conjugation of a double bond to a carbonyl group transmits the electrophilic character of the carbonyl carbon to the beta-carbon of the double bond. These conjugated carbonyl are called enones or α, β unsaturated carbonyls. A resonance description of this transmission is shown below.



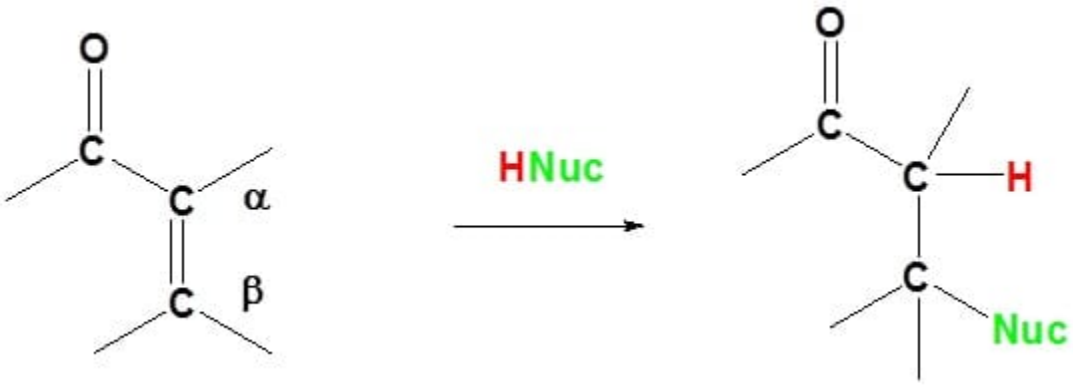
From this formula it should be clear that nucleophiles may attack either at the carbonyl carbon, as for any aldehyde, ketone or carboxylic acid derivative, or at the beta-carbon. These two modes of reaction are referred to as 1,2-addition and 1,4-addition respectively. A 1,4-addition is also called a conjugate addition.

Basic reaction of 1,2 addition

Here the nucleophile adds to the carbon which is in the one position. The hydrogen adds to the oxygen which is in the two position.



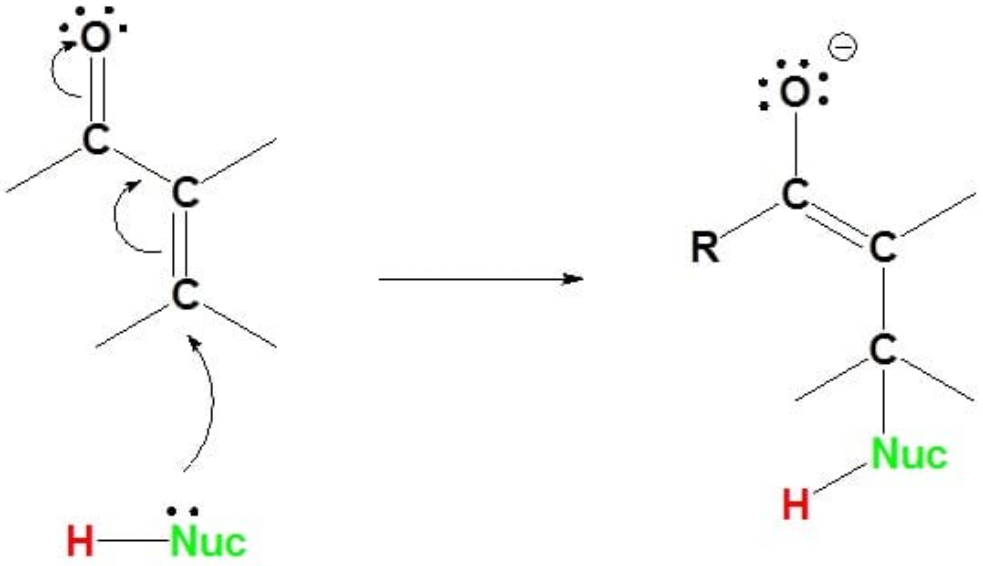
Basic reaction of 1,4 addition



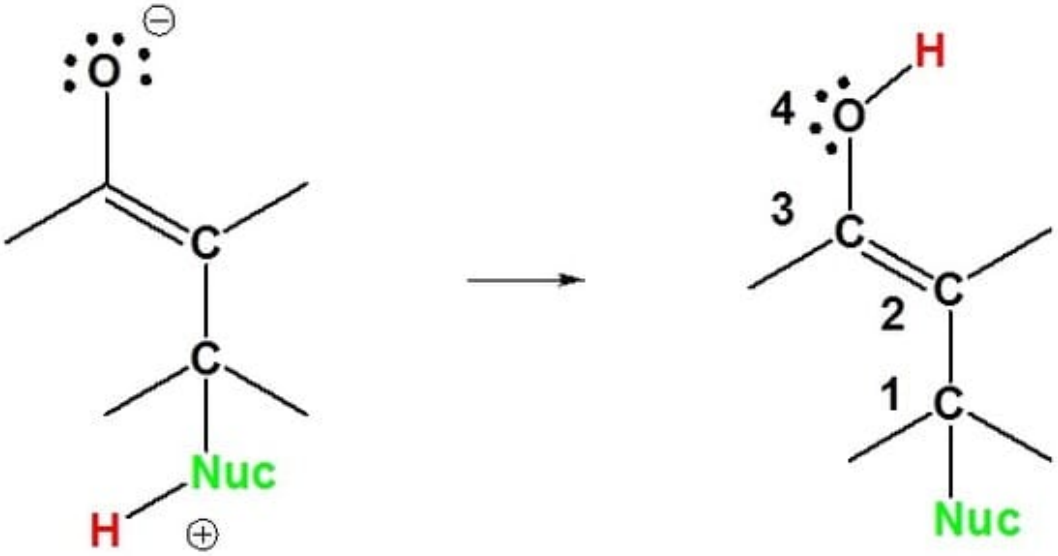
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

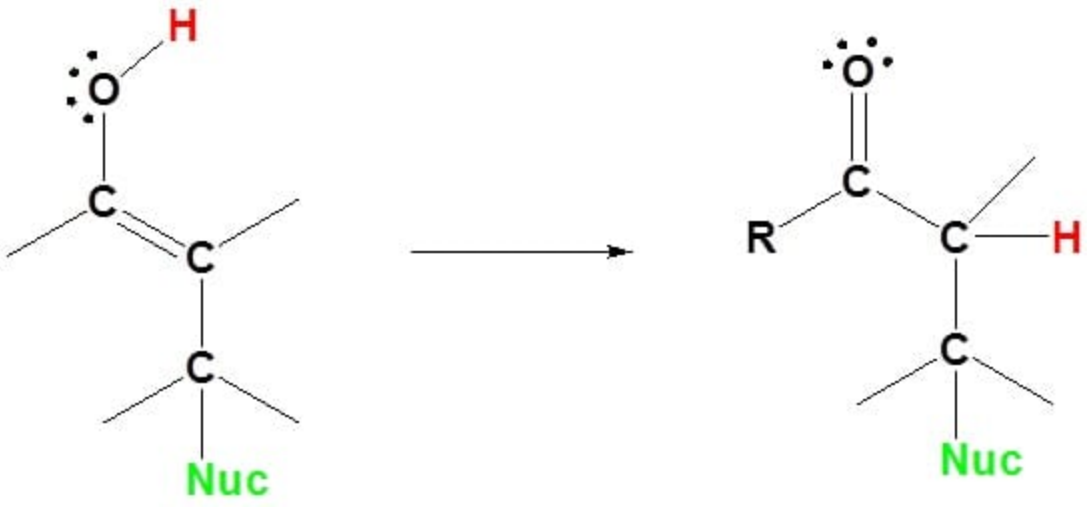


2) Proton Transfer

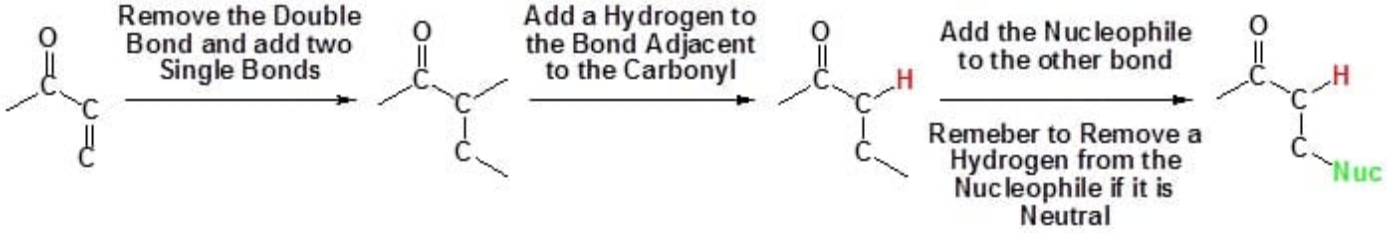


Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Going from reactant to products simplified



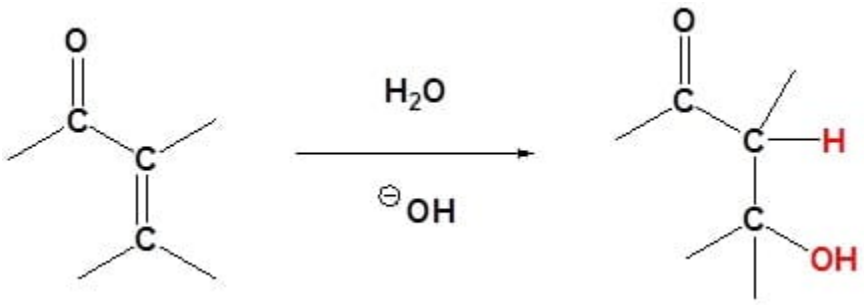
1,2 vs. 1,4 addition

Whether 1,2 or 1,4-addition occurs depends on multiple variables but mostly it is determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions.

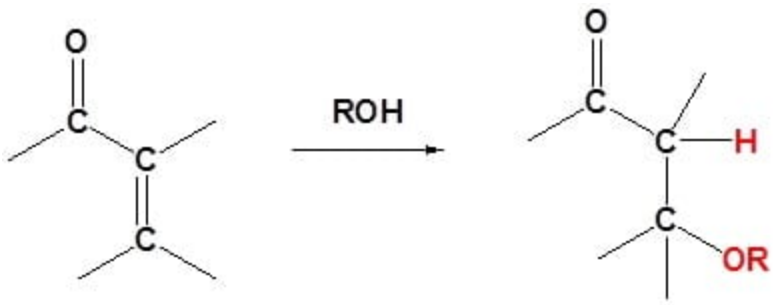
If the nucleophile is a weak base, such as alcohols or amines, then the 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this case 1,4-addition dominates because the stable carbonyl group is retained.

Nucleophiles which add 1,4 to α, β unsaturated carbonyls

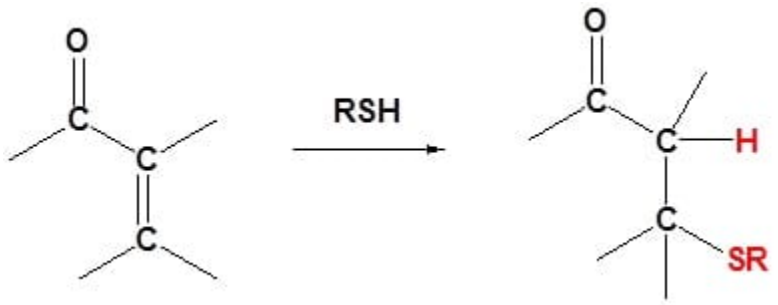
Water



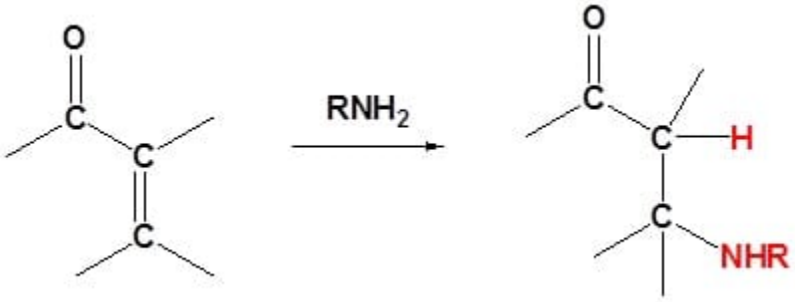
Alcohols



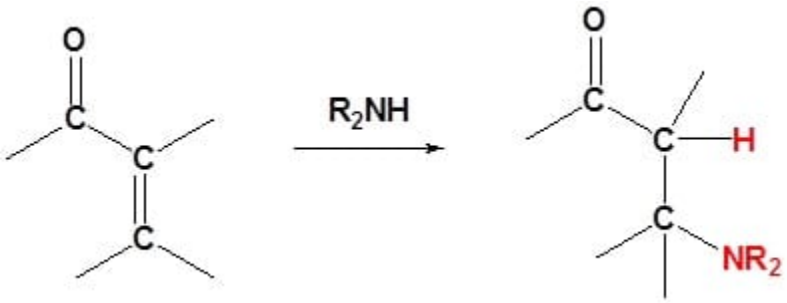
Thiols



1^{o} Amines



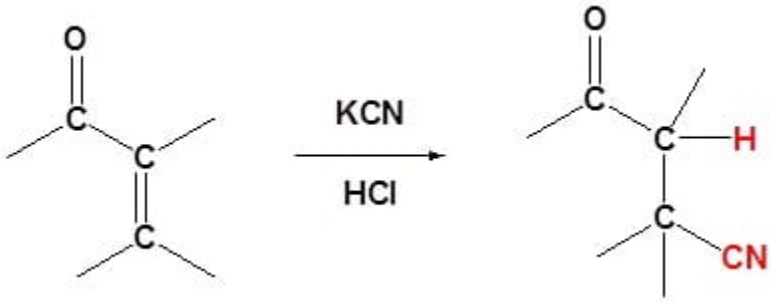
2^{o} Amines



HBr



Cyanides



Gilman Reagents

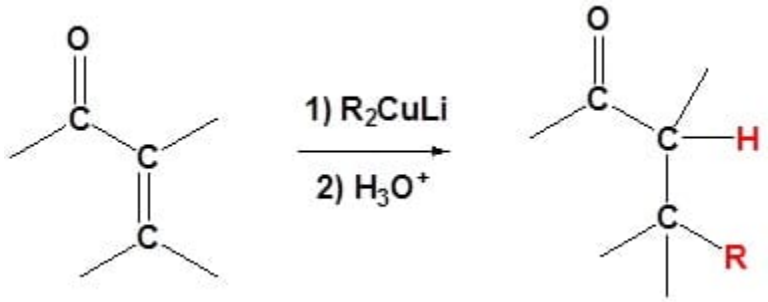
Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a lithium dimethylcopper reagent, which is referred to as a Gilman reagent. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organo lithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference will be exploited in different situations. In the case of α, β unsaturated carbonyls organocuprate reagents allow for an 1,4 addition of an alkyl group. As we will see later Grignard and Organolithium reagents add alkyl groups 1,2 to α, β unsaturated carbonyls

Organocuprate reagents are made from the reaction of organolithium reagents and CuI

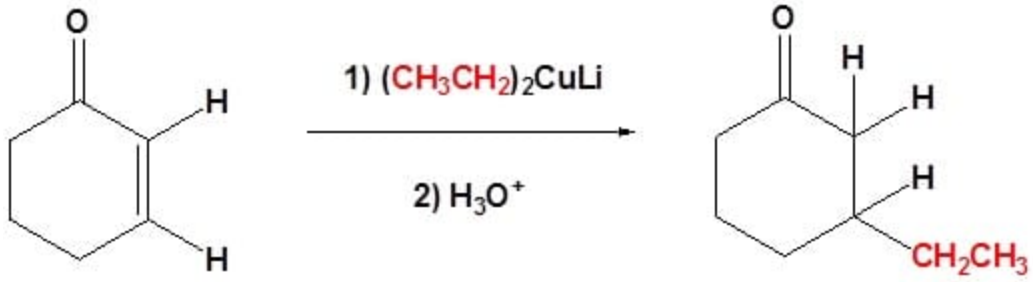
$$2RLi + CuI \rightarrow R_2CuLi + LiI \tag{18.9.1}$$

This acts as a source of R:$^-$

$$2CH_3Li + CuI \rightarrow (CH_3)_2CuLi + LiI \tag{18.9.2}$$

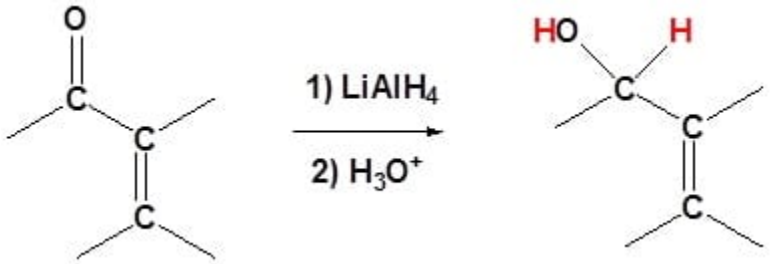


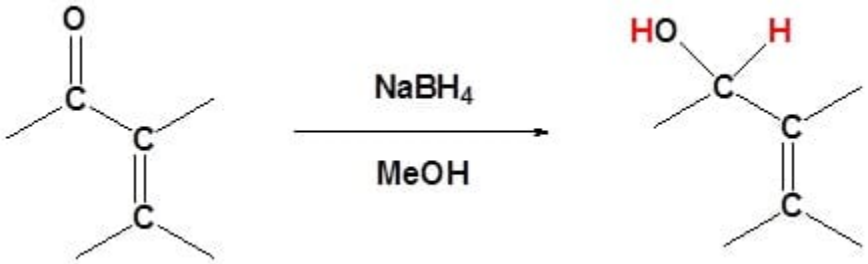
Example



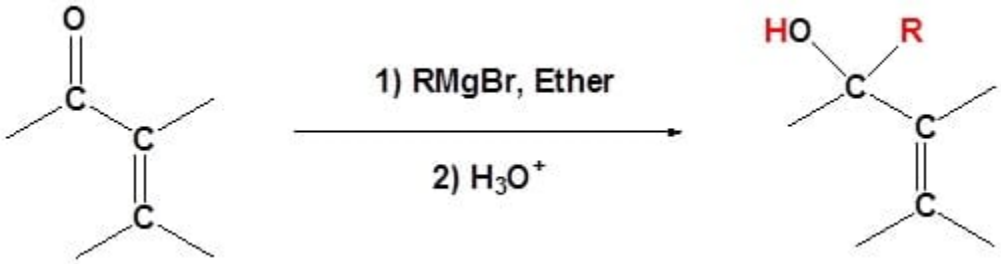
Nucleophiles which add 1,2 to α, β unsaturated carbonyls

Metal Hydrides

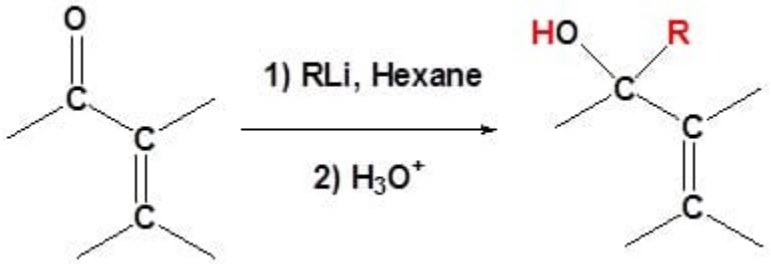




Grignard Reagents



Organolithium Reagents



Contributors

Prof. Steven Farmer (Sonoma State University)

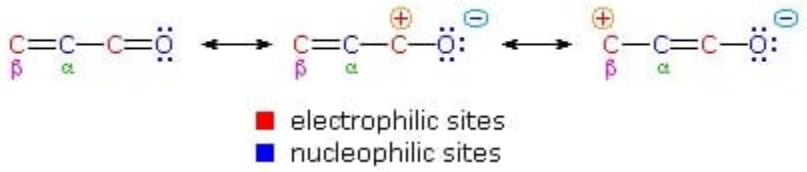
William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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18.10: 1,2- and 1,4-Additions of Organometallic Reagents

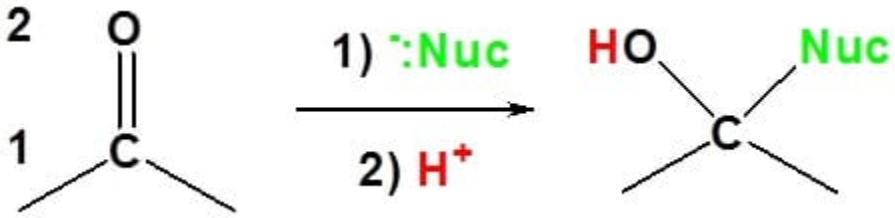
One of the largest and most diverse classes of reactions is composed of nucleophilic additions to a carbonyl group. Conjugation of a double bond to a carbonyl group transmits the electrophilic character of the carbonyl carbon to the beta-carbon of the double bond. These conjugated carbonyl are called enones or α, β unsaturated carbonyls. A resonance description of this transmission is shown below.



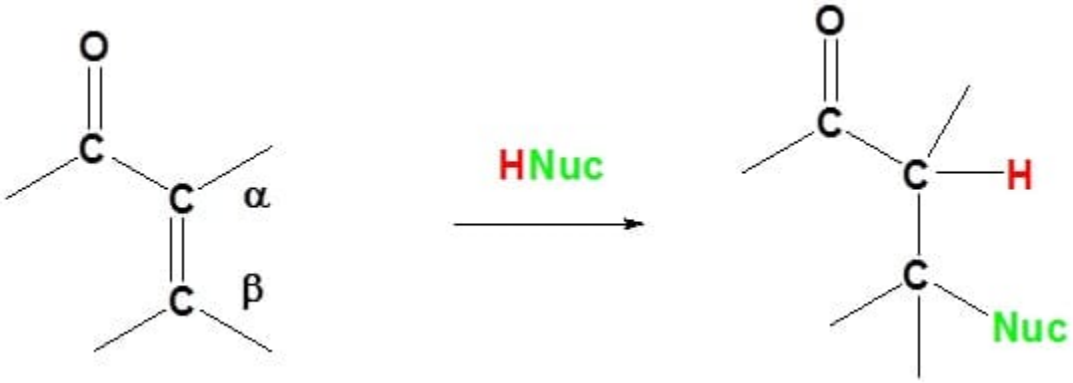
From this formula it should be clear that nucleophiles may attack either at the carbonyl carbon, as for any aldehyde, ketone or carboxylic acid derivative, or at the beta-carbon. These two modes of reaction are referred to as 1,2-addition and 1,4-addition respectively. A 1,4-addition is also called a conjugate addition.

Basic reaction of 1,2 addition

Here the nucleophile adds to the carbon which is in the one position. The hydrogen adds to the oxygen which is in the two position.



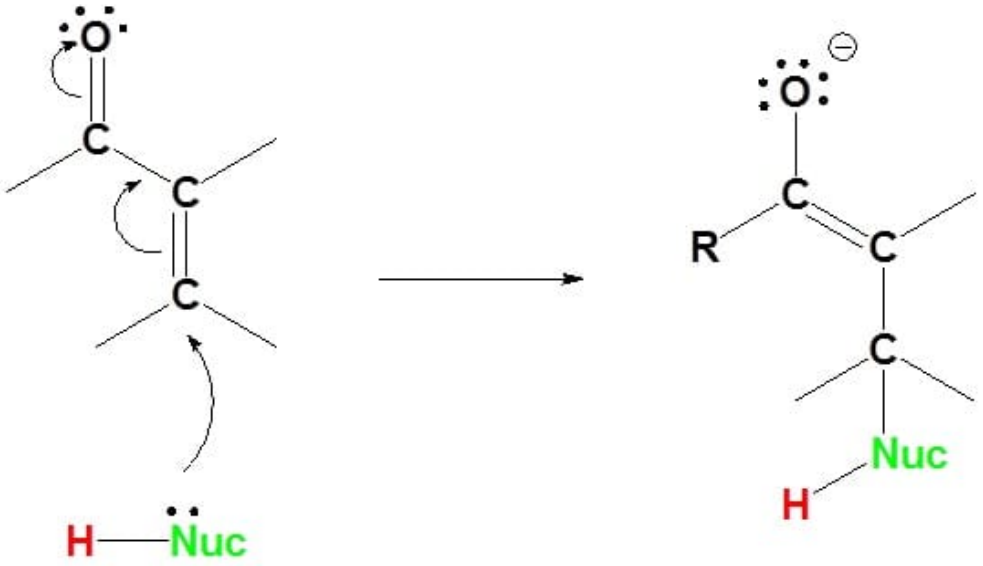
Basic reaction of 1,4 addition



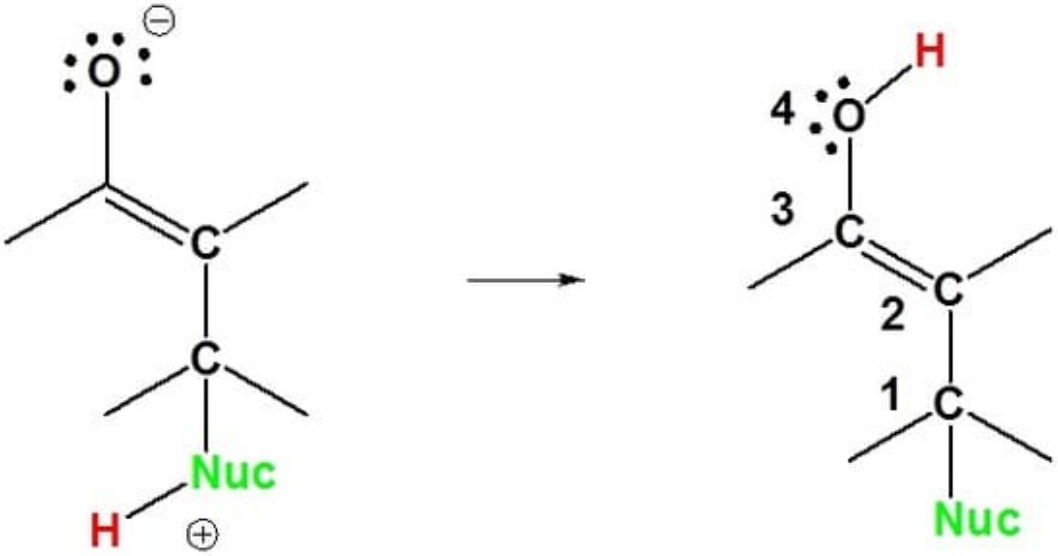
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

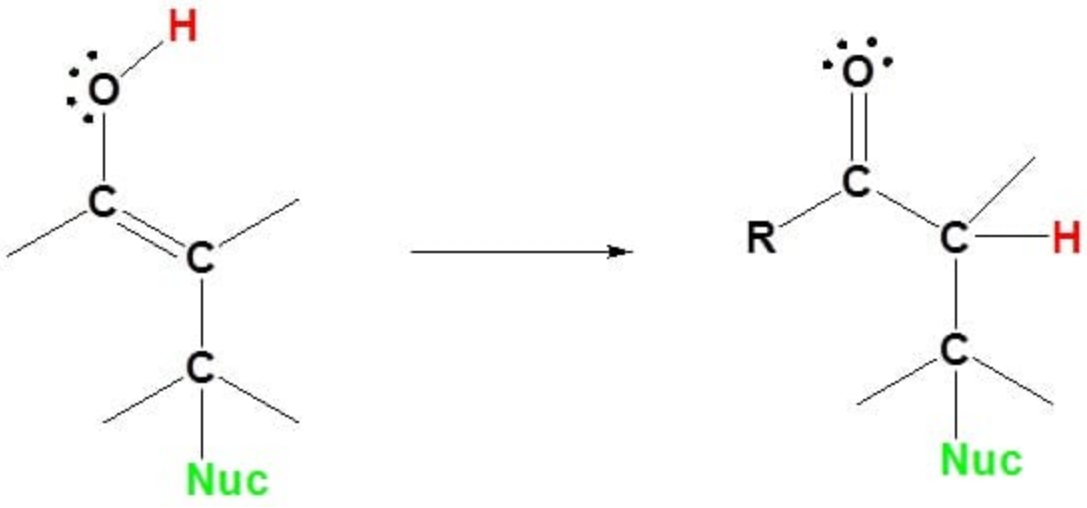


2) Proton Transfer

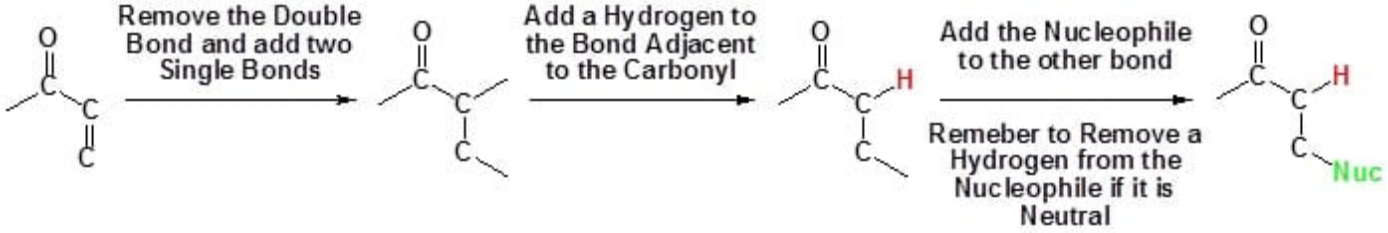


Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Going from reactant to products simplified



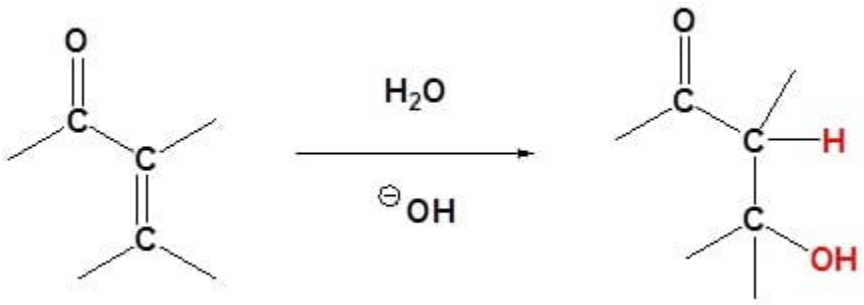
1,2 vs. 1,4 addition

Whether 1,2 or 1,4-addition occurs depends on multiple variables but mostly it is determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions.

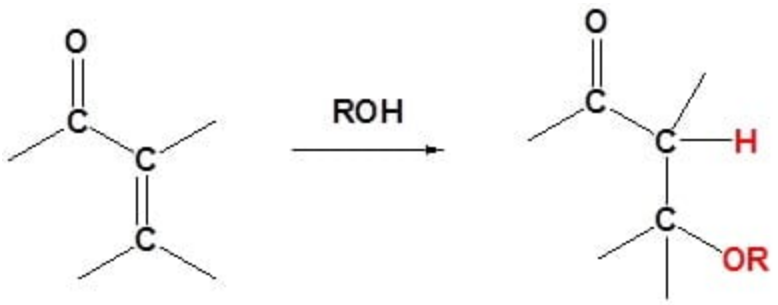
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Nucleophiles which add 1,4 to α, β unsaturated carbonyls

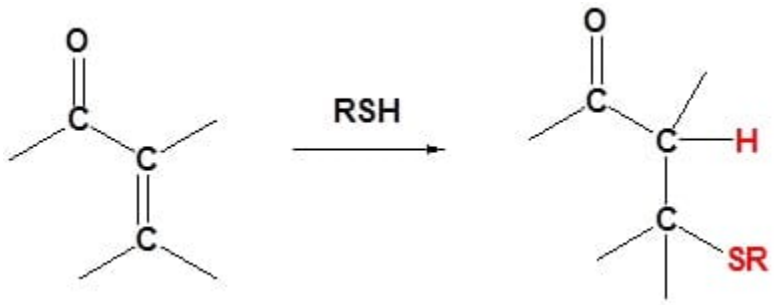
Water



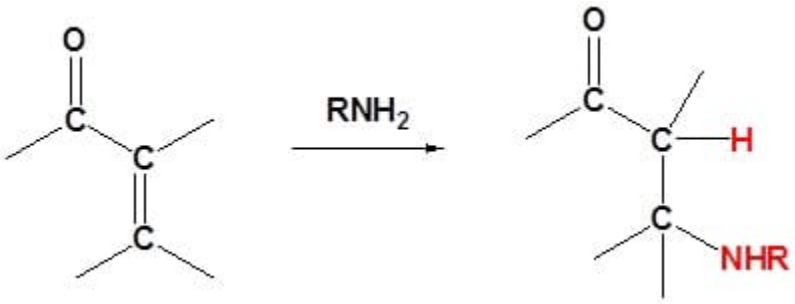
Alcohols



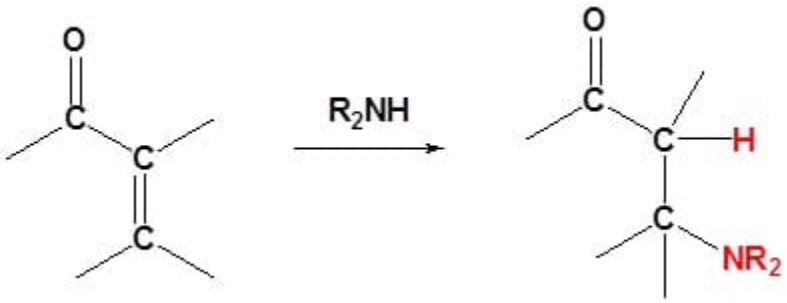
Thiols



1^{o} Amines



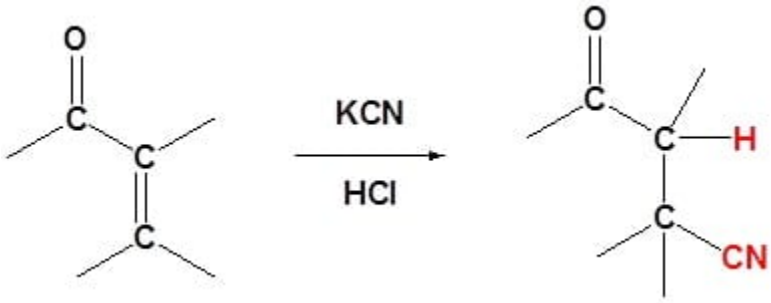
2^{o} Amines



HBr



Cyanides



Gilman Reagents

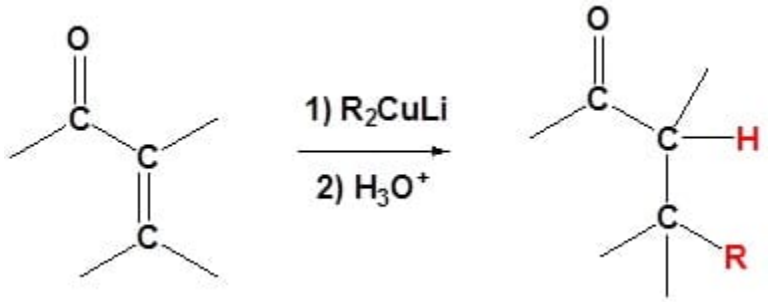
Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a lithium dimethylcopper reagent, which is referred to as a Gilman reagent. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organo lithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference will be exploited in different situations. In the case of α, β unsaturated carbonyls organocuprate reagents allow for an 1,4 addition of an alkyl group. As we will see later Grignard and Organolithium reagents add alkyl groups 1,2 to α, β unsaturated carbonyls

Organocuprate reagents are made from the reaction of organolithium reagents and CuI

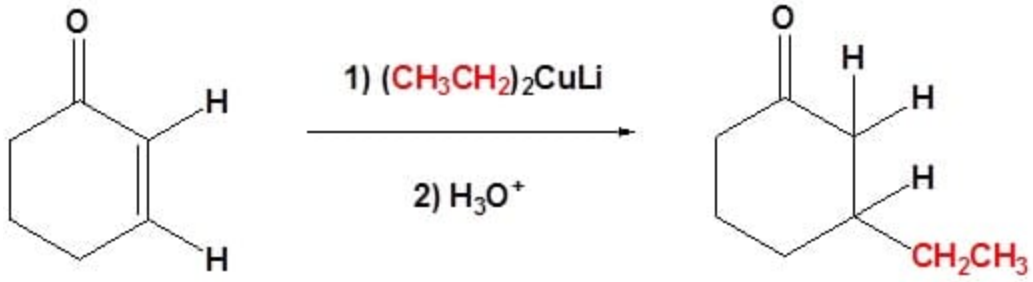
$$2RLi + CuI \rightarrow R_2CuLi + LiI \tag{18.10.1}$$

This acts as a source of R:$^-$

$$2CH_3Li + CuI \rightarrow (CH_3)_2CuLi + LiI \tag{18.10.2}$$

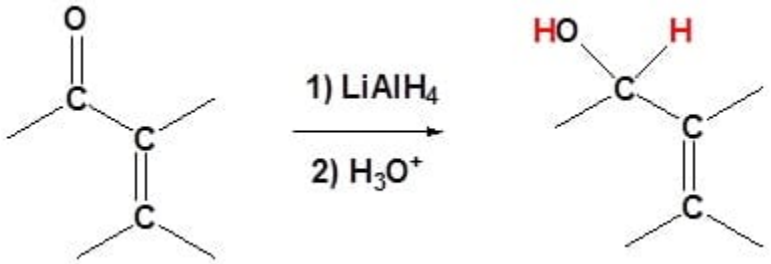


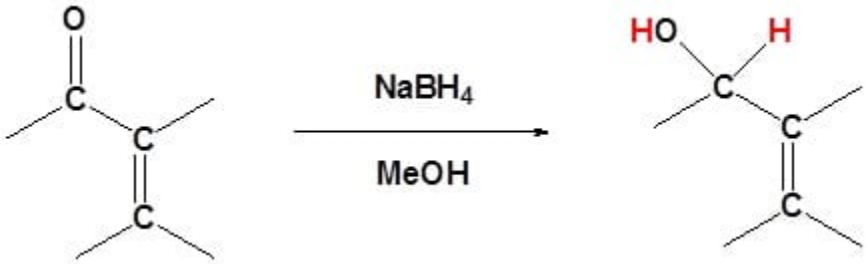
Example



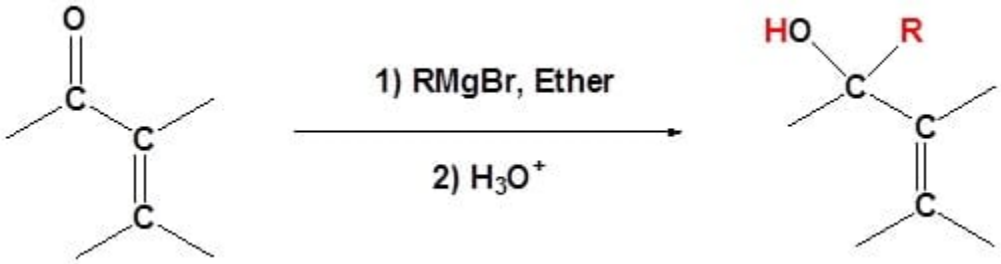
Nucleophiles which add 1,2 to α, β unsaturated carbonyls

Metal Hydrides

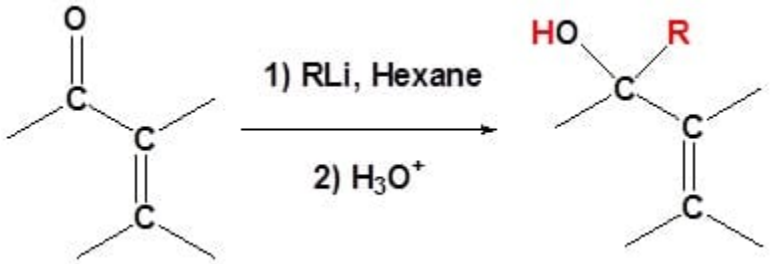




Grignard Reagents



Organolithium Reagents



Contributors

Prof. Steven Farmer (Sonoma State University)

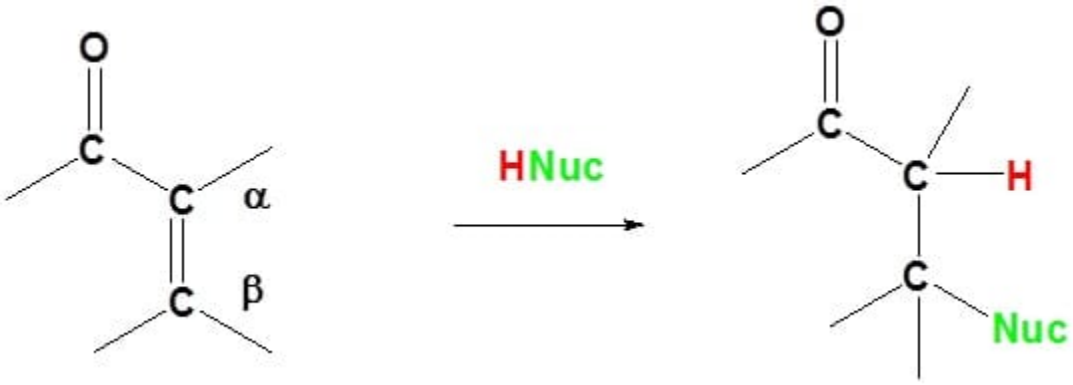
William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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18.11: Conjugate Additions of Enolate Ions: Michael Addition and Robinson Annulation

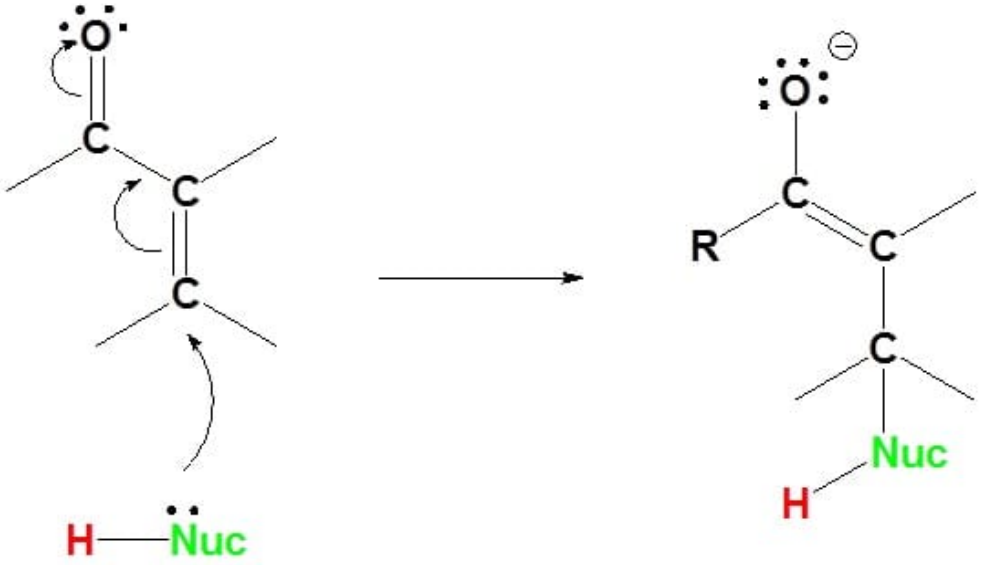
Basic reaction of 1,4 addition



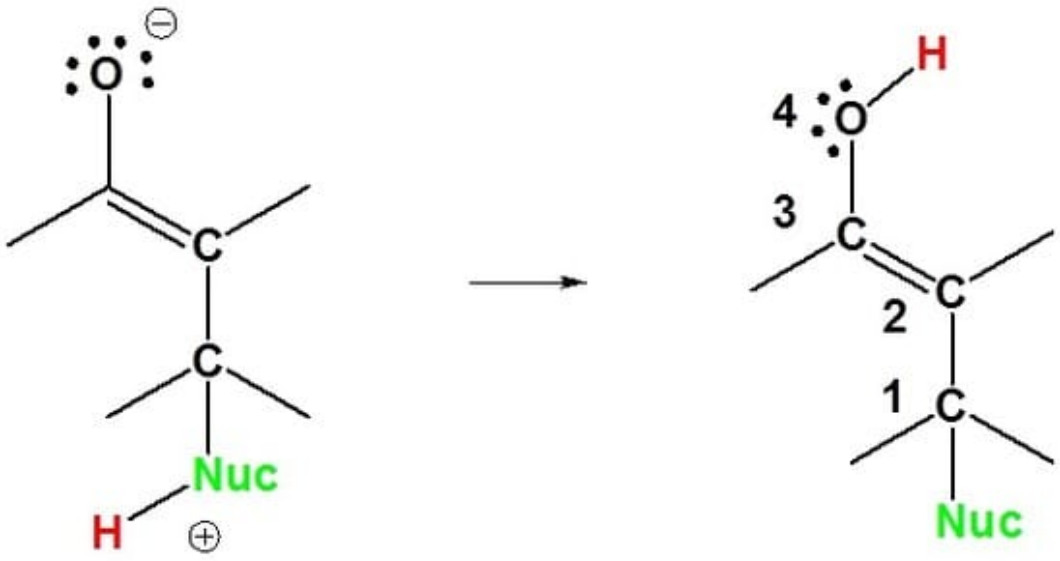
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

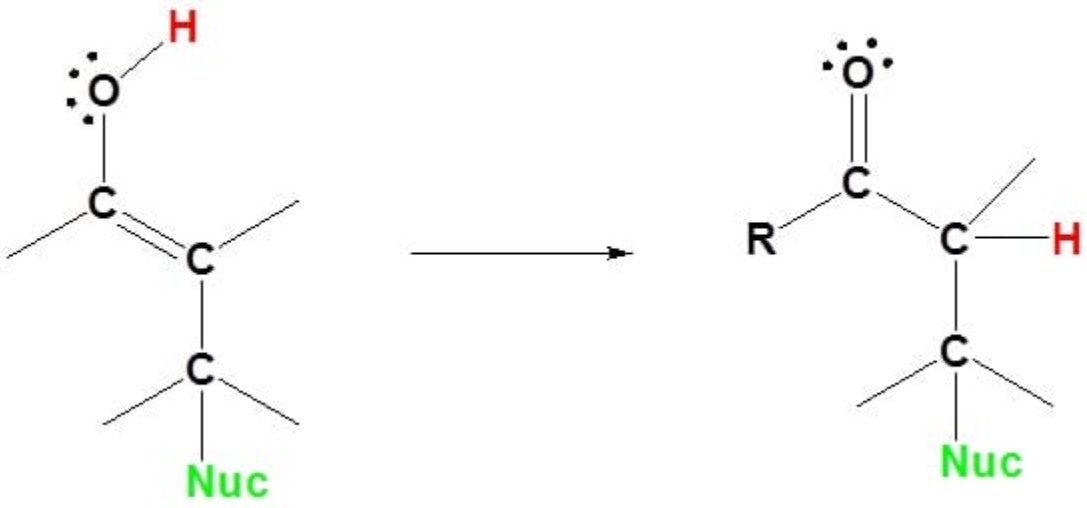


2) Proton Transfer



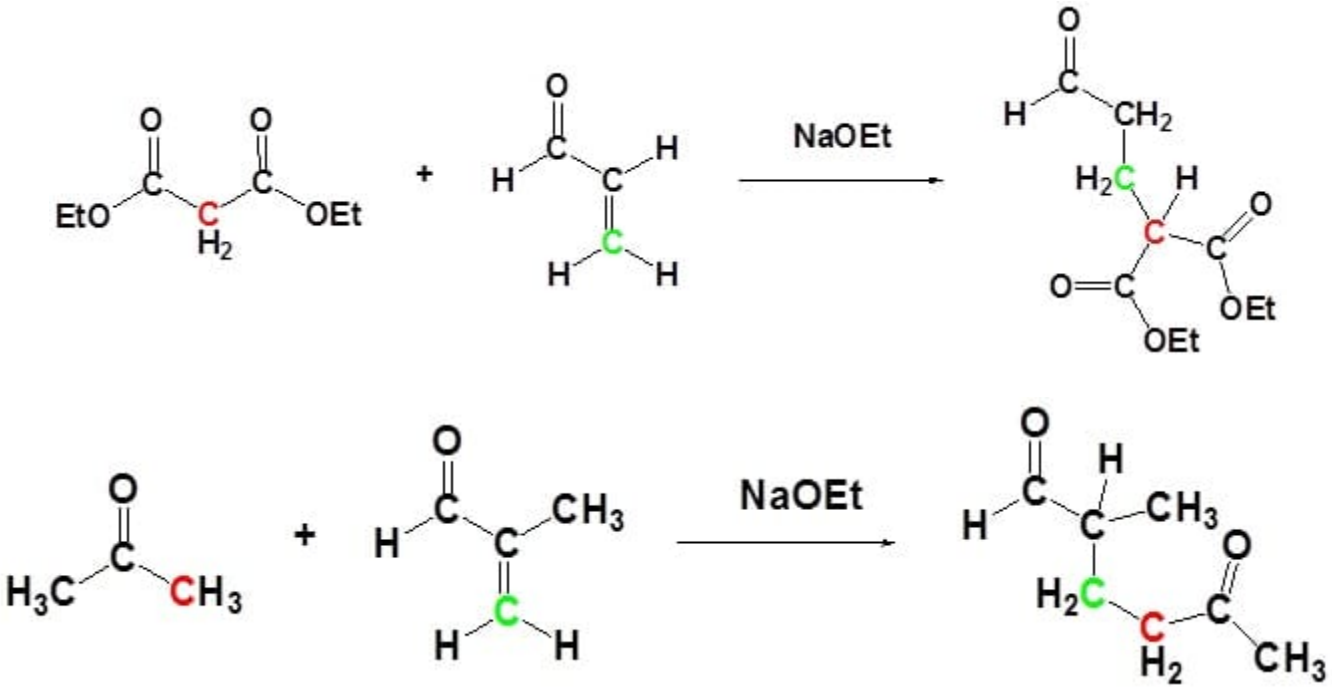
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds is a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942).

Examples of Michael Additions

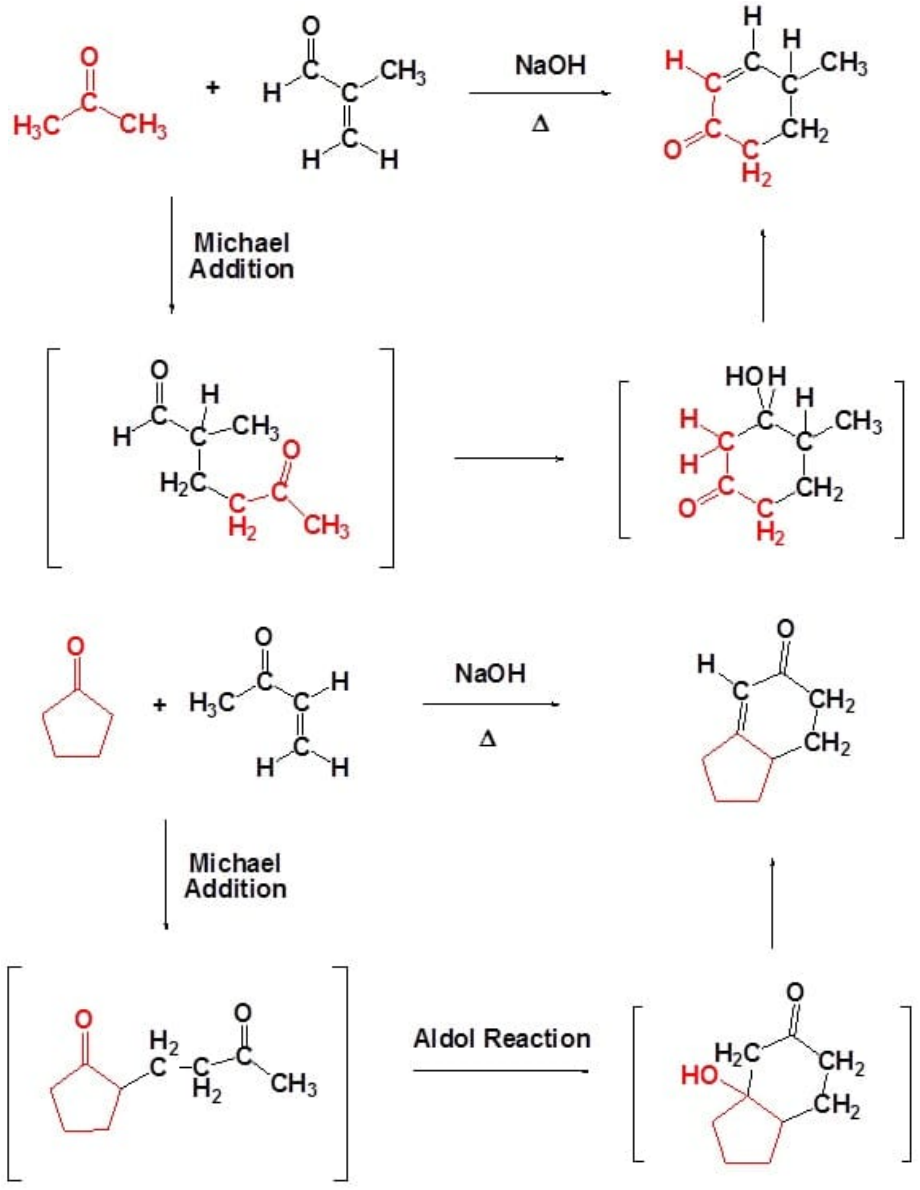


Contributors

- Prof. Steven Farmer (Sonoma State University)

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

Examples of Robinson Annulations



Contributors

- Prof. Steven Farmer (Sonoma State University)

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19: CARBOXYLIC ACIDS

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

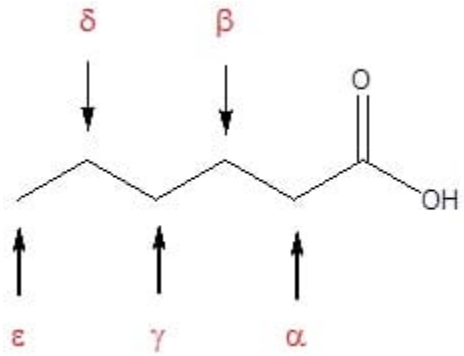
19.1: Naming the Carboxylic Acids
19.2: Structural and Physical Properties of Carboxylic Acids
19.3: Spectroscopy and Mass Spectrometry of Carboxylic Acids
19.4: Acidic and Basic Character of Carboxylic Acids
19.5: Carboxylic Acid Synthesis in Industry
19.6: Methods for Introducing the Carboxy Functional Group
19.7: Substitution at the Carboxy Carbon: The Addition-Elimination Mechanism
19.8: Carboxylic Acid Derivatives: Alkanoyl (Acyl) Halides and Anhydrides
19.9: Carboxylic Acid Derivatives: Esters
19.10: Carboxylic Acid Derivatives: Amides
19.11: Reduction of Carboxylic Acids by Lithium Aluminum Hydride
19.12: Bromination Next to the Carboxy Group: The Hell-Volhard-Zelinsky Reaction
19.13: Biological Activity of Carboxylic Acids

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19.1: Naming the Carboxylic Acids

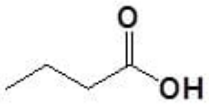
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-anoic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of aldehydes, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



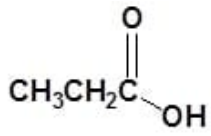
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 °C	101 °C
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 °C	118 °C
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 °C	141 °C
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 °C	164 °C
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 °C	186 °C
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 °C	205 °C
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 °C	223 °C
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 °C	239 °C
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 °C	253 °C
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 °C	219 °C

Example (Common Names Are in Red)



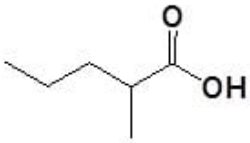
Butanoic acid

(Butyric Acid)



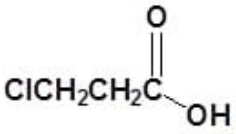
Propanoic acid

(Propionic Acid)



2-Methylpentanoic acid

(β-Methylvaleric acid)

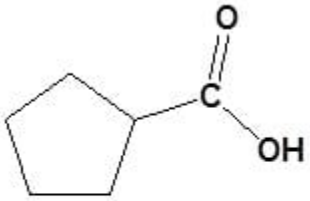


3-Chloropropanoic acid

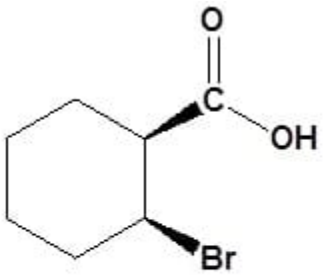
(γ-Chloropropionic acid)

Naming carboxyl groups added to a ring

When a carboxyl group is added to a ring the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.



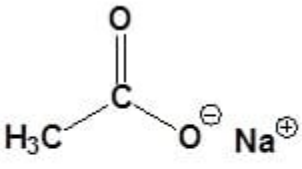
Cyclopentanecarboxylic acid



Cis-2-Bromocyclohexanecarboylic acid

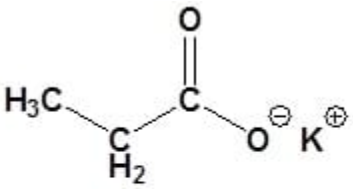
Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



Sodium ethanoate

(Sodium Acetate)

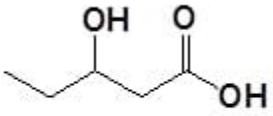


Potassium Propanoate

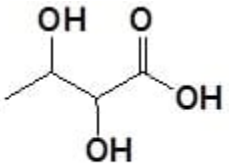
(Potassium propionate)

Naming carboxylic acids which contain other functional groups

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

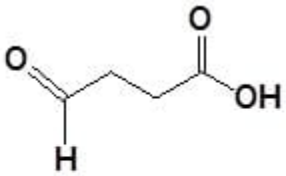


3-Hydroxypentanoic acid

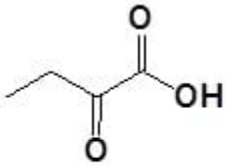


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups the carbonyl is named as a "Oxo" substituent.

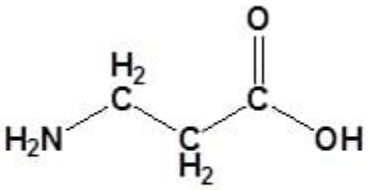


4-Oxobutanoic acid

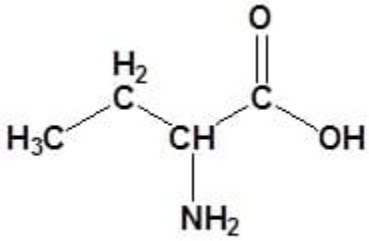


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group the amine is named as an "amino" substituent.



3-Aminopropanoic acid

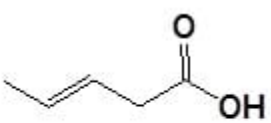


2-Aminobutanoic acid

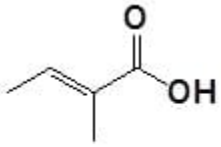
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.



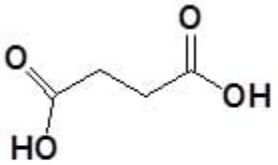
Trans-3-pentenoic acid



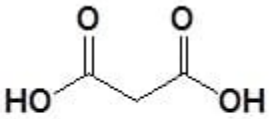
(E)-2-Methyl-2-butenoic acid

Naming dicarboxylic acids

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain.



Butanedioic acid



Propanedioic acid

Contributors

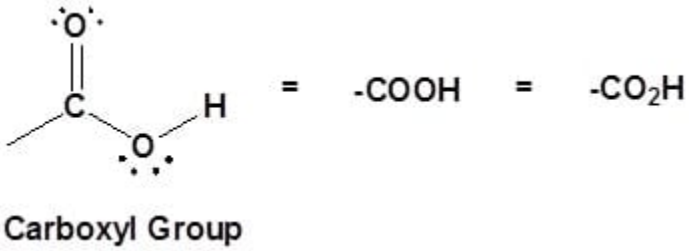
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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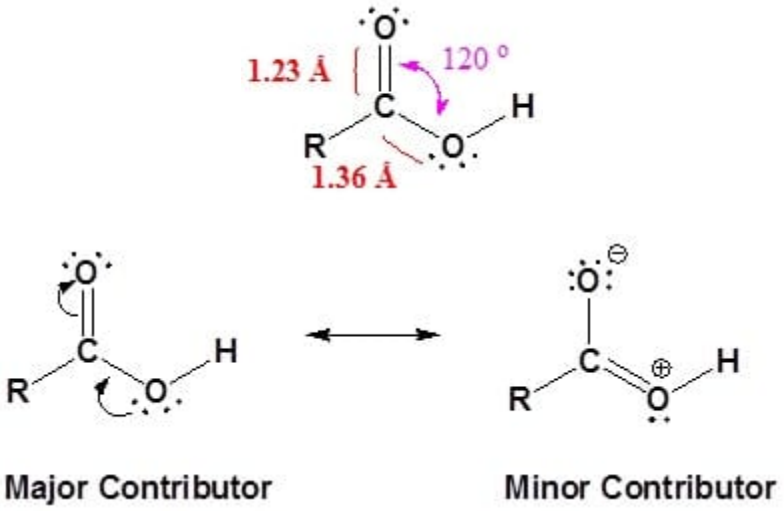
19.2: Structural and Physical Properties of Carboxylic Acids

Structure of the carboxyl acid group

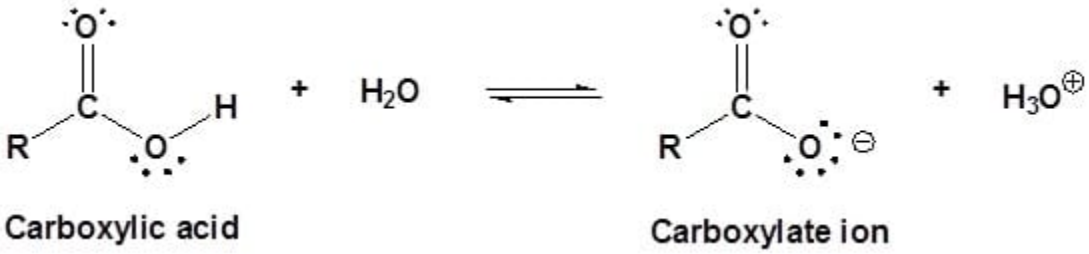
Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



The carbon and oxygen in the carbonyl are both sp2 hybridized which give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp2 hybridized which allows one of its lone pair electrons to conjugate with the pi system of the carbonyl group. This make the carboxyl group planar an can represented with the following resonance structure.



Carboxylic acids are named such because they can donate a hydrogen to produce a carboxylate ion. The factors which affect the acidity of carboxylic acids will be discussed later.



Contributors

- Prof. Steven Farmer (Sonoma State University)

Physical Properties of Some Carboxylic Acids

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Saturated			Unsaturated		
Formula	Common Name	Melting Point	Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon atoms have melting points higher than the odd numbered homologs having one more or one less carbon. This reflects differences in intermolecular attractive forces in the crystalline state. In the table of fatty acids we see that the presence of a cis-double bond significantly lowers the melting point of a compound. Thus, palmitoleic acid melts over 60° lower than palmitic acid, and similar decreases occur for the C_{18} and C_{20} compounds. Again, changes in crystal packing and intermolecular forces are responsible.

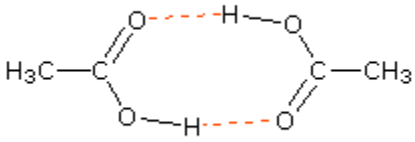
The factors that influence the relative boiling points and water solubilities of various types of compounds were discussed earlier. In general, dipolar attractive forces between molecules act to increase the boiling point of a given compound, with hydrogen bonds being an extreme example. Hydrogen bonding is also a major factor in the water solubility of covalent compounds To refresh your understanding of these principles Click Here. The following table lists a few examples of these properties for some similar sized polar compounds (the non-polar hydrocarbon hexane is provided for comparison).

Physical Properties of Some Organic Compounds

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility

$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 °C	very soluble
$CH_3(CH_2)_4OH$	1-pentanol	88	138 °C	slightly soluble
$CH_3(CH_2)_3CHO$	pentanal	86	103 °C	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 °C	moderately soluble
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 °C	slightly soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216 °C	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	165 °C	very soluble
$CH_3(CH_2)_4NH_2$	1-aminobutane	87	103 °C	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	140 °C	slightly soluble
$CH_3(CH_2)_4CH_3$	hexane	86	69 °C	insoluble

The first five entries all have oxygen functional groups, and the relatively high boiling points of the first two is clearly due to hydrogen bonding. Carboxylic acids have exceptionally high boiling points, due in large part to dimeric associations involving two hydrogen bonds. A structural formula for the dimer of acetic acid is shown here. When the mouse pointer passes over the drawing, an electron cloud diagram will appear. The high boiling points of the amides and nitriles are due in large part to strong dipole attractions, supplemented in some cases by hydrogen bonding.



Contributors

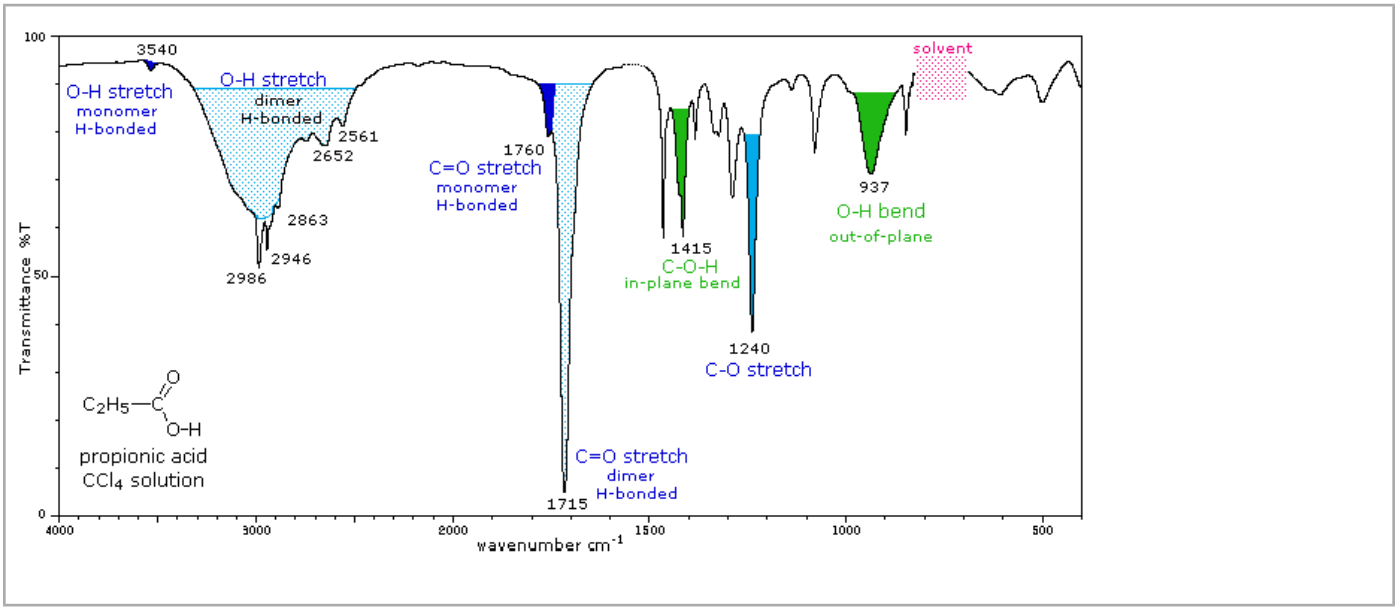
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19.3: Spectroscopy and Mass Spectrometry of Carboxylic Acids

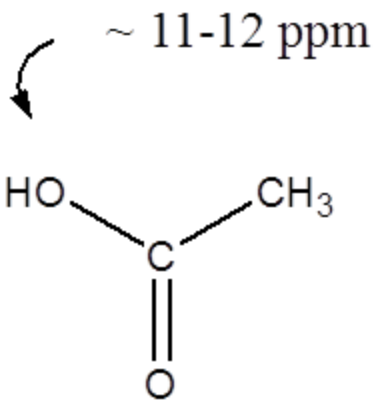
IR

The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of a CCl_4 solution of propionic acid (propanoic acid), shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases. The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}. This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 are characteristic of the dimer. In ether solvents a sharper hydrogen bonded monomer absorption near 3500 cm^{-1} is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

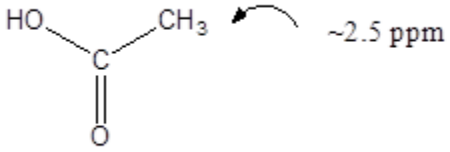


NMR

The combination of anisotropy and electronegativity causes the O-H hydrogen in a carboxylic acid to be very deshielded.



Hydrogen environments adjacent to a carboxylic acid are shifted to the region of 2.5-3.0 ppm.Deshielding occurs due to the fact that the sp^2 hybridized carbon the the carboxylic acid is more electronegative than a sp^3 hybridized carbon.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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19.4: Acidic and Basic Character of Carboxylic Acids

Objectives

After completing this section, you should be able to

1. identify the form that carboxylic acids take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentages of dissociated and undissociated acids [A^-] and [HA] in a solution, given the pK_a value of the acid and the pH of the solution.
3. explain why cellular carboxylic acids are always referred to by the name of their anion.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Henderson-Hasselbalch equation
- physiological pH

Organic molecules in buffered solution: The Henderson-Hasselbalch equation

The environment inside a living cell, where most biochemical reactions take place, is an aqueous buffer with pH ~ 7 (or sometimes referred to as the physiological pH). Recall from your General Chemistry course that a buffer is a solution of a weak acid and its conjugate base. The key equation for working with buffers is the Henderson-Hasselbalch equation:

The Henderson-Hasselbalch equation:

$$\mathrm{pH} = \mathrm{pK_a} + \log\left(\frac{concentration\ of\ conjugate\ base}{concentration\ of\ weak\ acid}\right)$$

The equation tells us that if our buffer is an equimolar solution of a weak acid and its conjugate base, the pH of the buffer will equal the pK_a of the acid (because the log of 1 is equal to zero). If there is more of the acid form than the base, then of course the pH of the buffer is lower than the pK_a of the acid.

The Henderson-Hasselbalch equation is particularly useful when we want to think about the protonation state of different biomolecule functional groups in a pH 7 buffer. When we do this, we are always assuming that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids.).

Imagine an aspartic acid residue located on the surface of a protein in a human cell. Being on the surface, the side chain is in full contact with the pH 7 buffer surrounding the protein. In what state is the side chain functional group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)?

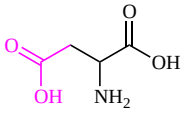


Figure 20.3.1: Aspartic acid with the carboxylic acid side-chain highlighted. (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the Henderson-Hasselbalch equation, we fill in our values for the pH of the buffer and a rough pKa approximation of pK_a = 5 for the carboxylic acid functional group. Doing the math, we find that the ratio of carboxylate to carboxylic acid is about 100 to 1: the carboxylic acid is almost completely ionized (in the deprotonated state) inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules: in the physiological environment, carboxylic acids are almost completely deprotonated. Indeed, often cellular carboxylic acids are often referred to by the name of their anion. So rather than pyruvic acid, or acetic acid or lactic acid, it is pyruvate, acetate or lactate.

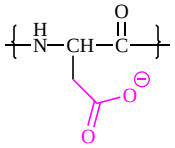


Figure 20.3.2: Aspartate (as part of a protein or polypeptide). (CC BY-SA 4.0; Layne Morsch via LibreTexts)

While we are most interested in the state of molecules at pH 7, the Henderson-Hasselbalch equation can of course be used to determine the protonation state of functional groups in solutions buffered to other pH levels. The exercise below provide some practice in this type of calculation.

Exercises

Exercise 20.3.1

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pK_a of acetic acid is 4.8.

Solution

This is a direct application of the Henderson-Hasselbalch equation.

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right)$$

The ratio of base to acid is 40/30, or 1.33. Therefore, substituting these values and the pK_a results in

$$\begin{aligned} pH &= 4.8 + \log\left(\frac{40}{30}\right) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

Exercise 20.3.2

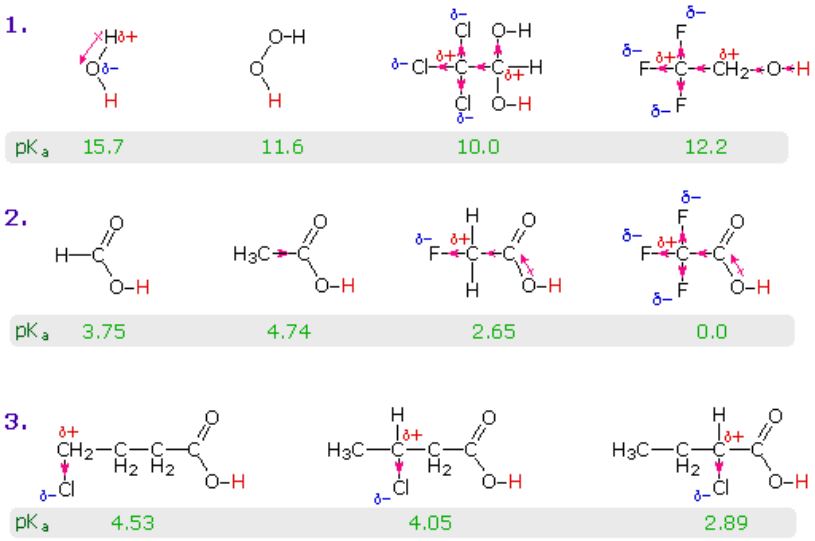
What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pK_a = 4.8) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

Answer available at the end of this section.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group. The following diagram illustrates this factor for several simple inorganic and organic compounds (row #1), and shows how inductive electron withdrawal may also increase the acidity of carboxylic acids (rows #2 & 3). The acidic hydrogen is colored red in all examples.



Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen, as noted earlier in a discussion of carbocation stability. Electronegative substituents increase acidity by inductive electron withdrawal. As expected, the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect (isomers in the 3rd row). Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing (last three entries in the table of pK_a values).

For additional information about substituent effects on the acidity of carboxylic acids Click Here

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 20.3.2

We use the Henderson-Hasselbalch equation and let the base to acid ratio be x.

For pH = 2.8:

$$2.8 = 4.8 + \log x$$

$x = 0.01 to 1$

- pH 3.8, the ratio is 0.10 to 1
- pH 4.8, the ratio is 1.0 to 1
- pH 5.8, the ratio is 10 to 1
- pH 6.8, the ratio is 100 to 1

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19.5: Carboxylic Acid Synthesis in Industry

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19.6: Methods for Introducing the Carboxy Functional Group

Objectives

After completing this section, you should be able to

1. describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
   a. the oxidation of alkylbenzenes.
   b. the oxidative cleavage of alkenes.
   c. the oxidation of primary alcohols and aldehydes.
2. discuss, in detail, the hydrolysis of nitriles:
   a. write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
   b. identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
   c. identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
   d. identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
3. discuss, in detail, the carboxylation of Grignard reagents:
   a. write an equation describing the formation of a carboxylic acid from a Grignard reagent.
   b. identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
   c. identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
   d. write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

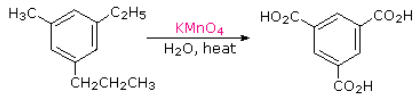
Study Notes

Review the methods of obtaining carboxylic acids presented in earlier sections:

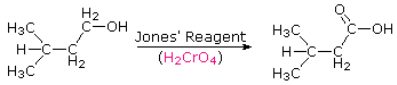
1. oxidation of aromatic compounds—Section 16.9.
2. oxidative cleavage of alkenes—Section 8.8.
3. oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text, and the following diagram summarizes most of these. To review the previous discussion of any of these reaction classes simply click on the number (**1** to **4**) or descriptive heading for the group.

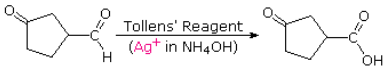
1. Oxidation of Arene Side-Chains



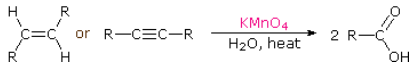
2. Oxidation of 1°-Alcohols



3. Oxidation of Aldehydes



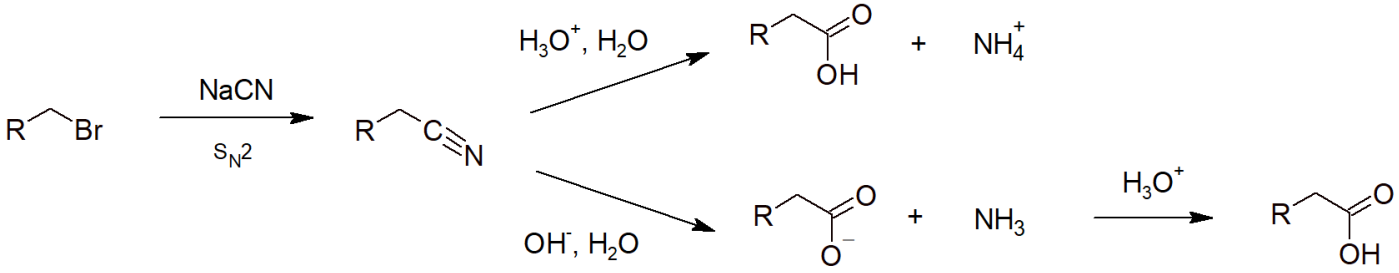
4. Oxidative Cleavage of Alkenes and Alkynes



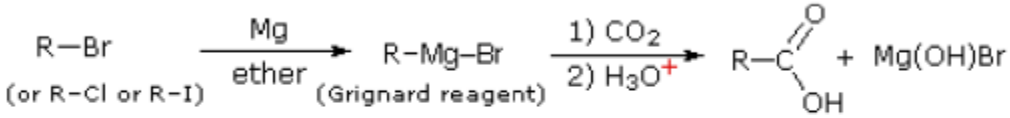
Two other useful procedures for preparing carboxylic acids involve hydrolysis of nitriles and carboxylation of organometallic intermediates. As shown in the following diagram, both methods begin with an organic halogen compound and the carboxyl group eventually replaces the halogen. Both methods require two steps, but are complementary in that the nitrile intermediate in the first procedure is generated by a S_N2 reaction, in which cyanide anion is a nucleophilic precursor of the carboxyl group. The hydrolysis may be either acid or base-catalyzed, but the latter give a carboxylate salt as the initial product.

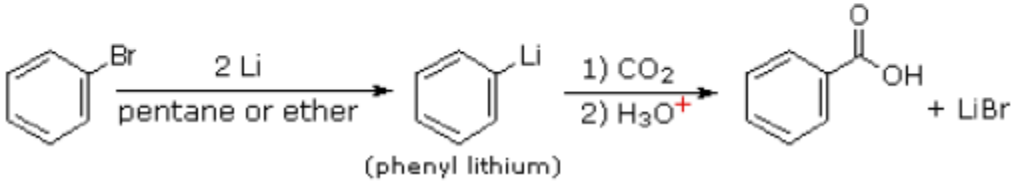
In the second procedure the electrophilic halide is first transformed into a strongly nucleophilic metal derivative, and this adds to carbon dioxide (an electrophile). The initial product is a salt of the carboxylic acid, which must then be released by treatment with strong aqueous acid.

Hydrolysis of Nitriles



Carboxylation of Organometallic Reagents





An existing carboxylic acid may be elongated by one methylene group, using a homologation procedure called the **Arndt-Eistert**

reaction. To learn about this useful method Click Here.

Worked Example 20.5.1

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1^{o} alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

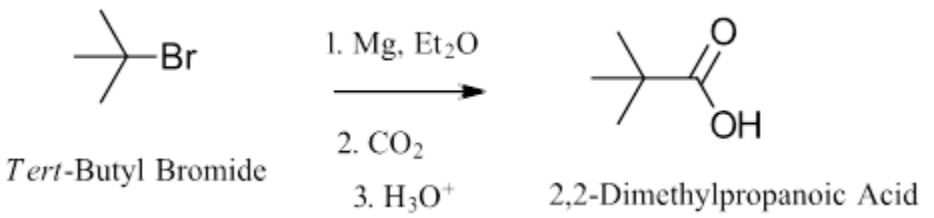
a) Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.

b) Benzyl Bromide → Benzoic Acid

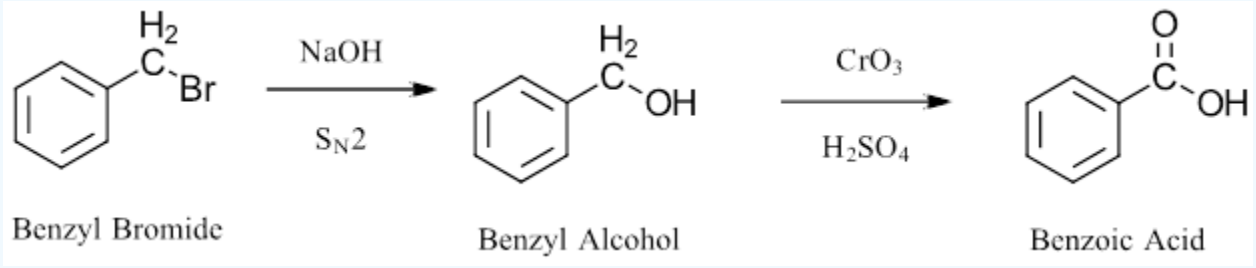
c) 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

Solution

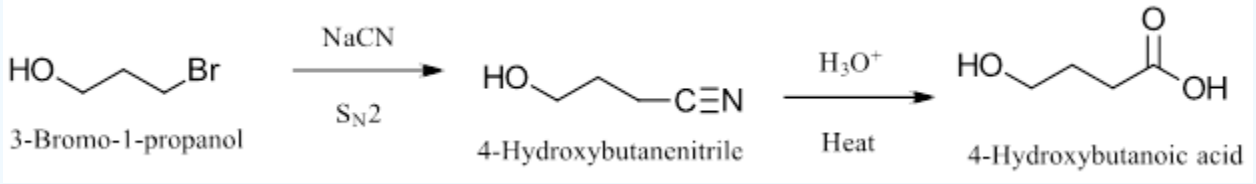
a) The product contains one more carbon than the reactant so the oxidation of a 1^{o} alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.



b) The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.



c) The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effect method because the presence of an incompatible alcohol functional group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.

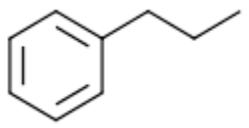


Exercises

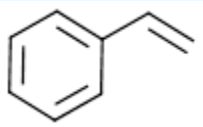
Exercise 20.5.1

Show how the following molecules can be used to synthesize benzoic acid:

a)



b)



c)

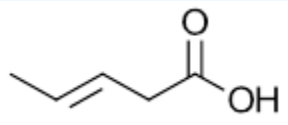


Answer available at the end of this section.

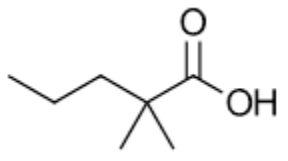
Exercise 20.5.2

Please give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

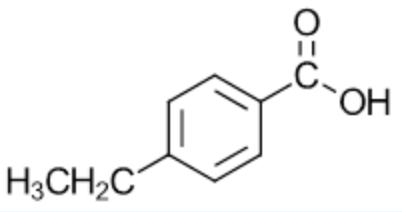
a)



b)



c)

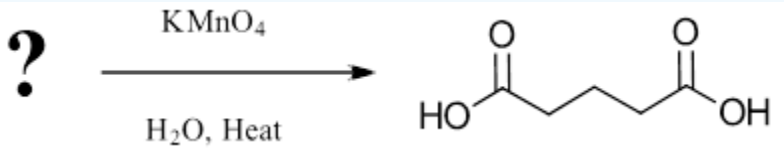


Answer available at the end of this section.

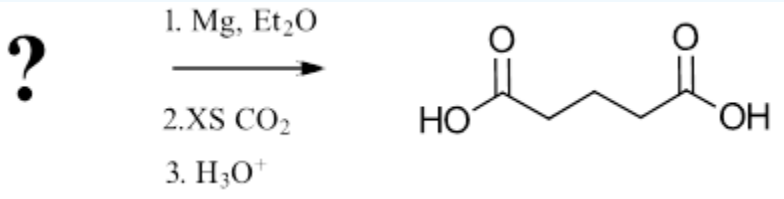
Exercise 20.5.3

Please give the possible reactants for the following reactions:

a) There are at least four possible answers for question a.



b)



Answer available at the end of this section.

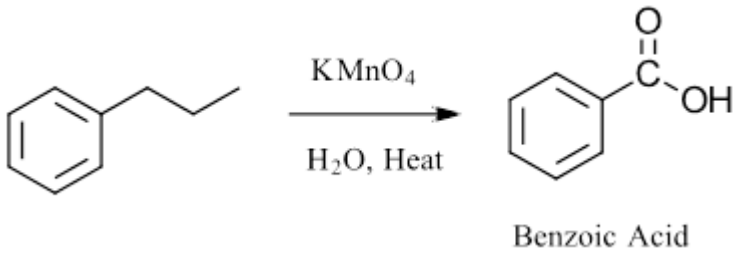
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

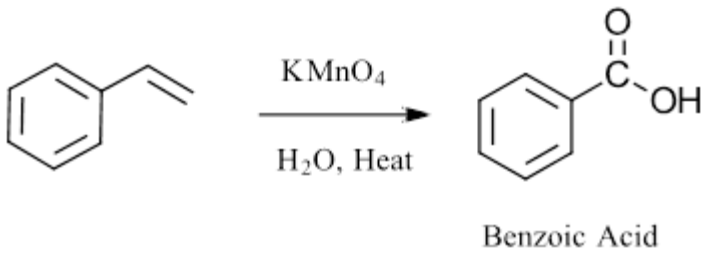
Exercise 20.5.1

a)



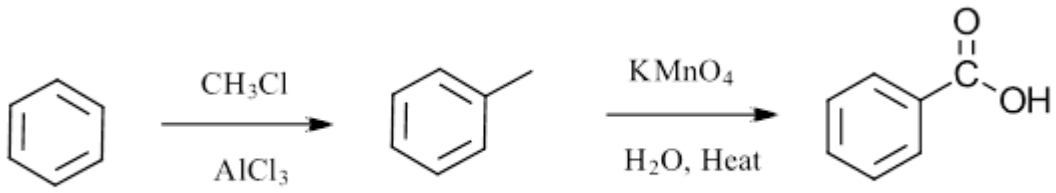
Benzoic Acid

b)



Benzoic Acid

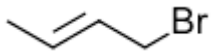
c)



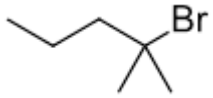
Benzoic Acid

Exercise 20.5.2

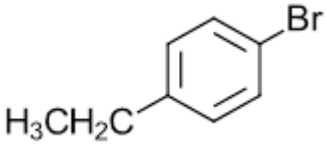
a)



b)

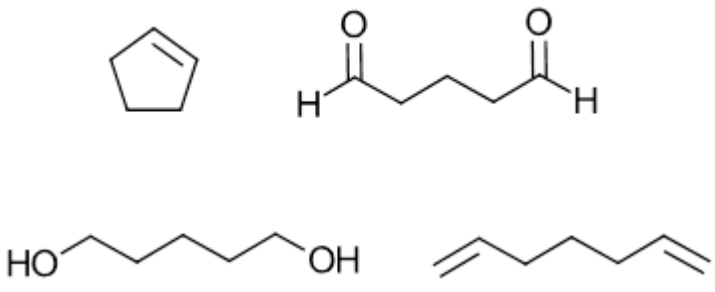


c)

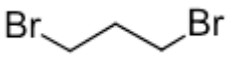


Exercise 20.5.3

a)



b)



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19.7: Substitution at the Carboxy Carbon: The Addition-Elimination Mechanism

Objectives

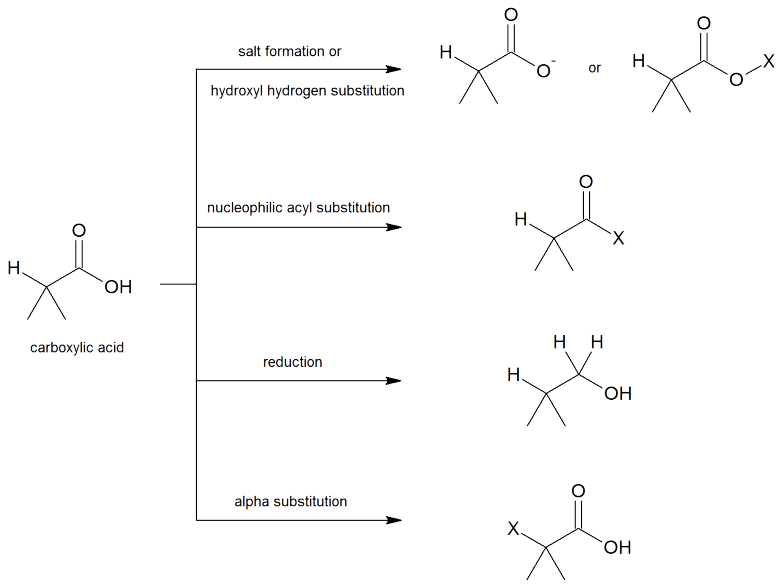
After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

Study Notes

You may wish to review Section 17.4 which discusses reduction of carbonyl compounds to form alcohols and Sections 20.2–20.4 which highlights the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 21) and alpha substitutions (Chapter 22) are discussed later in more detail.

Four Categories of Carboxylic Acid Reactions

The scheme summarizes some of the general reactions that carboxylic acids undergo.

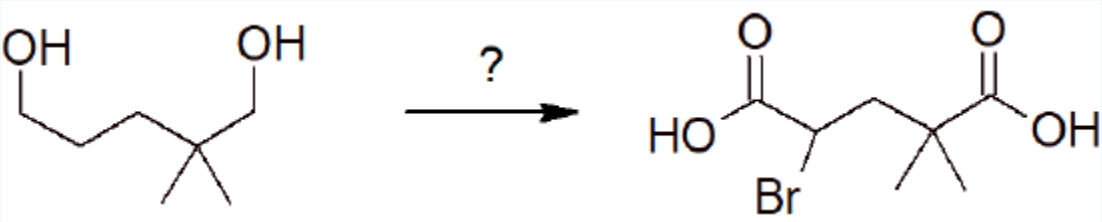


Four general reaction categories are represented here: (1) As carboxylic acid deprotonates quite readily, it is quite easy to form a carboxylate salt or to substitute the hydroxyl hydrogen. (2) The category of nucleophilic acyl substitution represents the substitution of the whole hydroxyl group, which we will see later in more detail leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). (3) Like other carbonyl compounds, carboxylic acids can be reduced by reagents like $LiAlH_4$. (4) While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha site.

Exercises

Exercise 20.6.1

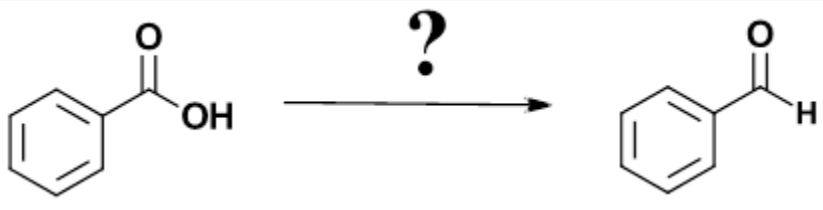
Show how the following transformation can be performed. Multiple steps may be required.



Answer available at the end of this section.

Exercise 20.6.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer available at the end of this section.

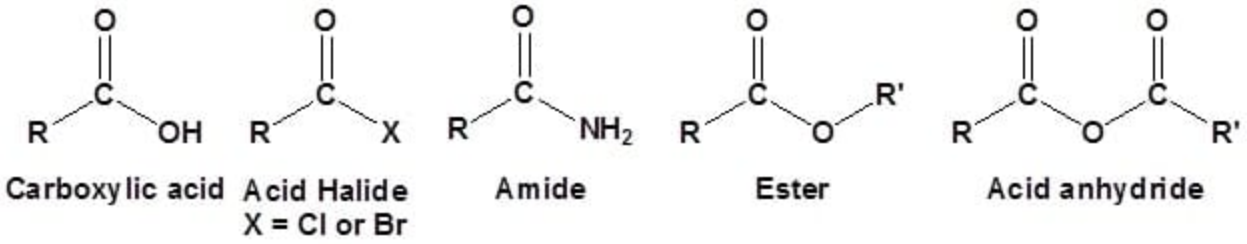
Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

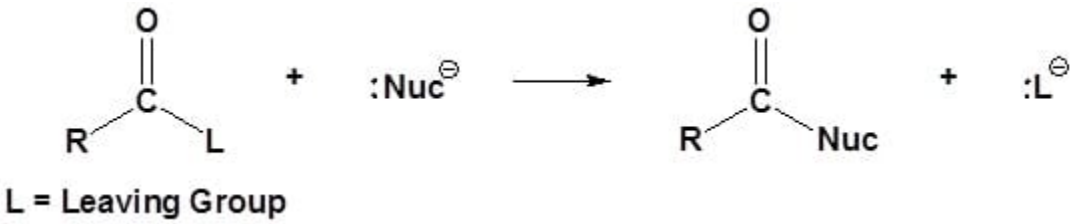
1. Study Notes
2. Four Categories of Carboxylic Acid Reactions
3.
4. Exercises
    1. Exercise 20.6.1
    2. Exercise 20.6.2
5. Contributors and Attributions
6. Introduction
7. General reaction
8. General mechanism
9. Contributors

Introduction

Carboxylic acid derivatives are functional groups whose chemistry is closely related. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

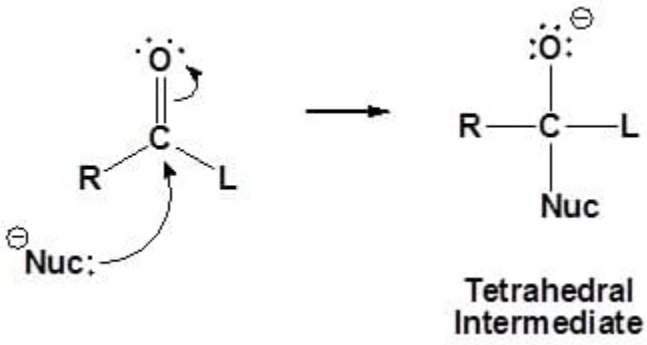


General reaction

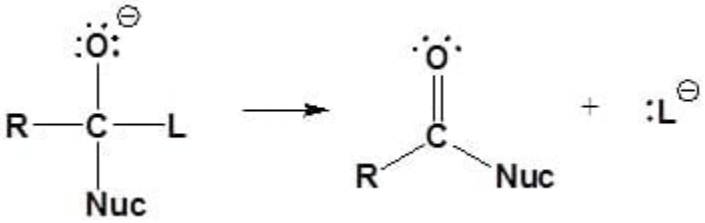


General mechanism

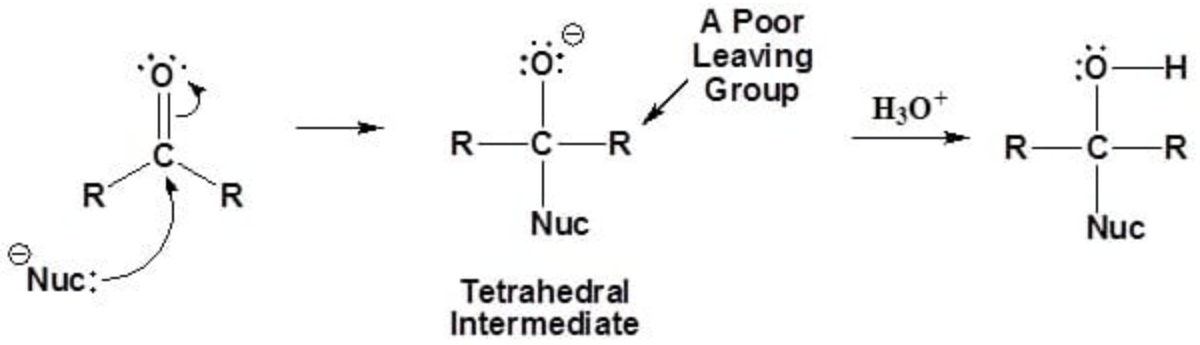
1) Nucleophilic attack on the carbonyl



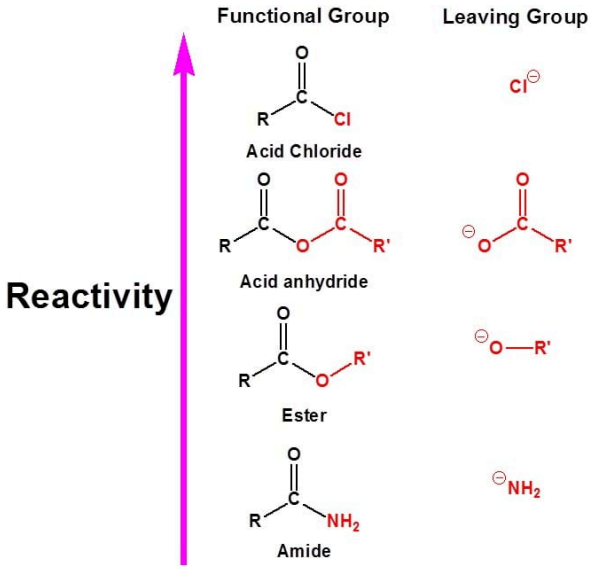
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.

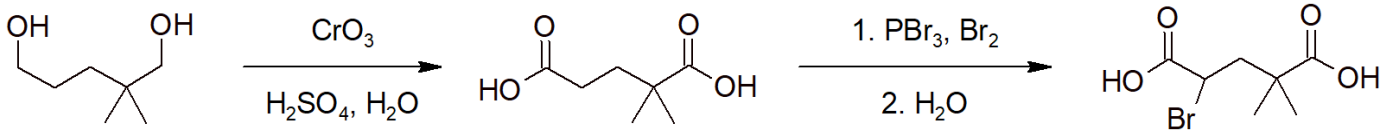


Contributors

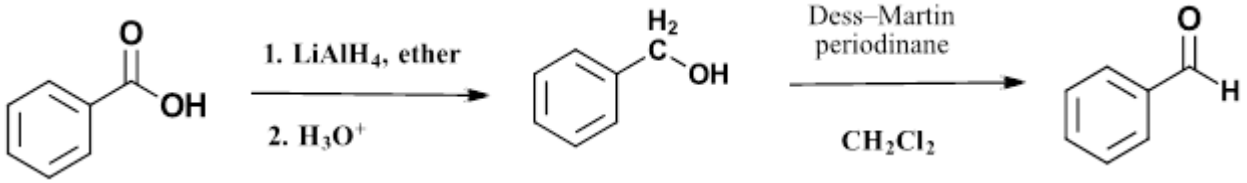
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 20.6.1



Exercise 20.6.2

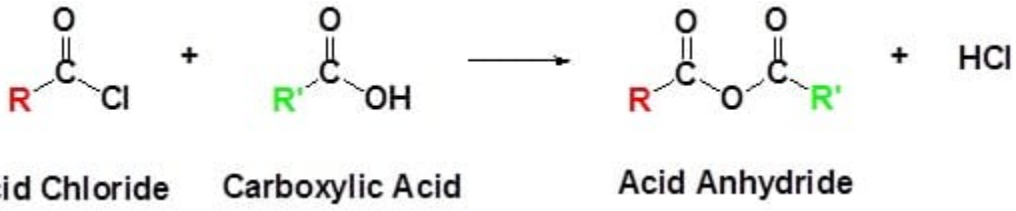


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- 20.6: Reactions of Carboxylic Acids - An Overview by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

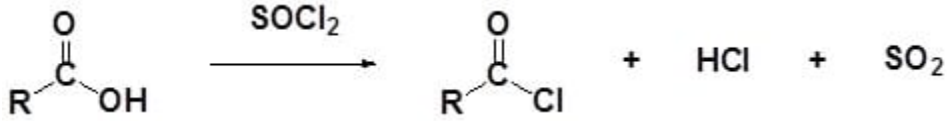
19.8: Carboxylic Acid Derivatives: Alkanoyl (Acyl) Halides and Anhydrides

Acid Chlorides react with carboxylic acids to form anhydrides

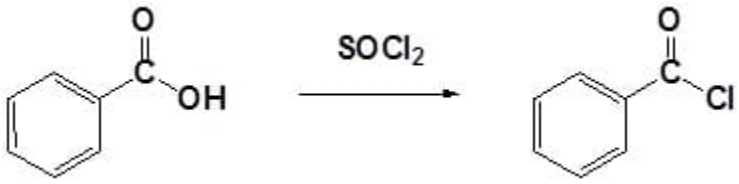


Carboxylic acids react with Thionyl Chloride ($SOCl_2$) to form acid chlorides.

During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

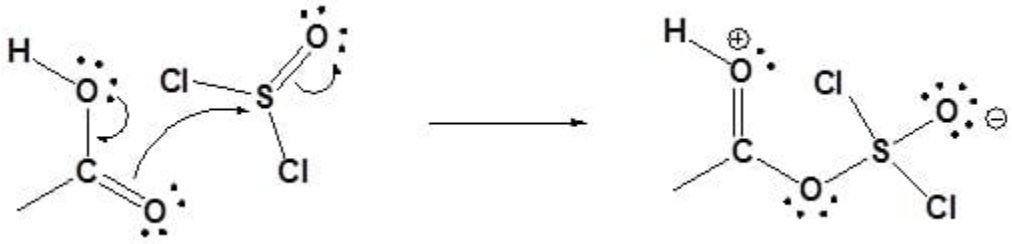


Example

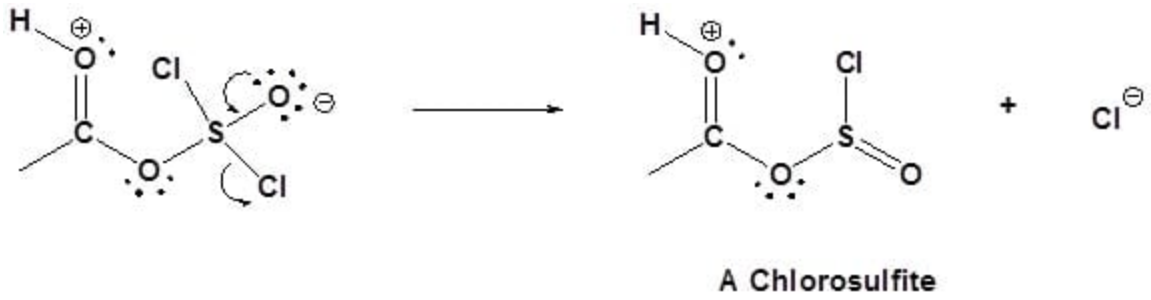


Mechanism

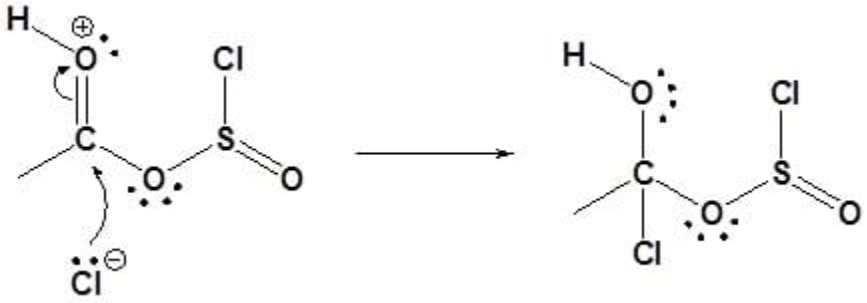
1) Nucleophilic attack on Thionyl Chloride



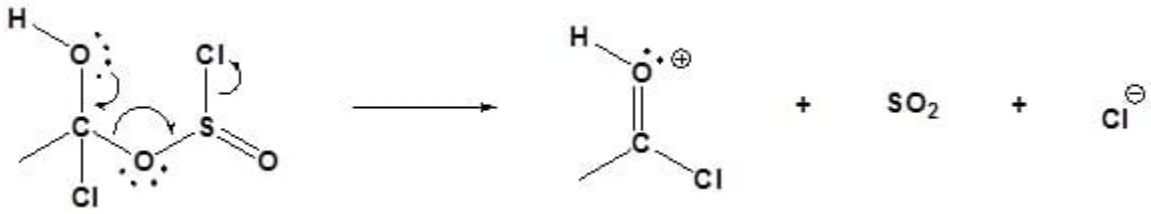
2) Removal of Cl leaving group



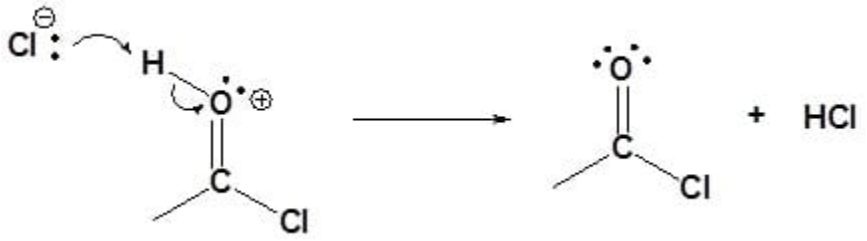
3) Nucleophilic attack on the carbonyl



4) Leaving group removal



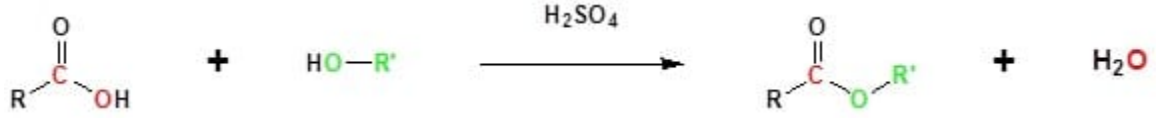
5) Deprotonation



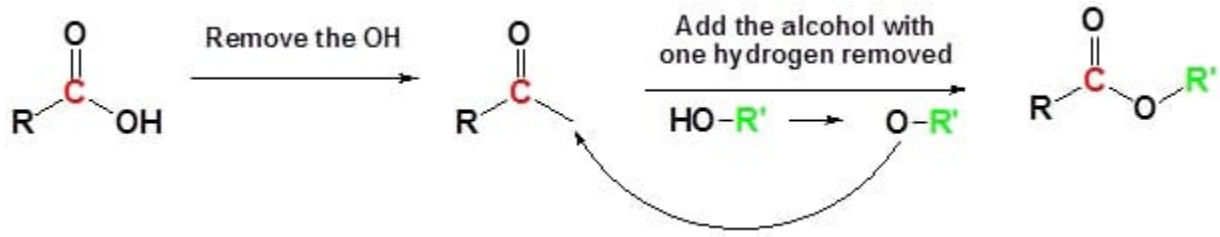
Carboxylic acids can react with alcohols to form esters in a process called Fischer esterification.

Usually the alcohol is used as the reaction solvent. An acid catalyst is required.

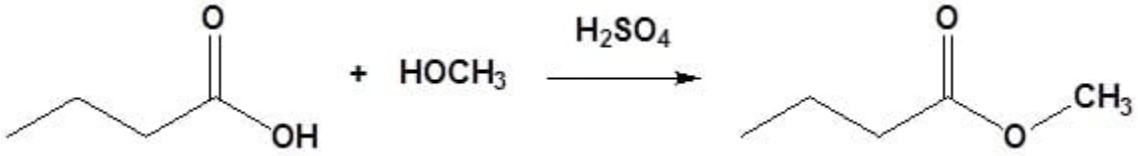
Basic Reaction



Going from reactants to products simplified

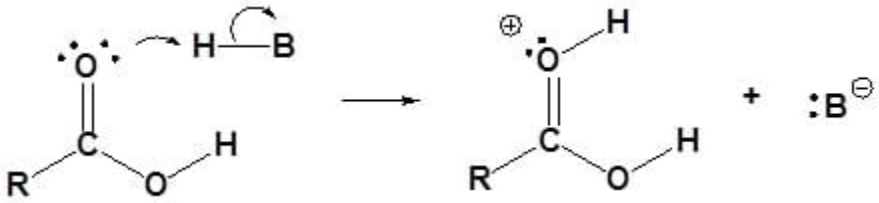


Example

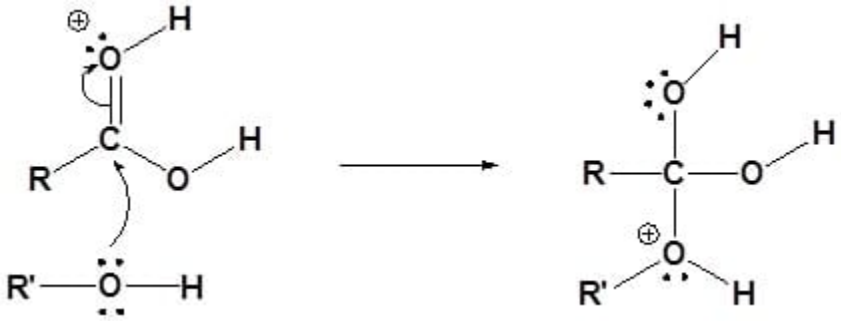


Mechanism

1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



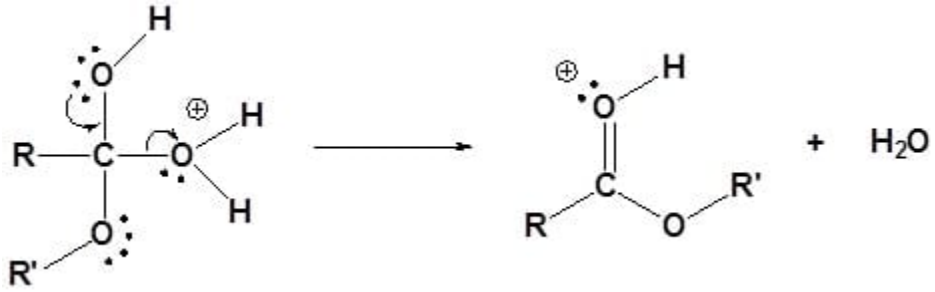
2) Nucleophilic attack on the carbonyl



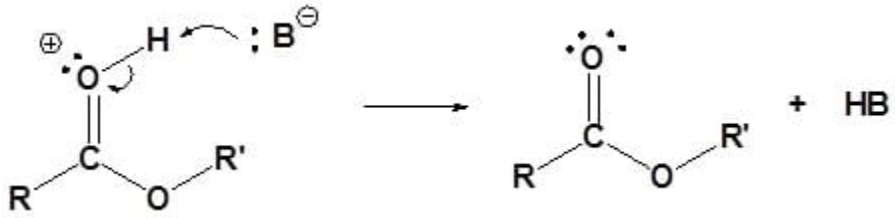
3) Proton transfer



4) Water leaves



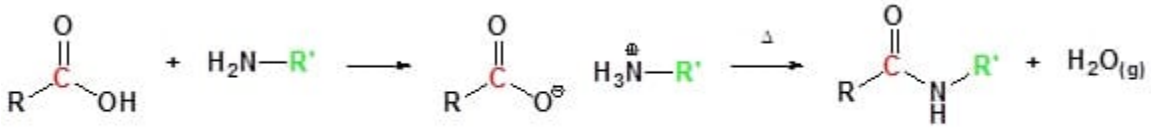
5) Deprotonation



Conversion of Carboxylic Acids to Amides

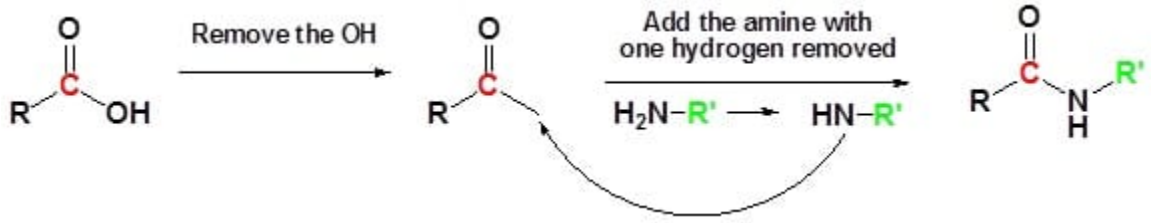
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.

General Reaction



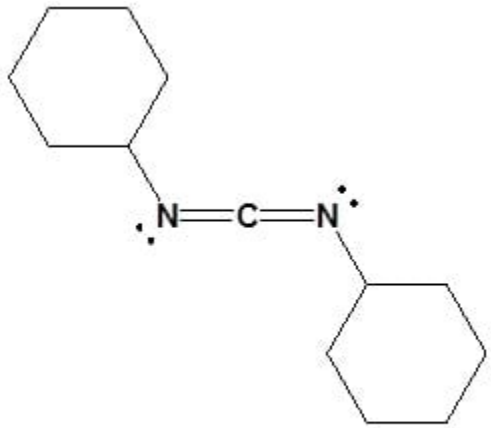
Ammonium Carboxylate Salt

Going from reactants to products simply



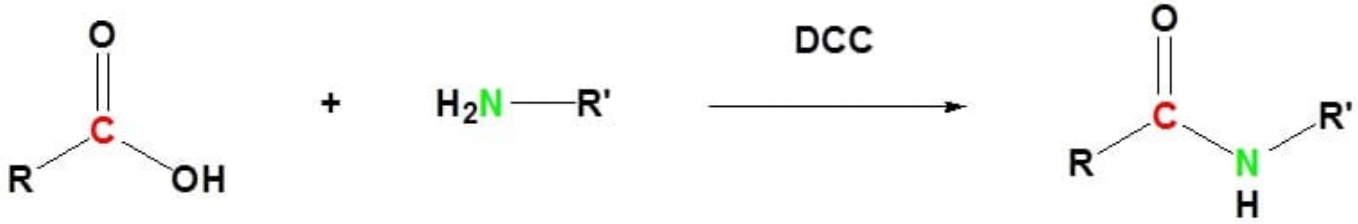
Conversion of Carboxylic acids to amide using DCC as an activating agent

The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the DCC molecule to form a good leaving group which can then be displaced by an amine during nucleophilic substitution. DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.



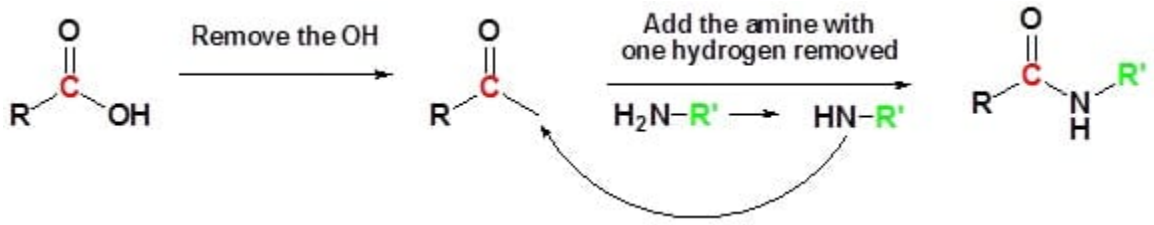
Dicyclohexylcarbodiimide (DCC)

Basic reaction



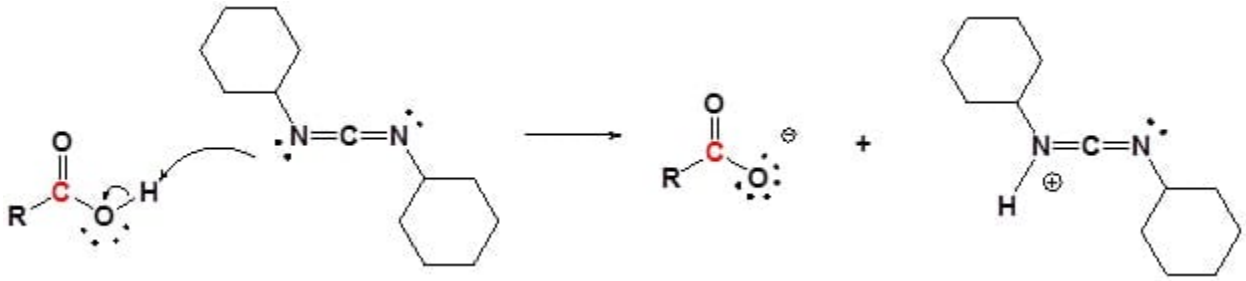
Carboxylic Acid Amine Amide

Going from reactants to products simplified

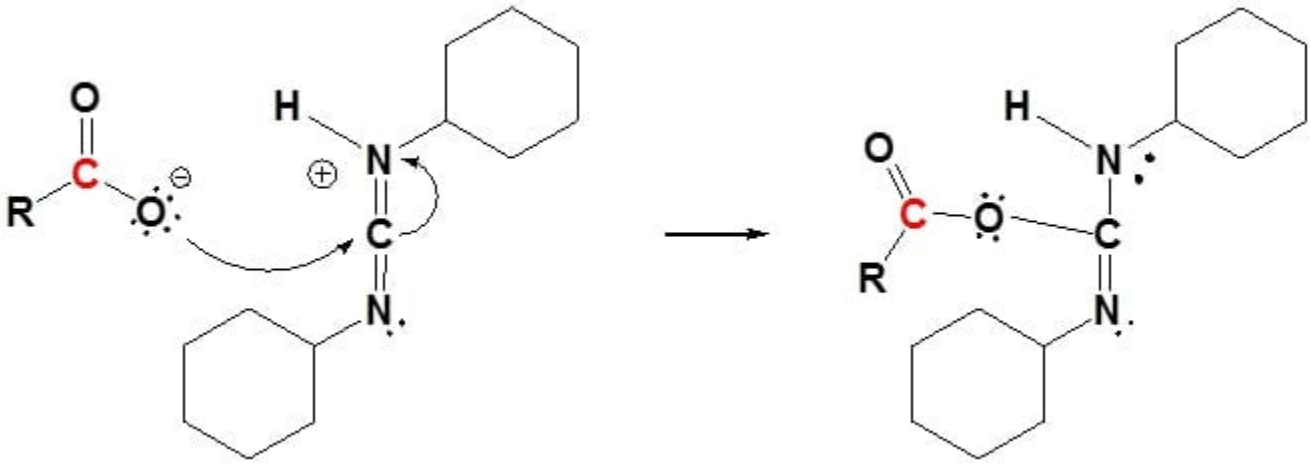


Mechanism

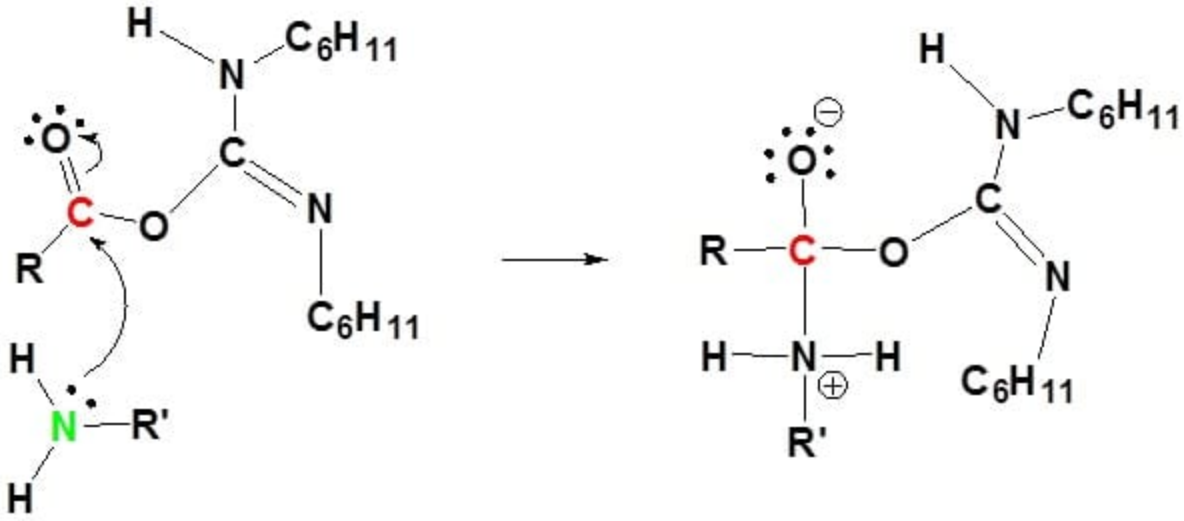
1) Deprotonation



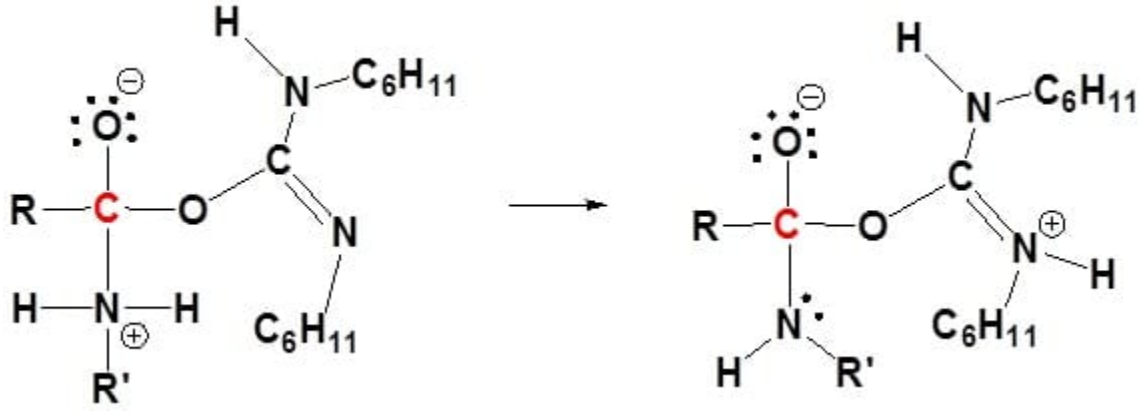
2) Nucleophilic attack by the carboxylate



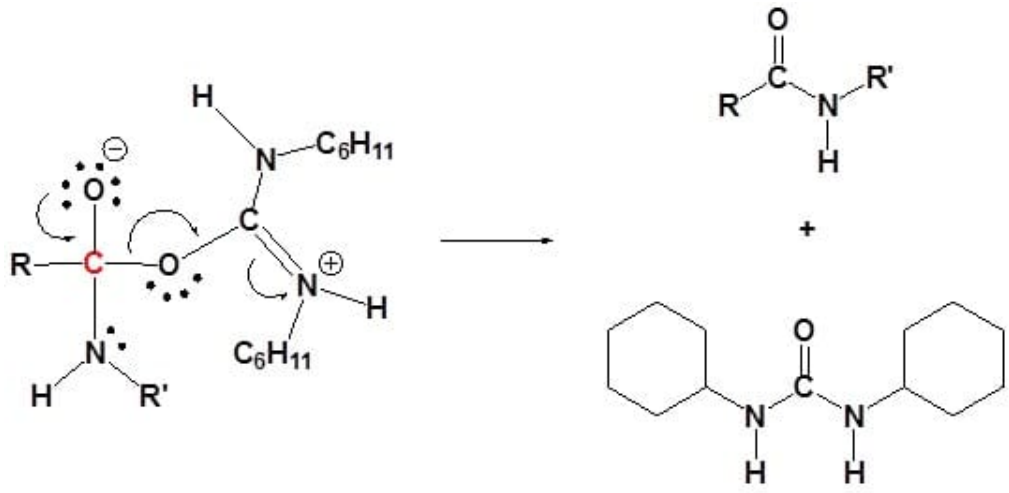
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal



Dicyclohexylurea

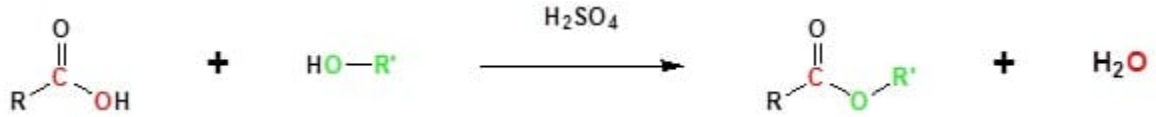
Contributors

- Prof. Steven Farmer (Sonoma State University)

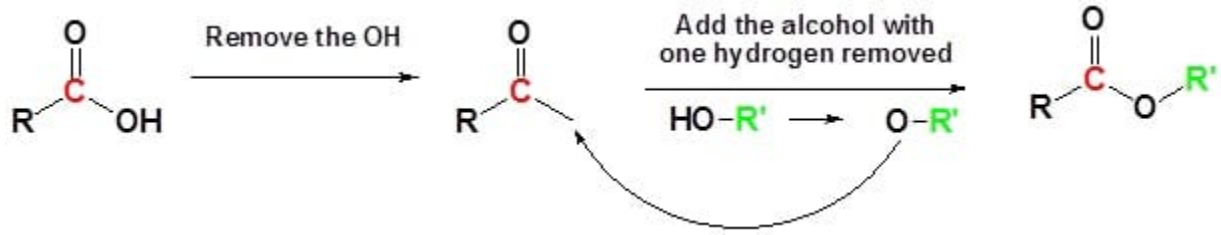
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19.9: Carboxylic Acid Derivatives: Esters

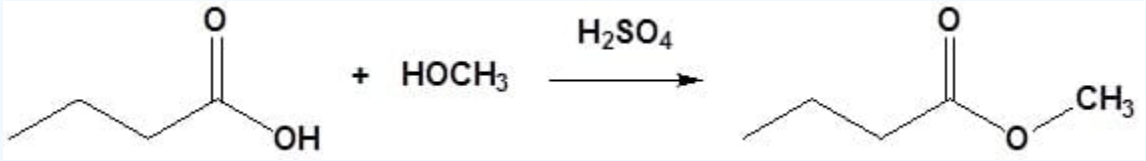
Fischer esterification is the esterification of a Carboxylic acid by heating it with an alcohol in the presence of a strong acid as the catalyst.



Going from reactants to products simplified



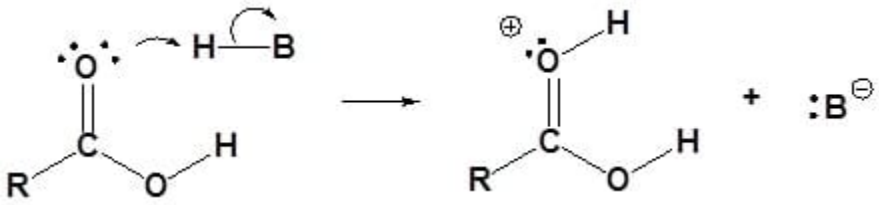
Example



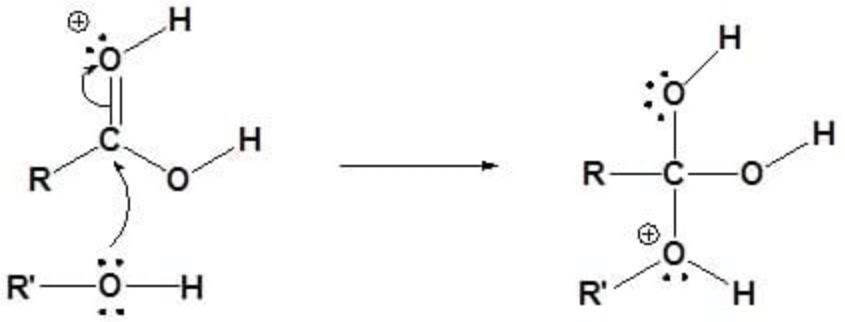
Mechanism

The overall reaction is reversible; to drive the reaction to completion, it is necessary to exploit Le Chateliers principle, which can be done either by continuously removing the water formed from the system or by using a large excess of the alcohol.

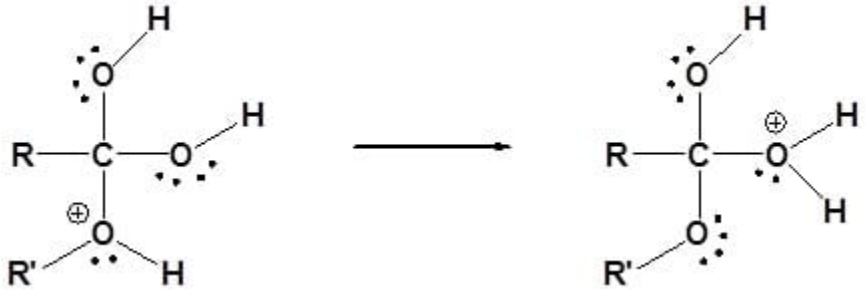
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



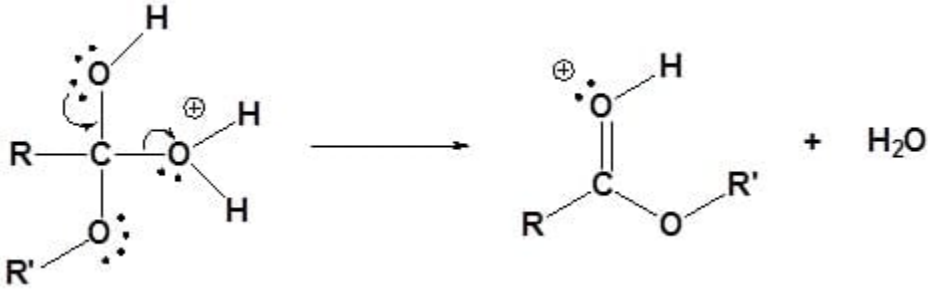
2) Nucleophilic attack on the carbonyl



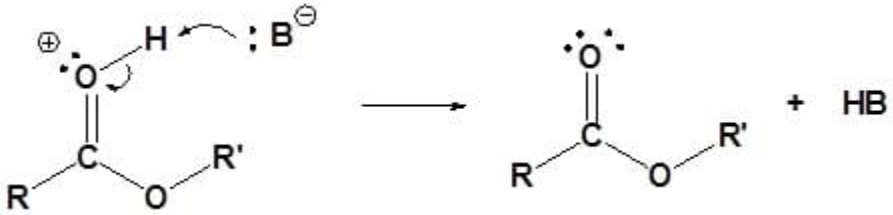
3) Proton transfer



4) Water leaves



5) Deprotonation



Contributors

- Prof. Steven Farmer (Sonoma State University)

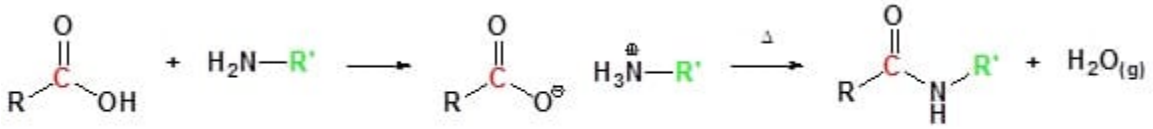
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- Fischer Esterification is licensed CC BY-NC-SA 4.0.

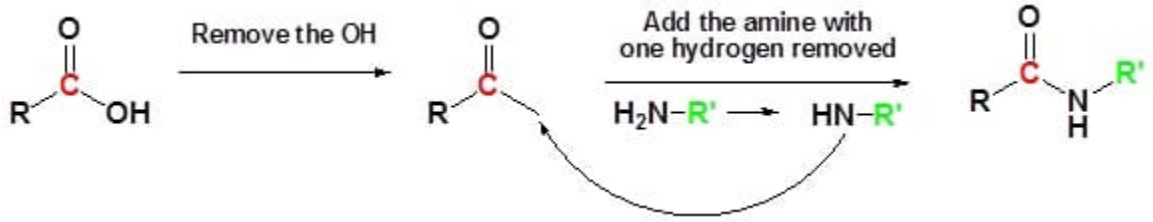
19.10: Carboxylic Acid Derivatives: Amides

The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.

General Reaction



Going from reactants to products simply



Contributors

Prof. Steven Farmer (Sonoma State University)

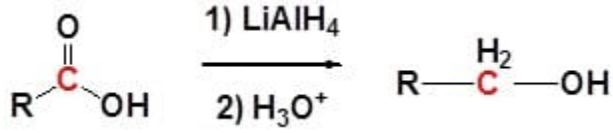
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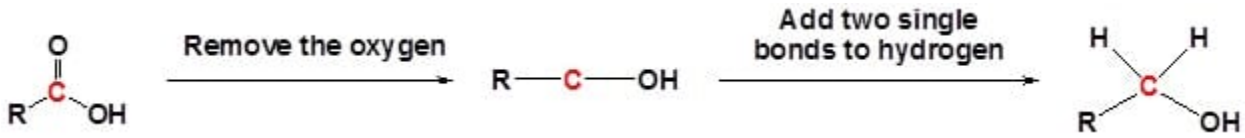
- Conversion of a Carboxylic Acid to an Amide is licensed CC BY-NC-SA 4.0.

19.11: Reduction of Carboxylic Acids by Lithium Aluminum Hydride

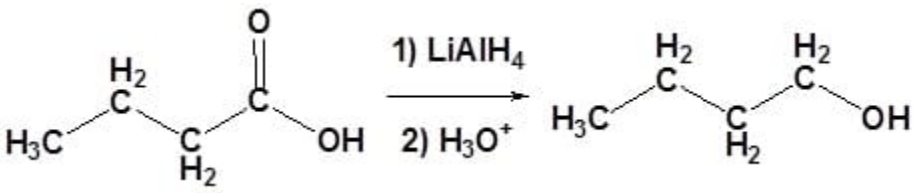
Carboxylic acids can be converted to 1^{o} alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.

General reaction



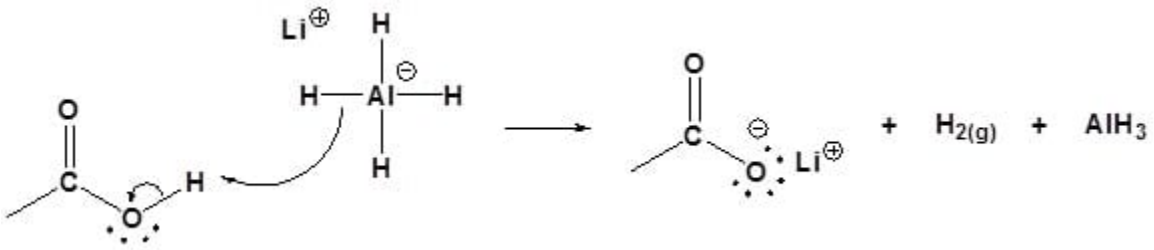


Example

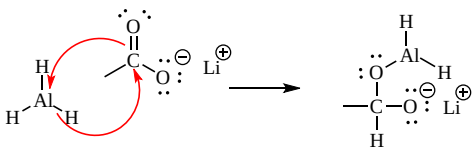


Possible Mechanism

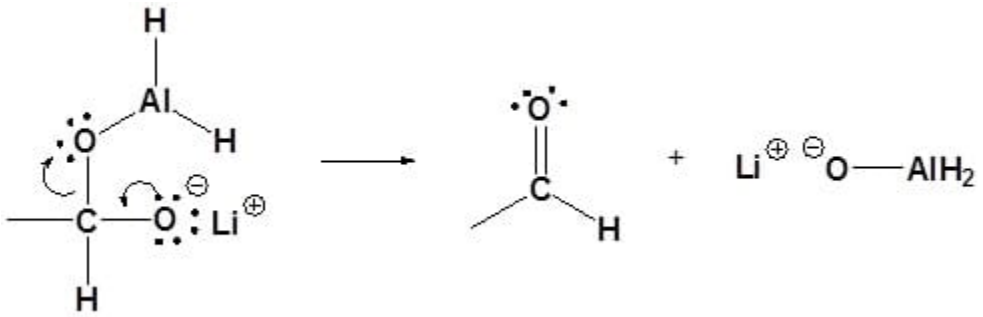
1) Deprotonation



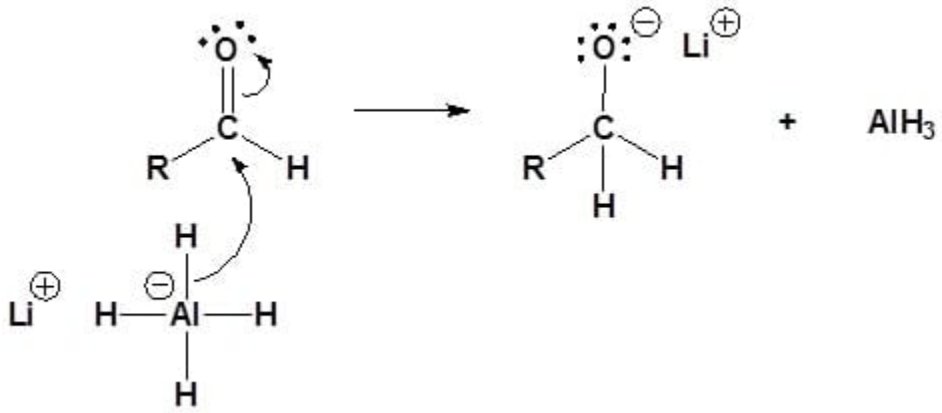
2) Nucleophilic attack by the hydride anion



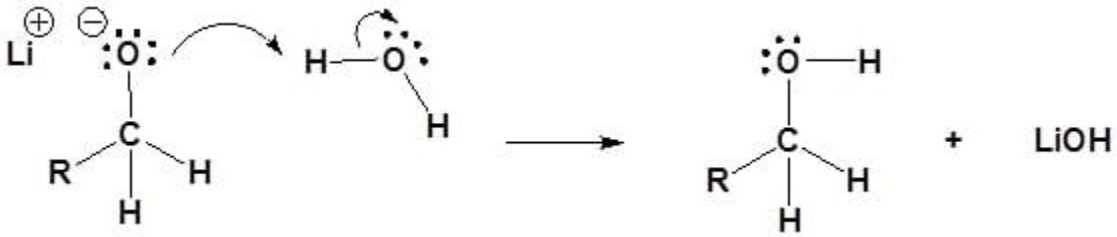
3) Leaving group removal



4) Nucleophilic attack by the hydride anion



5) The alkoxide is protonated



Contributors

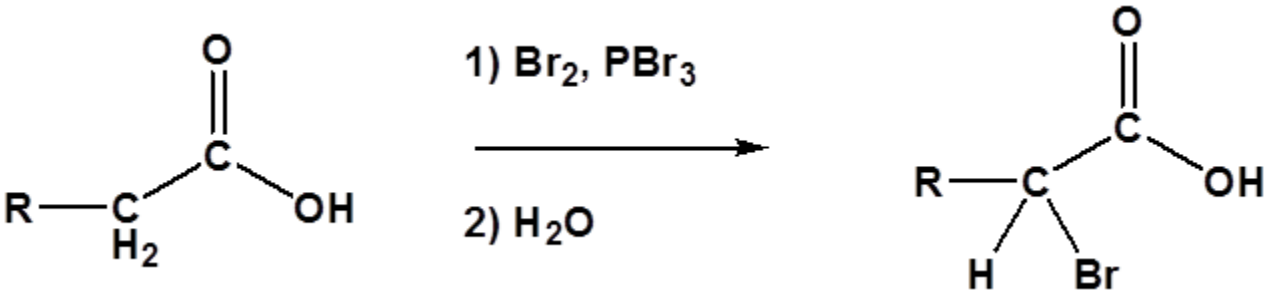
- Prof. Steven Farmer (Sonoma State University)

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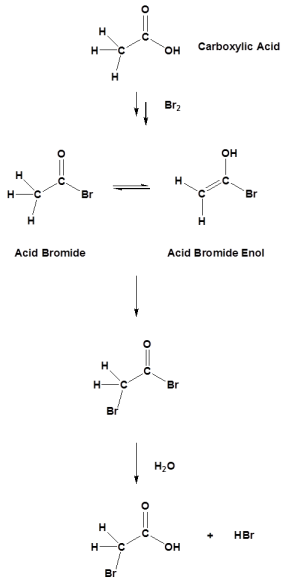
- Conversion of carboxylic acids to alcohols using LiAlH4 is licensed CC BY-NC-SA 4.0.

19.12: Bromination Next to the Carboxy Group: The Hell-Volhard-Zelinsky Reaction

Although the alpha bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with acids, esters, and amides. This is because only aldehydes and ketones enolize to a sufficient extent to allow the reaction to occur. However, carboxylic acids, can be brominated in the alpha position with a mixture of Br_2 and PBr_3 in a reaction called the Hell-Volhard-Zelinskii reaction.



The mechanism of this reaction involves an acid bromide enol instead of the expected carboxylic acid enol. The reaction stats with the reaction of the carboxylic acid with PBr_3 to form the acid bromide and HBr. The HBr then catalyzes the formation of the acid bromide enol which subsequently reacts with Br_2 to give alpha bromination. Lastly, the acid bromide reacts with water to reform the carboxylic acid.



Contributors

Prof. Steven Farmer (Sonoma State University)

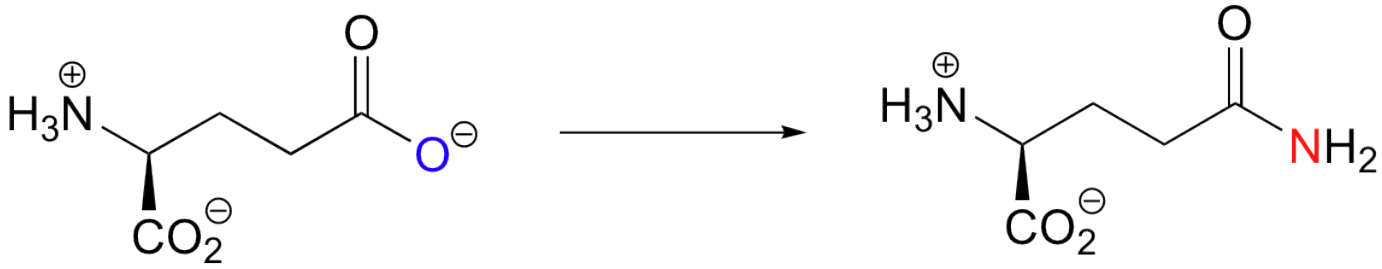
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- Hell-Volhard-Zelinskii Reaction is licensed CC BY-NC-SA 4.0.

19.13: Biological Activity of Carboxylic Acids

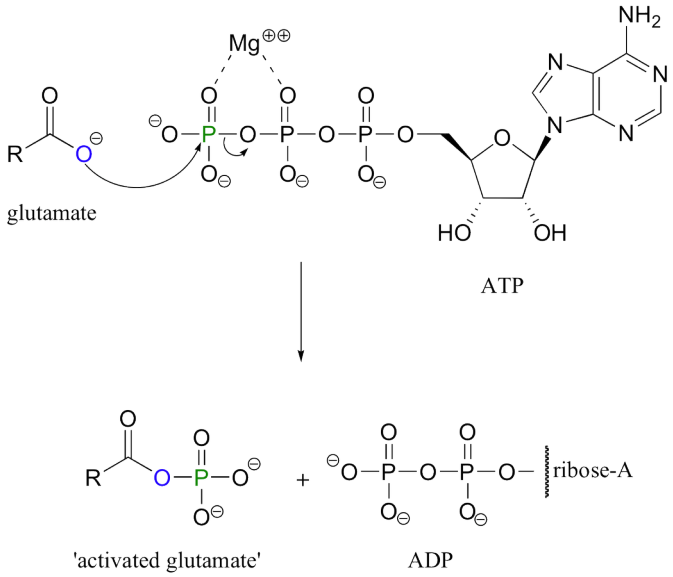
Glutamine synthetase

You have already learned that the carboxylate functional group is a very unreactive substrate for an enzyme-catalyzed acyl substitution reactions. How, then, does a living system accomplish an 'uphill' reaction such as the one shown below, where glutamate (a carboxylate) is converted to glutamine (an amide)?



glutamate glutamine

It turns out that this conversion is not carried out directly. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with from chapter 10: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

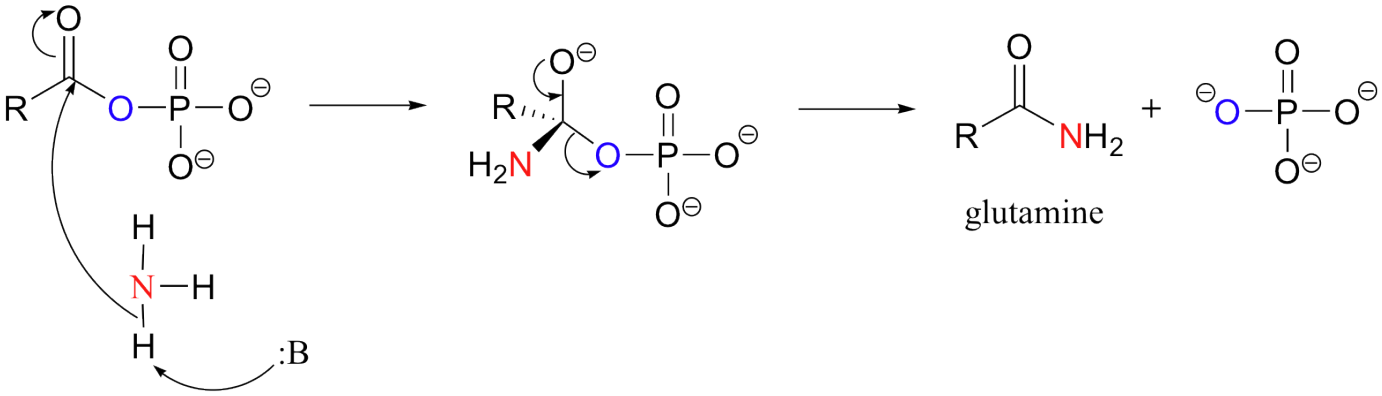


glutamate ATP

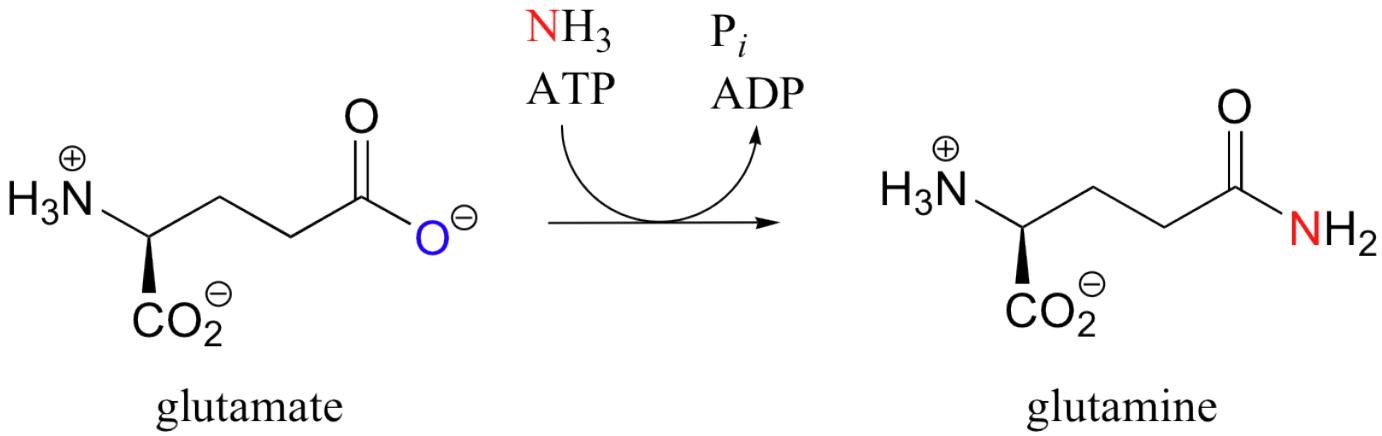
'activated glutamate' ADP

Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

The acyl phosphate version of glutamate is now ready to be converted directly to an amide (glutamine) *via* a nucleophilic acyl substitution reaction, as an ammonia molecule attacks the carbonyl and the phosphate is expelled.

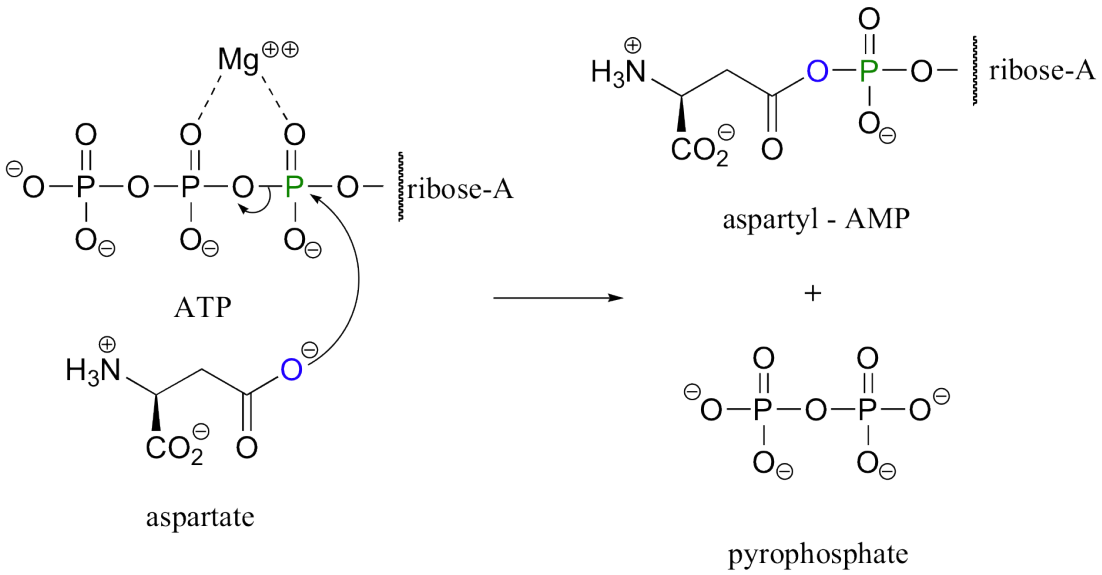


Overall, this reaction can be written as:



Asparagine synthetase

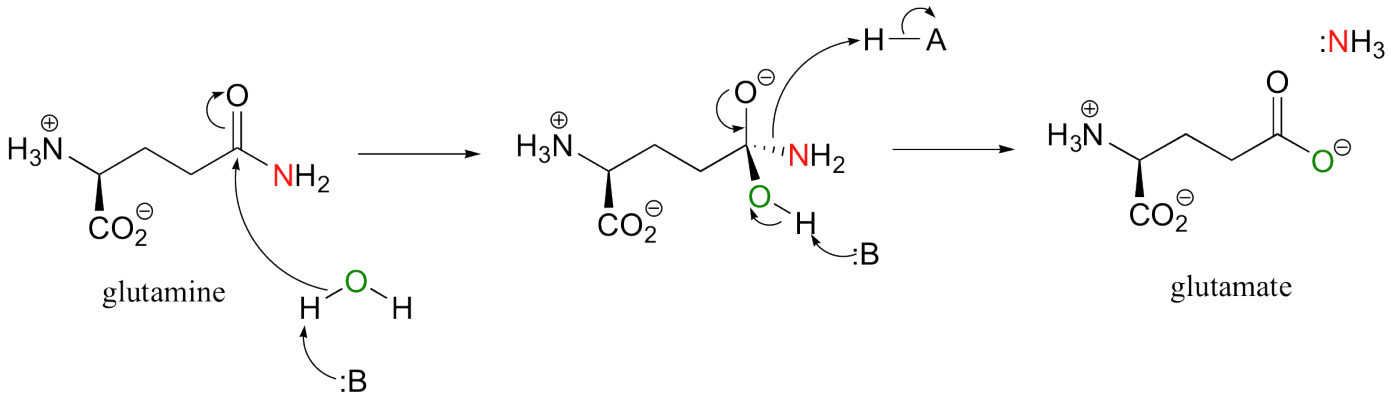
Another common form of activated carboxylate group is an acyl adenosine phosphate. Consider another amino acid reaction, the conversion of aspartate to asparagine. In the first step, the carboxylate group of aspartate must be activated:



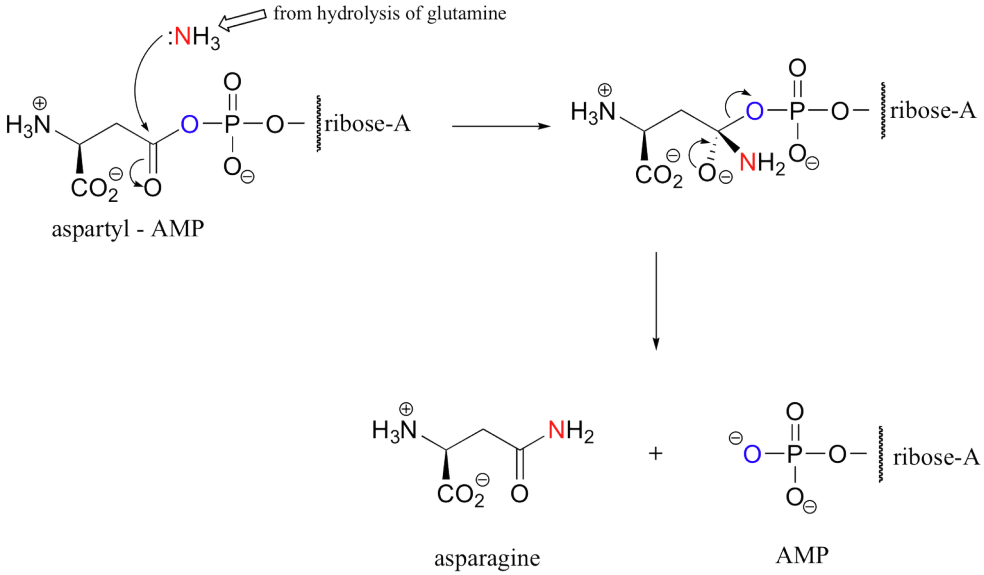
Once again, ATP provides the energy for driving the uphill reaction. This time, however, the activated carboxylate takes the form

of an acyl adenosine (mono)phosphate. All that has happened is that the carboxylate oxygen has attacked the a-phosphate of ATP rather than the g-phosphate.

The reactive acyl-AMP version of aspartate is now ready to be converted to an amide (asparagine) via nucleophilic attack by ammonia. In the case of glutamine synthase, the source of ammonia was free ammonium ion in solution. In the case of asparagine synthase, the NH_3 is derived from the hydrolysis of glutamine (this is simply another acyl substitution reaction):

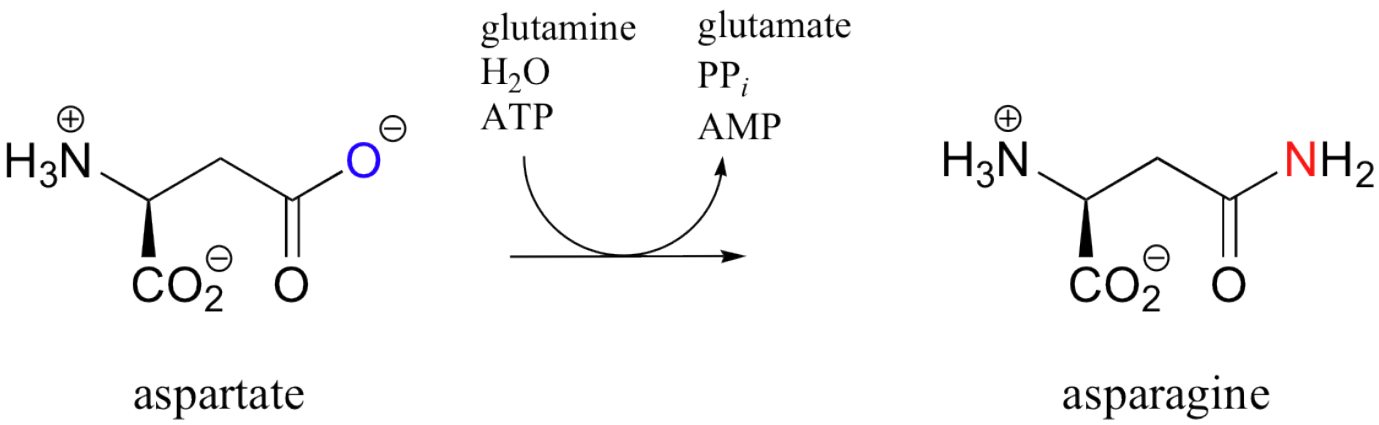


The hydrolysis reaction is happening in the same enzyme active site – as the NH_3 is expelled in the hydrolysis of glutamine, it immediately turns around and acts as the nucleophile in the conversion of aspartyl-AMP to asparagine:



Keep in mind that the same enzyme is also binding ATP and using it to activate aspartate – this is a busy construction zone!

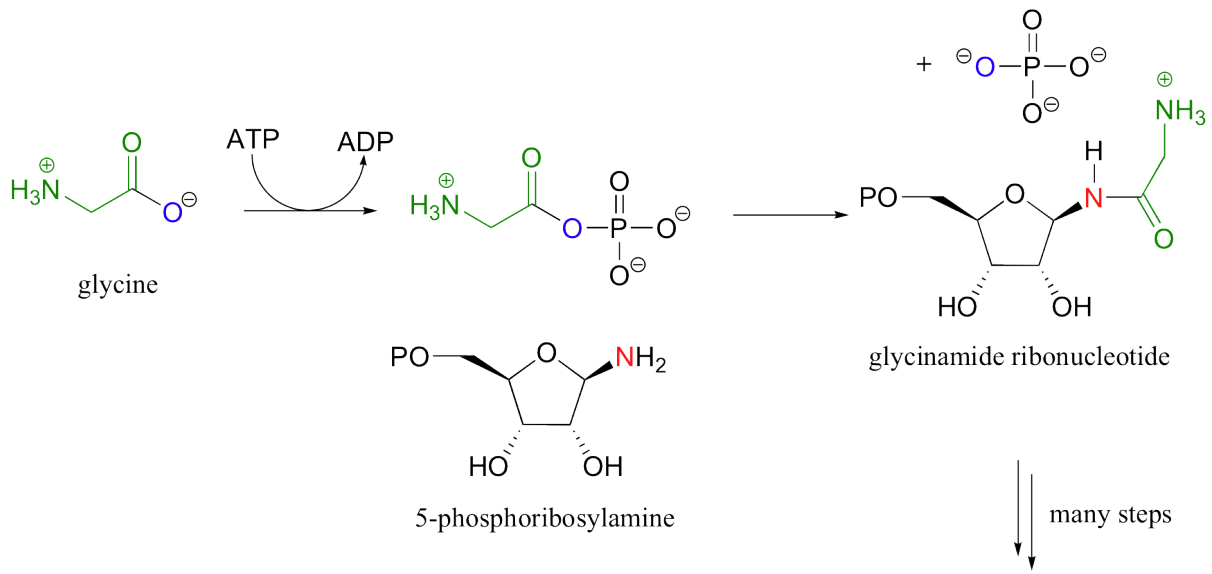
Overall, this reaction can be written in condensed form as:

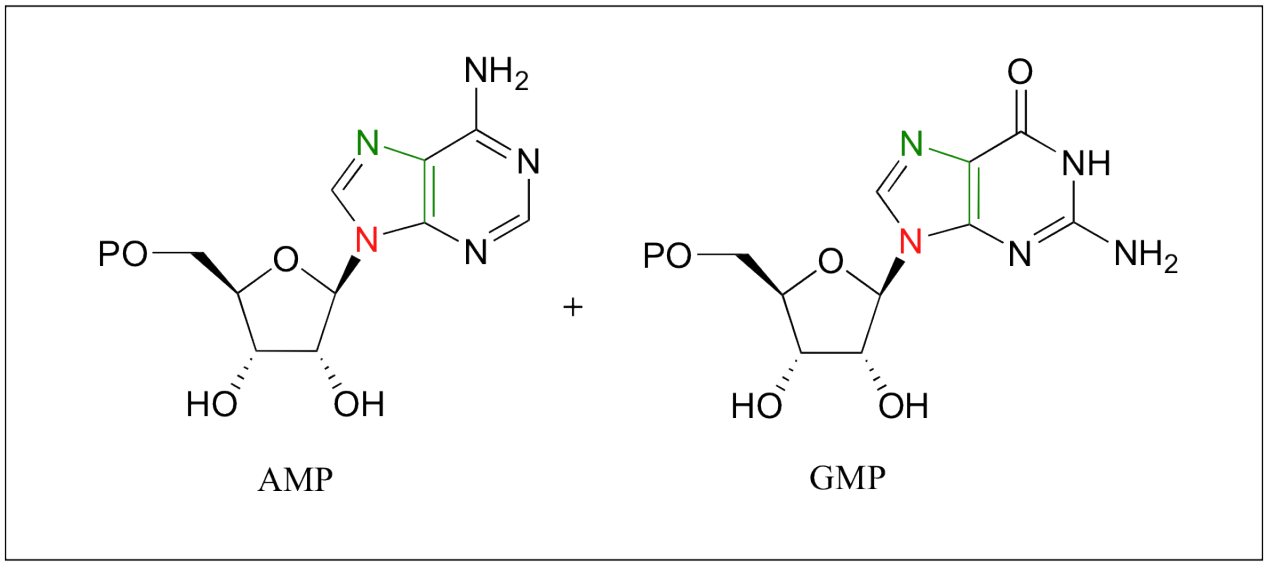


The use of glutamine as a 'carrier' for ammonia is a fairly common strategy in metabolic pathways. This strategy makes sense, as it allows cells to maintain a constant source of NH_3 for reactions that require it, without the need for high solution concentrations of free ammonia.

Glycinamide ribonucleotide synthetase

One of the early steps in the construction of purine bases (the adenine and guanine bases in DNA and RNA) involves an acyl substitution reaction with an acyl phosphate intermediate. In this case, the attacking nucleophile is not ammonia but a primary amine. The strategy, however, is similar to that of glutamine synthase. The carboxylate group on glycine is converted to an acyl phosphate, at the cost of one ATP molecule. The acyl group is then transferred to 5-phosphoribosylamine, resulting in an amide product.





Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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20: CARBOXYLIC ACID DERIVATIVES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

20.1: Relative Reactivities, Structures, and Spectra of Carboxylic Acid Derivatives

20.2: Chemistry of Alkanoyl Halides

20.3: Chemistry of Carboxylic Anhydrides

20.4: Chemistry of Esters

20.5: Esters in Nature: Waxes, Fats, Oils, and Lipids

20.6: Amides: The Least Reactive Carboxylic Acid Derivatives

20.7: Amidates and Their Halogenation: The Hofmann Rearrangement

20.8: Alkanenitriles: A Special Class of Carboxylic

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20.1: Relative Reactivities, Structures, and Spectra of Carboxylic Acid Derivatives

Objectives

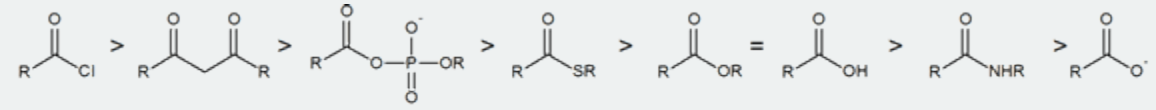
After completing this section, you should be able to

1. compare the reactions of carboxylic acid derivatives with nucleophiles to the reactions of aldehydes and ketones with nucleophiles.
2. arrange a given list of carboxylic acid derivatives in order of increasing or decreasing reactivity towards nucleophiles.
3. explain the difference in reactivity towards nucleophiles of two or more given carboxylic acid derivatives.
4. explain why esters and amides are commonly found in nature, but acid halides and acid anhydrides are not.

Study Notes

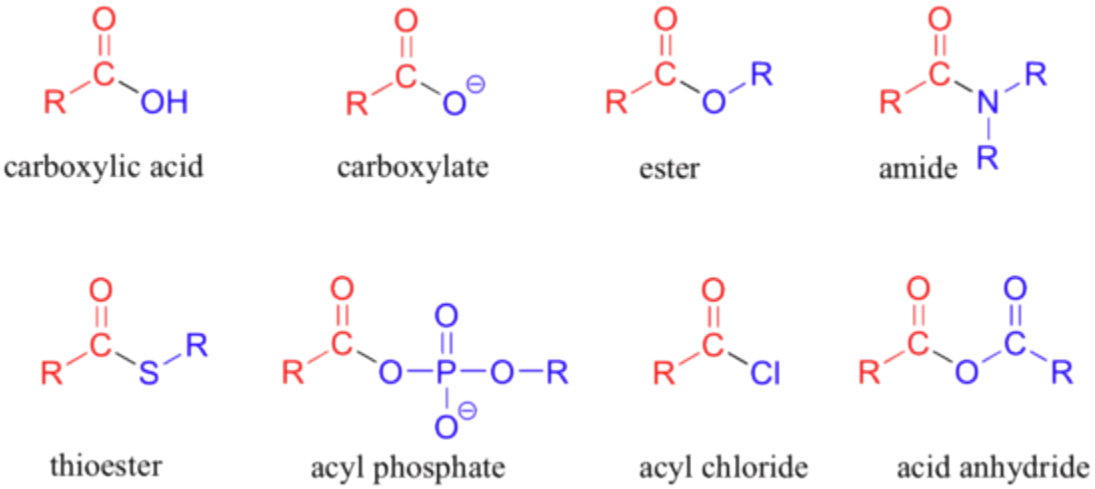
The general nucleophilic acyl substitution reaction, and its mechanism, were discussed earlier in "III. General Reactions of Carbonyl Compounds." Review if necessary.

The reading describes the relative reactivities of "biologically relevant acyl groups." Both acid anhydrides and acid halides readily react with water and cannot exist for any length of time in living organisms. The following scheme illustrates the relative reactivities of most carboxylic acid derivatives that you will encounter.

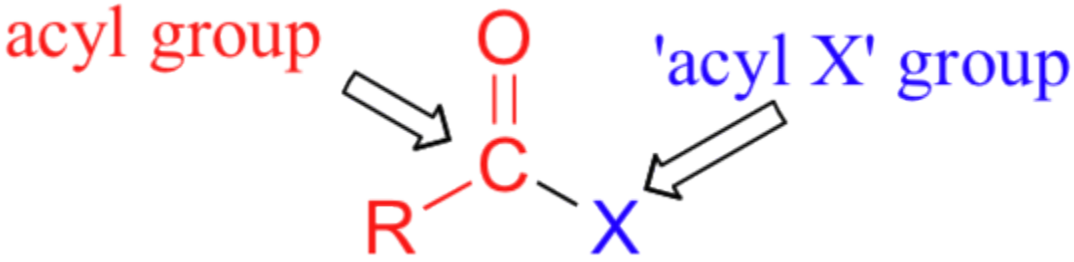


Carboxylic acid derivatives and acyl groups

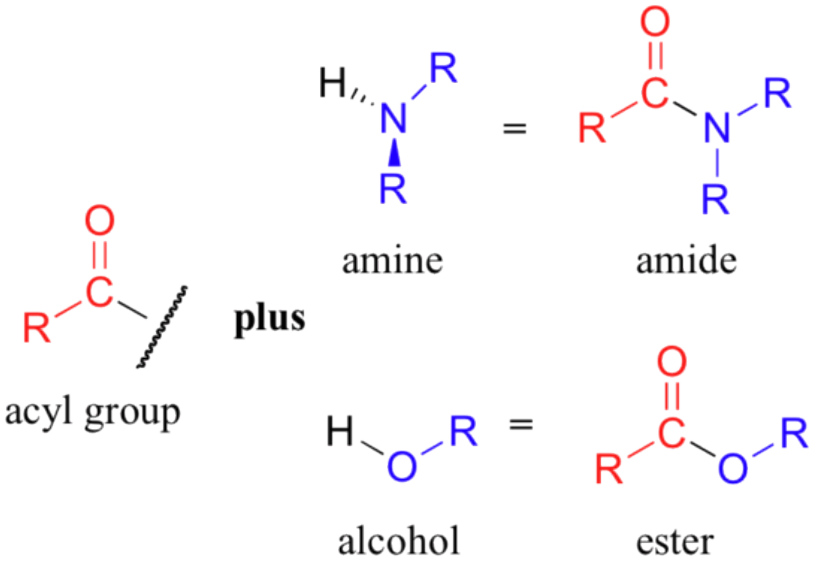
The functional groups that undergo nucleophilic acyl substitutions are called carboxylic acid derivatives: these include carboxylic acids themselves, carboxylates (deprotonated carboxylic acids), amides, esters, thioesters, and acyl phosphates. Two more examples of carboxylic acid derivatives which are less biologically relevant but important in laboratory synthesis are carboxylic acid anyhydrides and acid chlorides.



The carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, or sulfur – bonded directly to the carbonyl carbon. You can think of a carboxylic acid derivative as having two sides. One side is the carbonyl group and the attached alkyl group: this is called an **acyl group** (in the specific case where R is a methyl group, the term **acetyl group** is used). One the other side is the heteroatom-containing group: in this text, we will sometimes refer to this component as the 'acyl X' group (this, however, is *not* a standard term in organic chemistry).



Notice that the acyl X groups are simply deprotonated forms of other functional groups: in an amide, for example, the acyl X group is an amine, while in an ester the acyl X group is an alcohol.

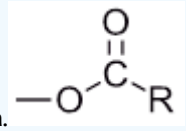


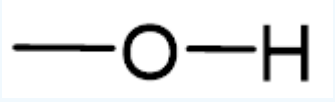
Example 21.2.1

What is the 'Y' group in:

a. an acid anhydride?
b. a carboxylic acid?

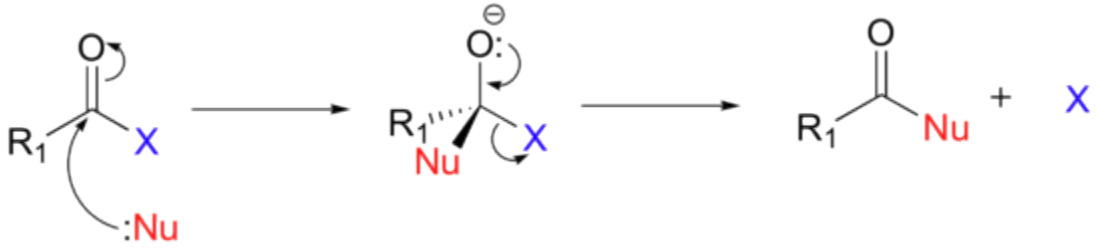
Answers

a. 

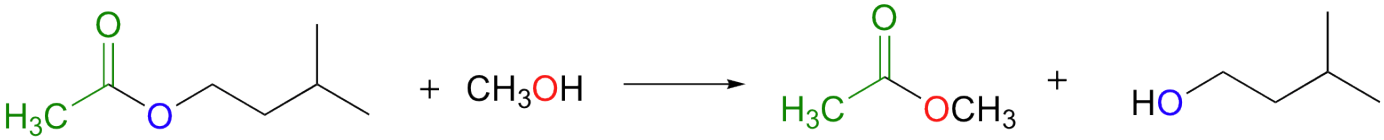
b. 

The nucleophilic acyl substitution reaction

The fact that the atom adjacent to the carbonyl carbon in carboxylic acid derivatives is an electronegative heteroatom – rather than a carbon like in ketones or a hydrogen like in aldehydes - is critical to understanding the reactivity of these functional groups. Just like in aldehydes and ketones, carboxylic acid derivatives are attacked from one side of their trigonal planar carbonyl carbon by a nucleophile, converting this carbon to tetrahedral (sp^3) geometry. In carboxylic acid derivatives, the acyl X group is a potential leaving group. What this means is that the tetrahedral product formed from attack of the nucleophile on the carbonyl carbon is not the product: it is a *reactive intermediate*. The tetrahedral intermediate rapidly collapses: the carbon-oxygen double bond re-forms, and the acyl X group is expelled.

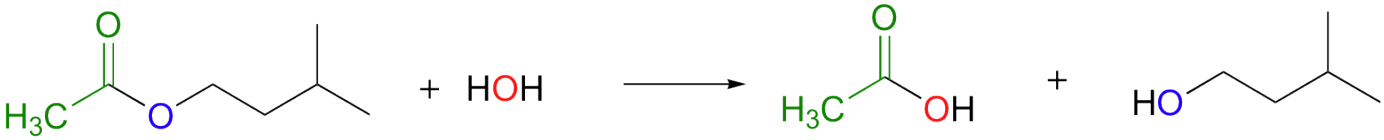


Notice that in the product, the nucleophile becomes the new acyl X group. This is why this reaction type is called a nucleophilic acyl *substitution*: one acyl X group is substituted for another. For example, in the reaction below, one alcohol X group (3-methyl-1-butanol) is replaced by another alcohol X group (methanol), as one ester is converted to another.



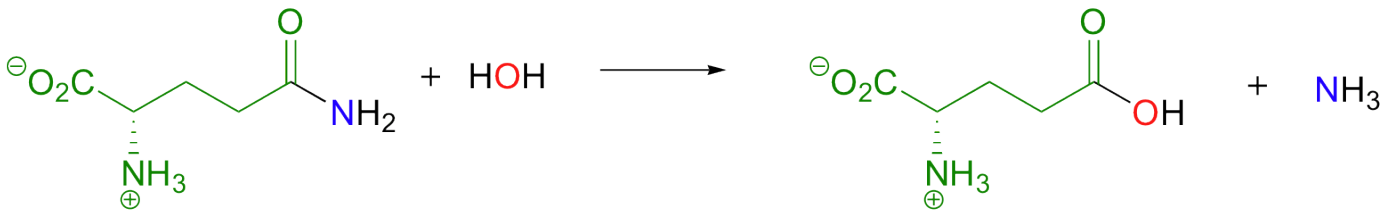
Another way of looking at this reaction is to picture the *acyl* group being transferred from one acyl X group to another: in the example above, the acetyl group is being transferred from 3-methyl-1-butanol to methanol. For this reason, nucleophilic acyl substitutions are also commonly referred to as **acyl transfer** reactions.

When the incoming nucleophile in an acyl substitution is a water molecule, the reaction is also referred to as an acyl hydrolysis. For example, the following reaction can be described as the hydrolysis of an ester (to form a carboxylic acid and an alcohol).



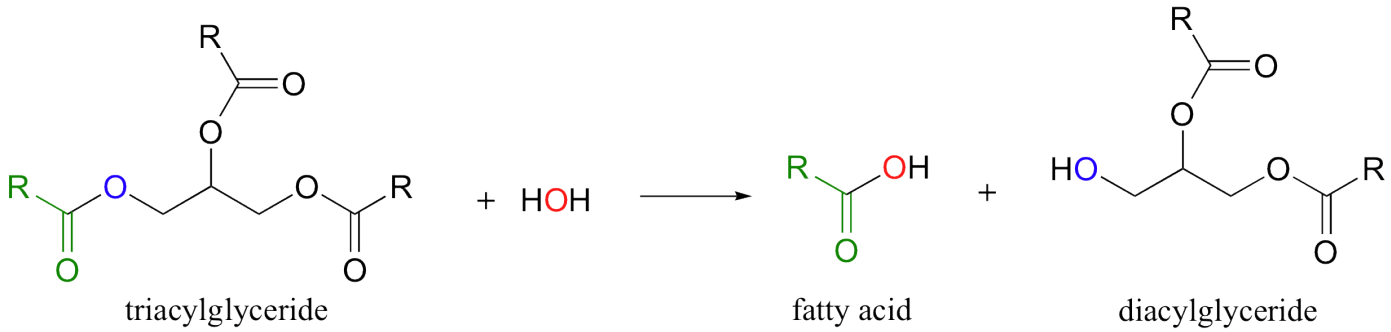
We could also describe this reaction as the transfer of an acyl group from an alcohol to a water molecule.

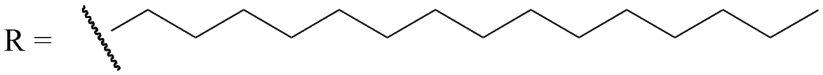
In a similar vein, the hydrolysis of an amide to form a carboxylic acid could be described as the transfer of an acyl group from ammonia (NH_3) to water.



glutamine glutamate

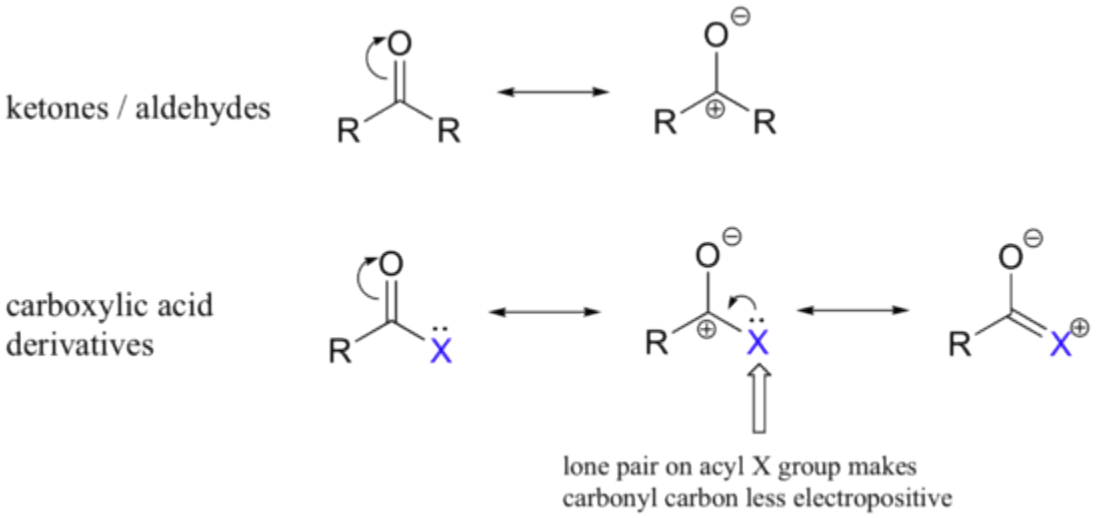
As we will see in later sections of this chapter the hydrolysis of esters and amides are particularly important reaction types in biochemical pathways. When your body digests the fat in a hamburger, for example, enzymes in your pancreas called lipases first catalyze ester hydrolysis reactions to free the fatty acids (we'll look more closely at this reaction in section 12.4D).



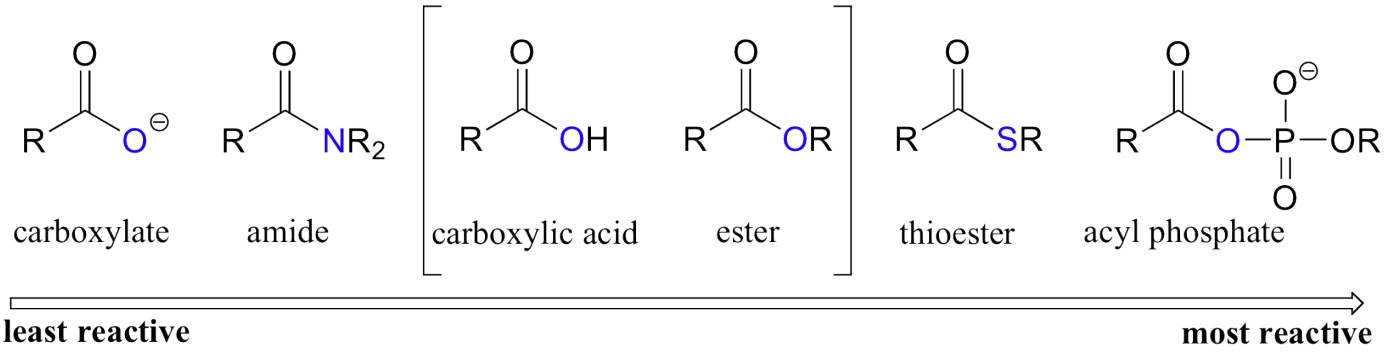


The relative reactivity of carboxylic acid derivatives

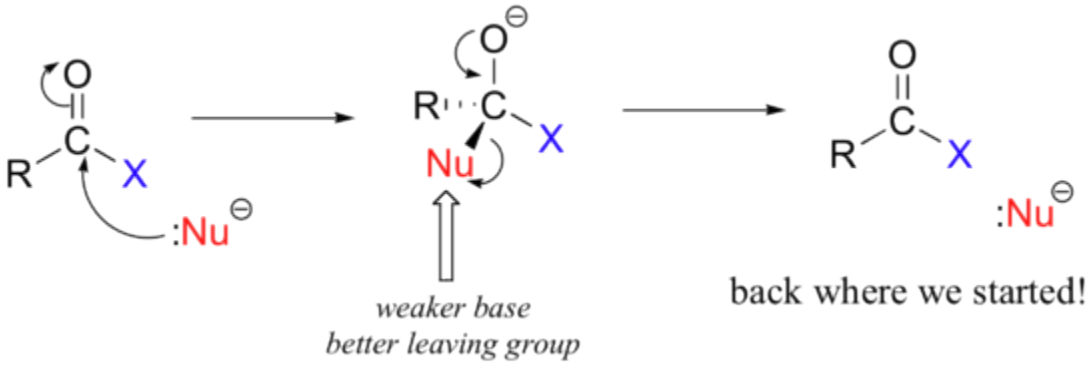
The relative reactivity of the carboxylic acid derivatives is an important concept to understand before entering into a detailed examination of nucleophilic acyl substitutions. As a general rule, the carbonyl carbon in an acyl group is less electrophilic than that in an aldehyde or ketone. This is because in carboxylic acid derivatives, the partial positive charge on the carbon is stabilized somewhat by resonance effects from the adjacent heteroatom.



Among the carboxylic acid derivatives, carboxylate groups are the least reactive towards nucleophilic acyl substitution, followed by amides, then esters and (protonated) carboxylic acids, thioesters, and finally acyl phosphates, which are the most reactive among the biologically relevant acyl groups.



The different reactivities of the functional groups can be understood by evaluating the basicity of the leaving group in each case - remember from section 8.5 that weaker bases are better leaving groups! A thioester is more reactive than an ester, for example, because a thiolate (RS^-) is a weaker base than an alkoxide (RO^-). In general, if the incoming nucleophile is a weaker base than the 'acyl X' group that is already there, the first nucleophilic step will simply reverse itself and we'll get the starting materials back:

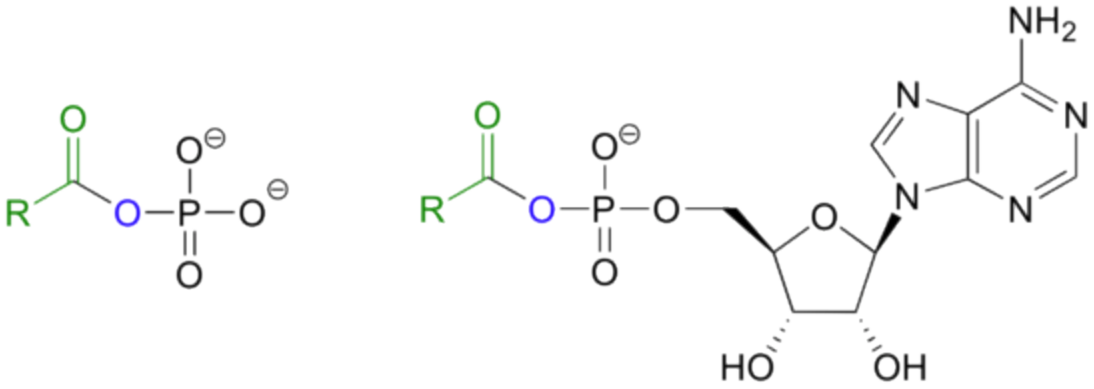


This is why it is not possible to *directly* convert an ester, for example, into a thioester by an acyl substitution reaction – this would be an uphill reaction.

Here's another way to think about the relative reactivites of the different carboxylic acid derivatives: consider the relative electrophilicity, or degree of partial positive charge, on the carbonyl carbon in each species. This depends on how much electron density the neighboring heteroatom on the acyl X group is able to donate: greater electron donation by the heteroatom implies lower partial positive charge on the carbonyl carbon, which in turn implies lower electrophilicity.

The negatively charged oxygen on the carboxylate group has lots of electron density to donate, thus the carbonyl carbon is not very electrophilic. In amides, the nitrogen atom is a powerful electron donating group by resonance - recall that the carbon-nitrogen bond in peptides has substantial double-bond character - thus amides are relatively unreactive. Amides *do* undergo acyl substitution reactions in biochemical pathways, but these reactions are inherently slow and the enzymes catalyzing them have evolved efficient strategies to lower the activation energy barrier.

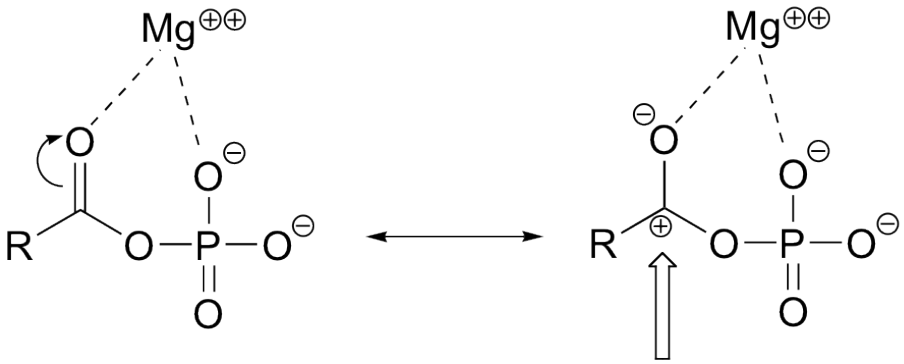
Carboxylic acids and esters are in the middle range of reactivity, while thioesters are somewhat more reactive. The most reactive of the carboxylic acid derivatives frequently found in biomolecules are the acyl phosphates. These are most often present in two forms: the simple acyl monophosphate, and the acyl-adenosine monophosphate.



acyl monophosphate

acyl adenosine monophosphate (acyl AMP)

Both are highly reactive to acyl substitution reactions, and are often referred to as '**activated acyl groups**' or '**activated carboxylic acids**'. The high reactivity of acyl phosphates is due mainly to the ability to form complexes with magnesium ions.



coordination to Mg^{2+} makes this resonance structure more important

very electrophilic carbon

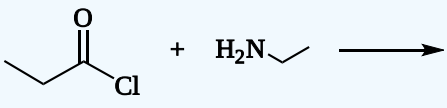
The magnesium ion acts as a Lewis acid to accept electron density from the oxygen end of the acyl carbonyl bond, thus greatly increasing the degree of partial positive charge - and thus the electrophilicity - of the carbonyl carbon. The magnesium ion also balances negative charge on the phosphate, making it an excellent leaving group.

In our examination of acyl substitution reactions, we will start with the formation and reactions of the highly reactive acyl phosphates. We will then discuss how thioesters play a key role in the acyl substitution reactions of lipid metabolism. Finally, we will take a look at some important acyl substitution reactions involving esters, as well as the formation and cleavage of the amide linkages in the peptide bonds of proteins.

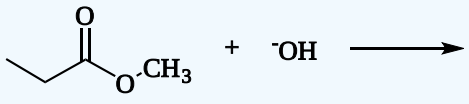
Worked Example 21.2.1

Draw the expected products of the following reactions:

a)

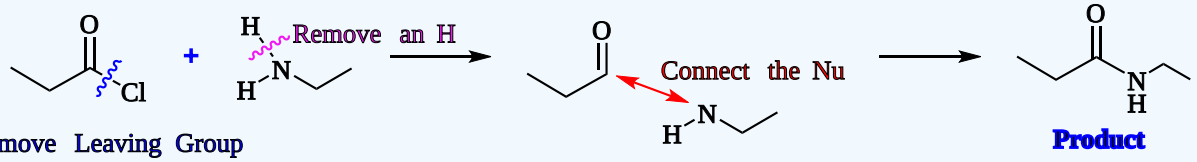


b)

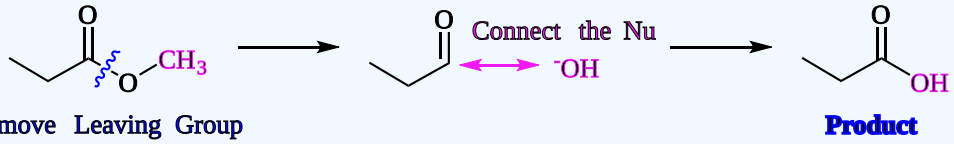


Solution

a) The nucleophile is neutral.



b) The nucleophile is negatively charged.

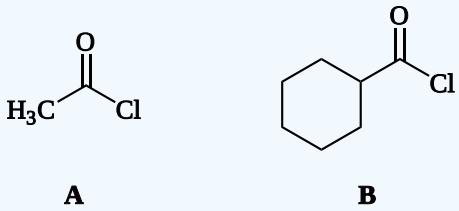


Exercises

Exercise 21.2.1

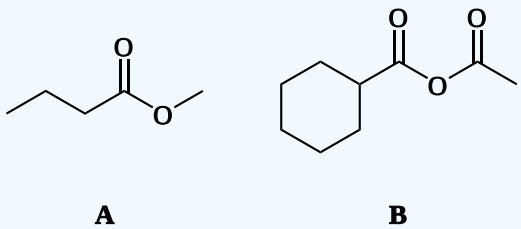
Which of the following compounds would be expected to be the most reactive towards nucleophilic acyl substitution? Briefly explain your answer.

a)



A **B**

b)



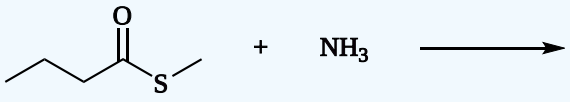
A **B**

Answer available at the end of this section.

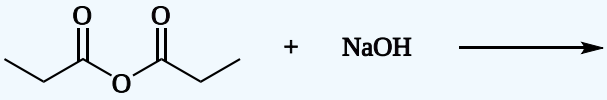
Exercise 21.2.2

Draw the expected products of the following reactions:

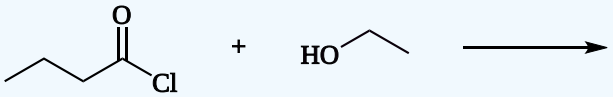
a)



b)



c)



Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Answers

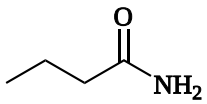
Exercise 21.2.1

a) Compound A would expected to be the more reactive. For two compounds with the same carboxylic acid derivative group the one with the least steric crowding on the acyl side is typically the most reactive.

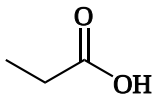
b) Compound B would be expected to be the more reactive. In general acid anhydrides are more reactive than ester.

Exercise 21.2.2

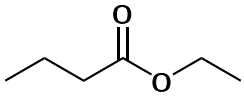
a)



b)



c)



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- 21.2: Nucleophilic Acyl Substitution Reactions by Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg is licensed CC BY-SA 4.0.

20.2: Chemistry of Alkanoyl Halides

Objectives

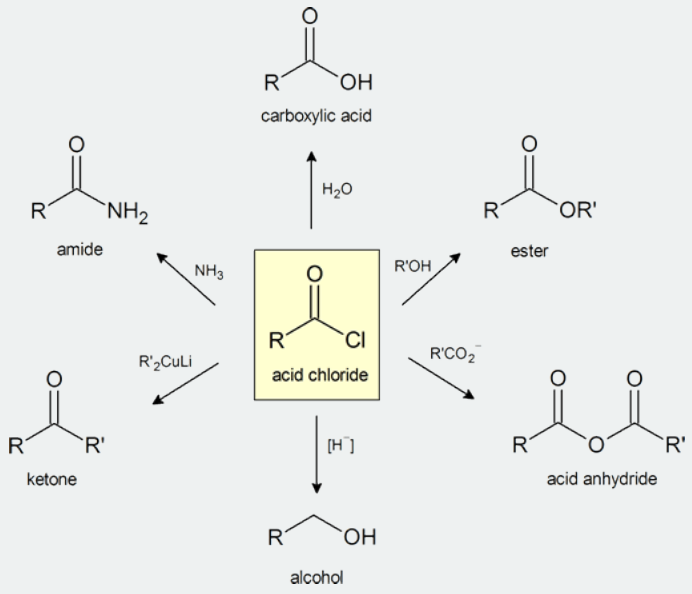
After completing this section, you should be able to

1. identify the reagent normally used to convert a carboxylic acid to an acid bromide.
2. write equations to show how an acid halide may be converted into each of the following: a carboxylic acid, an ester, an amide.
3. write a detailed mechanisms for the reaction of an acid halide with each of the following: water, an alcohol, ammonia, a primary or secondary amine.
4. identify the product formed when a given acid halide reacts with any of the following reagents: water, an alcohol, a primary or secondary amine.
5. identify the acid halide, the reagents, or both, needed to prepare a given carboxylic acid, ester or amide.
6. identify the product formed when a given acid halide reacts with water, a given alcohol, ammonia, or a given primary or secondary amine.
7. identify lithium aluminum hydride as a reagent for reducing acid halides to primary alcohols, and explain the limited practical value of this reaction.
8. identify the partial reduction of an acid halide using lithium tri-*tert*-butoxyaluminum to form an aldehyde.
9. write an equation to describe the formation of a tertiary alcohol by the reaction of an acid halide with a Grignard reagent.
10. write a detailed mechanism for the reaction of an acid halide with a Grignard reagent.
11. identify the product formed from the reaction of a given acid halide with a given Grignard reagent.
12. identify the acid halide, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
13. write an equation to illustrate the reaction of an acid halide with a lithium diorganocopper reagent.
14. identify the product formed from the reaction of a given acid halide with a given lithium diorganocopper reagent.
15. identify the acid halide, the lithium diorganocopper reagent, or both, that must be used to prepare a given ketone.

Study Notes

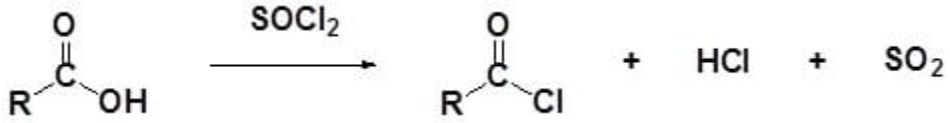
This figure provides a convenient general summary of a few of the reactions described in Section 21.4.

Note that $LiAlH_4$ is a common reagent for hydride [H^-] reduction of and acid chloride to an alcohol.

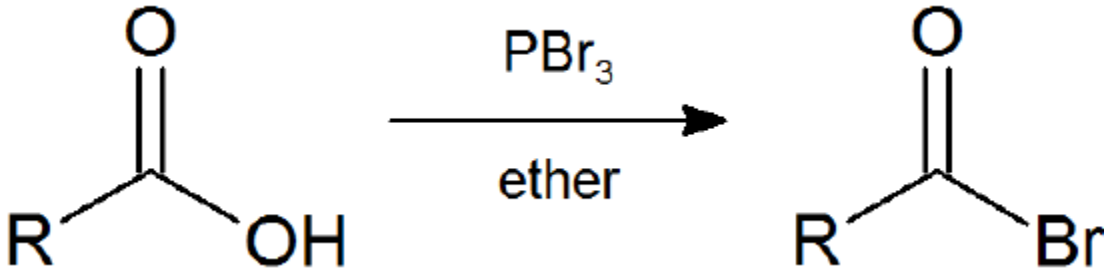


Formation of Acid Halides

Carboxylic acids react with thionyl chloride ($SOCl_2$) to form acid chlorides. During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

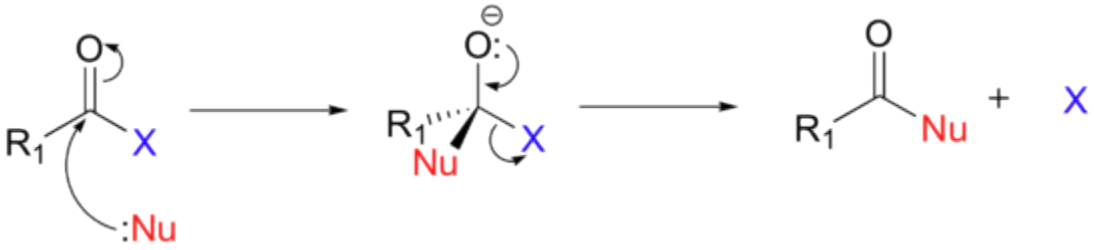


Earlier (Section 10.5) we saw that primary and secondary alcohols react with PBr_3 to afford the corresponding alkyl bromide. In a similar fashion acid bromides can be formed from the carboxylic acid.



Nucleophilic Acyl Substitution Mechanism

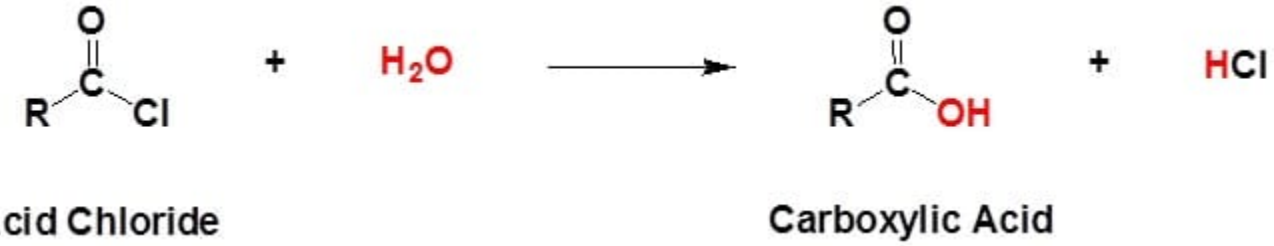
If you understand the mechanism of a typical nucleophilic acyl substitution, the reaction of an acyl halide with water, an alcohol or ammonia should not present you with any difficulty.



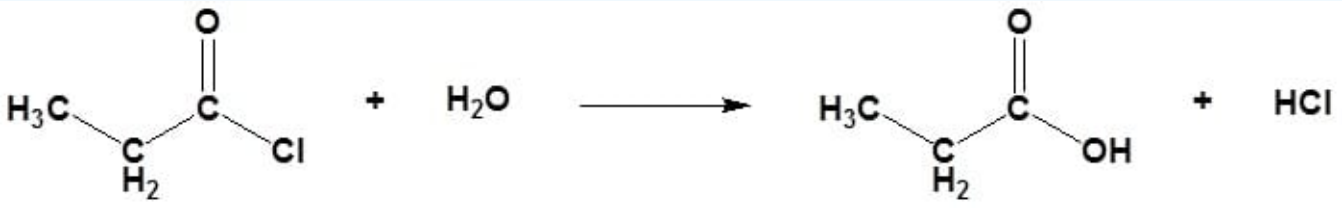
X = Cl, Br :Nu = H_2O, ROH, NH_2R, NHR_2 etc.

Acid chlorides react with water to form carboxylic acids.

General reaction

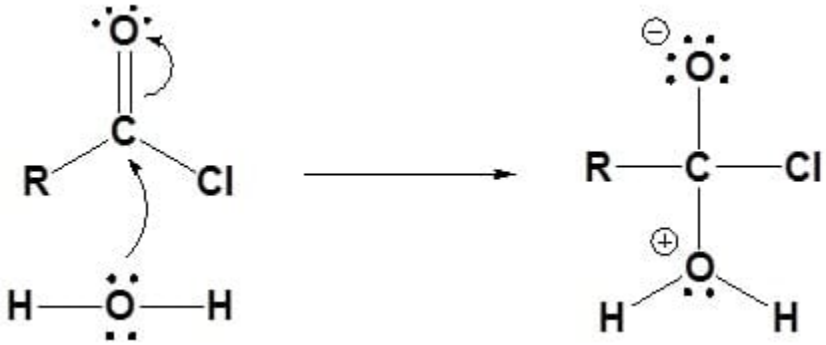


Example 21.4.1

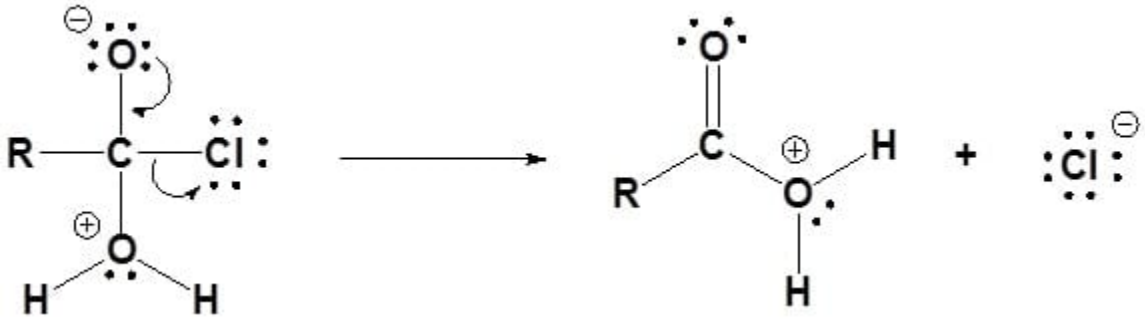


Mechanism

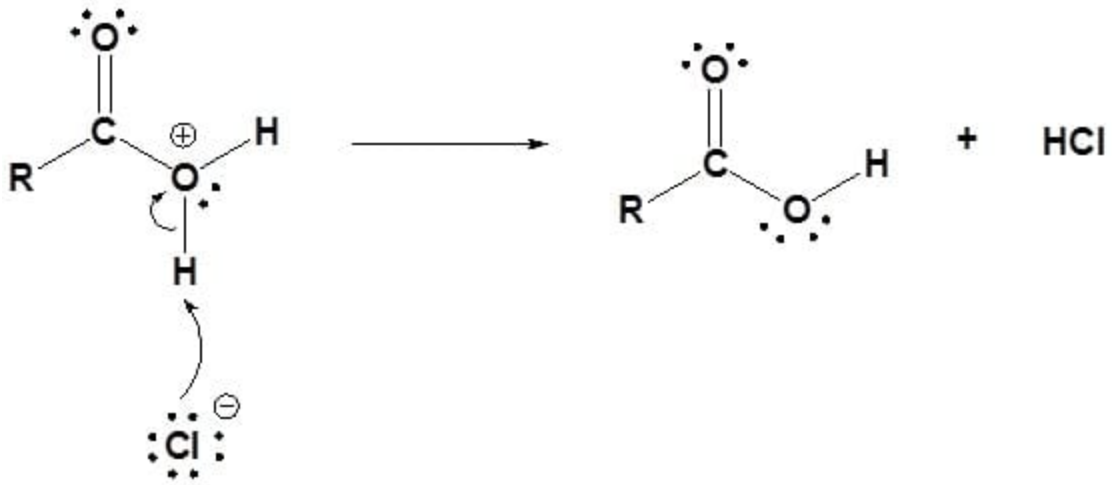
1) Nucleophilic attack by water



2) Leaving group is removed



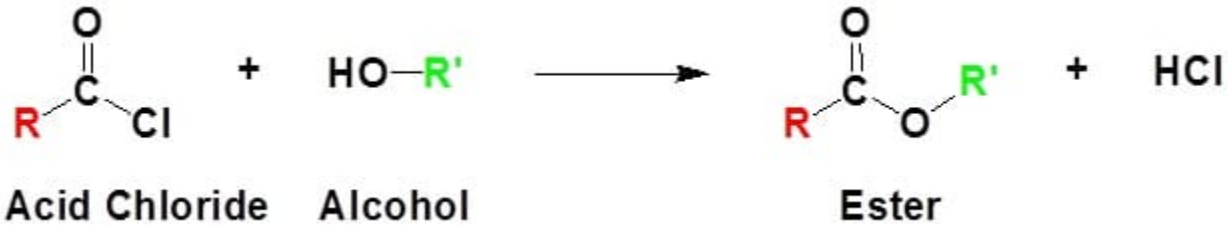
3) Deprotonation



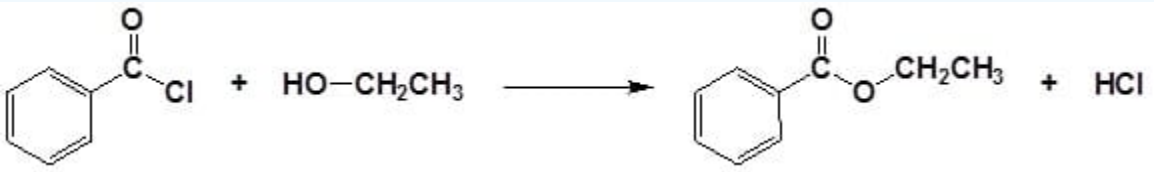
Acid chlorides react with carboxylic acids to form anhydrides



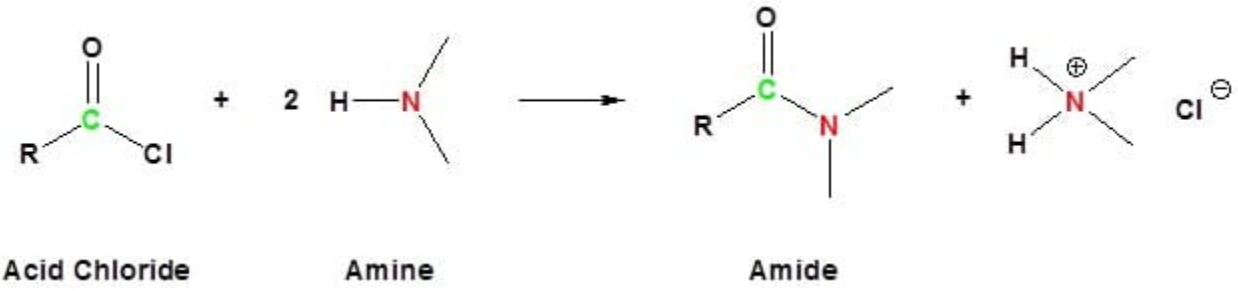
Acid chlorides react with alcohols to form esters



Example 21.4.2

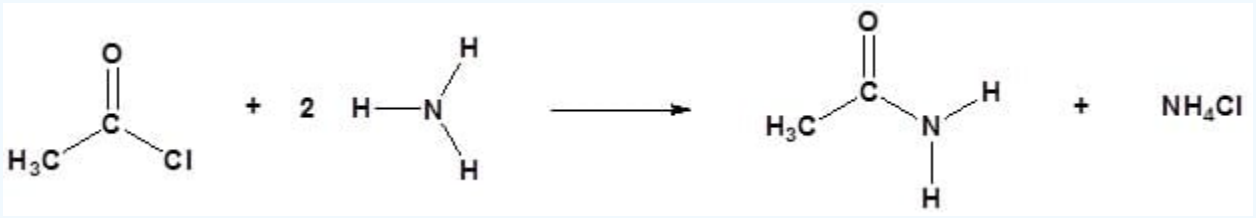


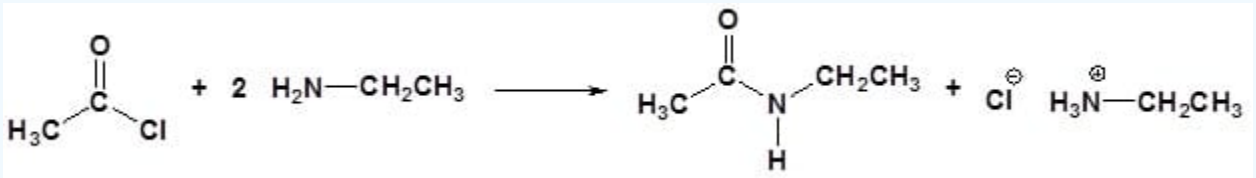
Acid chlorides react with ammonia, 1° amines and 2° amines to form amides.



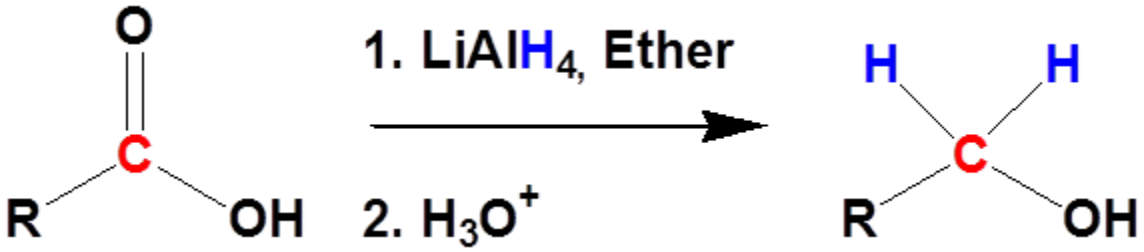
Acid Chloride Amine Amide

Example 21.4.3

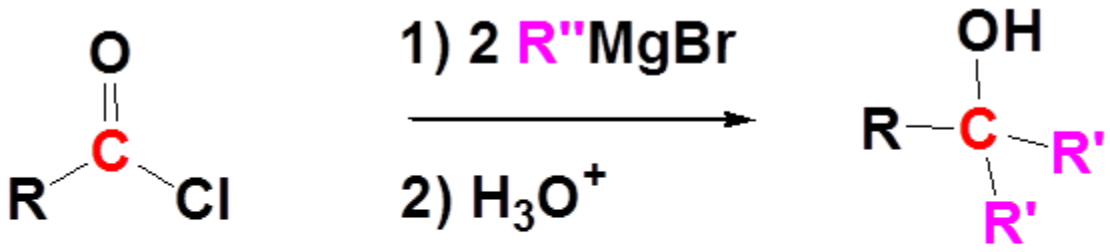




Acid Chlorides can be Reduced to form 1° Alcohols

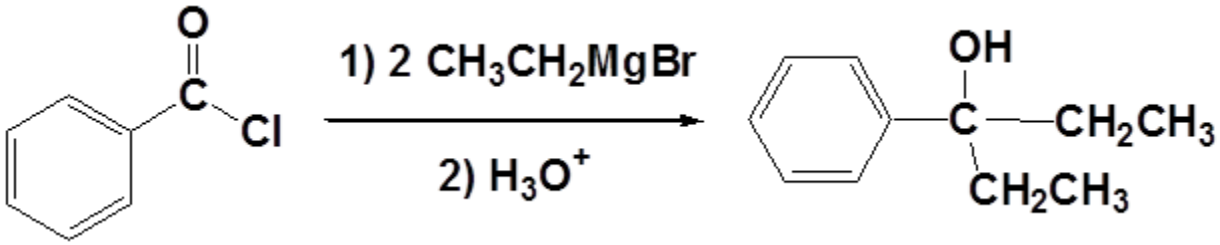


Grignard reagents convert acid chloride to 3° alcohols

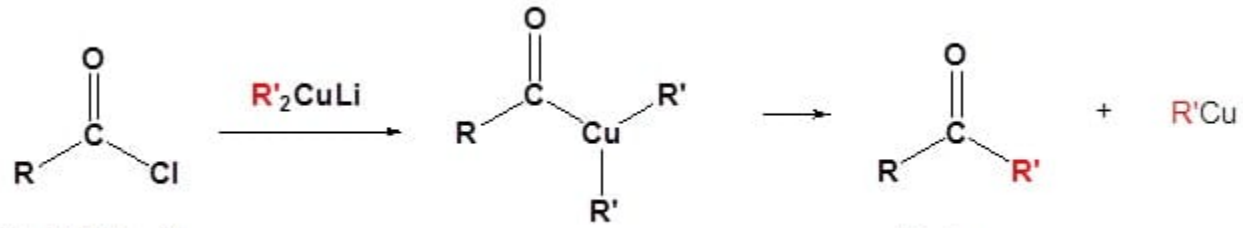


Acid Chloride

3° Alcohol



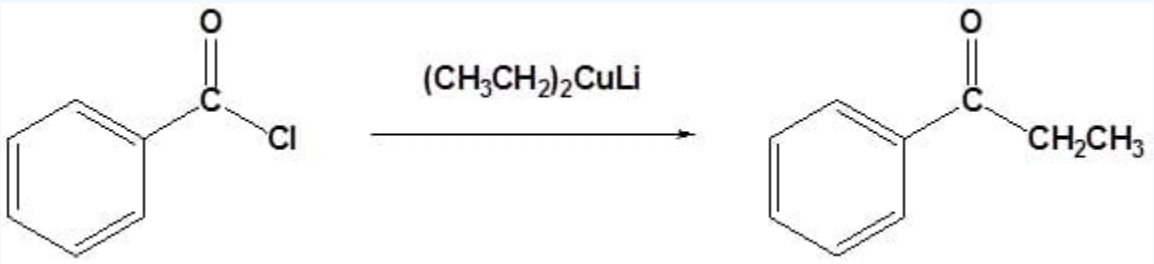
Organocuprate reagents convert acid chlorides to ketones.



Acid Chloride

Ketone

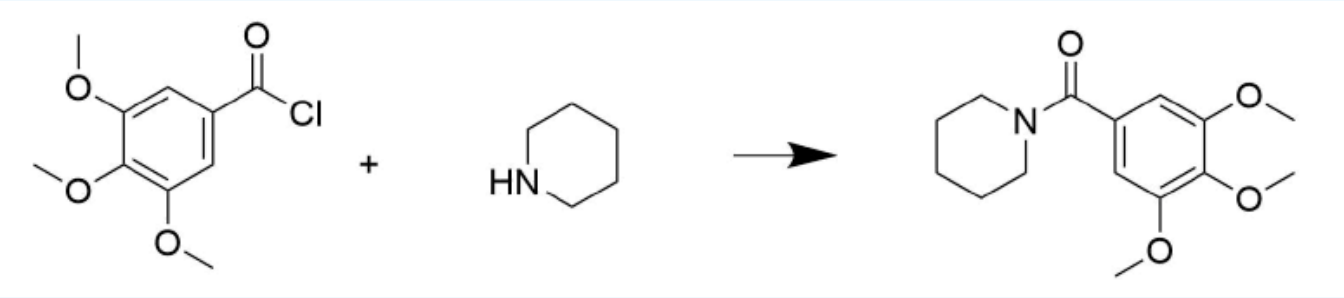
Example 21.4.4



Exercises

Exercise 21.4.1

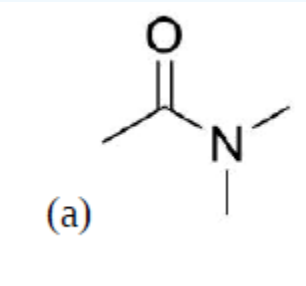
Draw the mechanism for the following reaction.

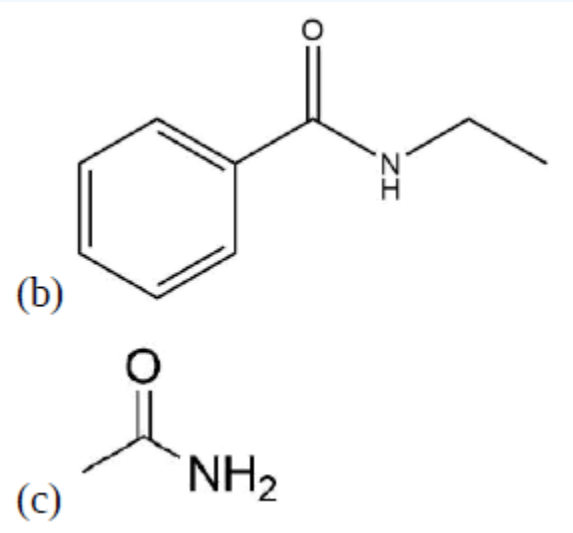


Answer available at the end of this section.

Exercise 21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.





Answer available at the end of this section.

Questions

Q21.4.1

Draw the mechanism for the following reaction

21.11 Question.png

Q21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.

(a)21.12 A (N N Dimethylacetamide).png

(b) 21.12 B (N Ehtylbenzamide).png

(c) 21.12 C (Acetamide).png

Solutions

S21.4.1

21.11 answer.png

S21.4.2

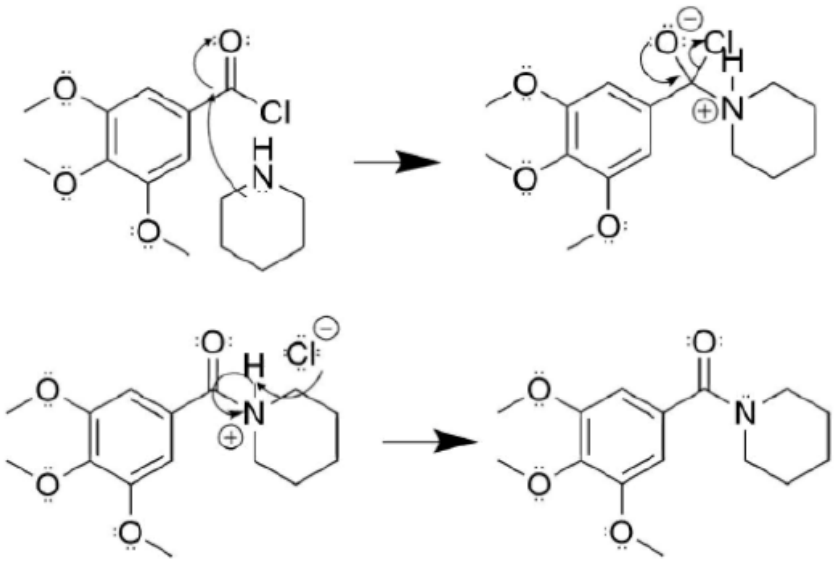
a. Acetyl chloride and dimethylamine
b. Benzoyl chloride and ethylamine
c. Acetyl chloride and ammonia

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 21.4.1



Exercise 21.4.2

a) Acetyl chloride and dimethylamine

b) Benzoyl chloride and ethylamine

c) Acetyl chloride and ammonia

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20.3: Chemistry of Carboxylic Anhydrides

Objectives

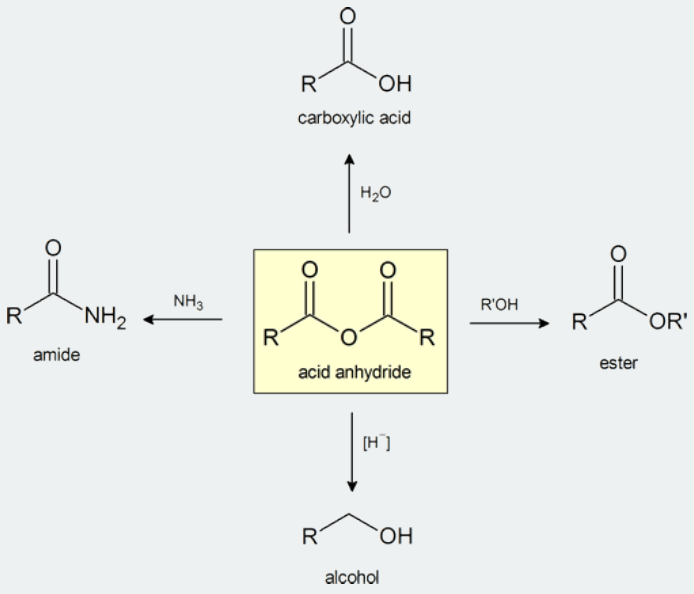
After completing this section, you should be able to

1. write an equation to illustrate the preparation of an acid anhydride from an acid halide and the sodium salt of a carboxylic acid.
2. identify the product formed from the reaction of a given acid halide with the sodium salt of a given carboxylic acid.
3. identify the acid halide, carboxylate salt, or both, required to prepare a given acid anhydride.
4. write an equation to describe the reaction of an acid anhydride with each of the following: water, alcohol, ammonia, a primary or secondary amine, lithium aluminum hydride.
5. identify the product formed when a given acid anhydride is reacted with any of the reagents listed in Objective 4, above.
6. write a detailed mechanism for the reaction of an acid anhydride with any of the reagents listed in Objective 4, above.
7. identify the acid anhydride, the nucleophilic reagent, or both, needed to prepare a specified carboxylic acid, ester, amide, or primary alcohol.

Study Notes

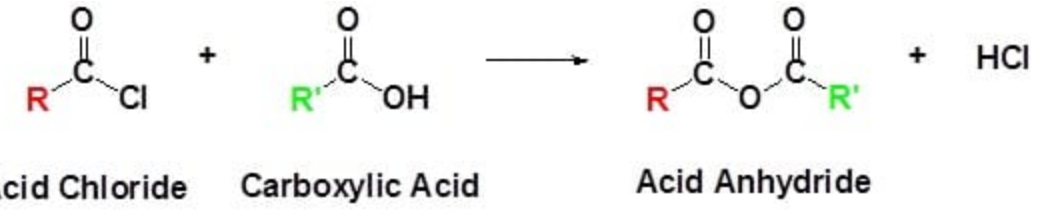
The reactions described in this section are, in principle, identical to those discussed in Section 21.4. Once you have understood the mechanism of nucleophilic acyl substitution, these reactions should not present you with any great difficulty, and memorization can be kept to a minimum.

This figure provides a convenient general summary of a few of the reactions described in Section 21.5. Note that from a synthetic perspective the ester- and amide-forming reactions are the most common, so they are the focus of this section.



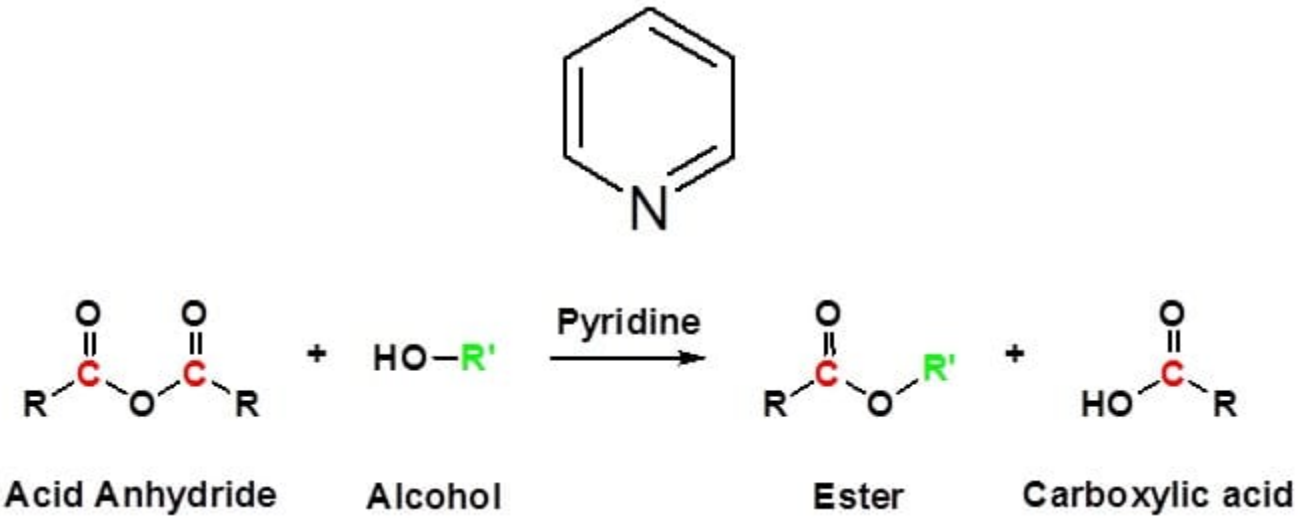
Preparation of Acid Anhydrides

Acid Chlorides react with carboxylic acids to form anhydrides

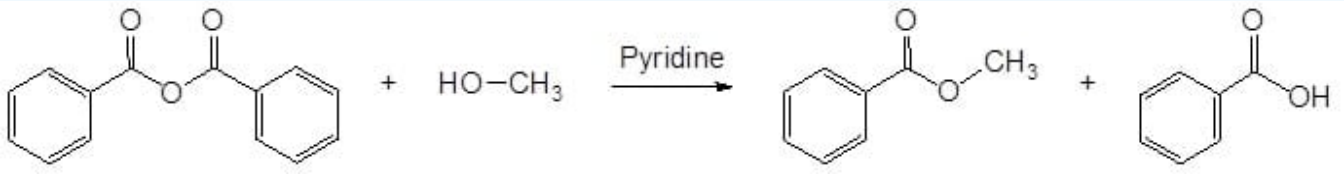


Acid Anhydrides react with alcohols to form esters

Reactions of anhydrides use Pyridine as a solvent

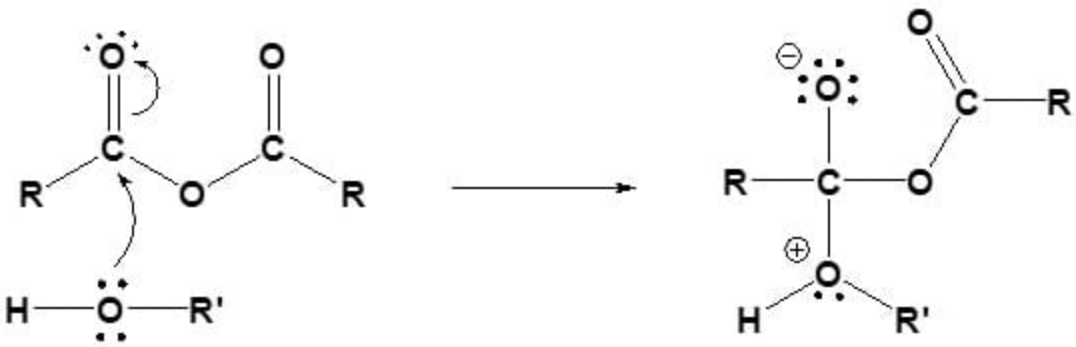


Example 21.5.1

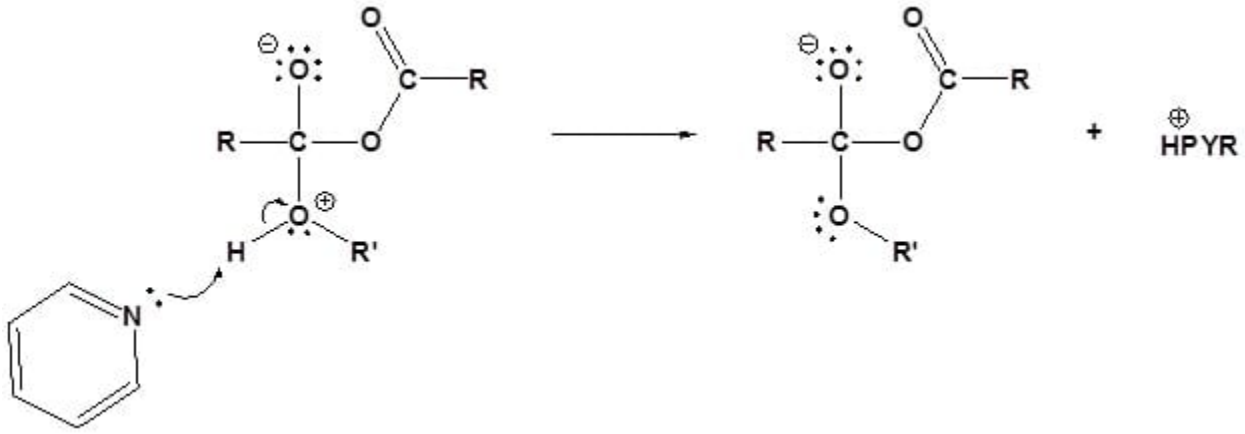


Mechanism

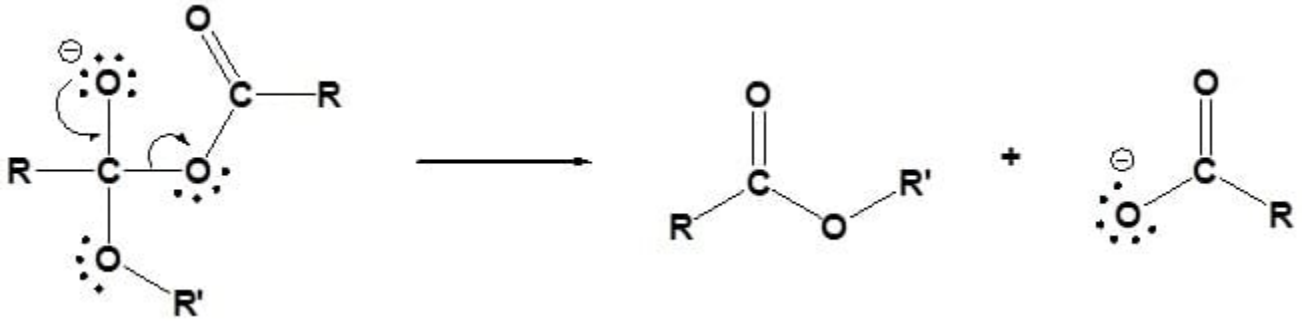
1) Nucleophilic Attack by the Alcohol



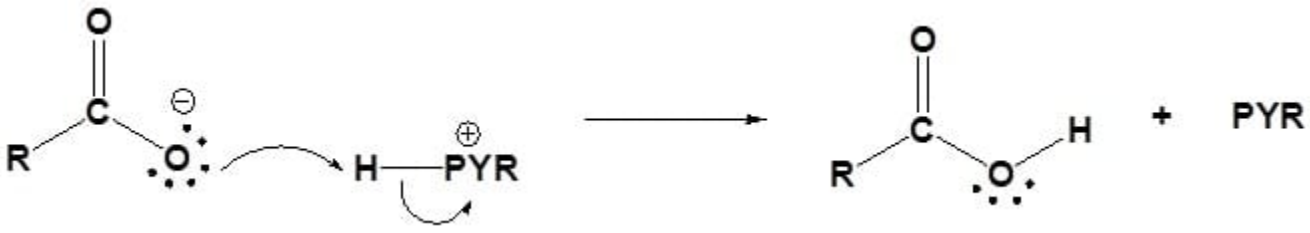
2) Deprotonation by pyridine



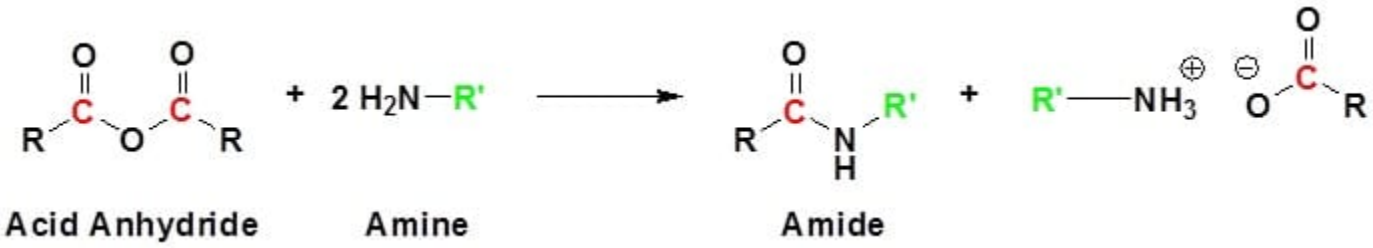
3) Leaving group removal



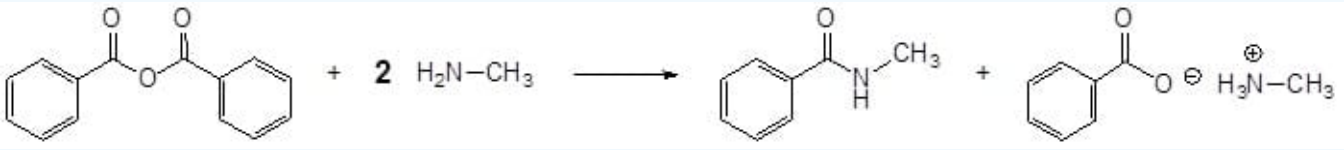
4) Protonation of the carboxylate



Acid Anhydrides react with amines to form amides

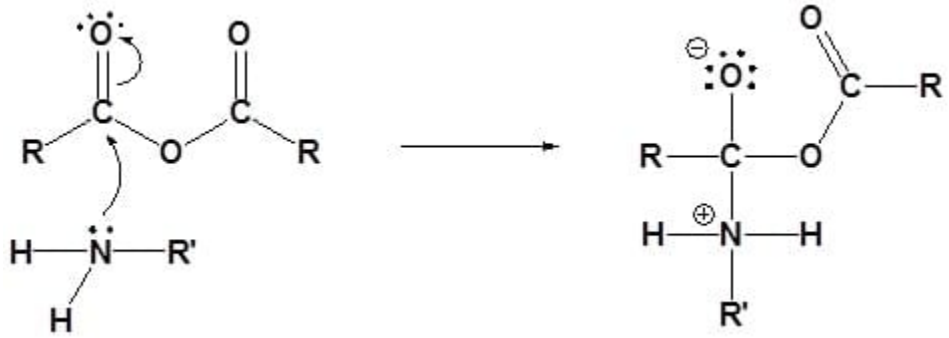


Example 21.5.2

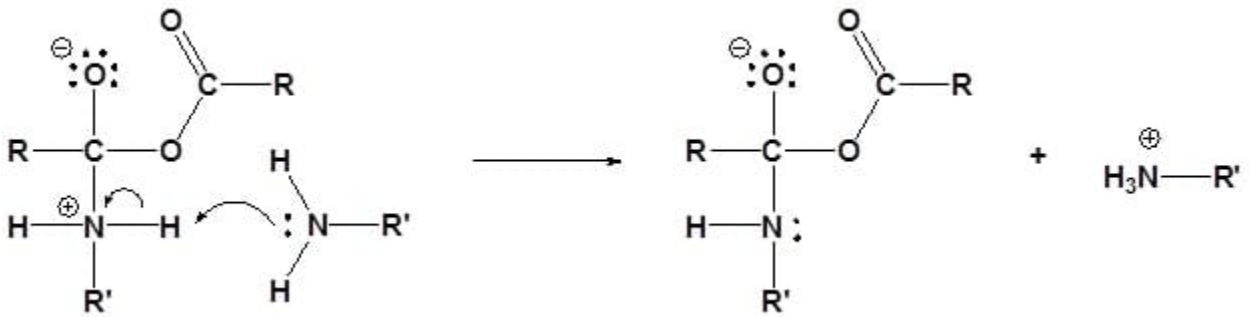


Mechanism

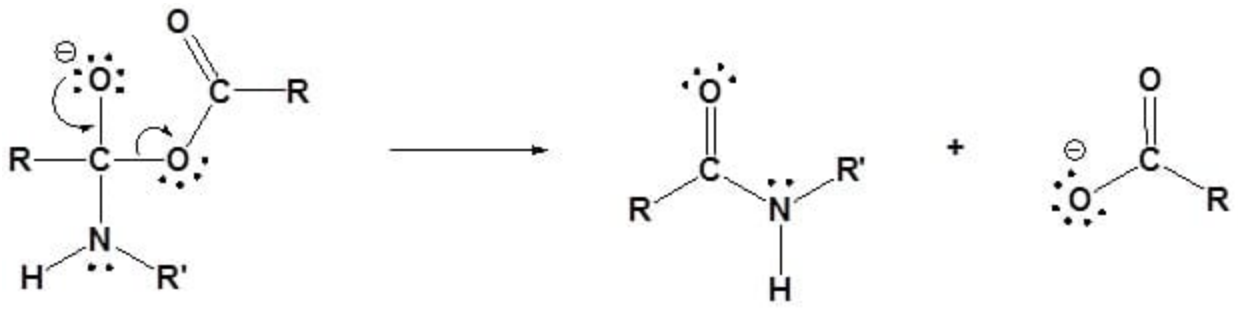
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



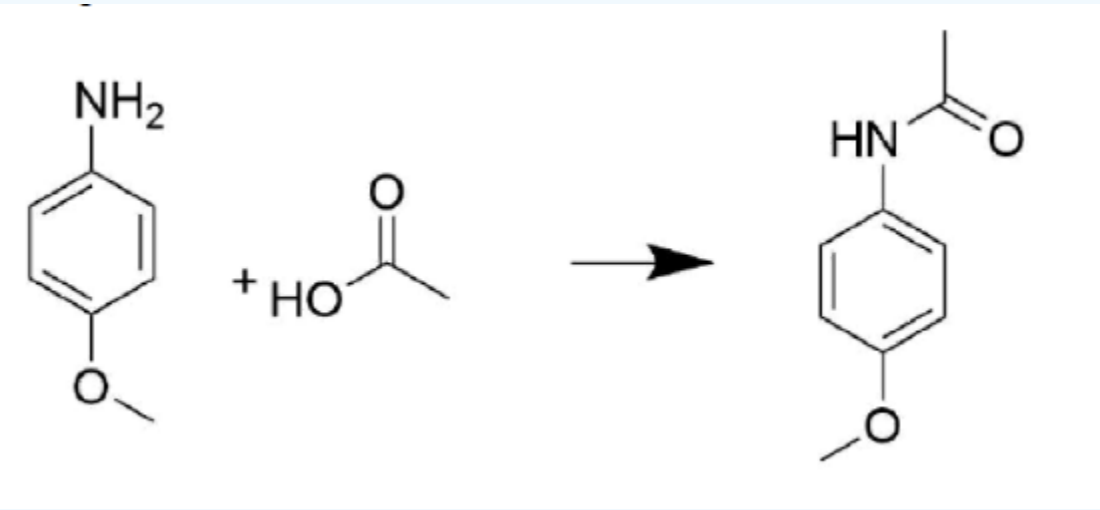
3) Leaving group removal



Exercises

Exercise 21.5.1

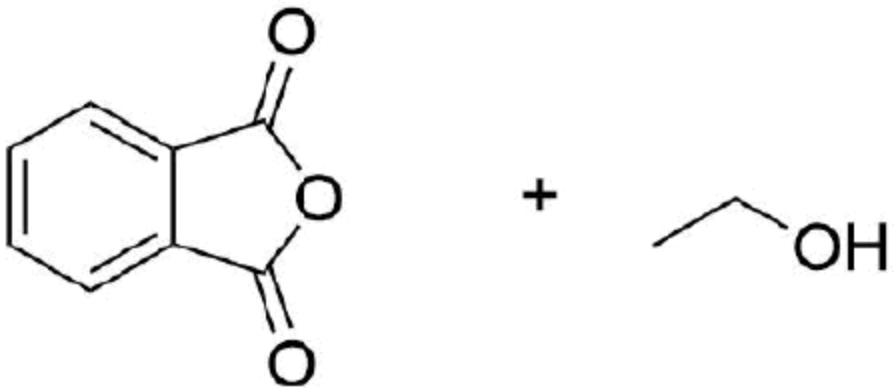
Draw out the mechanism for the following reaction.



Answer available at the end of this section.

Exercise 21.5.2

Draw the product of the reaction between these two molecules.



Answer available at the end of this section.

Questions

Q21.5.1

Draw out the mechanism for the following reaction.

21.14 Problem.png

Q21.5.2

Draw the product of the reaction between these two molecules.

21.15 Problem.png

Solutions

S21.5.1

21.14 Solution.png

S21.5.1

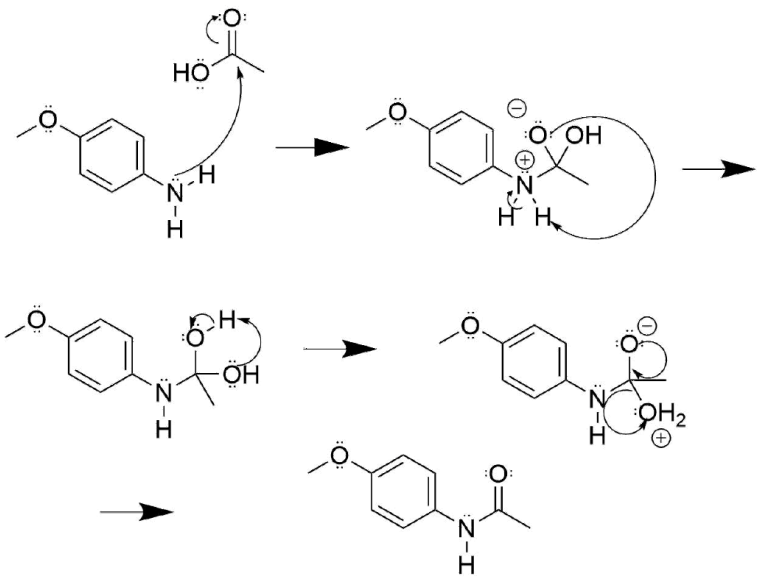
21.15 Solution.png

Contributors and Attributions

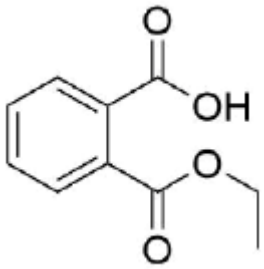
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise 21.5.1



Exercise 21.5.2



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20.4: Chemistry of Esters

Objectives

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

Study Notes

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

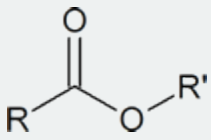
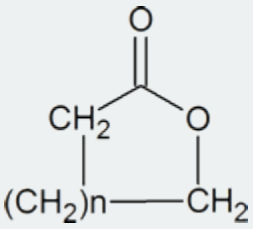


Table 21.1 Structures and characteristic odours of selected esters

IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum

IUPAC name	R	R′	Aroma
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

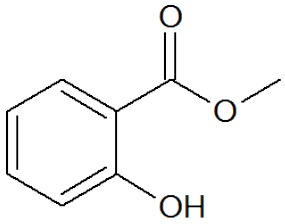
A “lactone” is a cyclic ester and has the general structure



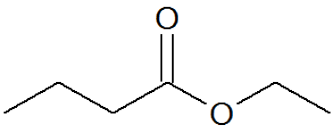
By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

Introduction

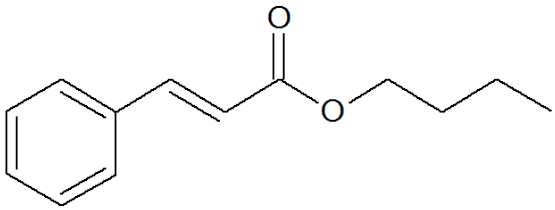
Esters are readily synthesized and naturally abundant contributing to the flavors and aromas in many fruits and flowers.



oil of wintergreen

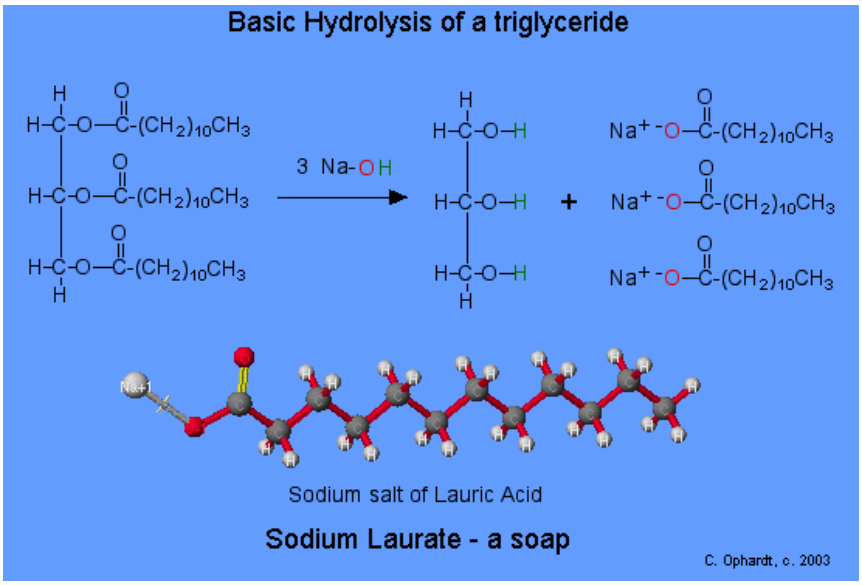


pineapple



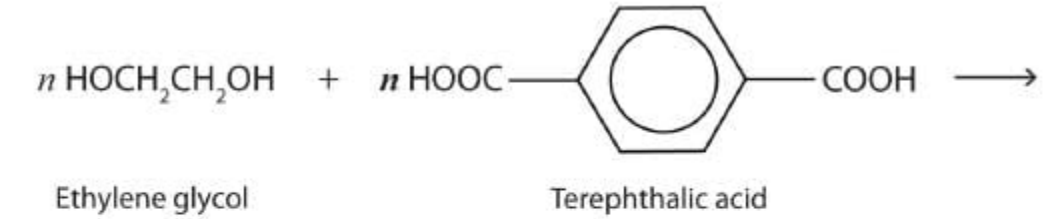
chocolate

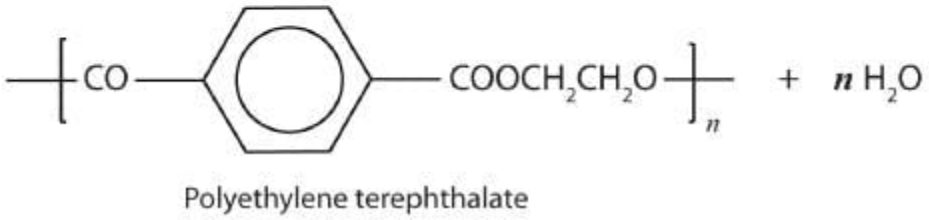
They also make up the bulk of animal fats and vegetable oils—glycerides (fatty acid esters of glycerol). Soap is produced by a saponification (basic hydrolysis) reaction of a fat or oil.



Esters are also present in a number of important biological molecules and have several commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

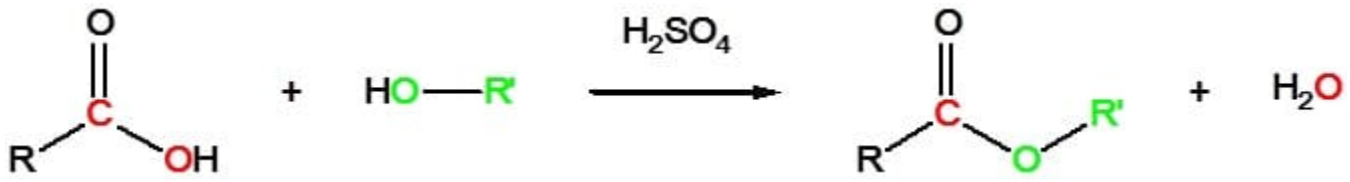
The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:



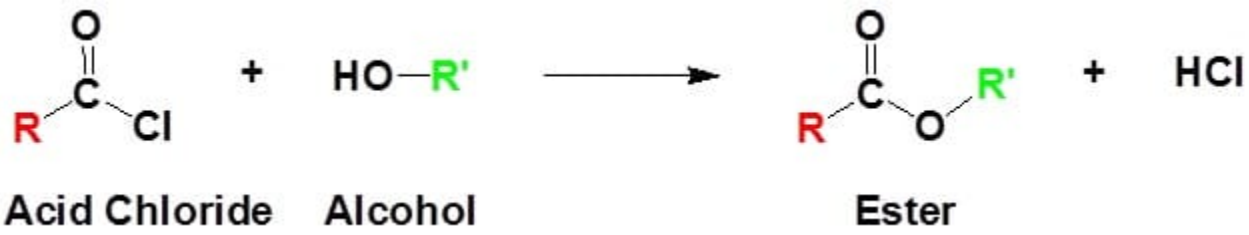


Preparation of Esters

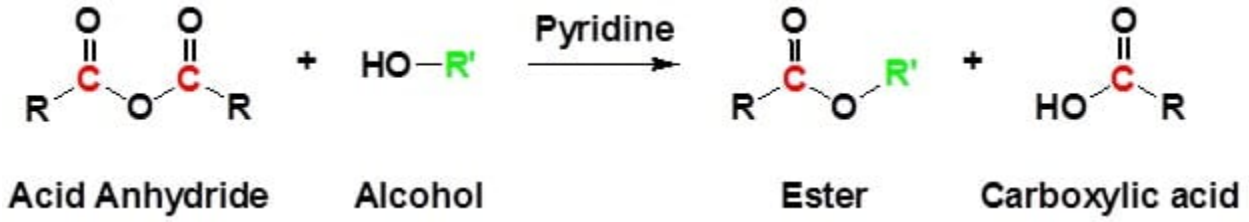
Carboxylic acids can react with alcohols to form esters



Acid chlorides react with alcohols to form esters

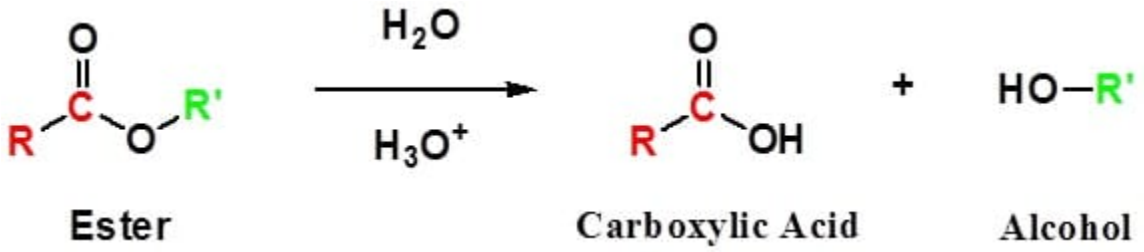


Acid Anhydrides react with alcohols to form esters

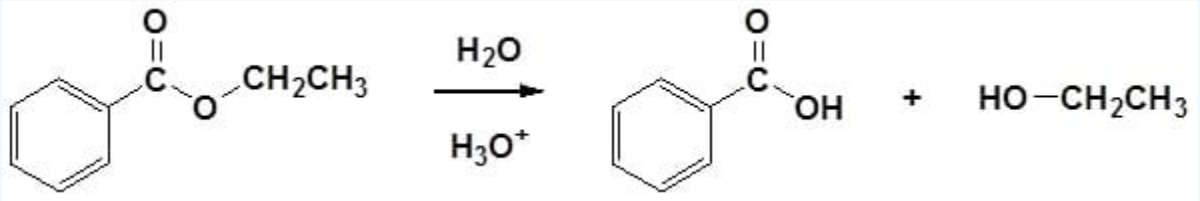


Conversion of Ester into Carboxylic acids: Hydrolysis

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a catalytic amount of acid.

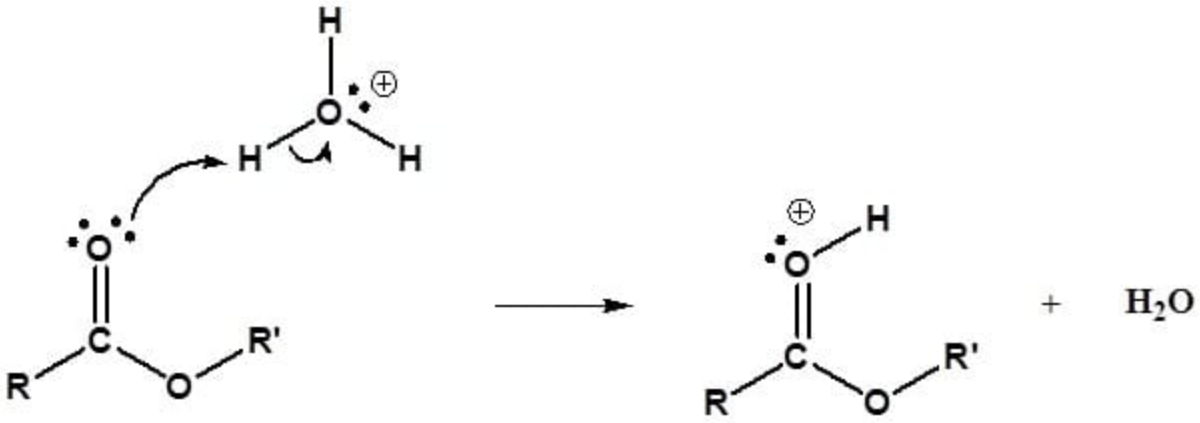


Example 21.6.1

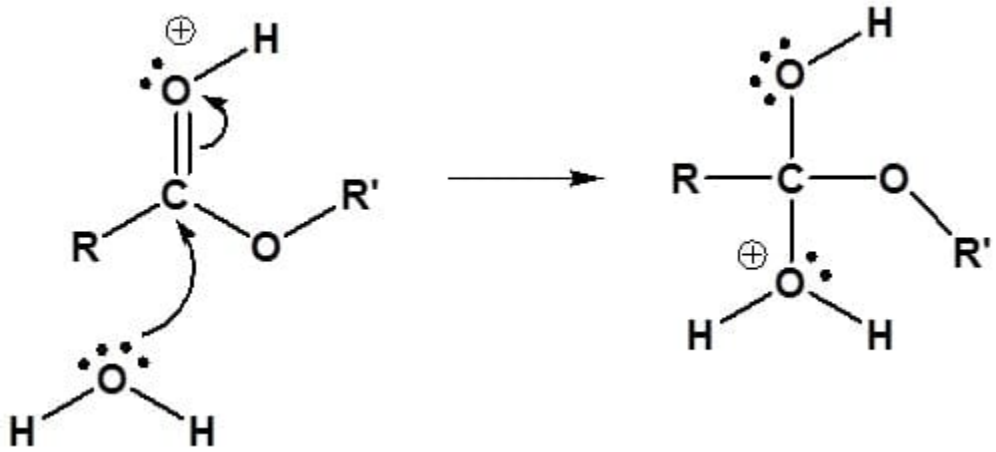


Mechanism

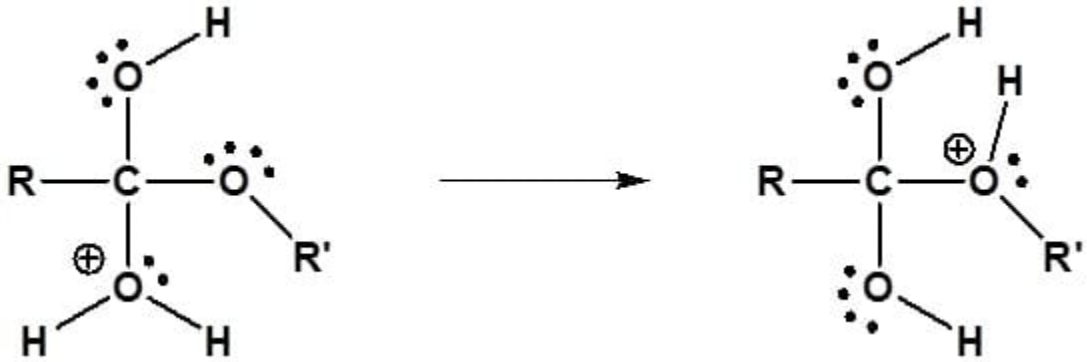
1) Protonation of the Carbonyl



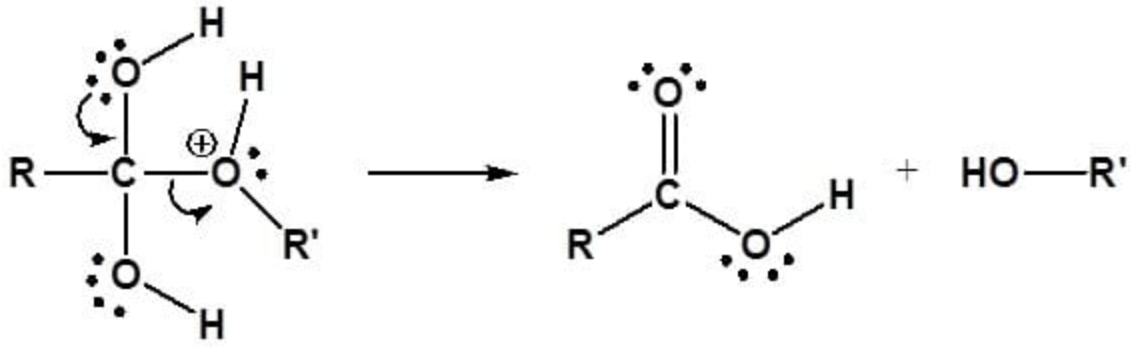
2) Nucleophilic attack by water



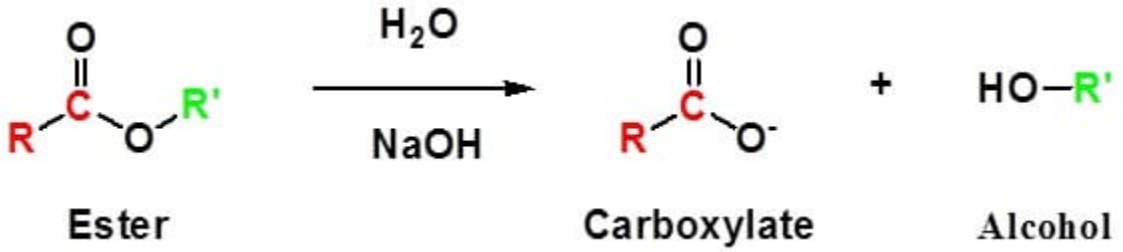
3) Proton transfer



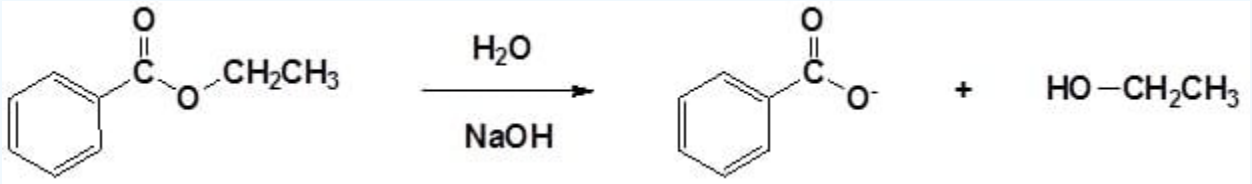
4) Leaving group removal



Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a base. The reaction is called a saponification from the Latin *sapo* which means soap. The name comes from the fact that soap used to me made by the ester hydrolysis of fats. Due to the basic conditions a carboxylate ion is made rather than a carboxylic acid.

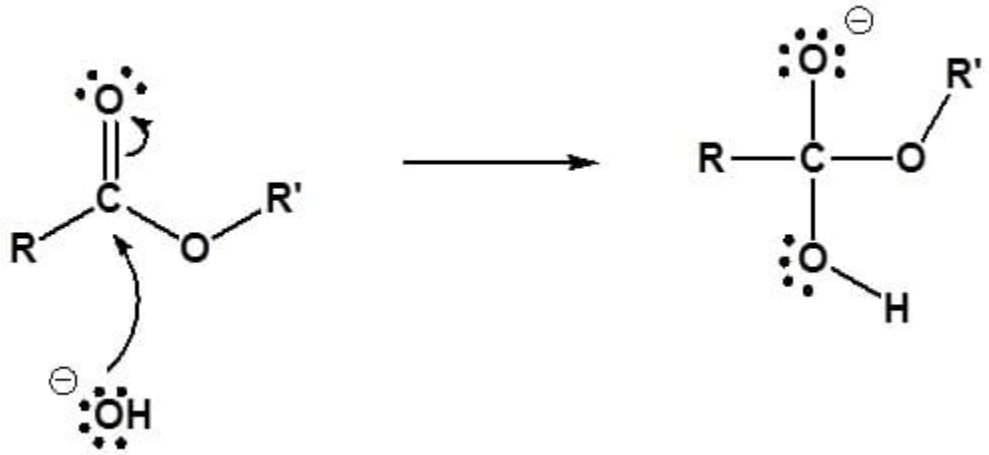


Example 21.6.2

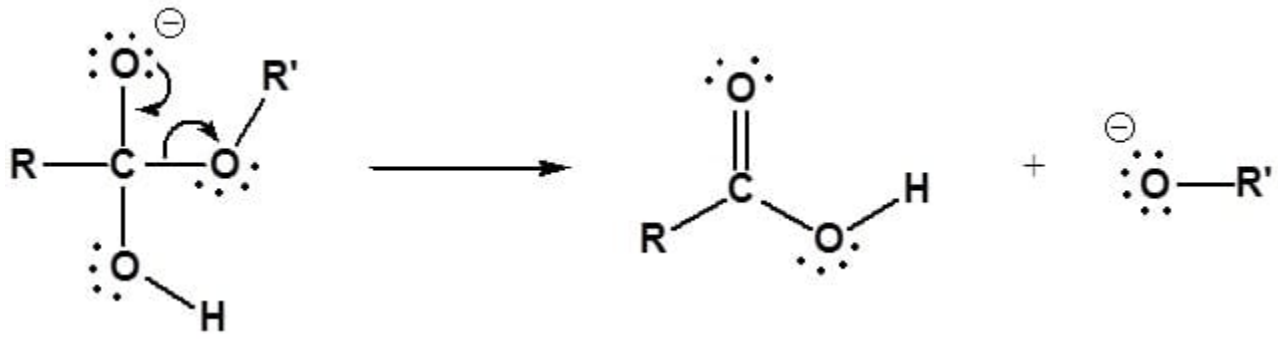


Mechanism

1) Nucleophilic attack by hydroxide



2) Leaving group removal

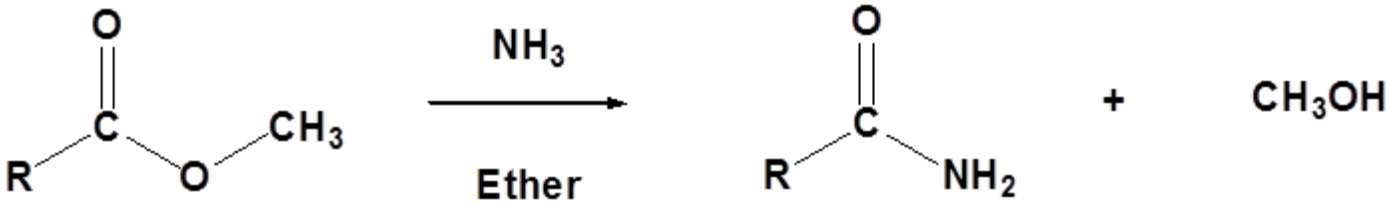


3) Deprotonation



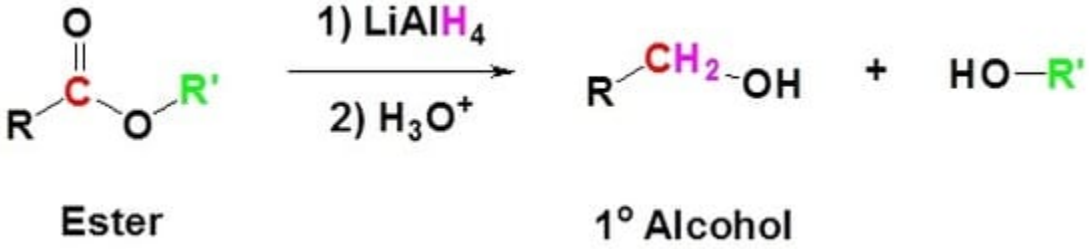
Conversion of Esters into Amides: Aminolysis

Esters reaction with ammonia and alkyl amines to yield amides.

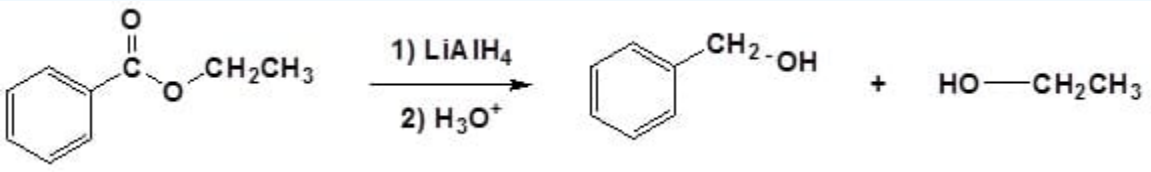


Conversion of Ester into Alcohols: Reduction

Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride ($NaBH_4$) is not a strong enough reducing agent to perform this reaction.

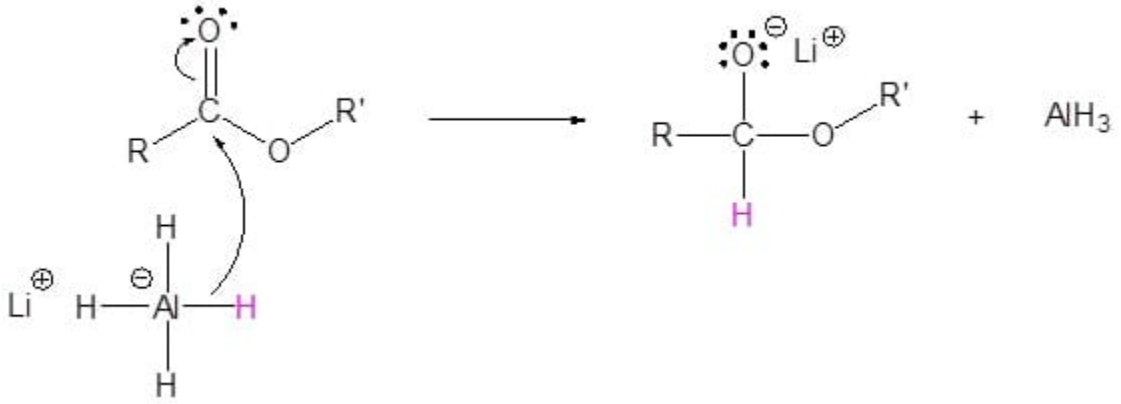


Example 21.6.3

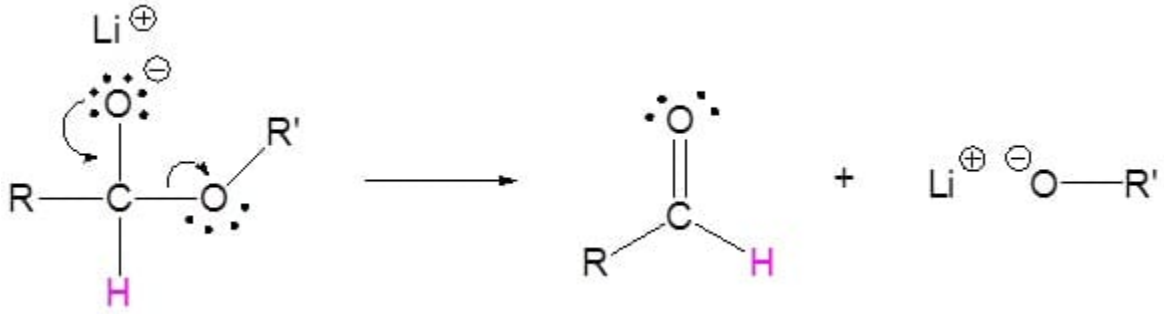


Mechanism

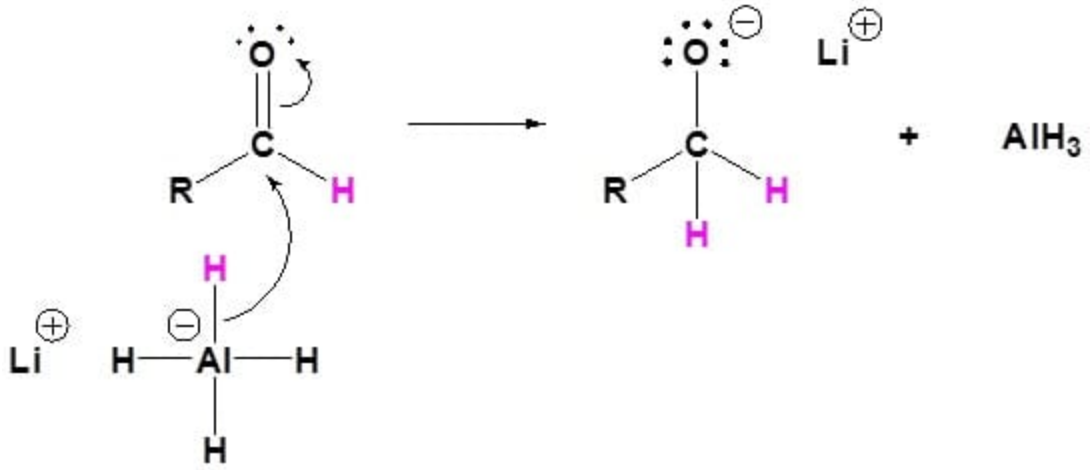
1) Nucleophilic attack by the hydride



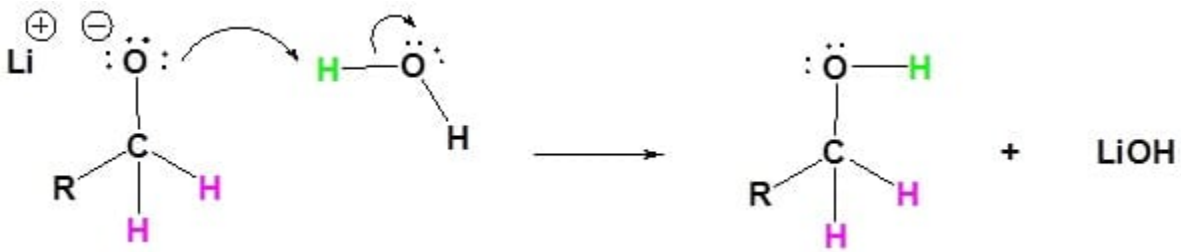
2) Leaving group removal



3) Nucleopilic attack by the hydride anion

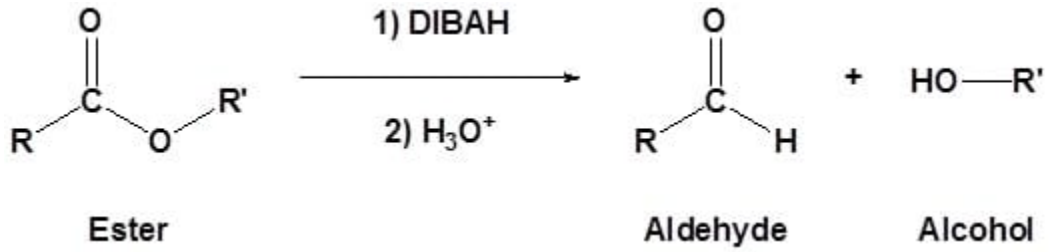


4) The alkoxide is protonated

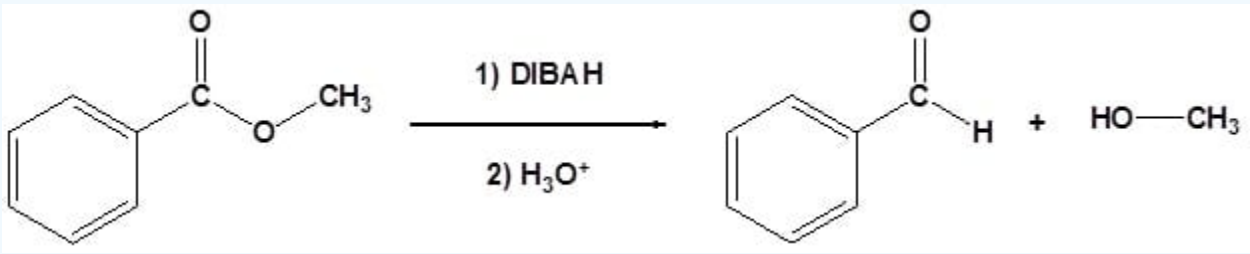


Esters can be converted to aldehydes using diisobutylaluminum hydride (DIBAH)

The reaction is usually carried out at -78 ^{o}C to prevent reaction with the aldehyde product.



Example 21.6.4

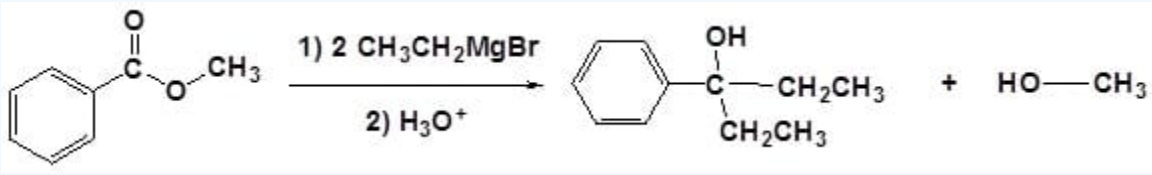


Addition of Grignard reagents convert esters to 3° alcohols.

In effect the Grignard reagent adds twice.

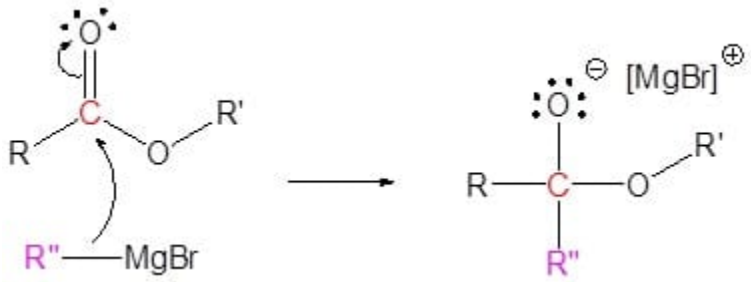


Example 21.6.5

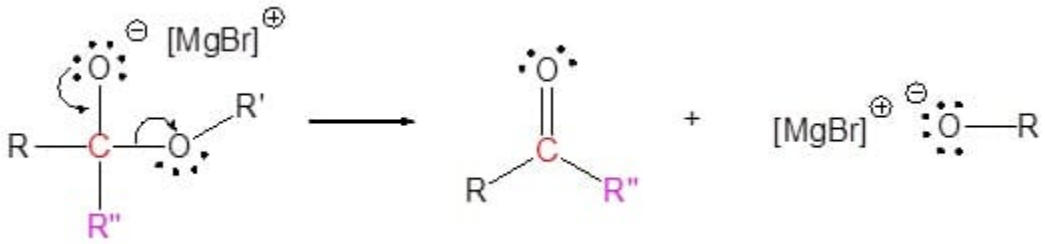


Mechanism

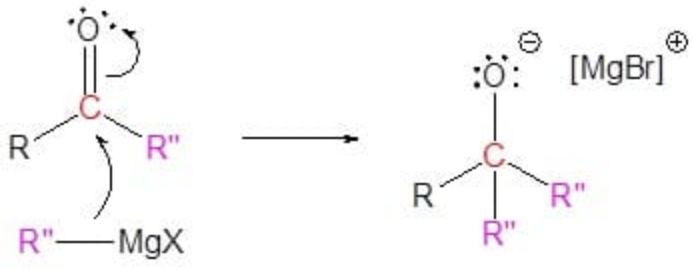
1) Nucleophilic attack



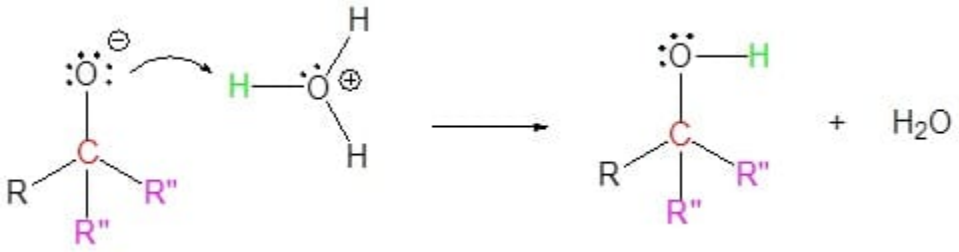
2) Leaving group removal



3) Nucleophilic attack



4) Protonation



Exercises

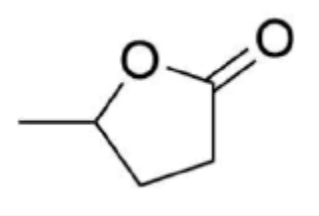
Exercise 21.6.1

Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid
produce an ester?

Answer available at the end of this section.

Exercise 21.6.2

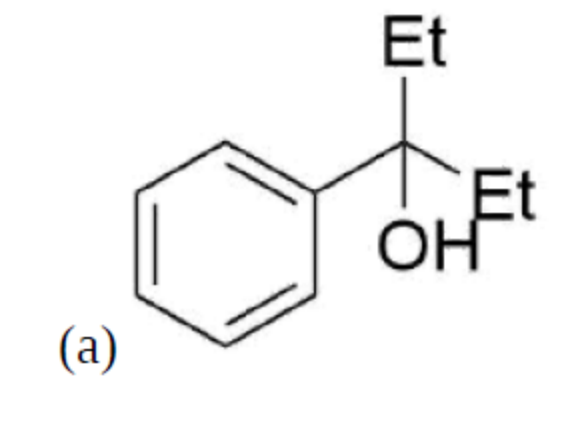
Draw the product of the reaction between the following molecule and LiAlH, and the product of the reaction between the following
molecule and DIBAL.

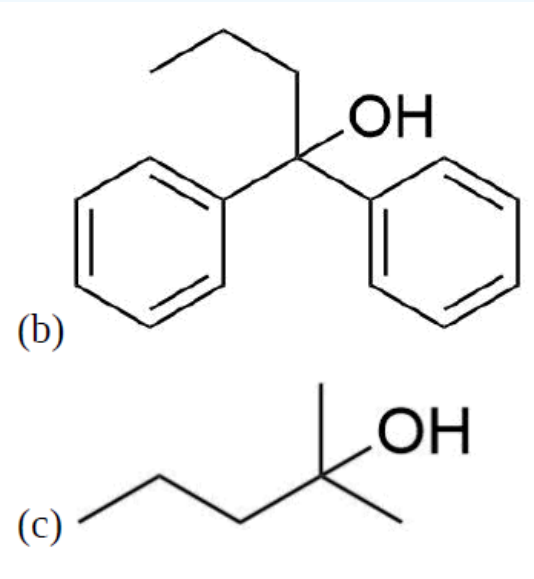


Answer available at the end of this section.

Exercise 21.6.3

How might you Prepare the following molecules from esters and Grignards?





Answer available at the end of this section.

Questions

Q21.6.1

Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

Q21.6.2

Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.

21.17 Problem.png

Q21.6.3

How might you Prepare the following molecules from esters and Grignards?

(a)21.19 Problem A.png

(b)21.19 Problem B.png

(c)21.19 Problem C.png

Solutions

S21.6.1

The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

S21.6.2

21-6c.png

S21.6.3

(a)21.19 Solution A.png

(b) 21.19 Solution B.png

(c)21.19 Solution C.png

.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

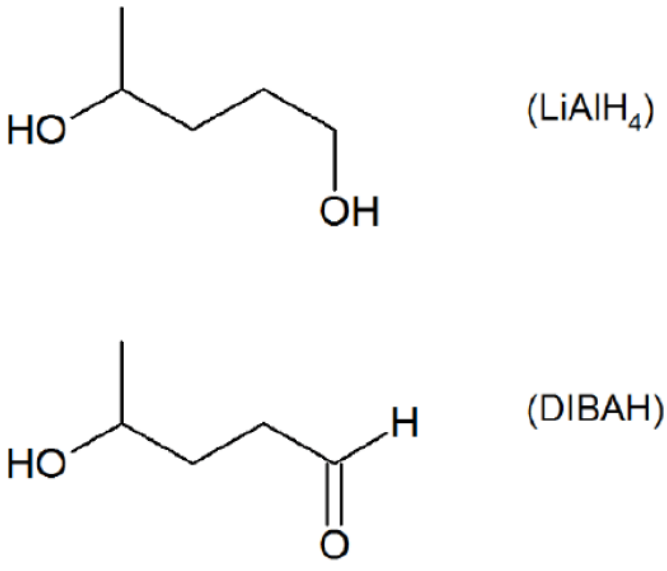
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Answers

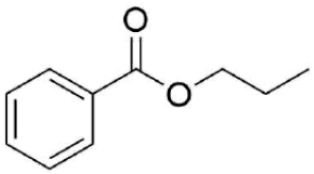
Exercise 21.6.1

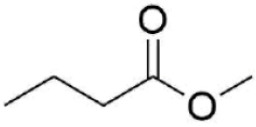
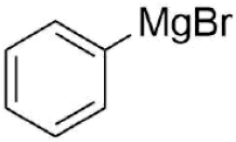
The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

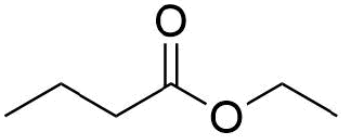
Exercise 21.6.2



Exercise 21.6.3

(a)  + 2 EtMgBr

(b)  + 2 

(c)  + 2 CH_3MgBr

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20.5: Esters in Nature: Waxes, Fats, Oils, and Lipids

27.01 Waxes, Fats, and Oils 27.03 Phospholipids

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20.6: Amides: The Least Reactive Carboxylic Acid Derivatives

Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

Key Terms

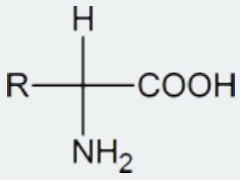
Make certain that you can define, and use in context, the key term below.

- lactam

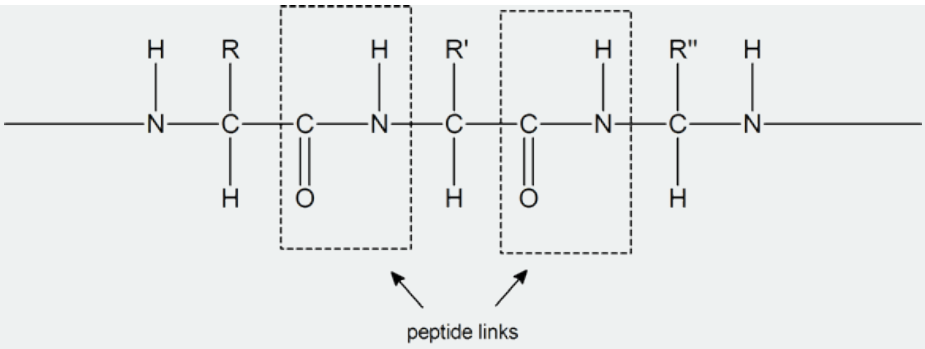
Study Notes

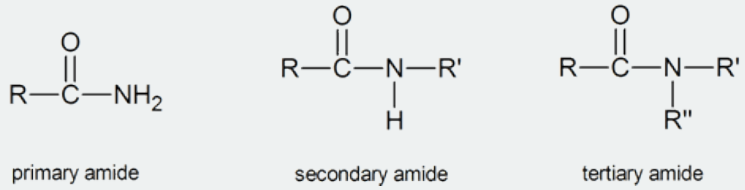
As the chapter which deals with amino acids and proteins is optional, it is possible for you to complete this course without studying these compounds in detail. However, because of their importance in biological systems, it is essential for all students completing this course to have some knowledge of their structure and properties.

When we talk about amino acids, we are generally referring to α-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:

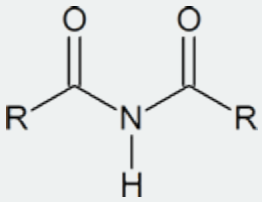


Notice that such compounds contain a chiral carbon atom (unless R = H). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in secondary amides

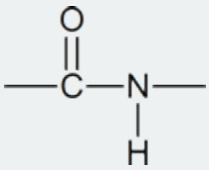




Note: Although the terms secondary amide and tertiary amide have been used here, this usage is not in agreement with IUPAC recommendations. According to IUPAC, the secondary amide shown above should be referred to as an *N*-substituted primary amide, and the tertiary amide should be referred to as a *N*, *N*-disubstituted primary amide. IUPAC reserves the term secondary amide for compounds of the type

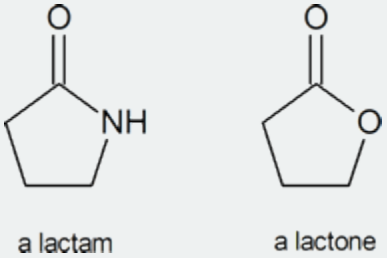


Because of the presence of the amide link in proteins,

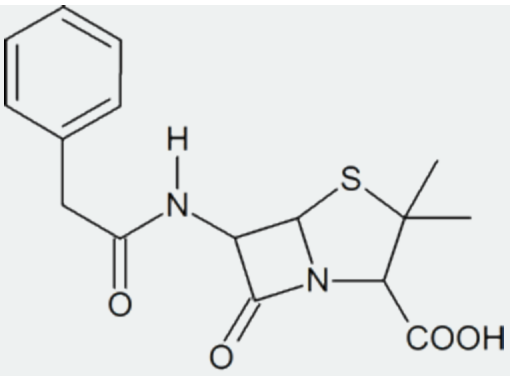


we can expect the properties of these compounds to resemble those of secondary amides.

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:



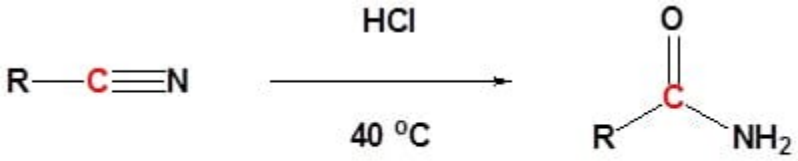
Among the most important molecules that contain lactam rings are the penicillins:



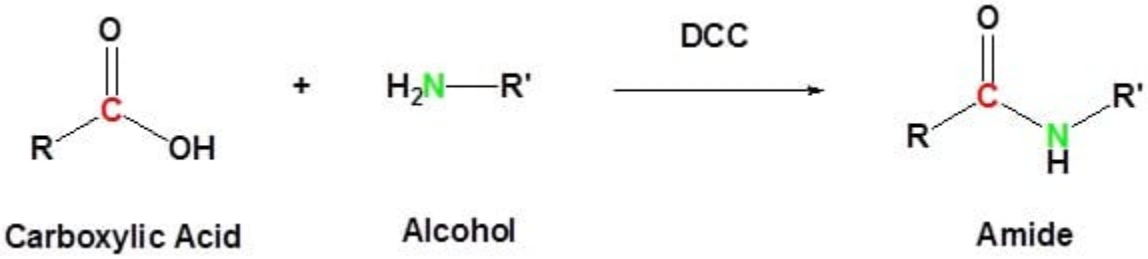
penicillin G (benzylpenicillin)

Preparation of Amides

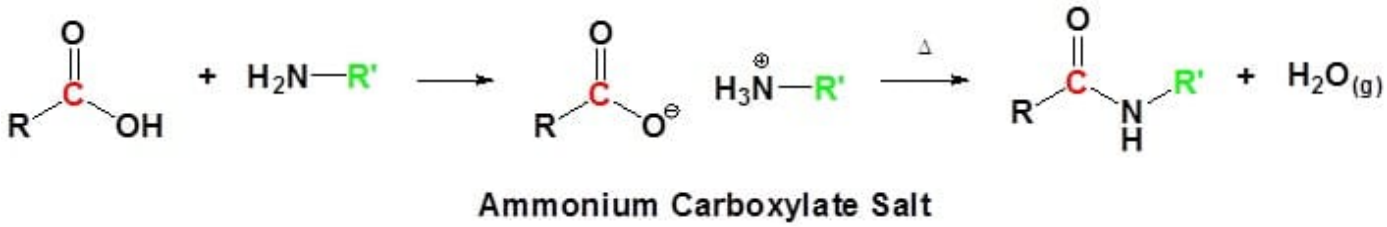
Nitriles can be converted to amides. This reaction can be acid or base catalyzed



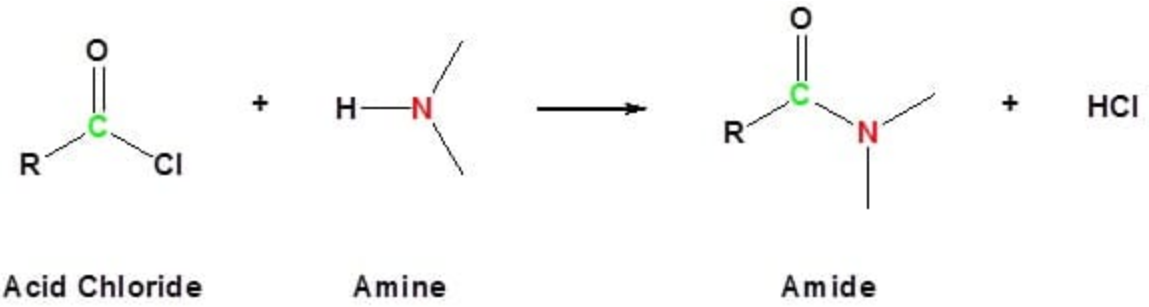
Carboxylic acid can be converted to amides by using DCC as an activating agent



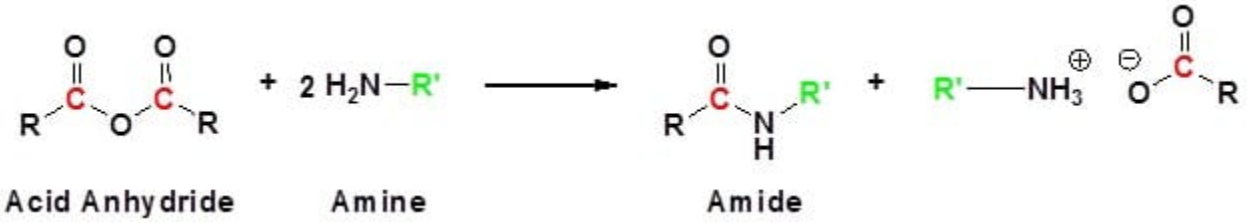
Direct conversion of a carboxylic acid to an amide by reaction with an amine.



Acid chlorides react with ammonia, 1^{o} amines and 2^{o} amines to form amides



Acid Anhydrides react with ammonia, 1^{o} amines and 2^{o} amines to form amides



Conversion of Amides into Carboxylic Acids: Hydrolysis

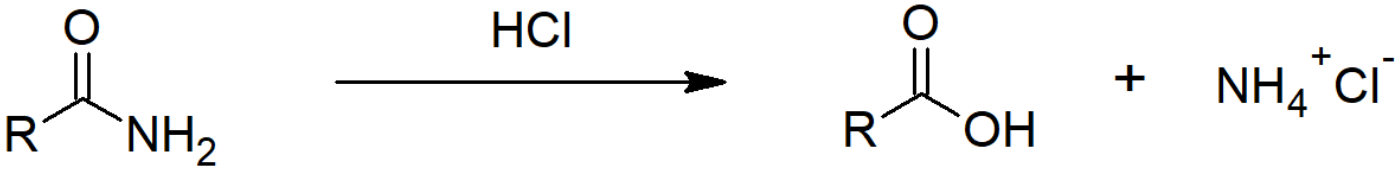
This page describes the hydrolysis of amides under both acidic and alkaline conditions. It also describes the use of alkaline hydrolysis in testing for amides.

What is hydrolysis?

Technically, hydrolysis is a reaction with water. That is exactly what happens when amides are hydrolyzed in the presence of dilute acids such as dilute hydrochloric acid. The acid acts as a catalyst for the reaction between the amide and water. The alkaline hydrolysis of amides actually involves reaction with hydroxide ions, but the result is similar enough that it is still classed as hydrolysis.

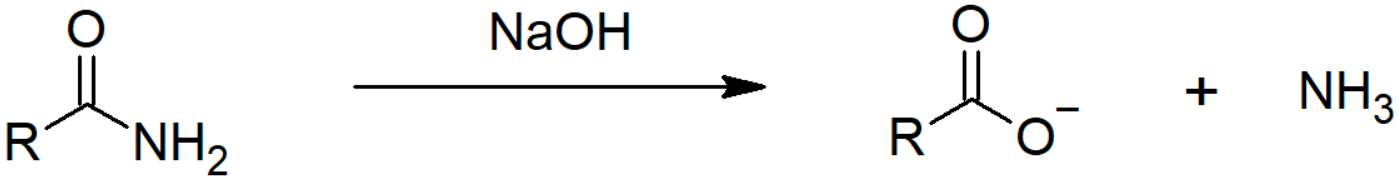
Hydrolysis under acidic conditions

Taking ethanamide as a typical amide. If ethanamide is heated with a dilute acid (such as dilute hydrochloric acid), ethanoic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and ethanoic acid.



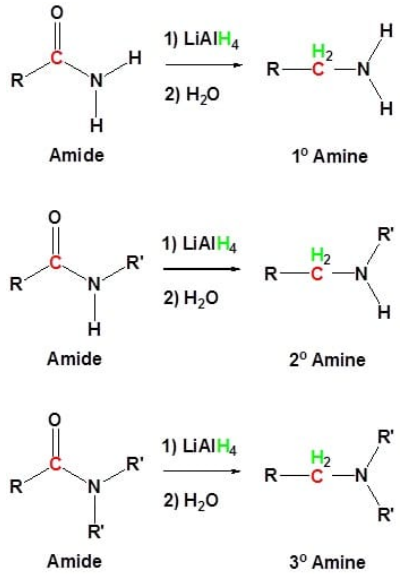
Hydrolysis under alkaline conditions

Also, if ethanamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium ethanoate.

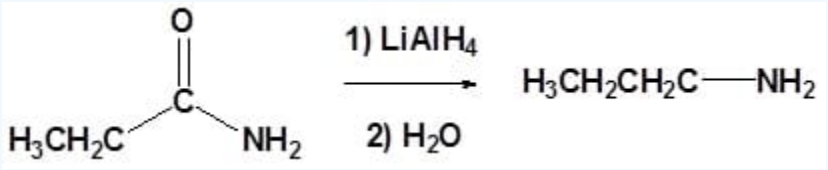


Conversion of Amides into Amines: Reduction

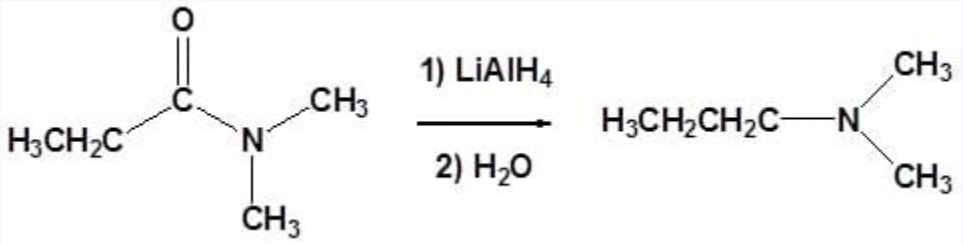
Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$.



Example 21.7.1: Amide Reductions

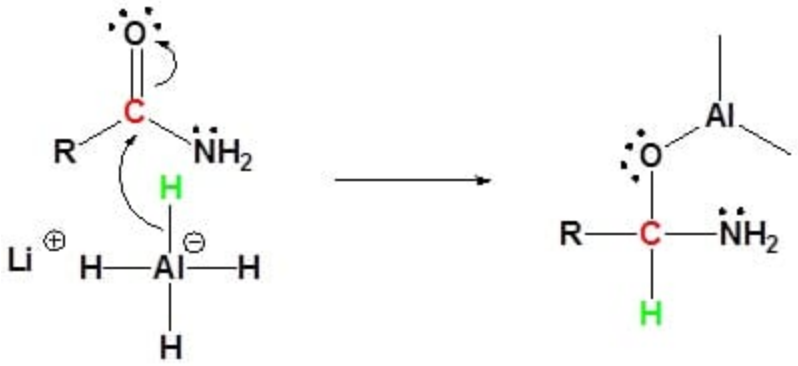


Alkyl groups attached to the nitrogen do not affect the reaction.

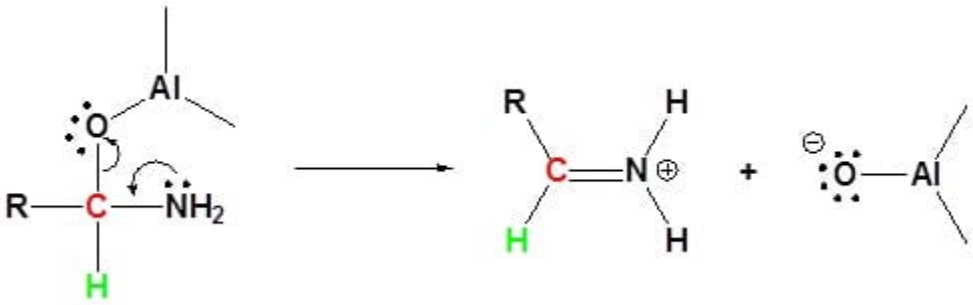


Mechanism

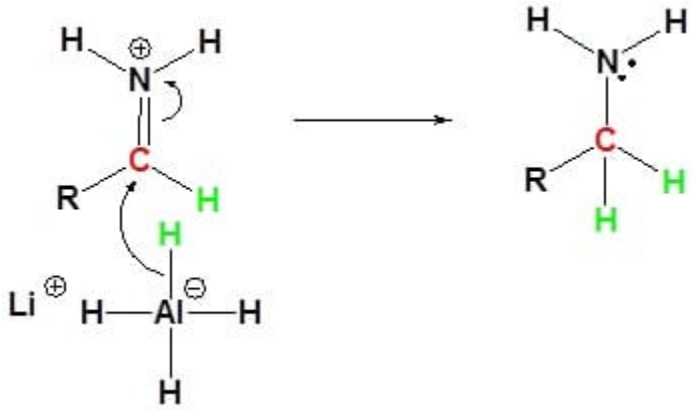
1) Nucleophilic attach by the hydride



2) Leaving group removal

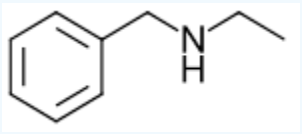


3) Nucleophilic attach by the hydride



Example 21.7.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



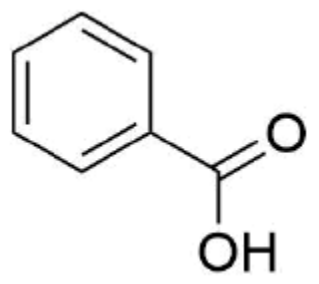
Answer available at the end of this section.

Exercises

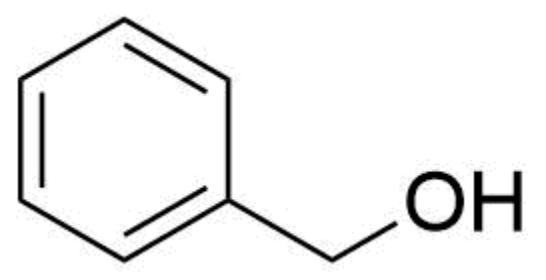
Exercise 21.7.1

How would you prepare the following compounds from N-Propypl benzamide?

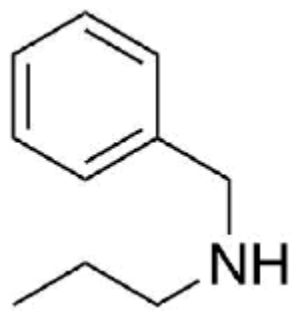
(a)



(b)



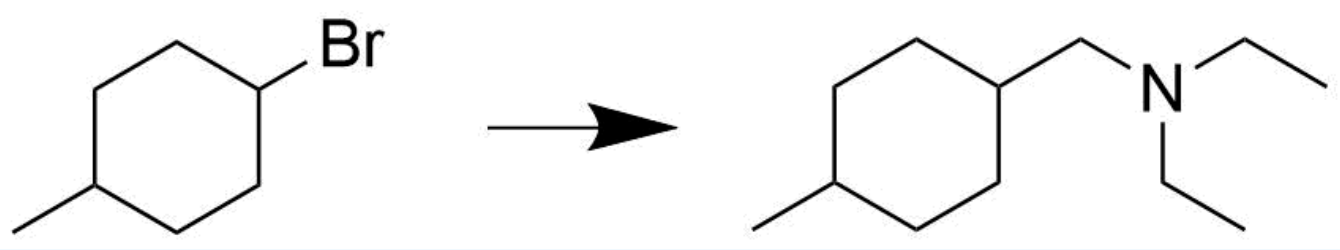
(c)



Answer available at the end of this section.

Exercise 21.7.2

Propose a synthesis pathway for the following conversion:



Answer available at the end of this section.

Questions

Q21.7.1

How would you prepare the following compounds from N-Propypl benzamide?

(a)21.20 Problem A.png

(b) 21.20 Problem B.png

(c)21.20 Problem C.png

Q21.7.2

Propose a synthesis for the following.

21.21 Problem.png

Solutions

S21.7.1

a. NaOH, H_2O
b. NaOH, H_2O, then LAH
c. LAH

S21.7.2

21.21 Solution.png

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

Answers

Example 21.7.1

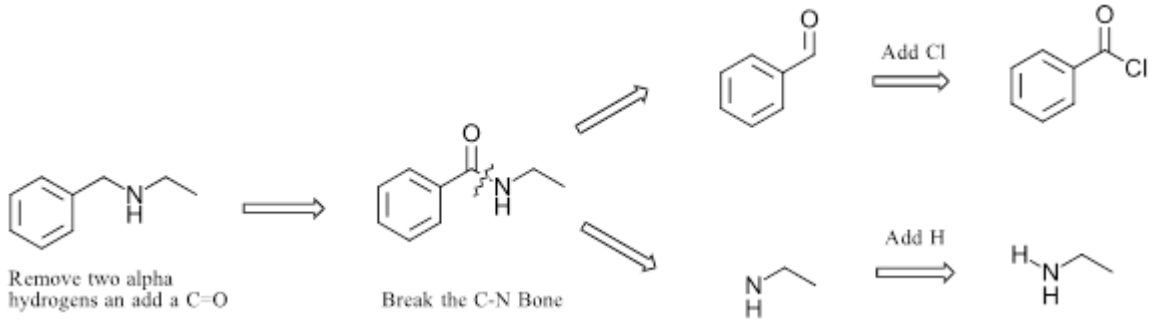
One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond

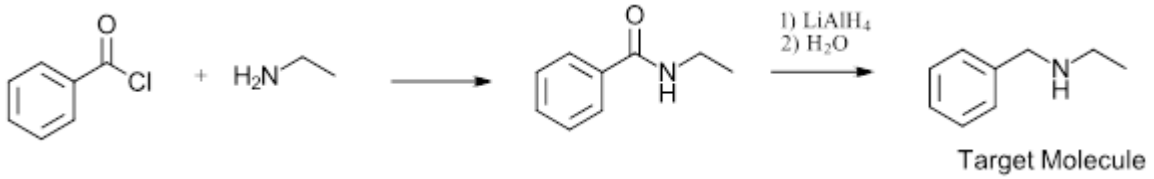
separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1° amine. In the forward reaction pathway, the acid chloride and the 1° amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

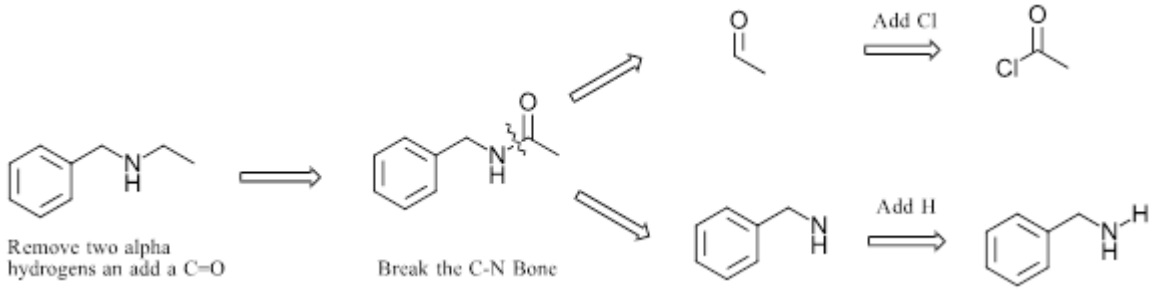
Pathway 1



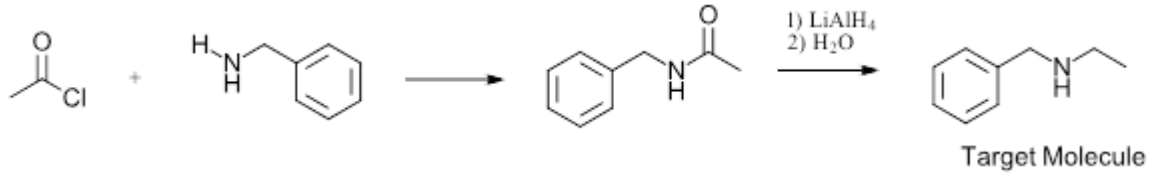
Solution 1



Pathway 2



Solution 2



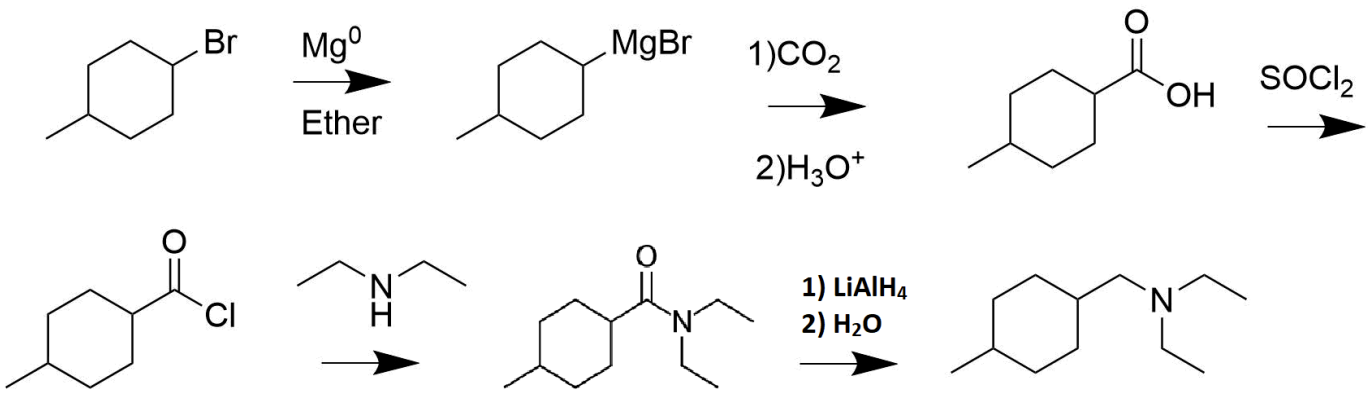
Exercise 21.7.1

(a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

Exercise 21.7.2

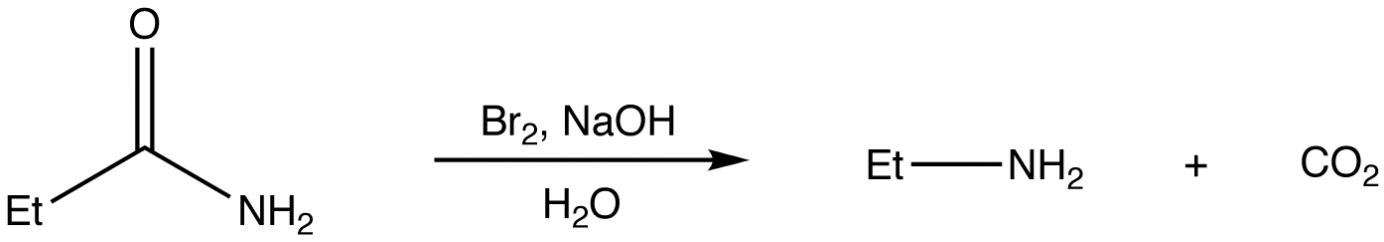


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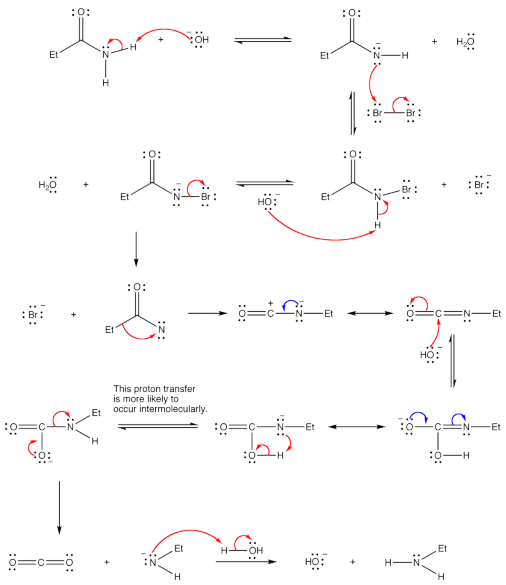
- 21.7: Chemistry of Amides by Dietmar Kennepohl, Jim Clark, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

20.7: Amidates and Their Halogenation: The Hofmann Rearrangement

Hofmann rearrangement, also known as Hofmann degradation and not to be confused with Hofmann elimination, is the reaction of a primary amide with a halogen (chlorine or bromine) in strongly basic (sodium or potassium hydroxide) aqueous medium, which converts the amide to a primary amine. For example:



Mechanism:



Contributors

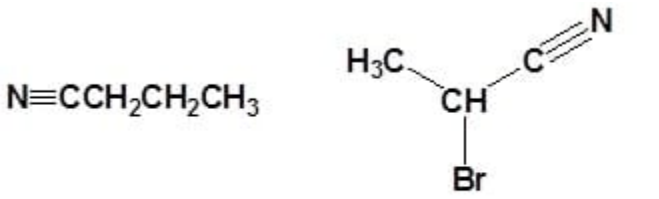
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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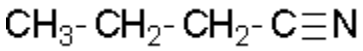
20.8: Alkanenitriles: A Special Class of Carboxylic

Name the parent alkane (include the carbon atom of the nitrile as part of the parent) followed with the word -nitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.



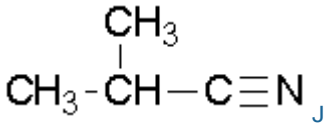
Butane nitrile 2-Bromopropane nitrile

Cycloalkanes are followed by the word -carbonitrile. The substituent name is cyano.

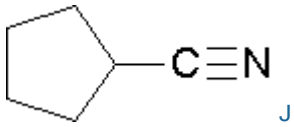


- 1-butanenitrile or 1-cyanopropane

Try to name the following compounds using these conventions



J

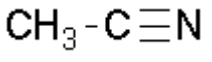


J

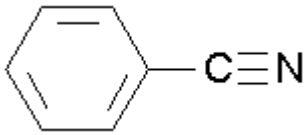
Try to draw structures for the following compounds

- butanedinitrile J
- 2-methycyclohexanecarbonitrile J

Some common names that you should know are...



acetonitrile



benzonitrile

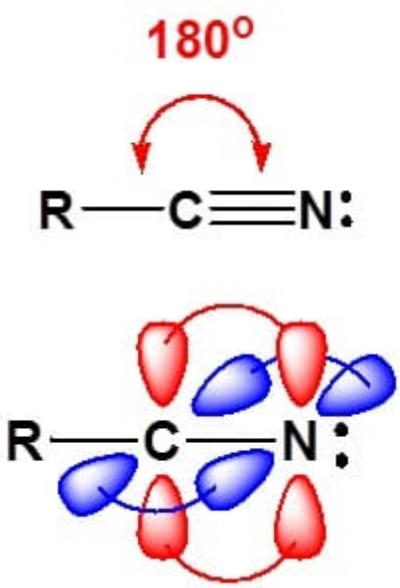
Try to draw a structure for the following compound

- 2-methoxybenzonitrile J

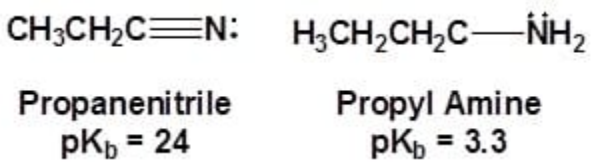
Contributors

- Prof. Steven Farmer (Sonoma State University)
- Richard Banks (Boise State University)

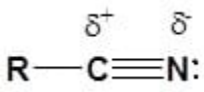
The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bond in the triple bond. The R-C-N bond angle in and nitrile is 180° which give a nitrile functional group a linear shape.



The lone pair electrons on the nitrogen are contained in a *sp* hybrid orbital which makes them much less basic and an amine. The 50% character of an *sp* hybrid orbital close to the nucleus and therefore less basic compared to other nitrogen containing compounds such as amines.



The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.



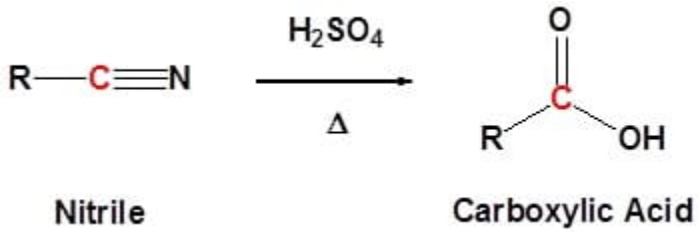
	Boiling Point
$CH_3CH_2C{\equiv}N$	96-98 °C
Propanenitrile	
$CH_3CH_2C{\equiv}C{-}H$	8.1 °C
Butyne	
$CH_3CH_2CH_2CH_3$	-1-1 °C
Butane	

Contributors

- Prof. Steven Farmer (Sonoma State University)

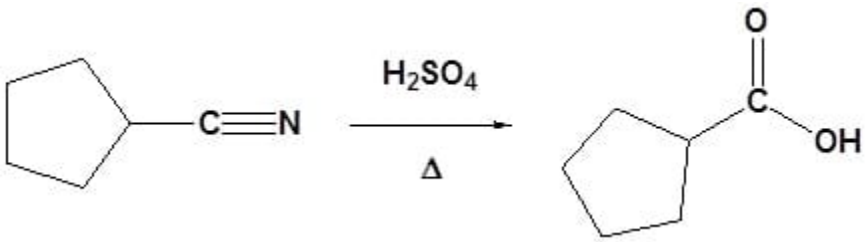
Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.

General Reaction



Nitrile Carboxylic Acid

Example

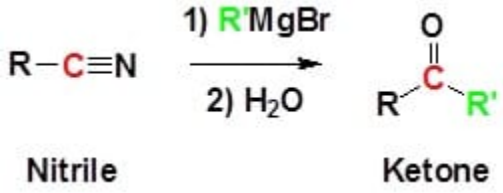


Contributors

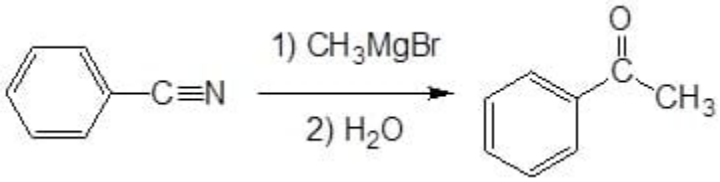
Prof. Steven Farmer (Sonoma State University)

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

General Reaction

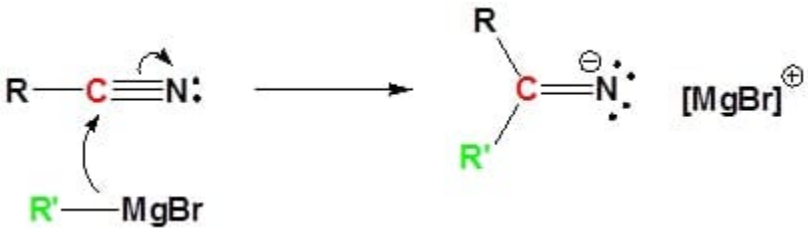


Example



Mechanism

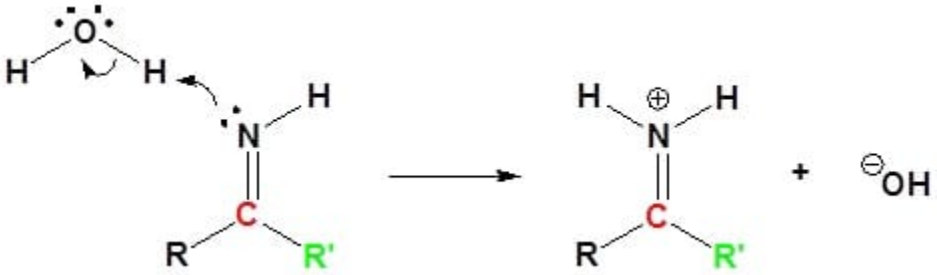
1) Nucleophilic Attack by the Grignard Reagent



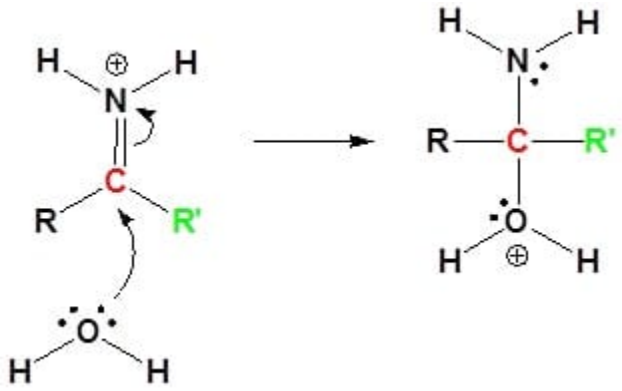
2) Protonation



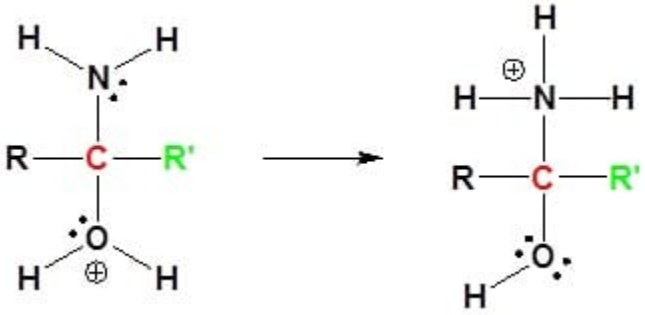
3) Protonation



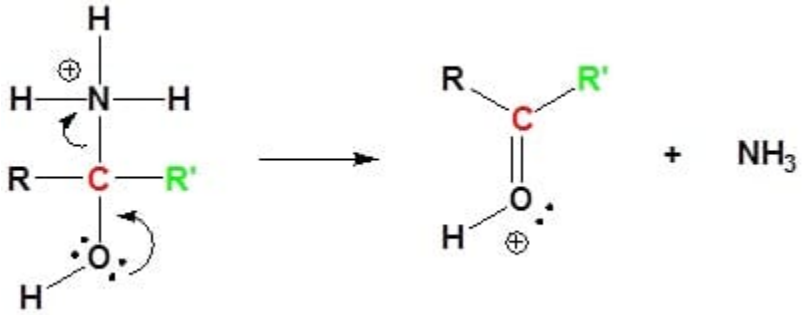
4) Nucleophilic attack by water



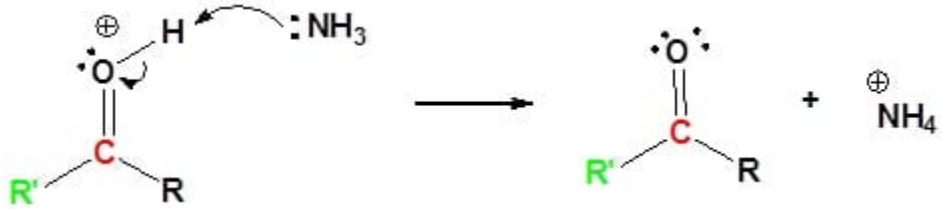
5) Proton Transfer



6) Leaving group removal



7) Deprotonation

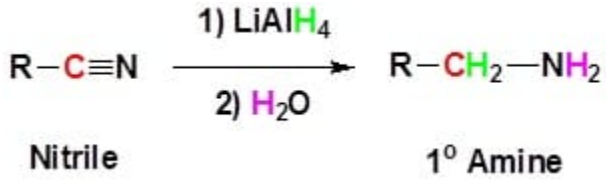


Contributors

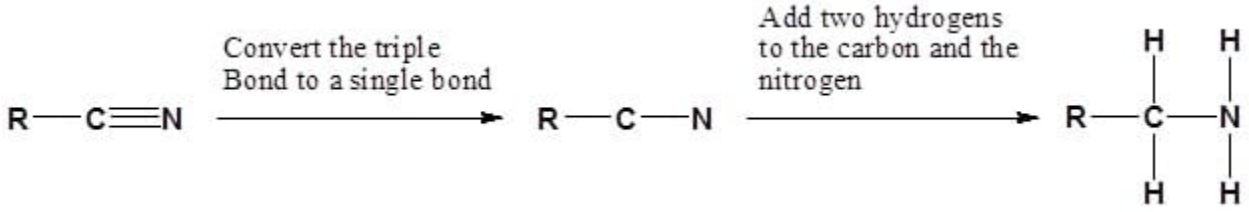
Prof. Steven Farmer (Sonoma State University)

Nitriles can be converted to 1° amines by reaction with $LiAlH_4$. During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.

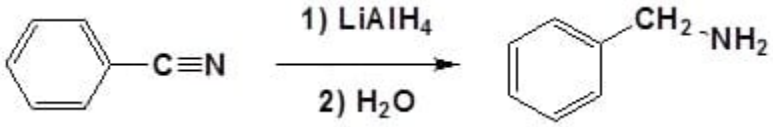
General Reaction



Going from reactants to products simplified

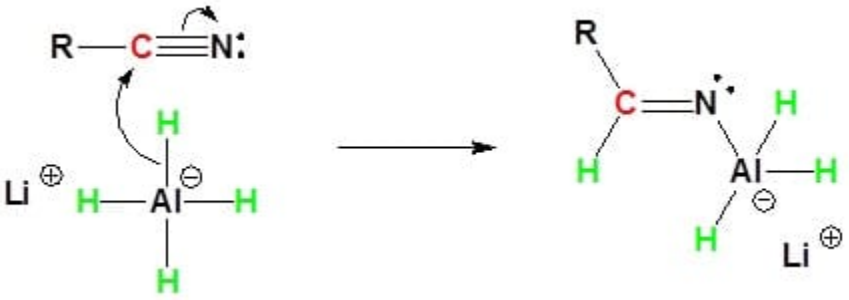


Example

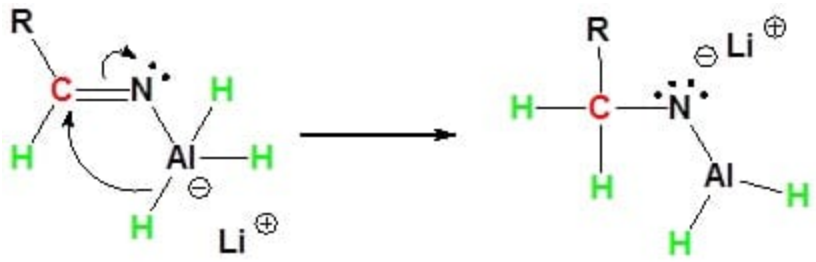


Mechanism

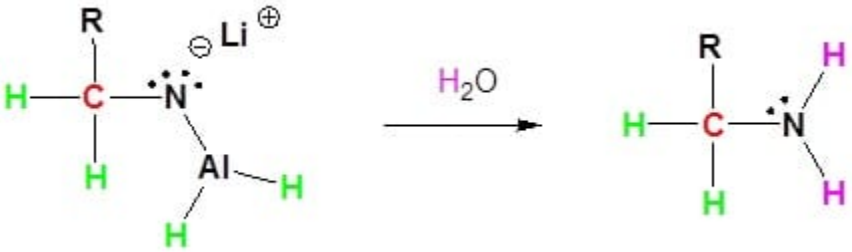
1) Nucleophilic Attack by the Hydride



2) Second nucleophilic attack by the hydride.



3) Protonation by addition of water to give an amine



Contributors

Prof. Steven Farmer (Sonoma State University)

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21: AMINES AND THEIR DERIVATIVES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

- Topic hierarchy

21.1: Naming the Amines
21.2: Structural and Physical Properties of Amines
21.3: Spectroscopy of the Amine Group
21.4: Acidity and Basicity of Amines
21.5: Synthesis of Amines by Alkylation
21.6: Synthesis of Amines by Reductive Amination
21.7: Synthesis of Amines from Carboxylic Amides
21.8: Quaternary Ammonium Salts: Hofmann Elimination
21.9: Mannich Reaction: Alkylation of Enols by Iminium Ions
21.10: Nitrosation of Amines

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21.1: Naming the Amines

Objectives

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

Key Terms

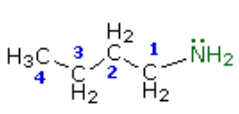
Make certain that you can define, and use in context, the key terms below.

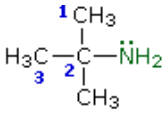
- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

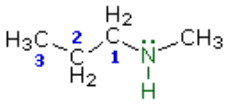
Study Notes

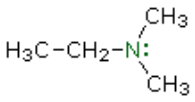
You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group. The nomenclature of amines is complicated by the fact that several different nomenclature systems exist, and there is no clear preference for one over the others. Furthermore, the terms primary (1°), secondary (2°) & tertiary (3°) are used to classify amines in a completely different manner than they were used for alcohols or alkyl halides. **When applied to amines these terms refer to the number of alkyl (or aryl) substituents bonded to the nitrogen atom**, whereas in other cases they refer to the nature of an alkyl group. The four compounds shown in the top row of the following diagram are all $C_4H_{11}N$ isomers. The first two are classified as 1°-amines, since only one alkyl group is bonded to the nitrogen; however, the alkyl group is primary in the first example and tertiary in the second. The third and fourth compounds in the row are 2° and 3°-amines respectively. A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a quaternary (4°)-ammonium cation. For example, $(CH_3)_4N^{(+)}\ Br^{(-)}$ is tetramethylammonium bromide.

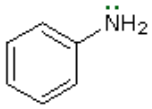

a 1° amine

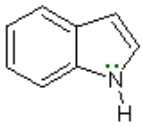

a 1° amine

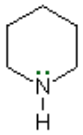

a 2° amine

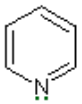

a 3° amine

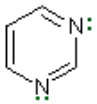
IUPAC name	1-aminobutane	2-amino-2-methylpropane	1-methylaminopropane	dimethylaminoethane
CA name	butanamine	2-methyl-2-propanamine	N-methylpropanamine	N,N-dimethylethanamine
Common name	n-butylamine	tert-butylamine	methylpropylamine	ethyldimethylamine


aniline


indole


piperidine


pyridine


pyrimidine


pyrrolidine


pyrrole


imidazole

- The IUPAC names are listed first and colored blue. This system names amine functions as substituents on the largest alkyl group. The simple -NH substituent found in 1°-amines is called an **amino group**. For 2° and 3°-amines a compound prefix (e.g. dimethylamino in the fourth example) includes the names of all but the root alkyl group.
- The Chemical Abstract Service has adopted a nomenclature system in which the suffix **-amine** is attached to the root alkyl name. For 1°-amines such as butanamine (first example) this is analogous to IUPAC alcohol nomenclature (-ol suffix). The additional nitrogen substituents in 2° and 3°-amines are designated by the prefix **N-** before the group name. These CA names are colored magenta in the diagram.
- Finally, a common system for simple amines names each alkyl substituent on nitrogen in alphabetical order, followed by the suffix **-amine**. These are the names given in the last row (colored black).

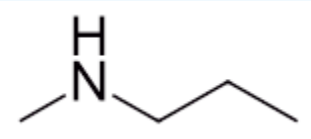
Many aromatic and heterocyclic amines are known by unique common names, the origins of which are often unknown to the chemists that use them frequently. Since these names are not based on a rational system, it is necessary to memorize them. There is a systematic nomenclature of heterocyclic compounds, but it will not be discussed here.

Exercises

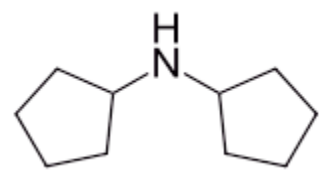
Exercise 24.1.1

Name the following compounds:

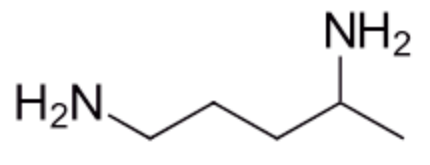
a)



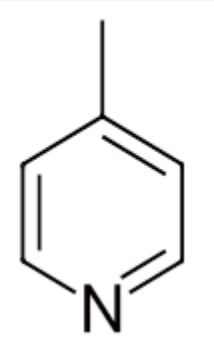
b)



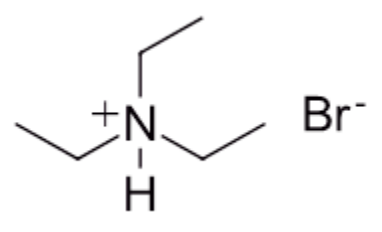
c)



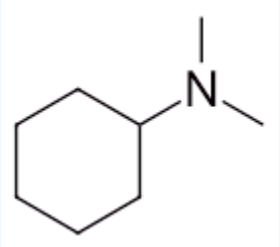
d)



e)



f)



Answer available at the end of this section.

Exercise 24.1.2

Draw the structures corresponding to the following names:

a) 3-Bromo-pentan-2-amine

b) Cyclopentanamine

c) *Trans*-3-ethylcyclohexanamine

d) Sec-butyl-*tert*-butyl amine

e) N,N-Dimethyl-3-pentanamine

f) 4-Methyl-2-hexanamine

g) 6-Bromo-4-amino-2-heptanol

Answer available at the end of this section.

Exercise 24.1.3

Draw the structures of the following heterocyclic compounds:

a) 4-Methoxyindole

b) 1,4-Dimethylpyrrole

c) 3-(N,N-Dimethylamino)pyridine

d) 2-Aminopyrimidine

Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

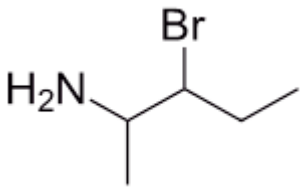
Answers

Exercise 24.1.1

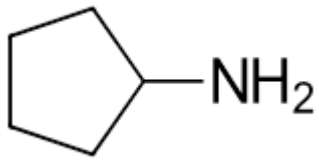
a) N-Methylpropylamine
b) Dicyclopentylamine
c) 1,4-Pentanediamine
d) 4-Methylpyridine
e) Triethylammonium Bromide
f) N,N-Dimethylcyclohexylamine

Exercise 24.1.2

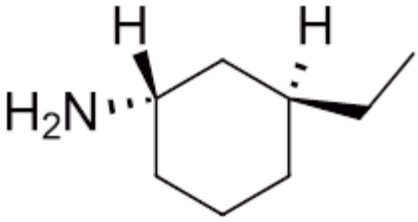
a)



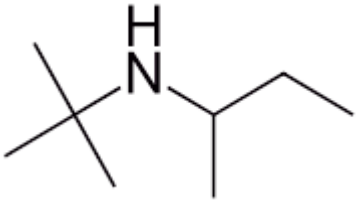
b)



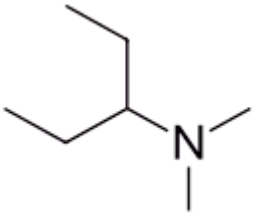
c)



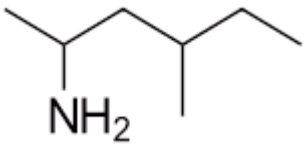
d)



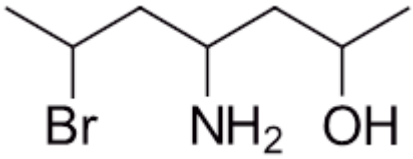
e)



f)

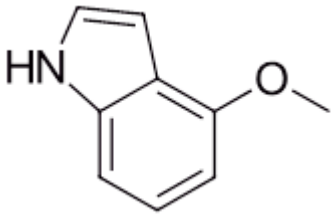


g)

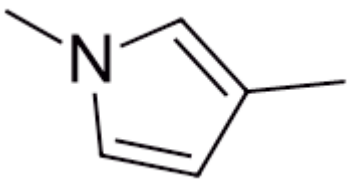


Exercise 24.1.3

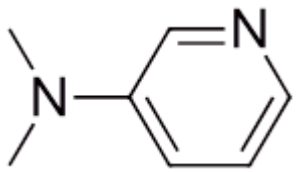
a)



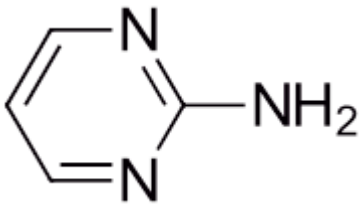
b)



c)



d)



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21.2: Structural and Physical Properties of Amines

Objectives

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

Key Terms

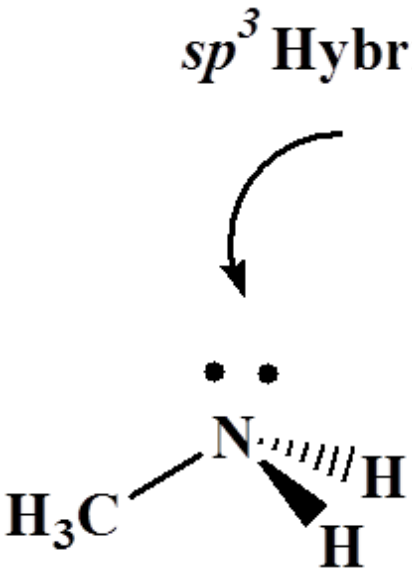
Make certain that you can define, and use in context, the key term below.

- pyramidal inversion

Study Notes

Molecular models may help you to understand pyramidal inversion.

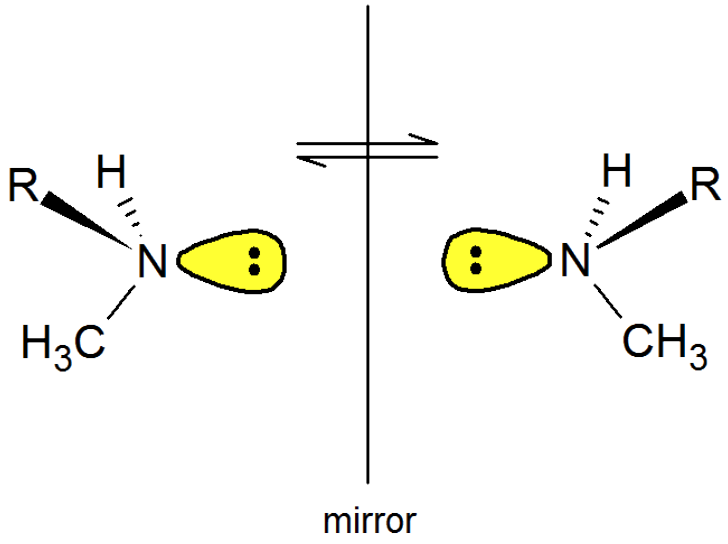
Amines typically have three bonds and one pair of lone pair electrons. This makes the nitrogen sp^3 hybridized, trigonal pyramidal, with a bond angle of roughly 109.5°.



Stereogenic Nitrogen

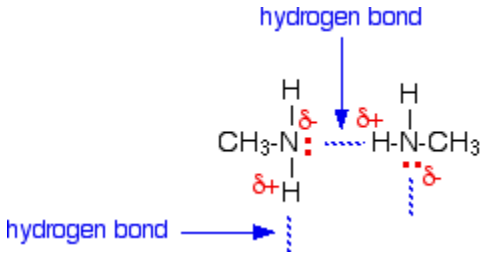
Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram (the remainder of the molecule is represented by *R*, and the electron pair is colored yellow). If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. It rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp^2-hybridized transition state, leading to a mixture of

interconverting *R* and *S* configurations. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of *R* and *S* configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. The take-home message is that nitrogen does not contribute to isolable stereoisomers.



Boiling Point and Water Solubility

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines (light green columns) demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1°-amines is roughly half the increase observed for equivalent alcohols.



Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point °C	-88.6°	65°	-6.0°	-42°	78.5°	16.6°

The second table illustrates differences associated with isomeric 1°, 2° & 3°-amines, as well as the influence of chain branching. Since 1°-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2°-amines, which in turn should boil higher than isomeric 3°-amines (no hydrogen bonding). Indeed, 3°-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3°-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 °C.

Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$

Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point °C	-0.5°	97°	48°	37°	-12°	82°	34°	3°

The water solubility of 1° and 2°-amines is similar to that of comparable alcohols. As expected, the water solubility of 3°-amines and ethers is also similar. These comparisons, however, are valid only for pure compounds in neutral water. The basicity of amines (next section) allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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21.3: Spectroscopy of the Amine Group

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum that shows absorptions resulting from the N$\ce{-}$H bonds of primary and secondary amines.
2. describe a characteristic change that occurs in the infrared spectrum of an amine when a small amount of mineral acid is added to the sample.
3. use ^{1}H NMR spectra in determining the structure of an unknown amine.
4. use the “nitrogen rule” of mass spectrometry to determine whether a compound has an odd or even number of nitrogen atoms in its structure.
5. predict the prominent peaks in the mass spectrum of a given amine.
6. use the mass spectrum of an unknown amine in determining its structure.

Key Terms

Make certain that you can define, and use in context, the key term below.

- nitrogen rule

Study Notes

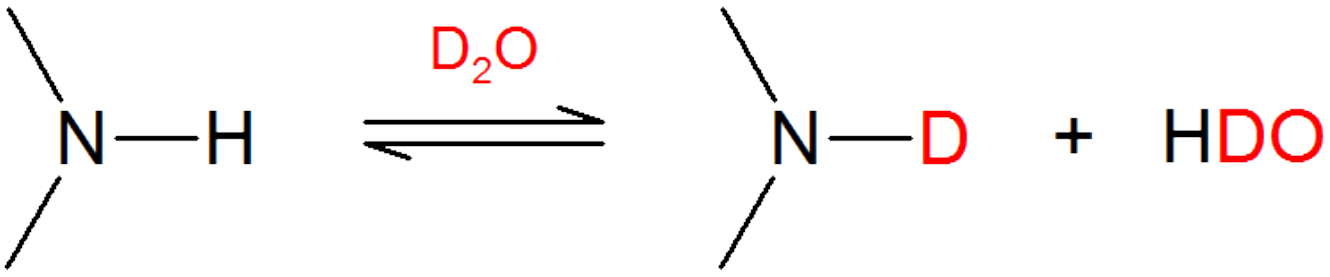
You should note the spectroscopic similarities between amines and alcohols: both have infrared absorptions in the 3300–3360 cm^{-1} region, and in both cases, the proton that is attached to the heteroatom gives rise to an often indistinct signal in the ^{1}H NMR spectrum.

^{1}H NMR of Amines

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration.

The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm.

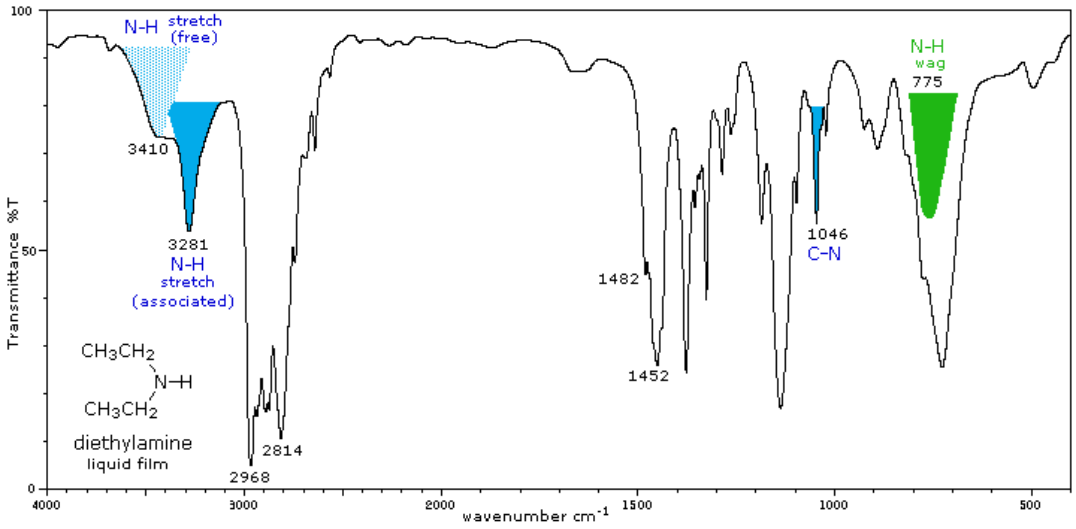
Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuteriums, thus making these resonances "disappear." Addition of a few drops of D_2O causing a signal to vanish can help confirm the presence of -NH.

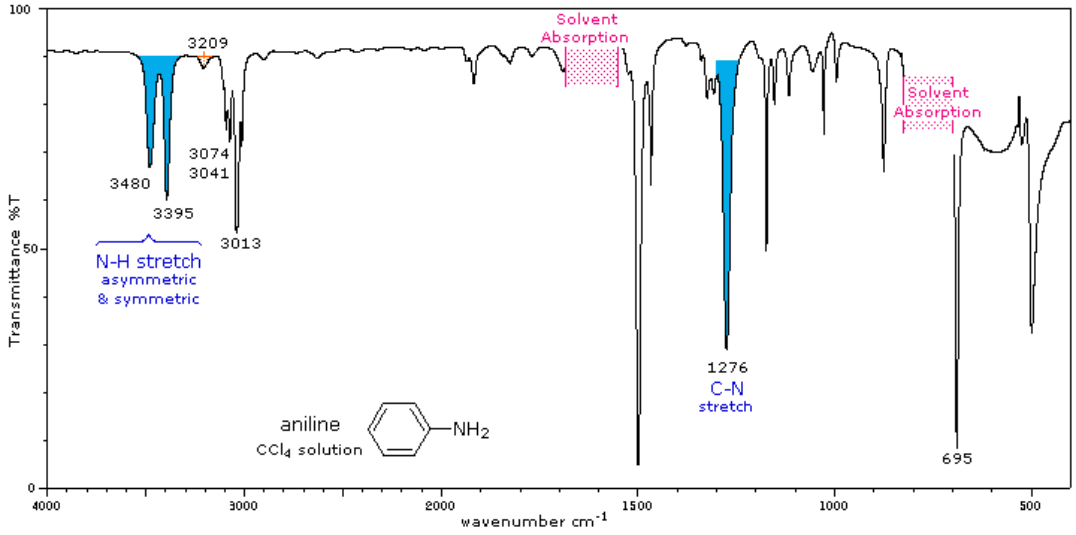


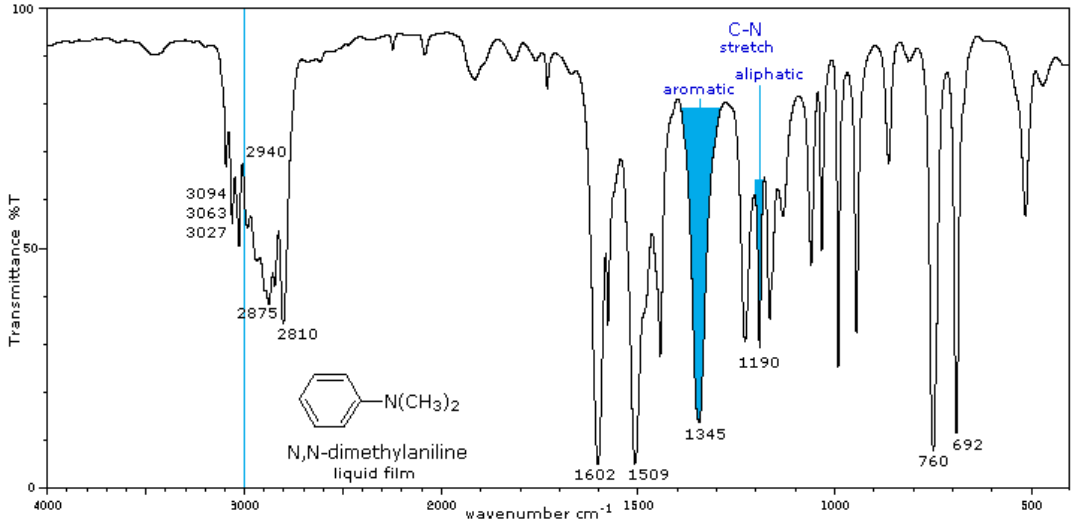
IR

The infrared spectrum of aniline is shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

Amine Class	Stretching Vibrations	Bending Vibrations	
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.	
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.	
Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.	


N-H stretch (free)
3410
3281
N-H stretch (associated)
CH3CH2
N-H
CH3CH2
diethylamine
liquid film
2968
2814
1482
1452
1046
C-N
N-H wag
775
Transmittance %T
wavenumber cm-1

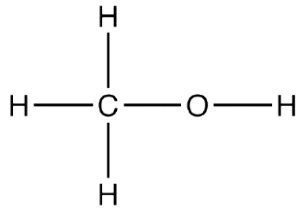

3209
3480
3395
3074
3041
3013
N-H stretch asymmetric & symmetric
Solvent Absorption
Solvent Absorption
1276
C-N stretch
695
aniline
CCl4 solution
NH2
Transmittance %T
wavenumber cm-1


C-N stretch
aromatic
aliphatic
2940
3094
3063
3027
2875
2810
1190
1345
1602
1509
760
692
N(CH3)2
N,N-dimethylaniline
liquid film
Transmittance %T
wavenumber cm-1

Nitrogen Rule

The nitrogen rule states that a molecule that has no or even number of nitrogen atoms has an even nominal mass, whereas a molecule that has an odd number of nitrogen atoms has an odd nominal mass.

eg. 1:



molecular formula = CH_4O

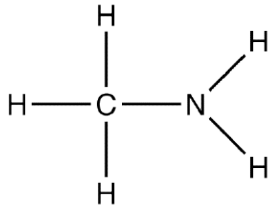
nominal mass = (1x12) + (4x1) + (1x16)

= 32

N atoms = 0

nominal mass = 32 (even #)

eg. 2:



molecular formula = CH_5N

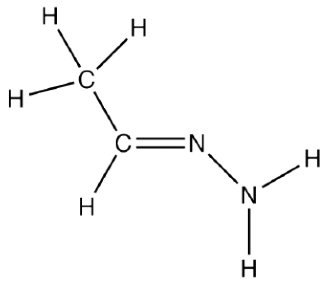
nominal mass = (1x12) + (5x1) + (1x14)

= 31

N atoms = 1 (odd #)

nominal mass = 31 (odd #)

eg. 3:



molecular formula = $C_2H_6N_2$

nominal mass = (2x12) + (6x1) + (2x14)

= 58

N atoms = 2 (even #)

nominal mass = 58 (even #)

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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21.4: Acidity and Basicity of Amines

Objectives

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

Key Terms

Make certain that you can define, and use in context, the key term below.

- amide

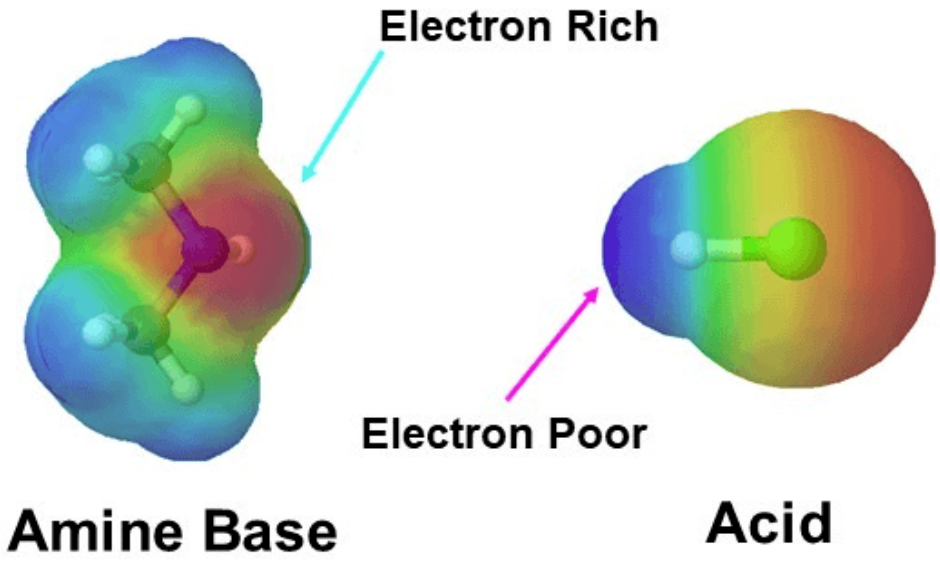
Study Notes

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 19.8).

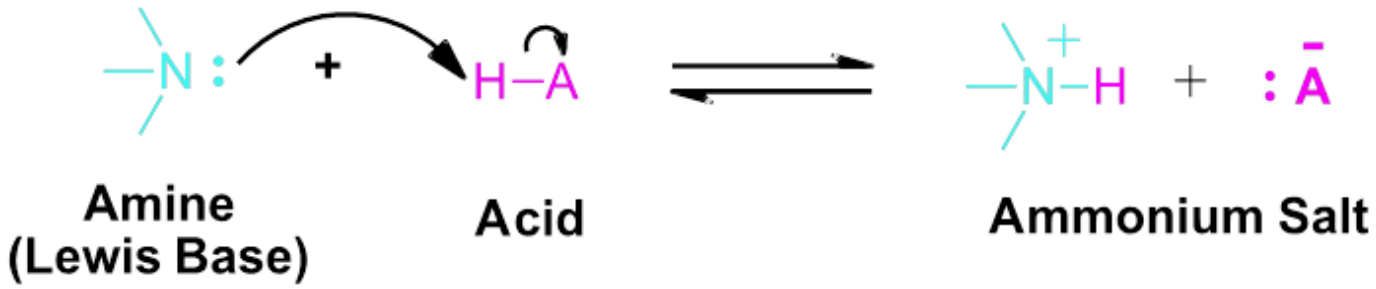
The ammonium ions of most simple aliphatic amines have a pK_a of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher pK_a) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher pK_a than the latter.

Basicity of nitrogen groups

In this section we consider the relative basicity of amines. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic and nucleophilic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen. The lone pair electrons makes the nitrogen in amines electron dense, which is represents by a red color in the electrostatic potential map present below left. Amine are basic and easily react with the hydrogen of acids which are electron poor as seen below.



Amines are one of the only neutral functional groups which are considered bases which is a consequence of the presence of the lone pair electrons on the nitrogen. During an acid/base reaction the lone pair electrons attack an acidic hydrogen to form a N-H bond. This gives the nitrogen in the resulting ammonium salt four single bonds and a positive charge.



Amines react with water to establish an equilibrium where a proton is transferred to the amine to produce an ammonium salt and the hydroxide ion, as shown in the following general equation:

$$RNH2_{(aq)} + H_2O_{(l)} \rightleftharpoons RNH3^+_{(aq)} + OH^-_{(aq)} \tag{21.4.1}$$

The equilibrium constant for this reaction is the base ionization constant (K_b), also called the base dissociation constant:

$$K_b = \frac{[RNH3^+][OH^-]}{[NH2]} \tag{21.4.2}$$

$$pK_b = -\log K_b$$

Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous basicity constant K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

However, Kb values are often not used to discuss relative basicity of amines. It is common to compare basicity's of amines by using the K_a's of their conjugate acids, which is the corresponding ammonium ion. Fortunately, the K_a and K_b values for amines are directly related.

Consider the reactions for a conjugate acid-base pair, RNH_3^+ – RNH_2:

$$\mathrm{RNH_3}^+(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_2}(aq) + \mathrm{H_3O}^+(aq) \quad K_\mathrm{a} = \frac{[RNH2][H3O]}{[RNH3+]} \tag{21.4.3}$$

$$\mathrm{RNH_2}(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_3}^+(aq) + \mathrm{OH}^-(aq) \quad K_\mathrm{b} = \frac{[RNH3+][OH-]}{[RNH2]} \tag{21.4.4}$$

Adding these two chemical equations together yields the equation for the autoionization for water:

$$\cancel{\mathrm{RNH_3}^+(aq)} + \mathrm{H_2O}(l) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O}^+(aq) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{OH}^-(aq) + \cancel{\mathrm{RNH_3}^+(aq)} \tag{21.4.5}$$

$$2\,\mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O}^+(aq) + \mathrm{OH}^-(aq) \tag{21.4.6}$$

Given that the *K* expression for a chemical equation formed from adding two or more other equations is the mathematical product of the input equations' *K* constants.

$$K_a \text{ X } K_b = \{2\ H_2O\} / (H_3O^+)\{OH^-\} = Kw$$

$$K_\mathrm{a} = \frac{K_\mathrm{w}}{K_\mathrm{b}} \tag{21.4.7}$$

$$pK_a + pK_b = 14$$

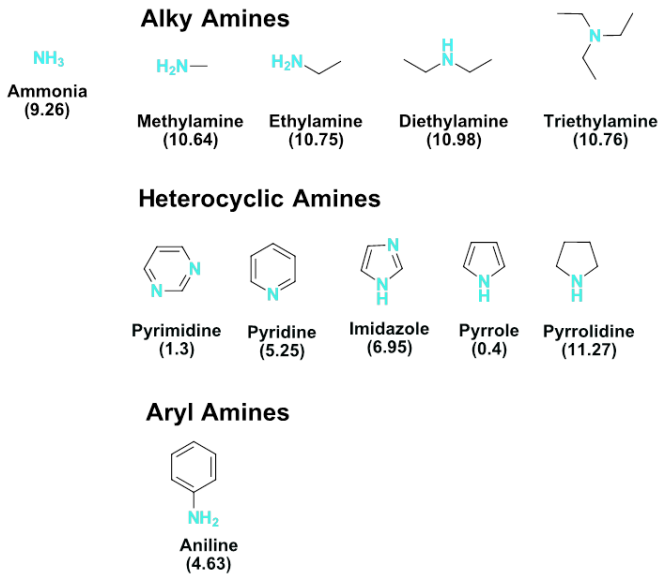
Thus if the K_a for an ammonium ion is know the K_b for the corresponding amine can be calculated using the equation $K_b = K_w / K_a$. This relationship shows that as an ammonium ion becomes more acidic (K_a increases / pK_a decreases) the correspond base becomes weaker (K_b decreases / pK_b increases)

Weaker Base = Larger K_a and Smaller pK_a of the Ammonium ion

Stronger Base = Smaller K_a and Larger pK_a of the Ammonium ion

Like ammonia, most amines are Brønsted-Lowry and Lewis bases, but their base strength can be changed enormously by substituents. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their aqueous solutions are basic (have a pH of 11 to 12, depending on concentration).

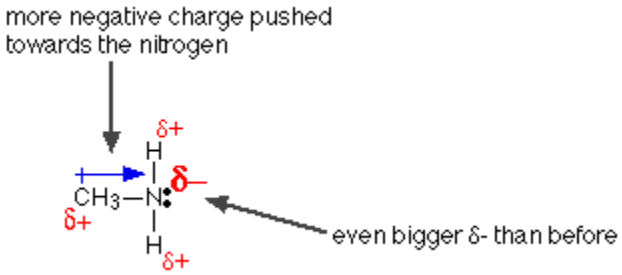
Aromatic herterocyclic amines (such as pyrimidine, pyridine, imidazole, pyrrole) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In each case the heterocyclic nitrogen is sp^2 hybridized. The increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton compared to sp^3 hybridized nitrogens. The very low basicity of pyrrole reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. Imidazole (pK_a = 6.95) is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.



Basicity of common amines (pK_a of the conjugate ammonium ions)

Inductive Effects in Nitrogen Basicity

Alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonia. The small amount of extra negative charge built up on the nitrogen atom makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.

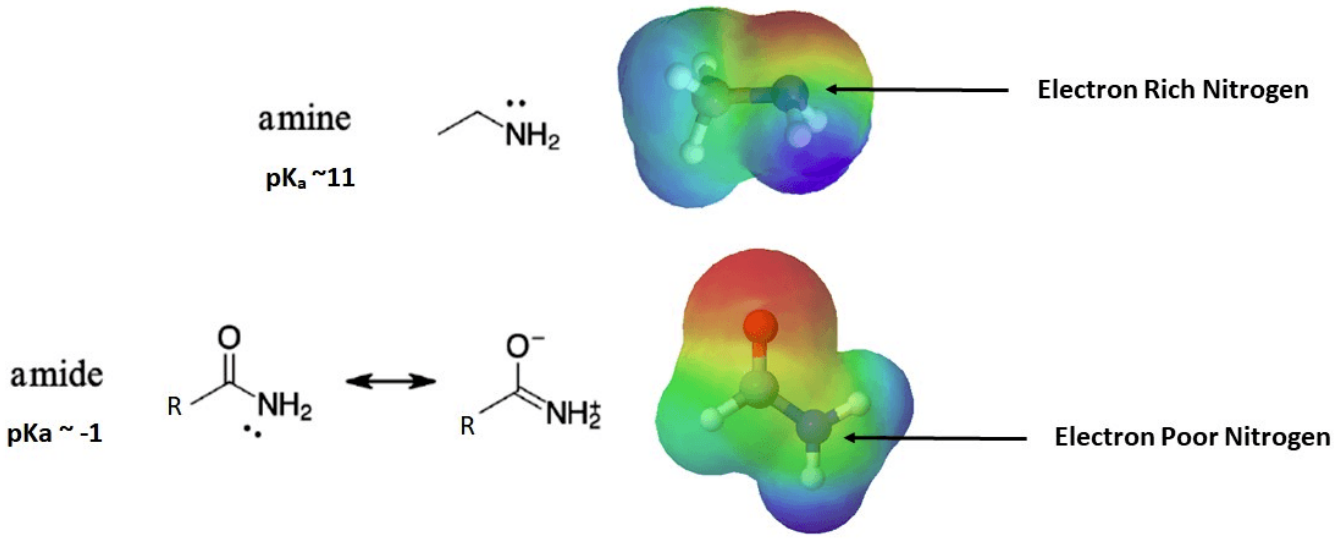


Compound	pK_a of the conjugate acid
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

Comparing the Basicity of Alkylamines to Amides

The nitrogen atom is strongly basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the electron lone pair of an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not as available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map shows the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost

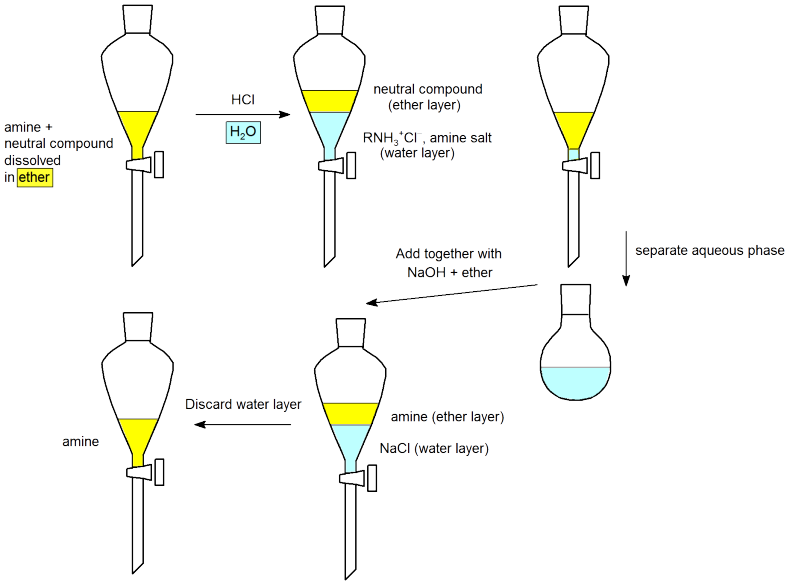
completely shifted towards the oxygen. This greatly decreases the basicity of the lone pair electrons on the nitrogen in an amide.



Comparison of amines and amides to rationalize the the pK_a values of their conjugate acids

Amine Extraction in the Laboratory

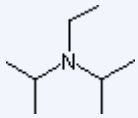
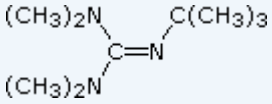
Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines one can take advantage of their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water. The salt will extract into the aqueous phase leaving behind neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.



Important Reagent Bases

The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying

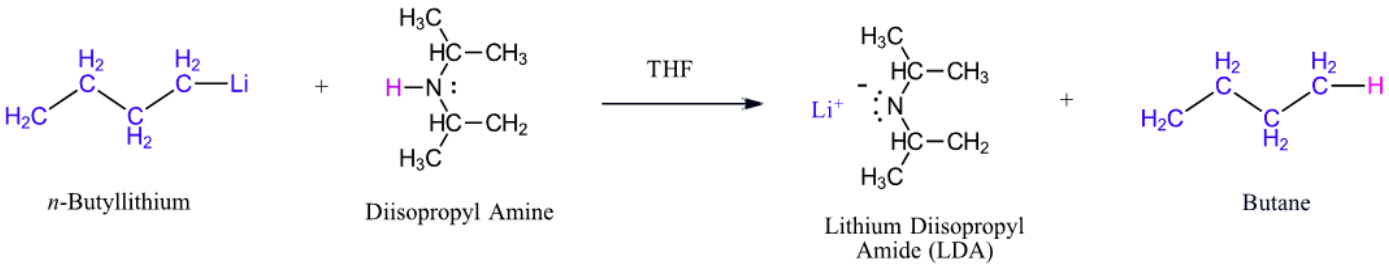
strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amine bases, and fill the gap in base strength between amines and amide salts.

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LD
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH$
pK_a of conjugate acid	5.3	10.7	11.4	14	19	26	35

Basicity of common amines (pK_a of the conjugate ammonium ions)

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

In addition to acting as a base, 1° and 2° amines can act as very weak acids. Their N-H proton can be removed if they are reacted with a strong enough base. An example is the formation of lithium diisopropylamide (LDA, $LiN[CH(CH_3)_2]_2$) by reacting *n*-butyllithium with diisopropylamine (pK_a 36) **(Section 22-5)**. LDA is a very strong base and is commonly used to create enolate ions by deprotonating an alpha-hydrogen from carbonyl compounds **(Section 22-7)**.

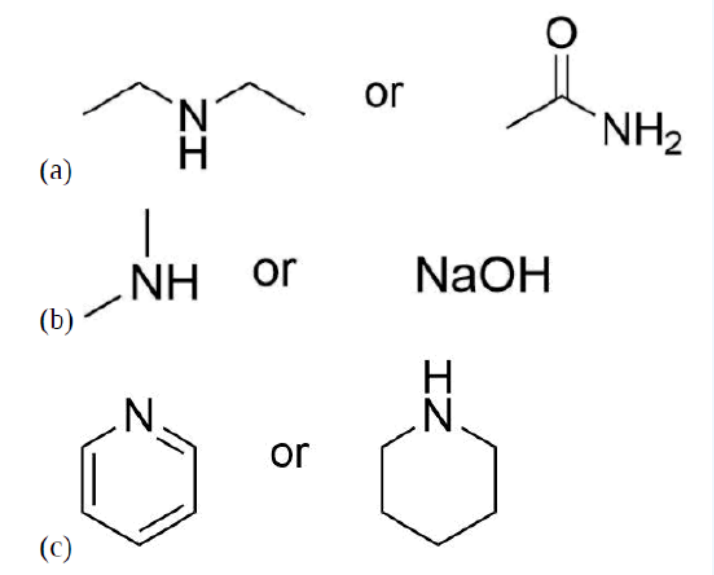


n-Butyllithium + Diisopropyl Amine → Lithium Diisopropyl Amide (LDA) + Butane

Exercises

Exercise 24.3.1

Select the more basic compound from each of the following pairs of compounds.



Answer available at the end of this section.

Exercise \24.3.2

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Answer available at the end of this section.

Questions

Q24.3.1

Select the more basic amine from each of the following pairs of compounds.

(a)24.4 Problem A.png

(b)24.4 Problem B.png

(c)24.4 Problem C.png

Q24.3.2

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Solutions

S24.3.1

(a)24.4 Solution A.png

(b)24.4 Solution B.png

(c)24.4 Solution C.png

S24.3.2

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Objectives

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

Study Notes

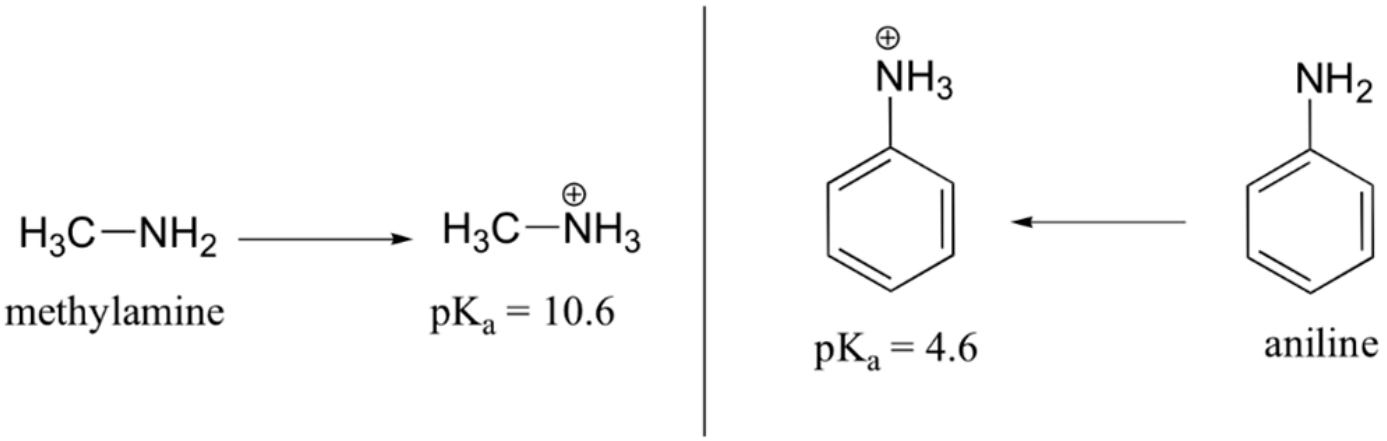
With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering $\Delta G°$.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

Note that the arylammonium ion derived from aniline, $PhNH_3^+$, is commonly referred to as the anilinium ion.

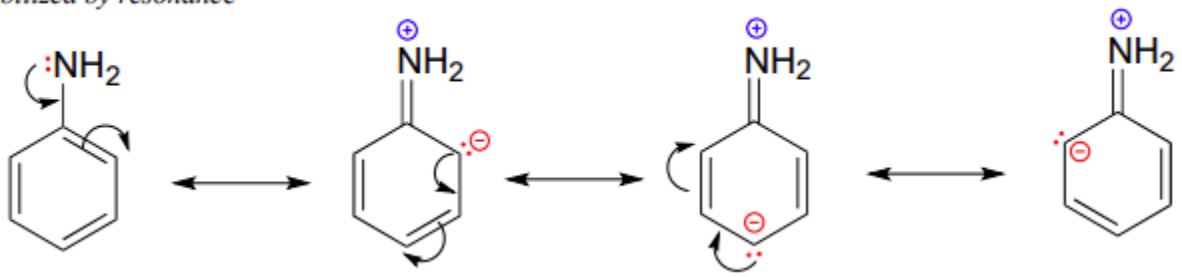
Basicity of Aniline

Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).

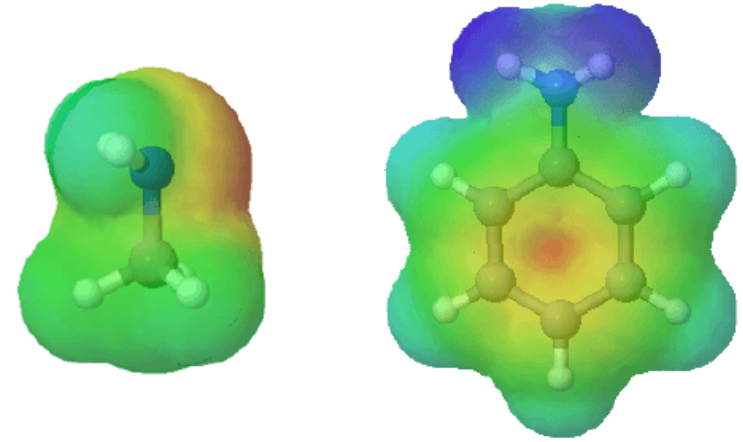


This difference is basicity can be explained by the observation that, in aniline, the lone pair of electrons on the nitrogen are delocalized by the aromatic p system, making it less available for bonding to H^+ and thus less basic. The lone pair electrons of aniline are involved in four resonance forms making them more stable and therefore less reactive relative to alkylamines.

lone pair is stabilized by resonance

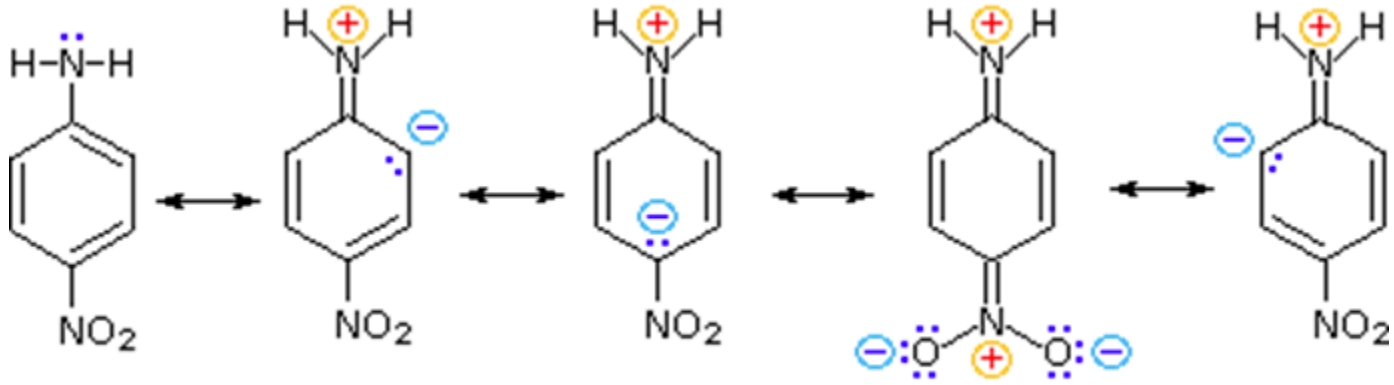


The effect of delocalization can be seen when viewing the electrostatic potential maps of aniline an methyl amine. The nitrogen of methyl amine has a significant amount of electron density on its nitrogen, shown as a red color, which accounts for it basicity compared to aniline. While the electron density of aniline's nitrogen is delocalized in the aromatic ring making it less basic.



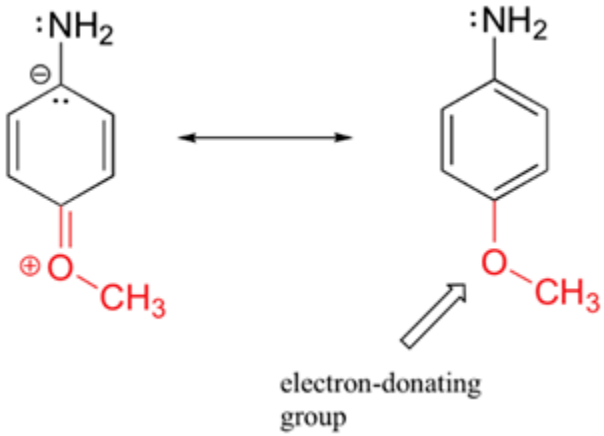
Basicity of Substituted Arylamines

The addition of substituents onto the aromatic ring can can make arylamines more or less basic. Substituents which are electron-withdrawing (-Cl, -CF_3, -CN, -NO_2) decrease the electron density in the aromatic ring and on the amine making the arylamine less basic. In particular, the nitro group of *para*-nitroaniline allows for an additional resonance form to be drawn, which further stabilizes the lone pair electrons from the nitrogen, making the substituted arylamine less basic than aniline. This effect is analogous to the one discussed for the acidity of substituted phenols in **Section 17.2.**



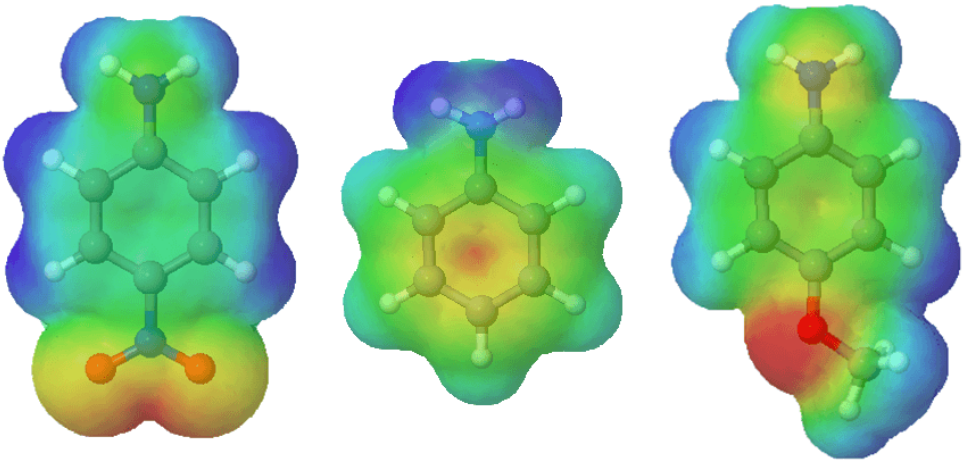
Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Substituents which are electron-donating (-CH_3, -OCH_3, -NH_2) increase the electron density in the aromatic ring and on the amine making the arylamine more basic. In the case of *para*-methoxyaniline, the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the substituted arylamine more basic than aniline.



Increased Basicity of para-Methoxyaniline due to Electron-Donation

The shifting electron density of aniline, *p*-nitroaniline, and *p*-methoxyaniline are seen in their relative electrostatic potential maps. For *p*-Nitroaniline virtually all of the electron density, shown as a red/yellow color. is pulled toward the electron-withdrawing nitro group. In *p*-methoxyaninline the electron donating methoxy group donates electron density into the ring. The amine in p-methoxyaniline is shown to have more electron density, shown as a yellow color, when compared to the amine in aniline.



p-Nitroaniline Aniline *p*-Methoxyaniline

Exercise

Exercise 24.4.1

Using the knowledge of the electron donating or withdrawing effects of subsituents gained in Section 16.6, rank the following compound in order of decreasing basicity.
a) *p*-Nitroaniline, methyl p-aminobenzoate, *p*-chloroaniline
b) *p*-Bromoaniline, *p*-Aminobenzonitrile, *p*-ethylaniline
c) p-(Trifluoromethyl)aniline, *p*-methoxyaniline, *p*-methylaniline

Answers available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

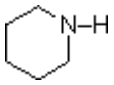
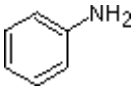
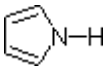
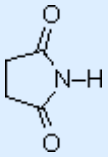
Acidity of AminesEdit section

We normally think of amines as bases, but it must be remembered that 1° and 2°-amines are also very weak acids (ammonia has a $pK_a = 34$). In this respect it should be noted that **pK_a is being used as a measure of the acidity of the amine itself rather than its conjugate acid, as in the previous section**. For ammonia this is expressed by the following hypothetical equation:

$$NH_3 + H_2O \longrightarrow NH_2^{(-)} + H_2O\text{-}H^{(+)}$$

The same factors that decreased the basicity of amines increase their acidity. This is illustrated by the following examples, which are shown in order of increasing acidity. It should be noted that the first four examples have the same order and degree of increased acidity as they exhibited decreased basicity in the previous table. The first compound is a typical 2°-amine, and the

three next to it are characterized by varying degrees of nitrogen electron pair delocalization. The last two compounds (shaded blue) show the influence of adjacent sulfonyl and carbonyl groups on N-H acidity. From previous discussion it should be clear that the basicity of these nitrogens is correspondingly reduced.

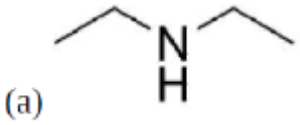
Compound					$C_6H_5SO_2NH_2$	
pK_a	33	27	19	15	10	9.6

The acids shown here may be converted to their conjugate bases by reaction with bases derived from weaker acids (stronger bases). Three examples of such reactions are shown below, with the acidic hydrogen colored red in each case. For complete conversion to the conjugate base, as shown, a reagent base roughly a million times stronger is required.

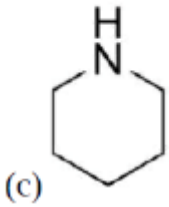
$C_6H_5SO_2NH_2 + KOH \longrightarrow C_6H_5SO_2NH^{(-)}\ K^{(+)} + H_2O$	a sulfonamide base
$(CH_3)_3COH + NaH \longrightarrow (CH_3)_3CO^{(-)}\ Na^{(+)} + H_2$	an alkoxide base
$(C_2H_5)_2NH + C_4H_9Li \longrightarrow (C_2H_5)_2N^{(-)}\ Li^{(+)} + C_4H_{10}$	an amide base

Answers

Exercise 24.3.1







Exercise \24.3.2

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49

Exercise 24.4.1

a) *p*-Chloroaniline, methyl p-aminobenzoate, *p*-nitroaniline
b) *p*-Ethylaniline, *p*-Bromoaniline, *p*-aminobenzonitrile
c) *p*-Methoxyaniline, *p*-methylaniline, *p*-(trifluoromethyl)aniline

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21.5: Synthesis of Amines by Alkylation

This page summarises the reactions of amines as nucleophiles. This includes their reactions with halogenoalkanes (haloalkanes or alkyl halides), with acyl chlorides (acid chlorides) and with acid anhydrides.

Amines by direct nucleophilic substitution

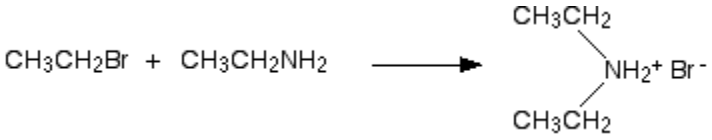
A nucleophile is something which is attracted to, and then attacks, a positive or slightly positive part of another molecule or ion. All amines contain an active lone pair of electrons on the very electronegative nitrogen atom. It is these electrons which are attracted to positive parts of other molecules or ions.

The reactions of primary amines with halogenoalkanes

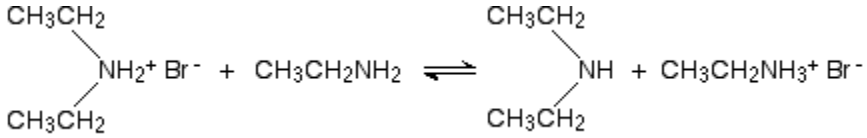
You get a complicated series of reactions on heating to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

Making secondary amines and their salts

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



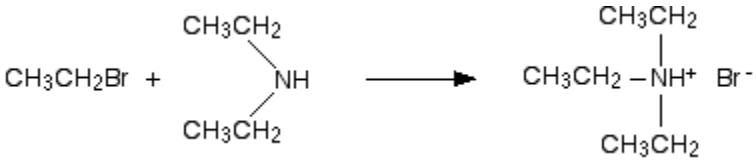
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



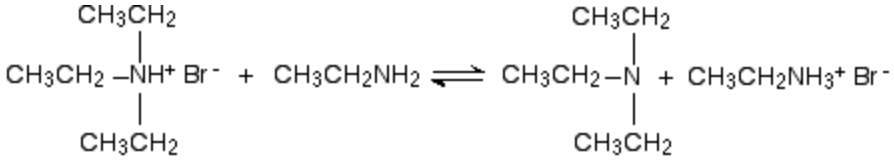
Making tertiary amines and their salts

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



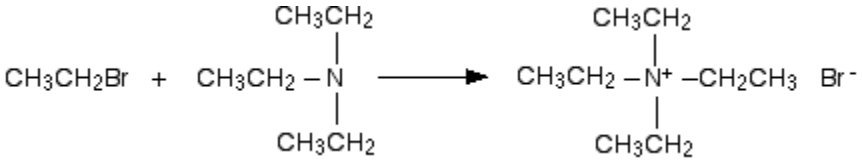
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

Making a quaternary ammonium salt

The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



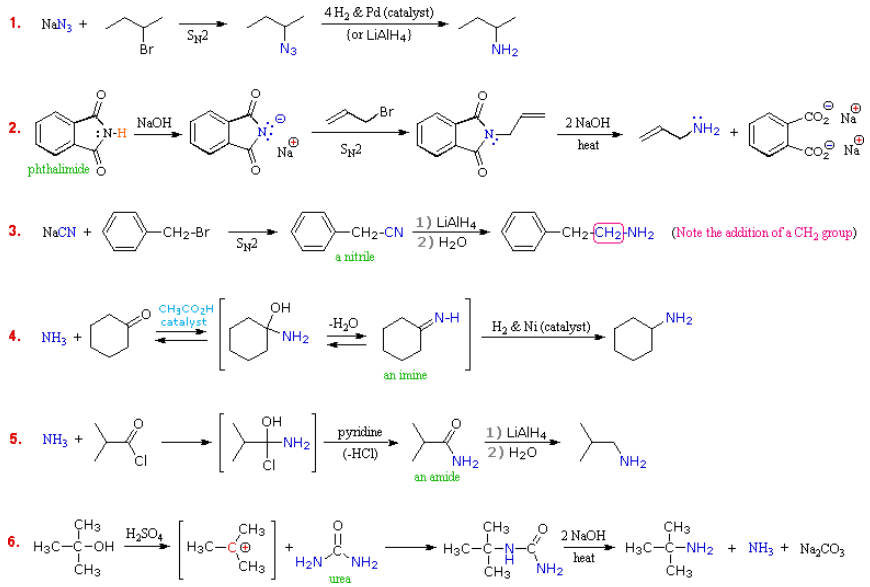
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1°-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$N_3^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-N_3 or R_2CH-N_3	$LiAlH_4$ or 4 H_2 & Pd	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$C_6H_5SO_2NH^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NHSO_2C_6H_5$ or R_2CH-$NHSO_2C_6H_5$	Na in NH_3 (liq)	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$CN^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-CN or R_2CH-CN	$LiAlH_4$	Reduction	RCH_2-CH_2NH_2 or R_2CH-CH_2NH_2
NH_3	RCH=O or R_2C=O	Addition / Elimination	RCH=NH or R_2C=NH	H_2 & Ni or $NaBH_3CN$	Reduction	RCH_2-NH_2 or R_2CH-NH_2
NH_3	RCOX	Addition / Elimination	RCO-NH_2	$LiAlH_4$	Reduction	RCH_2-NH_2
NH_2CONH_2 (urea)	$R_3C^{(+)}$	S_N1	R_3C-$NHCONH_2$	NaOH soln.	Hydrolysis	R_3C-NH_2

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an S_N2 reaction with a modestly electrophilic alkyl halide reactant. For example #2 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system by a methylene group (CH_2). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an E2 elimination.



The methods illustrated by examples #4 and #5 proceed by attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by $LiAlH_4$.

The 6th example is a specialized procedure for bonding an amino group to a 3°-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3°-alkyl-substituted urea is then hydrolyzed to give the amine.

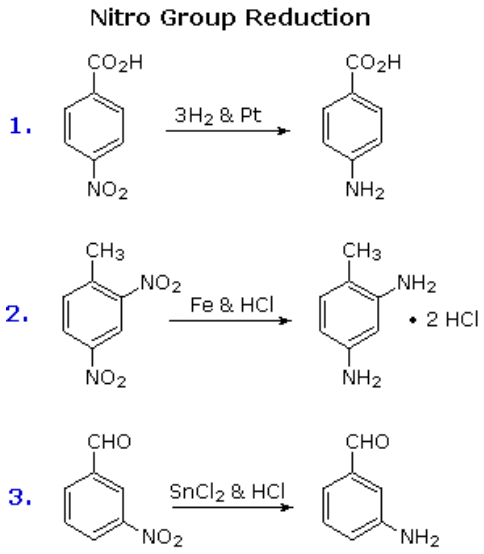
One important method of preparing 1°-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($NO_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1°-amine by any of several reduction procedures.

The Hofmann rearrangement of 1°-amides provides an additional synthesis of 1°-amines. To learn about this useful procedure Click Here.

Reduction of Other Functional Groups that Contain Nitrogen

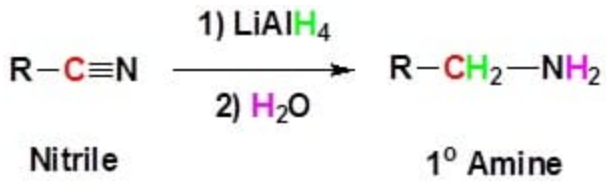
Reduction of Nitro Groups

Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

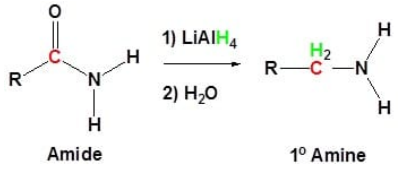


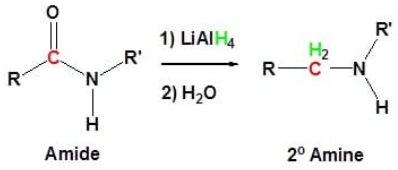
Nitriles can be converted to 1° amines by reaction with $LiAlH_4$

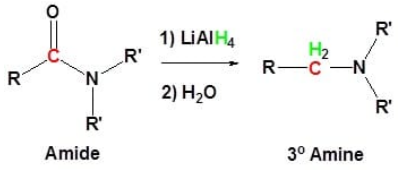
During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$

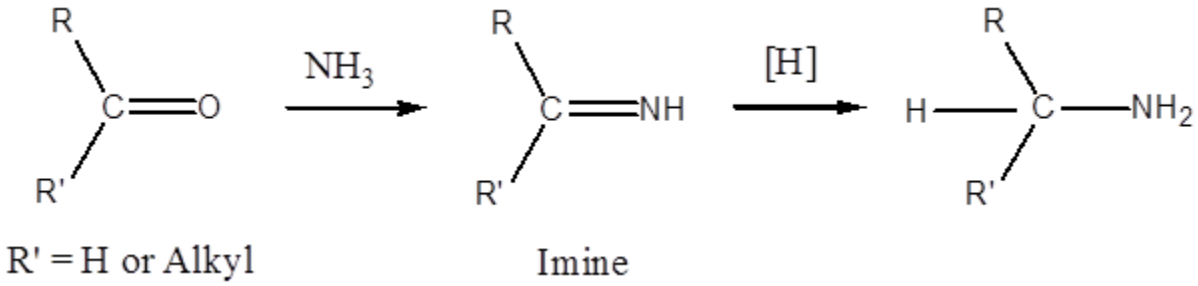


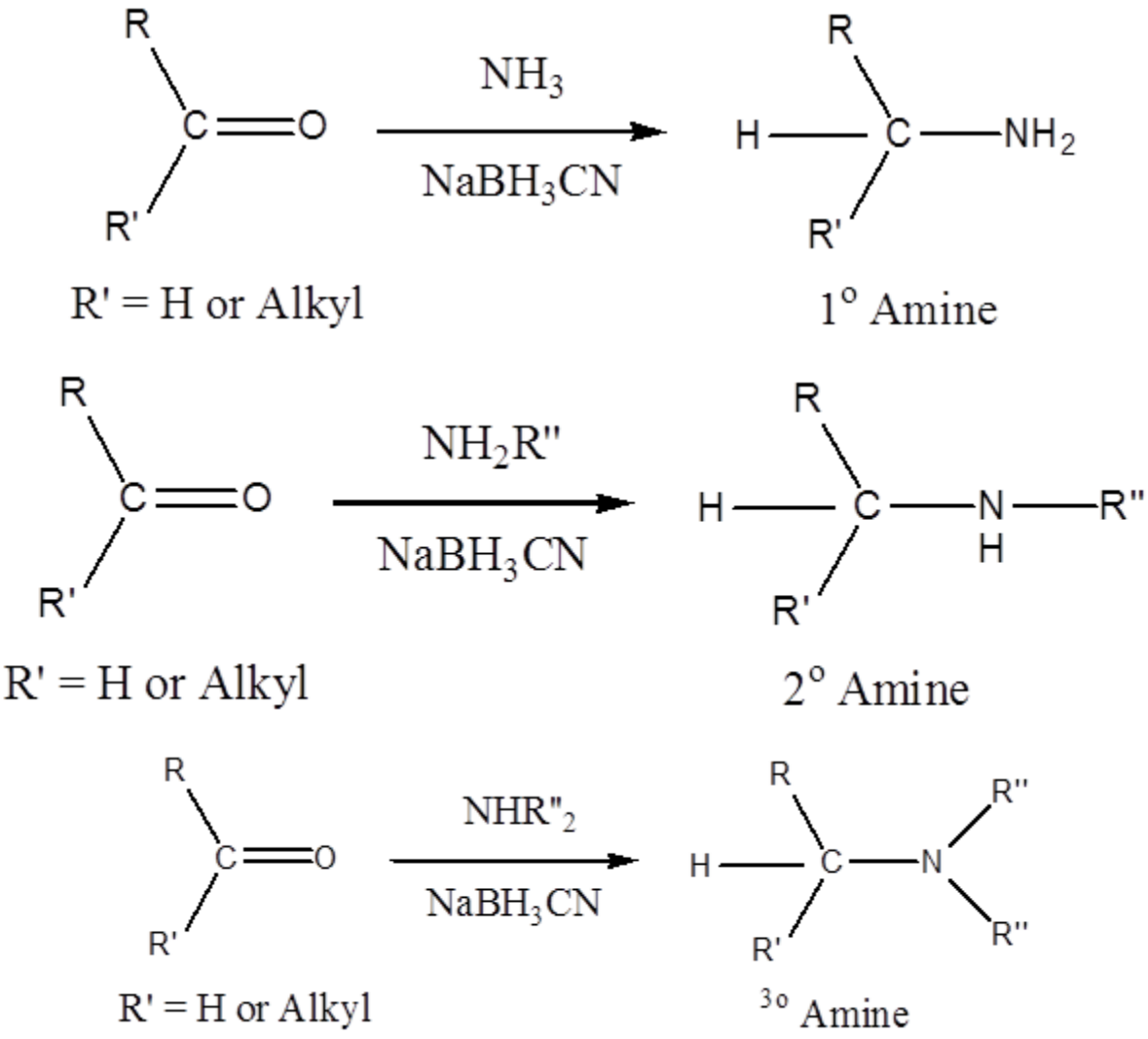




Reductive amination

Aldehydes and ketones can be converted into 1^{o}, 2^{o} and 3^{o} amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophiic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).





Contributors

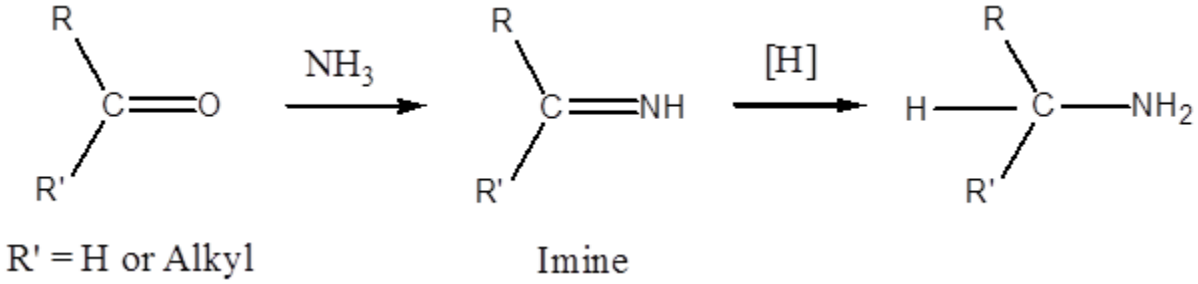
- Jim Clark (Chemguide.co.uk)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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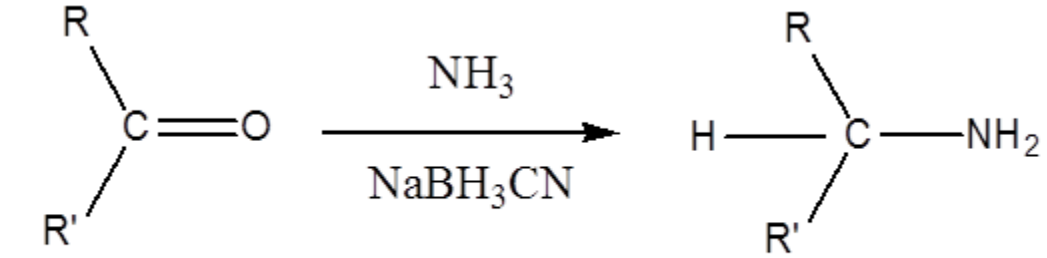
21.6: Synthesis of Amines by Reductive Amination

Reductive Amination

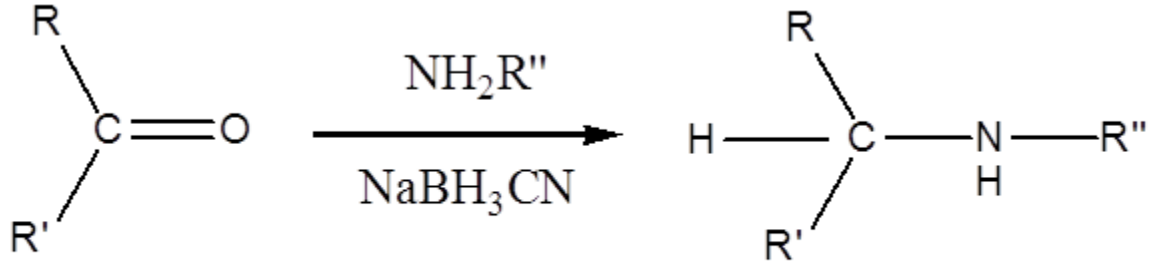
Aldehydes and ketones can be converted into 1^{o}, 2^{o} and 3^{o} amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophiic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).



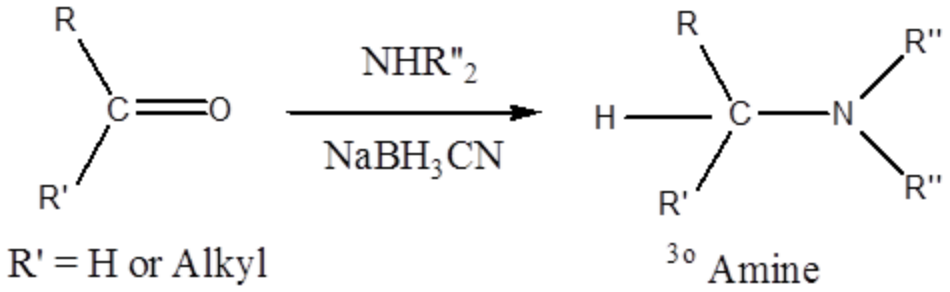
R' = H or Alkyl Imine



R' = H or Alkyl 1° Amine



R' = H or Alkyl 2° Amine



R' = H or Alkyl

3o Amine

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21.7: Synthesis of Amines from Carboxylic Amides

Objectives

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

Key Terms

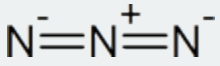
Make certain that you can define, and use in context, the key terms below.

- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

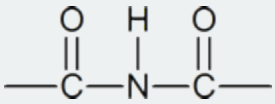
Study Notes

You may wish to review the mechanism of S_N2 reactions which is discussed in some detail in Sections 11.2 and 11.3.

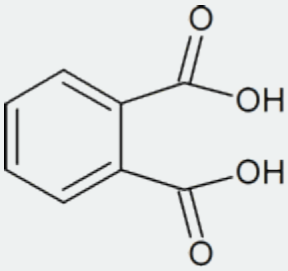
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



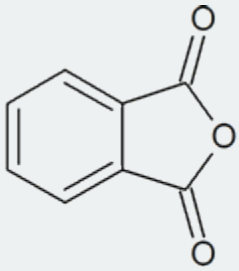
An “imide” is a compound in which an N$\ce{-}$H group is attached to two carbonyl groups; that is,



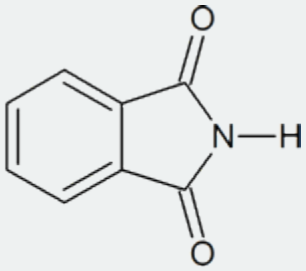
You should note the commonly used trivial names of the following compounds.



phthalic acid



phthalic anhydride



phthalimide

The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

If necessary, review the reduction of nitriles (Section 20.7) and the reduction of amides (Section 21.7).

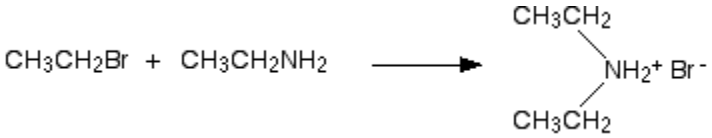
Before you read the section on reductive amination you may wish to remind yourself of the structure of an imine (see Section 19.8).

The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term “rearrangement” is not really appropriate. There is a rearrangement step in the overall degradation process, however: this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

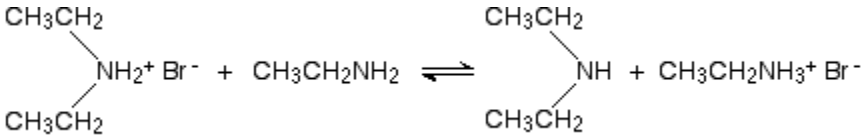
You get a complicated series of reactions on heating primary amines with halogenoalkanes to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

Making secondary amines and their salts

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



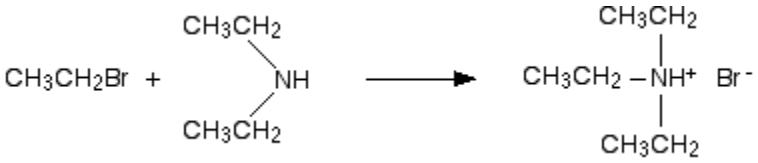
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



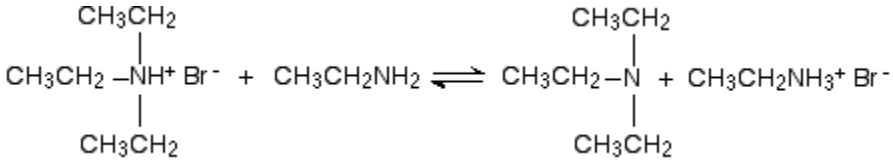
Making tertiary amines and their salts

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



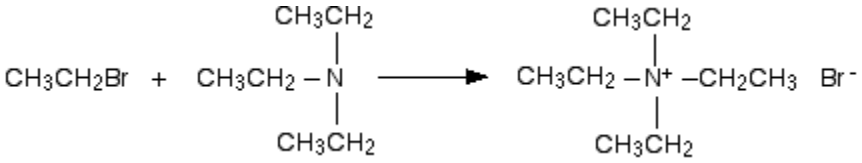
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

Making a quaternary ammonium salt

The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

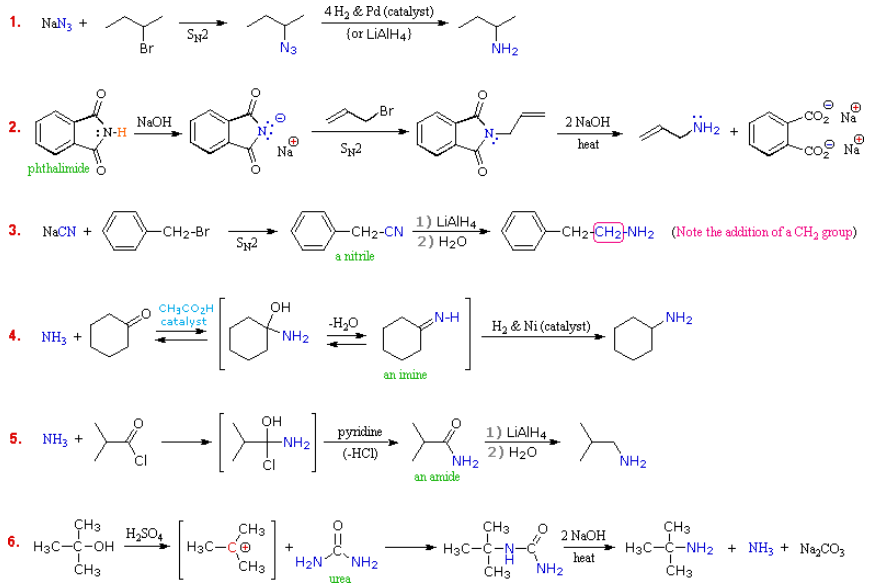
Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1°-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$N_3^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-N_3 or R_2CH-N_3	$LiAlH_4$ or 4 H_2 & Pd	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$C_6H_5SO_2NH^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NHSO_2C_6H_5$ or R_2CH-$NHSO_2C_6H_5$	Na in NH_3 (liq)	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$CN^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-CN or R_2CH-CN	$LiAlH_4$	Reduction	RCH_2-CH_2NH_2 or R_2CH-CH_2NH_2
NH_3	RCH=O or R_2C=O	Addition / Elimination	RCH=NH or R_2C=NH	H_2 & Ni or $NaBH_3CN$	Reduction	RCH_2-NH_2 or R_2CH-NH_2
NH_3	RCOX	Addition / Elimination	RCO-NH_2	$LiAlH_4$	Reduction	RCH_2-NH_2
NH_2CONH_2 (urea)	$R_3C^{(+)}$	S_N1	R_3C-$NHCONH_2$	NaOH soln.	Hydrolysis	R_3C-NH_2

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an S_N2 reaction with a modestly electrophilic alkyl halide reactant. For example #2 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system by a methylene group (CH_2). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an E2 elimination.



The methods illustrated by examples #4 and #5 proceed by attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by $LiAlH_4$.

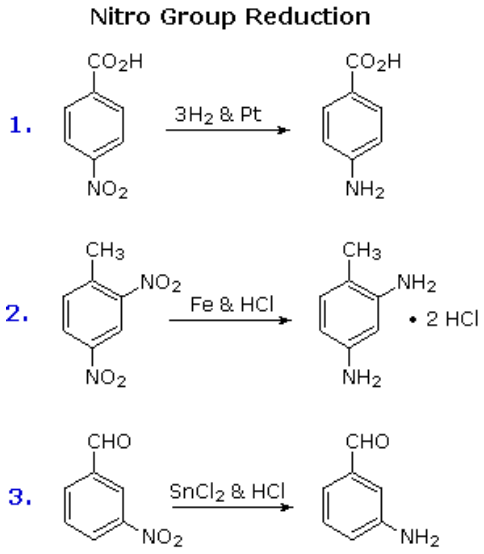
The 6th example is a specialized procedure for bonding an amino group to a 3°-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3°-alkyl-substituted urea is then hydrolyzed to give the amine. One important method of preparing 1°-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($NO_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1°-amine by any of several reduction procedures.

The Hofmann rearrangement of 1°-amides provides an additional synthesis of 1°-amines.

Reduction of Other Functional Groups that Contain Nitrogen

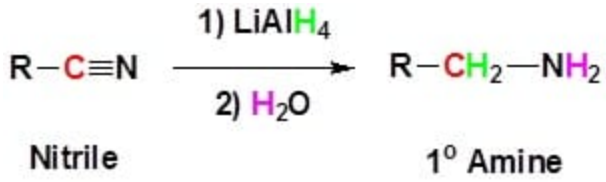
Reduction of Nitro Groups

Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

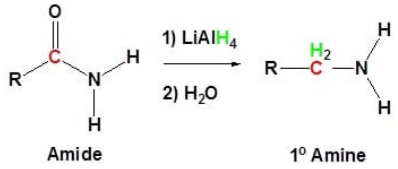


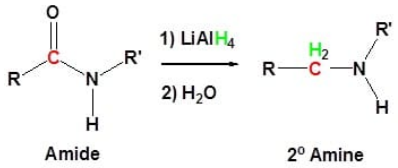
Nitriles can be converted to 1° amines by reaction with $LiAlH_4$

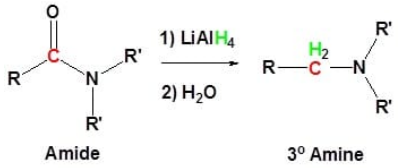
During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$

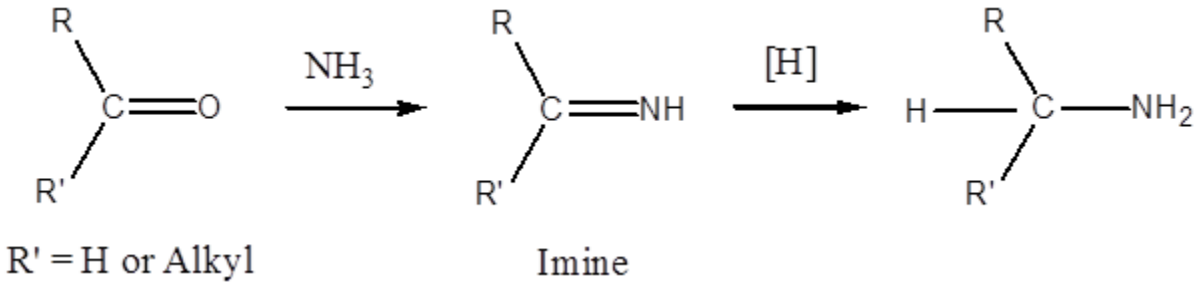


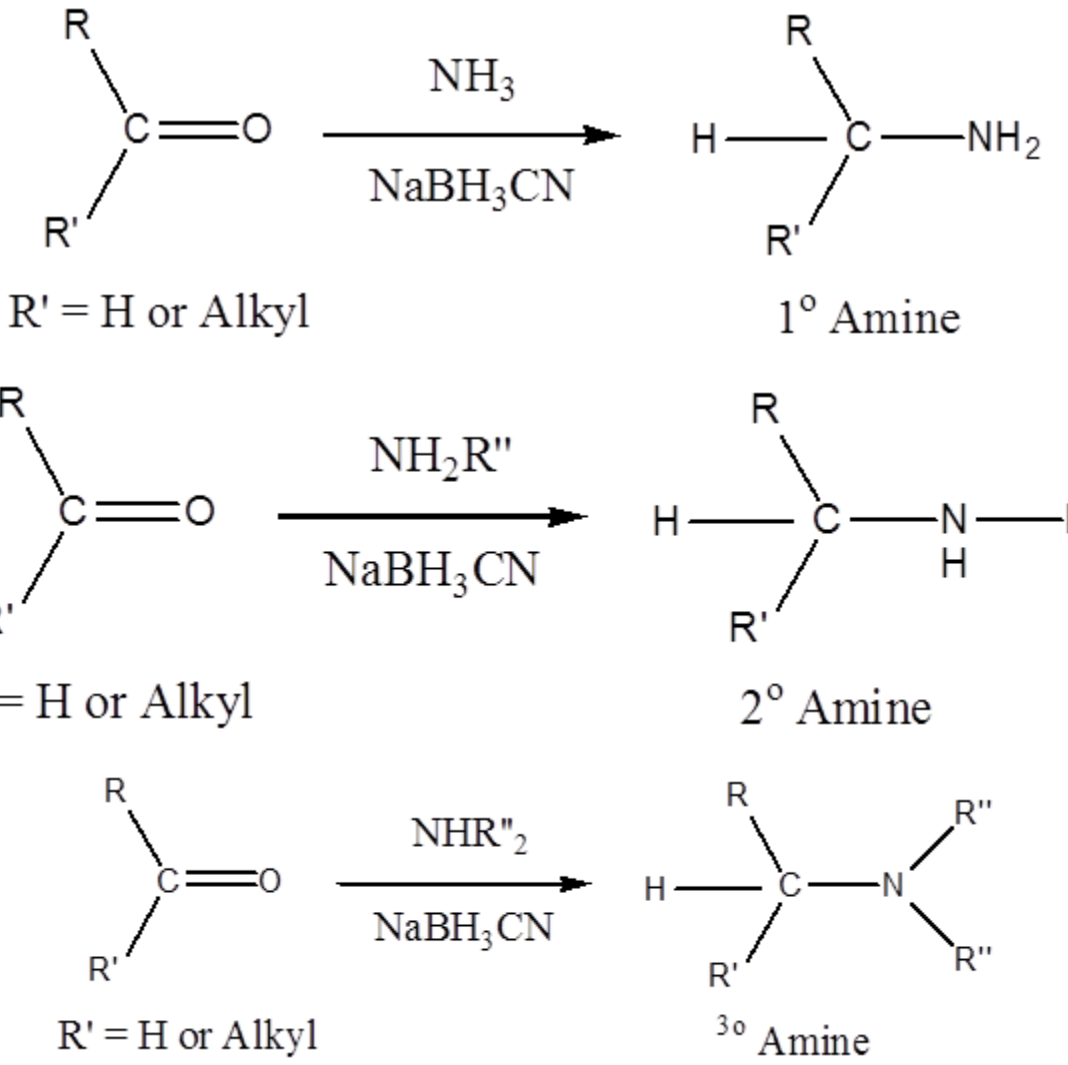




Reductive Amination

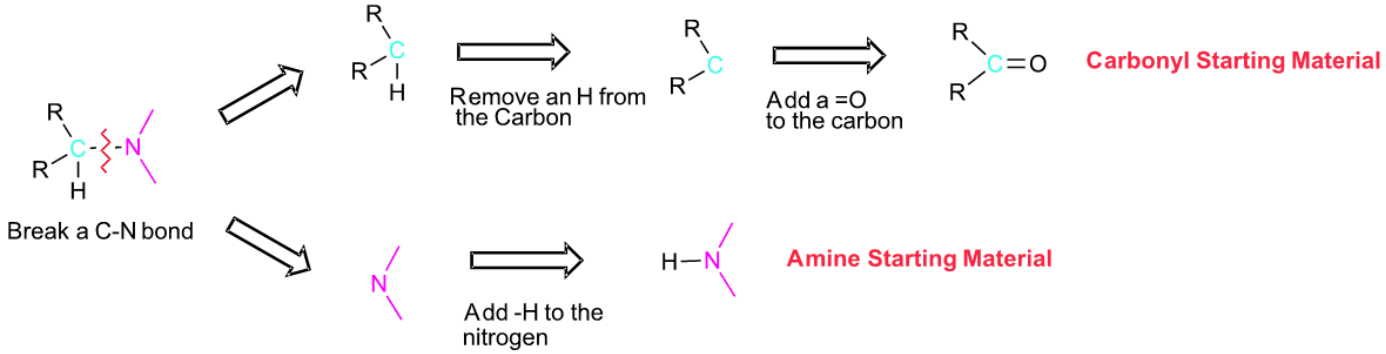
Aldehydes and ketones can be converted into 1^o, 2^o and 3^o amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophiic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).





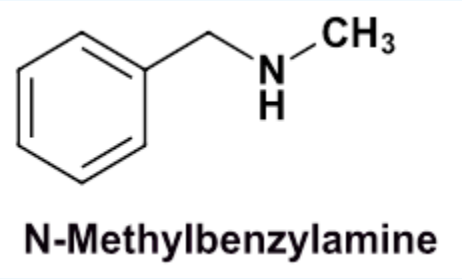
Planning a Synthesis using a Reductive Amination

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



Worked Exercise 24.6.1

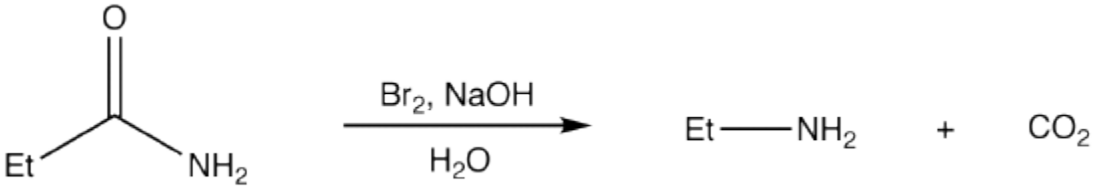
Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.



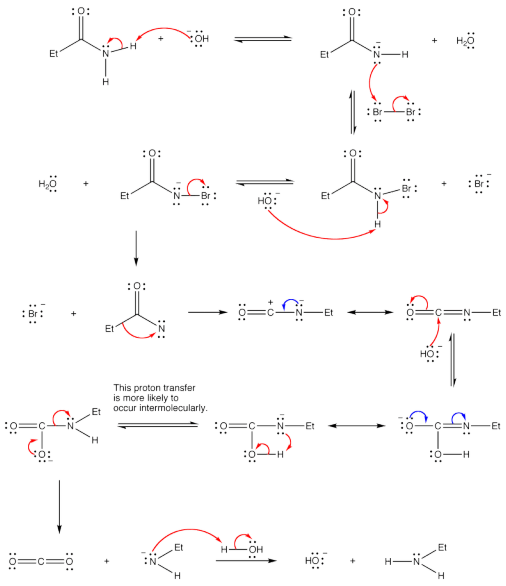
Answer available at the end of this section.

Hofmann rearrangement

Hofmann rearrangement, also known as Hofmann degradation and not to be confused with Hofmann elimination, is the reaction of a primary amide with a halogen (chlorine or bromine) in strongly basic (sodium or potassium hydroxide) aqueous medium, which converts the amide to a primary amine. For example:

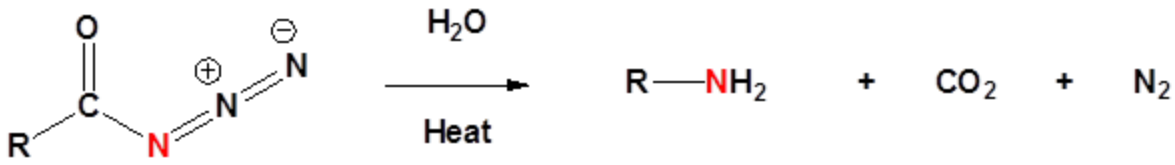


Mechanism:

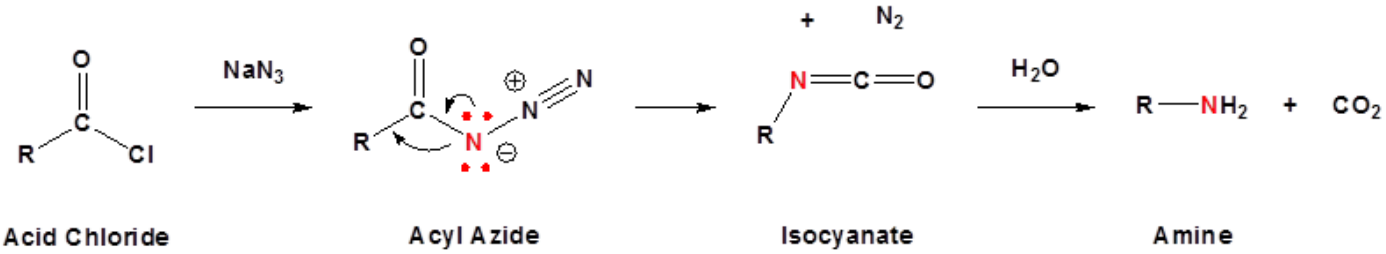


Curtius Rearrangement

The Curtius rearrangement involves an acyl azide.

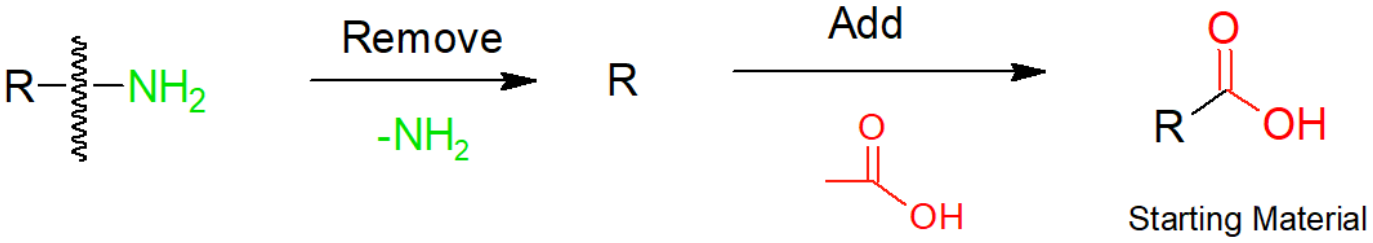


The mechanism of the Curtius rearrangement involves the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen.



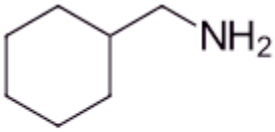
Planning a Synthesis using a Hofman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements both are best made from an acid chloride, synthesis of amines using these reaction are best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product - the key break is the C-NH_2 bond. The amine is removed and replaced with a -CO_2H fragment to provide the required carboxylic acid starting material.



Worked Example 24.6.2

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



(Cyclohexylmethyl)amine

Answer available at the end of this section.

Exercises

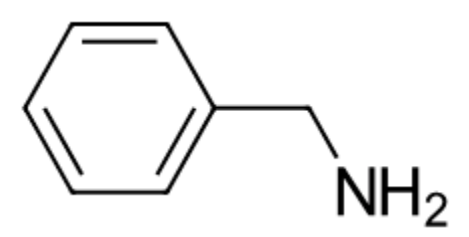
Exercise 24.6.1

Propose structures of the starting materials needed to make the the following amines using the reduction of a nitrile or an amide:

a) $CH_3CH_2CH_2CH_2NH_2$

b) $(CH_3CH_2)_2NH$

c)



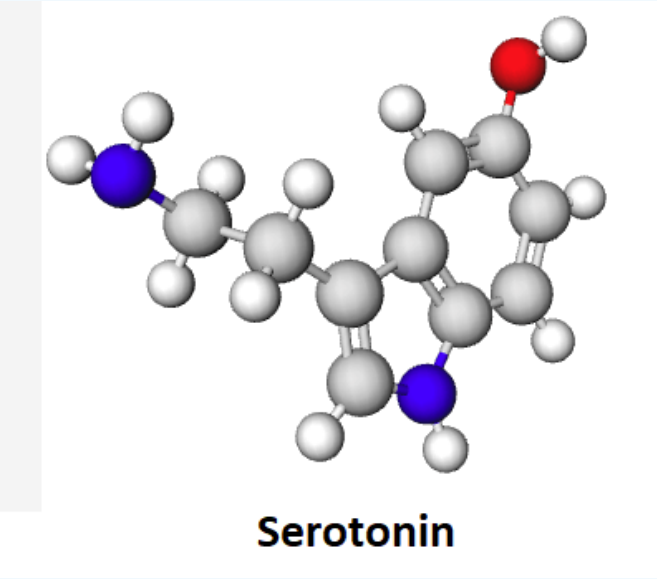
e) N-Propylaniline

Answer available at the end of this section.

Exercise 24.6.2

1) Write the mechanism for the base promoted hydrolysis of an N-alkyl phthalimide to create a 1^o amine and the phthalate ion.

2) Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.



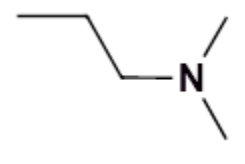
Answers available at the end of this section.

Exercise 24.6.3

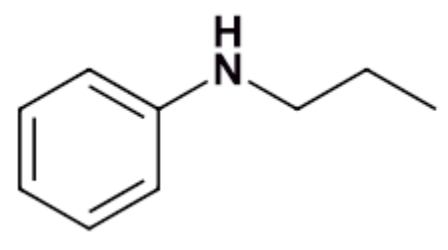
Provide starting materials which could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

1)

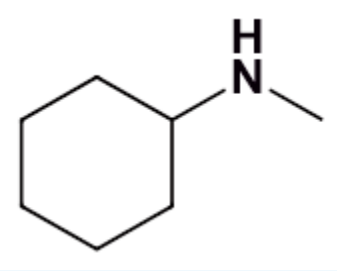
a)



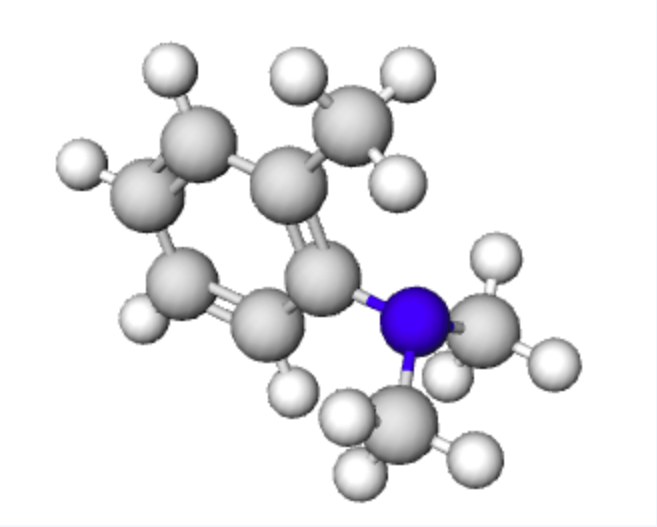
b)



c)



2) Please give the starting materials which could provide the following molecule using a reductive amination.

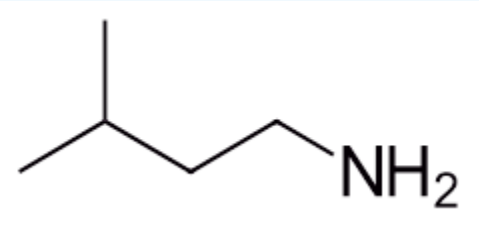


Answer available at the end of this section.

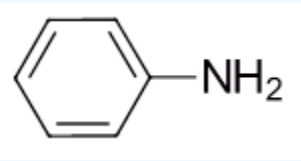
Exercises 24.6.4

1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a)



b)



Answers available at the end of this section.

Contributors and Attributions

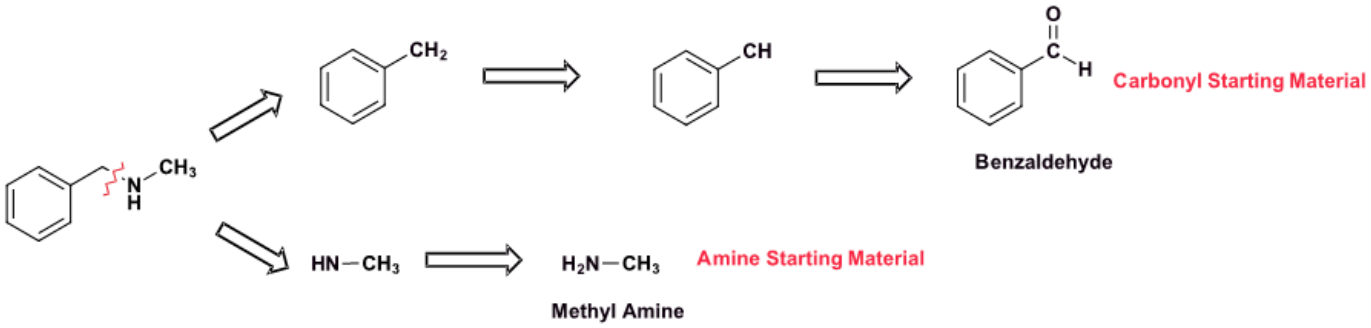
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Jim Clark (Chemguide.co.uk)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

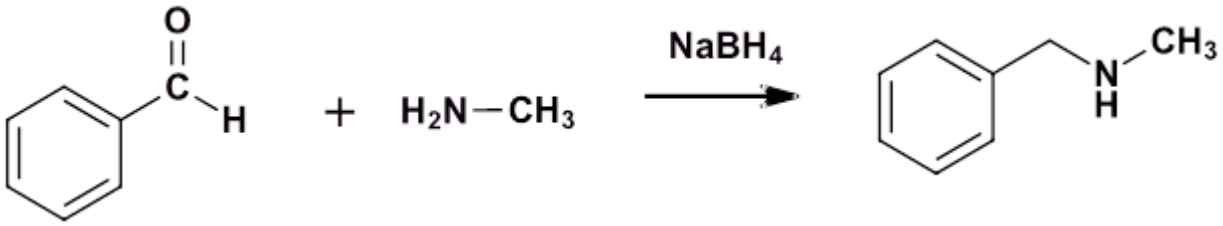
Answers

Worked Exercise 24.6.1

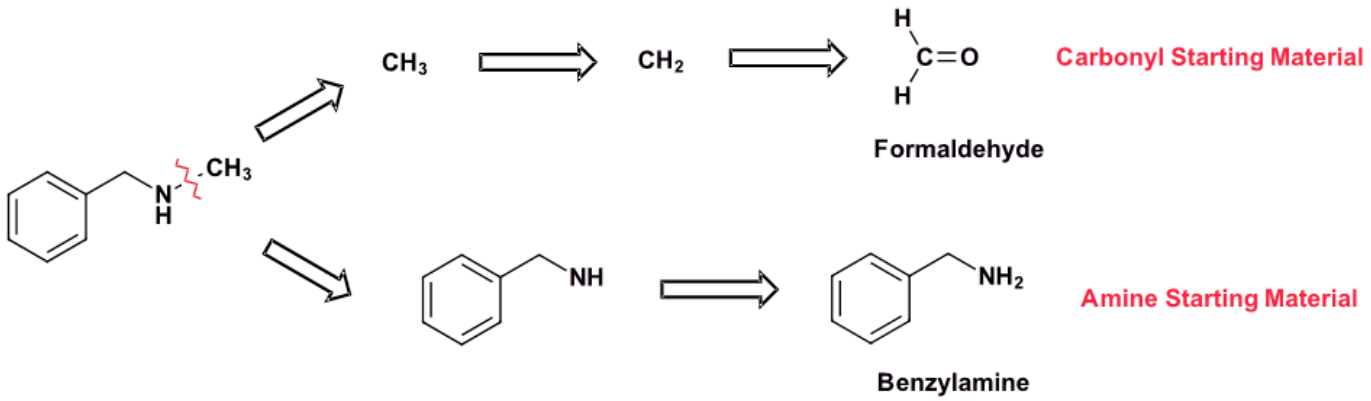
Pathway 1



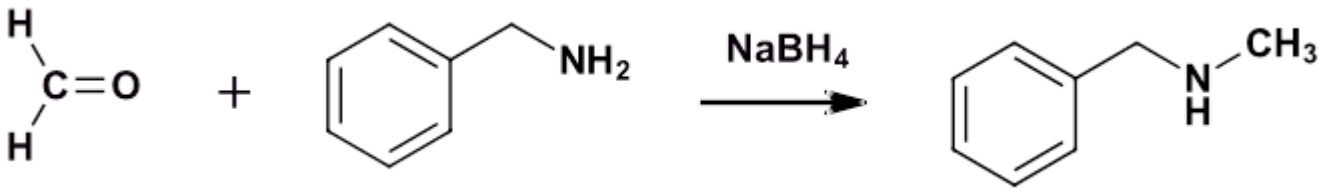
Solution 1



Pathway 2



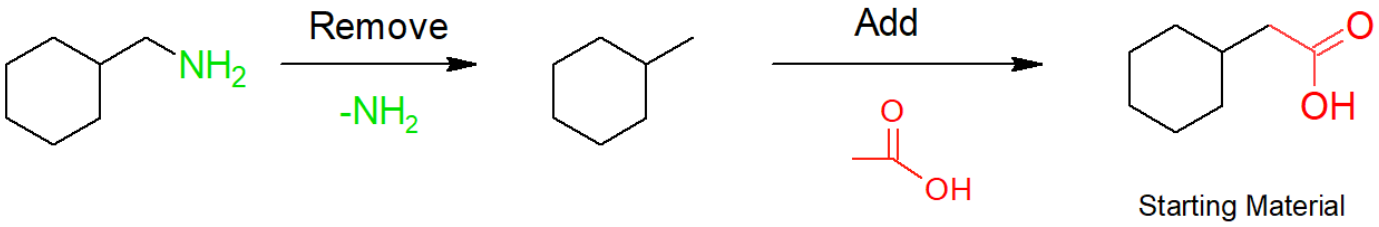
Solution 2



Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

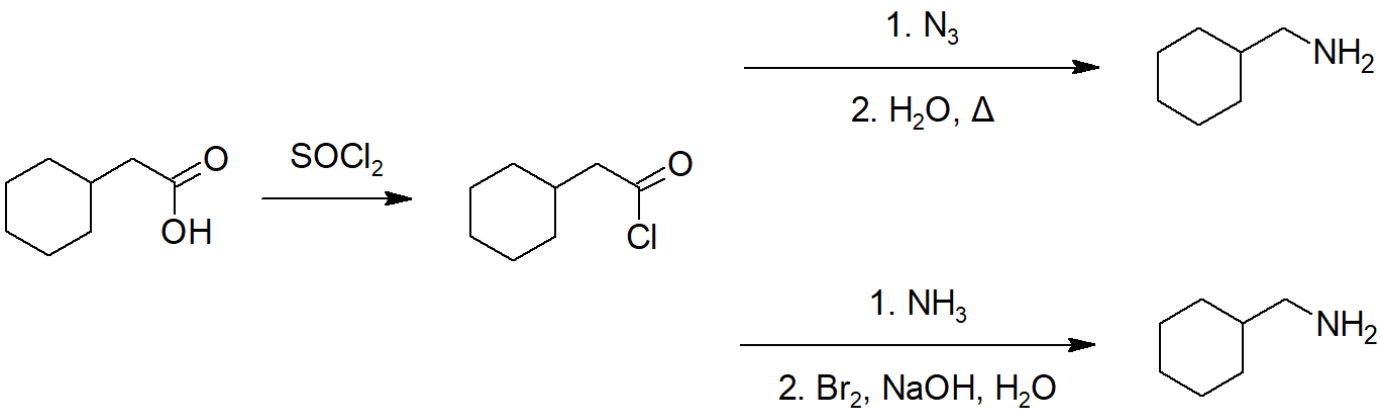
Worked Example 24.6.2

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



Solution

The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.

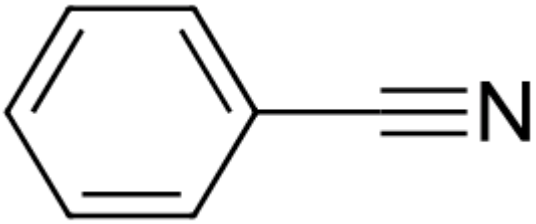


Exercise 24.6.1

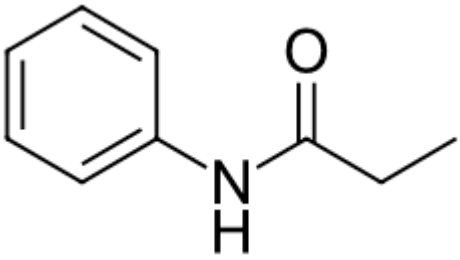
a) $CH_3CH_2CH_2CONH_2$

b) $CH_3CONHCH_2CH_3$

c)

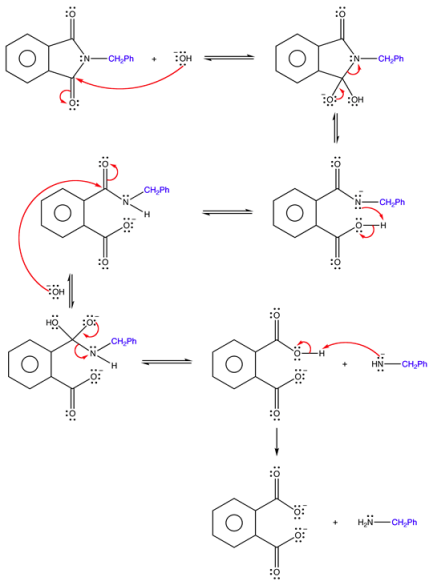


e)

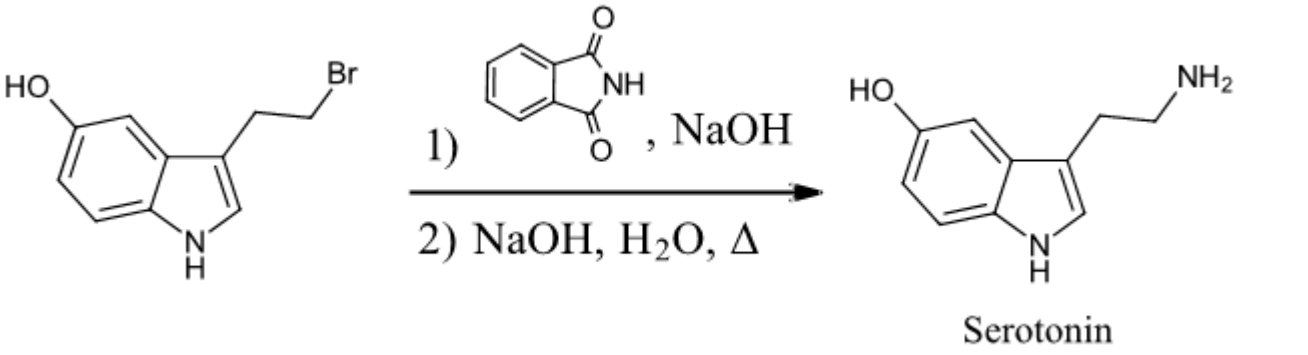


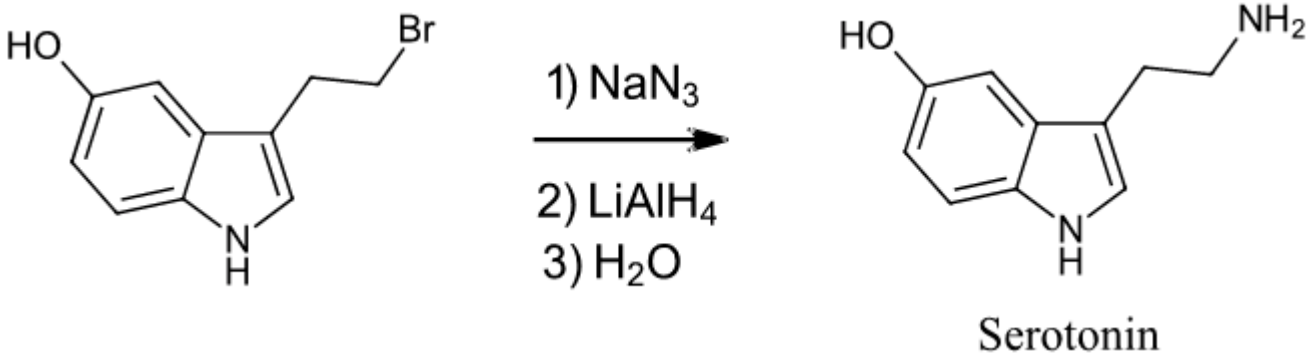
Exercise 24.6.2

1)



2)

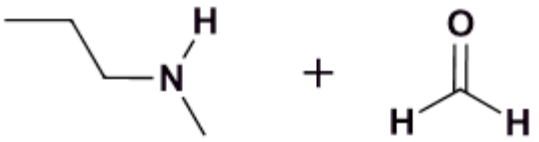




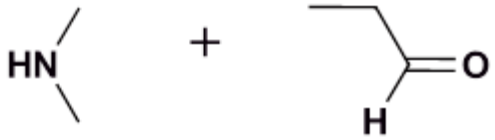
Exercise 24.6.3

1)

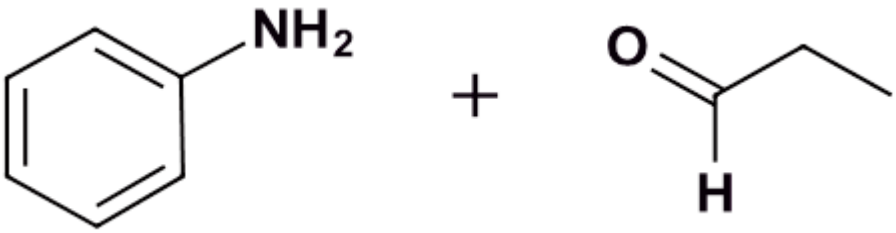
a)



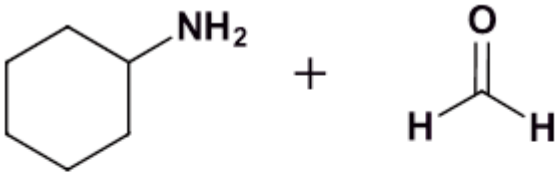
And



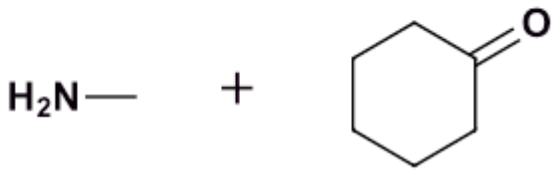
b)



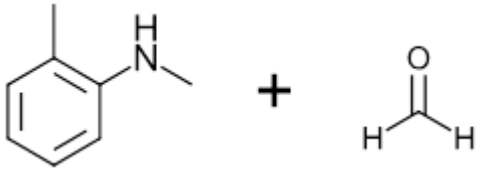
c)



And



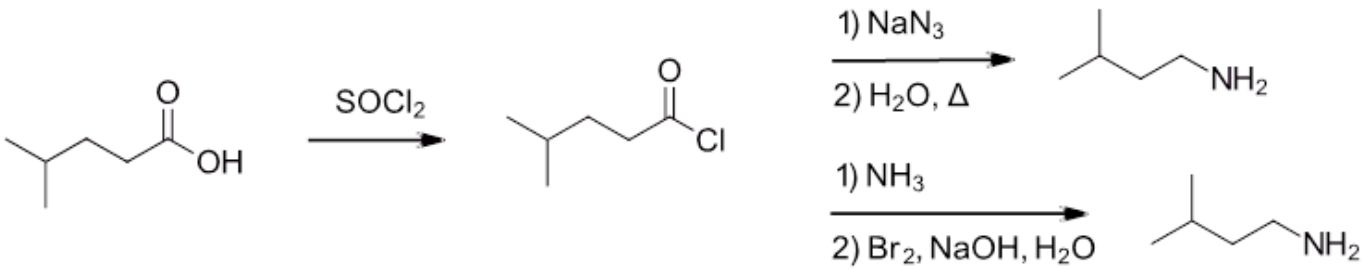
2)



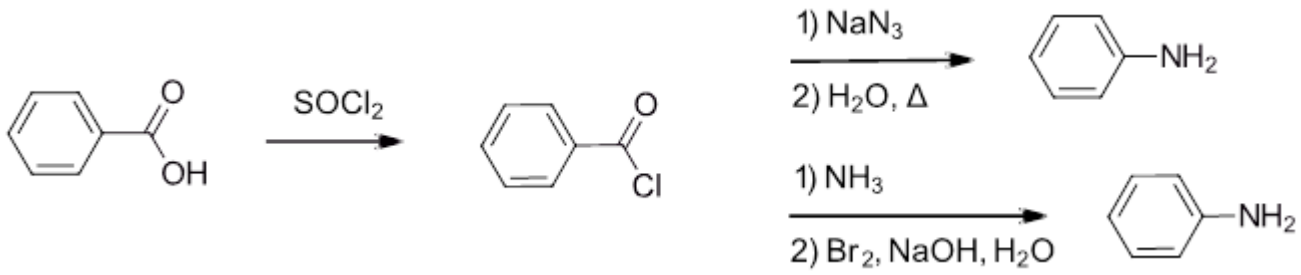
Exercises 24.6.4

1)

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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21.8: Quaternary Ammonium Salts: Hofmann Elimination

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. In the case of alcohols and ethers, a useful technique for enhancing the reactivity of the oxygen function was to modify the leaving group ($OH^{(-)}$ or $OR^{(-)}$) to improve its stability as an anion (or equivalent). This stability is conveniently estimated from the strength of the corresponding conjugate acids.

As noted earlier, 1° and 2°-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a nucleophilic leaving group. For example, heating an amine with HBr or HI does not normally convert it to the corresponding alkyl halide, as in the case of alcohols and ethers. In this context we note that the acidity of the putative ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. The loss of nitrogen from diazonium intermediates is a notable exception in this comparison, due to the extreme stability of this leaving group (the conjugate acid of N_2 would be an extraordinarily strong acid).

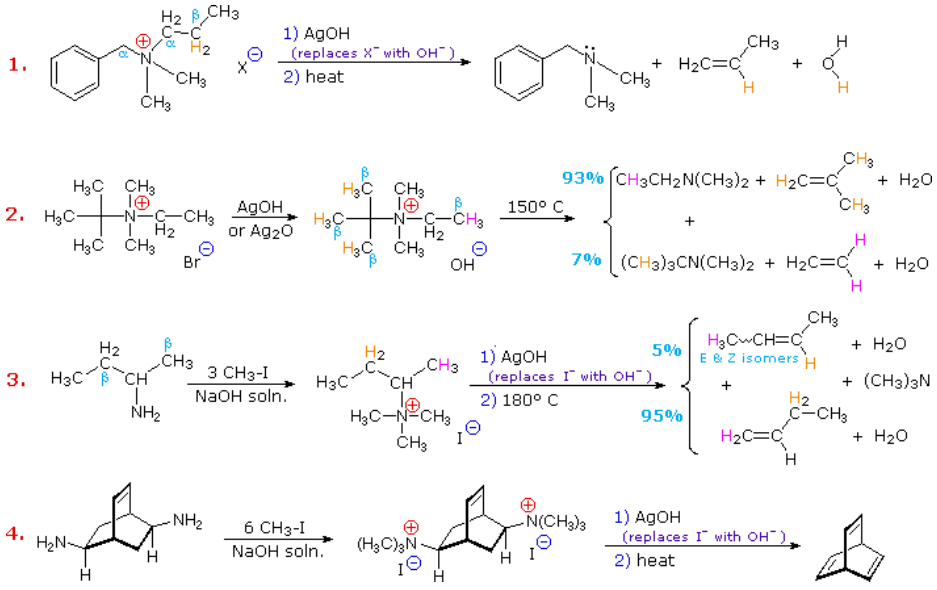
One group of amine derivatives that have proven useful in S_N2 and E2 reactions is that composed of the tetraalkyl (4°-) ammonium salts. Most applications involving this class of compounds are eliminations, but a few examples of S_N2 substitution have been reported.

C_6H_5–$N(CH_3)_3^{(+)}$ $Br^{(-)}$ + R-$S^{(-)}$ $Na^{(+)}$	acetone & heat ⟶	R-S-CH_3 + C_6H_5–$N(CH_3)_2$ + NaBr

$(CH_3)_4N^{(+)}$ $OH^{(-)}$	heat ⟶	CH_3–OH + $(CH_3)_3N$

Hofmann Elimination

Elimination reactions of 4°-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4°-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 °C) to effect the E2-like elimination of a 3°-amine. Example #1 below shows a typical Hofmann elimination. Obviously, for an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, as noted earlier in examining elimination reactions of alkyl halides.



In example #2 above, two of the alkyl substituents on nitrogen have beta-hydrogens, all of which are on methyl groups (colored

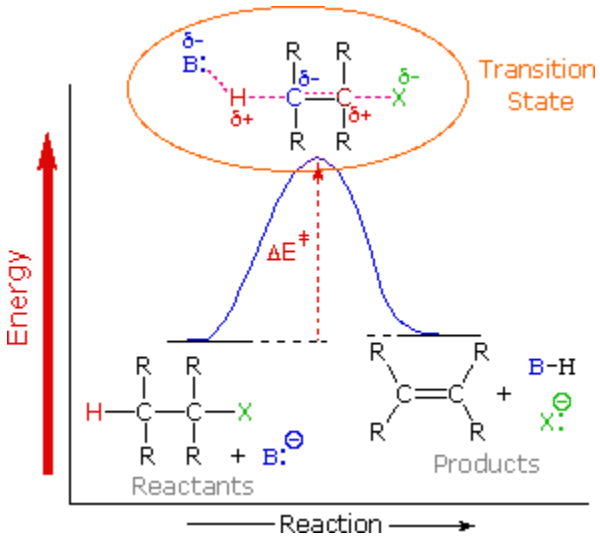
orange & magenta). The chief product from the elimination is the alkene having the more highly substituted double bond, reflecting not only the 3:1 numerical advantage of those beta-hydrogens, but also the greater stability of the double bond.

Example #3 illustrates two important features of the Hofmann elimination:

1. Simple amines are easily converted to the necessary 4°-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction). Exhaustive methylation is shown again in example #4.
2. When a given alkyl group has two different sets of beta-hydrogens available to the elimination process (colored orange & magenta here), the major product is often the alkene isomer having the less substituted double bond.

The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**, and contrasts strikingly with the Zaitsev Rule formulated for dehydrohalogenations and dehydrations. In cases where other activating groups, such as phenyl or carbonyl, are present, the Hofmann Rule may not apply. Thus, if 2-amino-1-phenylpropane is treated in the manner of example #3, the product consists largely of 1-phenylpropene (E & Z-isomers).

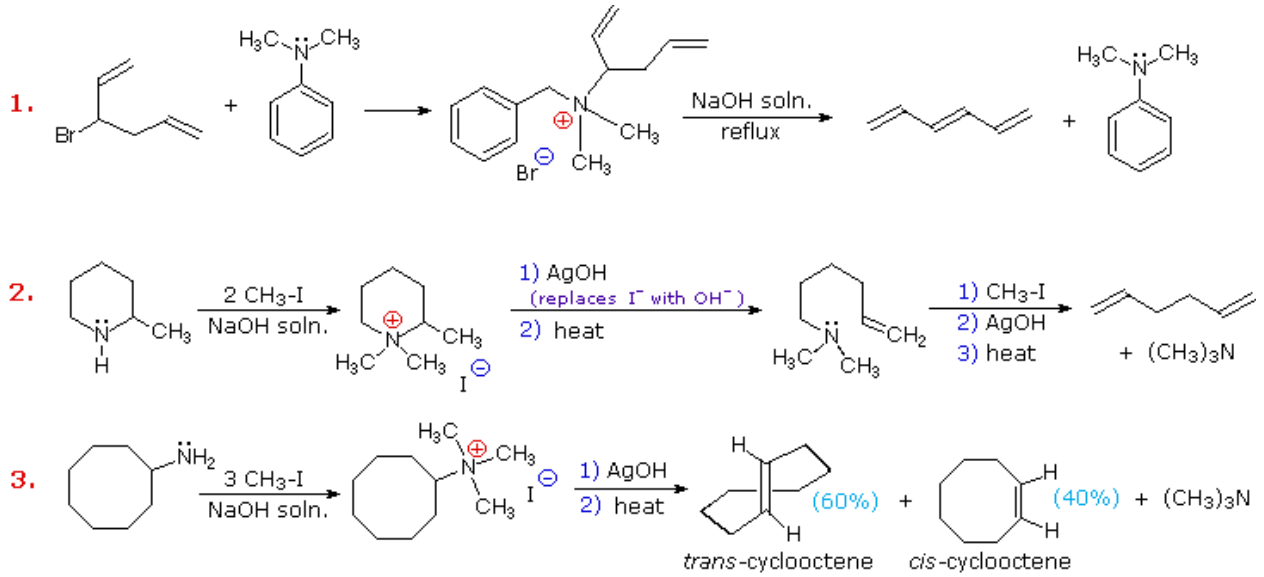
To understand why the base-induced elimination of 4°-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state, first described for dehydrohalogenation. The energy diagram shown earlier for a single-step bimolecular E2 mechanism is repeated below.



The E2 transition state is less well defined than is that of S_N2 reactions. More bonds are being broken and formed, with the possibility of a continuum of states in which the extent of C–H and C–X bond-breaking and C=C bond-making varies. For example, if the bond to the leaving group (X) is substantially broken relative to the other bond changes, the transition state approaches that for an E1 reaction (initial ionization followed by a fast second step). At the other extreme, if the acidity of the beta-hydrogens is enhanced, then substantial breaking of C–H may occur before the other bonds begin to be affected. For most simple alkyl halides it was proper to envision a balanced transition state, in which there was a synchronous change in all the bonds. Such a model was consistent with the **Zaitsev Rule**.

When the leaving group X carries a positive charge, as do the 4°-ammonium compounds discussed here, the inductive influence of this charge will increase the acidity of both the alpha and the beta-hydrogens. Furthermore, the 4°-ammonium substituent is much larger than a halide or hydroxyl group and may perturb the conformations available to substituted beta-carbons. It seems that a combination of these factors acts to favor base attack at the least substituted (least hindered and most acidic) set of beta-hydrogens. The favored anti orientation of the leaving group and beta-hydrogen, noted for dehydrohalogenation, is found for many Hofmann eliminations; but syn-elimination is also common, possibly because the attraction of opposite charges orients the hydroxide base near the 4°-ammonium leaving group.

Three additional examples of the Hofmann elimination are shown in the following diagram. Example #1 is interesting in two respects. First, it generates a 4°-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.



Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3°-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to sever the nitrogen from the remaining molecular framework.

Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

Contributors

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21.9: Mannich Reaction: Alkylation of Enols by Iminium Ions

The acid-catalyzed reaction of an enolizable aldehyde or an enolizable ketone with an imminium ion, usually generated in situ by the reaction of formaldehyde with a secondary amine, followed by a base to give a β-aminoaldehyde of a β-aminoketone, respectively, is known as the Mannich reaction. The product of the Mannich reaction is called the Mannich base.

- Gamini Gunawardena from the OChemPal site (Utah Valley University)

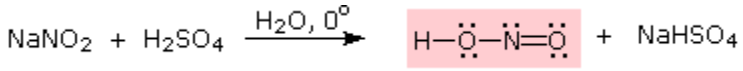
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21.10: Nitrosation of Amines

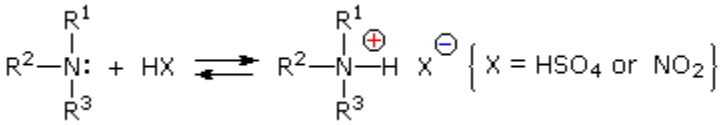
Nitrous acid (HNO_2 or $HONO$) reacts with aliphatic amines in a fashion that provides a useful test for distinguishing primary, secondary and tertiary amines.

- 1°-Amines + HONO (cold acidic solution) → Nitrogen Gas Evolution from a Clear Solution
- 2°-Amines + HONO (cold acidic solution) → An Insoluble Oil (N-Nitrosamine)
- 3°-Amines + HONO (cold acidic solution) → A Clear Solution (Ammonium Salt Formation)

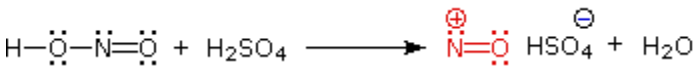
Nitrous acid is a Brønsted acid of moderate strength (pK_a = 3.3). Because it is unstable, it is prepared immediately before use in the following manner:



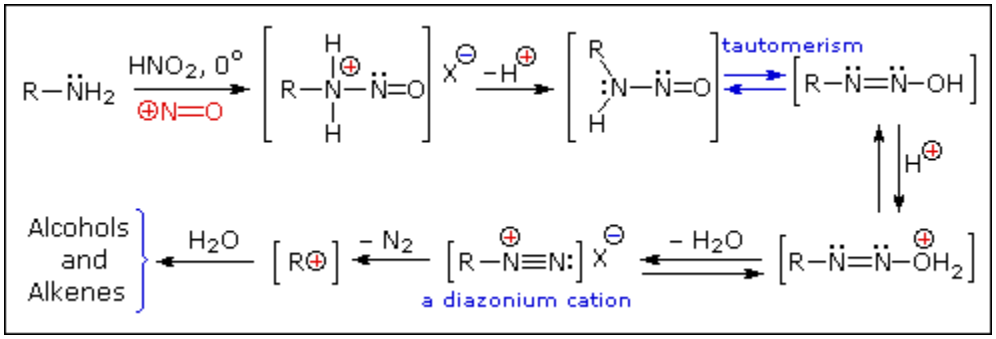
Under the acidic conditions of this reaction, all amines undergo reversible salt formation:



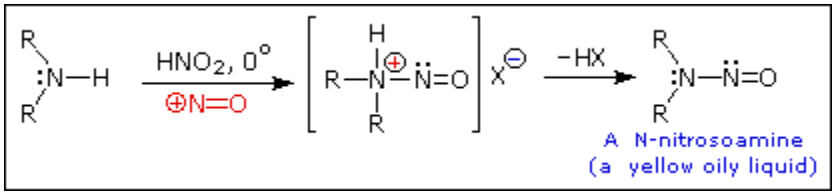
This happens with 3°-amines, and the salts are usually soluble in water. The reactions of nitrous acid with 1°- and 2°- aliphatic amines may be explained by considering their behavior with the nitrosonium cation, $NO^{(+)}$, an electrophilic species present in acidic nitrous acid solutions.



Primary Amines



Secondary Amines

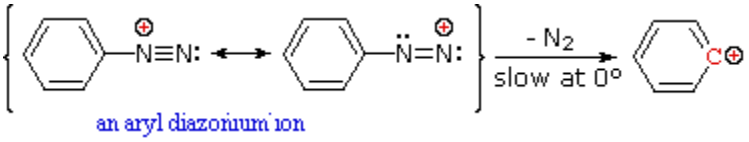


The distinct behavior of 1°, 2° & 3°-aliphatic amines is an instructive challenge to our understanding of their chemistry, but is

of little importance as a synthetic tool. The S_N1 product mixtures from 1°-amines are difficult to control, and rearrangement is common when branched primary alkyl groups are involved. The N-nitrosamines formed from 2°-amines are carcinogenic, and are not generally useful as intermediates for subsequent reactions.

Aryl Amines

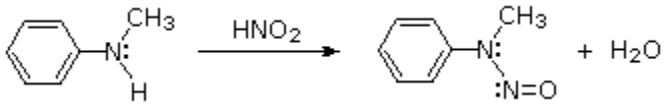
Nitrous acid reactions of 1°-aryl amines generate relatively stable diazonium species that serve as intermediates for a variety of aromatic substitution reactions. Diazonium cations may be described by resonance contributors, as in the bracketed formulas shown below. The left-hand contributor is dominant because it has greater bonding. Loss of nitrogen is slower than in aliphatic 1°-amines because the C-N bond is stronger, and aryl carbocations are comparatively unstable.



Aqueous solutions of these diazonium ions have sufficient stability at 0° to 10 °C that they may be used as intermediates in a variety of nucleophilic substitution reactions. For example, if water is the only nucleophile available for reaction, phenols are formed in good yield.

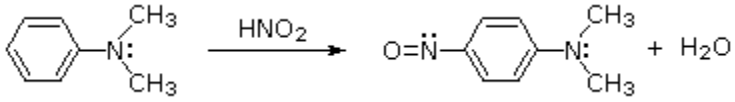
2°-Aryl Amines:

2°-Aryl amines give N-nitrosamine derivatives on reaction with nitrous acid, and thus behave identically to their aliphatic counterparts.



3°-Aryl Amines:

Depending on ring substitution, 3°-Aryl amines may undergo aromatic ring nitrosation at sites ortho or para to the amine substituent. The nitrosonium cation is not sufficiently electrophilic to react with benzene itself, or even toluene, but highly activated aromatic rings such as amines and phenols are capable of substitution. Of course, the rate of reaction of $NO^{(+)}$ directly at nitrogen is greater than that of ring substitution, as shown in the previous example. Once nitrosated, the activating character of the amine nitrogen is greatly diminished; and N-nitrosoaniline derivatives, or indeed any amide derivatives, do not undergo ring nitrosation.



Contributors

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22: CHEMISTRY OF THE BENZENE SUBSTITUENTS: ALKYLBENZENES, PHENOLS, AND BENZENAMINES

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

22.1: Reactivity at the Phenylmethyl (Benzyl) Carbon: Benzylic Resonance Stabilization
22.2: Benzylic Oxidations and Reductions
22.3: Names and Properties of Phenols
22.4: Preparation of Phenols: Nucleophilic Aromatic Substitution
22.5: Alcohol Chemistry of Phenols
22.6: Electrophilic Substitution of Phenols
22.7: An Electrocyclic Reaction of the Benzene Ring: The Claisen Rearrangement
22.8: Oxidation of Phenols: Benzoquinones
22.9: Oxidation-Reduction Processes in Nature
22.10: Arenediazonium Salts
22.11: Electrophilic Substitution with Arenediazonium Salts: Diazo Coupling

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22.1: Reactivity at the Phenylmethyl (Benzyl) Carbon: Benzylic Resonance Stabilization

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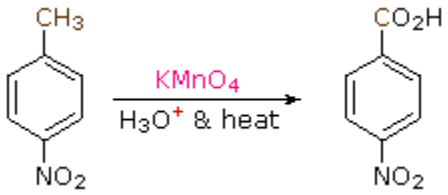
22.2: Benzylic Oxidations and Reductions

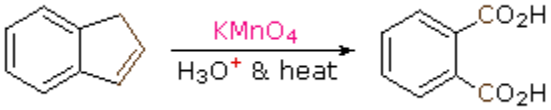
Oxidation of Alkyl Side-Chains

The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore, , and E1 reactions ofbenzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general benzylic activation is supported by the susceptibility of alkyl side-chains to oxidative degradation, as shown in the following examples (the oxidized side chain is colored). Such oxidations are normally effected by hot acidic pemanganate solutions, but for large scale industrial operations catalyzed air-oxidations are preferred. Interestingly, if the benzylic position is completely substituted this oxidative degradation does not occur (second equation, the substituted benzylic carbon is colored blue).

$C_6H_5–CH_2CH_2CH_2CH_3$ + $KMnO_4$ + $H_3O^{(+)}$ & heat	⟶	$C_6H_5–CO_2H$ + CO_2
p-$(CH_3)_3C–C_6H_4–CH_3$ + $KMnO_4$ + $H_3O^{(+)}$ & heat	⟶	p-$(CH_3)_3C–C_6H_4–CO_2H$

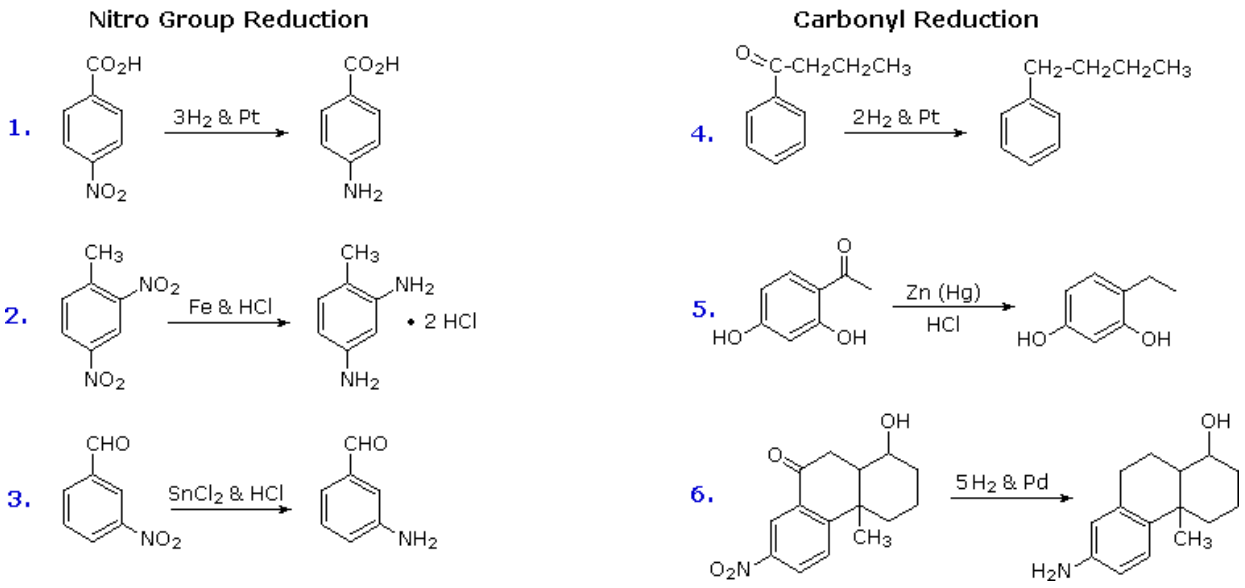
These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.





Reduction of Nitro Groups and Aryl Ketones

Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H2 + catalyst), or with reducing metals in acid. Examples of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).



Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

Contributors

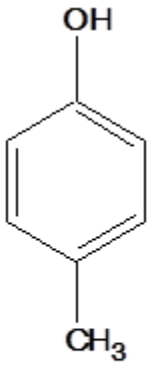
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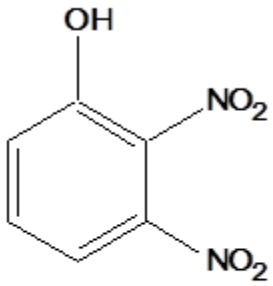
22.3: Names and Properties of Phenols

Naming phenols

Phenols are named using the rules for aromatic compounds discussed in seciton 15.1 Note! that *-phenol* is used rather than *-benzene*.



p-Metylphenol

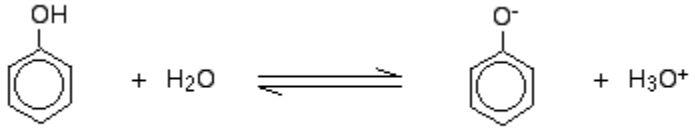


2,3-Dinitrophenol

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base.

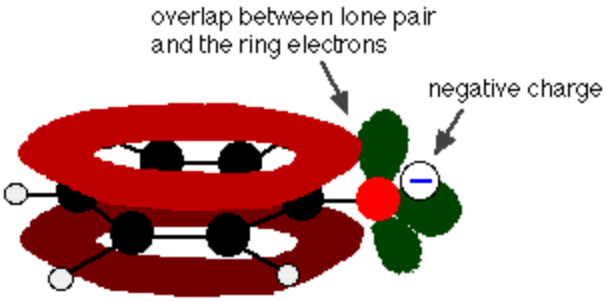
Why is phenol acidic?

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in solution in water:

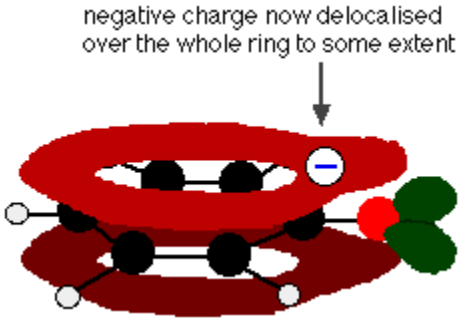


a **phenoxide** ion

Phenol is a very weak acid and the position of equilibrium lies well to the left. Phenol can lose a hydrogen ion because the phenoxide ion formed is stabilised to some extent. The negative charge on the oxygen atom is delocalised around the ring. The more stable the ion is, the more likely it is to form. One of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion.



Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

Properties of phenol as an acid

With indicators

The pH of a typical dilute solution of phenol in water is likely to be around 5 - 6 (depending on its concentration). That means that a very dilute solution isn't really acidic enough to turn litmus paper fully red. Litmus paper is blue at pH 8 and red at pH 5. Anything in between is going to show as some shade of "neutral". Phenol reacts with sodium hydroxide solution to give a colourless solution containing sodium phenoxide.



In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

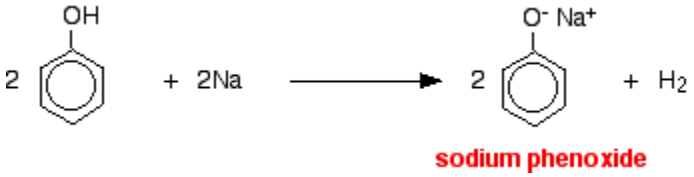
With sodium carbonate or sodium hydrogencarbonate

Phenol isn't acidic enough to react with either of these. Or, looked at another way, the carbonate and hydrogencarbonate ions aren't strong enough bases to take a hydrogen ion from the phenol. Unlike the majority of acids, phenol does not give carbon dioxide when you mix it with one of these. This lack of reaction is actually useful. You can recognise phenol because:

- It is fairly insoluble in water.
- It reacts with sodium hydroxide solution to give a colourless solution (and therefore must be acidic).
- It does not react with sodium carbonate or hydrogencarbonate solutions (and so must be only very weakly acidic).

With metallic sodium

Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off. The mixture left in the tube will contain sodium phenoxide.

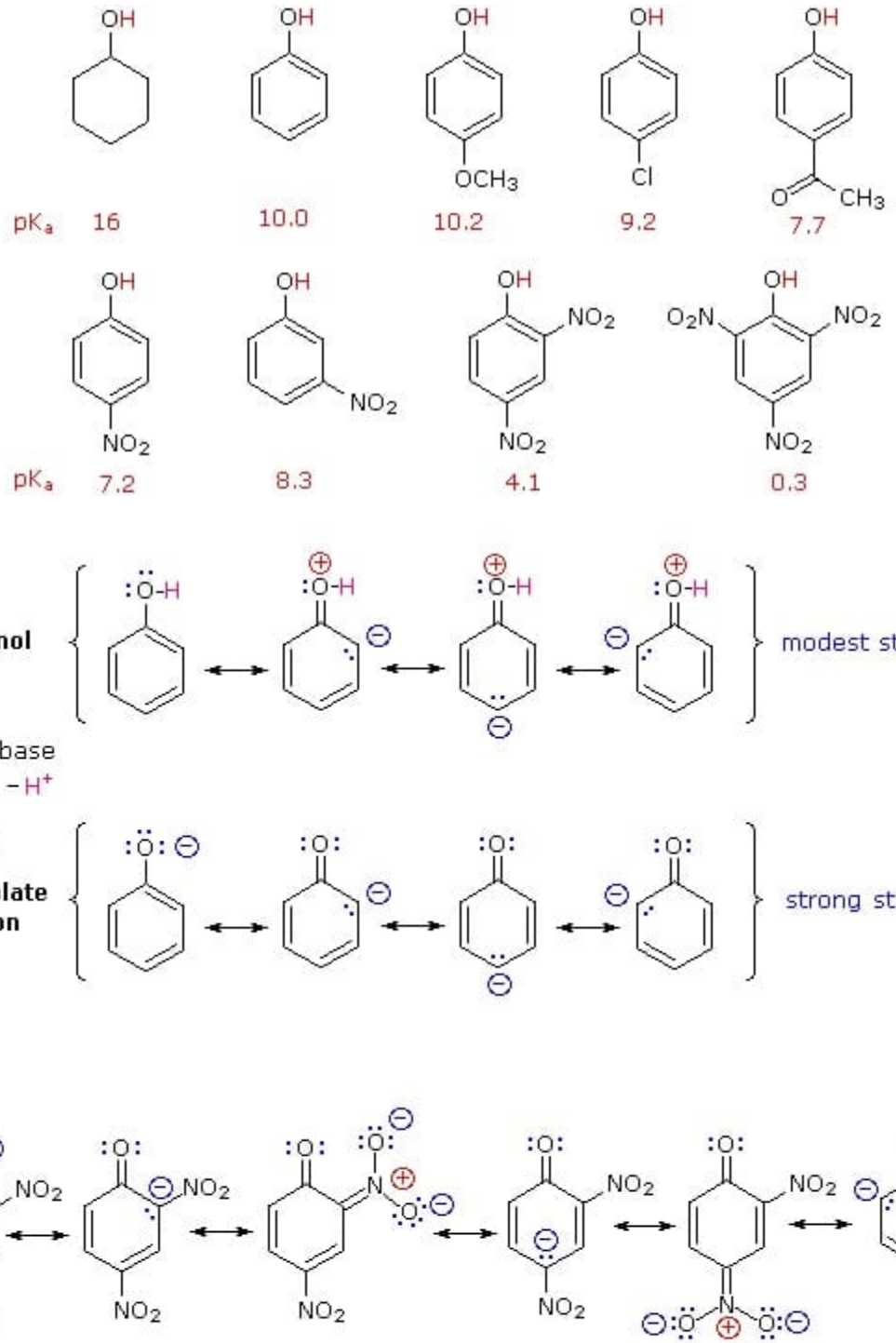


Contributors

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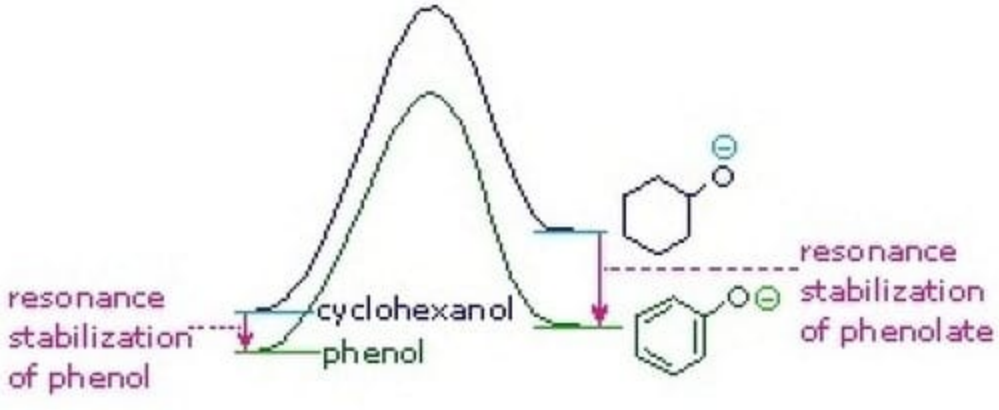
Jim Clark (Chemguide.co.uk)

Substitution of the hydroxyl hydrogen atom is even more facile with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. The alcohol cyclohexanol is shown for reference at the top left. It is noteworthy that the influence of a nitro substituent is over ten times stronger in the para-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. Furthermore additional nitro groups have an additive influence if they are positioned in ortho or para locations. The trinitro compound shown at the lower right is a very strong acid called picric acid.



Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.



The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

Contributors

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22.4: Preparation of Phenols: Nucleophilic Aromatic Substitution

Objectives

After completing this section, you should be able to

1. identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
2. write the detailed mechanism for a nucleophilic aromatic substitution reaction.
3. compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
4. identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Meisenheimer complex
- nucleophilic aromatic substitution

Study Notes

A *nucleophilic aromatic substitution reaction* is a reaction in which one of the substituents in an aromatic ring is replaced by a nucleophile.

A *Meisenheimer complex* is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.

reaction scheme showing Meisenheimer complex

Figure 16.2: The formation of a typical Meisenheimer complex

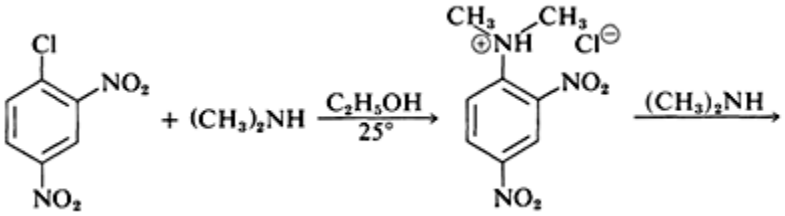
A Nucleophilic Aromatic Displacement Reactions of Aryl Halides

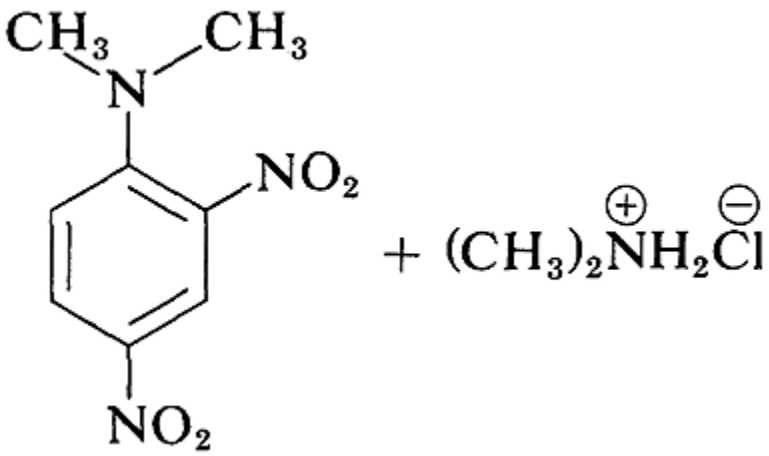
The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides (see Table 4-6). The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions (Table 14-6). However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid

a. when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and
b. when very strongly basic nucleophilic reagents are used.

Addition-Elimination Mechanism of Nucleophilic Substitution of Aryl Halides

Although the simple aryl halides are inert to the usual nucleophilic reagents, considerable activation is produced by strongly electron-attracting substituents provided these are located in either the ortho or para positions, or both. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by dimethylamine occurs readily in ethanol solution at room temperature. Under the same conditions chlorobenzene completely fails to react; thus the activating influence of the two nitro groups amounts to a factor of at least 10⁸:



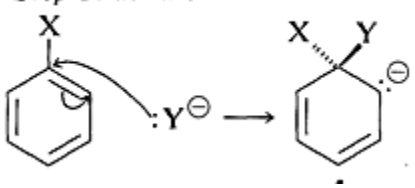


A related reaction is that of 2,4-dinitrofluorobenzene with the amino groups of peptides and proteins, and this reaction provides a means for analysis of the N-terminal amino acids in polypeptide chains. (See Section 25-7B.)

In general, the reactions of activated aryl halides closely resemble the SN2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., CH3O⊖, HO⊖, and RNH2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the more nucleophilic the attacking reagent, the faster the reaction. However, there must be more than a subtle difference in mechanism because an aryl halide is unable, to pass through the same type of transition state as an alkyl halide in SN2 displacements.

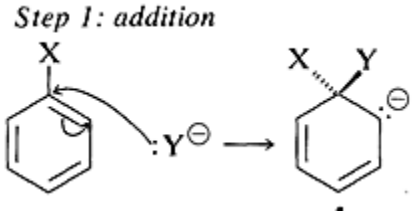
The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps that are closely analogous to those briefly described in Section 14-4 for alkenyl and alkynyl halides. The first step involves attack of the nucleophile Y:⊖ at the carbon bearing the halogen substituent to form an intermediate carbanion 4 (Equation 14-3). The aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp2 bonds) to tetrahedral (sp3 bonds).

Step 1: addition



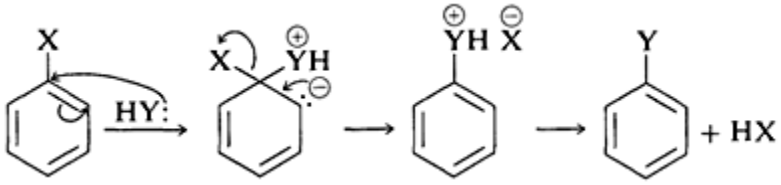
(only one of three valence-bond structures is shown) (14-3)

In the second step, loss of an anion, X⊖ or Y⊖, regenerates an aromatic system, and, if X⊖ is lost, the overall reaction is nucleophilic displacement of X by Y (Equation 14-4).

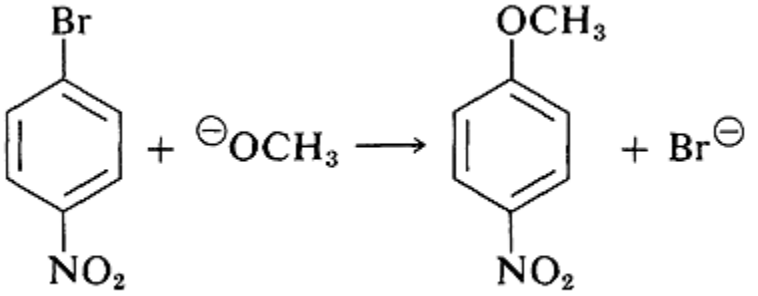


(only one of three valence-bond structures is shown) (14-3)

In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:

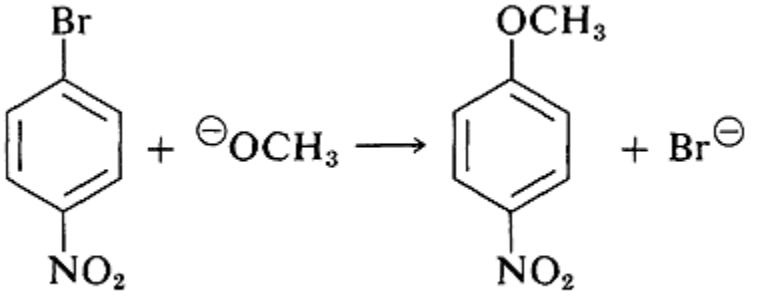


Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the intermediate 4, which we can express as a hybrid of the valence-bond structures 4a-4c, is too high in energy to be formed at any practical rate. Not only has 4 lost the aromatic stabilization of the benzene ring, but its formation results in transfer of negative charge to the ring carbons, which themselves are not very electronegative:



4-nitromethoxybenzene

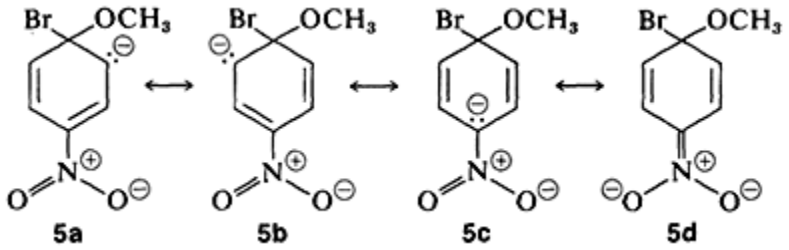
However, when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. As an example, consider the displacement of bromine by OCH3 in the reaction of 4-bromonitrobenzene and methoxide ion:

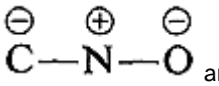
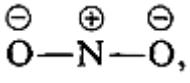


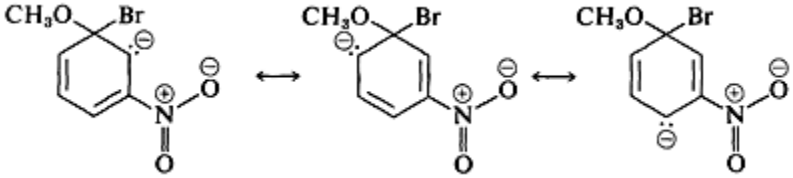
4-nitromethoxybenzene

The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures

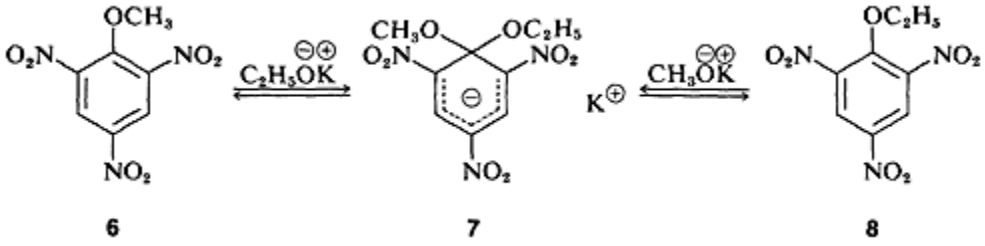
5a-5d. Of these structures 5d is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent:



Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and  ,



In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 6 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:

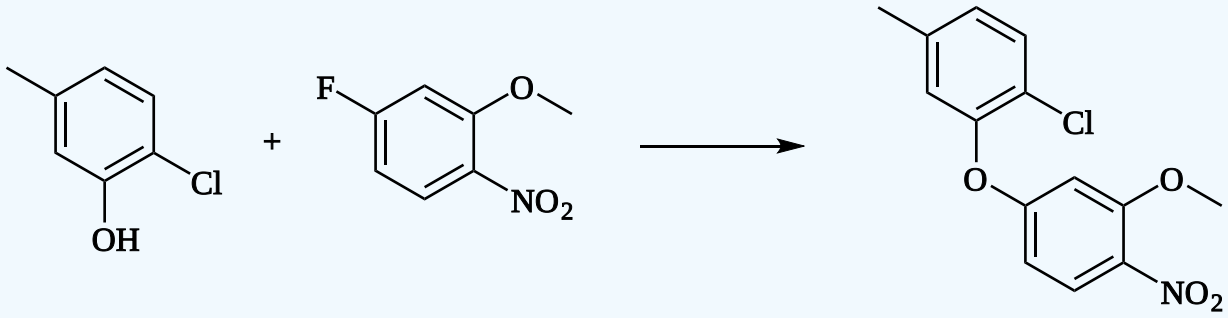


6 7 8

Exercise

Exercise 22.4.1

Propose a mechanism for the following reaction:



Answer available at the end of this section.

Questions

Q16.7.1

Propose a mechanism for the following reaction:

16-7-1qu.png

Solutions

S16.7.1

16.7.png

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition*. W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

Objectives

After completing this section, you should be able to

1. identify the reagents and conditions required to produce phenol from chlorobenzene on an industrial scale.
2. write the mechanism for the conversion of an alkyl halide to a phenol through a benzyne intermediate.
3. discuss the experimental evidence which supports the existence of benzyne intermediates.
4. discuss the bonding in benzyne, and hence account for its high reactivity.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- benzyne
- elimination-addition mechanism

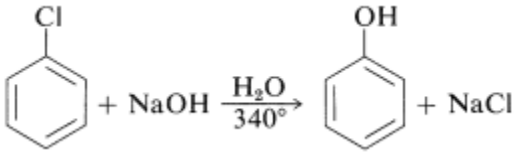
Study Notes

An elimination-addition mechanism involves the elimination of the elements of a small molecule from a substrate to produce a highly reactive intermediate, which then undergoes an addition reaction.

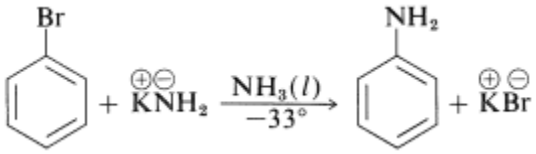
The elimination-addition mechanism of nucleophilic aromatic substitution involves the remarkable intermediate called benzyne or arynes.

14-6C Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution. Arynes

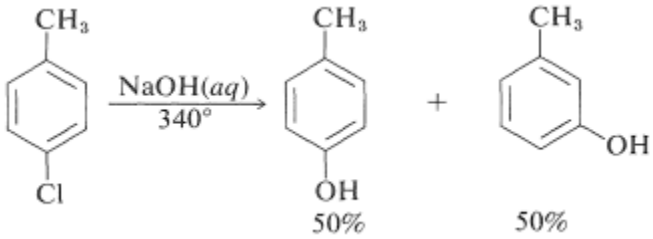
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect displacements with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, chlorobenzene reacts with sodium hydroxide solution at temperatures around 340° and this reaction was once an important commercial process for the production of benzenol (phenol):



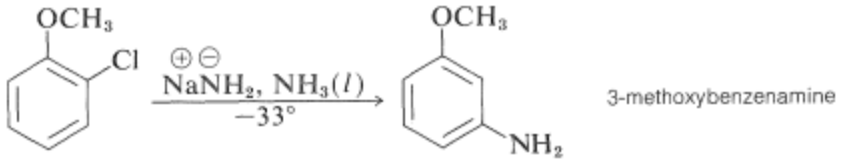
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines $\mathrm{ArNH_2}$ by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as -33° with liquid ammonia as solvent:



However, displacement reactions of this type differ from the previously discussed displacements of activated aryl halides in that rearrangement often occurs. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at 340° gives an equimolar mixture of 3- and 4-methylbenzenols:

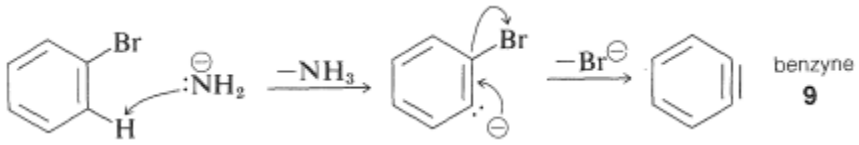


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change (Section 1-1H):



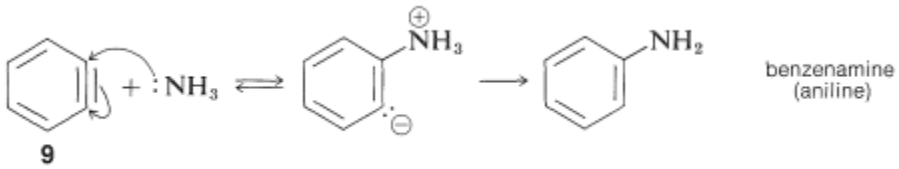
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (HX) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

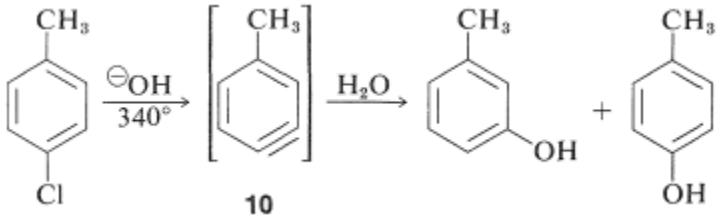


The product of the elimination reaction is a highly reactive intermediate 9 called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

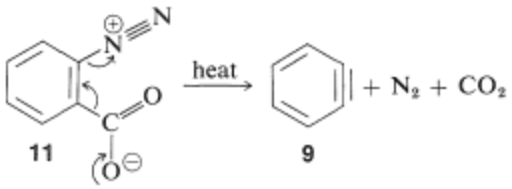
Addition



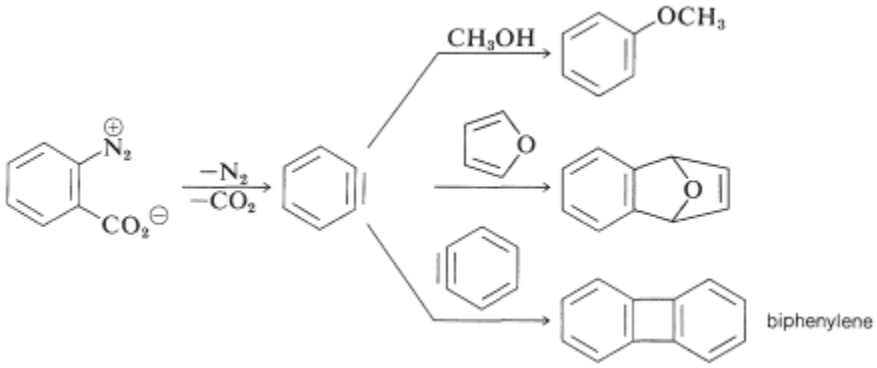
The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, 10, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



In the foregoing benzyne reactions the base that produces the benzyne in the elimination step is derived from the nucleophile that adds in the addition step. This need not always be so, depending on the reaction conditions. In fact, the synthetic utility of aryne reactions depends in large part of the success with which the aryne can be generated by one reagent but captured by another. One such method will be discussed in Section 14-10C and involves organometallic compounds derived from aryl halides. Another method is to generate the aryne by thermal decomposition of a 1,2-disubstituted arene compound such as 11, in which both substituents are leaving groups - one leaving with an electron pair, the other leaving without:



When 11 decomposes in the presence of an added nucleophile, the benzyne intermediate is trapped by the nucleophile as it is formed. Or, if a conjugated diene is present, benzyne will react with it by a [4 + 2] cycloaddition. In the absence of other compounds with which it can react, benzyne will undergo [2 + 2] cycloaddition to itself:



Exercise

Exercise 22.4.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer available at the end of this section.

Questions

Q16.8.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Solutions

S16.8.1

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.

16.8.png

Contributors and Attributions

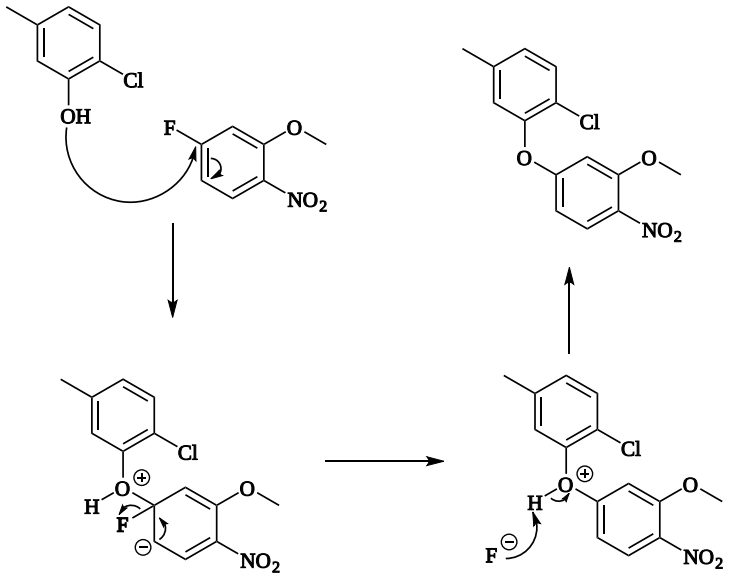
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

- Prof. Steven Farmer (Sonoma State University)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition*. W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

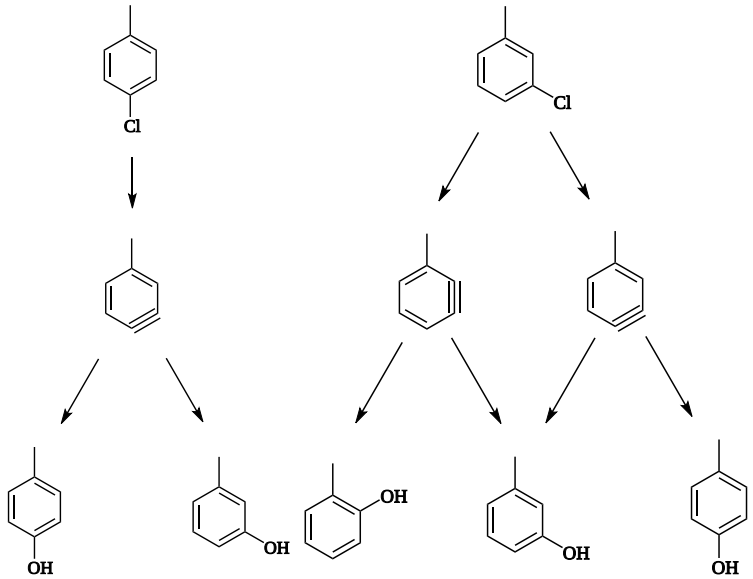
Answers

Exercise 22.4.1



Exercise 22.4.1

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



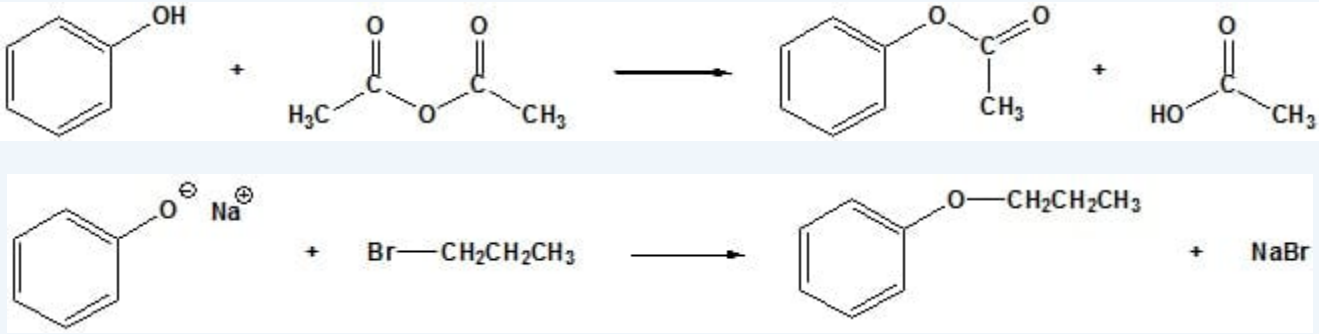
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- 16.8: Benzyne by Dietmar Kennepohl, James Kabrhel, John Roberts, Marjorie C. Caserio, Steven Farmer is licensed CC BY-SA 4.0.

22.5: Alcohol Chemistry of Phenols

As with the alcohols, the phenolic hydroxyl hydrogen is rather easily replaced by other substituents. For example, phenol reacts easily with acetic anhydride to give phenyl acetate. Likewise, the phenolate anion is an effective nucleophile in S_N2 reactions, as in the second example below.

Examples:



Contributors

Prof. Steven Farmer (Sonoma State University)

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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22.6: Electrophilic Substitution of Phenols

Over reaction of Aniline and Phenol

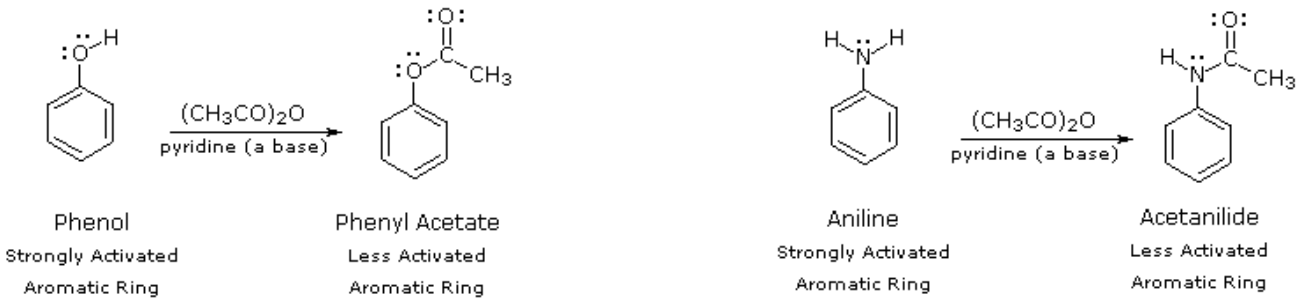
The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Bromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily. Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$C_6H_5–NH_2 + I_2 + NaHCO_3$		⟶	p-I–$C_6H_4–NH_2 + NaI + CO_2 + H_2O$

By acetylating the heteroatom substituent on phenol and aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$C_6H_5–NH_2 + (CH_3CO)_2O$	pyridine (a base) ⟶	$C_6H_5–NHCOCH_3$	HNO_3 , 5 °C ⟶	p-$O_2N–C_6H_4–NHCOCH_3$	$H_3O^{(+)}$ & heat ⟶	p-$O_2N–C_6H_4–NH$

The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.

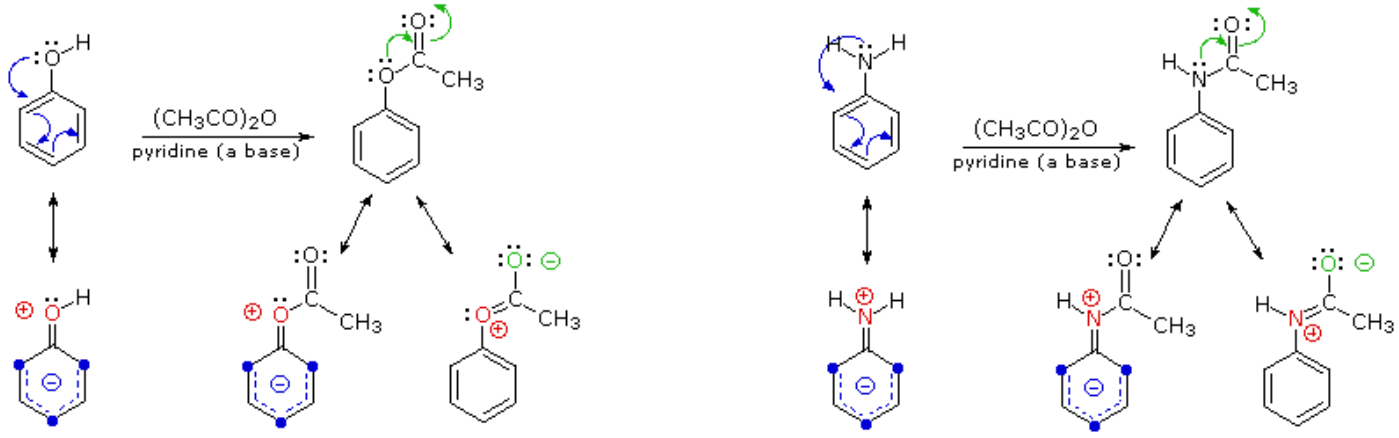


Phenol
Strongly Activated
Aromatic Ring

Phenyl Acetate
Less Activated
Aromatic Ring

Aniline
Strongly Activated
Aromatic Ring

Acetanilide
Less Activated
Aromatic Ring



Objectives

After completing this section, you should be able to:

1. explain why phenols and phenoxide ions are very reactive towards electrophilic aromatic substitution (see Section 16.4 of the textbook).
2. write an equation to illustrate the oxidation of a phenol or an arylamine to a quinone, and identify the reagents used to oxidize phenols.
3. write an equation to illustrate the reduction of a quinone to a hydroquinone, and identify the reagents used to reduce quinones.
4. describe, briefly, the biological importance of the redox properties of quinones.

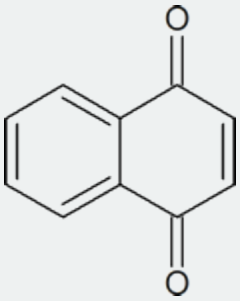
Key Terms

Make certain that you can define, and use in context, the key terms below.

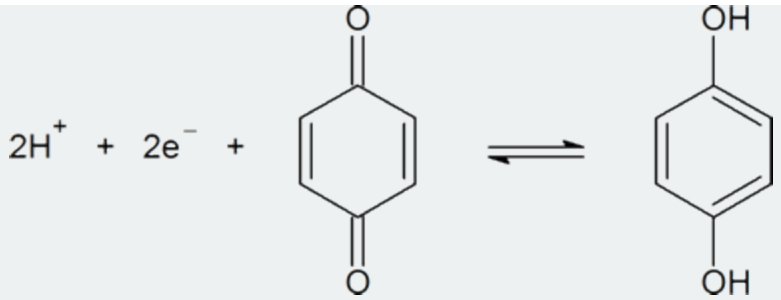
- hydroquinone
- quinone
- ubiquinone

Study Notes

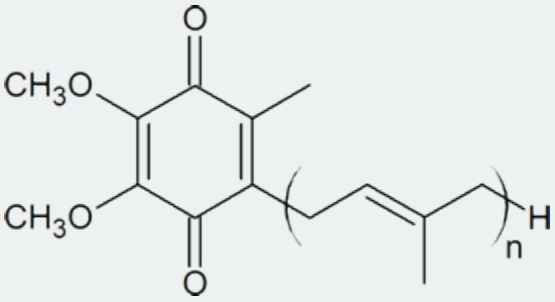
"Quinone" is a term used to describe cyclohexadiendiones in general, and *p*-benzoquinone in particular. In addition to benzene, other aromatic systems also give rise to quinones; for example, 1,4-naphthoquinone



"Hydroquinones" are produced by the reduction of quinones according to the following half-reaction:

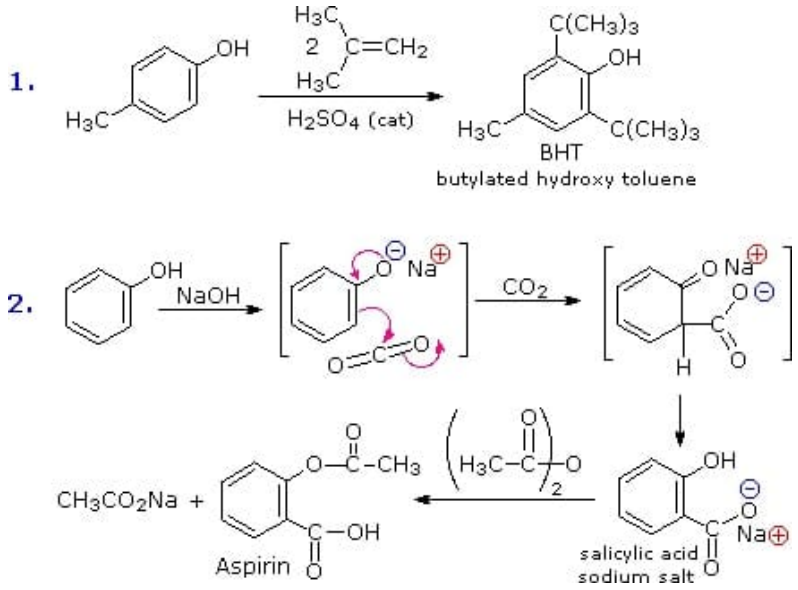


“Ubiquinones” are naturally occurring quinones whose role is to transfer a pair of electrons from one substance to another in enzyme-catalyzed reactions. Ubiquinones are also called coenzymes Q.



Electrophilic Aromatic Substitution Reactions

The facility with which the aromatic ring of phenols and phenol ethers undergoes electrophilic substitution has been noted. Two examples are shown in the following diagram. The first shows the Friedel-Crafts synthesis of the food preservative BHT from para-cresol. The second reaction is interesting in that it further demonstrates the delocalization of charge that occurs in the phenolate anion. Carbon dioxide is a weak electrophile and normally does not react with aromatic compounds; however, the negative charge concentration on the phenolate ring enables the carboxylation reaction shown in the second step. The sodium salt of salicylic acid is the major product, and the preference for ortho substitution may reflect the influence of the sodium cation. This is called the **Kolbe-Schmidt reaction**, and it has served in the preparation of aspirin, as the last step illustrates.

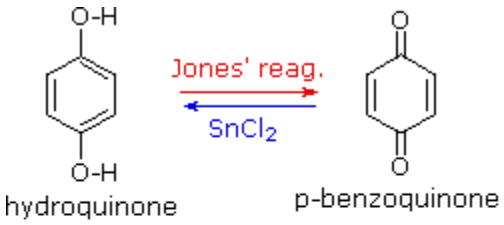


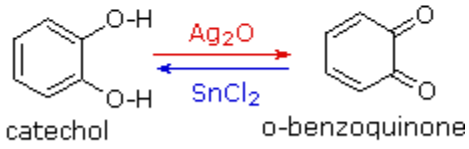
Oxidation of Phenols: Quinones

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone or simply quinone); an ortho isomer is also known. These compounds are easily reduced to their dihydroxybenzene analogs, and it is from these compounds that quinones are best prepared. Note that meta-quinones having similar structures do not exist. The redox equilibria between the dihydroxybenzenes hydroquinone and catechol and their quinone oxidation states are so facile that milder oxidants than chromate (Jones reagent) are generally preferred.

One such oxidant is **Fremy's salt**, shown on the right. Reducing agents other than stannous chloride (e.g. $NaBH_4$) may be used for the reverse reaction. The position of the quinone-hydroquinone redox equilibrium is proportional to the square of the hydrogen ion concentration, as shown by the following half-reactions (electrons are colored blue). The electrode potential for this interconversion may therefore be used to measure the pH of solutions.

Quinone + $2H^{(+)}$	$2e^{(-)}$ ⇌ $-2e^{(-)}$	Hydroquinone



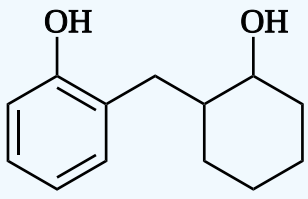


Fremy's Salt = $(KSO_3)_2NO$
a milder oxidant than chromate

Exercises

Exercise 17.10.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.

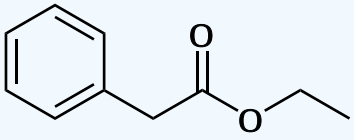


a. 1 equivalent of PBr_3
b. 1 equivalent of $SOCl_2$
c. Dess–Martin periodinane
d. 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst
e. Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Answer available at the end of this section.

Exercise 17.10.2

Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



a. 2 equivalents of RMgBr and H_3O^+ work-up
b. $LiAlH_4$ and H_3O^+ work-up
c. $NaBH_4$ and H_3O^+ work-up

Answer available at the end of this section.

Questions

Q17.10.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.

17.22q.png

(a) 1 equivalent of PBr_3 (b) 1 equivalent of $SOCl_2$ (c) Dess–Martin periodinane (d) 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst

(e) Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Q17.10.2

Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.

17.23q.png

(a) 2 equivalents of RMgBr and H_3O^+ work-up (b) $LiAlH_4$ and H_3O^+ work-up (c) $NaBH_4$ and H_3O^+ work-up

Solutions

S17.10.1

(a) 17.22a.png (b) 17.22b.png (c) 17.22c.png (d) 17.22d.png (e) 17.22e.png

S17.10.2

(a) 17.23a.png (b) 17.23b.png (c) No reaction. $NaBH_4$ is milder oxidant than $LiAlH_4$. It typically only reduces ketones and aldehydes.

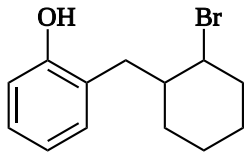
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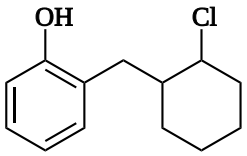
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

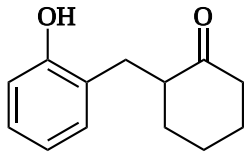
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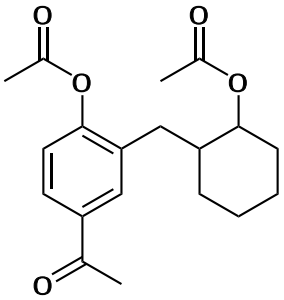
Answers

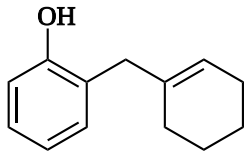
Exercise 17.10.1

a) 

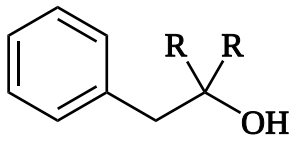
b) 

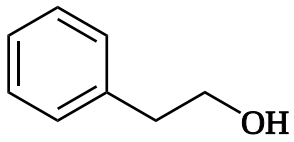
c) 

d) 

e) 

Exercise 17.10.2

a) 

b) 

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22.7: An Electrocyclic Reaction of the Benzene Ring: The Claisen Rearrangement

Objectives

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

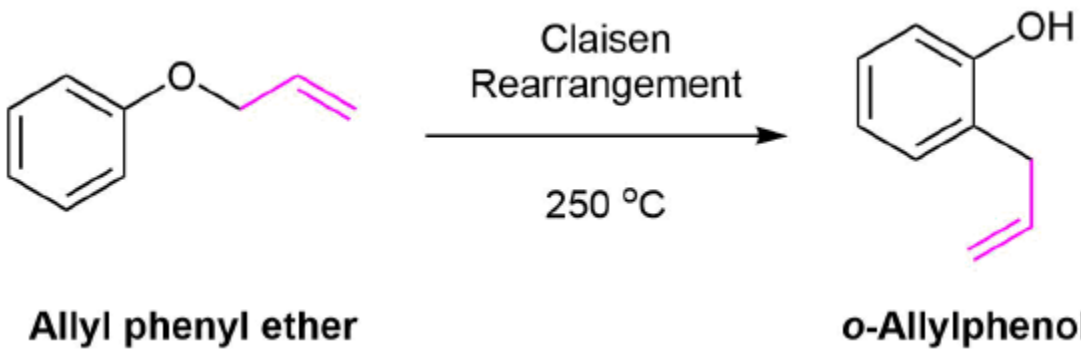
Key Terms

Make certain that you can define, and use in context, the key term below.

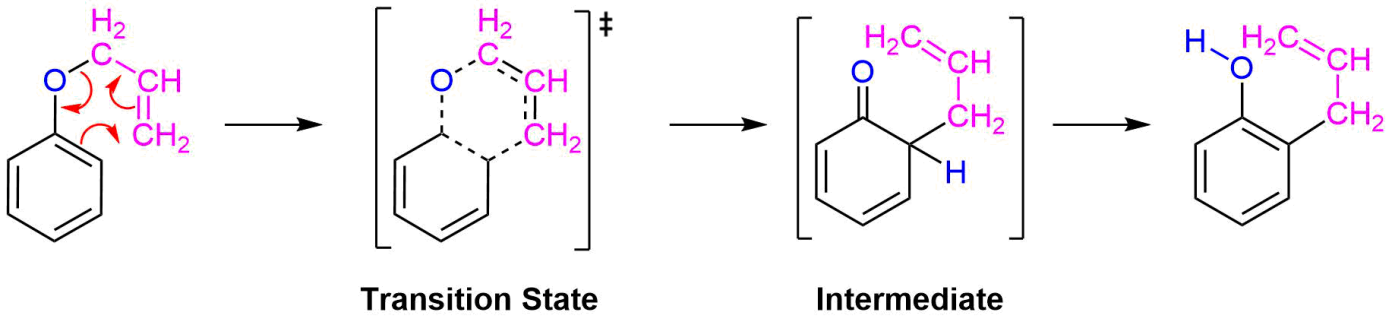
- Claisen rearrangement

Claisen Rearrangements

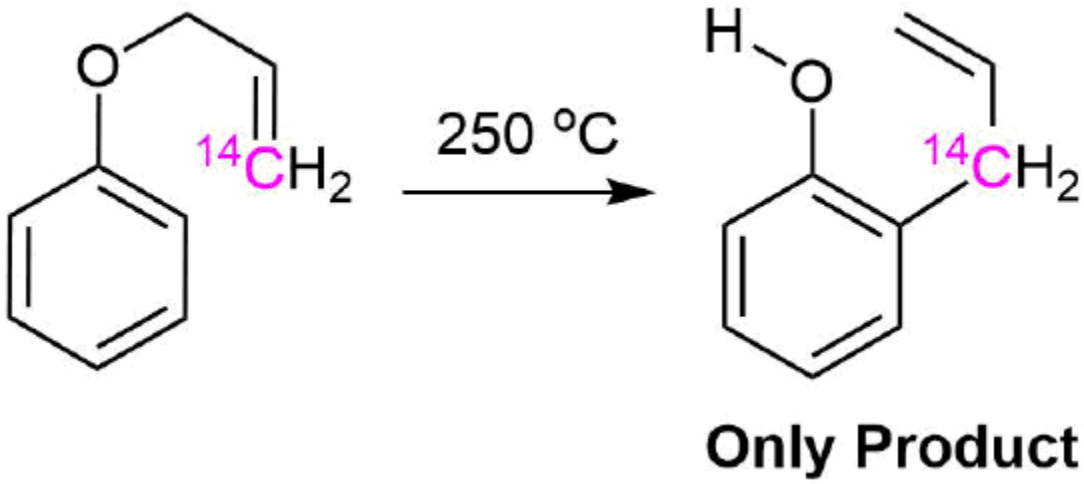
The Claisen rearrangement is a key organic reaction that involves the thermal rearrangement of allyl vinyl ethers to form β-aryl allyl ethers. This reaction is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 ^{o}C causes an intramolecular rearrangement to produce an *o*-allylphenol.



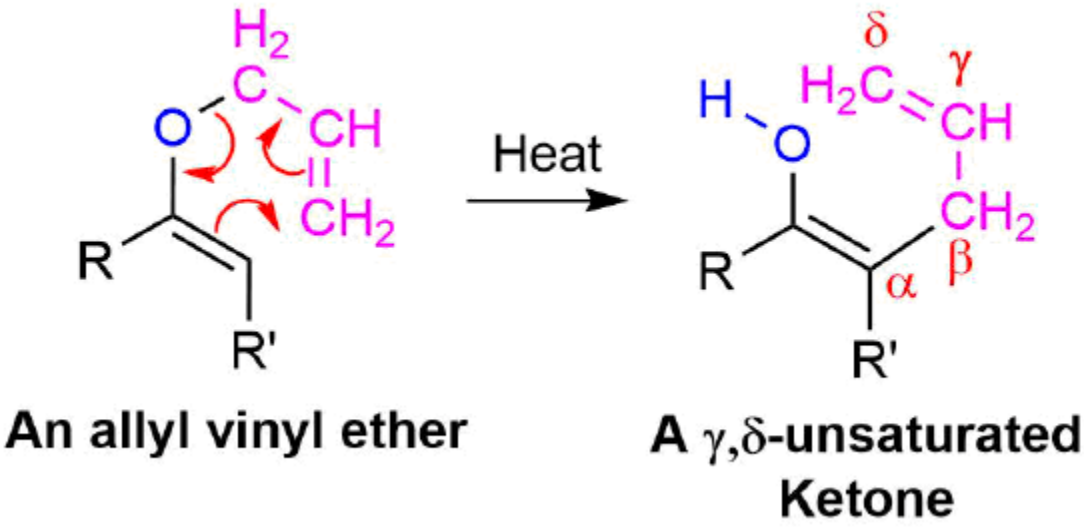
The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



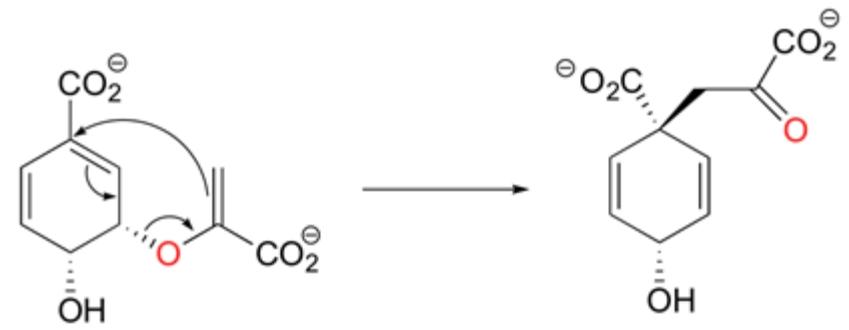
Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.



Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.

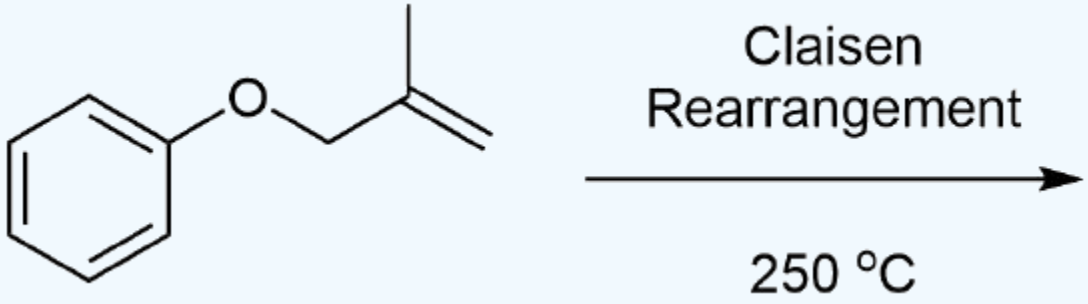


chorismate prephenate

Exercise 22.7.1

1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

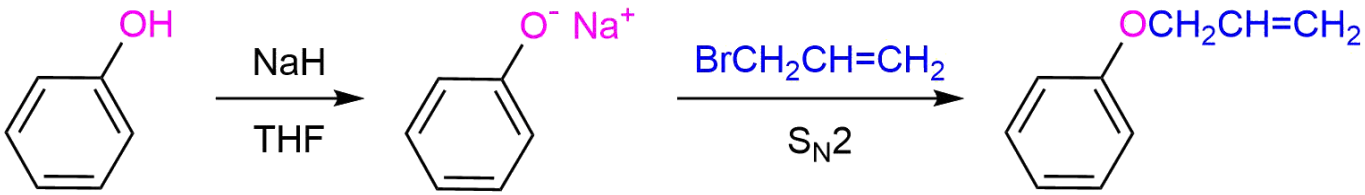


Answer available at the end of this section.

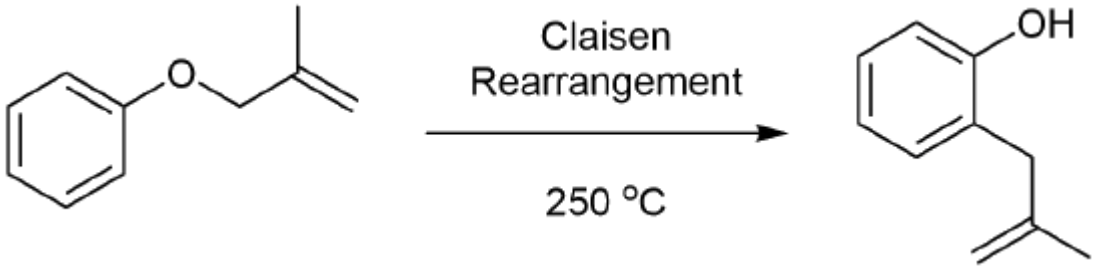
Answers

Exercise 22.7.1

1)



2)

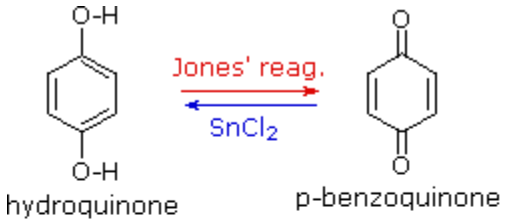


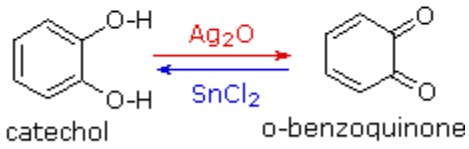
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22.8: Oxidation of Phenols: Benzoquinones

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone or simply quinone); an ortho isomer is also known. These compounds are easily reduced to their dihydroxybenzene analogs, and it is from these compounds that quinones are best prepared. Note that meta-quinones having similar structures do not exist. The redox equilibria between the dihydroxybenzenes hydroquinone and catechol and their quinone oxidation states are so facile that milder oxidants than chromate (Jones reagent) are generally preferred. One such oxidant is **Fremy's salt**, shown on the right. Reducing agents other than stannous chloride (e.g. $NaBH_4$) may be used for the reverse reaction. The position of the quinone-hydroquinone redox equilibrium is proportional to the square of the hydrogen ion concentration, as shown by the following half-reactions (electrons are colored blue). The electrode potential for this interconversion may therefore be used to measure the pH of solutions.





Fremy's Salt = $(KSO_3)_2NO$
a milder oxidant than chromate

Quinone + $2H^{(+)}$	$2e^{(-)}$ ⇌ $-2e^{(-)}$	Hydroquinone

Further Reading

Chemgapedia

Oxidation of Phenols

Carey 5th Ed Online

Phenol Oxidation

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22.9: Oxidation-Reduction Processes in Nature

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22.10: Arenediazonium Salts

Objectives

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. outline a possible synthetic route for the preparation of a given sulfa drug.
   c. identify the starting material, the necessary organic reagents, inorganic reagents, or both, and the intermediate compounds formed during the synthesis of a given sulfa drug.
   d. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

Key Terms

Make certain that you can define, and use in context, the key terms below.

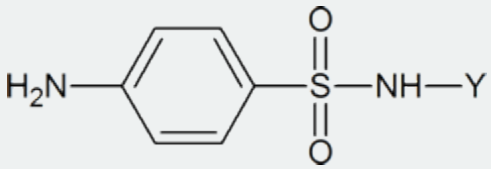
- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

Study Notes

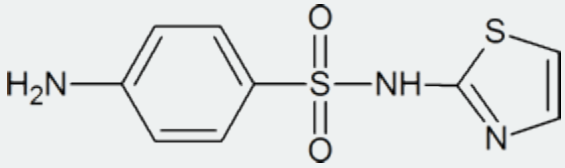
This section contains a considerable amount of new information. To absorb all of it, you should use the three subsections indicated in the reading: electrophilic aromatic substitution and overreaction of aniline (Objectives 1 and 2), the preparation of diazonium salts and the Sandmeyer reaction (Objectives 3 and 4), and diazonium coupling reactions (Objective 5).

The general process in which an aromatic amine is reacted with acetic anhydride, substituted, and then hydrolyzed is known as “protecting the amino group.”

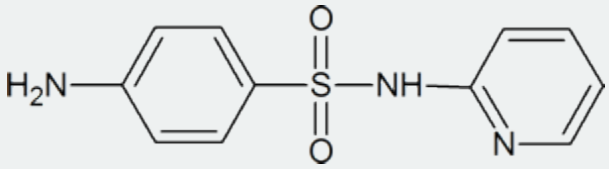
Sulfa drugs have the general formula



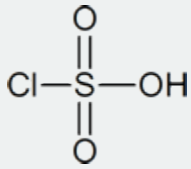
Typical examples are sulfathiazole



and sulfapyridine

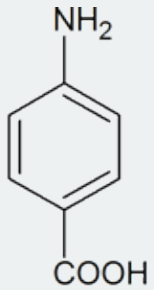


The reagent used to bring about the chlorosulfonation of acetanilide is chlorosulfuric acid

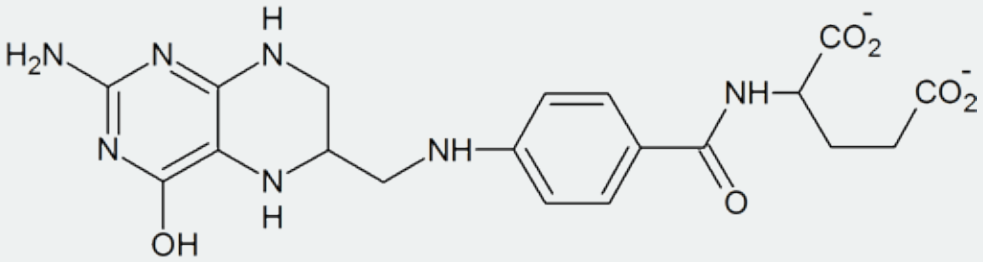


Sulfanilamide itself is toxic to humans, but derivatives of this compound, such as sulfathiazole, are less harmful to humans and are effective in killing many types of bacteria. The drugs work by "deceiving" the bacteria in the following way. To survive, many micro-organisms use *p*-aminobenzoic acid to synthesize folic acid, a coenzyme in a number of biochemical processes.

These micro-organisms cannot distinguish between sulfa drugs and *p*-aminobenzoic acid; so, when the drug is administered, the bacteria use it to produce a compound which has a structure similar to that of folic acid, but which is unable to act as a coenzyme in essential biochemical processes. The result is that many of the bacteria's amino acids and nucleotides cannot be made, and the bacteria die. Amino acids are discussed in Chapter 26; nucleotides are discussed in Section 28.1.

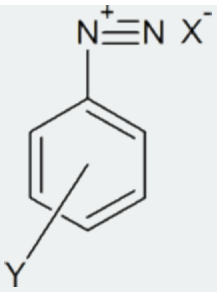


p-aminobenzoic acid



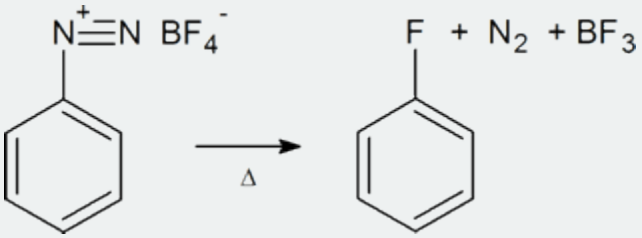
folic acid

An "arenediazonium salt" is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as diazonium salts.

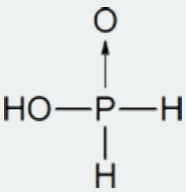
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

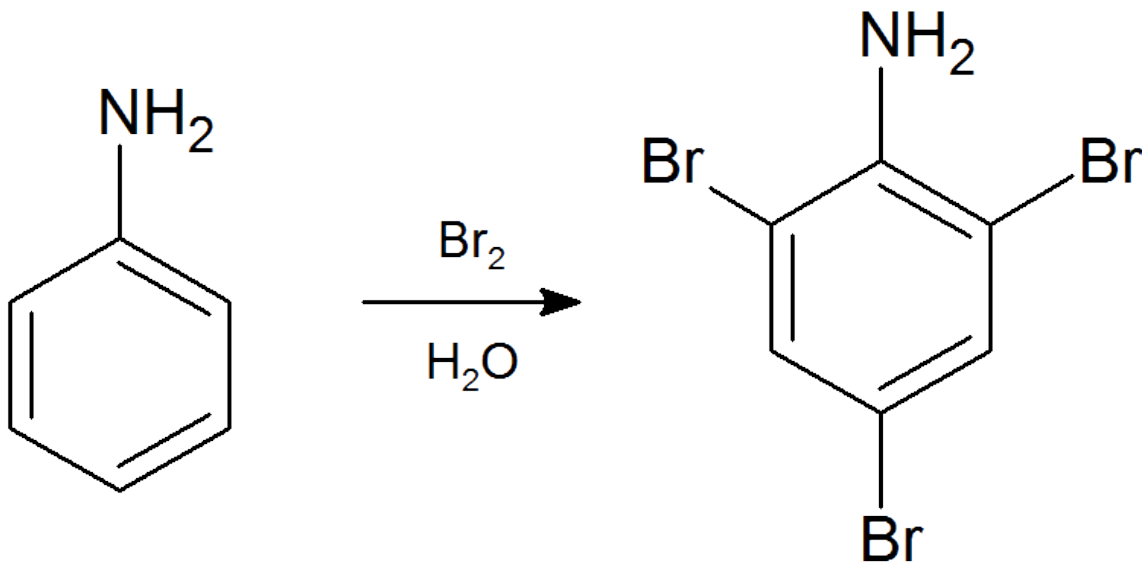
Hypophosphorous acid has the structure shown below:



The presence of the letters “azo” in a compound’s name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by an $\ce{-}$N$\ce{=}$N$\ce{-}$ linkage are usually very colourful.

Overreaction of Aniline

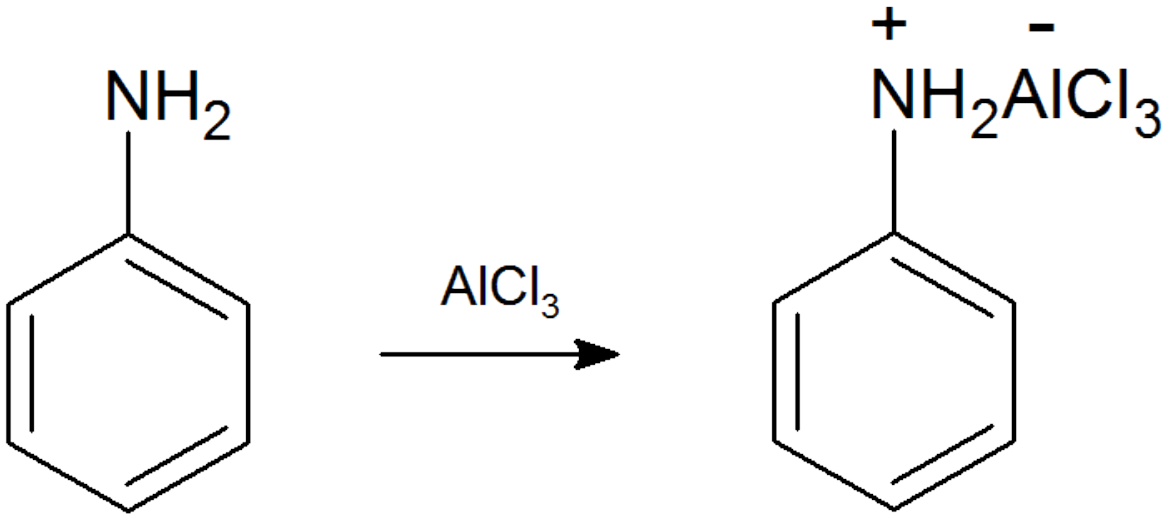
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.



Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$C_6H_5–NH_2 + I_2 + NaHCO_3$		⟶	p-I–C_6H_4–NH_2 + NaI + CO_2 + H_2O

In addition to overreactivity, we have previously seen (Section 16.3) that Friedel-Crafts reactions employing $AlCl_3$ catalyst does not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

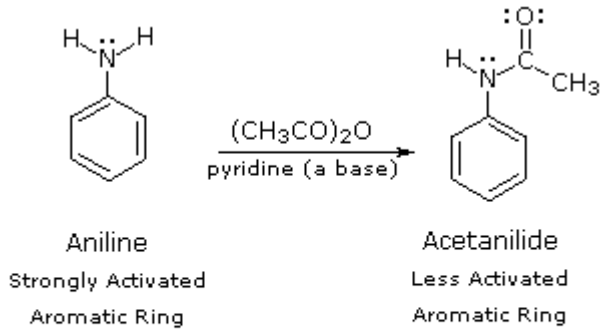
Modifying the Influence of Strong Activating Groups

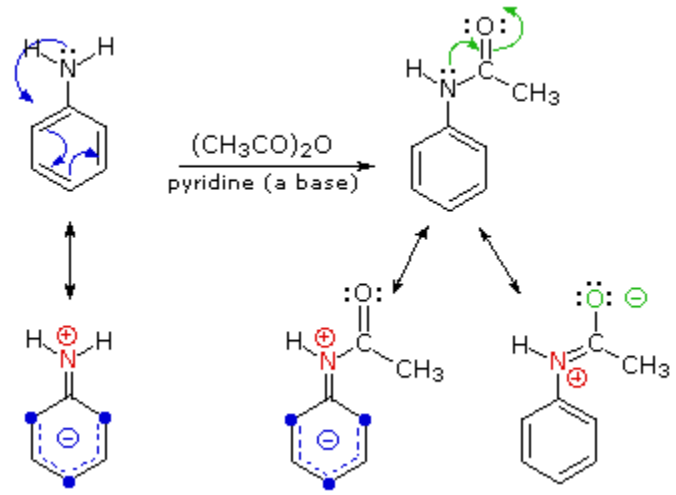
By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step),

to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$C_6H_5–NH_2 + (CH_3CO)_2O$	pyridine (a base) ⟶	$C_6H_5–NHCOCH_3$	HNO_3 , 5 °C ⟶	p-$O_2N–C_6H_4–NHCOCH_3$	$H_3O^{(+)}$ & heat ⟶	p-$O_2N–C_6H_4–NH$

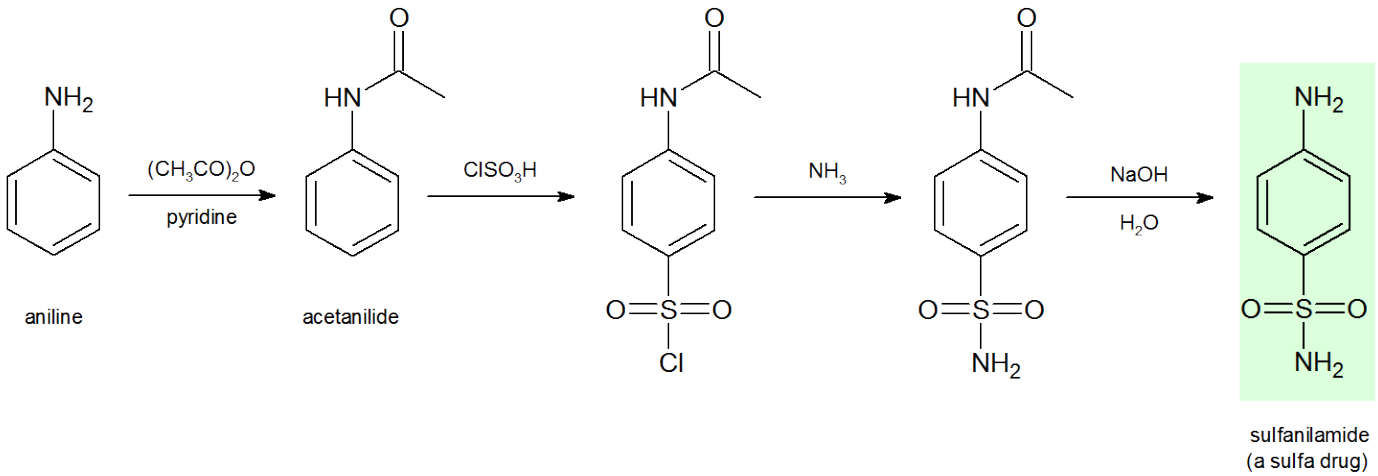
The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.





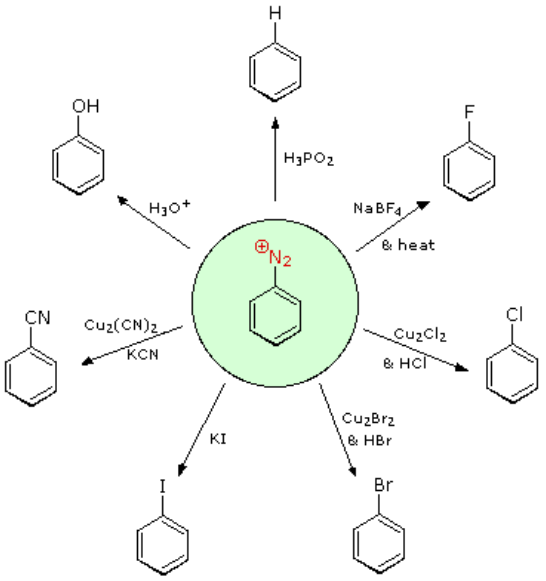
Sulfa Drug Synthesis

Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group. The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution. The corresponding acetanilide undergoes chlorosulfonation. The resulting 4-acetamidobenzenesulfanyl chloride is treated with ammonia to replace the chlorine with an amino group and affords 4-acetamidobenzenesulfonamide. The subsequent hydrolysis of the sulfonamide produces the sulfanilamide.



Diazonium Salts: The Sandmeyer Reaction

Aryl diazonium salts are important intermediates. They are prepared in cold (0 ° to 10 °C) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.

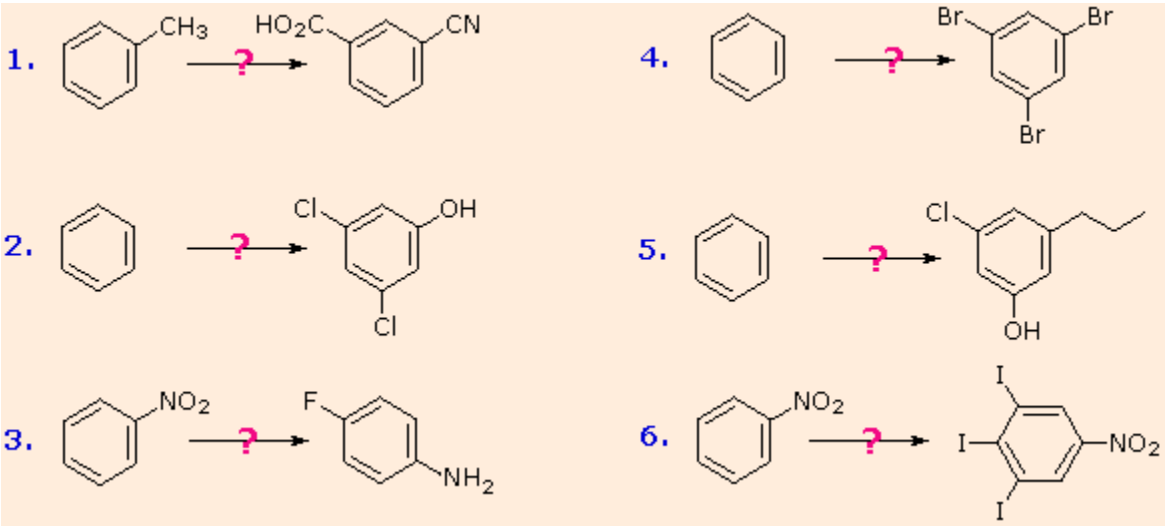


These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.
II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.
II. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

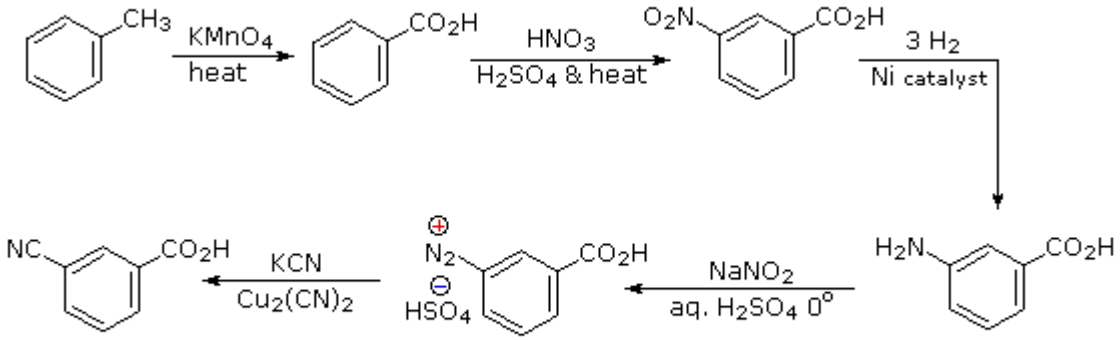
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



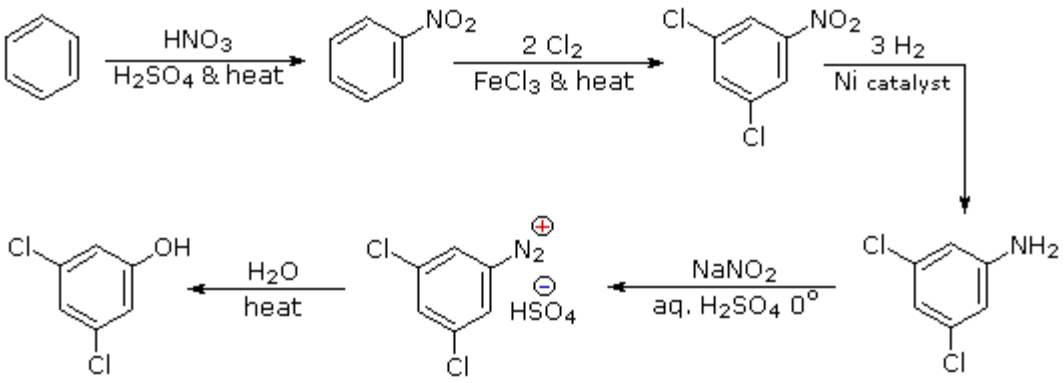
Answer 1:

It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



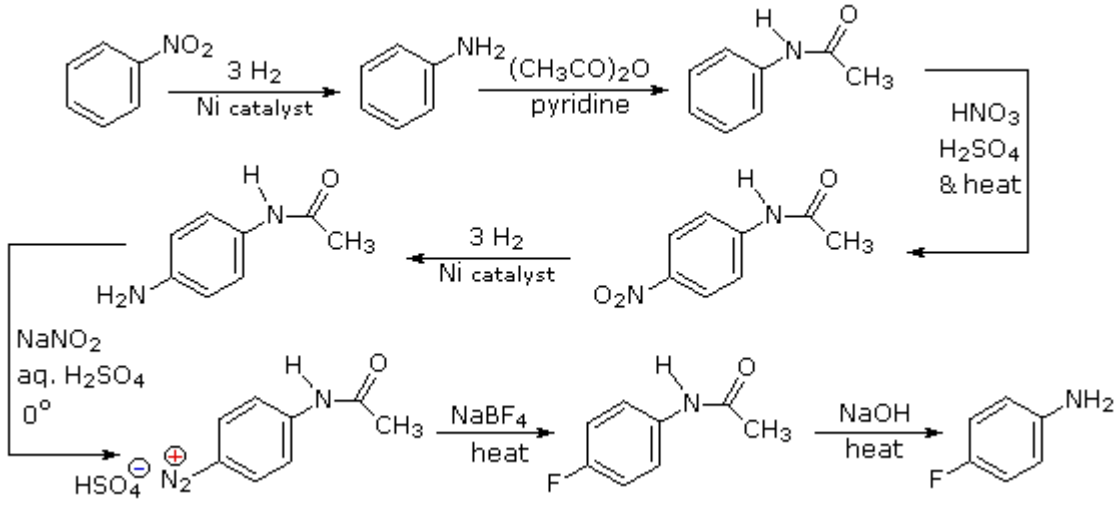
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



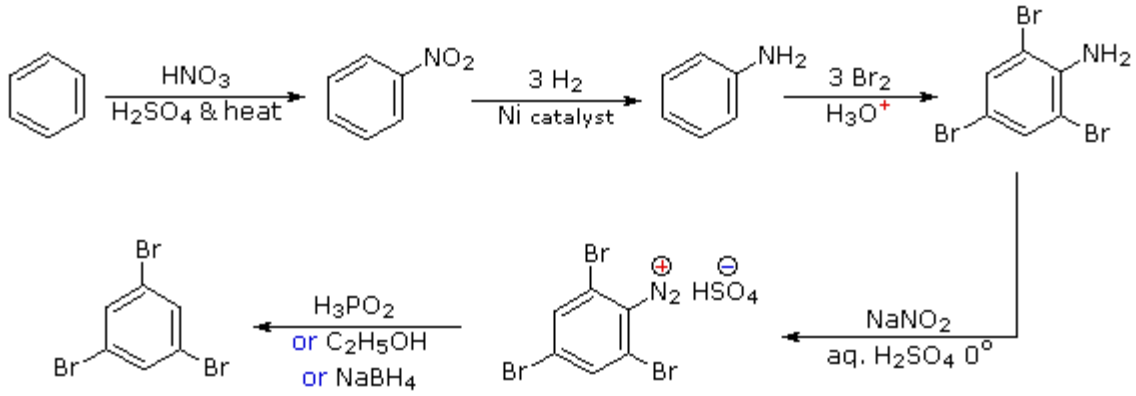
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



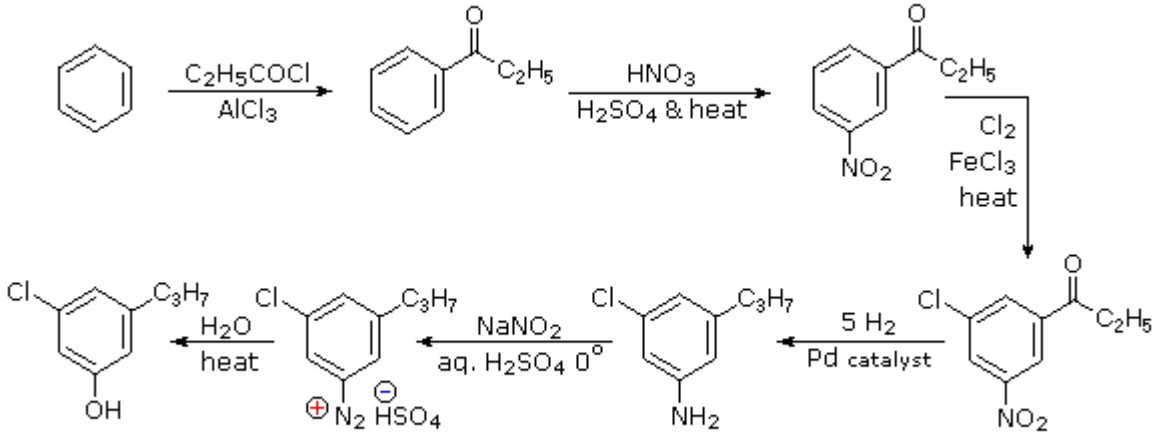
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



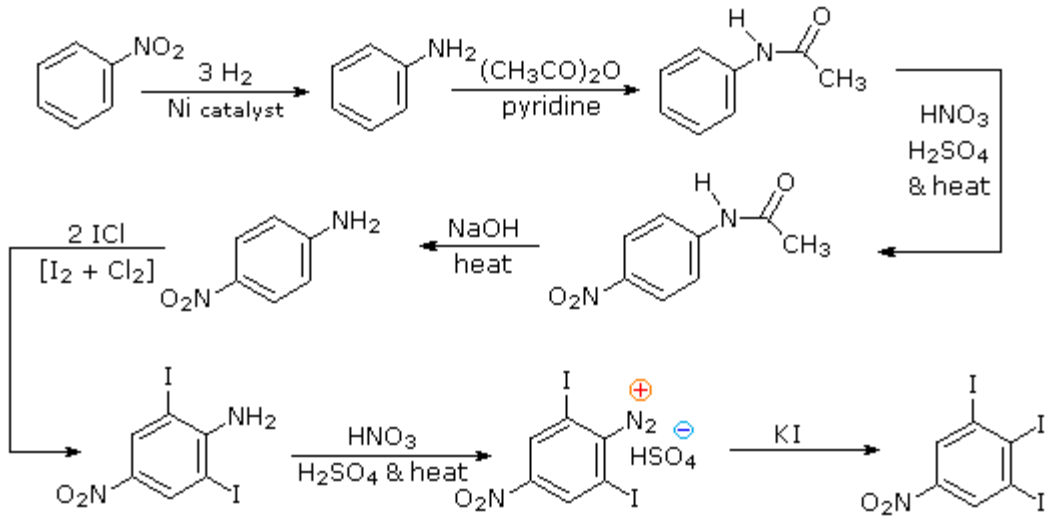
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



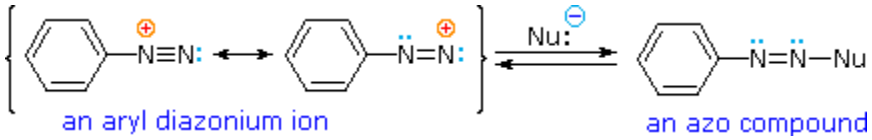
Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



Diazonium Coupling ReactionsEdit section

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



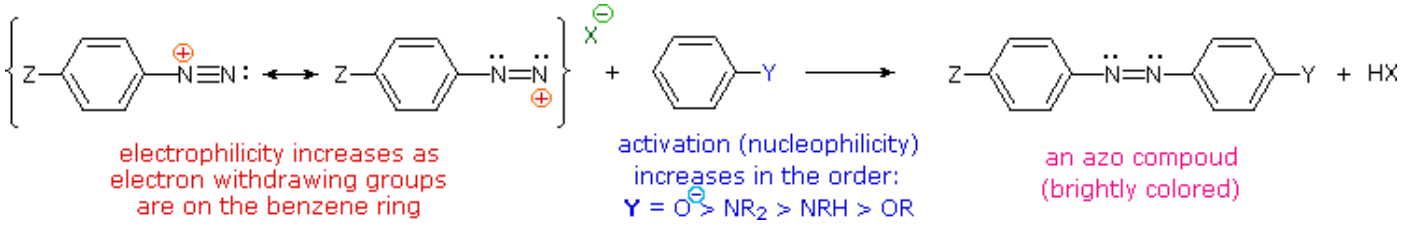
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$C_6H_5N_2^{(+)}$ $HSO_4^{(-)}$ + NaOH (cold solution)	⇌	$C_6H_5N_2$–OH + NaOH (cold)	⇌	$C_6H_5N_2$–$O^{(-)}$ $Na^{(+)}$
phenyldiazonium bisulfate		phenyldiazoic acid		sodium phenyldiazoate

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

Ar-$N_2^{(+)}$ $X^{(-)}$	$NaHSO_3$ ⟶	Ar-N=N-SO_3H	$NaHSO_3$ ⟶	Ar-NH-NH-SO_3H	H_2O ⟶	Ar-NH-NH_2 + H_2SO_4

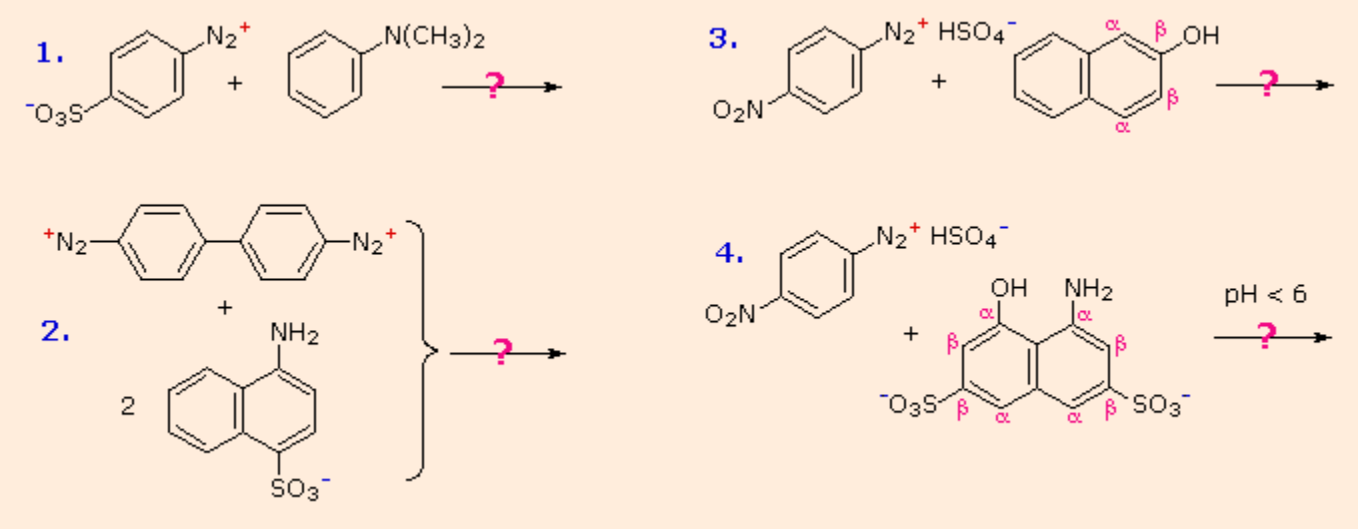
The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.
II. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

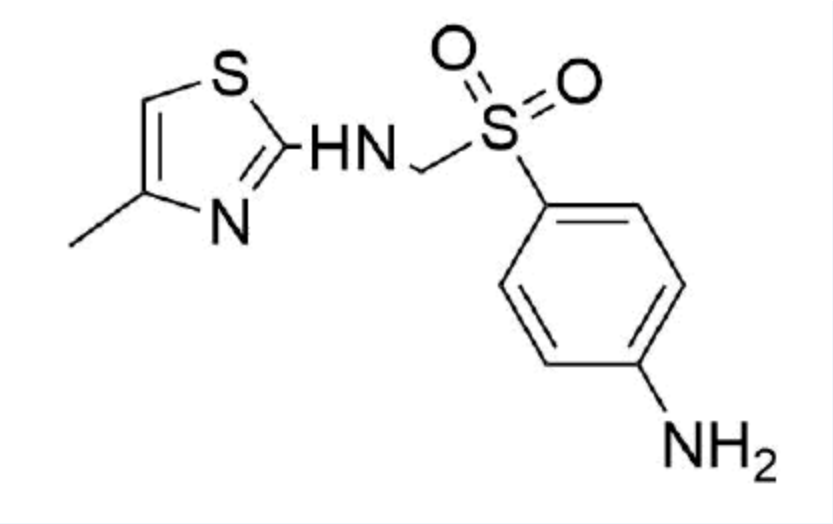
You should try to conceive a plausible product structure for each of the following couplings.



Exercises

Exercise 24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



Answer available at the end of this section.

Exercise 24.8.2

Propose a synthesis for each of the following compounds via benzene.

(a) N,N-Diethylaniline

(b) p-Bromoaniline

(c) m-Bromoaniline

(d) 2,4-Diethylaniline

Answer available at the end of this section.

Exercise 24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) p-Chlorobenzoic acid

(b) m-Chlorobenzoic acid

(c) m-Dichlorobenzene

(d) p-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Answer available at the end of this section.

Questions

Q24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.

24.16 Problem.png

Q24.8.2

Proposes synthesis for each of the following compounds via benzene.

(a) *N,N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

Q24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) *p*-Chlorobenzoic acid

(b) *m*-Chlorobenzoic acid

(c) *m*-Dichlorobenzene

(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Solutions

S24.8.1

24.16 Solution.png

S24.8.2

(a) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. Br_2, $FeBr_3$; 5. H_2O, NaOH

(c) 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. Zn(Hg), HCl

(d) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. EtCl, $AlCl_3$; 5. H_2O, NaOH

S24.8.3

(a) 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O

(b) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(c) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCl

(d) 1. CH_3CH_2Cl, $AlCl_3$: 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

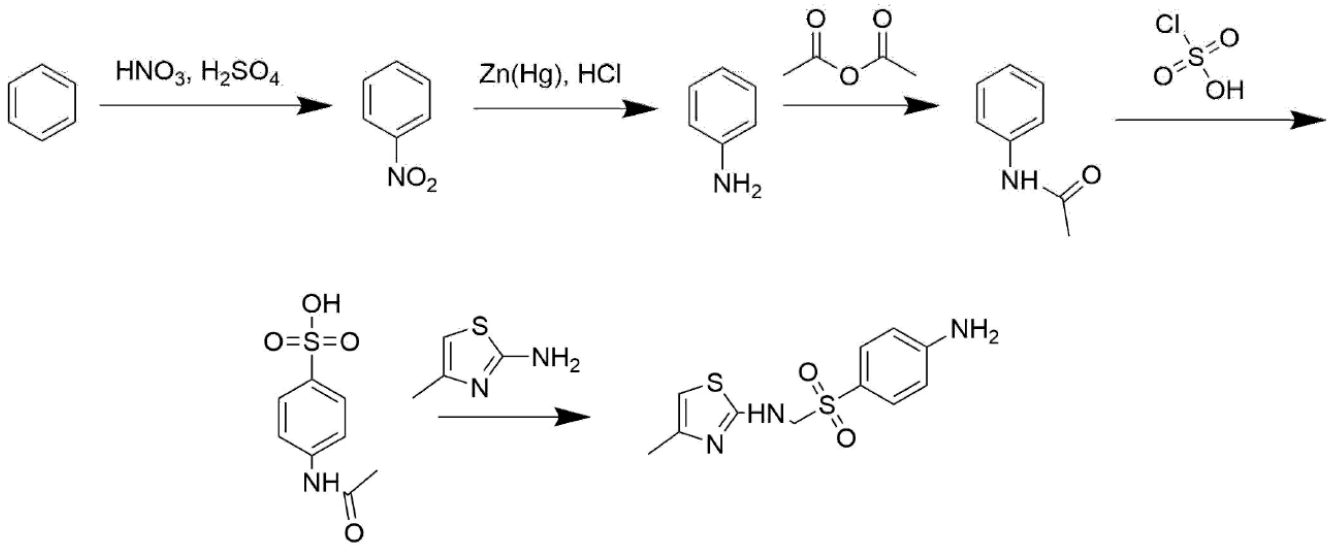
(e) 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Cl_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuCl

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 24.8.1



Exercise 24.8.2

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH

(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl

(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

Exercise 24.8.3

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH

(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl

(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

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22.11: Electrophilic Substitution with Arenediazonium Salts: Diazo Coupling

Objectives

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. outline a possible synthetic route for the preparation of a given sulfa drug.
   c. identify the starting material, the necessary organic reagents, inorganic reagents, or both, and the intermediate compounds formed during the synthesis of a given sulfa drug.
   d. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

Key Terms

Make certain that you can define, and use in context, the key terms below.

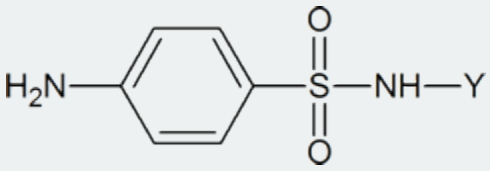
- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

Study Notes

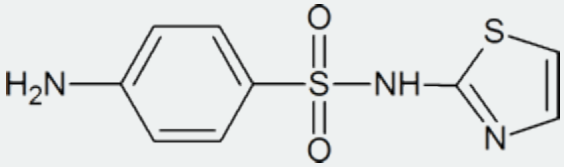
This section contains a considerable amount of new information. To absorb all of it, you should use the three subsections indicated in the reading: electrophilic aromatic substitution and overreaction of aniline (Objectives 1 and 2), the preparation of diazonium salts and the Sandmeyer reaction (Objectives 3 and 4), and diazonium coupling reactions (Objective 5).

The general process in which an aromatic amine is reacted with acetic anhydride, substituted, and then hydrolyzed is known as “protecting the amino group.”

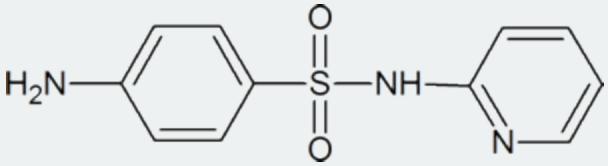
Sulfa drugs have the general formula



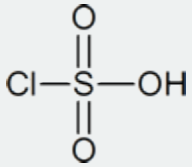
Typical examples are sulfathiazole



and sulfapyridine

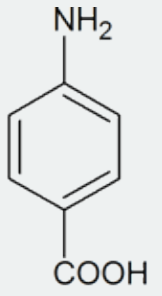


The reagent used to bring about the chlorosulfonation of acetanilide is chlorosulfuric acid

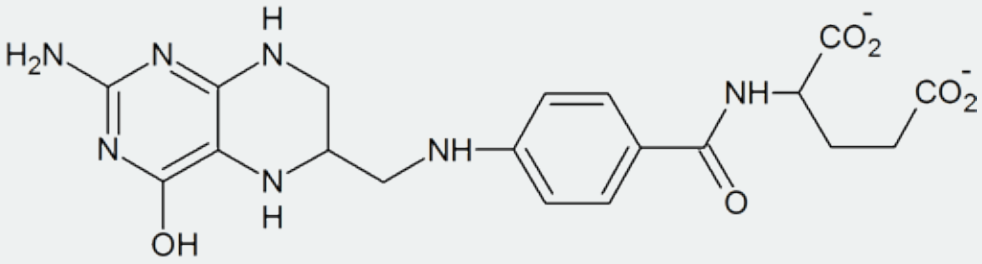


Sulfanilamide itself is toxic to humans, but derivatives of this compound, such as sulfathiazole, are less harmful to humans and are effective in killing many types of bacteria. The drugs work by “deceiving” the bacteria in the following way. To survive, many micro-organisms use *p*-aminobenzoic acid to synthesize folic acid, a coenzyme in a number of biochemical processes.

These micro-organisms cannot distinguish between sulfa drugs and *p*-aminobenzoic acid; so, when the drug is administered, the bacteria use it to produce a compound which has a structure similar to that of folic acid, but which is unable to act as a coenzyme in essential biochemical processes. The result is that many of the bacteria’s amino acids and nucleotides cannot be made, and the bacteria die. Amino acids are discussed in Chapter 26; nucleotides are discussed in Section 28.1.

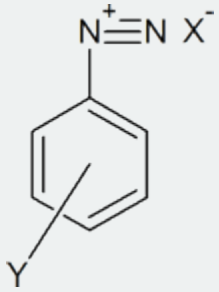


p-aminobenzoic acid



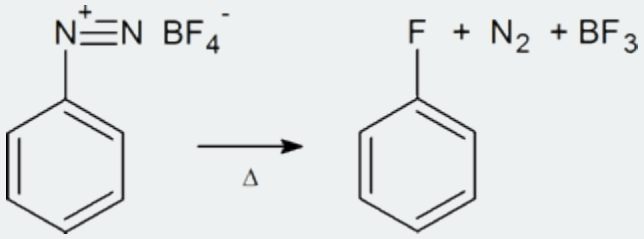
folic acid

An “arenediazonium salt” is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as diazonium salts.

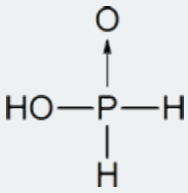
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

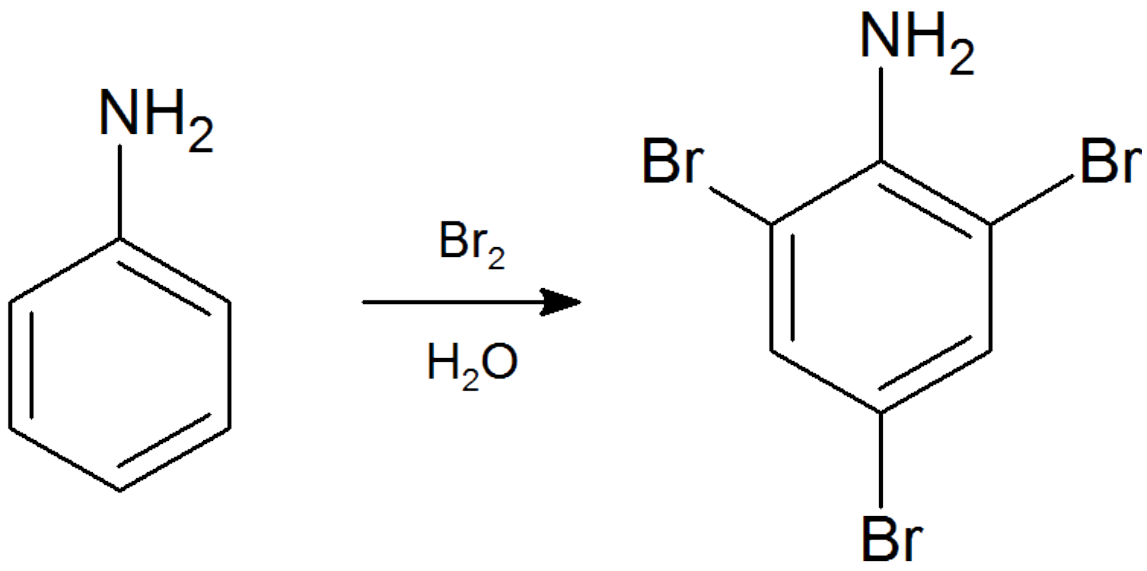
Hypophosphorous acid has the structure shown below:



The presence of the letters “azo” in a compound’s name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by an $\ce{-}$N$\ce{=}$N$\ce{-}$ linkage are usually very colourful.

Overreaction of Aniline

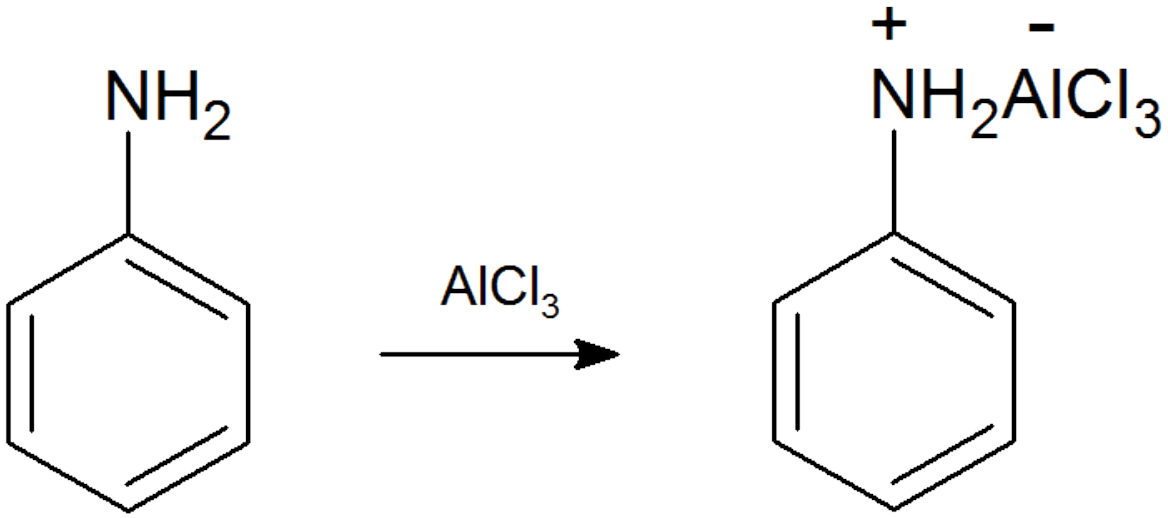
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino ($-NH_2$) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.



Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$C_6H_5–NH_2 + I_2 + NaHCO_3$		⟶	p-I–C_6H_4–NH_2 + NaI + CO_2 + H_2O

In addition to overreactivity, we have previously seen (Section 16.3) that Friedel-Crafts reactions employing $AlCl_3$ catalyst does not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

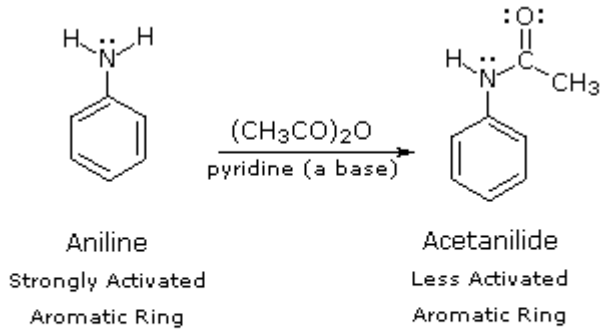
Modifying the Influence of Strong Activating Groups

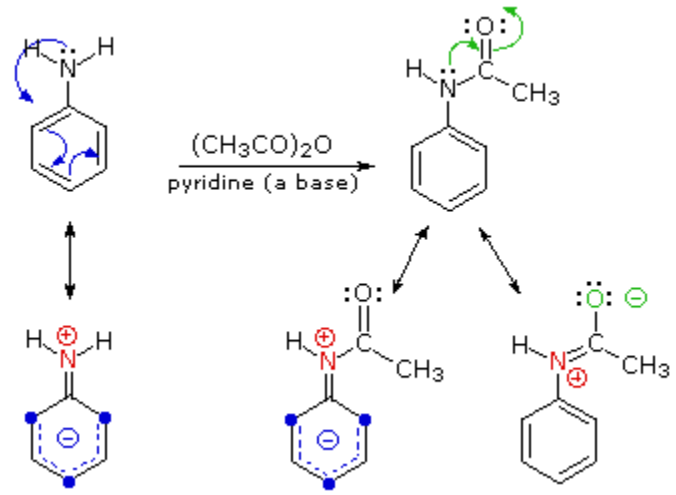
By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step),

to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$C_6H_5–NH_2 + (CH_3CO)_2O$	pyridine (a base) ⟶	$C_6H_5–NHCOCH_3$	HNO_3 , 5 °C ⟶	p-$O_2N–C_6H_4–NHCOCH_3$	$H_3O^{(+)}$ & heat ⟶	p-$O_2N–C_6H_4–NH$

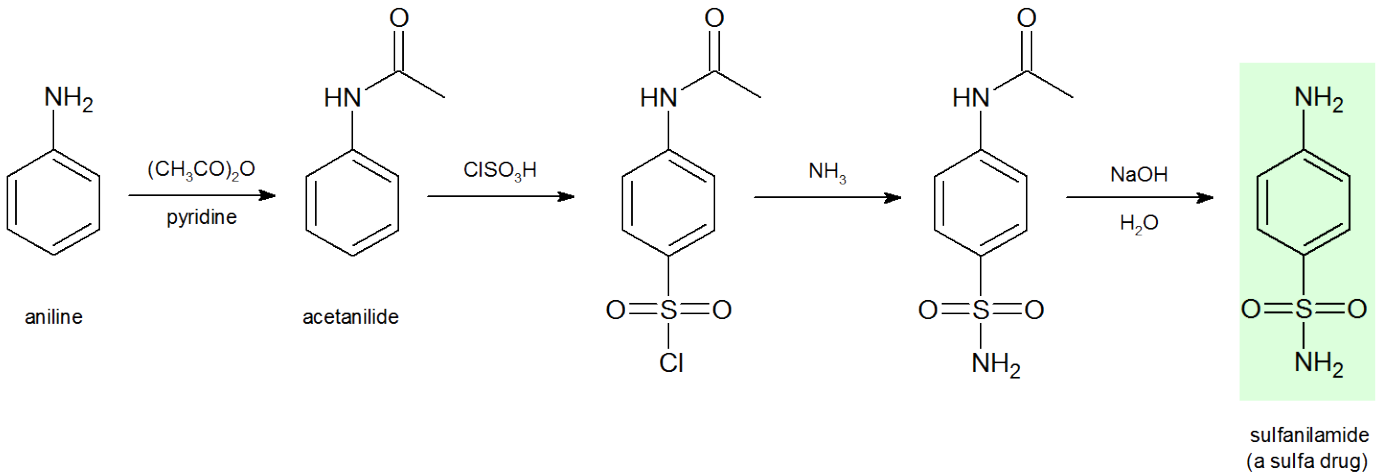
The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.





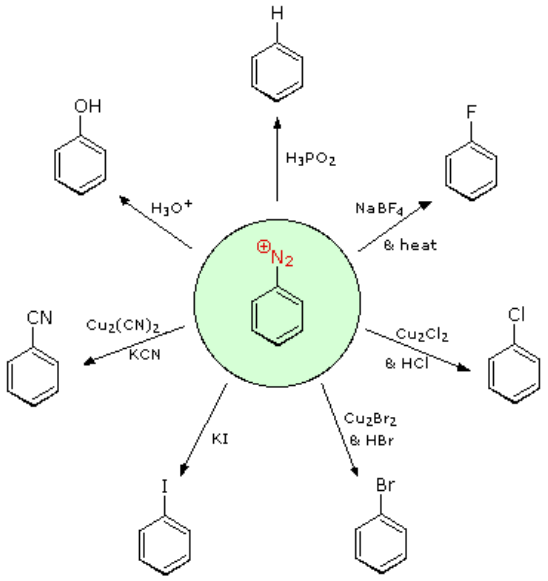
Sulfa Drug Synthesis

Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group. The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution. The corresponding acetanilide undergoes chlorosulfonation. The resulting 4-acetamidobenzenesulfanyl chloride is treated with ammonia to replace the chlorine with an amino group and affords 4-acetamidobenzenesulfonamide. The subsequent hydrolysis of the sulfonamide produces the sulfanilamide.



Diazonium Salts: The Sandmeyer Reaction

Aryl diazonium salts are important intermediates. They are prepared in cold (0 ° to 10 °C) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.

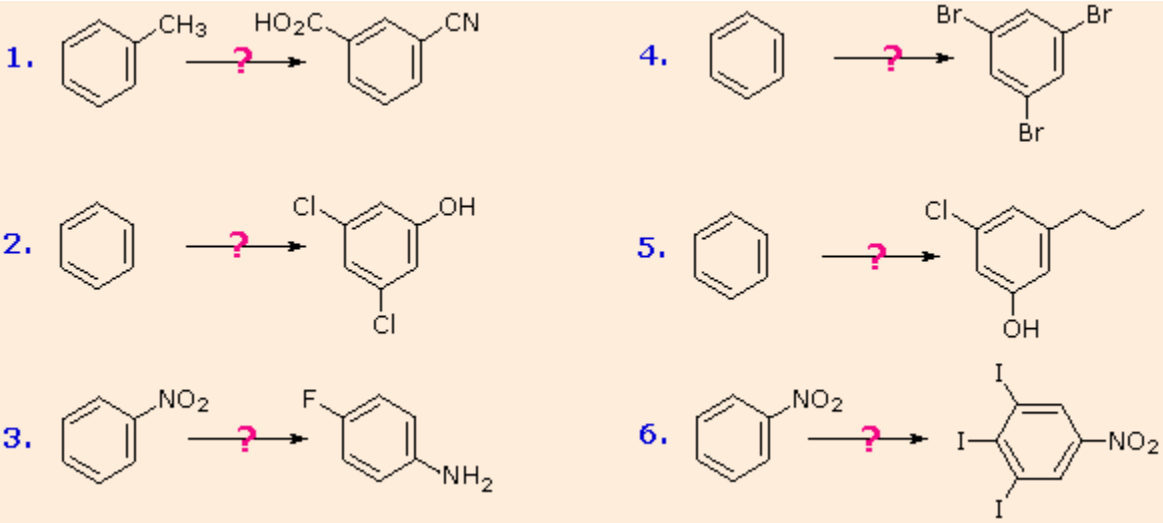


These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.
II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.
II. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

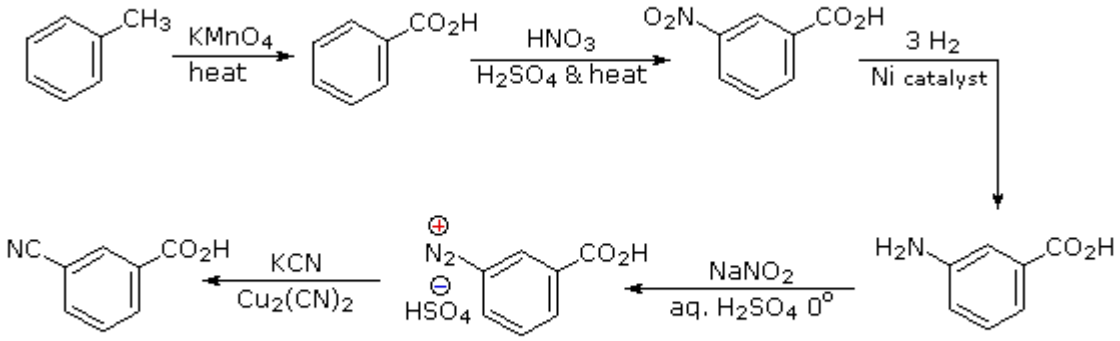
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



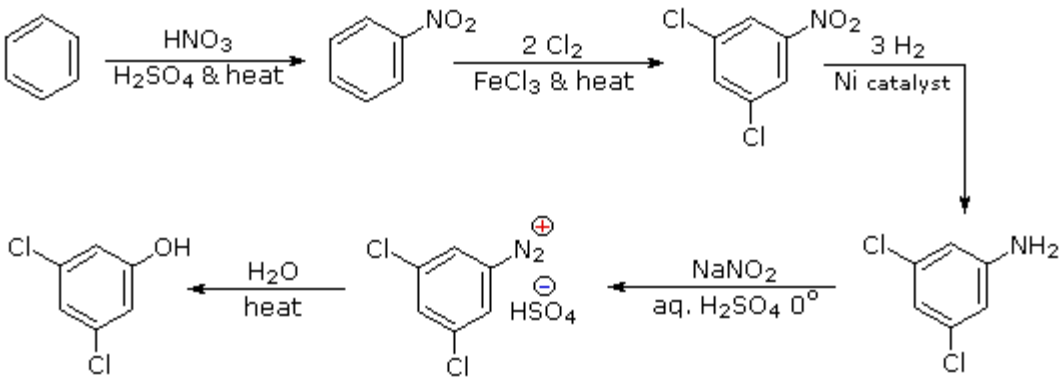
Answer 1:

It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



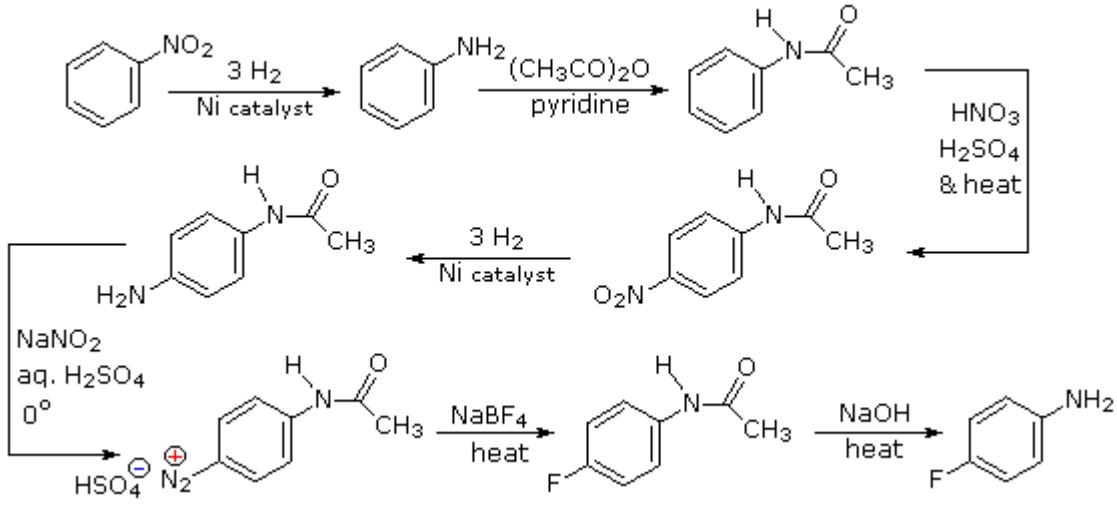
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



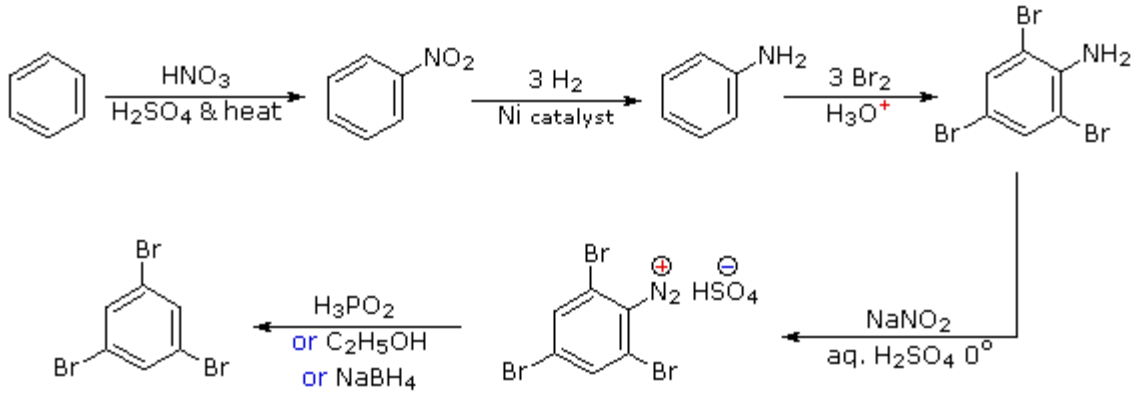
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



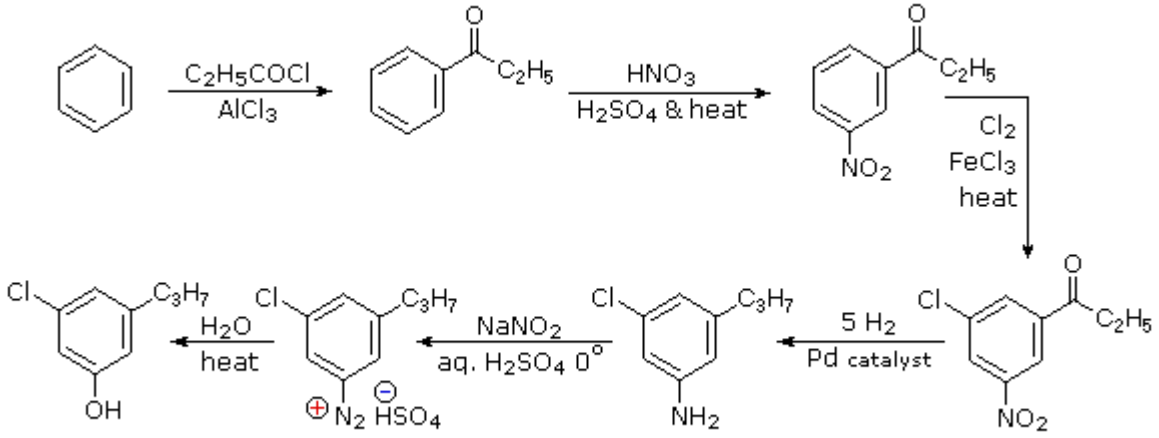
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



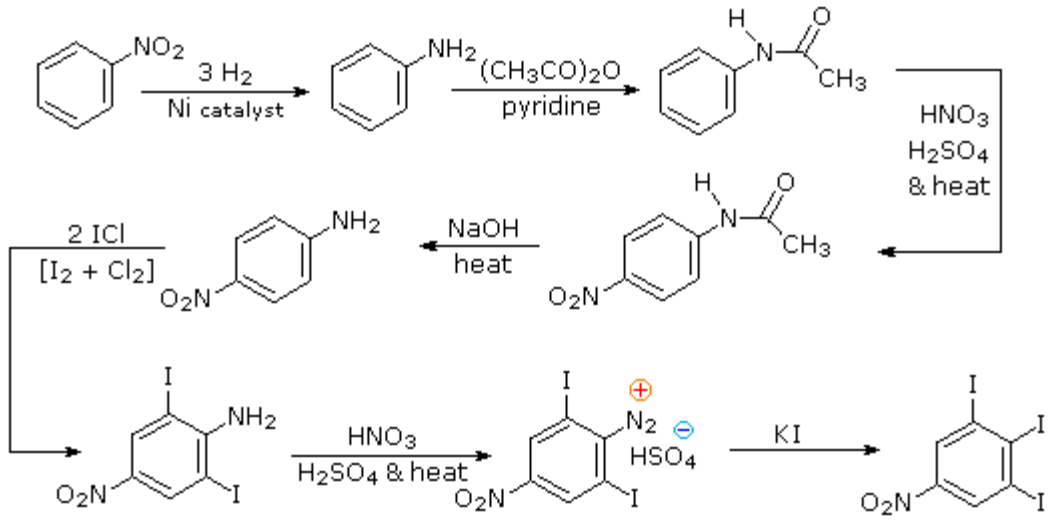
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



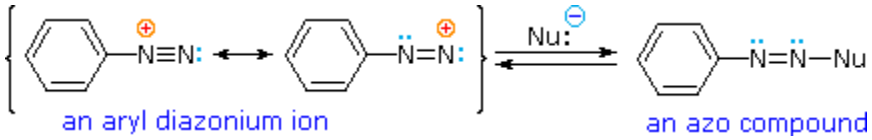
Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



Diazonium Coupling ReactionsEdit section

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



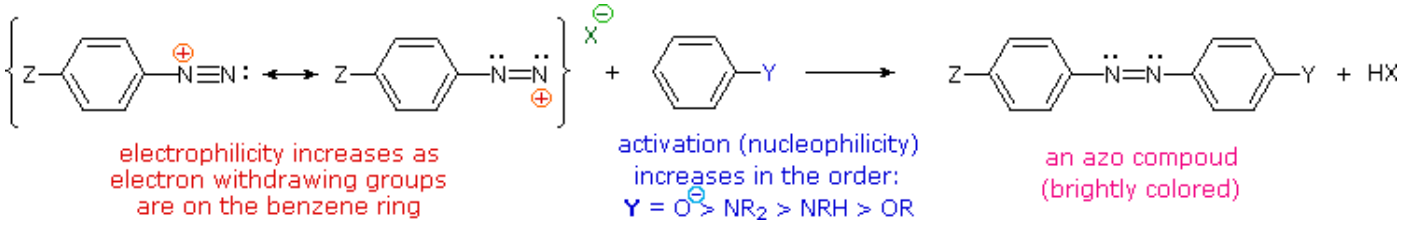
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$C_6H_5N_2^{(+)}$ $HSO_4^{(-)}$ + NaOH (cold solution)	⇌	$C_6H_5N_2$–OH + NaOH (cold)	⇌	$C_6H_5N_2$–$O^{(-)}$ $Na^{(+)}$
phenyldiazonium bisulfate		phenyldiazoic acid		sodium phenyldiazoate

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

Ar-$N_2^{(+)}$ $X^{(-)}$	$NaHSO_3$ ⟶	Ar-N=N-SO_3H	$NaHSO_3$ ⟶	Ar-NH-NH-SO_3H	H_2O ⟶	Ar-NH-NH_2 + H_2SO_4

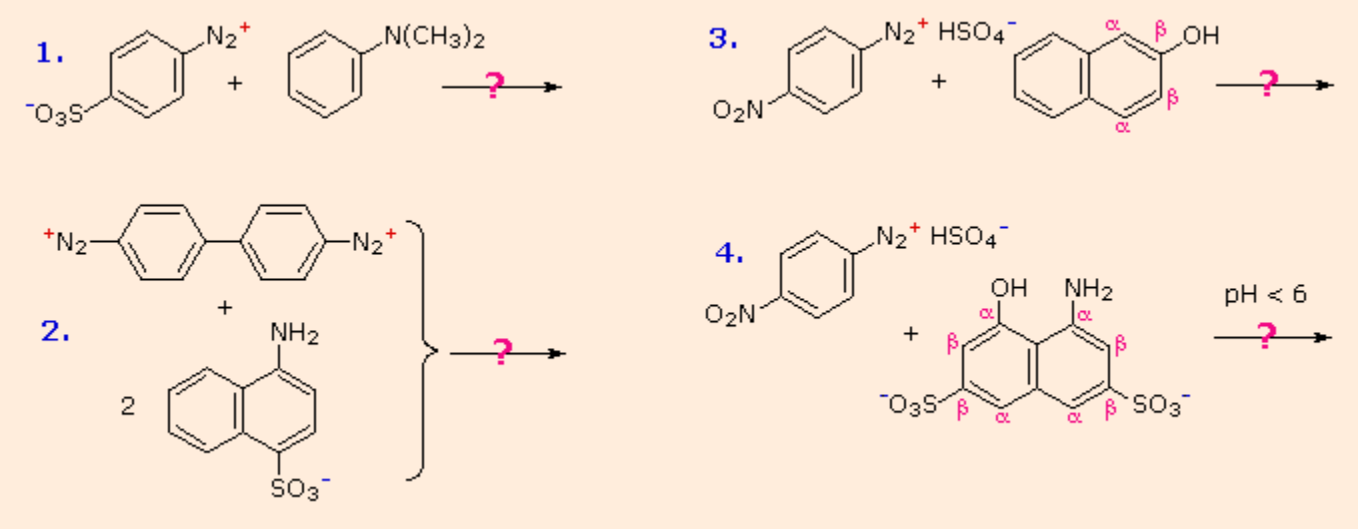
The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.
II. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

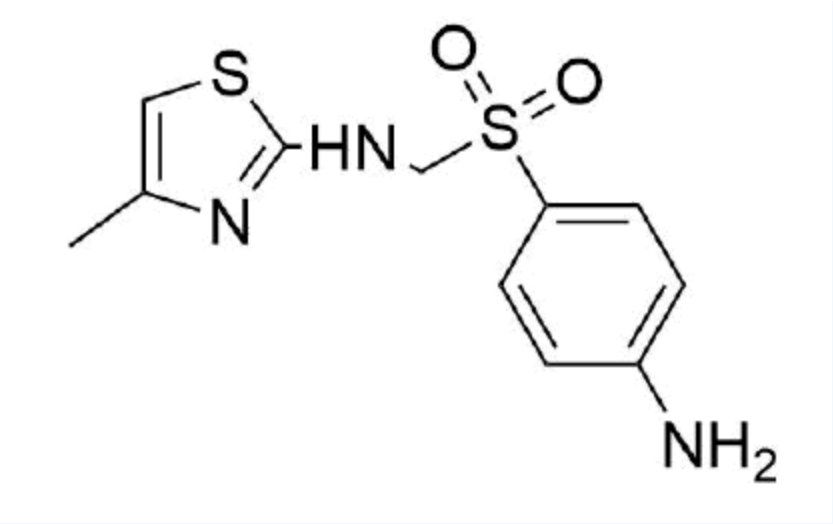
You should try to conceive a plausible product structure for each of the following couplings.



Exercises

Exercise 24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



Answer available at the end of this section.

Exercise 24.8.2

Propose a synthesis for each of the following compounds via benzene.

(a) N,N-Diethylaniline

(b) p-Bromoaniline

(c) m-Bromoaniline

(d) 2,4-Diethylaniline

Answer available at the end of this section.

Exercise 24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) p-Chlorobenzoic acid

(b) m-Chlorobenzoic acid

(c) m-Dichlorobenzene

(d) p-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Answer available at the end of this section.

Questions

Q24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.

24.16 Problem.png

Q24.8.2

Proposes synthesis for each of the following compounds via benzene.

(a) *N,N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

Q24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) *p*-Chlorobenzoic acid

(b) *m*-Chlorobenzoic acid

(c) *m*-Dichlorobenzene

(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Solutions

S24.8.1

24.16 Solution.png

S24.8.2

(a) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. Br_2, $FeBr_3$; 5. H_2O, NaOH

(c) 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. Zn(Hg), HCl

(d) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. EtCl, $AlCl_3$; 5. H_2O, NaOH

S24.8.3

(a) 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O

(b) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(c) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCl

(d) 1. CH_3CH_2Cl, $AlCl_3$: 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

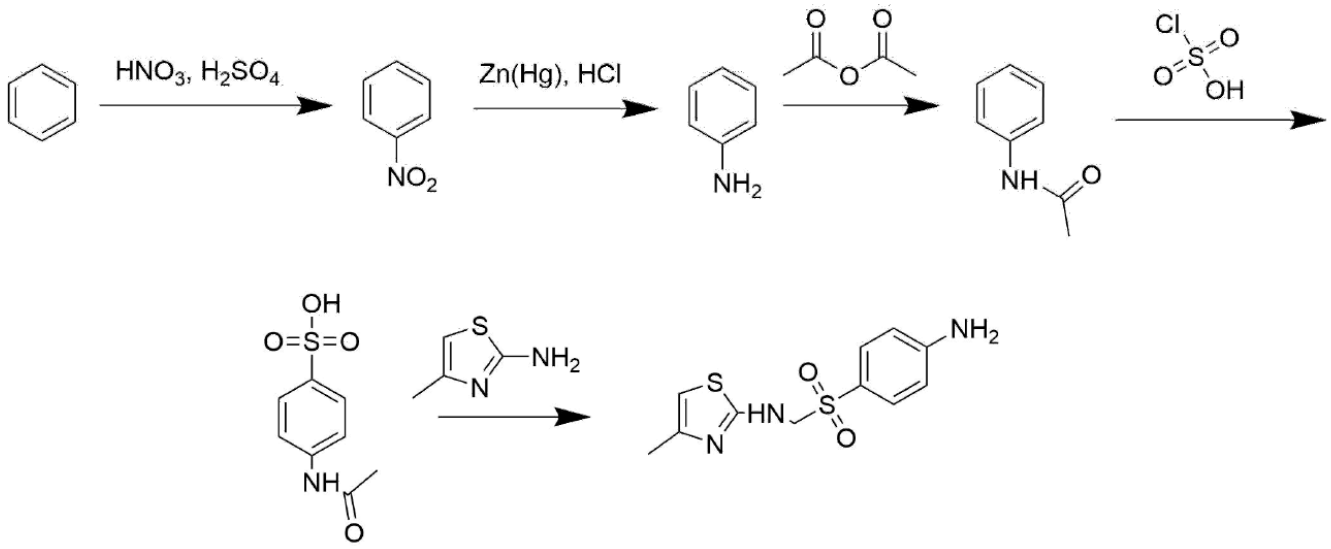
(e) 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Cl_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuCl

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 24.8.1



Exercise 24.8.2

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr
(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH
(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl
(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

Exercise 24.8.3

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr
(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH
(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl
(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

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23: ESTER ENOLATES AND THE CLAISEN CONDENSATION

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore

Ester Enolates and the Claisen Condensation: Synthesis of β-Dicarbonyl Compounds; Acyl Anion Equivalents



-  Topic hierarchy

23.1: B-Dicarbonyl Compounds: Claisen Condensations

23.2: B-Dicarbonyl Compounds as Synthetic Intermediates

23.3: B-Dicarbonyl Anion Chemistry: Michael Additions

23.4: Alkanoyl (Acyl) Anion Equivalents: Preparation of a-Hydroxyketones

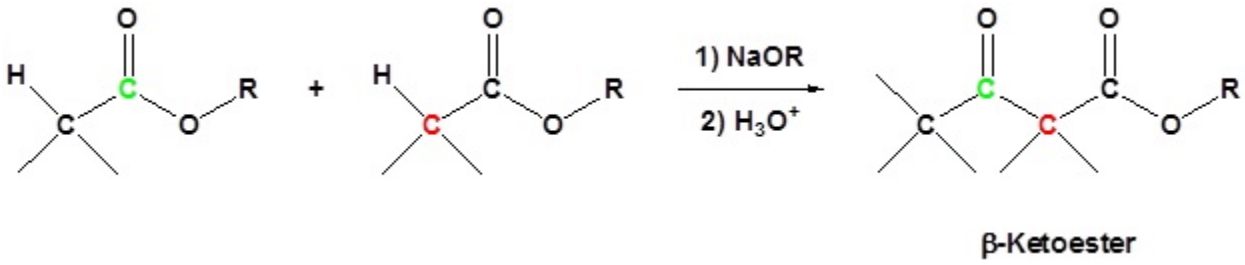
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23.1: B-Dicarbonyl Compounds: Claisen Condensations

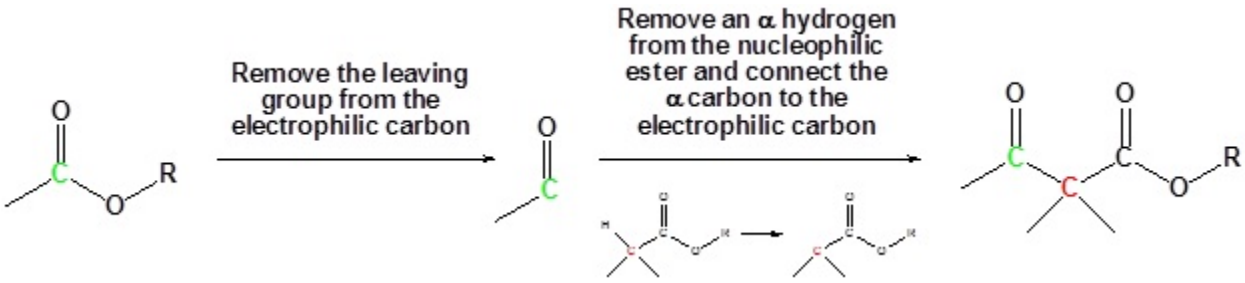
Because esters can contain α hydrogens they can undergo a condensation reaction similar to the aldol reaction called a **Claisen Condensation**. In a fashion similar to the aldol, one ester acts as a nucleophile while a second ester acts as the electrophile. During the reaction a new carbon-carbon bond is formed. The product is a β-keto ester. A major difference with the aldol reaction is the fact that hydroxide cannot be used as a base because it could possibly react with the ester. Instead, an alkoxide version of the alcohol used to synthesize the ester is used to prevent transesterification side products.

Claisen Condensation

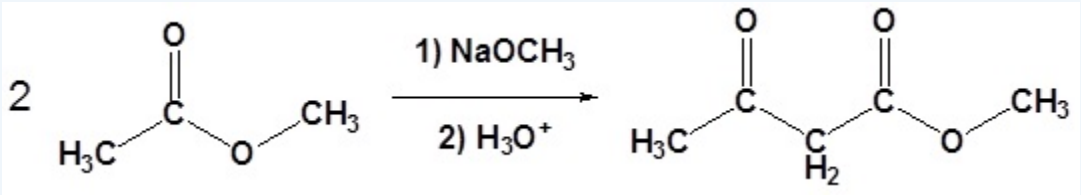
Basic reaction

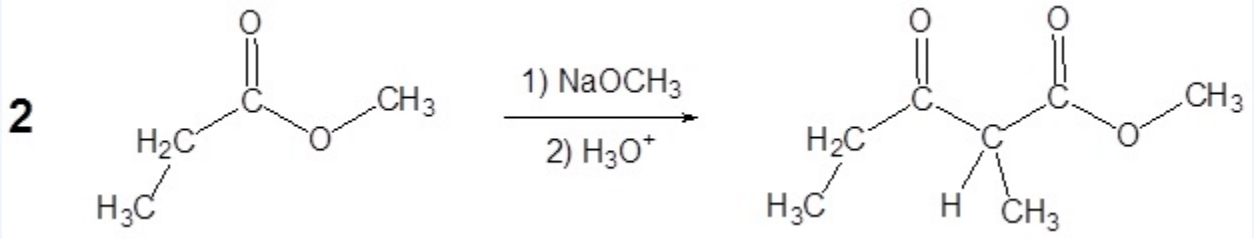


Going from reactants to products simply



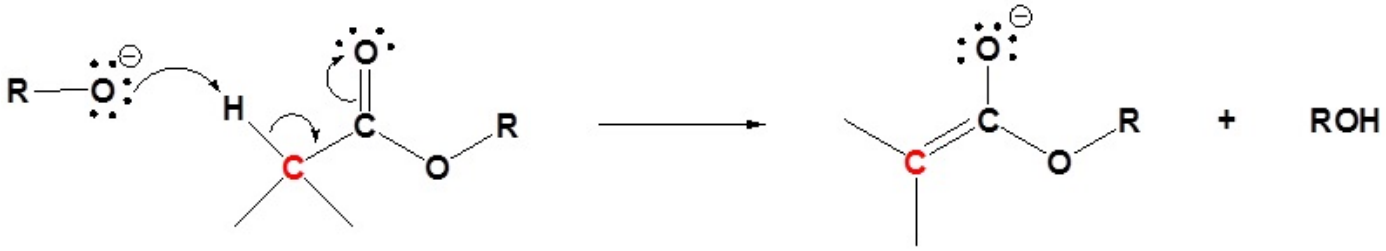
Example 1: Claisen Condensation



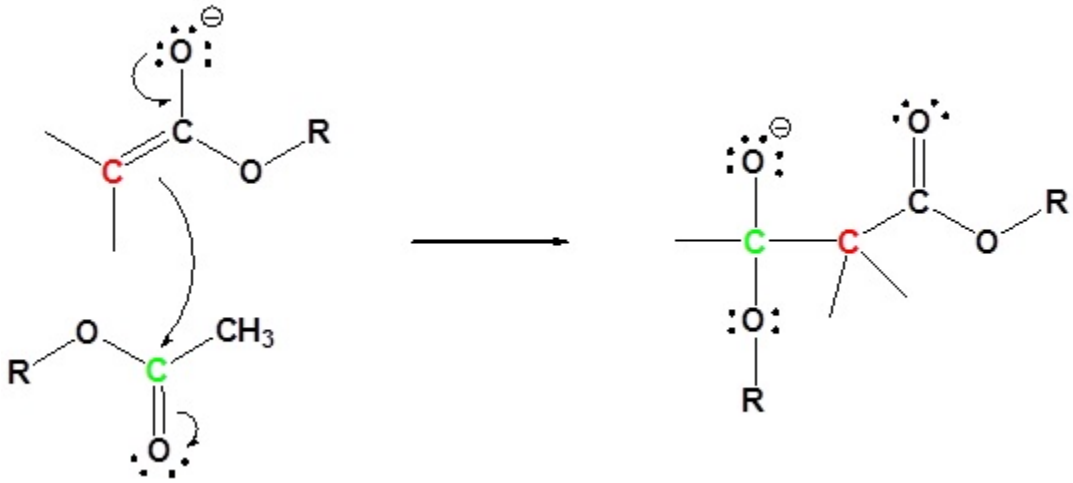


Claisen Condensation Mechanism

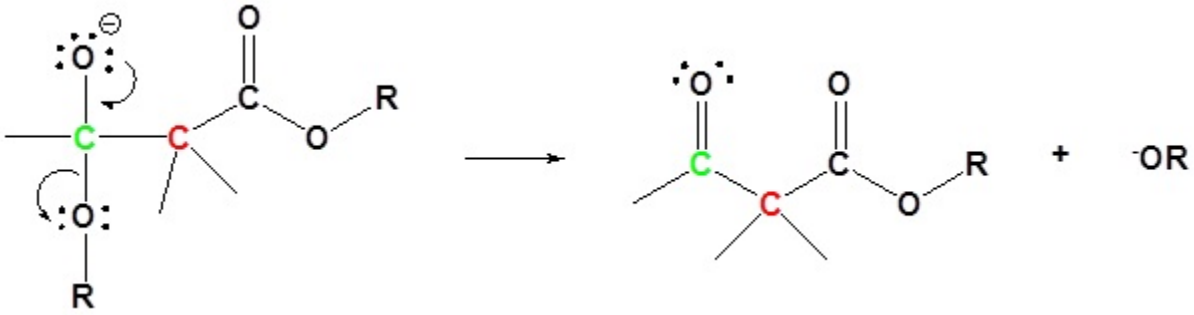
1) Enolate formation



2) Nucleophilic attack



3) Removal of leaving group



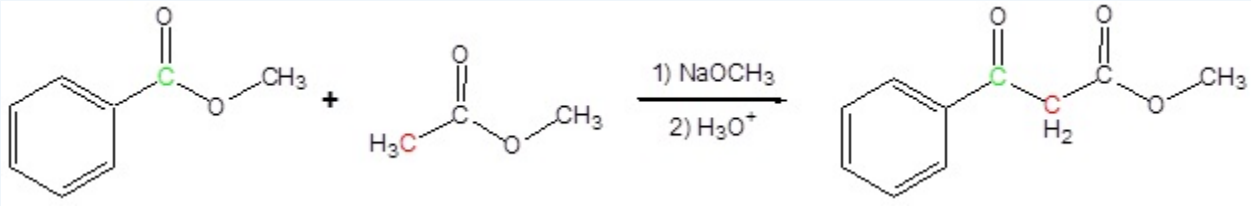
Contributor

- Prof. Steven Farmer (Sonoma State University)

Crossed Claisen Condensation

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures. Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.

Example 3: Crossed Claisen Condensation



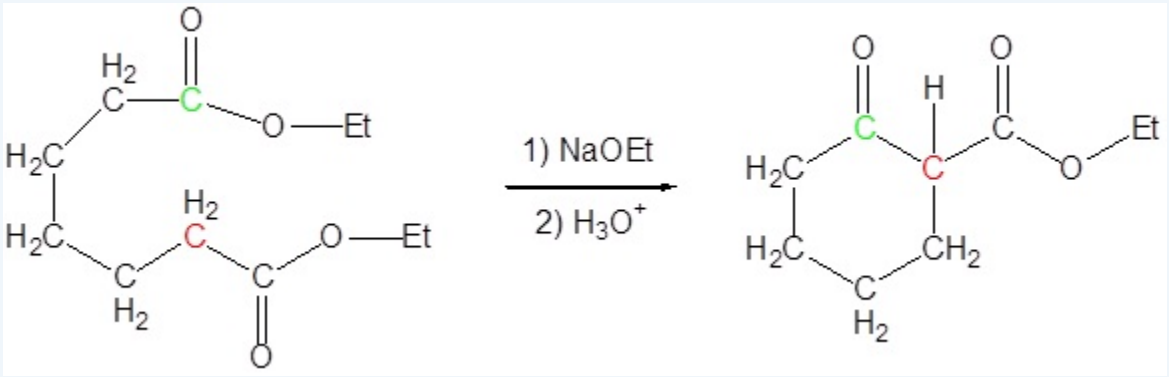
Contributors

- Prof. Steven Farmer (Sonoma State University)

Dieckmann Condensation

A diester can undergo an intramolecular reaction called a Dieckmann condensation.

Example 2: Dieckman Condensation



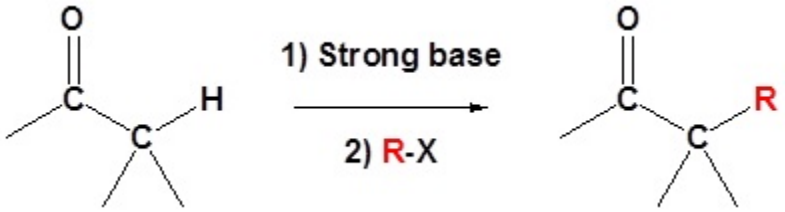
Contributors

- Prof. Steven Farmer (Sonoma State University)

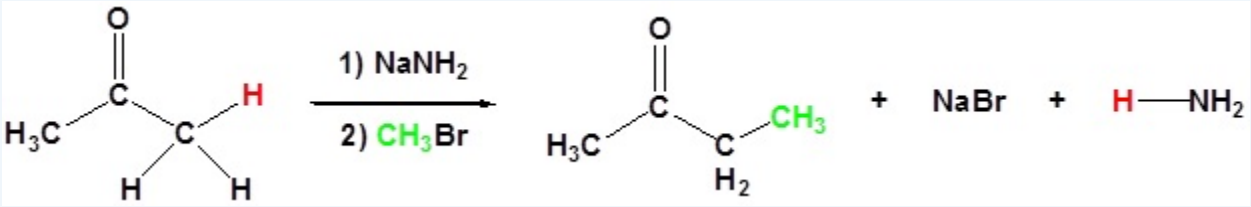
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23.2: B-Dicarbonyl Compounds as Synthetic Intermediates

Enolates can act as a nucleophile in S_N2 type reactions. Overall an α hydrogen is replaced with an alkyl group. This reaction is one of the more important for enolates because a carbon-carbon bond is formed. These alkylations are affected by the same limitations as S_N2 reactions previously discussed. A good leaving group, Chloride, Bromide, Iodide, Tosylate, should be used. Also, secondary and tertiary leaving groups should not be used because of poor reactivity and possible competition with elimination reactions. Lastly, it is important to use a strong base, such as LDA or sodium amide, for this reaction. Using a weaker base such as hydroxide or an alkoxide leaves the possibility of multiple alkylation's occurring.

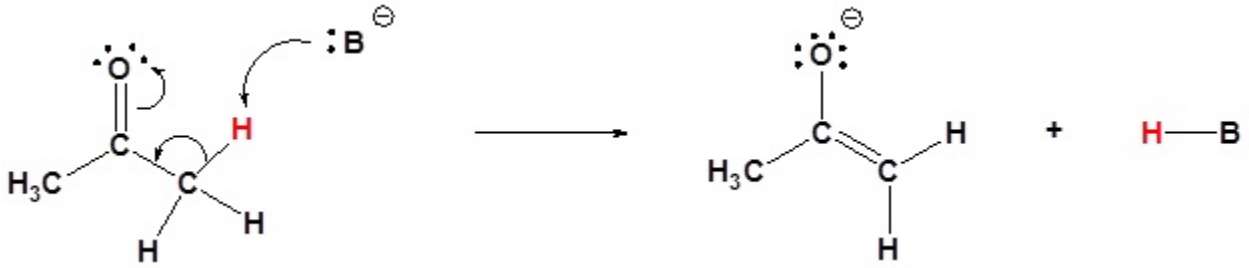


Example 1: Alpha Alkylation

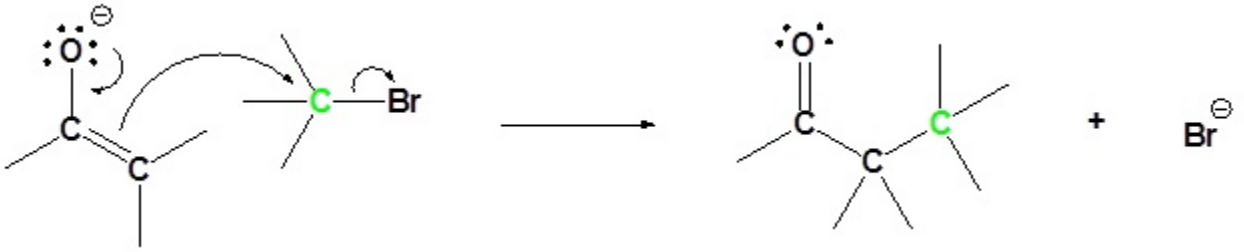


Mechanism

1) Enolate formation



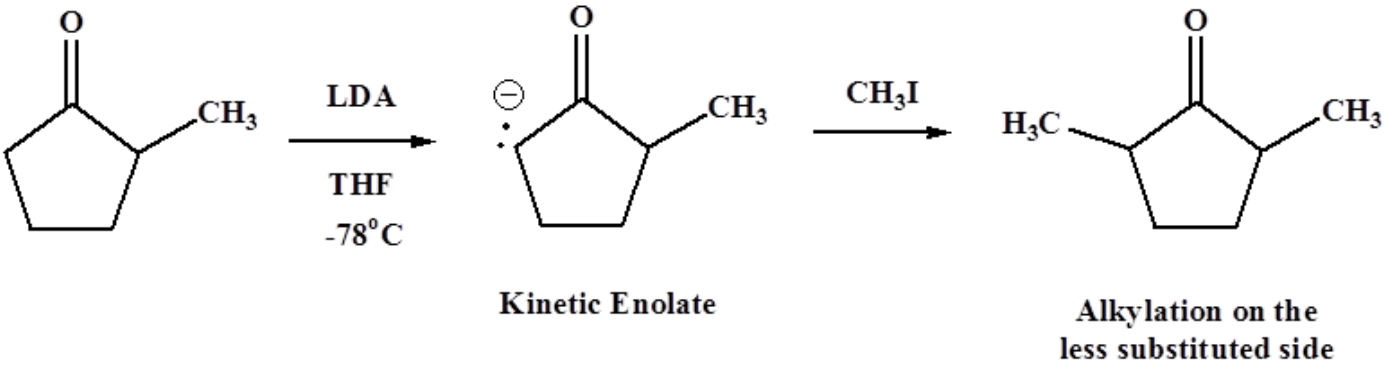
2) S_n2 attack



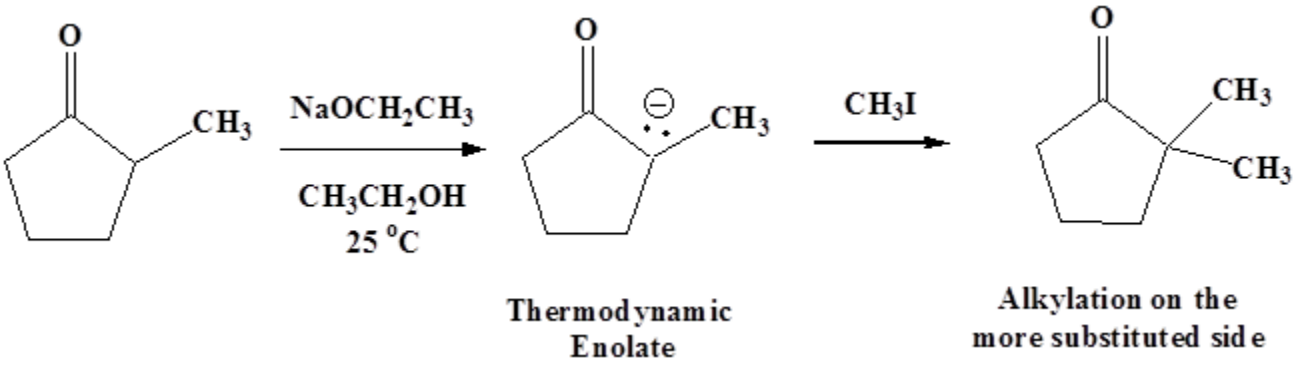
Alkylation of Unsymmetrical Ketones

Unsymmetrical ketones can be regioselctively alkylated to form one major product depending on the reagents.

Treatment with LDA in THF at -78°C tends to form the less substituted kinetic enolate.

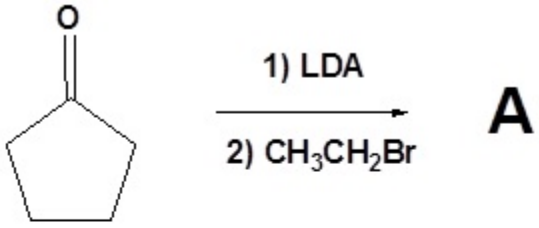


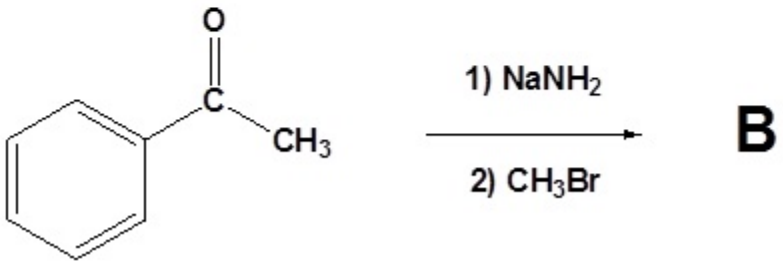
Using sodium ethoxide in ethanol at room temperature forms the more substituted thermodynamic enolate.



Problems

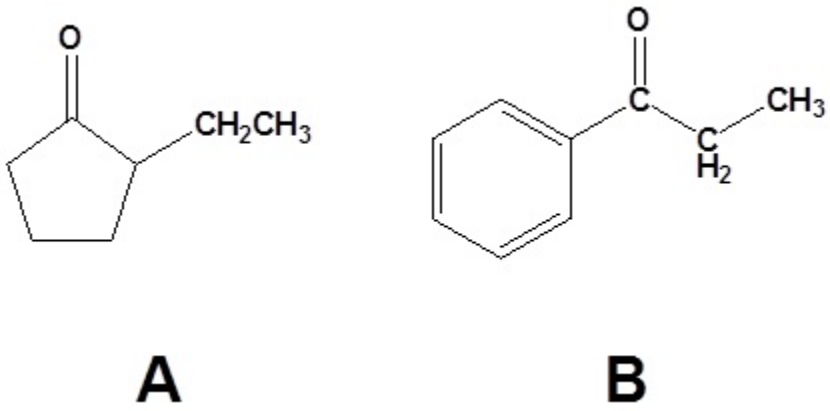
1) Please write the structure of the product for the following reactions.





Answers

1)

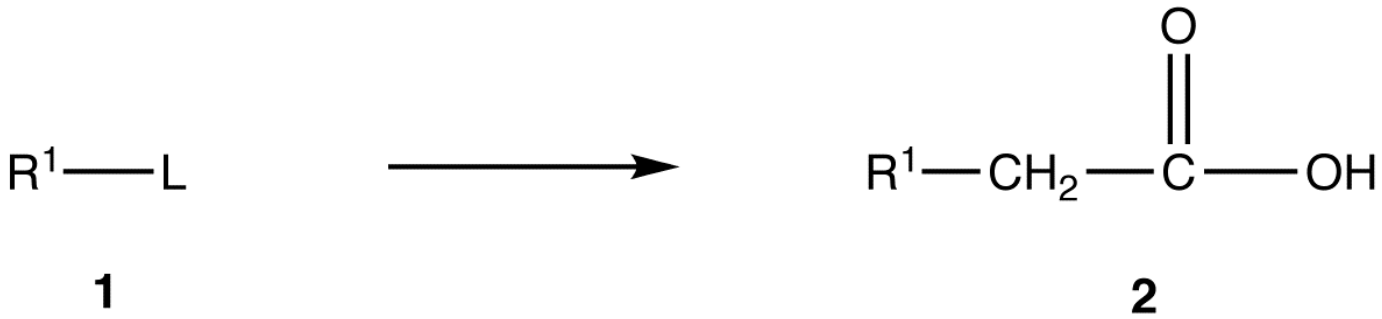


A B

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

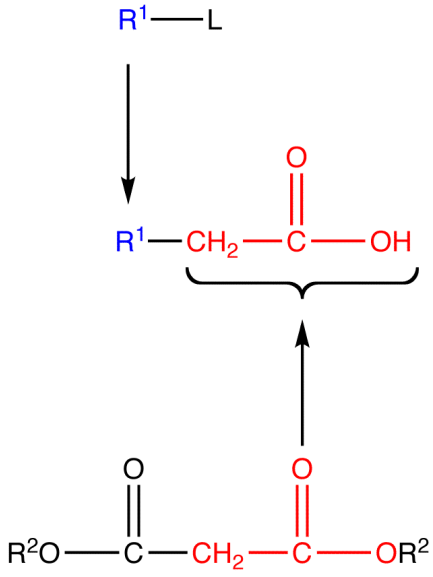
Malonic ester is a reagent specifically used in a reaction which converts alkyl halides to carboxylic acids called the Malonic Ester Synthesis. Malonic ester synthesis is a synthetic procedure used to convert a compound that has the general structural formula 1 into a carboxylic acid that has the general structural formula 2.



1 2

- R^1 = alkyl group
- L = leaving group

The group —CH_2CO_2H in 2 is contributed by a malonic ester, hence the term malonic ester synthesis.



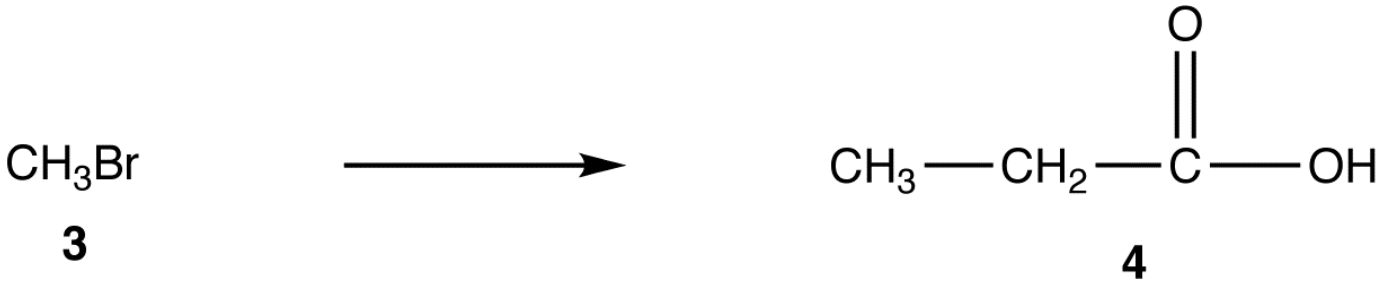
- R^2 = alkyl, aryl

Mechanism

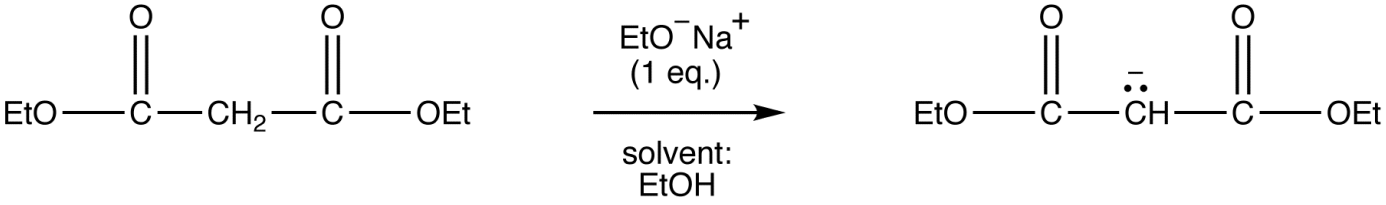
Malonic ester synthesis consists of four consecutive reactions that can be carried out in the same pot.

- reaction 1: acid-base reaction
- reaction 2: nucleophilic substitution
- reaction 3: ester hydrolysis (using saponification)
- reaction 4: decarboxylation

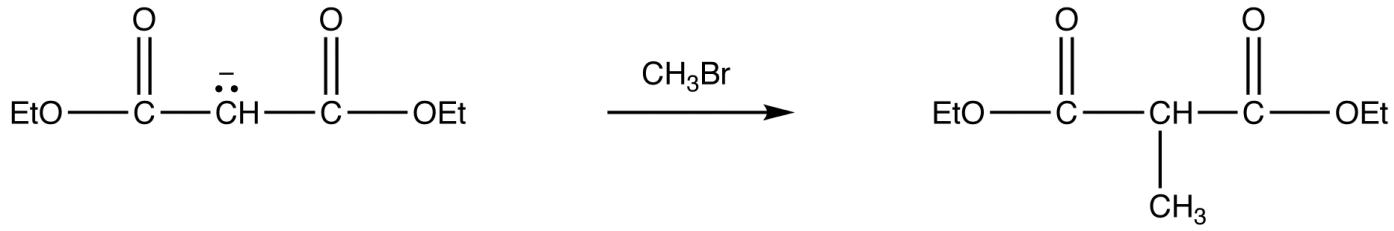
eg:



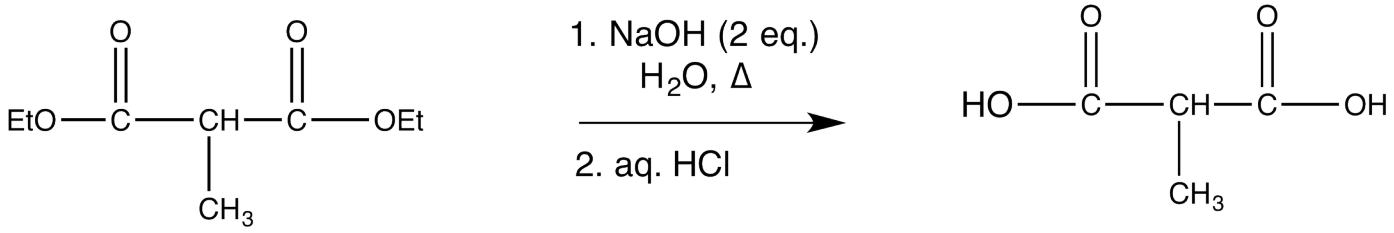
reaction 1:



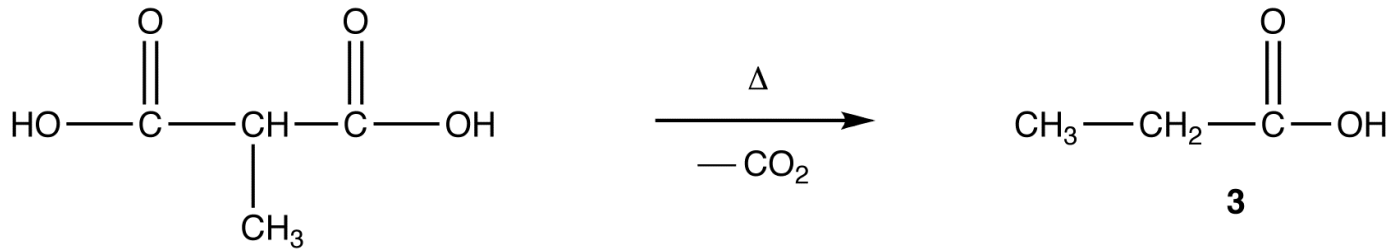
reaction 2:



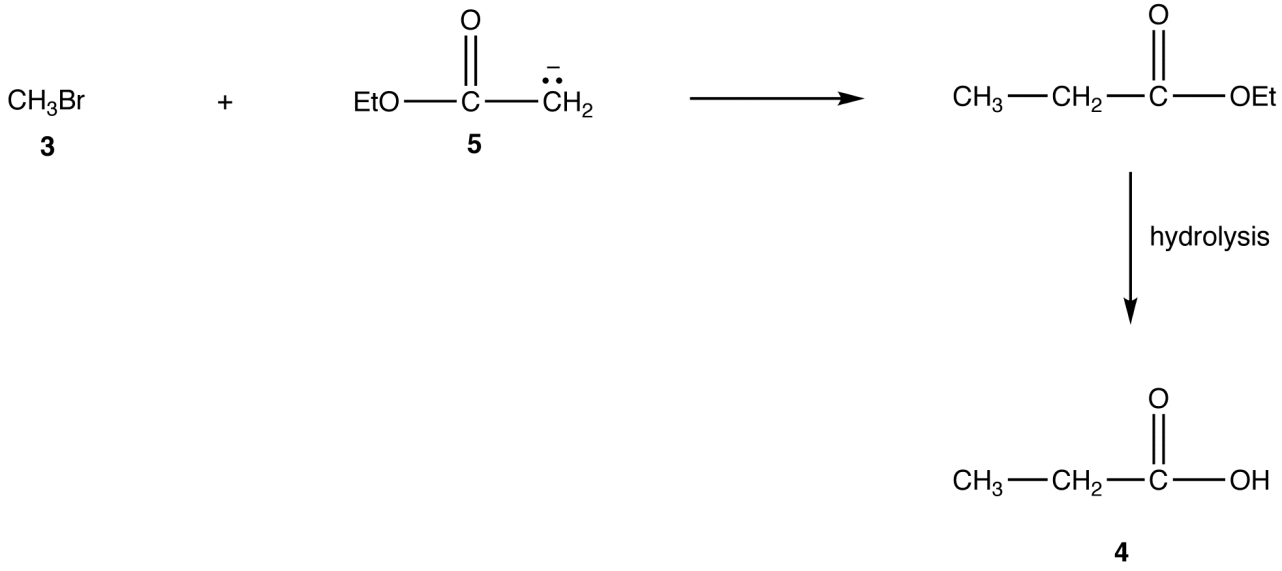
reaction 3:



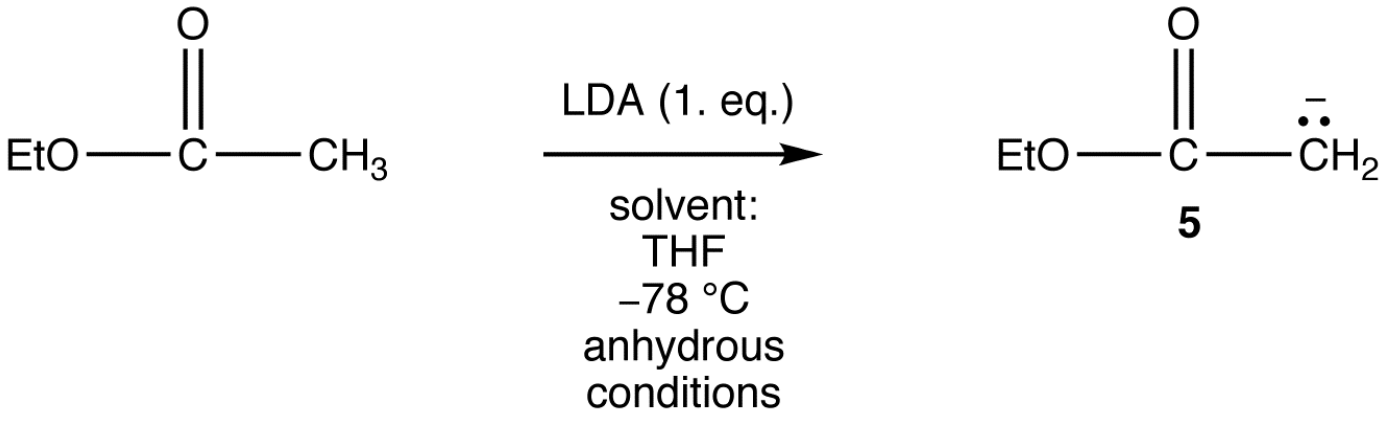
reaction 4:



A more direct method to convert **3** into **4** is the reaction of **3** with the enolate ion **(5)** of ethyl acetate followed by hydrolysis of the resultant ester.

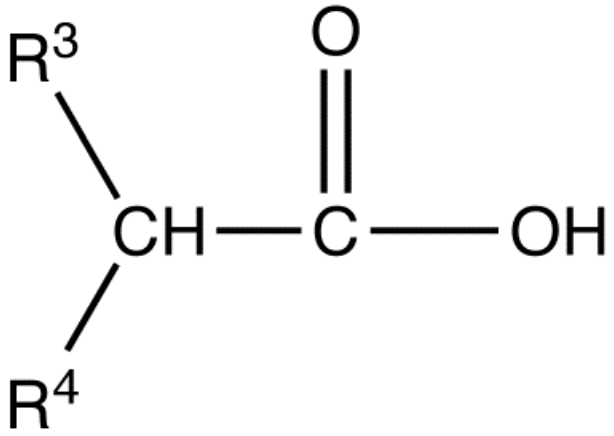


However, the generation of **5** from ethyl acetate quantitatively in high yield is not an easy task because the reaction requires a very strong base, such as LDA, and must be carried out at very low temperature under strictly anhydrous conditions.



Malonic ester synthesis provides a more convenient alternative to convert **3** to **4**.

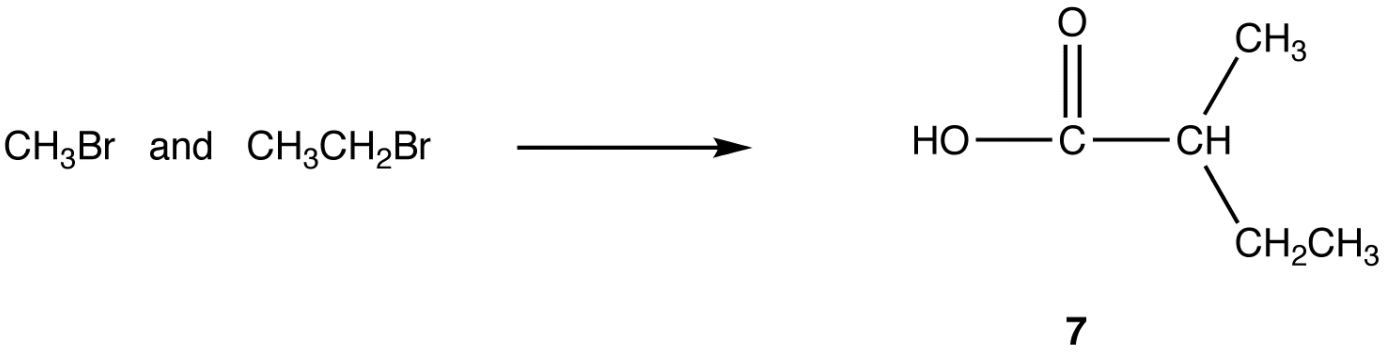
Malonic ester synthesis can be adapted to synthesize compounds that have the general structural formula **6**.



6

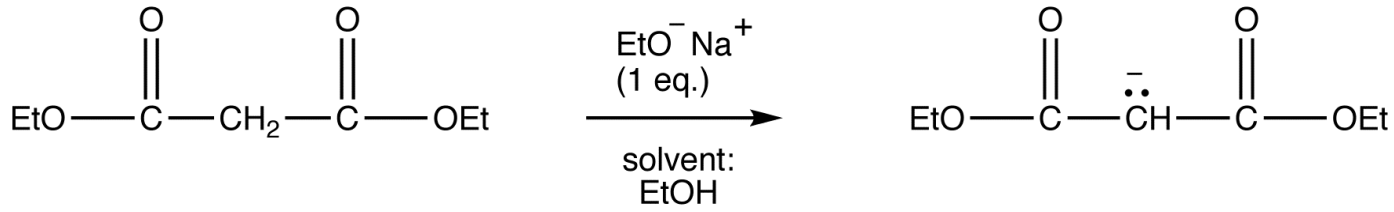
R^3, R^4 = identical or different alkyl groups

eg:

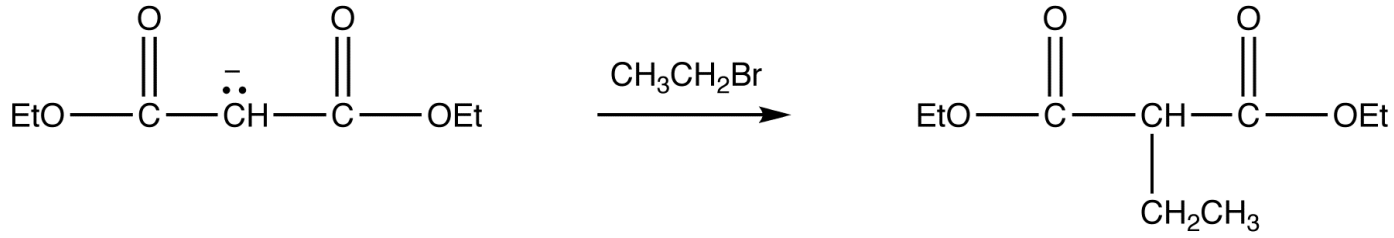


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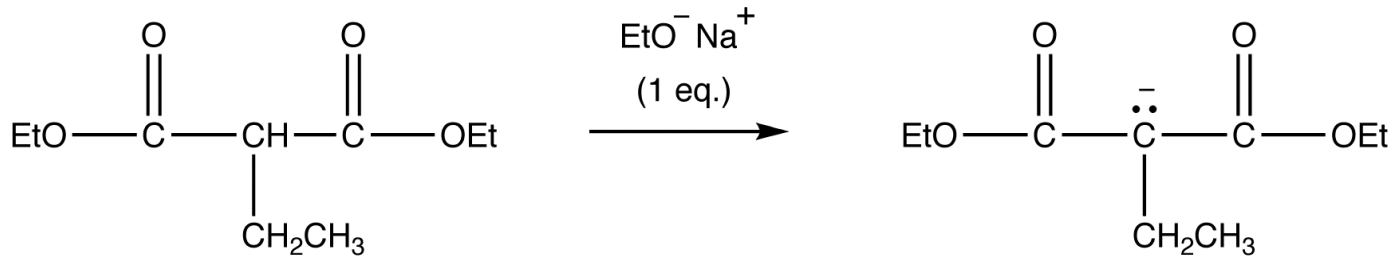
reaction 1:



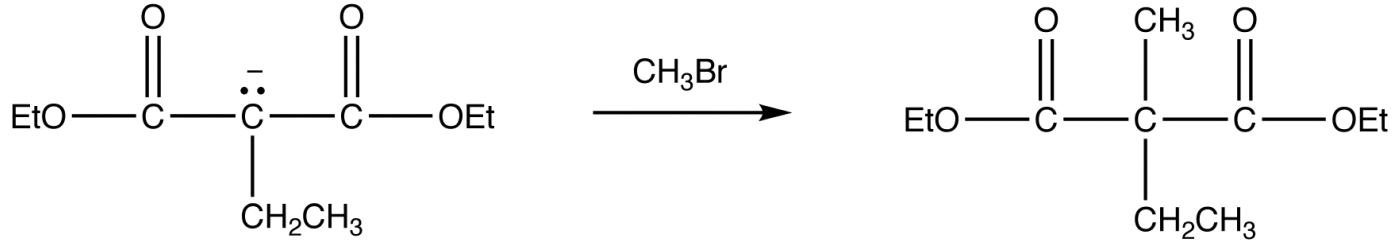
reaction 2:



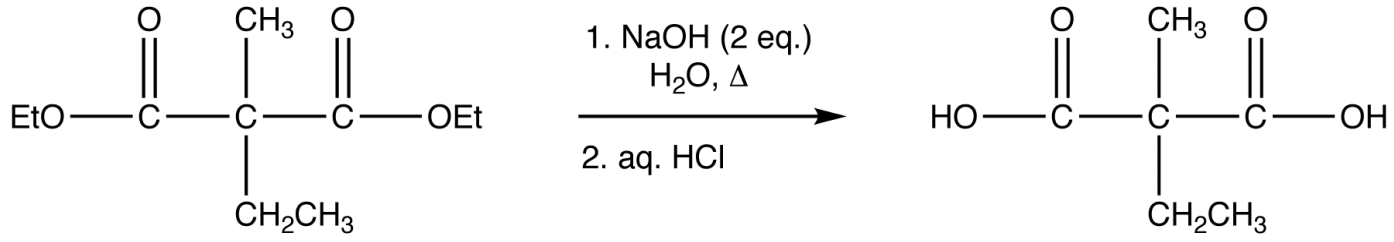
reaction 1 (repeat):



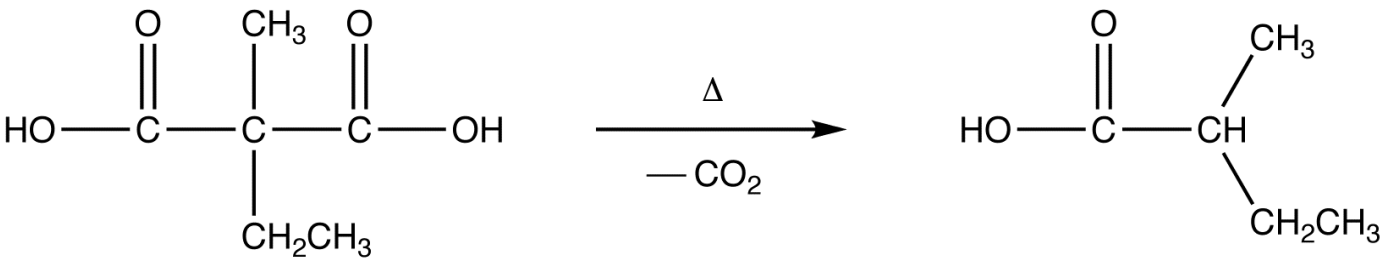
reaction 2 (repeat):



reaction 3:

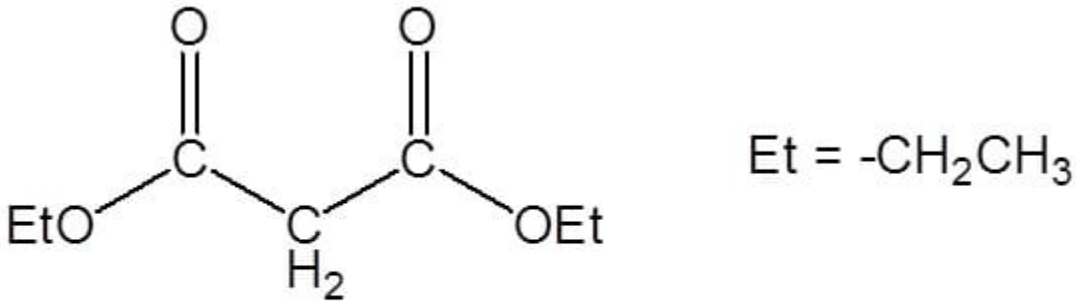


reaction 4:



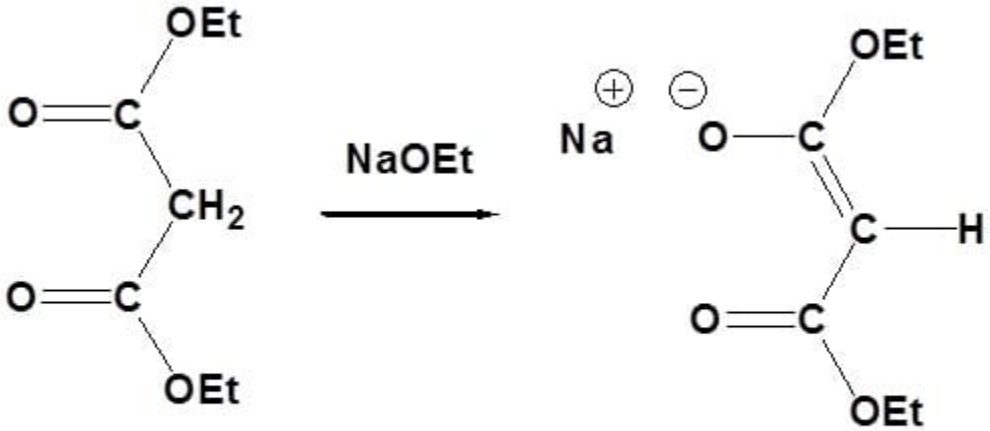
7

Malonic Ester Synthesis



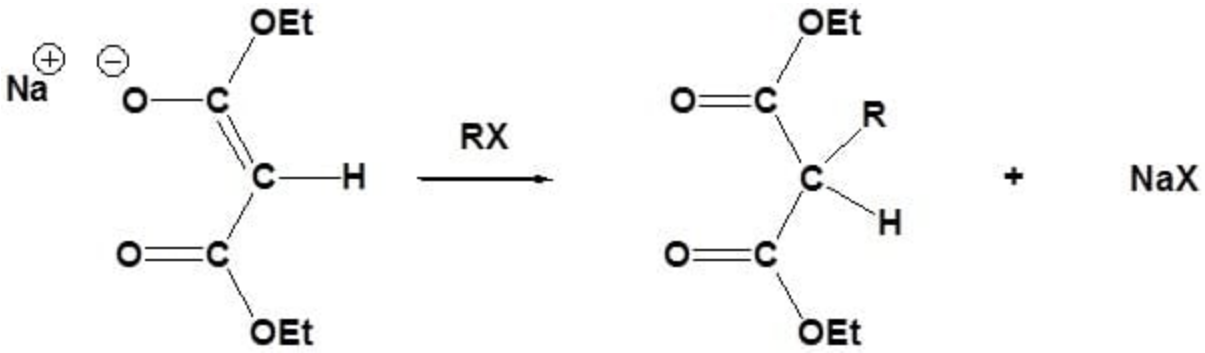
Malonic Ester

Due to the fact that Malonic ester's α hydrogens are adjacent to two carbonyls, they can be deprotonated by sodium ethoxide (NaOEt) to form Sodio Malonic Ester.

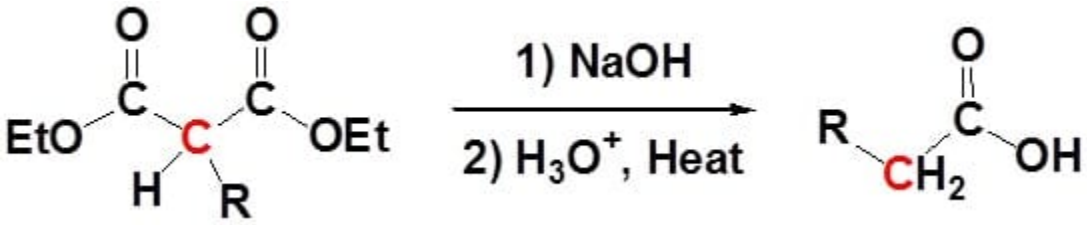


Malonic Ester **Sodio Malonic Ester**

Because Sodio Malonic Ester is an enolate, it can then be alkylated with alkyl halides.

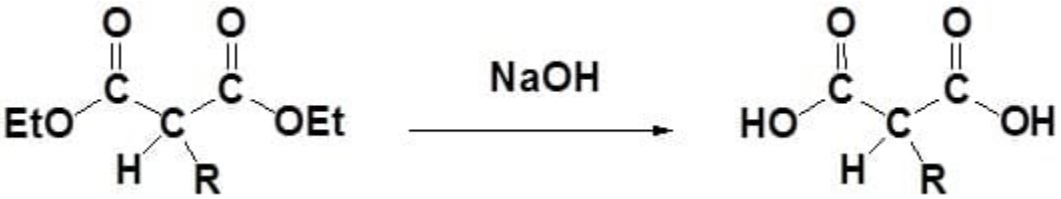


After alkylation the product can be converted to a dicarboxylic acid through saponification and subsequently one of the carboxylic acids can be removed through a decarboxylation step.

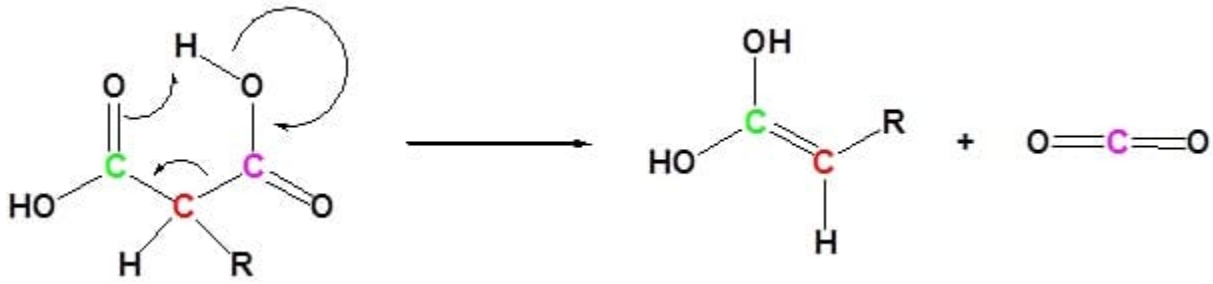


Mechanism

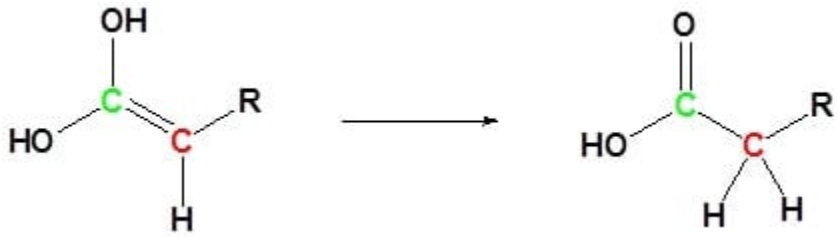
1) Saponification



2) Decarboxylation



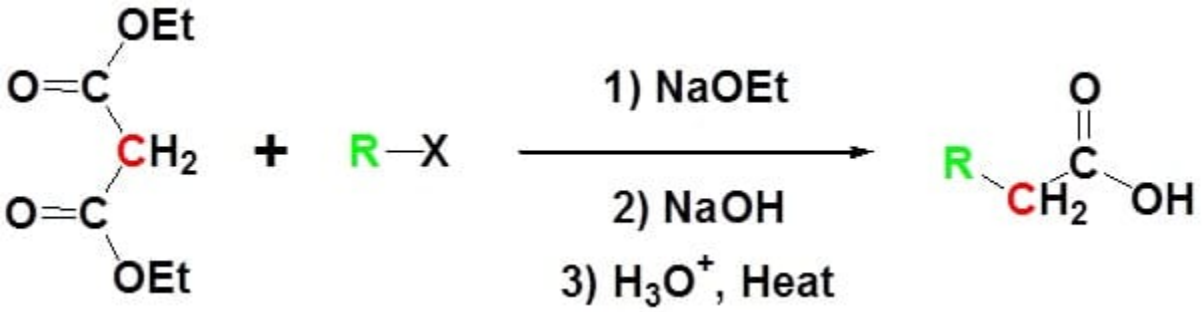
3) Tautomerization



All of the steps together form the Malonic ester synthesis.

$$RX \rightarrow RCH\text{-}_2CO_2H \tag{23.2.1}$$

Example

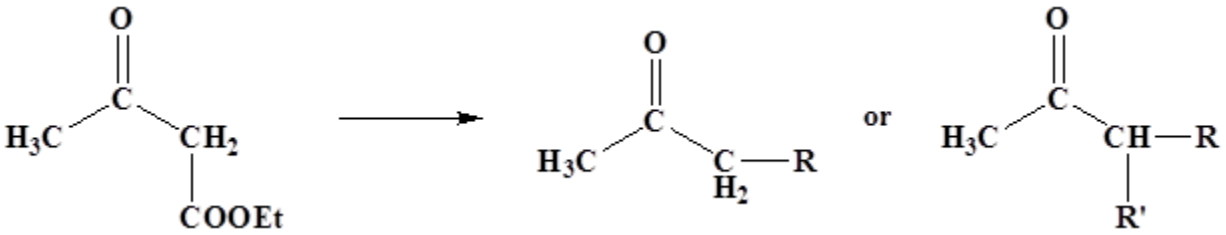


- Bernard E. Hoogenboom , Phillip J. Ihrig , Arne N. Langsjoen , Carol J. Linn and Stephen D. Mulder, The malonic ester synthesis in the undergraduate laboratory, *J. Chem. Educ.*, 1991, 68 (8), p 689

Contributors

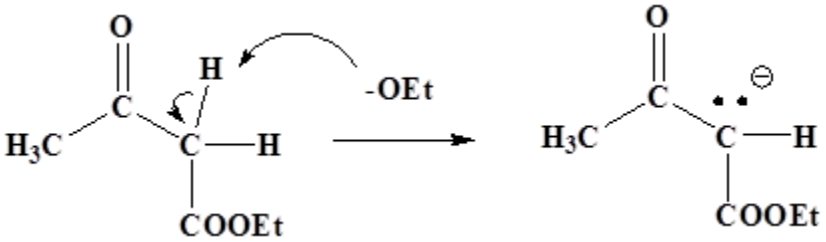
- Prof. Steven Farmer (Sonoma State University)
- ◦ Gamini Gunawardena from the OChemPal site (Utah Valley University)

The acetoacetic ester synthesis allows for the conversion of ethyl acetoacetate into a methyl ketone with one or two alkyl groups on the alpha carbon.

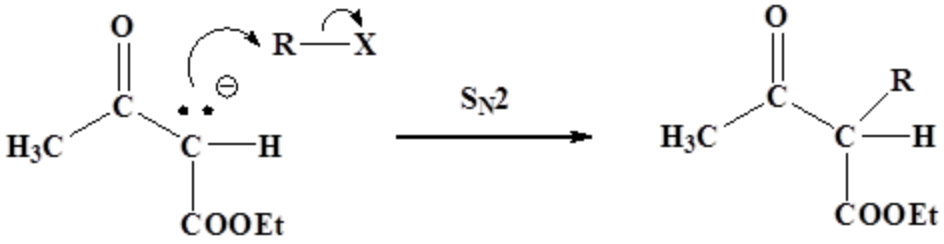


Steps

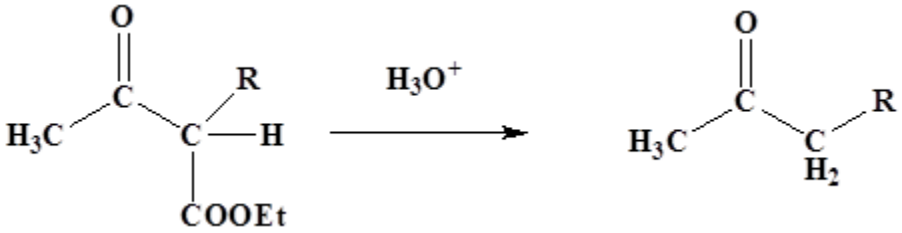
1) Deprotonation with ethoxide



2) Alkylation via and SN2 Reaction

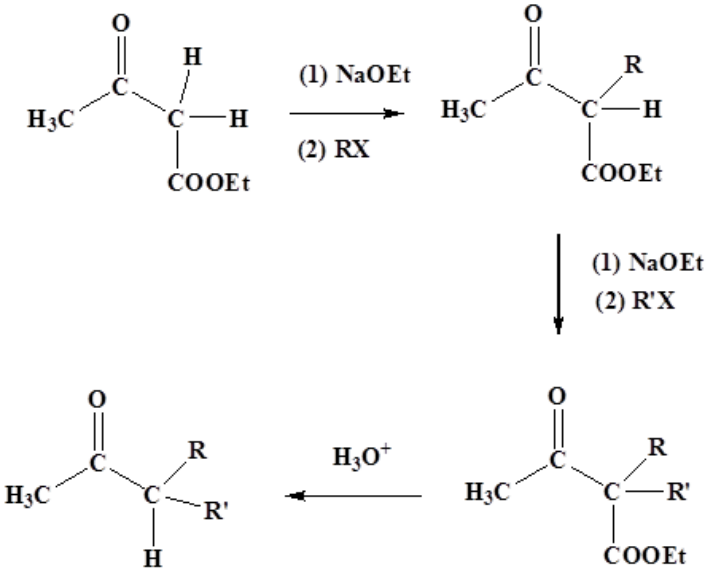


3) Hydrolysis and decarboxylation



Addition of a second alky group

After the first step and additional alkyl group can be added prior to the decarboxylation step. Overall this allows for the addition of two different alkyl groups.



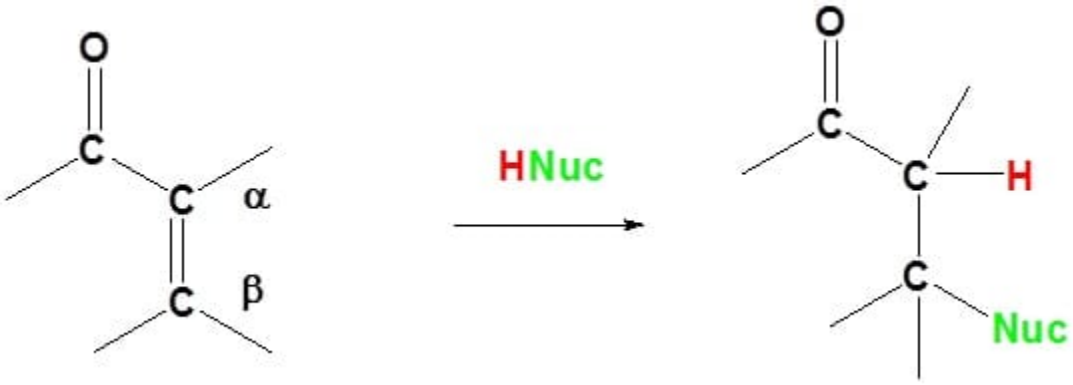
Contributors

- Prof. Steven Farmer (Sonoma State University)

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23.3: B-Dicarbonyl Anion Chemistry: Michael Additions

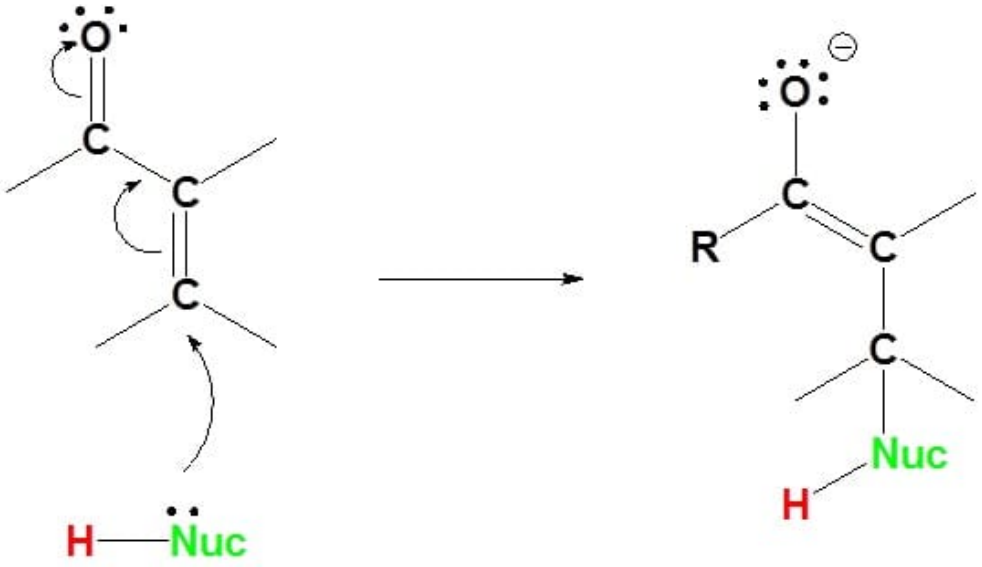
Basic reaction of 1,4 addition



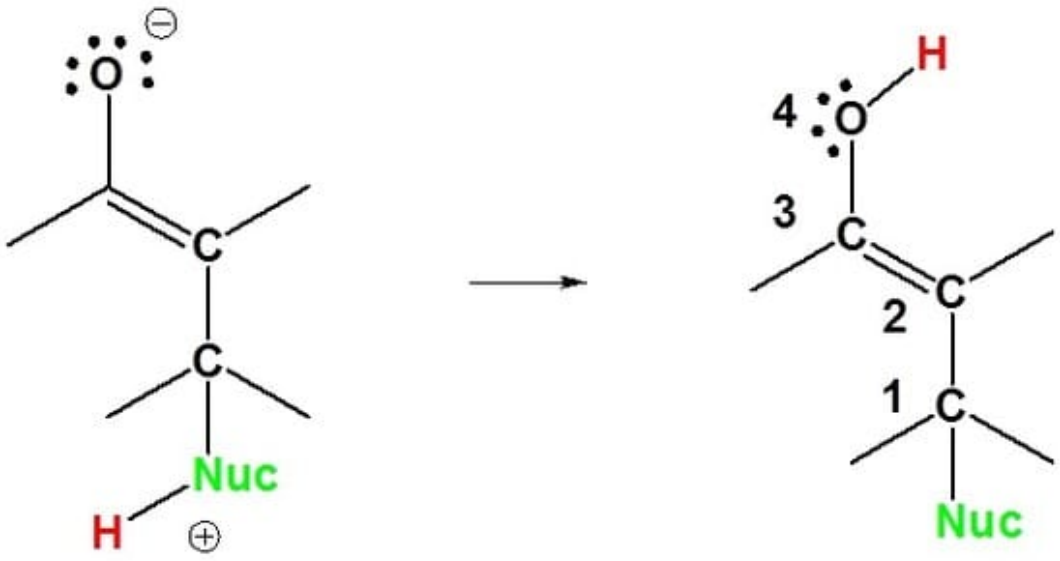
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

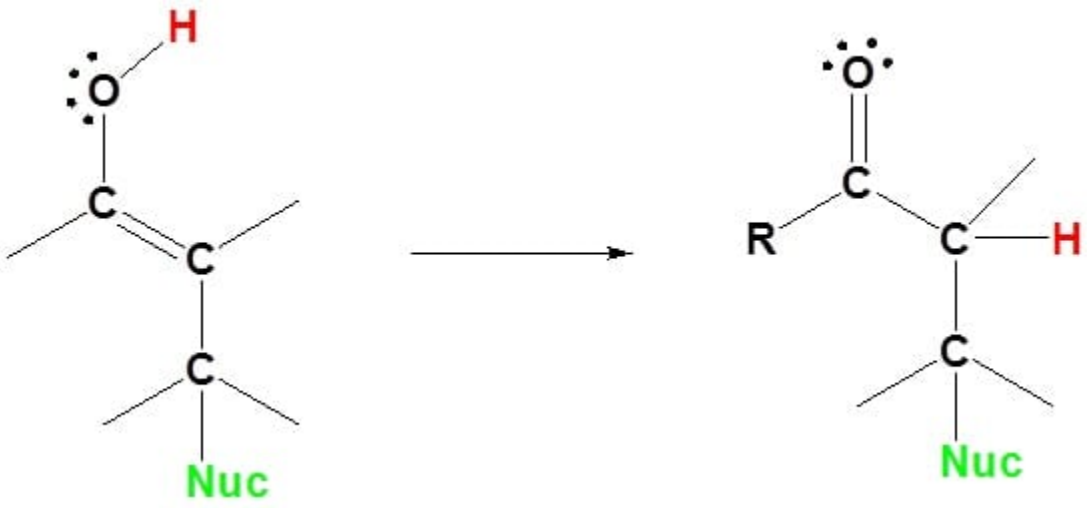


2) Proton Transfer



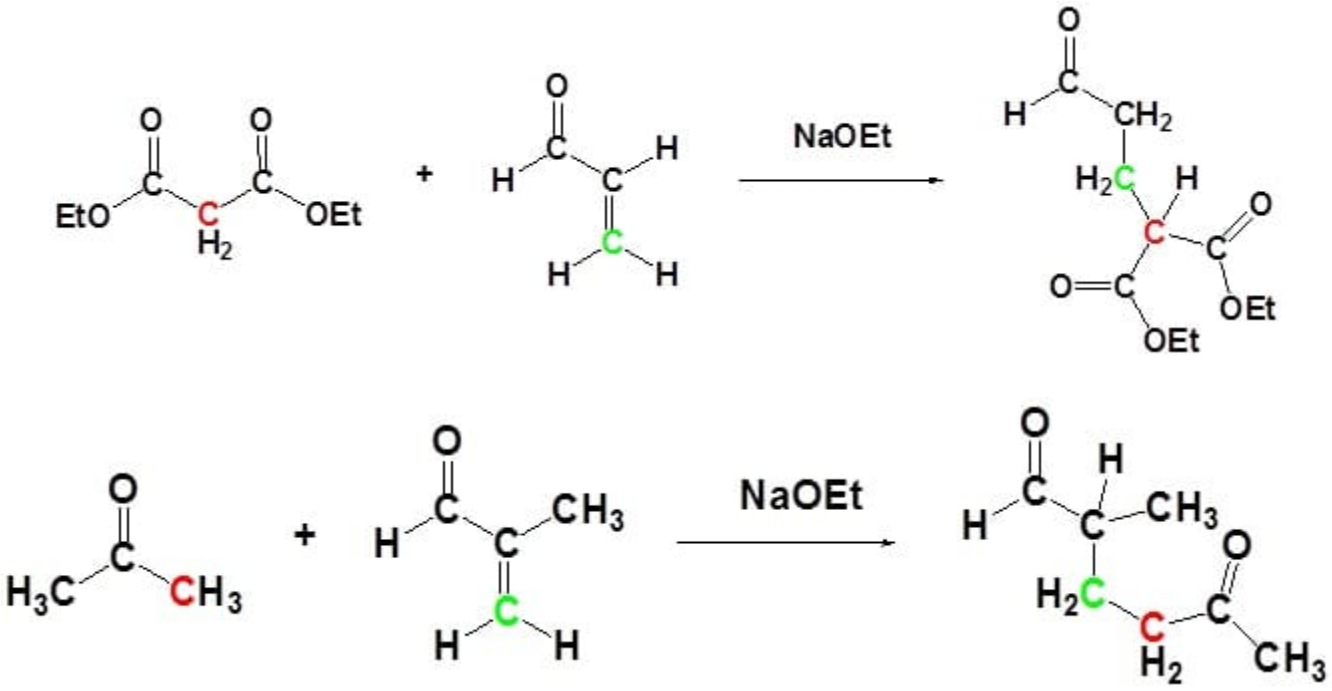
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds is a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942).

Examples of Michael Additions

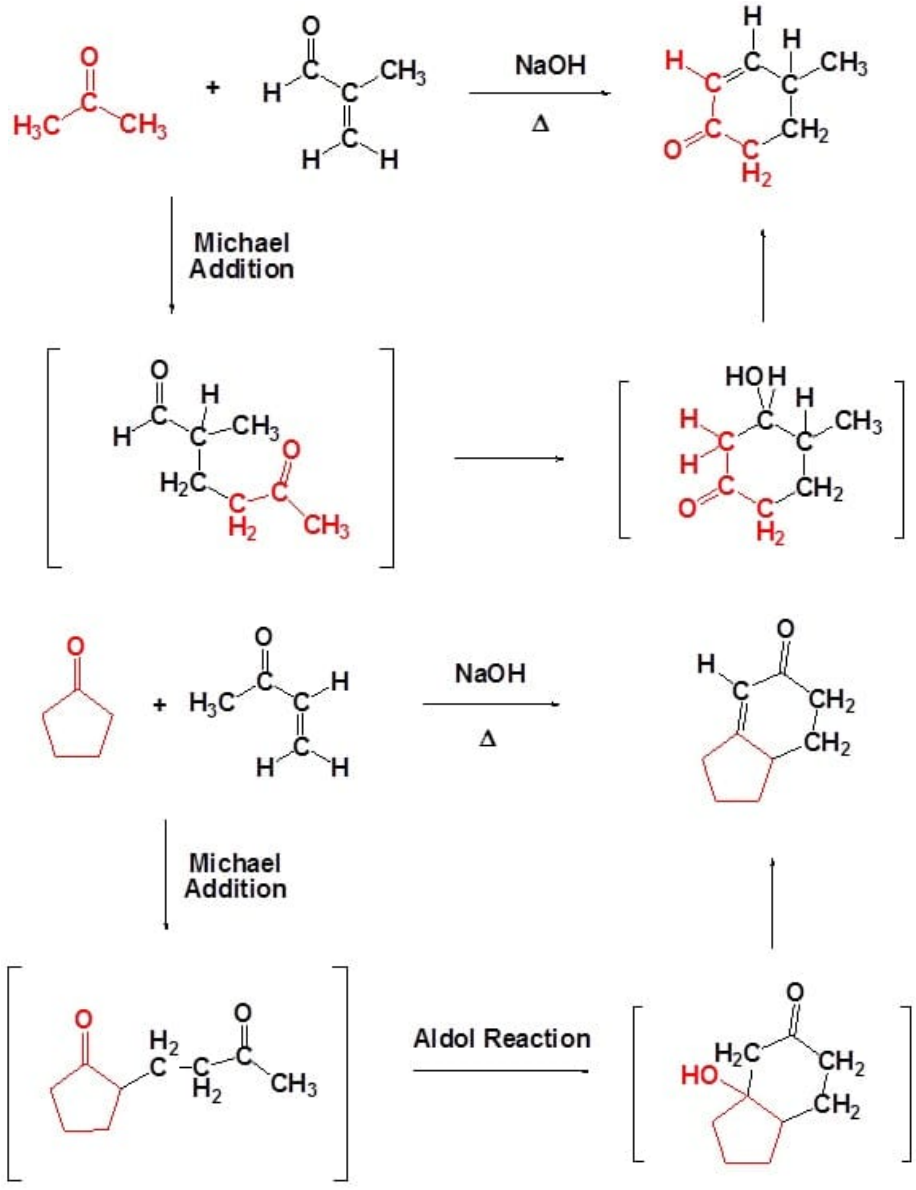


Contributors

- Prof. Steven Farmer (Sonoma State University)

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

Examples of Robinson Annulations



Contributors

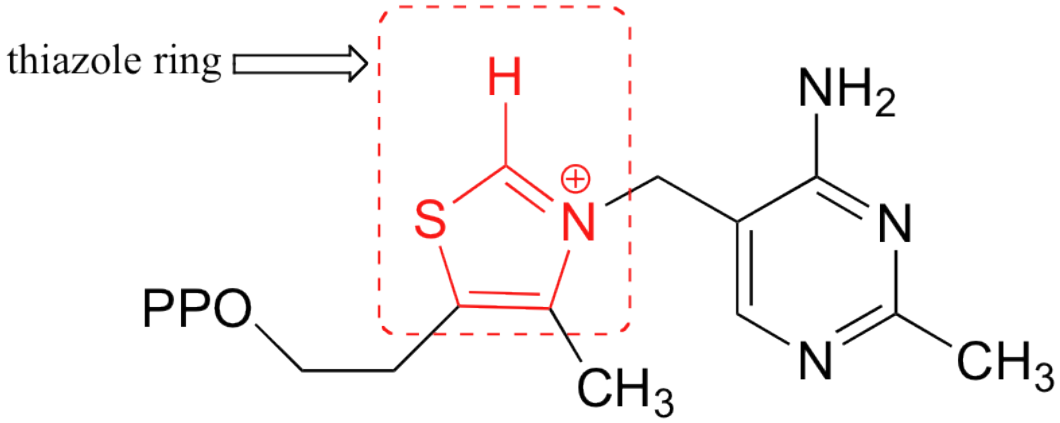
- Prof. Steven Farmer (Sonoma State University)

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23.4: Alkanoyl (Acyl) Anion Equivalents: Preparation of a-Hydroxyketones

Solutions to exercises

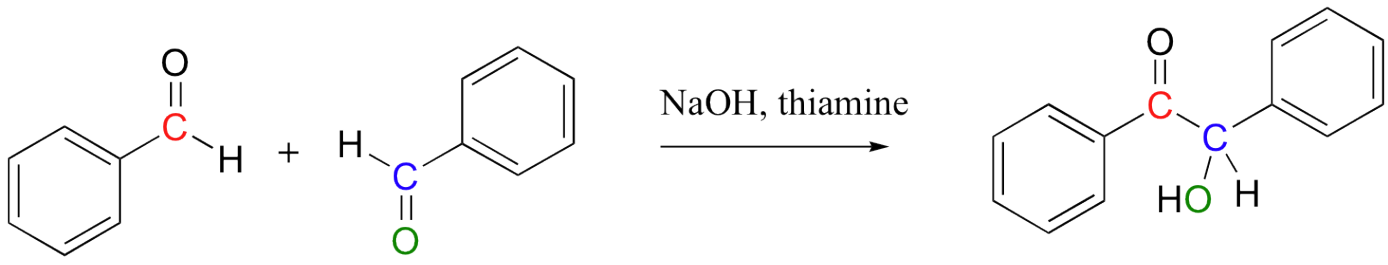
Thiamine diphosphate (TPP) is another very important coenzyme which, like PLP, acts as an electron sink to stabilize key carbanion intermediates. The important part of the TPP molecule from a catalytic standpoint is its thiazole ring.



thiamine diphosphate (TPP)

14.5A: The benzoin condensation reaction

In a very simple experiment that can performed in an undergraduate organic chemistry lab, benzaldehyde (a liquid compound at room temperature that is used as an artificial cherry flavoring) self-condenses to form benzoin (a crystalline solid) when stirred in ethanol with a catalytic amount of sodium hydroxide and thiamine.

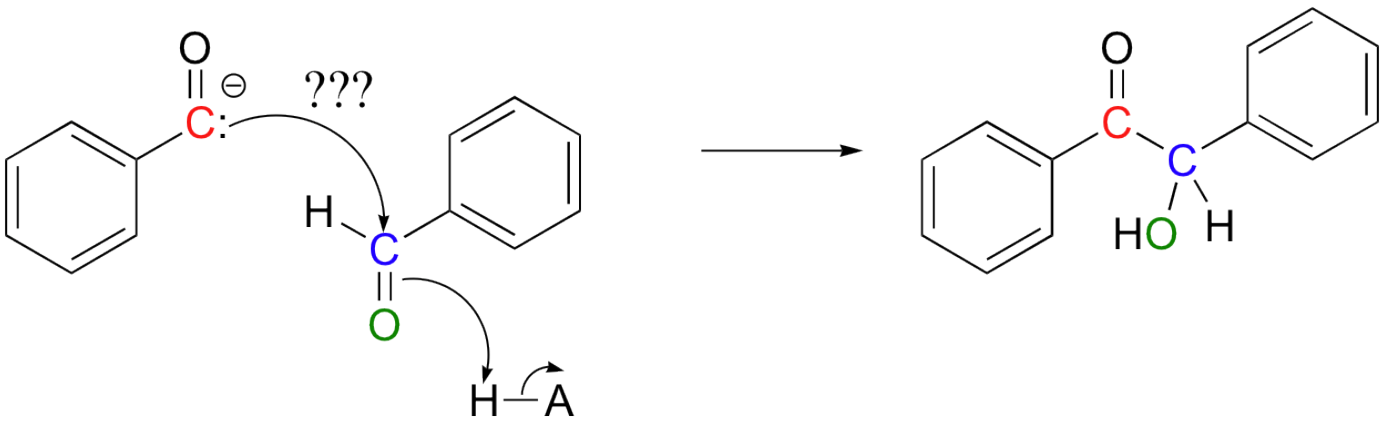


2 benzaldyhyde

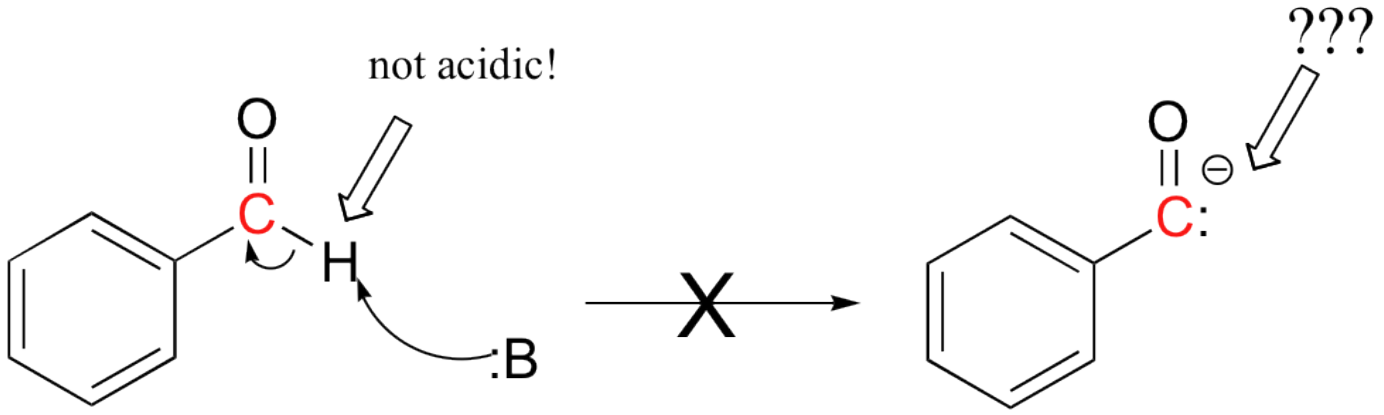
benzoin

The laboratory synthesis of benzoin is interesting because it mimics the mechanism of TPP-dependant enzymatic reactions in biological systems. This reaction is not catalyzed by an enzyme – rather, the thiamine molecule acts on its own, playing a similar catalytic role to that played by its diphosphate ester cousin (TPP) in enzymatic reactions.

Look carefully at the connectivity of the starting compounds and product in the benzoin condensation. Essentially what has happened is that the carbonyl carbon of one benzaldehyde molecule has somehow been turned into a nucleophile, and has attacked a second benzaldehyde molecule in a nucleophilic carbonyl addition reaction.

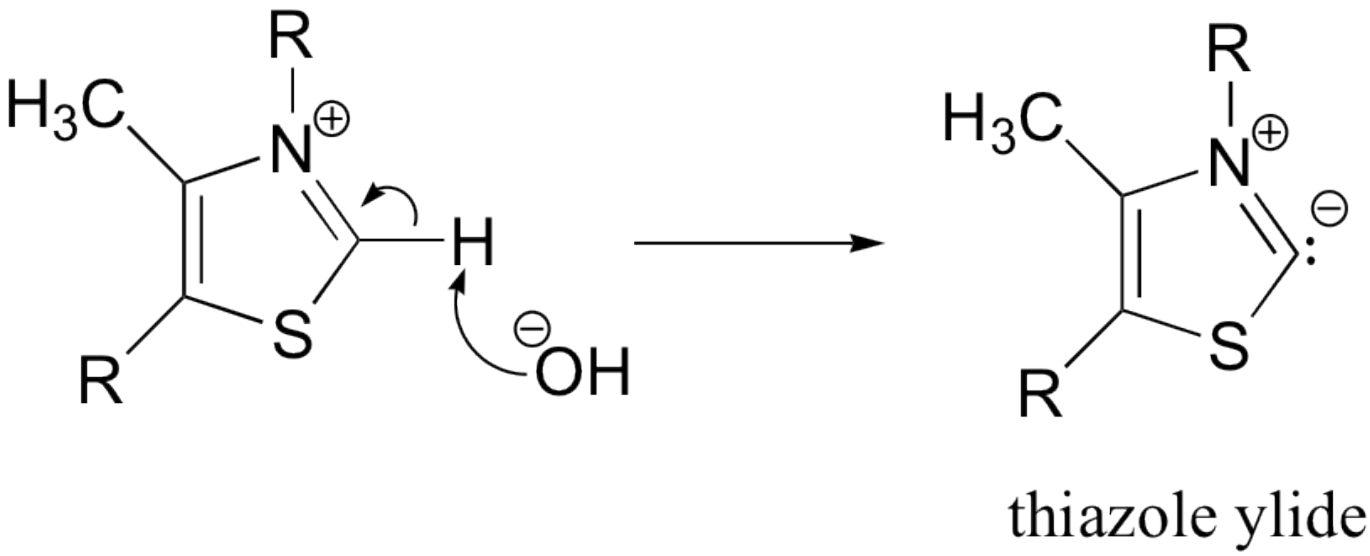


This probably seems quite strange - we know that carbonyl carbons are good electrophiles, but how can they be *nucleophilic*? For the aldehyde carbon to be a nucleophile, it would have to be deprotonated, and become a carbonyl anion. But aldehyde protons are not at all acidic!



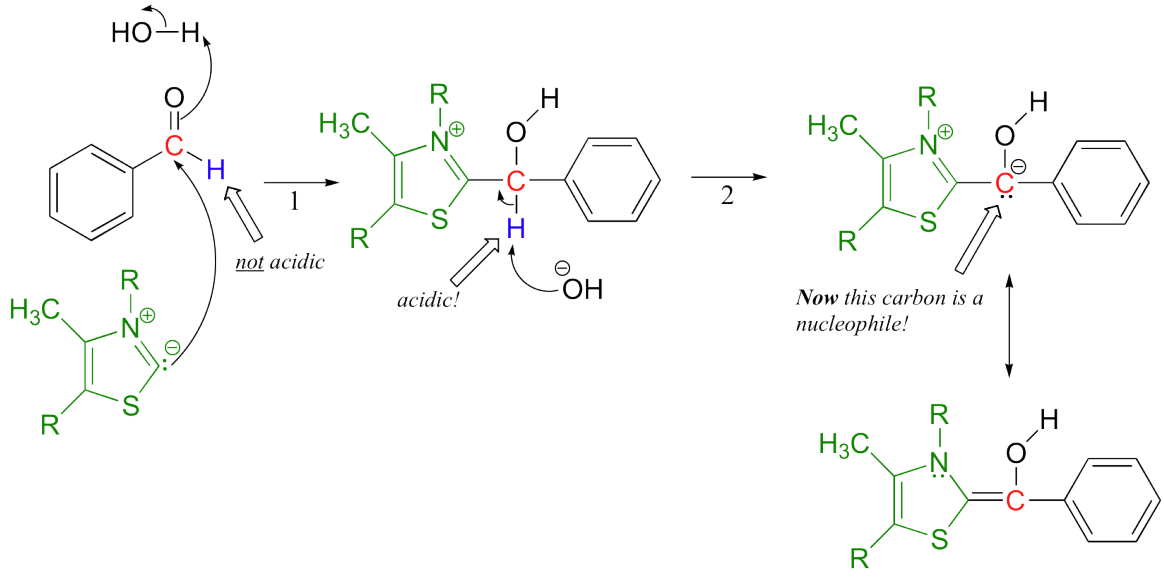
The thiamine catalyst is the key: it allows the formation of what is essentially the *equivalent* of a nucleophilic benzaldehyde carbanion. Let's follow the benzoin condensation reaction mechanism through step-by-step, and see how thiamine accomplishes this task.

The important part of the thiamine molecule is the thiazole ring (look again at the structure of thiamine diphosphate on the previous page), thus we will draw thiamine (and later, thiamine diphosphate) using R groups to depict the unreactive parts of the molecule. The first step of the benzoin condensation is deprotonation of thiamine by hydroxide.



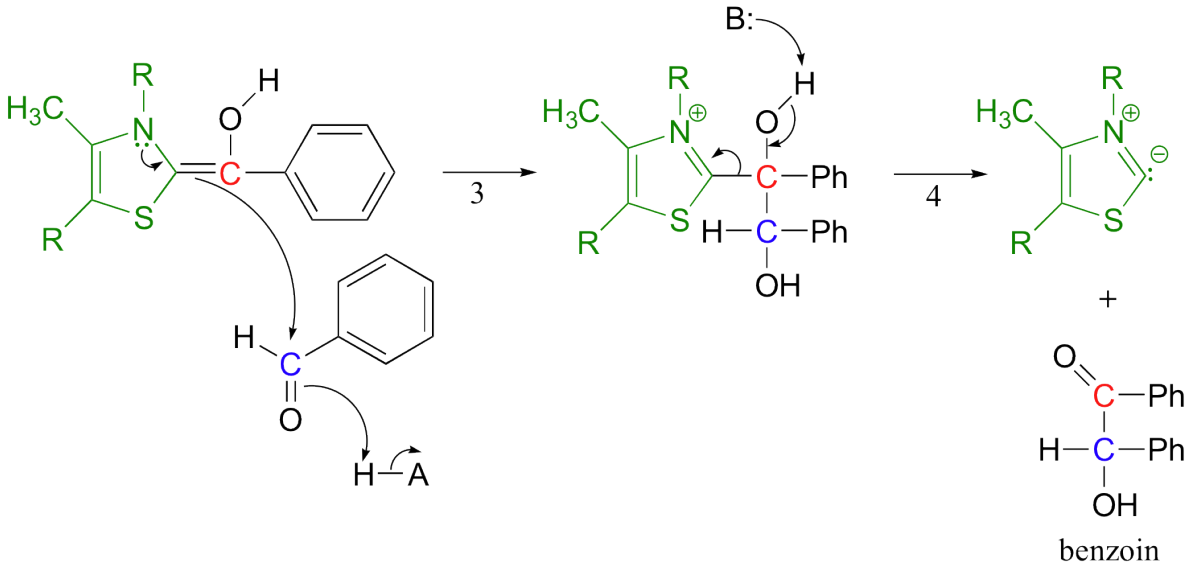
It may surprise you to learn that this proton is acidic. The reason for its acidity lies partly in the ability of the neighboring sulfur atom to accept, in its open d orbitals, some of the excess electron density of the conjugate base. Another reason is that the positive charge on the nitrogen helps to stabilize the negative charge on the conjugate base. The deprotonated thiazole is called an **ylide,** which is a species with adjacent positively and negatively charged atoms.

The negatively charged carbon on the thiazole ylide next attacks the carbonyl of the first benzaldehyde molecule in a nucleophilic carbonyl addition (from here on out, thiamine will be colored green in order to help you to focus on the chemistry going on with the substrate).



In the resulting molecule, *what used to be the aldehyde hydrogen is now acidic* - this is so because, when the proton is abstracted by hydroxide, the negative charge on the conjugate base is stabilized by resonance with the positively-charged thiazole ring of thiamine. This is the function of thiamine: *it acts as an electron sink*, accepting electron density so as to allow for the formation of what amounts to a carbonyl anion.

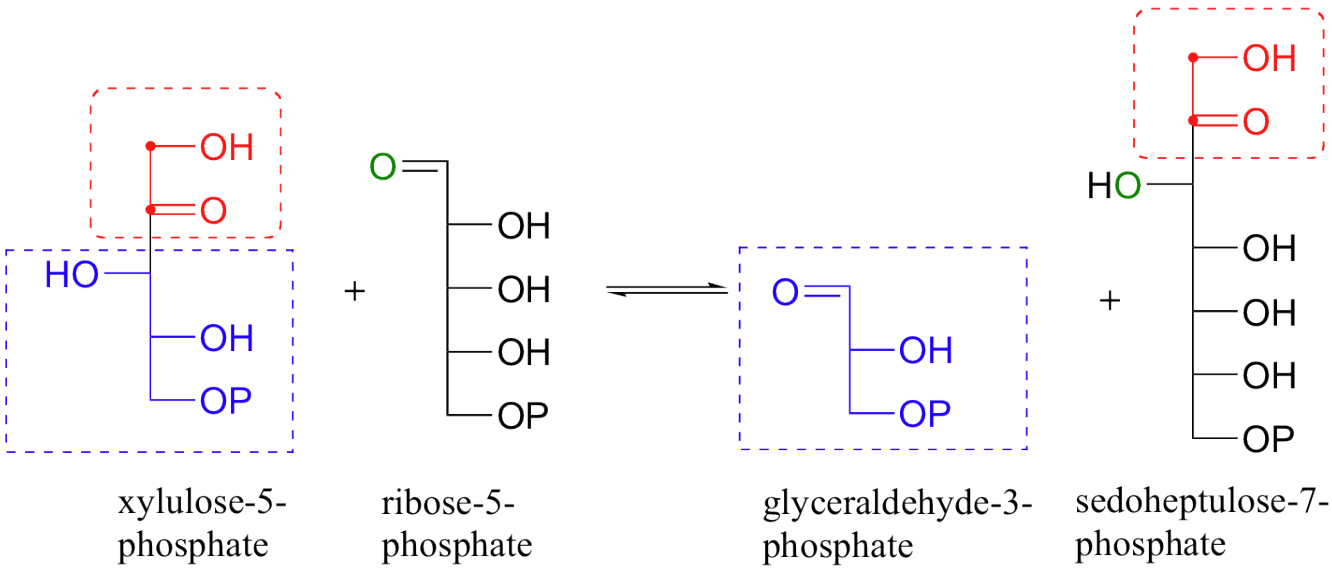
Now the first benzaldehyde molecule, assisted by thiamine, can finally act as a nucleophile, attacking the carbonyl of a second benzaldehyde (step 3).



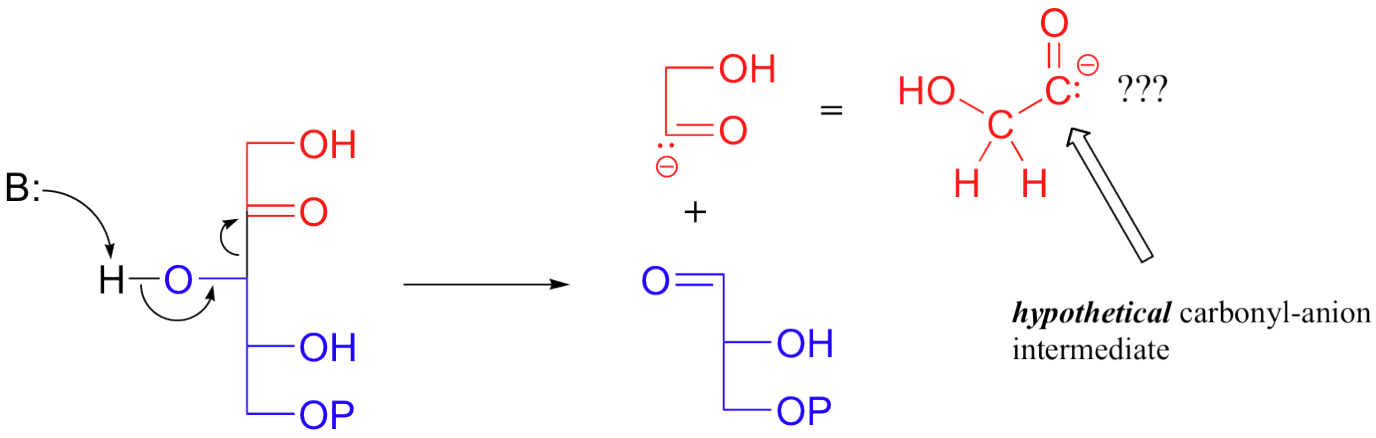
Once this is accomplished, the thiamine ylide can be kicked off as the original carbonyl on the first benzaldehyde re-forms (step 4). The thiamine ylide is now free to catalyze another reaction.

14.5B: The transketolase reaction

Now let's look at a biochemical reaction carried out by an enzyme called transketolase, with the assistance of thiamine diphosphate. Transketolase is one of a series of enzymes (along with ribulose-5-phosphate-3-epimerase, which we considered in section 13.2B) in the 'Calvin cycle' of carbon fixation in plants. Animals and bacteria also use transketolase in sugar metabolism. In the transketolase reaction, a 2-carbon unit (in the smaller, red box) is transferred between two sugar molecules:

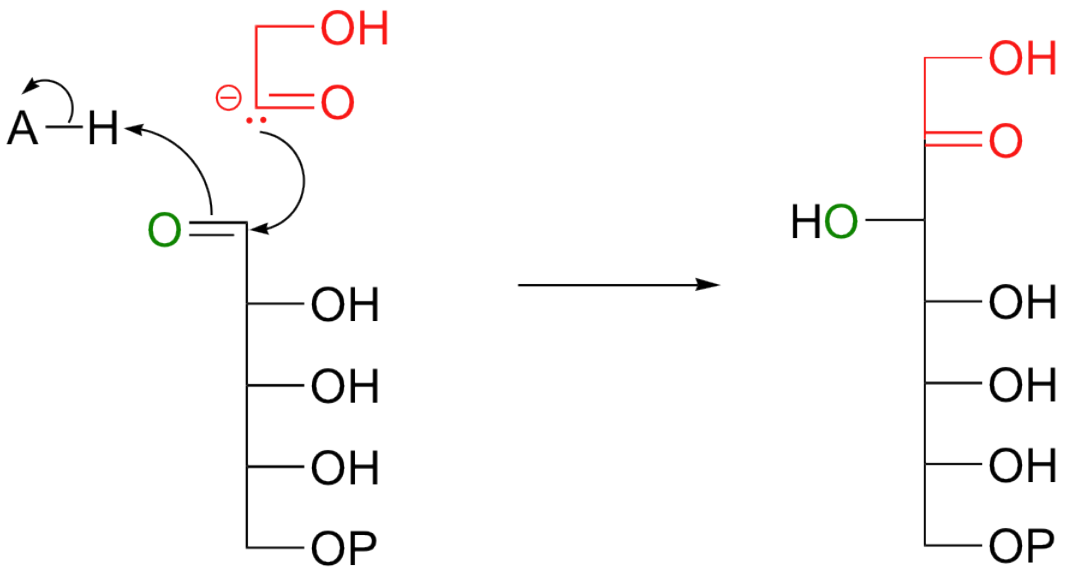


First, let's consider how this reaction might *hypothetically* proceed without the assistance of the TPP cofactor. The breaking off of the 2-carbon unit from fructose-6-phosphate might be depicted as a kind of retro-aldol event:

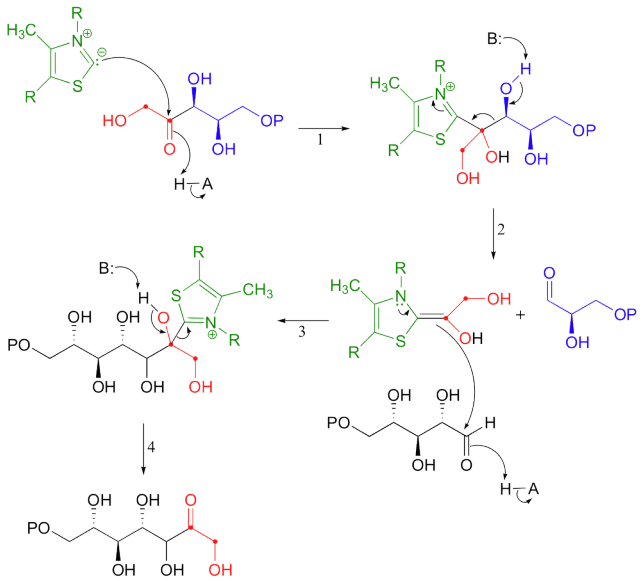


This would lead to glyceraldehyde-3-phosphate, the first product, plus an intermediate in the form of a carbonyl anion.

Continuing to think hypothetically, this strange 2-carbon ionic intermediate could attack the glyceraldehyde-3-phosphate carbonyl, resulting in sedoheptulose-7-phosphate, the second product.



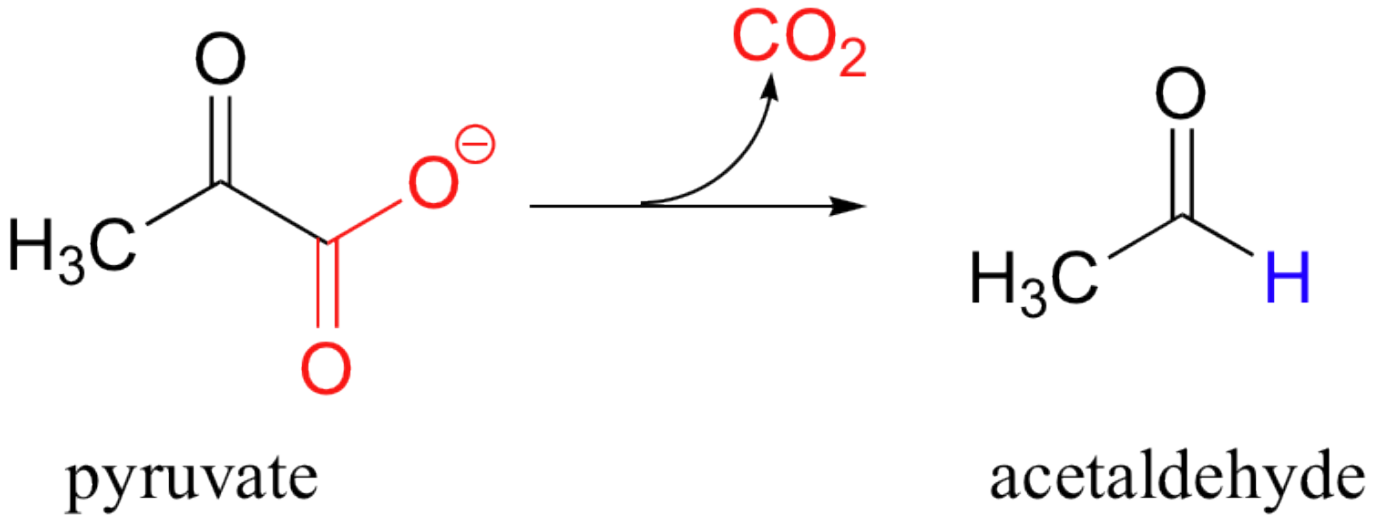
Everything in this hypothetical scenario is fine, chemically speaking, with one major exception: the carbonyl anion intermediate. It would be an extremely high energy, unlikely species. But we have seen something like this before, haven't we, in the non-enzymatic benzoin condensation reaction above! This is exactly the kind of carbanion that thiamine (this time in its diphosphate form, TPP) makes possible. The carbonyl anion is generated in different ways in the two reactions: in the benzoin condensation it is the result of the deprotonation of benzaldehyde, while in the transketolase it results from a retro-aldol-like cleavage. But that doesn't really matter - what does matter is that in each case, a thiazole ring is present to modify the starting carbonyl group and act as an electron sink, allowing it to take on a negative charge. Here, then, is the real (as opposed to hypothetical) transketolase reaction, with the role of TPP revealed.



Make sure that you can follow the electron movement throughout the mechanism, that you can see how TPP acts as an electron sink cofactor, and that you clearly recognize the mechanistic parallels to the benzoin condensation.

14.5C: Pyruvate decarboxylase

The thiamine diphosphate coenzyme also assists in the decarboxylation of an acyl group, such as in this reaction catalyzed by pyruvate decarboxylase (this is a key reaction in the fermentation of glucose to ethanol by yeast):



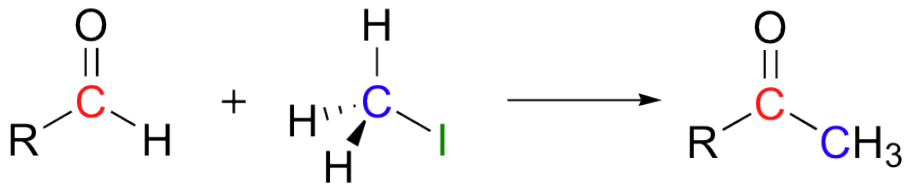
In this example, the TPP-stabilized carbonyl carbanion simply acts as a base rather than as a nucleophile, abstracting a proton from an enzymatic acid to form acetaldehyde.

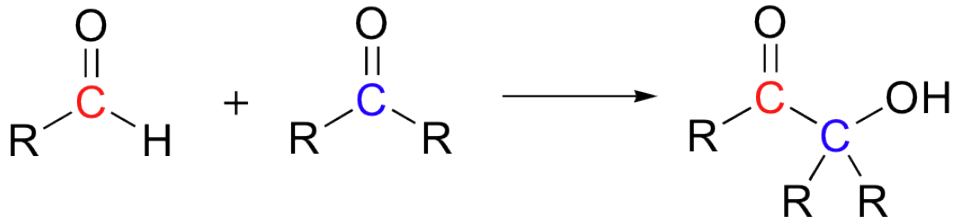
Example 14.7

Propose a mechanism for the reaction catalyzed by pyruvate decarboxylase.

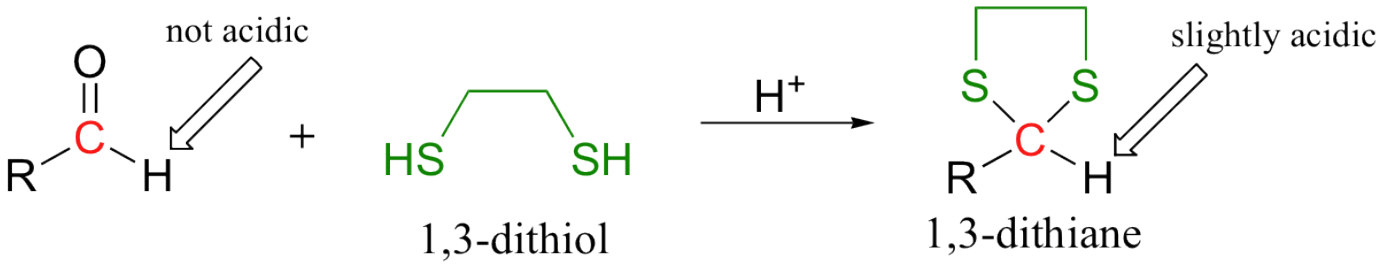
14.5D: Synthetic parallel - carbonyl nucleophiles *via* dithiane anions

Nature uses thiamine to generate the equivalent of a nucleophilic carbonyl anion, but with the specific exception of the benzoin condensation, a chemist working in an organic synthesis laboratory before the mid-1970's had no equivalent procedure. In 1975, E. J. Corey and Dieter Seebach reported that they had developed a method to accomplish reactions such as the following, in which aldehyde carbons act as nucleophiles in S_N2 and carbonyl addition reactions (*J. Org. Chem.* **1975**, *40*, 231).

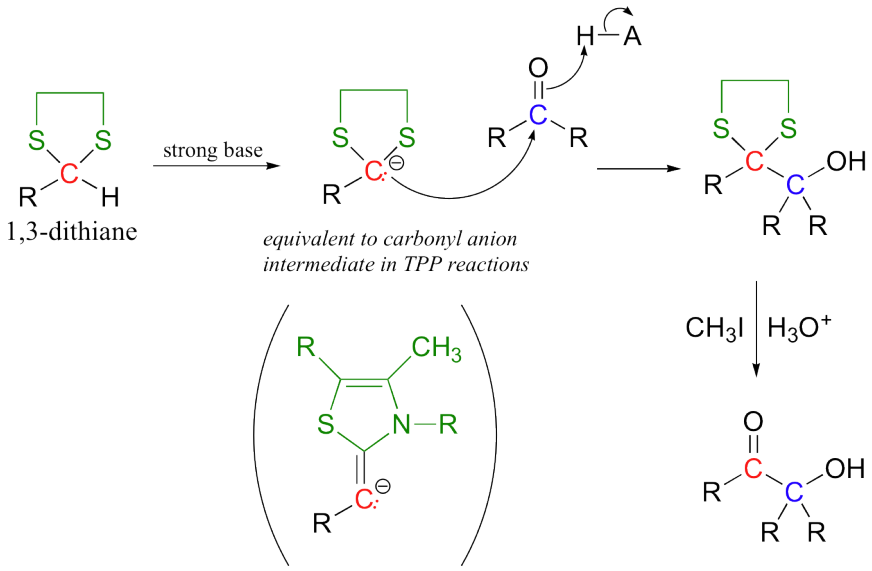




In this technique, the aldehyde is first converted to a cyclic thioketal using 1,3-propanedithiol and acid catalyst - this is the same as the method used to 'protect' aldehydes as cyclic acetals, discussed in section 11.4B, except that a di**thi**ol is used instead of a diol.



The original aldehyde proton is now somewhat acidic, because the empty d orbitals on the two adjacent sulfur atoms are able to delocalize excess electron density of the conjugate base. A strong base, such as an organolithium compound (section 13.6B) will deprotonate the cyclic thioacetal, which can then act as a nucleophile, attacking an alkyl halide or a carbonyl electrophile (the latter case is illustrated below):



The thioacetal can then be hydrolyzed back to an aldehyde group, a process that is facilitated by the use of methyl iodide.

Example 14.8

Show a mechanism for the hydrolysis of a cyclic thioacetal, in the presence of catalytic acid and methyl iodide. Propose a role for methyl iodide in this reaction.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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24: CARBOHYDRATES: POLYFUNCTIONAL COMPOUNDS IN NATURE

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

24.1: Names and Structures of Carbohydrates
24.2: Conformations and Cyclic Forms of Sugars
24.3: Anomers of Simple Sugars - Mutarotation of Glucose
24.4: Polyfunctional Chemistry of Sugars: Oxidation to Carboxylic Acids
24.5: Oxidative Cleavage of Sugars
24.6: Reduction of Monosaccharides to Alditols
24.7: Carbonyl Condensations with Amine Derivatives
24.8: Ester and Ether Formation: Glycosides
24.9: Step-by-Step Buildup and Degradation of Sugars
24.10: Relative Configurations of the Aldoses: An Exercise in Structure Determination
24.11: Complex Sugars in Nature: Disaccharides
24.12: Polysaccharides and Other Sugars in Nature

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24.1: Names and Structures of Carbohydrates

Objectives

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

Key Terms

Make certain that you can define, and use in context, the key terms below.

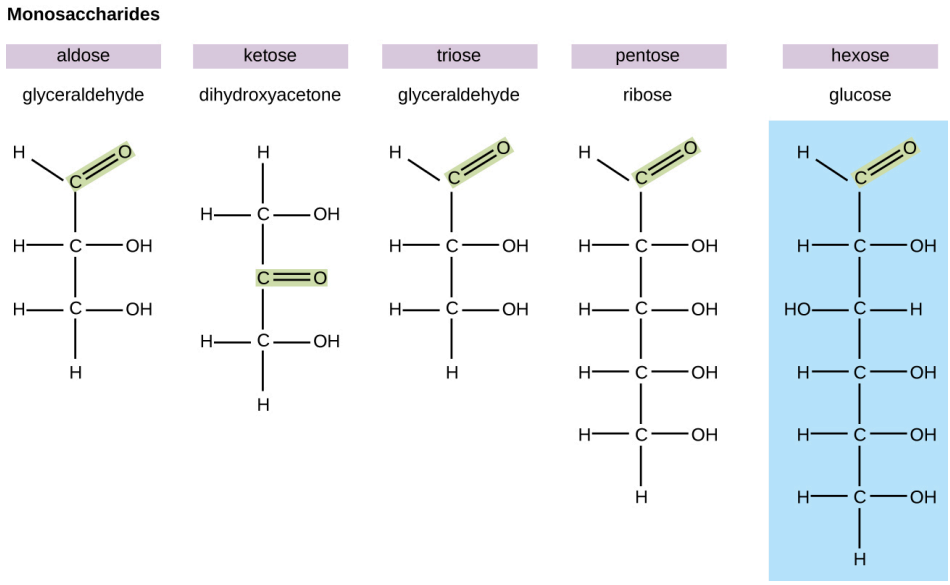
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

What Are Carbohydrates?

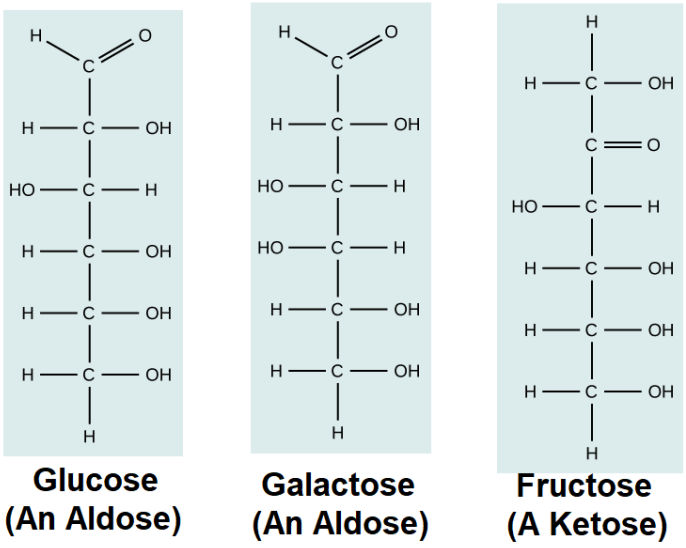
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" carbon atom chains in which water molecules attach to each carbon atom, leading to the term "carbohydrates." Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

Monosaccharides

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.



Complex Carbohydrates

The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

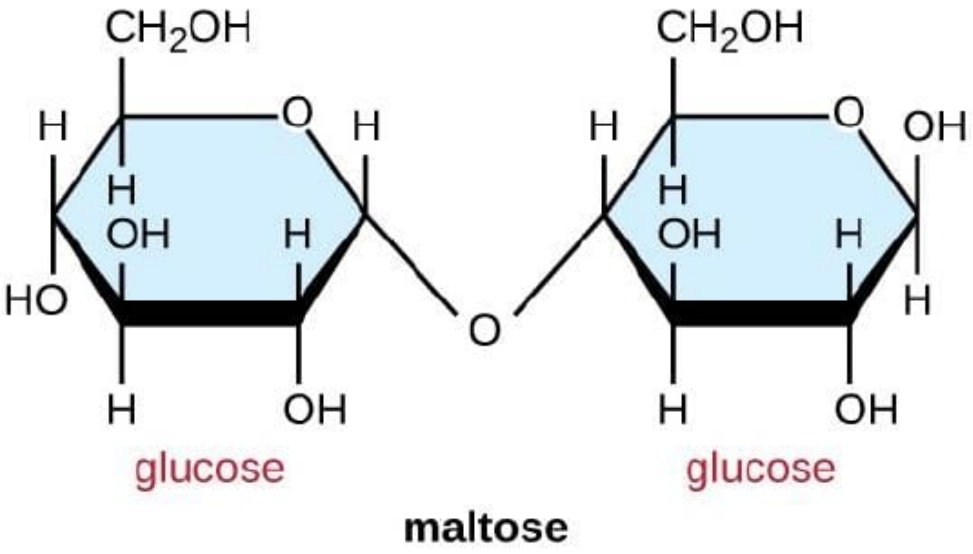
Disaccharides

Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the

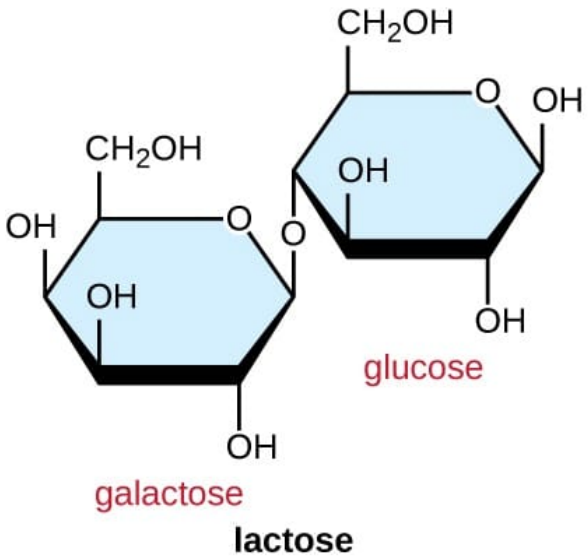
two monosaccharides is a glycosidic bond. **Glycosidic bonds** form between hydroxyl groups of the two saccharide molecules, an example of the dehydration synthesis described later in this chapter.

$$\text{monosaccharide—OH} + \text{HO—monosaccharide} \longrightarrow \underbrace{\text{monosaccharide—O—monosaccharide}}_{\text{disaccharide}}$$

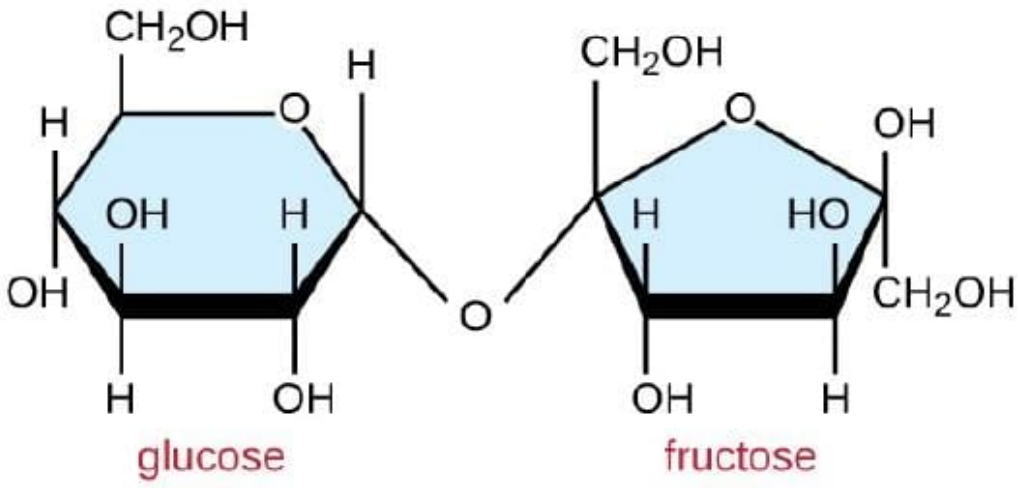
Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.



maltose



lactose



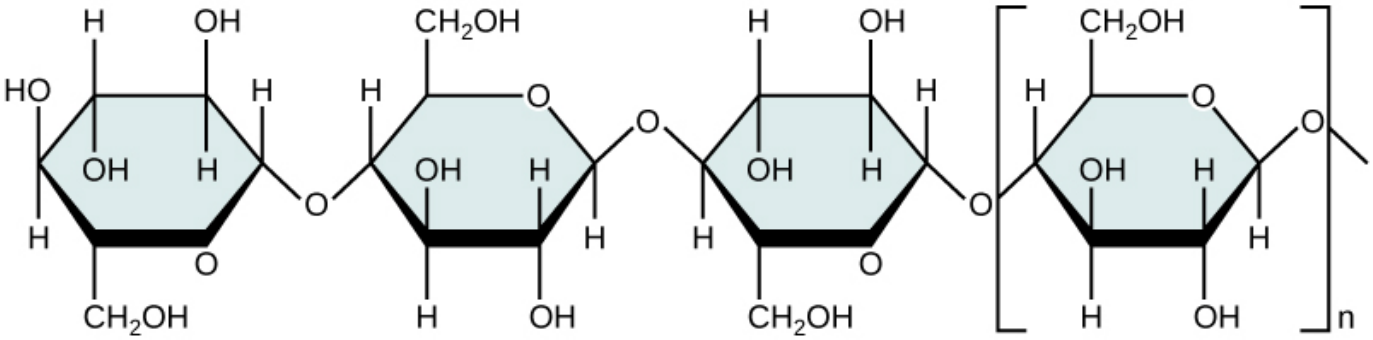
sucrose

Polysaccharides

Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.

Cellulose structure



Summary

Complexity	**Simple Carbohydrates** monosaccharides	**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides

Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.

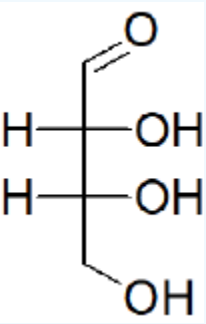
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

Exercise

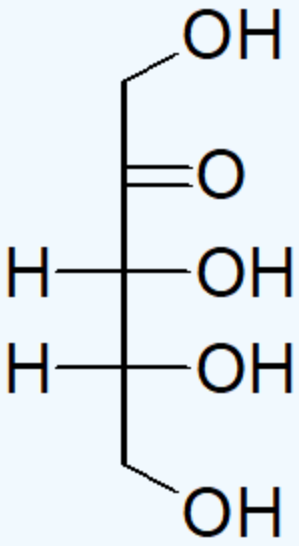
Exercise 25.1.1

Classify each of the following sugars.

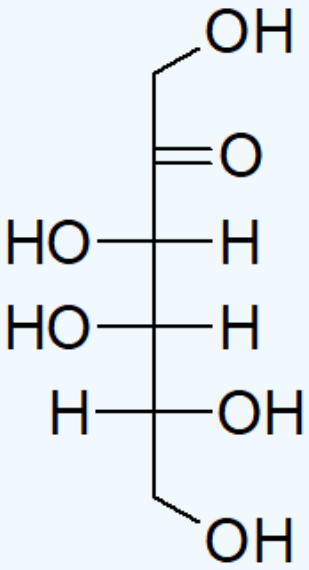
a)



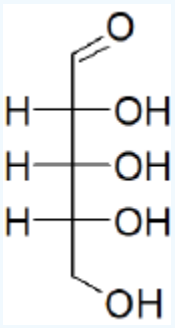
b)



c)



d)



Answer available at the end of this section.

Questions

Q25.1.1

Classify each of the following sugars.

(a)25.1 Problem A.png

(b)25.1 Problem B.png

(c)25.1 Problem C.png

(d)25.1 Problem D.png

Solutions

S25.1.1

(a) Aldoterose

(b) Ketopentose

(c) Ketohexose

(d) Aldopentose

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
2. draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.

Key Terms

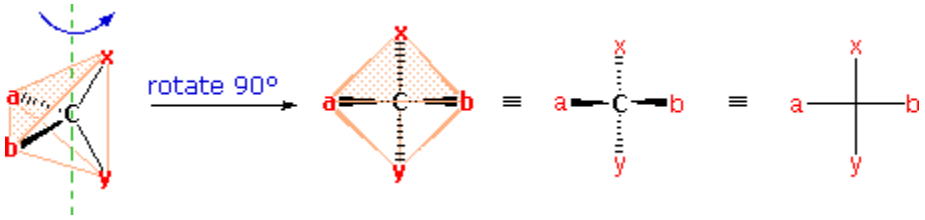
Make certain that you can define, and use in context, the key term below.

- Fischer projection

Study Notes

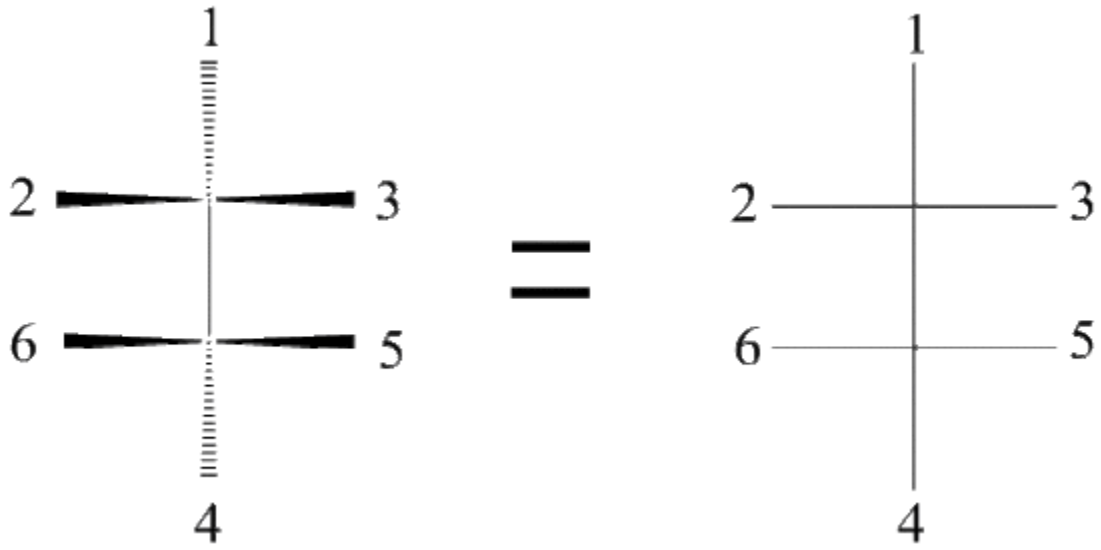
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and hatched line notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. In a Fischer projection drawing, the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines. The two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon). The two vertical bonds are directed behind the central carbon (away from the viewer). Since this is not the usual way in which we have viewed such structures, the following diagram shows how a stereogenic carbon positioned in the common two-bonds-in-a-plane orientation (x–C–y define the reference plane) is rotated into the Fischer projection orientation (the far right formula). When writing Fischer projection formulas it is important to remember these conventions. Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180° within the plane, thus maintaining this relationship. **The structure must not be flipped over or rotated by 90°**.

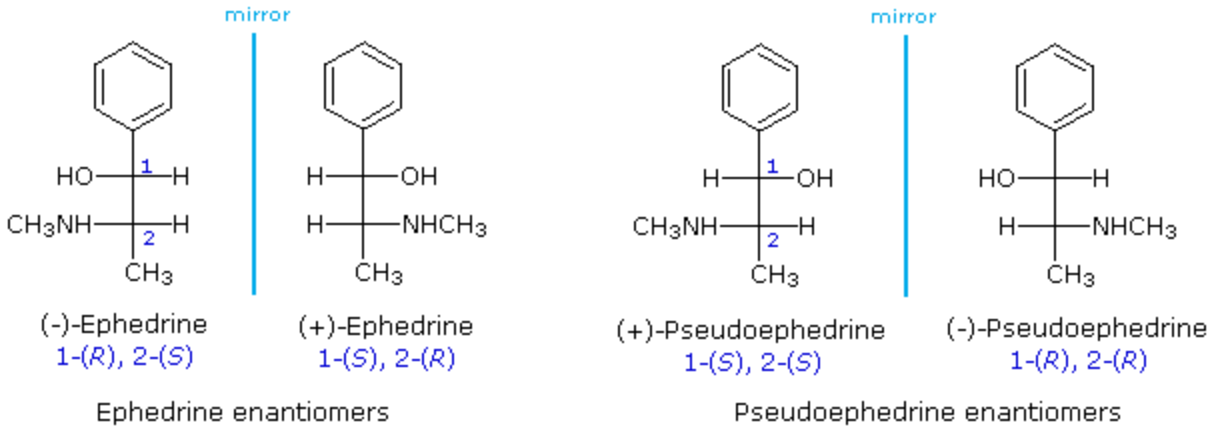


In the above diagram, if x = CO_2H, y = CH_3, a = H & b = OH, the resulting formula describes (*R*)-(–)-lactic acid. The mirror-image formula, where x = CO_2H, y = CH_3, a = OH & b = H, would, of course, represent (S)-(+)-lactic acid.

The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines represents the central carbon.

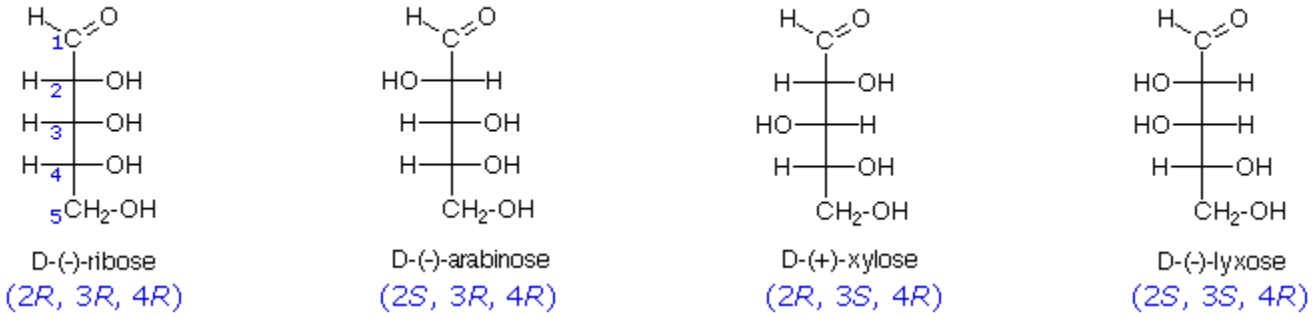


Using the Fischer projection notation, the stereoisomers of 2-methylamino-1-phenylpropanol are drawn in the following manner. Note that it is customary to set the longest carbon chain as the vertical bond assembly.



The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses. Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**. Fischer formulas for these isomers, which Fischer designated as the "D"-family, are shown in the diagram. Each of these compounds has an enantiomer, which is a member of the "L"-family so, as expected, there are eight stereoisomers in all. Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

How to make Fischer Projections

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

Example 25.2.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

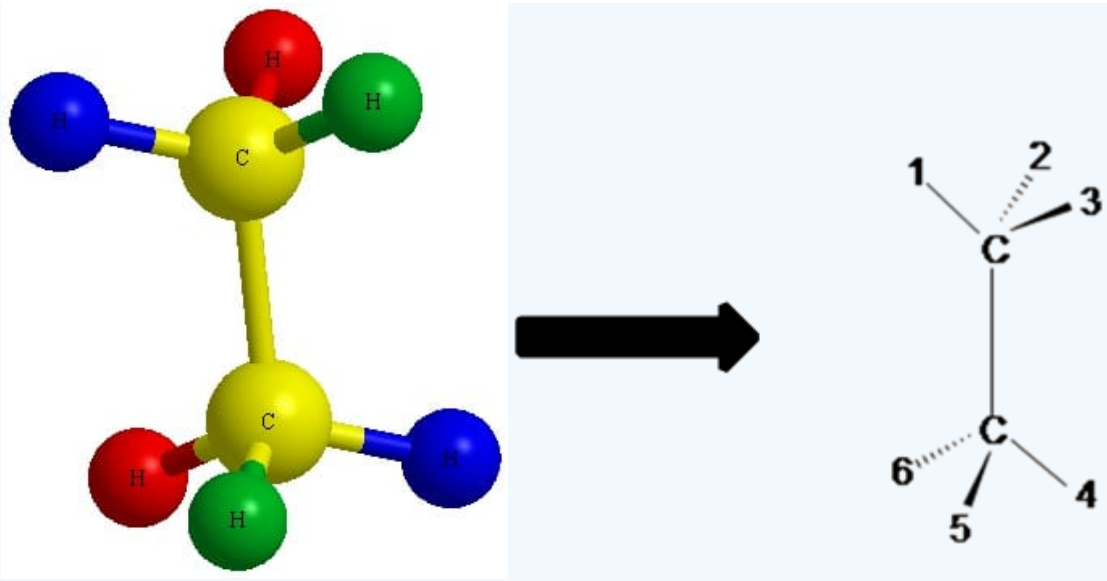


Figure A Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a "flat" Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

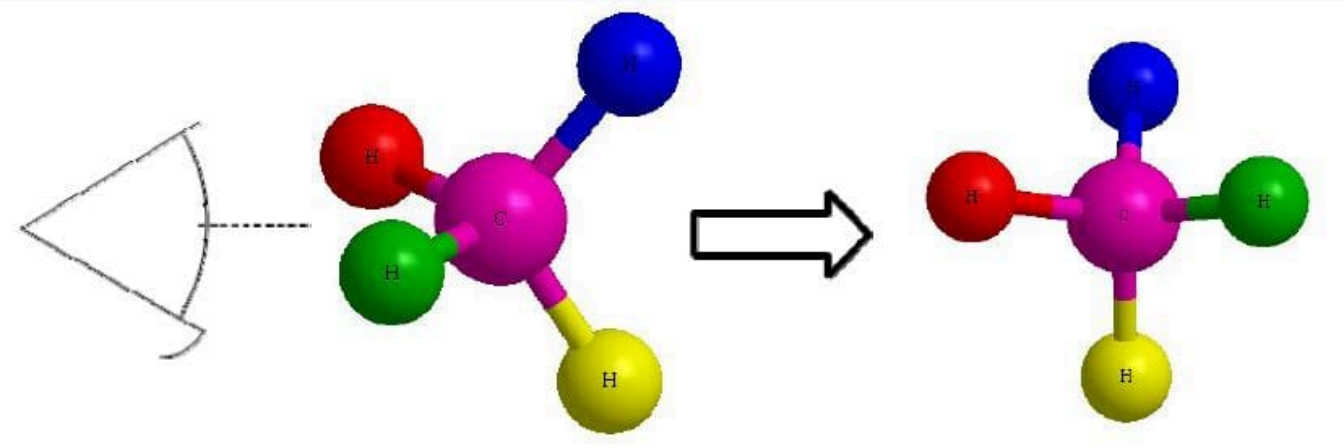
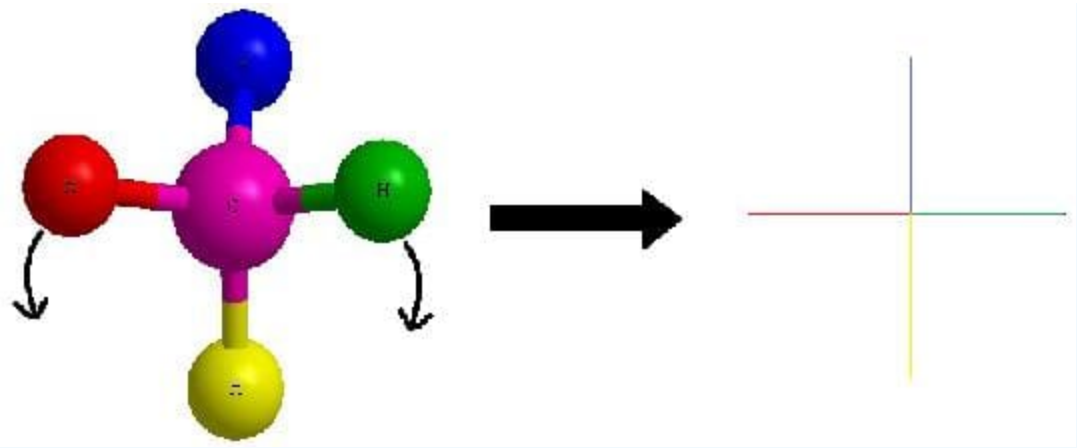


Figure C Figure D

Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.

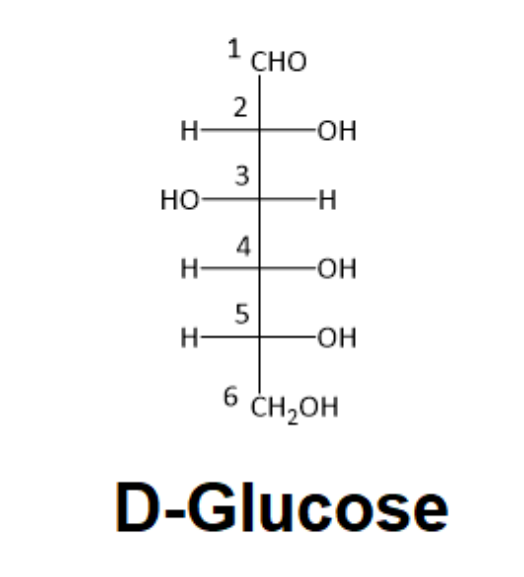


As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

Exercises

Exercise 25.2.1

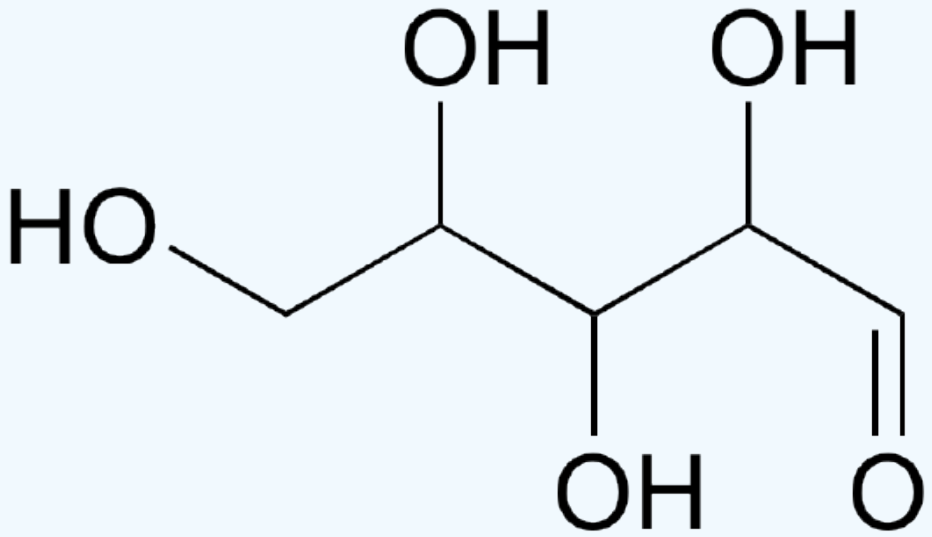
Determine if carbon #2 in D-glucose is R or S.



Answer available at the end of this section.

Exercise 25.2.2

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or S.



Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Objectives

After completing this section, you should be able to

1. identify a specific enantioner of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

Key Terms

Make certain that you can define, and use in context, the key terms below.

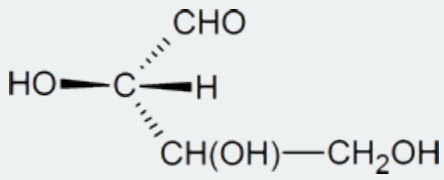
- D sugar
- L sugar

Study Notes

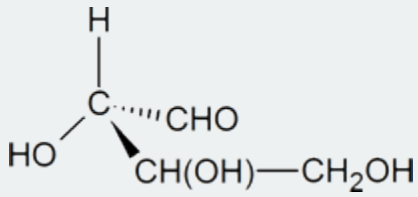
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

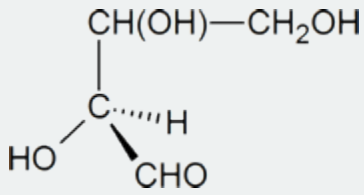
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



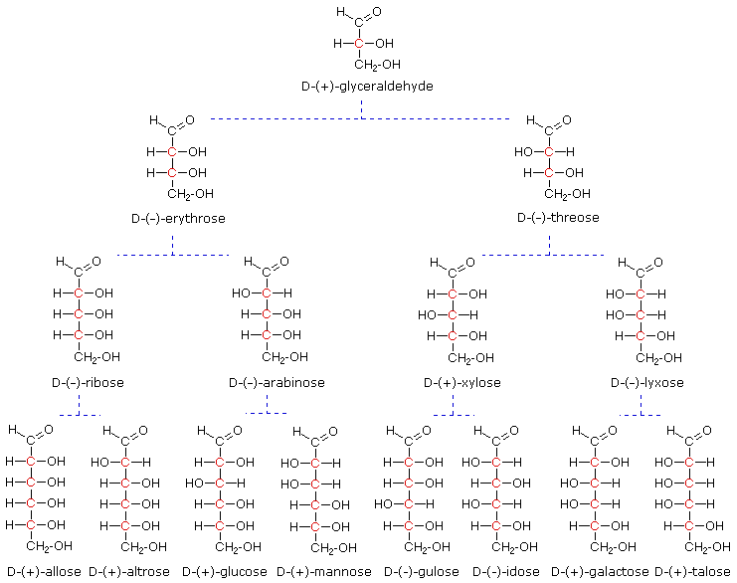
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

The Configuration of Glucose

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula. Click on this link for a review.

At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (+)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red. The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Fischer as the D / L designator site. If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family. A left directed hydroxyl group (the mirror image) then represented the L-family. Fischer's initial assignment of the D-configuration had a 50:50 chance of being right, but all his subsequent conclusions concerning the relative configurations of various aldoses were soundly based. In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L). It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

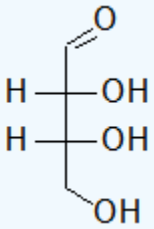


Exercise

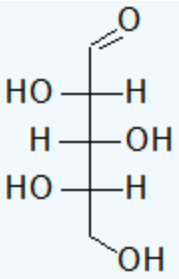
Exercise 24.1.1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

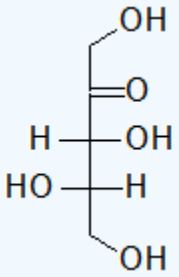
a)



b)



c)



Answer available at the end of this section.

Questions

Q25.3.1

Assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

(a)

25.6 Problem A.png

(b)

25.6 Problem B.png

(c)

25.6 Problem C.png

Solutions

S25.3.1

(a) From top to bottom, 2R, 3R, and it is a D sugar.

(b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

(c) From to to bottom, 3R, 4S, and it is an L sugar.

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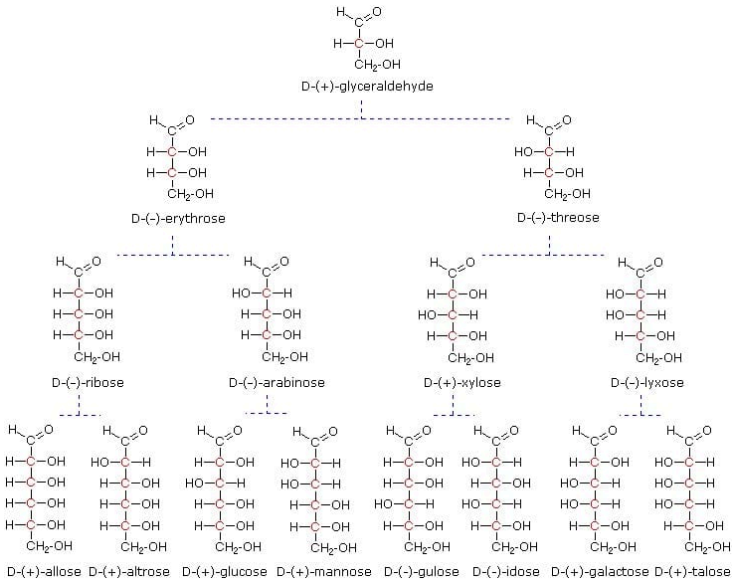
Objectives

After completing this section, you should be able to

1. draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. draw the Fischer projection of D-glyceraldehyde, D-ribose and D-glucose from memory.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula.

At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (+)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red.



The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Fischer as the D / L designator site. If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family. A left directed hydroxyl group (the mirror image) then represented the L-family. Fischer's initial assignment of the D-configuration had a 50:50 chance of being right, but all his subsequent conclusions concerning the relative configurations of various aldoses were soundly based. In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet (pronounced "buy foot"), proved that Fischer's choice was correct.

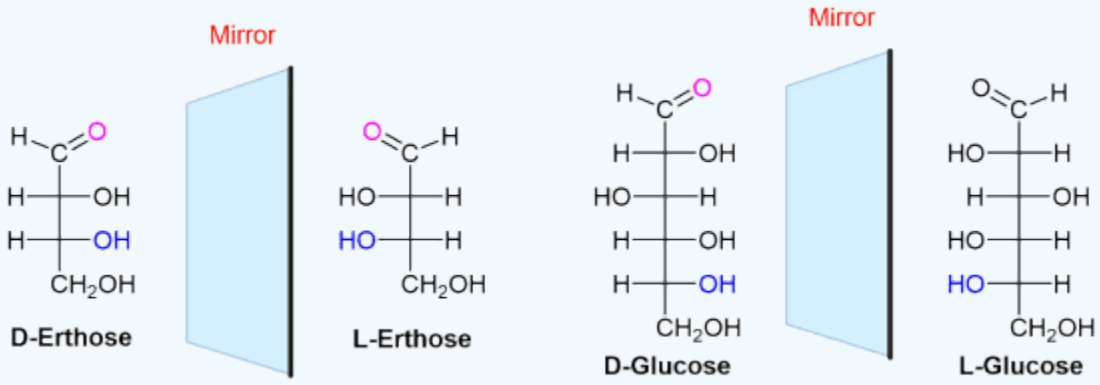
It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L). It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

Worked Example 25.4.1

Draw the Fisher projection of L-erythrose and L-Glucose

Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.

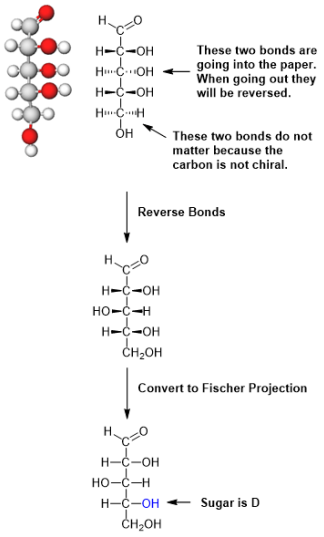


Worked Example 25.4.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

Solution

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.



Exercises

Exercise 25.4.1

For the following model of a sugar, please draw its Fischer projection and name it.

Answer available at the end of this section.

Exercise 25.4.2

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer available at the end of this section.

Exercise 25.4.3

Draw the Fischer projection of the following sugars.

a. L-Ribose
b. L-Galactose
c. L-Talose

Answer available at the end of this section.

Questions

Q25.4.1

Draw the following sugars.

(a) D-Xylose

(b) D-Galactose

(c) D-Allose

Solutions

S25.4.1

(a)

25.4.1 problem answer.svg

(b)

25.8 Solution B.png

(c)

25.8 Solution C.png

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

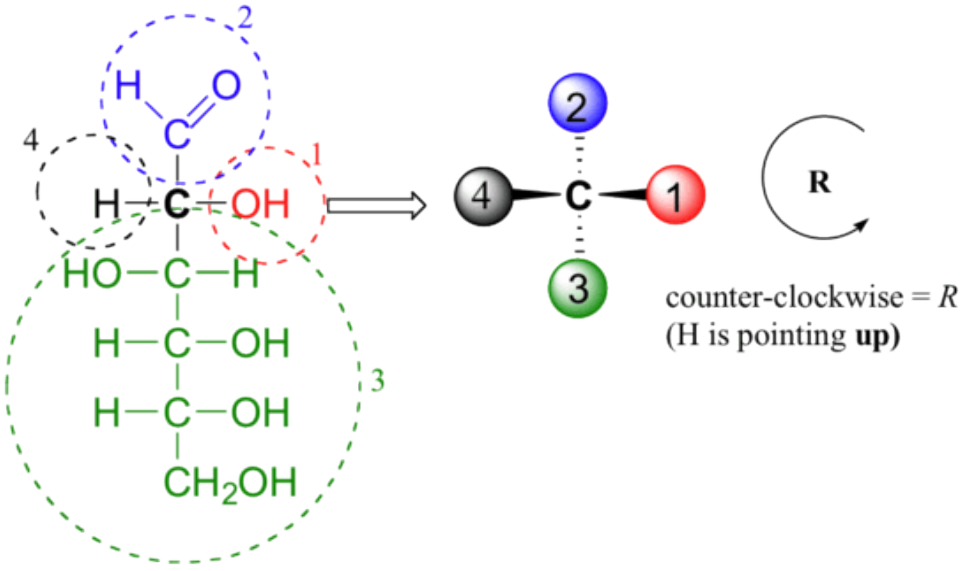
Answers

Exercise 25.1.1

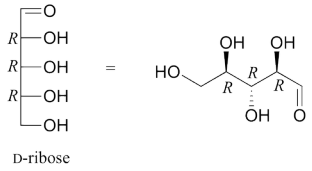
a) Aldoterose
b) Ketopentose
c) Ketohexose
d) Aldopentose

Exercise 25.2.1

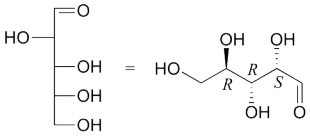
When deciding whether a stereocenter in a Fischer projection is *R* or S, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means S. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



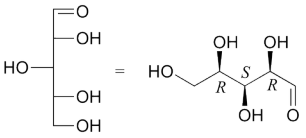
Exercise 25.2.2



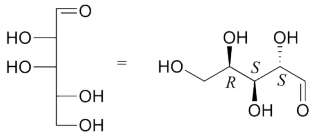
D-ribose



D-arabinose



D-xylose



D-lyxose

Exercise 24.1.1

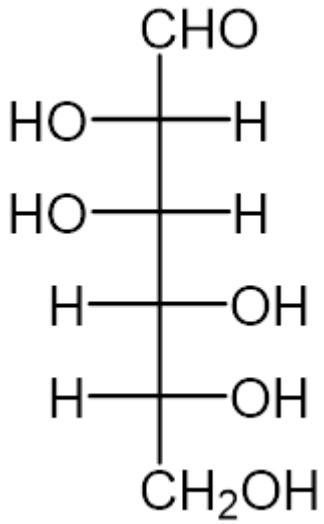
a) From top to bottom, 2R, 3R, and it is a D sugar.

b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

c) From to to bottom, 3R, 4S, and it is an L sugar.

Exercise 25.4.1

D-Mannose

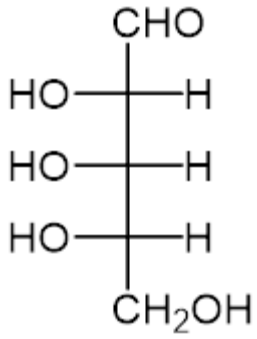


Exercise 25.4.2

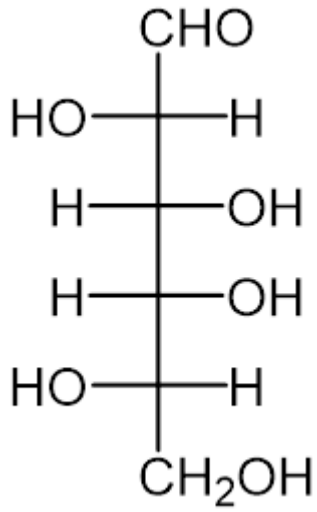
There would be 2^5 = 32 heptose stereoisomers. Half of these would be D-sugars or 16.

Exercise 25.4.3

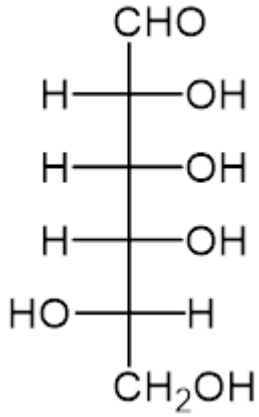
a)



b)



c)



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24.2: Conformations and Cyclic Forms of Sugars

Objectives

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

Key Terms

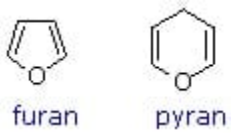
Make certain that you can define, and use in context, the key terms below.

- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

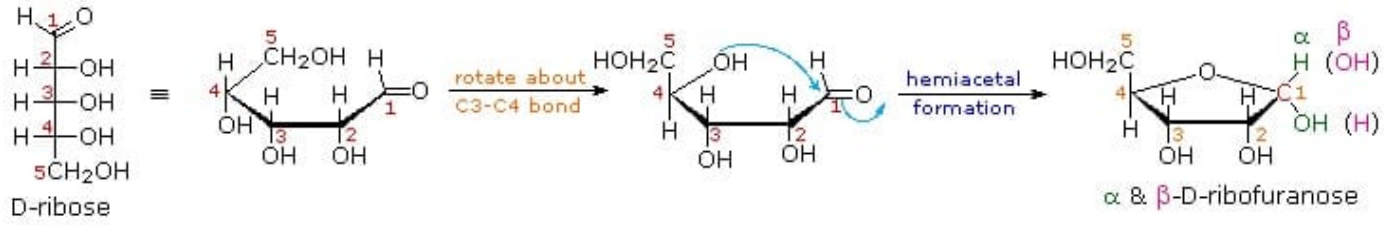
Study Notes

If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

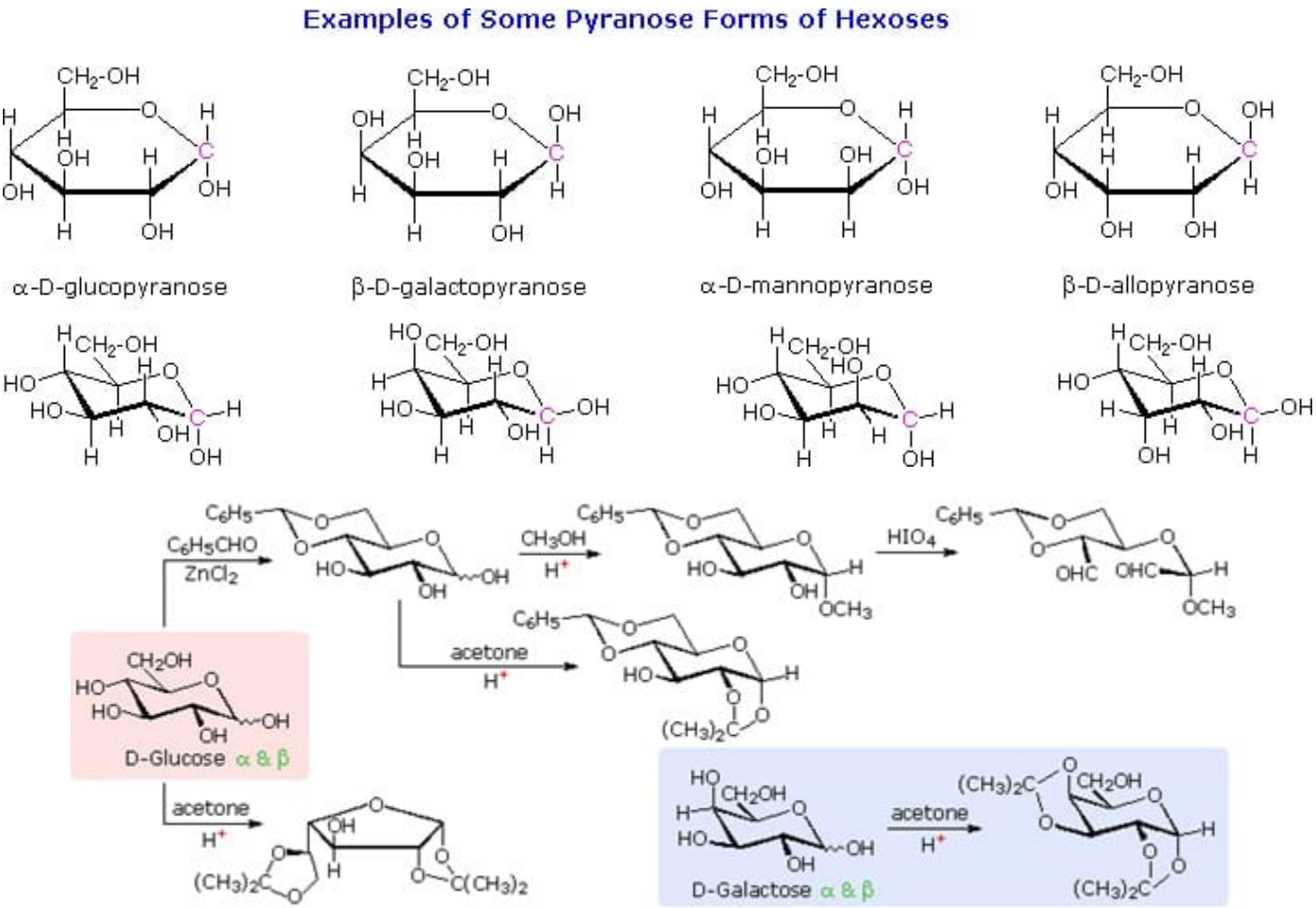
As noted above, the preferred structural form of many monosaccharides may be that of a cyclic hemiacetal. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown on the right. Ribose, an important aldopentose, commonly adopts a furanose structure, as shown in the following illustration. By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer. The anomeric carbon atom (colored red here) is placed on the right. The upper bond to this carbon is defined as beta, the lower bond then is alpha.



furan pyran



The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula, after the British chemist, Norman Haworth. As with the furanose ring, the anomeric carbon is placed on the right with the ring oxygen to the back of the edgewise view. In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring (beta is up & alpha is down). These Haworth formulas are convenient for displaying stereochemical relationships, but do not represent the true shape of the molecules. We know that these molecules are actually puckered in a fashion we call a chair conformation. Examples of four typical pyranose structures are shown below, both as Haworth projections and as the more representative chair conformers. The anomeric carbons are colored red.



The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features. Aldolhexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. The formation of acetal derivatives illustrates how subtle changes may alter this selectivity. A pyranose structure for D-glucose is drawn in the rose-shaded box on the left. Acetal derivatives have been prepared by acid-catalyzed reactions with benzaldehyde and acetone. As a rule, benzaldehyde forms six-membered cyclic acetals, whereas acetone prefers to form five-membered acetals. The top equation shows the formation and some reactions of the 4,6-O-benzylidene acetal, a commonly employed protective group. A methyl glycoside derivative of this compound (see below) leaves the C-2 and C-3 hydroxyl groups exposed to reactions such as the periodic acid cleavage, shown as the last step. The formation of an isopropylidene acetal at C-1 and C-2, center structure, leaves the C-3 hydroxyl as the only unprotected function. Selective oxidation to a ketone

is then possible. Finally, direct di-O-isopropylidene derivatization of glucose by reaction with excess acetone results in a change to a furanose structure in which the C-3 hydroxyl is again unprotected. However, the same reaction with D-galactose, shown in the blue-shaded box, produces a pyranose product in which the C-6 hydroxyl is unprotected. Both derivatives do not react with Tollens' reagent. This difference in behavior is attributed to the cis-orientation of the C-3 and C-4 hydroxyl groups in galactose, which permits formation of a less strained five-membered cyclic acetal, compared with the trans-C-3 and C-4 hydroxyl groups in glucose. Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.

Anomers of Simple Sugars: Mutarotation of Glucose

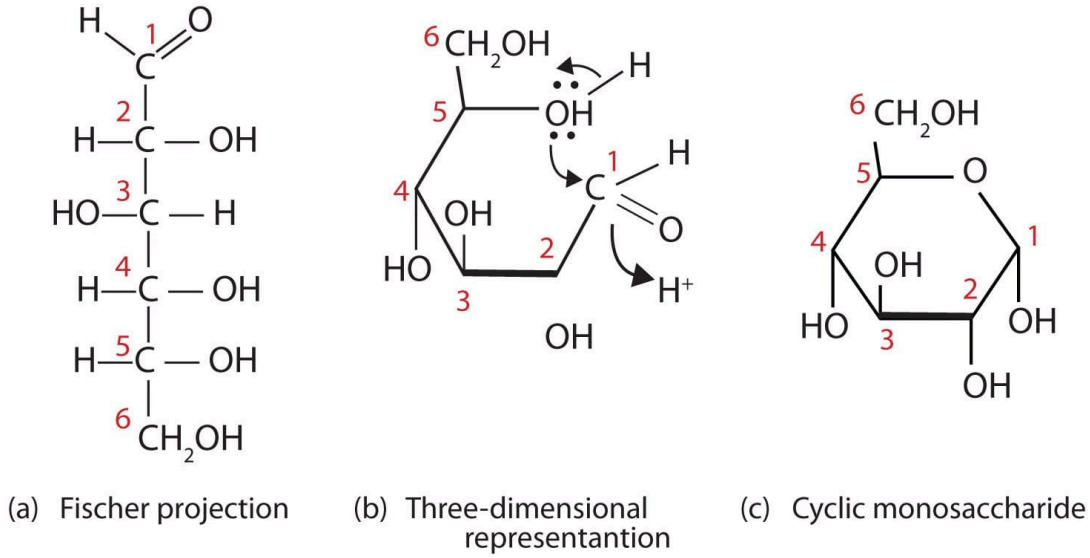


Figure 1: *Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.*

When a straight-chain monosaccharide, such as any of the structures shown in Figure 1, forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers, as shown in Figure 2. The structure shown on the left side of Figure 2, with the OH group on the first carbon atom projected downward, represent what is called the *alpha (α) form*. The structures on the right side, with the OH group on the first carbon atom pointed upward, is the *beta (β) form*. These two stereoisomers of a cyclic monosaccharide are known as anomers; they differ in structure around the anomeric carbon—that is, the carbon atom that was the carbonyl carbon atom in the straight-chain form.

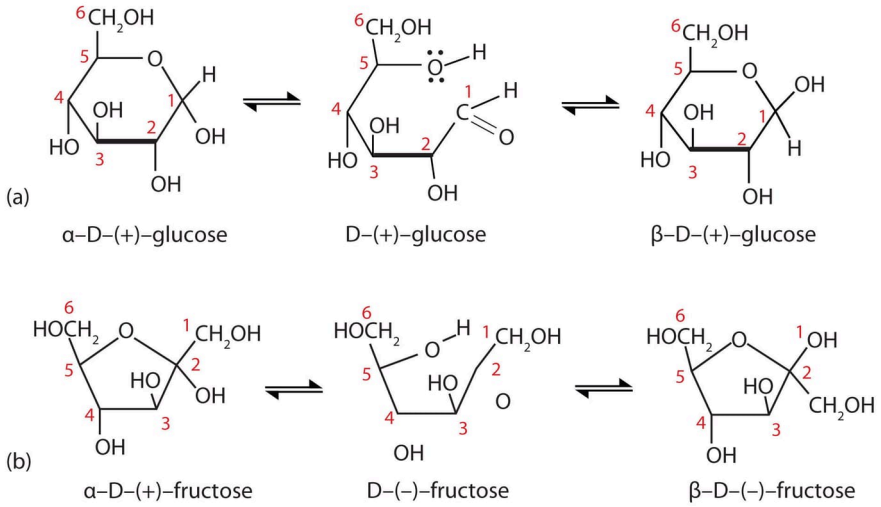


Figure 2: *Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as mutarotation, which is shown for D-glucose (a) and D-fructose (b).*

It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium (part (a) of Figure 2). You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.

Even though only a small percentage of the molecules are in the open-chain aldehyde form at any time, the solution will nevertheless exhibit the characteristic reactions of an aldehyde. As the small amount of free aldehyde is used up in a reaction, there is a shift in the equilibrium to yield more aldehyde. Thus, *all* the molecules may eventually react, even though very little free aldehyde is present at a time.

Commonly, (e.g., in Figures 1 and 2) the cyclic forms of sugars are depicted using a convention first suggested by Walter N. Haworth, an English chemist. The molecules are drawn as planar hexagons with a darkened edge representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the right in a Fischer projection appears below the plane of the ring in a Haworth projection, and any group written to the left in a Fischer projection appears above the plane in a Haworth projection.

The difference between the α and the β forms of sugars may seem trivial, but such structural differences are often crucial in biochemical reactions. This explains why we can get energy from the starch in potatoes and other plants but not from cellulose, even though both starch and cellulose are polysaccharides composed of glucose molecules linked together.

Summary

Monosaccharides that contain five or more carbons atoms form cyclic structures in aqueous solution. Two cyclic stereoisomers can form from each straight-chain monosaccharide; these are known as anomers. In an aqueous solution, an equilibrium mixture forms between the two anomers and the straight-chain structure of a monosaccharide in a process known as mutarotation.

Exercises

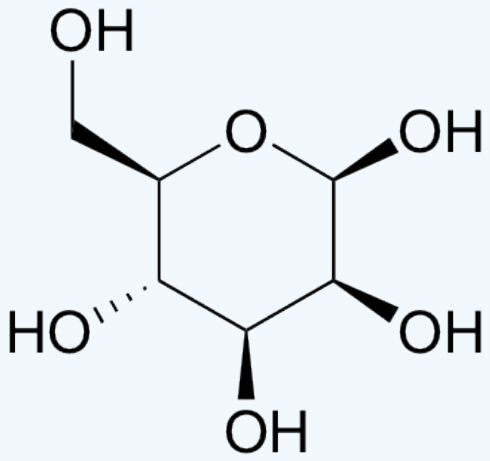
Exercise 25.5.1

Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer available at the end of this section.

Exercise 25.5.2

Draw the two chair conformations of the sugar called mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.



mannose

Answer available at the end of this section.

Exercise 25.5.3

Draw the cyclic structure of α-D-altrose.

Answer available at the end of this section.

Exercise 25.5.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer available at the end of this section.

Exercise 25.5.5

Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

Answer available at the end of this section.

Exercise 25.5.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

Answer available at the end of this section.

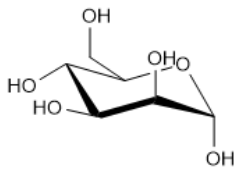
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

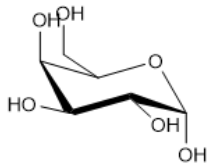
Answers

Exercise 25.5.1

Because the both have two axial OH's their chair conformations should be roughly the same stability.

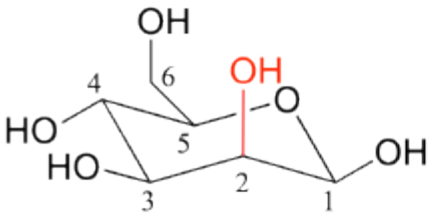


a-D-Mannose

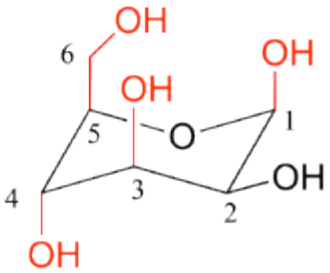


a-D-Galactose

Exercise 25.5.2

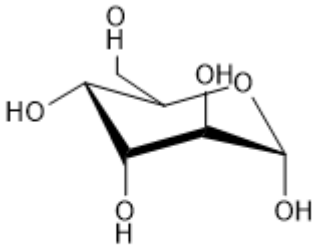


major chair form of mannose
(only one substituent axial)



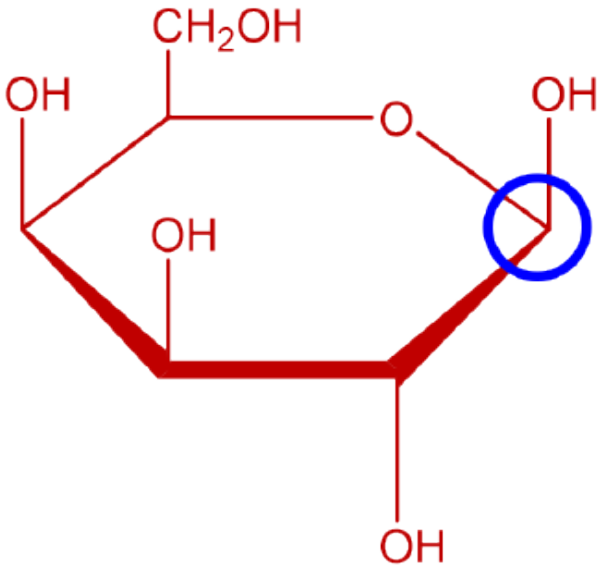
minor chair form of mannose
(four substituents axial)

Exercise 25.5.3



a-D-Altrose

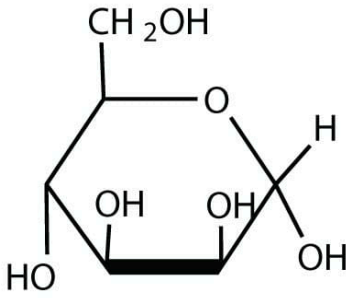
Exercise 25.5.4



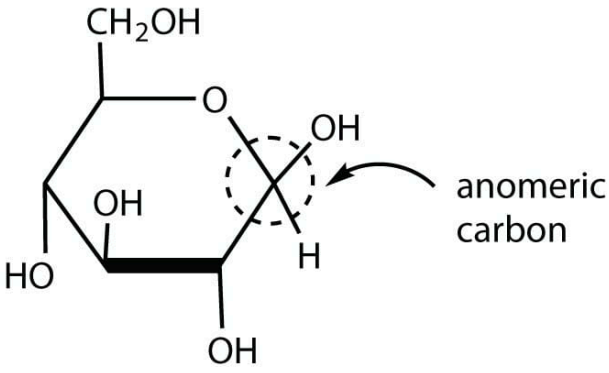
anomeric carbon

To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

Exercise 25.5.5



Exercise 25.5.6



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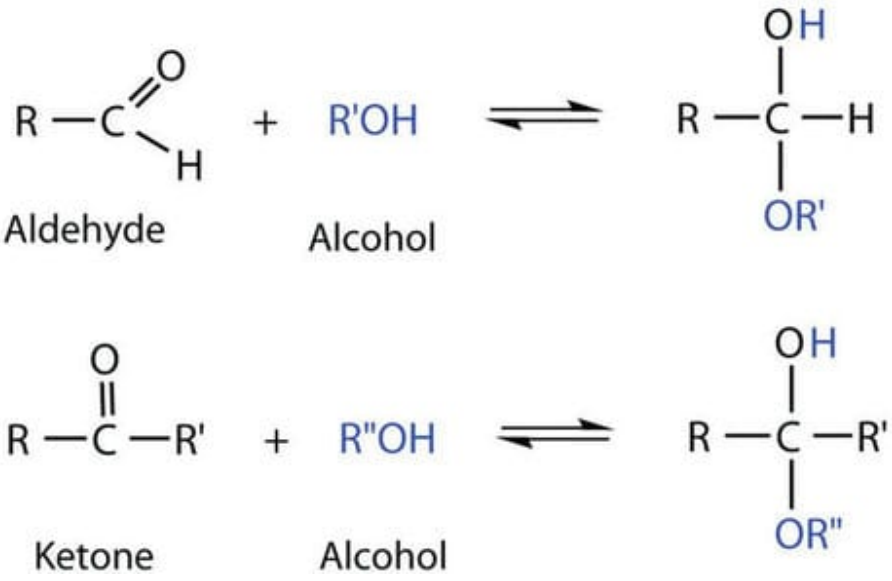
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24.3: Anomers of Simple Sugars - Mutarotation of Glucose

Learning Objectives

- Define what is meant by anomers and describe how they are formed.
- Explain what is meant by mutarotation.

So far we have represented monosaccharides as linear molecules, but many of them also adopt cyclic structures. This conversion occurs because of the ability of aldehydes and ketones to react with alcohols:



You might wonder why the aldehyde reacts with the OH group on the fifth carbon atom rather than the OH group on the second carbon atom next to it. Recall that cyclic alkanes containing five or six carbon atoms in the ring are the most stable. The same is true for monosaccharides that form cyclic structures: rings consisting of five or six carbon atoms are the most stable.

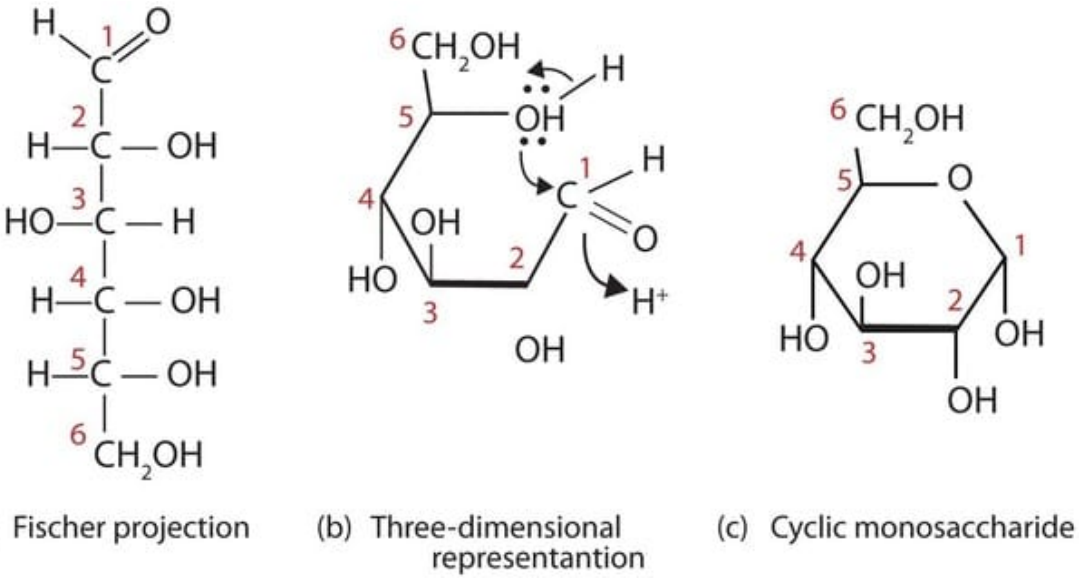


Figure 24.3.1: Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.

When a straight-chain monosaccharide, such as any of the structures shown in Figure 24.3.1, forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers, as shown in Figure 24.3.2. The structure shown on the left side of Figure 24.3.2, with the OH group on the first carbon atom projected downward, represent what is called the *alpha (α) form*. The structures on the right side, with the OH group on the first carbon atom pointed upward, is the *beta (β) form*. These two stereoisomers of a cyclic monosaccharide are known as anomers; they differ in structure around the anomeric carbon—that is, the carbon atom that was the carbonyl carbon atom in the straight-chain form.

It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium (part (a) of Figure 24.3.2). You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.

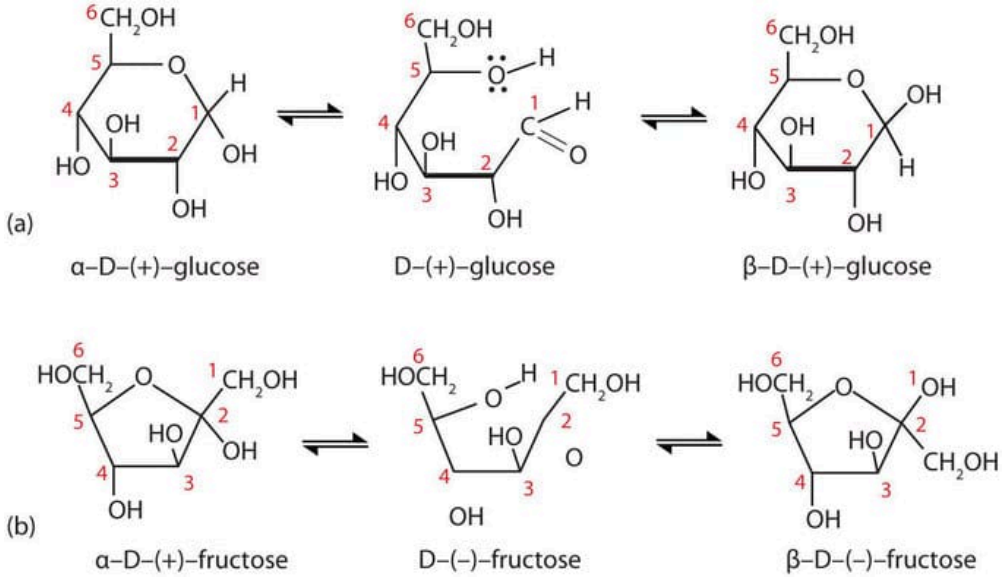


Figure 24.3.2: Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as *mutarotation*, which is shown for D-glucose (a) and D-fructose (b).

Even though only a small percentage of the molecules are in the open-chain aldehyde form at any time, the solution will nevertheless exhibit the characteristic reactions of an aldehyde. As the small amount of free aldehyde is used up in a reaction, there is a shift in the equilibrium to yield more aldehyde. Thus, *all* the molecules may eventually react, even though very little free aldehyde is present at a time.

Commonly, (e.g., in Figures 24.3.1 and 24.3.2) the cyclic forms of sugars are depicted using a convention first suggested by Walter N. Haworth, an English chemist. The molecules are drawn as planar hexagons with a darkened edge representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the right in a Fischer projection appears below the plane of the ring in a Haworth projection, and any group written to the left in a Fischer projection appears above the plane in a Haworth projection.

The difference between the α and the β forms of sugars may seem trivial, but such structural differences are often crucial in biochemical reactions. This explains why we can get energy from the starch in potatoes and other plants but not from cellulose, even though both starch and cellulose are polysaccharides composed of glucose molecules linked together.

Summary

Monosaccharides that contain five or more carbons atoms form cyclic structures in aqueous solution. Two cyclic stereoisomers can form from each straight-chain monosaccharide; these are known as anomers. In an aqueous solution, an equilibrium mixture

forms between the two anomers and the straight-chain structure of a monosaccharide in a process known as mutarotation.

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24.4: Polyfunctional Chemistry of Sugars: Oxidation to Carboxylic Acids

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

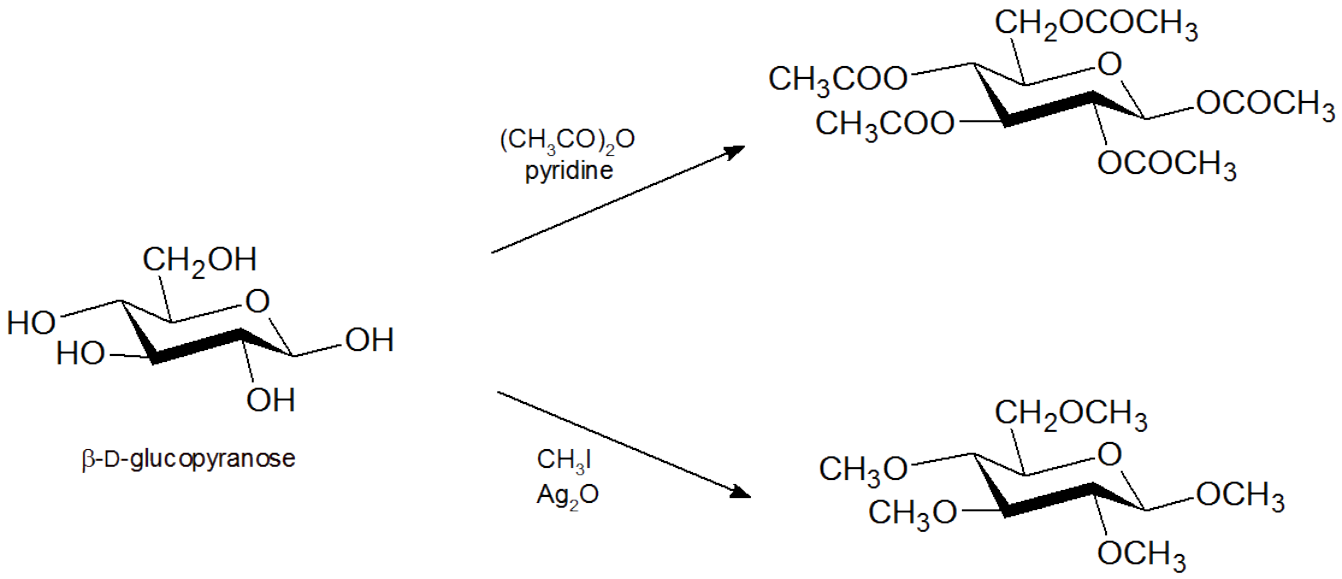
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

Ester and Ether Formation

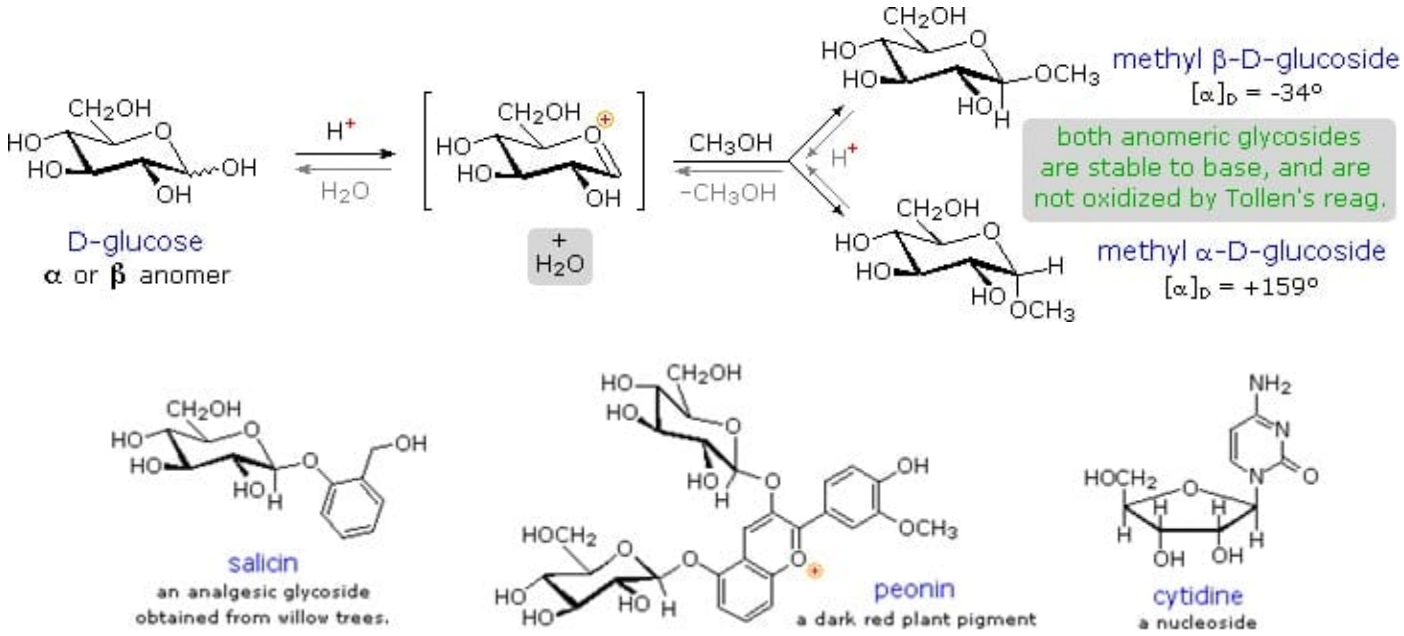
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.

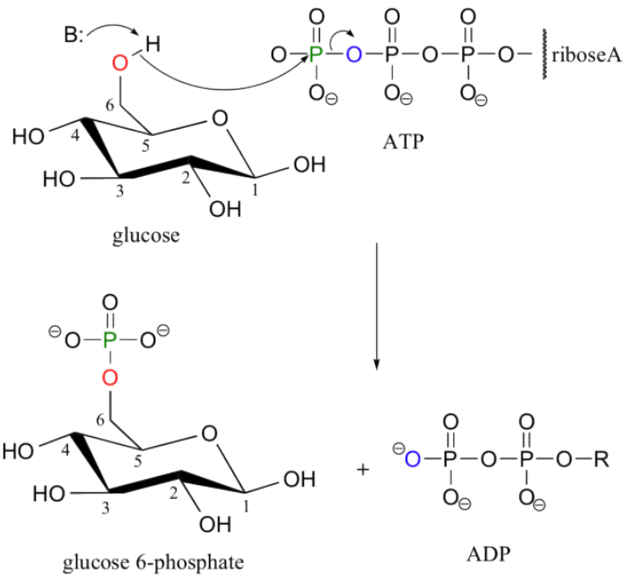


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin. A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).

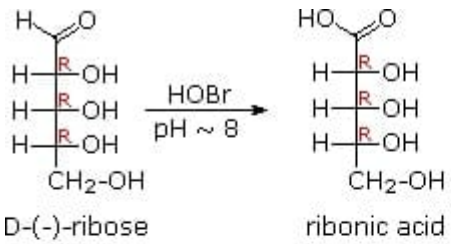


OxidationEdit section

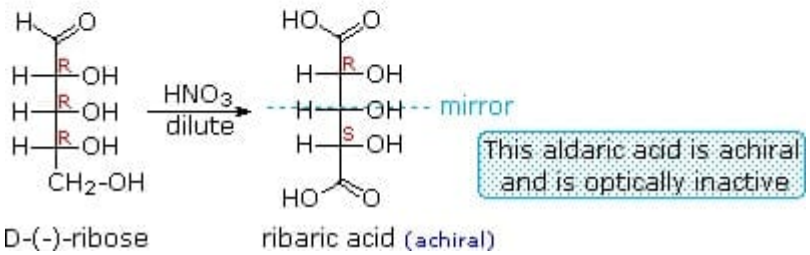
As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2° hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

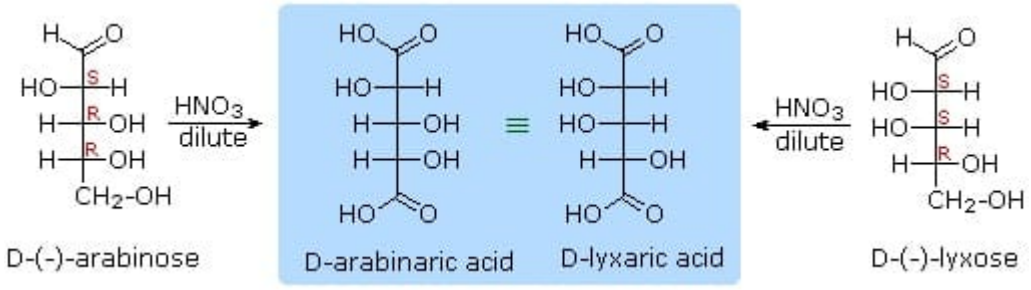
1.



2.



3.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

Reduction

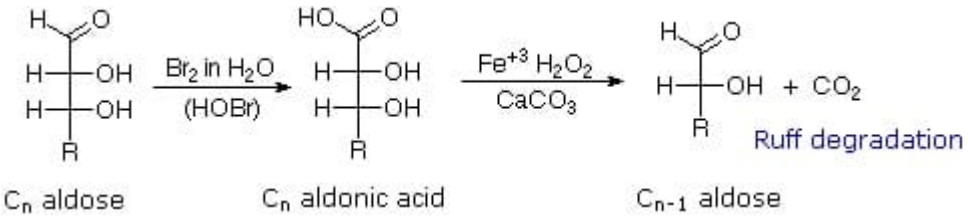
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

Table: Derivatives of $HOCH_2(CHOH)_nCHO$

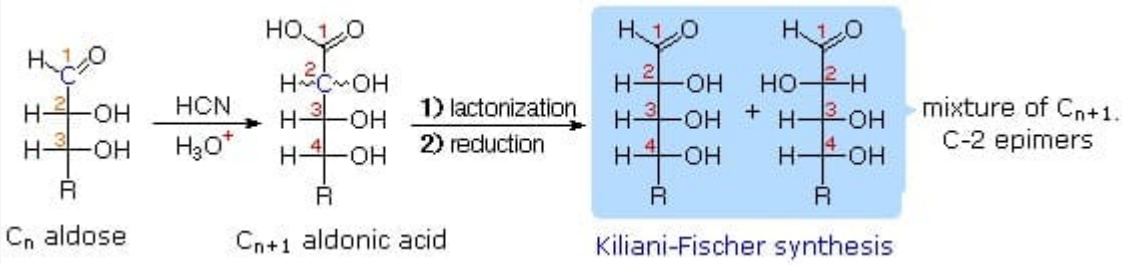
$HOBr$ Oxidation	$\longrightarrow$	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	$\longrightarrow$	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	$\longrightarrow$	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening

1. Ruff Degradation

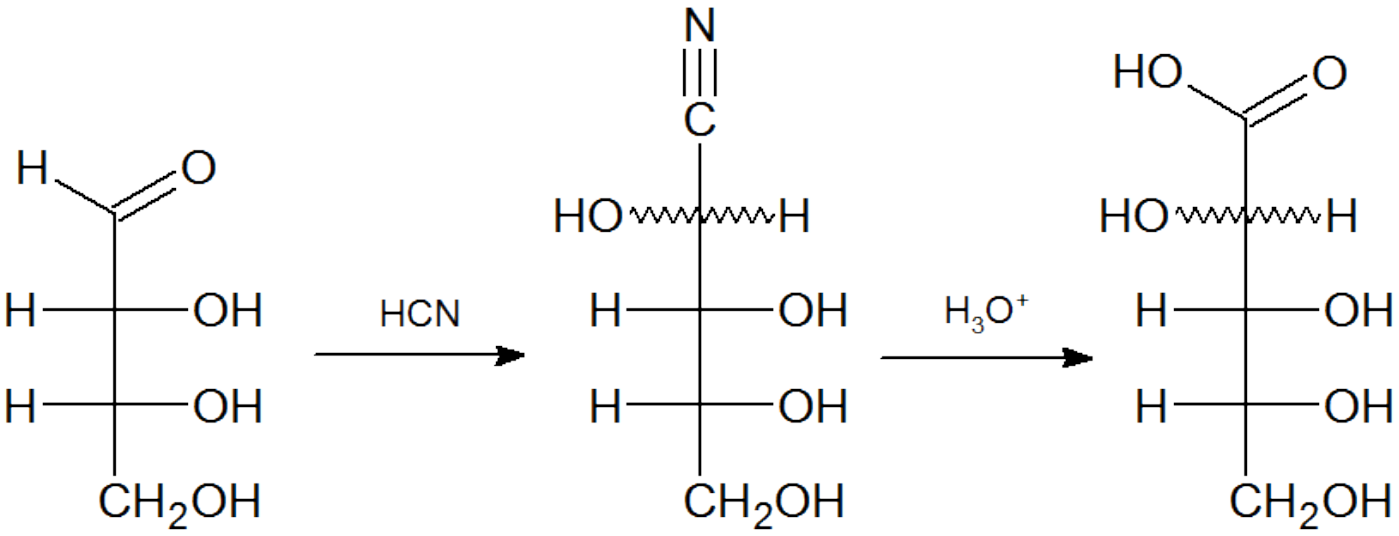


2. Kiliani-Fischer Synthesis



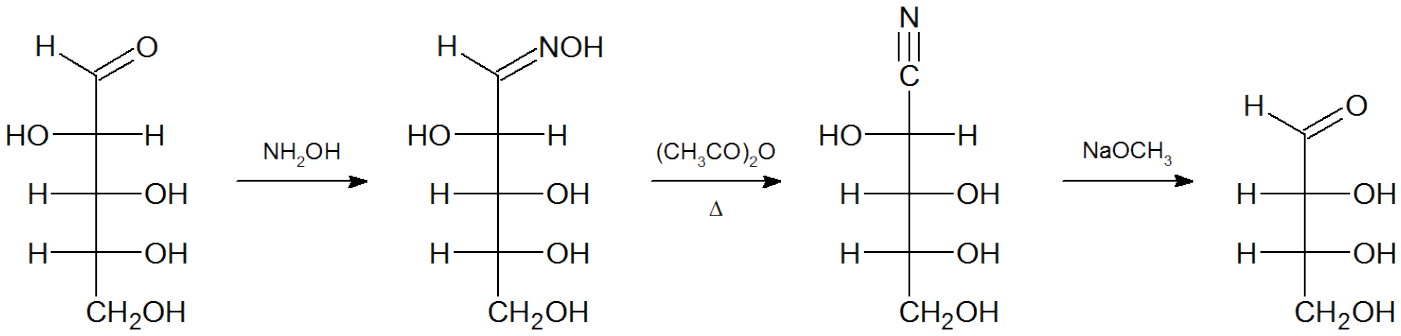
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



Exercises

Exercise 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer available at the end of this section.

Exercise 25.6.2

1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer available at the end of this section.

Exercise 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer available at the end of this section.

Exercise 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer available at the end of this section.

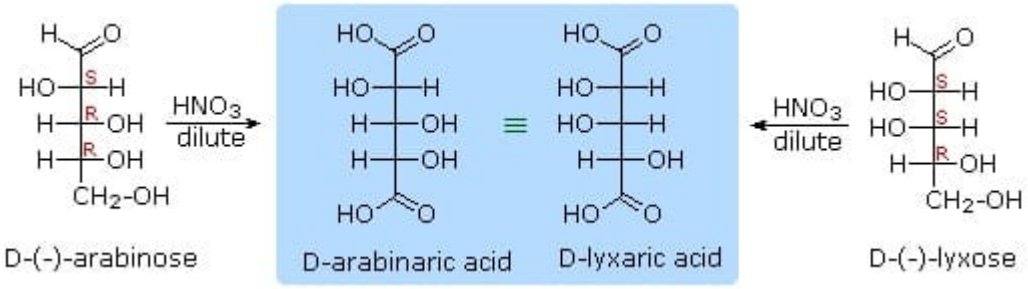
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 25.6.1

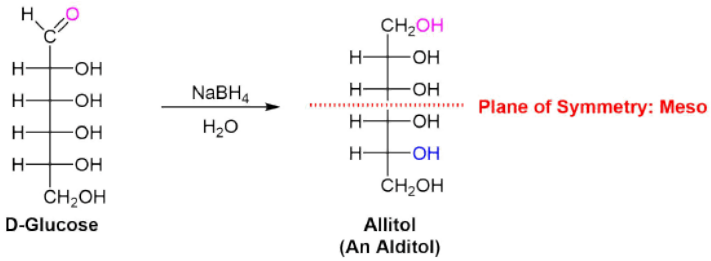
1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

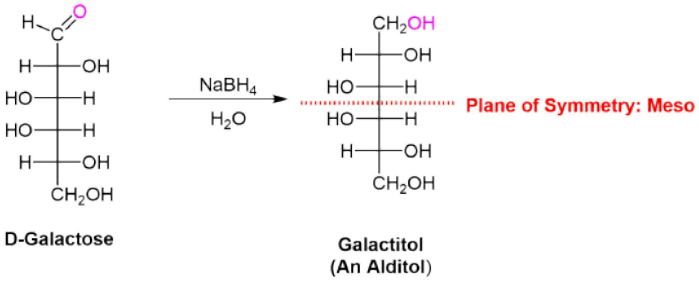


2) D-Allose and D-galactose.

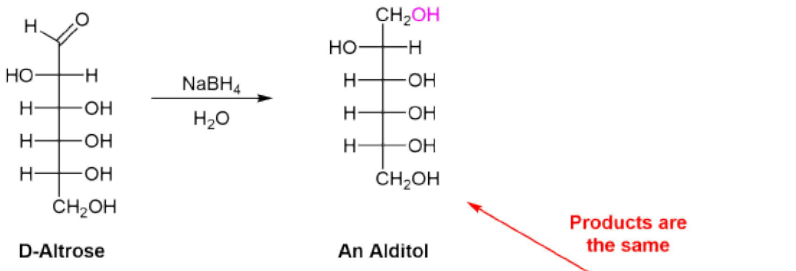
Exercise 25.6.2

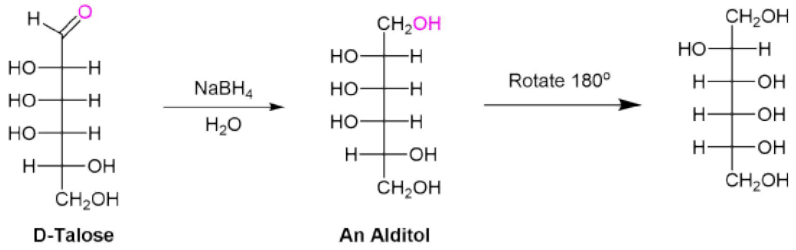
1)





2)





Exercise 25.6.3

1) D-Gluose and D-idose

2) D-Threose

Exercise 25.6.4

D-Ribose and D-arabinose

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24.5: Oxidative Cleavage of Sugars

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24.6: Reduction of Monosaccharides to Alditols

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

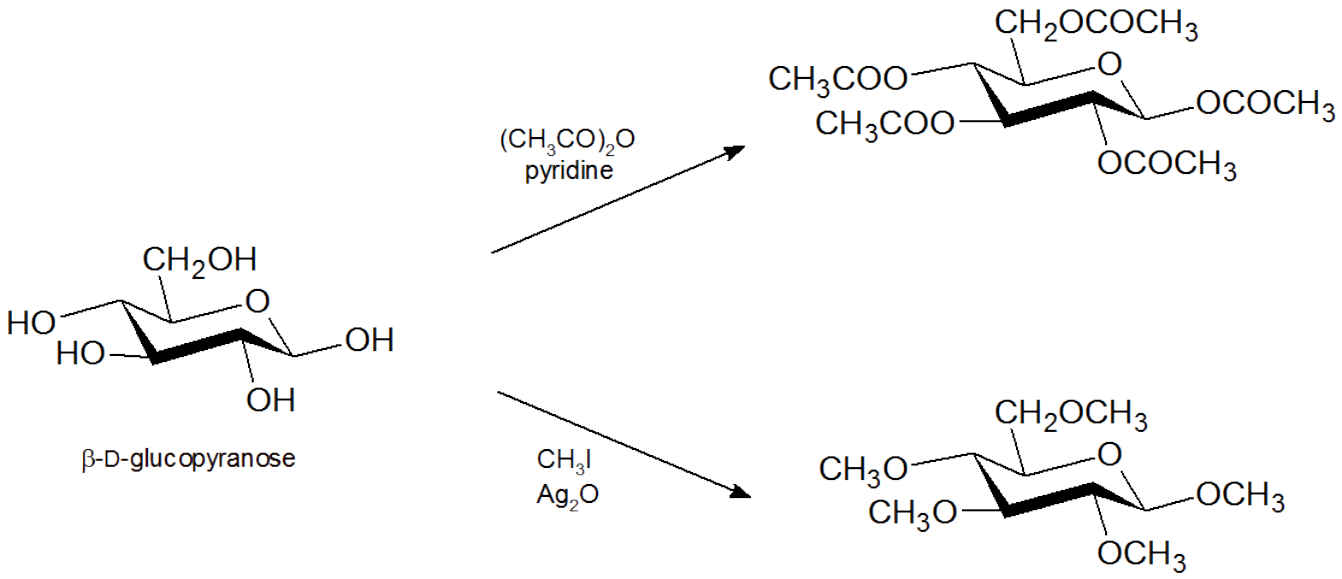
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

Ester and Ether Formation

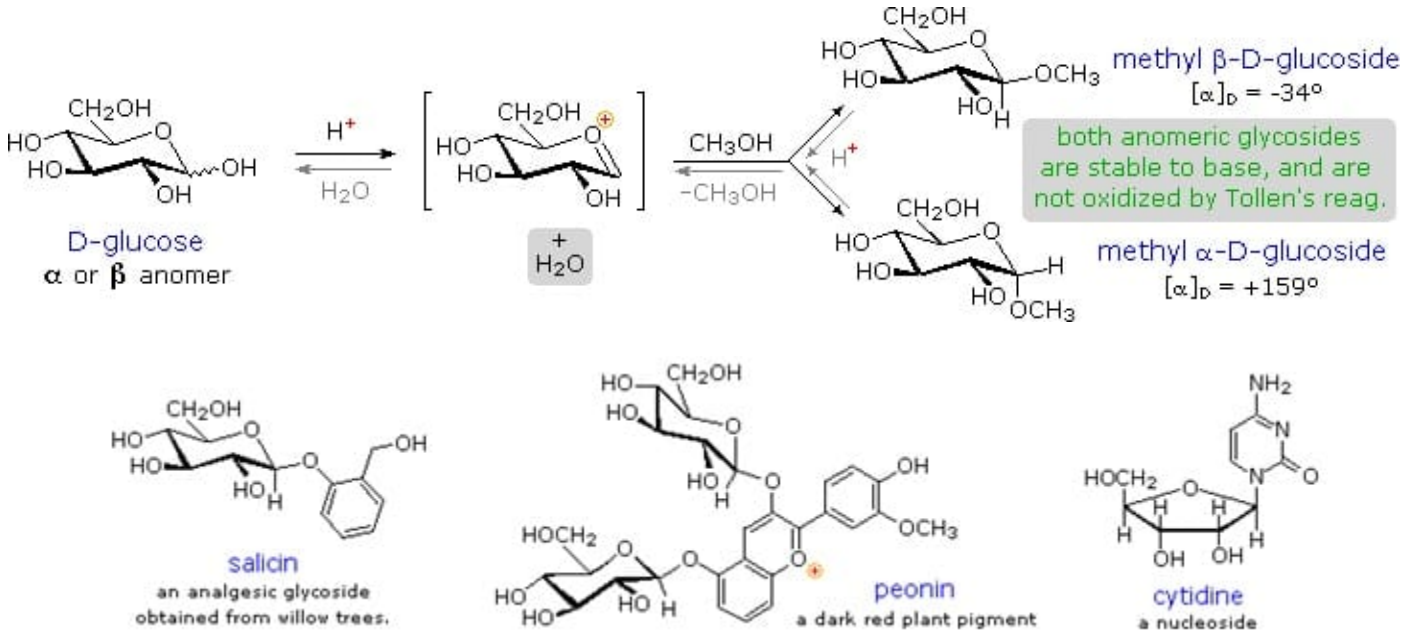
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.

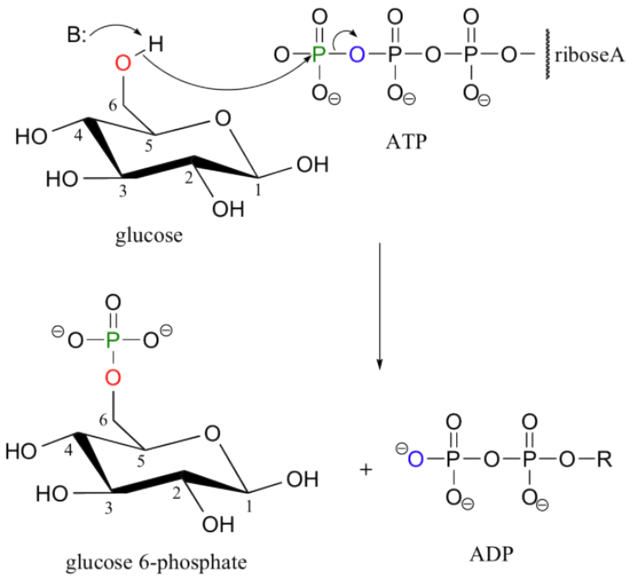


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin. A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).

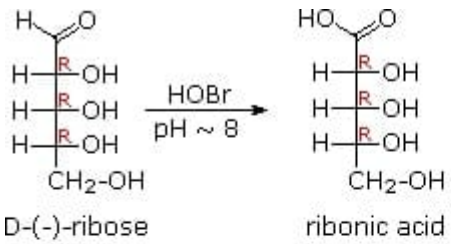


OxidationEdit section

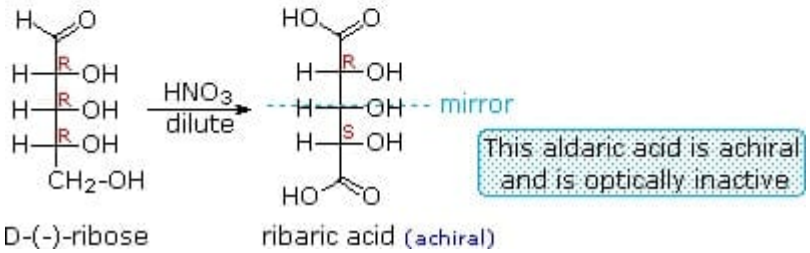
As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2° hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

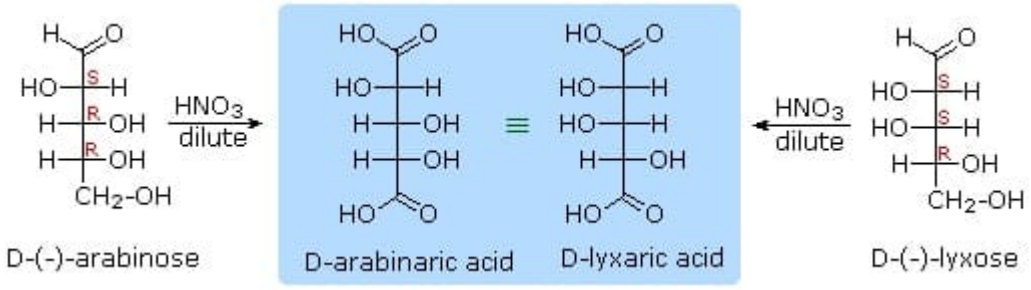
1.



2.



3.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

Reduction

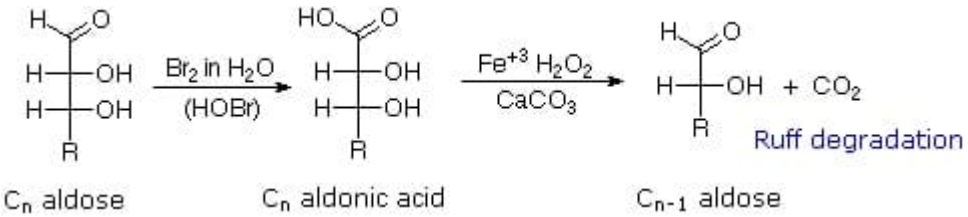
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

Table: Derivatives of $HOCH_2(CHOH)_nCHO$

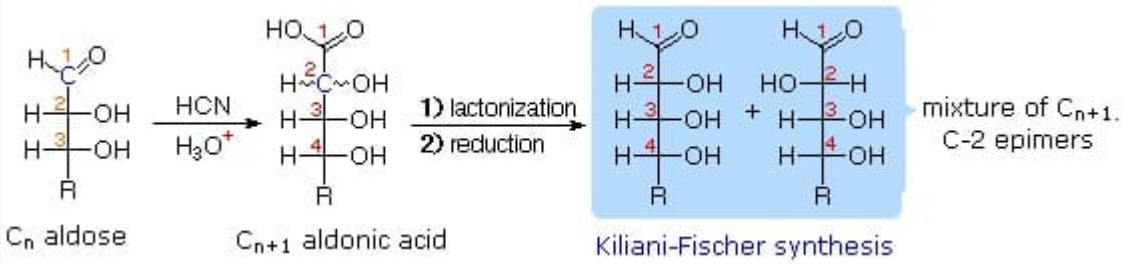
$HOBr$ Oxidation	$\longrightarrow$	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	$\longrightarrow$	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	$\longrightarrow$	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening

1. Ruff Degradation

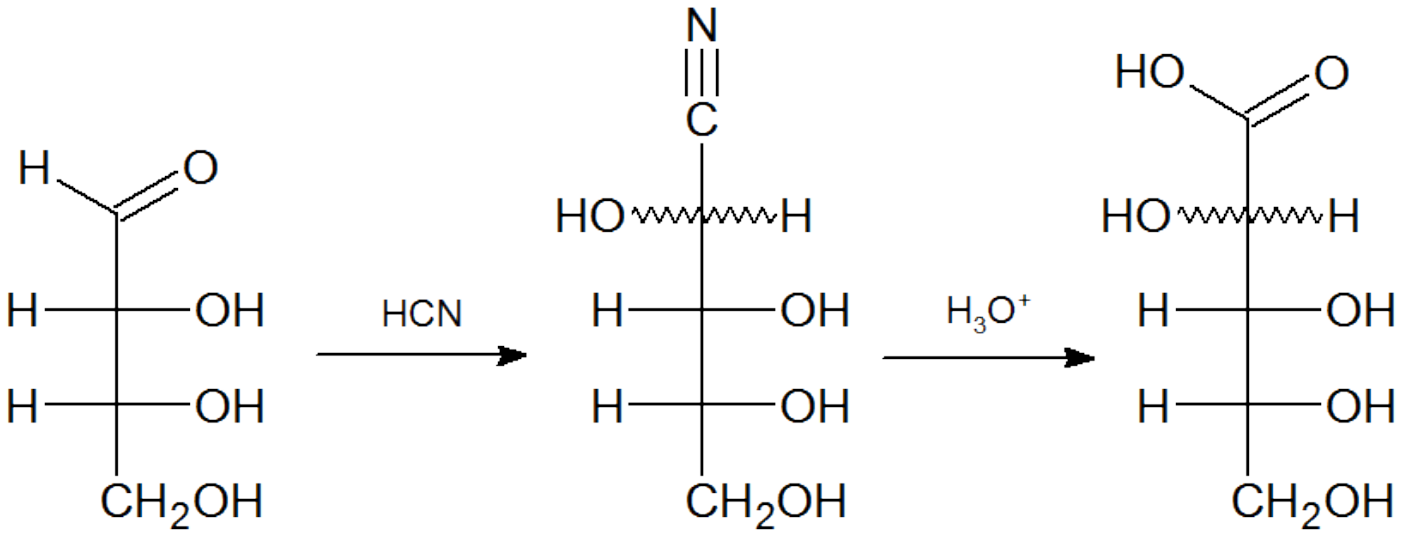


2. Kiliani-Fischer Synthesis



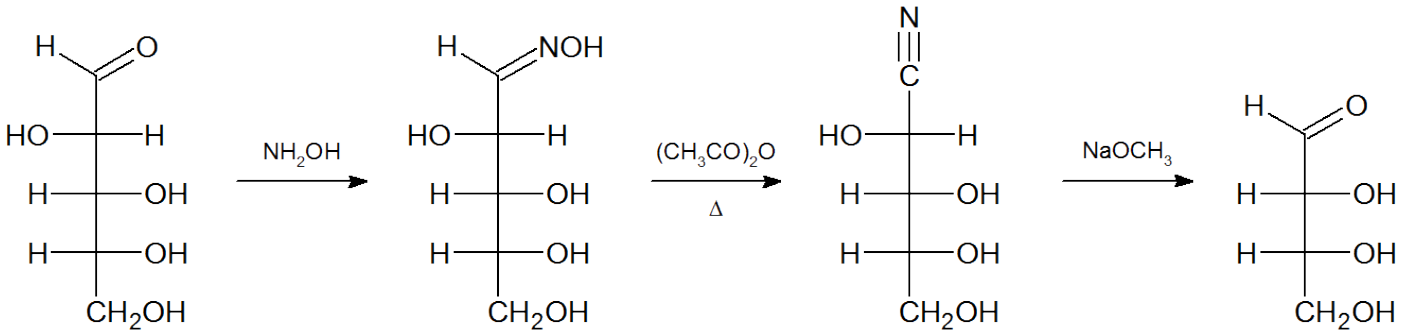
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



Exercises

Exercise 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer available at the end of this section.

Exercise 25.6.2

1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer available at the end of this section.

Exercise 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer available at the end of this section.

Exercise 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer available at the end of this section.

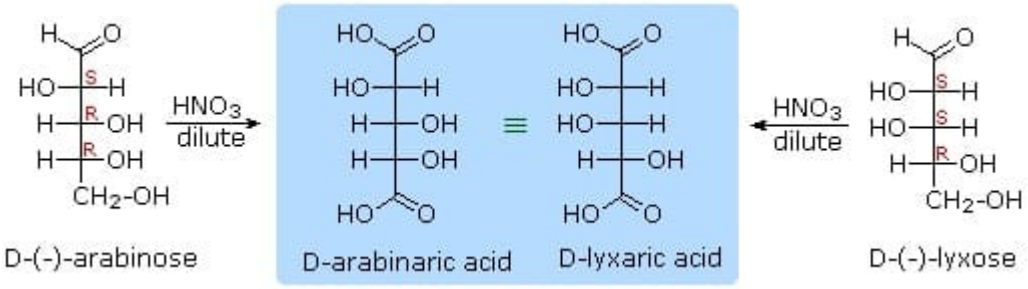
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 25.6.1

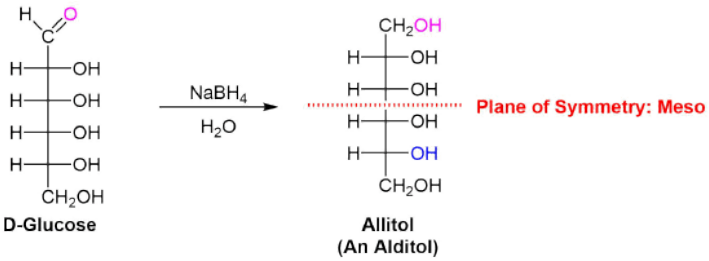
1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

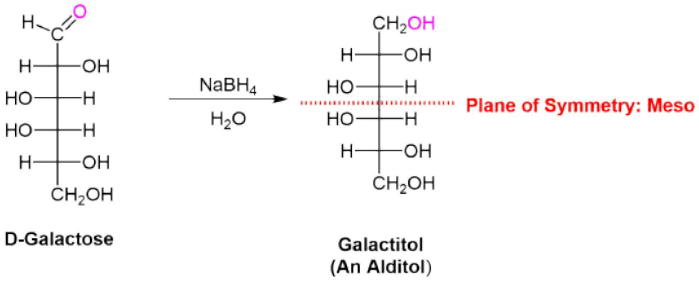


2) D-Allose and D-galactose.

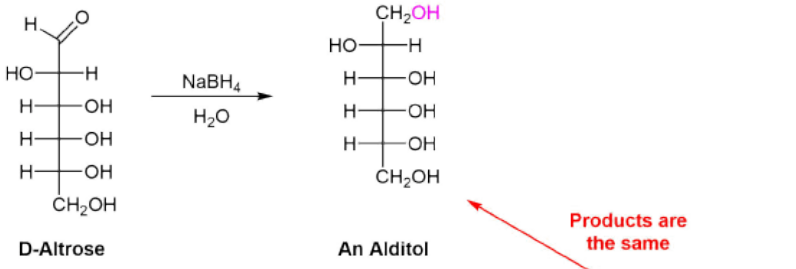
Exercise 25.6.2

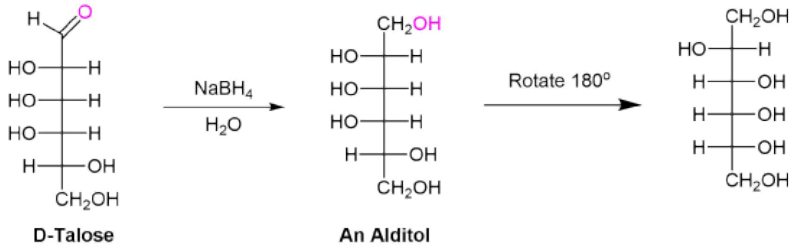
1)





2)





Exercise 25.6.3

1) D-Gluose and D-idose

2) D-Threose

Exercise 25.6.4

D-Ribose and D-arabinose

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24.7: Carbonyl Condensations with Amine Derivatives

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

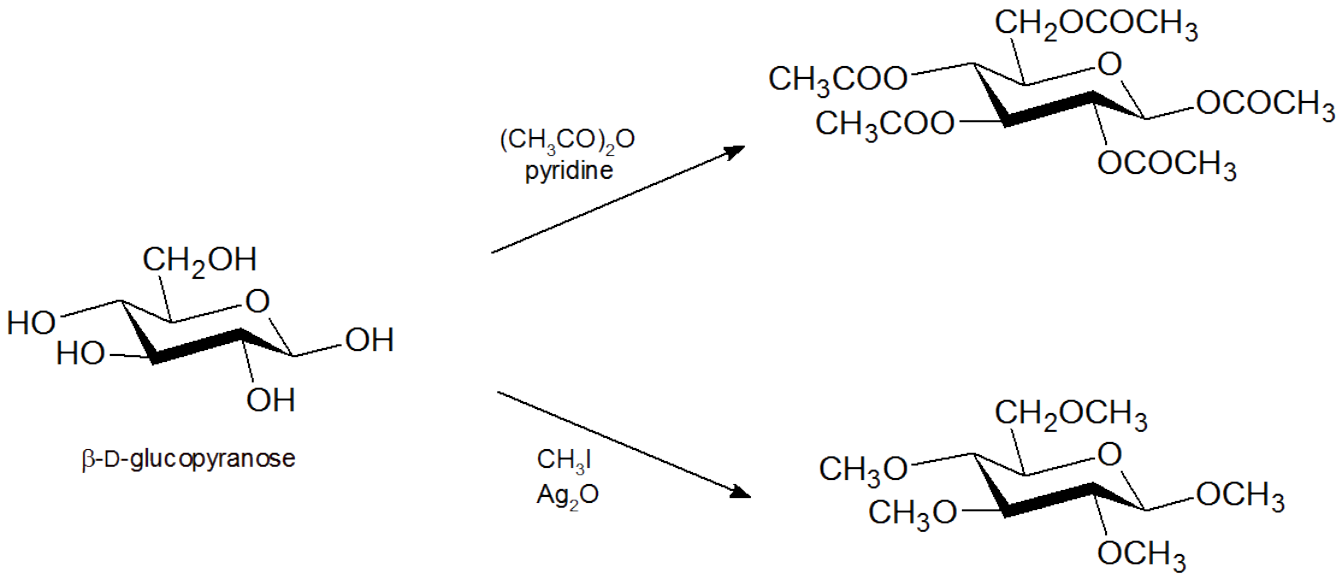
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

Ester and Ether Formation

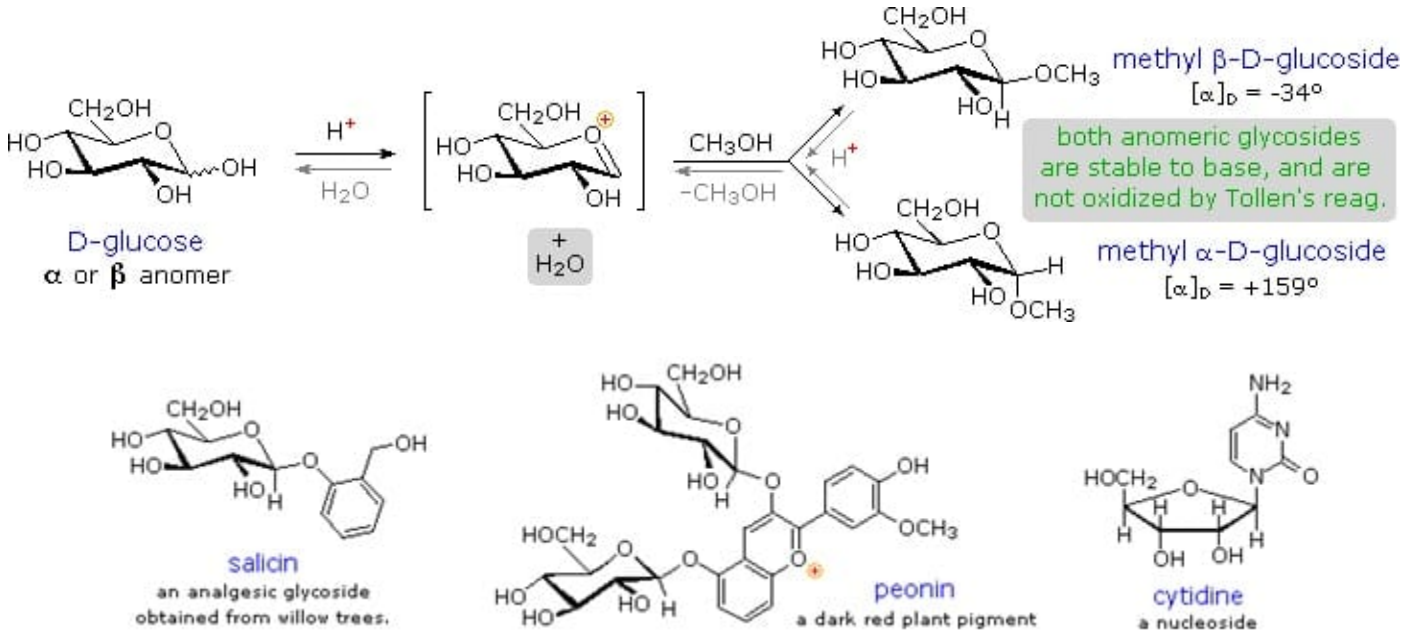
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.

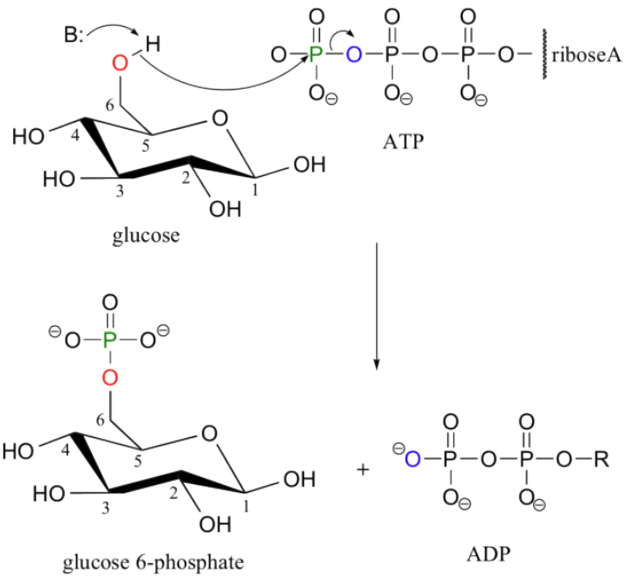


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

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Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).

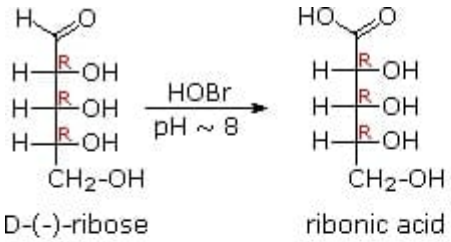


OxidationEdit section

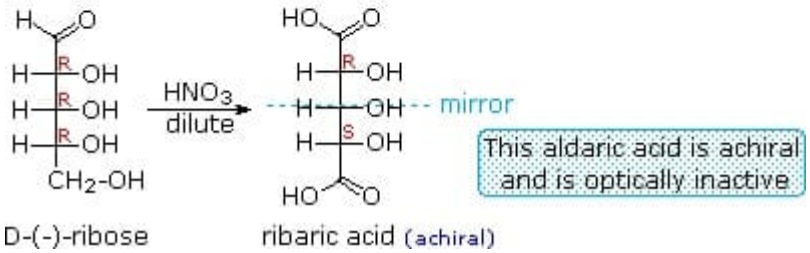
As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2° hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

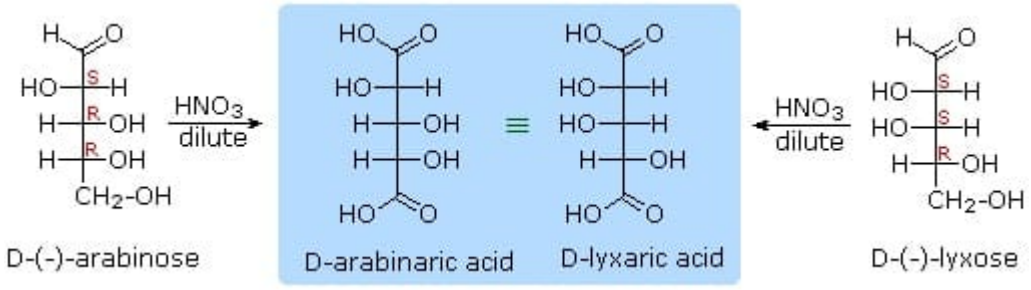
1.



2.



3.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

Reduction

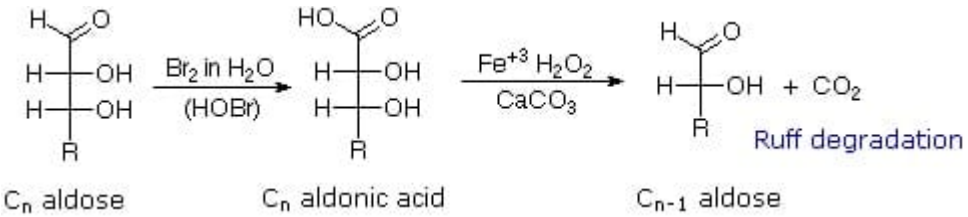
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

Table: Derivatives of $HOCH_2(CHOH)_nCHO$

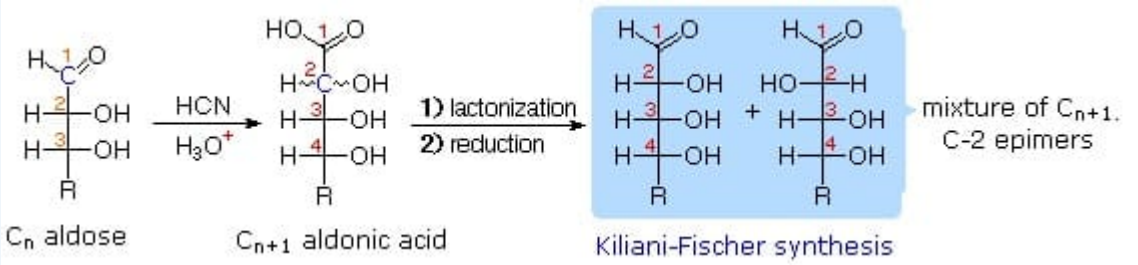
$HOBr$ Oxidation	$\longrightarrow$	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	$\longrightarrow$	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	$\longrightarrow$	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening

1. Ruff Degradation

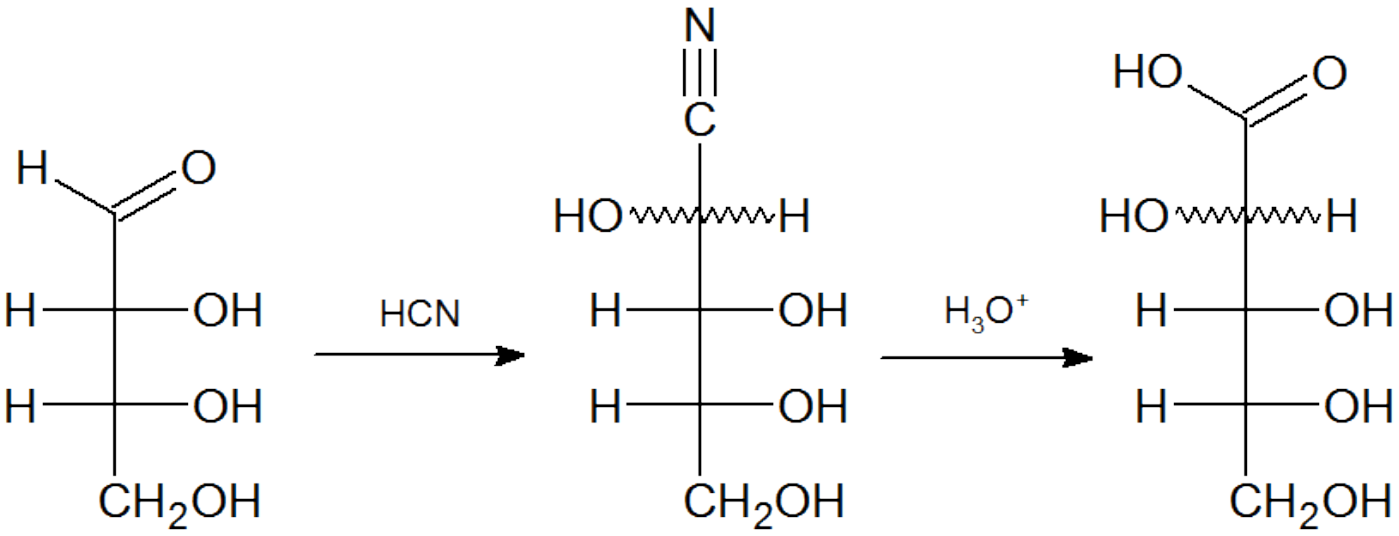


2. Kiliani-Fischer Synthesis



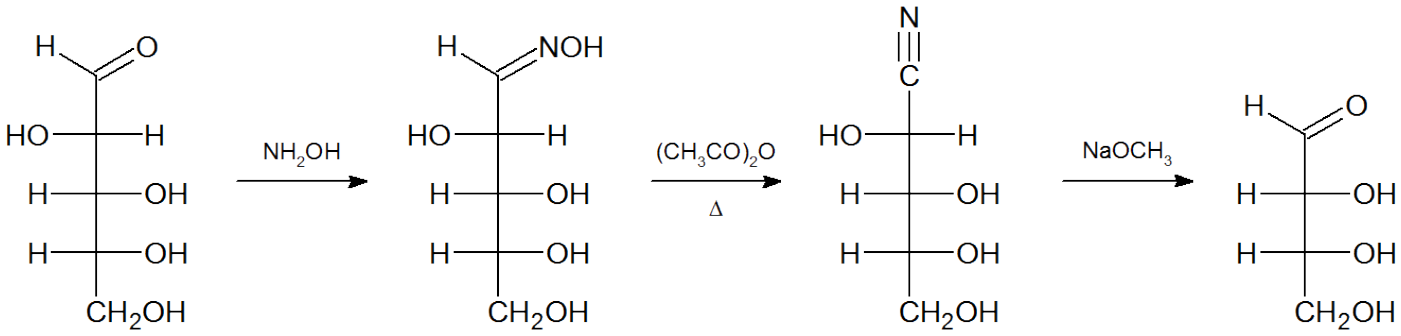
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



Exercises

Exercise 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer available at the end of this section.

Exercise 25.6.2

1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer available at the end of this section.

Exercise 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer available at the end of this section.

Exercise 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer available at the end of this section.

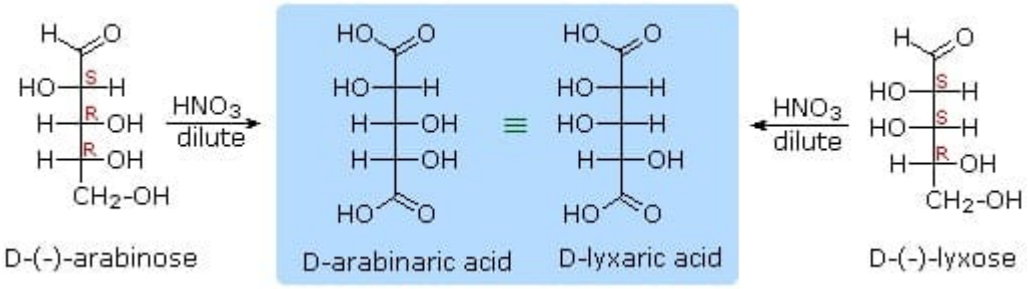
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Answers

Exercise 25.6.1

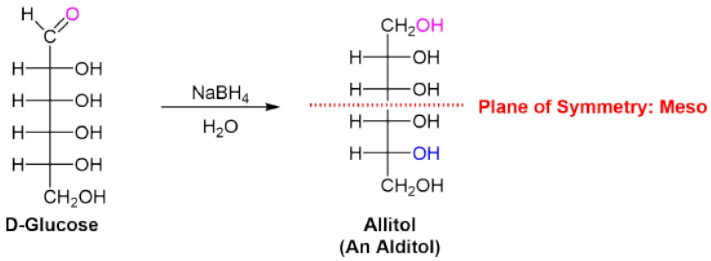
1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

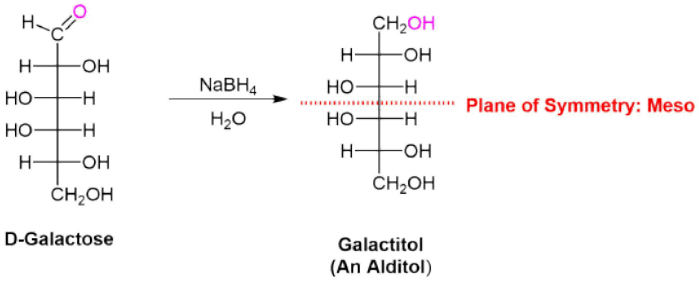


2) D-Allose and D-galactose.

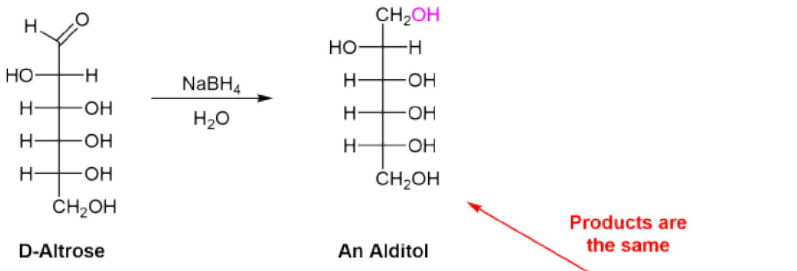
Exercise 25.6.2

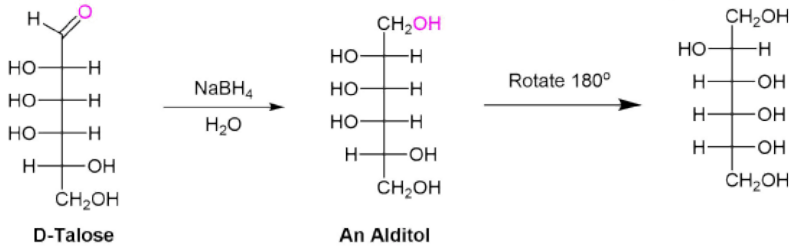
1)





2)





Exercise 25.6.3

1) D-Gluose and D-idose

2) D-Threose

Exercise 25.6.4

D-Ribose and D-arabinose

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24.8: Ester and Ether Formation: Glycosides

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

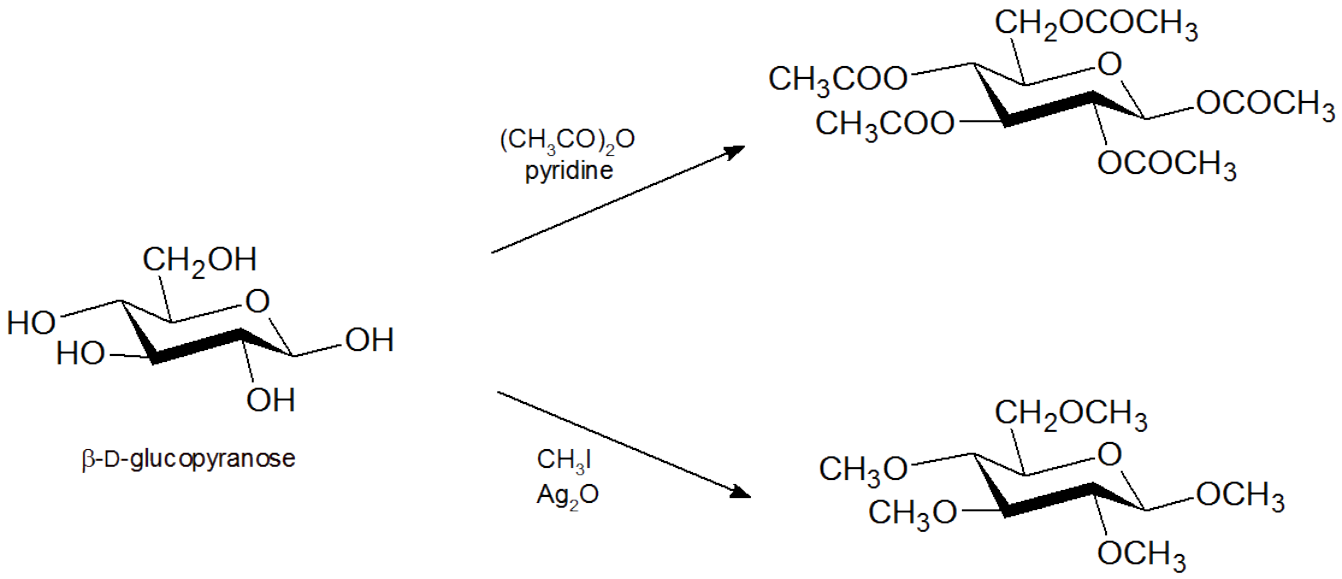
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

Ester and Ether Formation

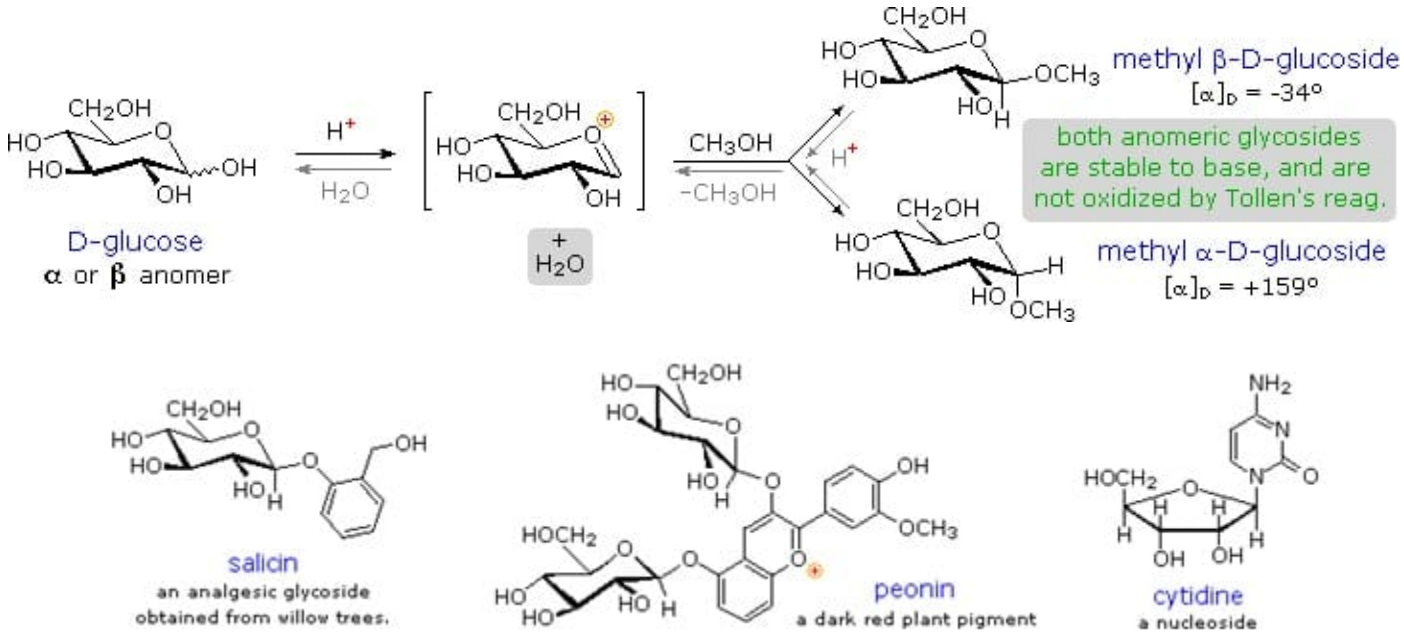
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.

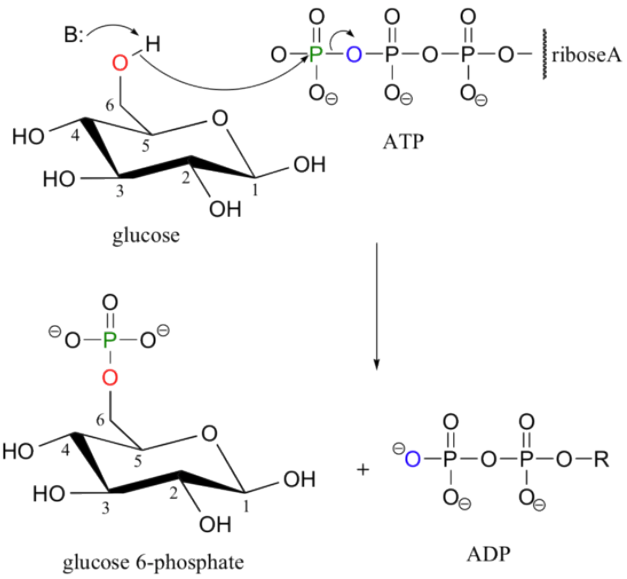


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin. A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).



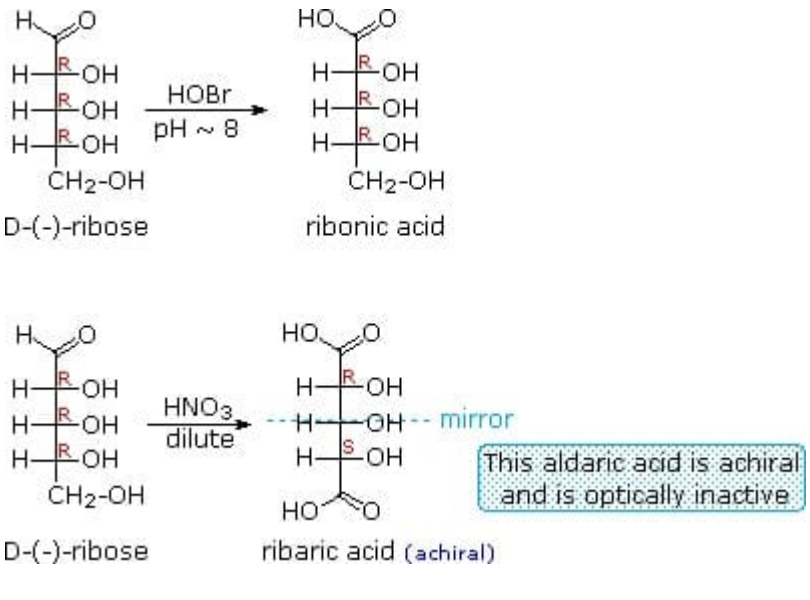
OxidationEdit section

As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

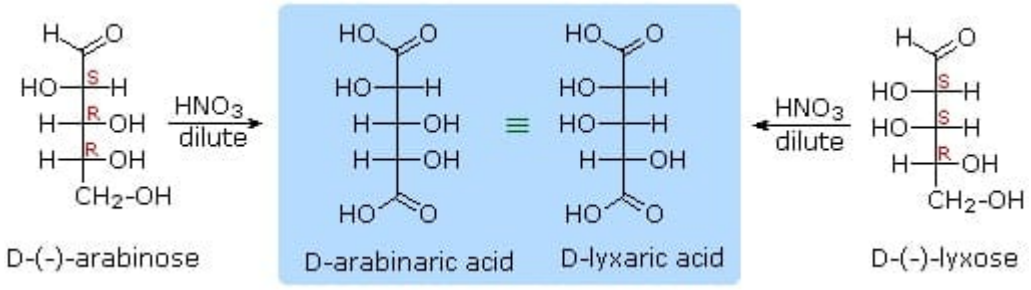
When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2° hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

1.

2.



3.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

Reduction

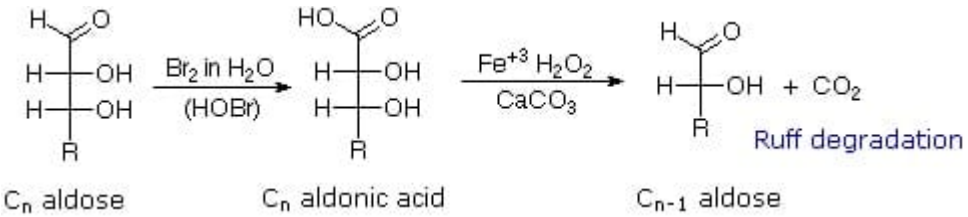
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

Table: Derivatives of $HOCH_2(CHOH)_nCHO$

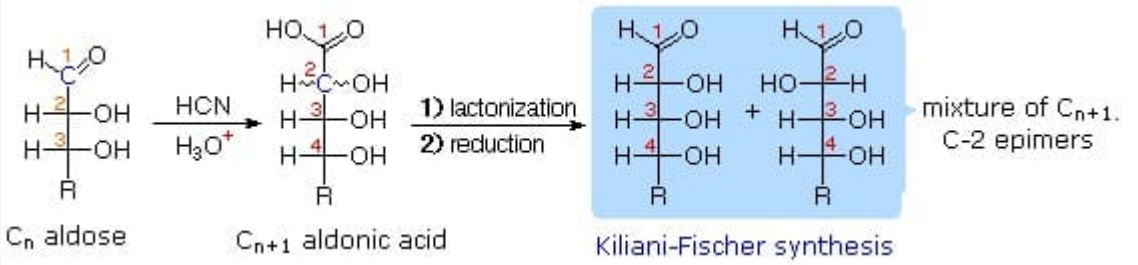
$HOBr$ Oxidation	$\longrightarrow$	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	$\longrightarrow$	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	$\longrightarrow$	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening

1. Ruff Degradation

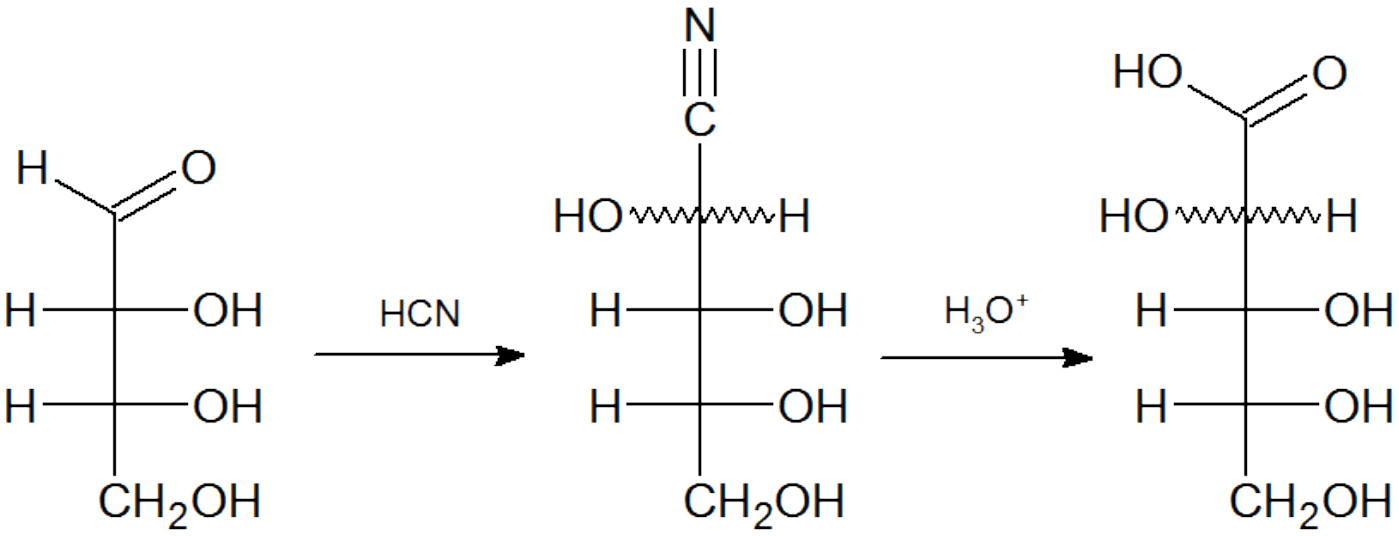


2. Kiliani-Fischer Synthesis



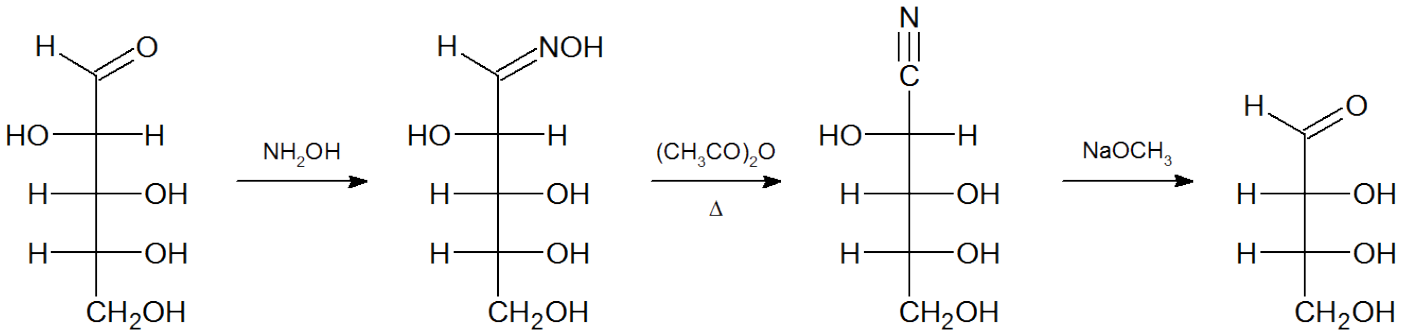
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



Exercises

Exercise 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer available at the end of this section.

Exercise 25.6.2

1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer available at the end of this section.

Exercise 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer available at the end of this section.

Exercise 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer available at the end of this section.

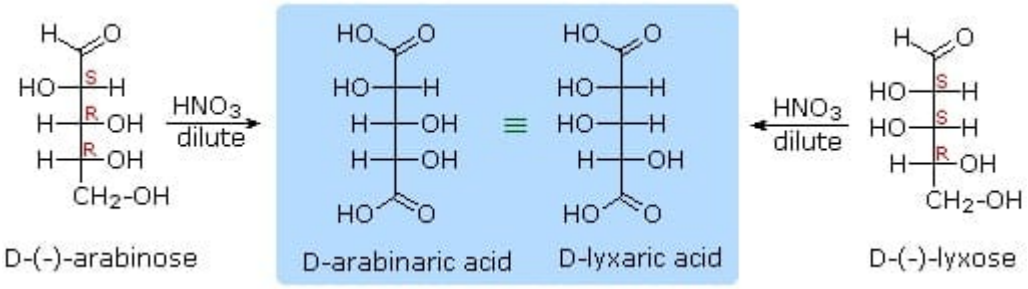
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 25.6.1

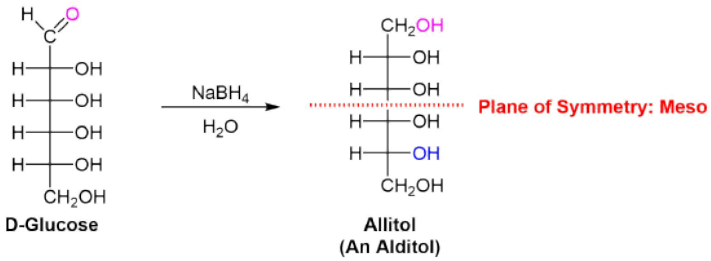
1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

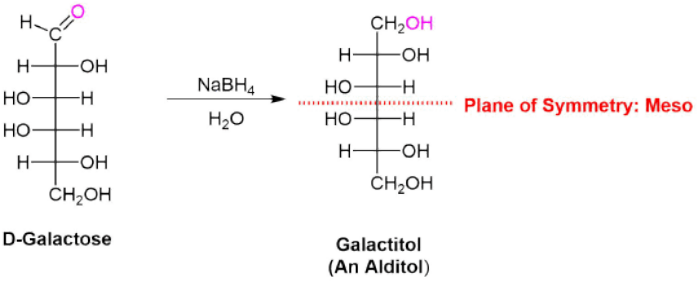


2) D-Allose and D-galactose.

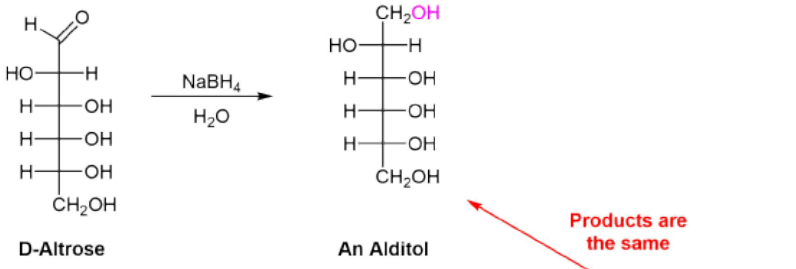
Exercise 25.6.2

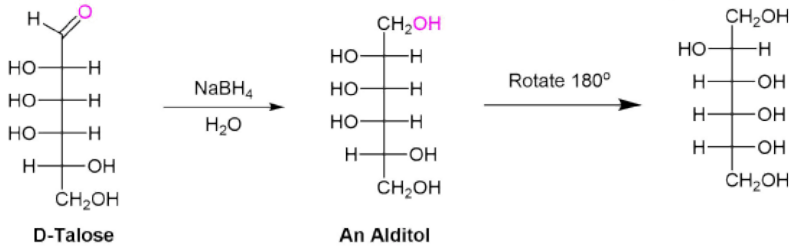
1)





2)





Exercise 25.6.3

1) D-Gluose and D-idose

2) D-Threose

Exercise 25.6.4

D-Ribose and D-arabinose

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24.9: Step-by-Step Buildup and Degradation of Sugars

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

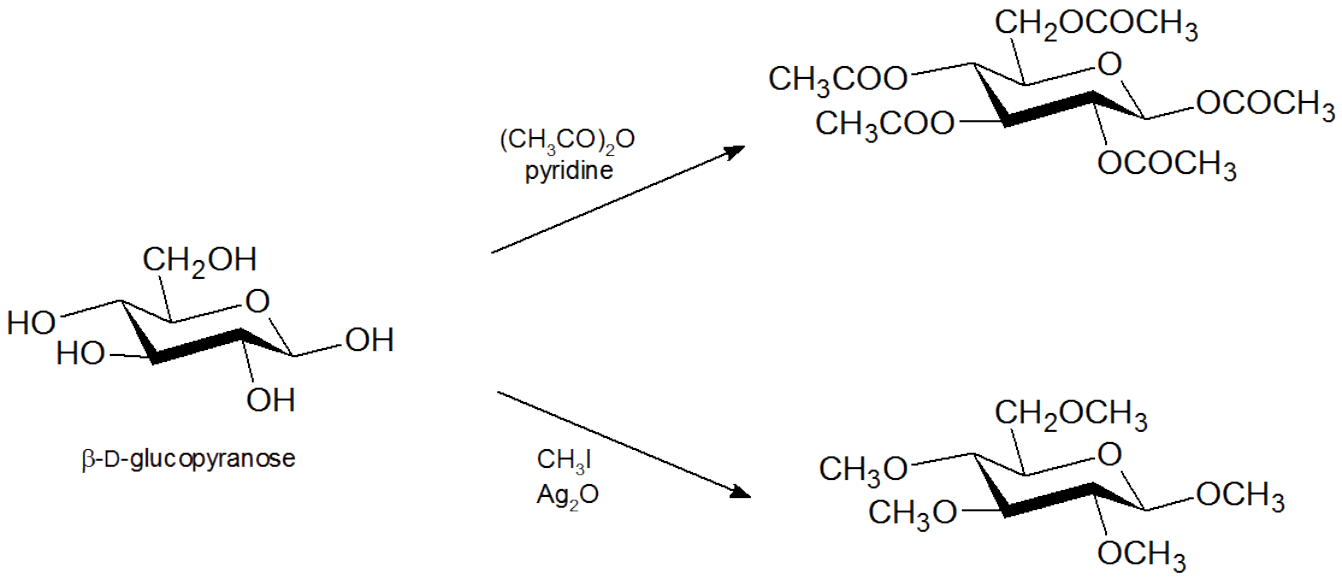
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

Ester and Ether Formation

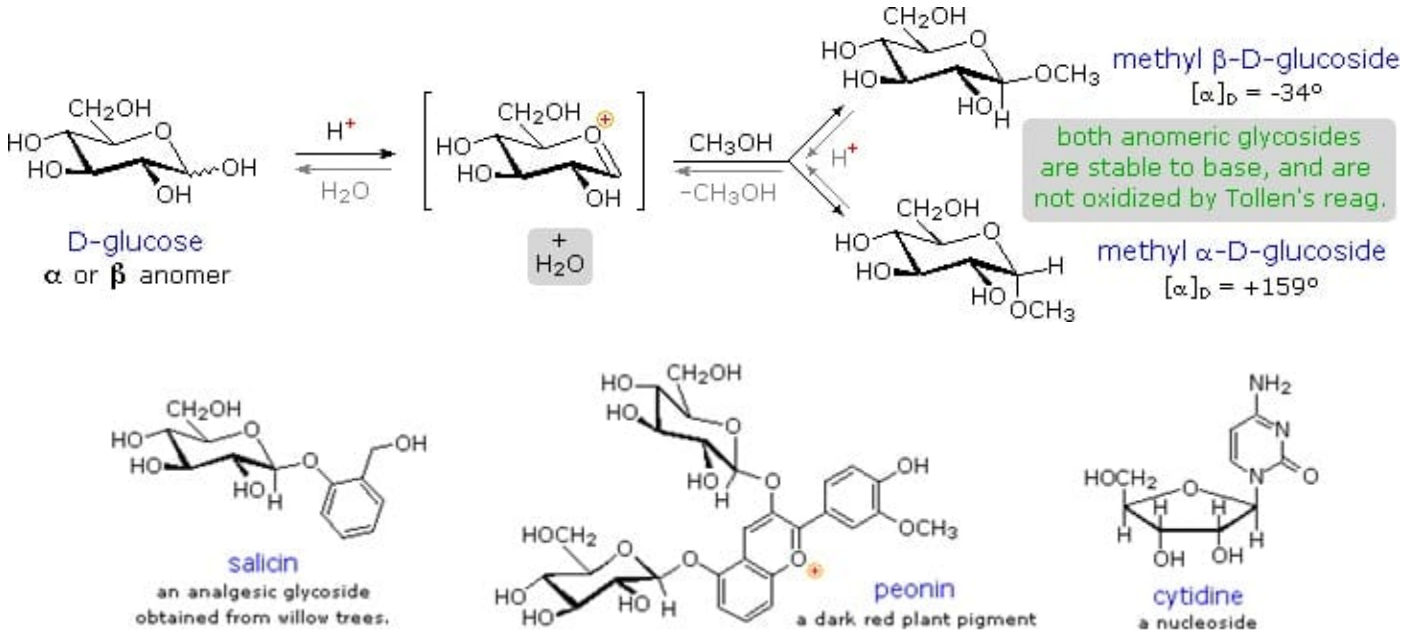
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.

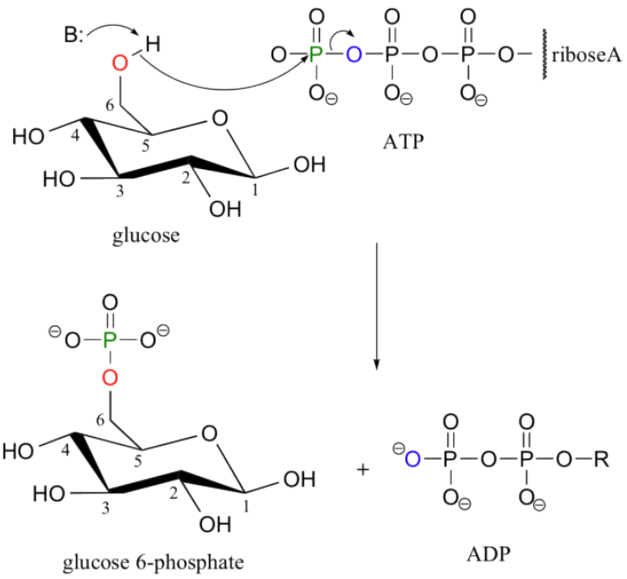


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin. A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).

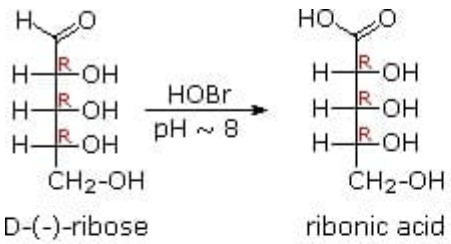


OxidationEdit section

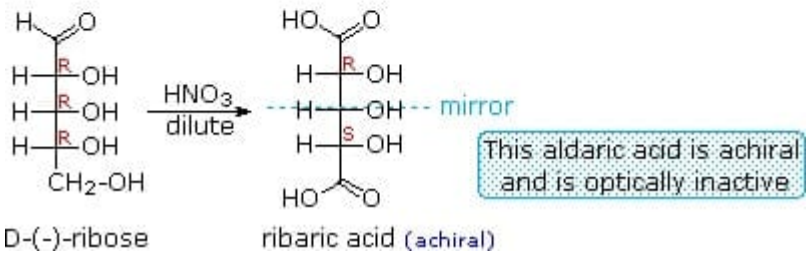
As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2° hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

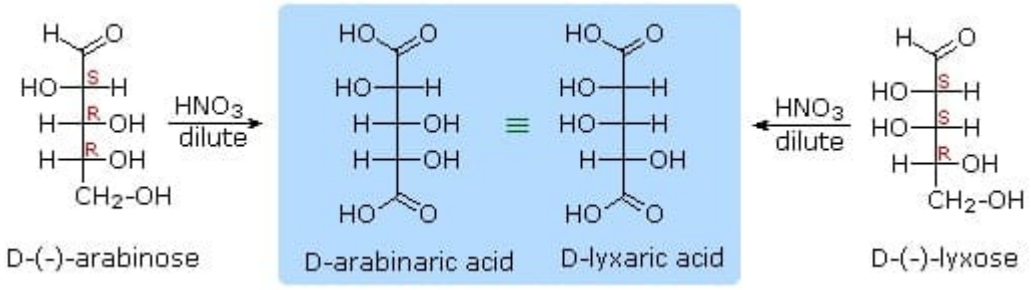
1.



2.



3.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

Reduction

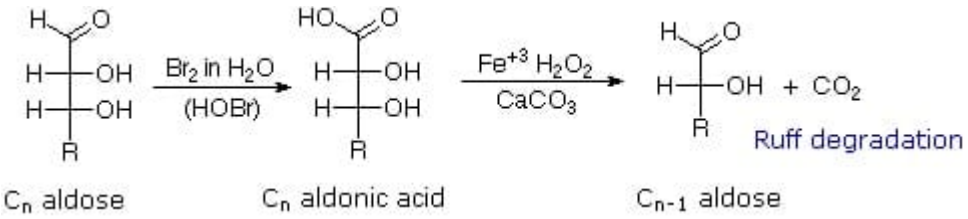
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

Table: Derivatives of $HOCH_2(CHOH)_nCHO$

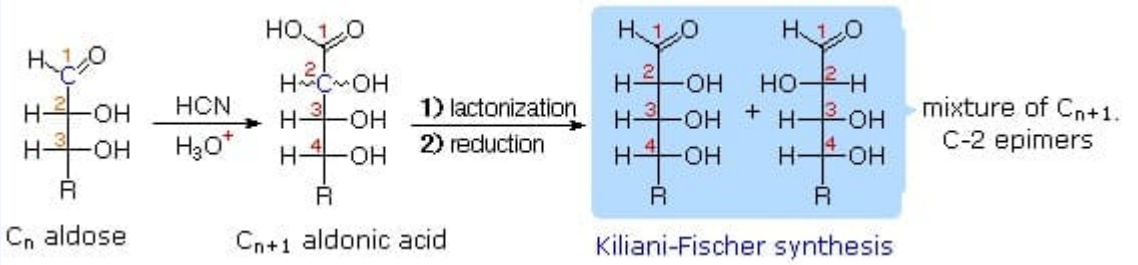
$HOBr$ Oxidation	$\longrightarrow$	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	$\longrightarrow$	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	$\longrightarrow$	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening

1. Ruff Degradation

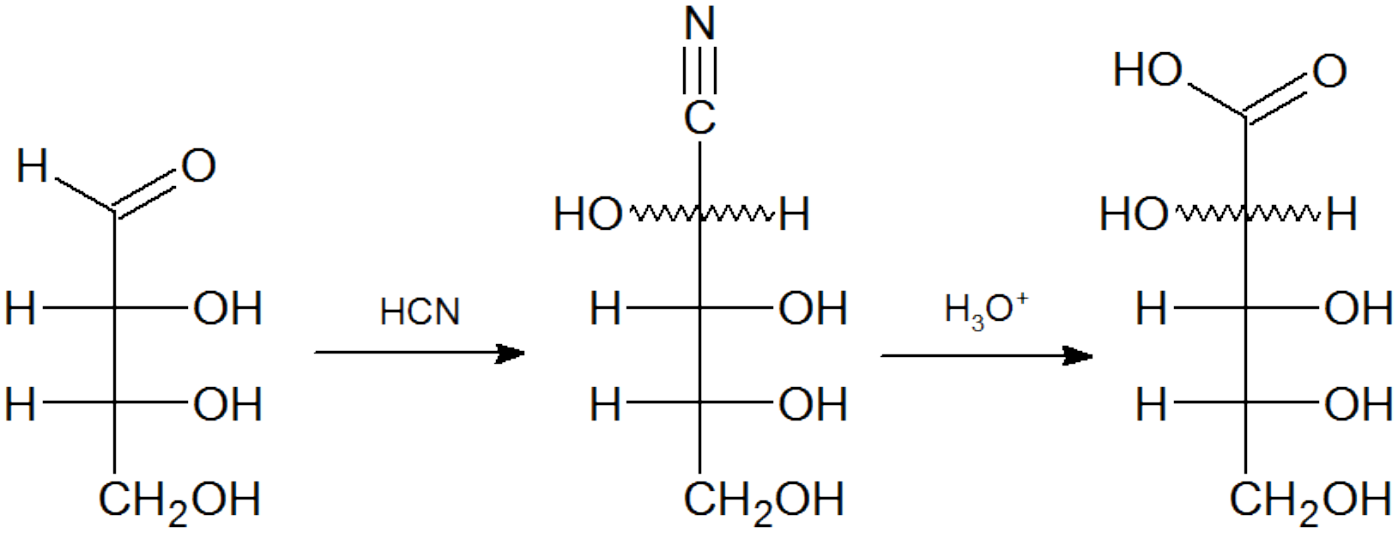


2. Kiliani-Fischer Synthesis



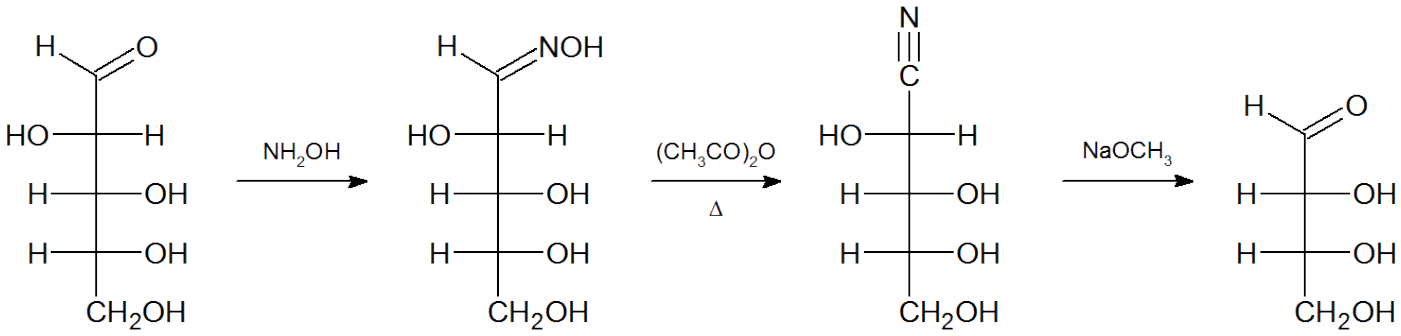
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



Exercises

Exercise 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer available at the end of this section.

Exercise 25.6.2

1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer available at the end of this section.

Exercise 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer available at the end of this section.

Exercise 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer available at the end of this section.

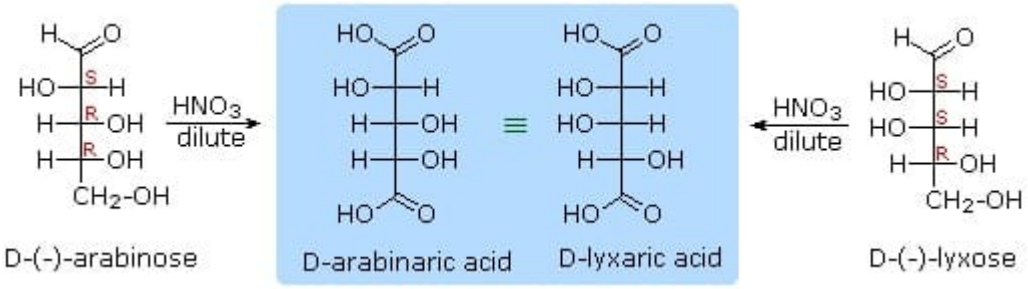
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 25.6.1

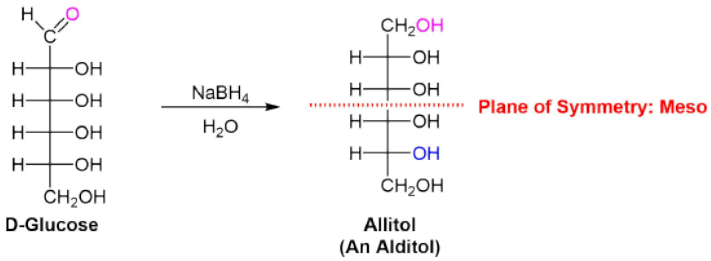
1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.

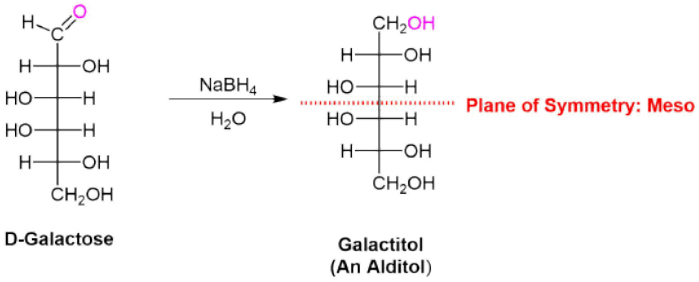


2) D-Allose and D-galactose.

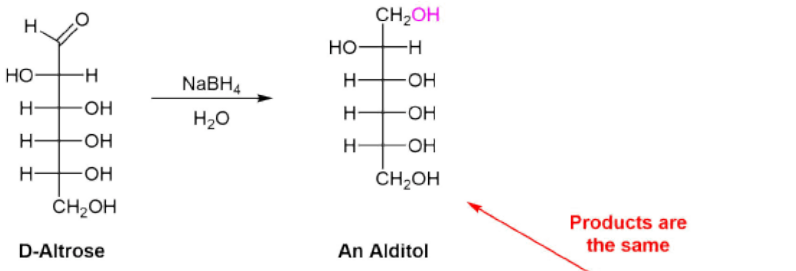
Exercise 25.6.2

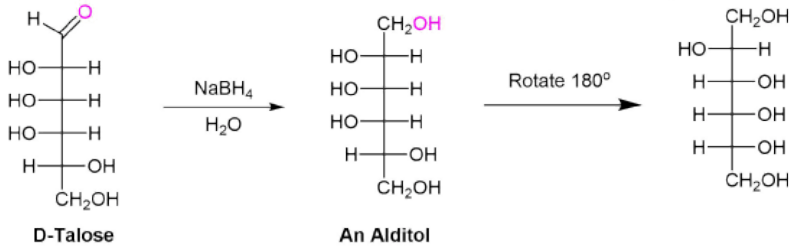
1)





2)





Exercise 25.6.3

1) D-Gluose and D-idose

2) D-Threose

Exercise 25.6.4

D-Ribose and D-arabinose

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24.10: Relative Configurations of the Aldoses: An Exercise in Structure Determination

Objectives

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If α- or β-D-glucose were one of the monosaccharide units, its structure would not be provided.

5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

Key Terms

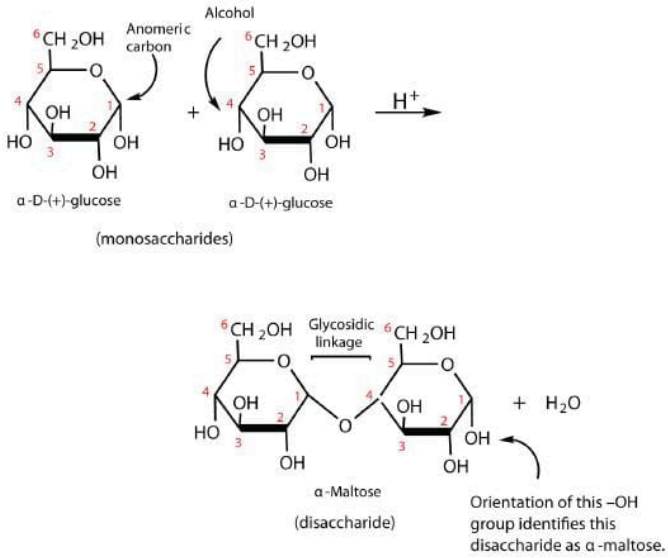
Make certain that you can define, and use in context, the key terms below.

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

Study Notes

Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.



The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water. We'll consider each sugar in more detail.

Maltose

Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose.

$$\text{maltose} \xrightarrow{\text{H}^+ \text{ or maltase}} 2 \text{ D-glucose} \tag{24.10.1}$$

Maltose is a reducing sugar. Thus, its two glucose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. The glucose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule (that is, an α-1,4-glycosidic linkage; see Figure 1). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucose can be in either the α or the β position, as shown in Figure 1.

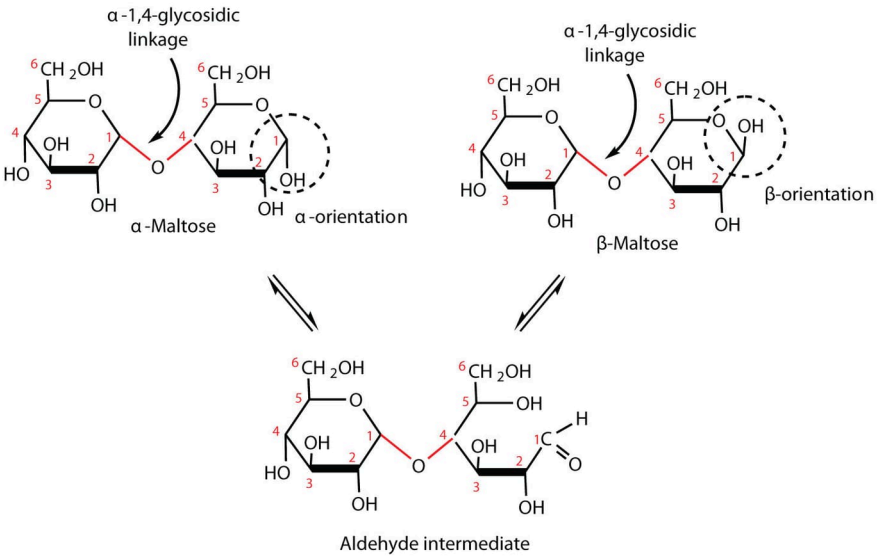
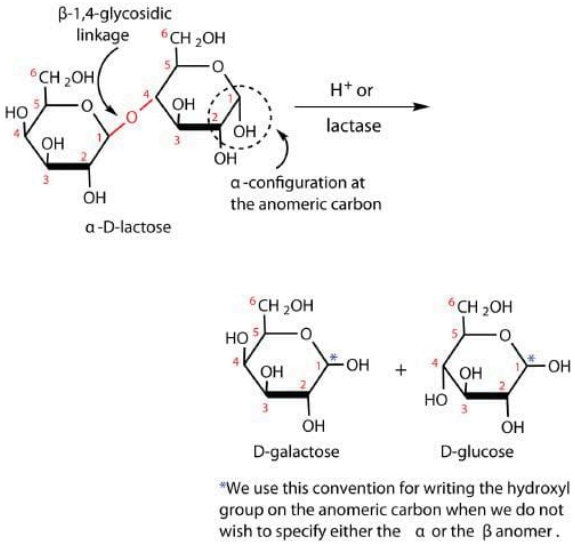


Figure 1 *An Equilibrium Mixture of Maltose Isomers*

Lactose

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

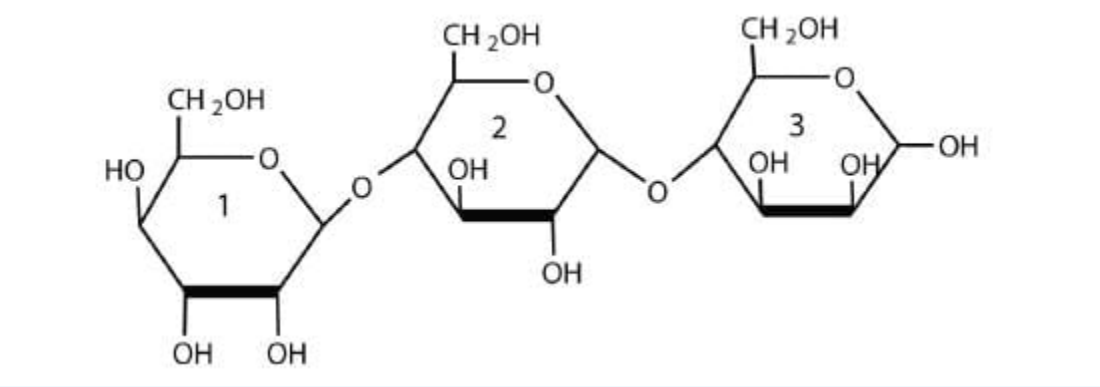
Lactose is a reducing sugar composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond (the bond from the anomeric carbon of the first monosaccharide unit being directed upward). The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*:



Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the "souring" of milk.

Example 25.8.1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

To Your Health: Lactose Intolerance and Galactosemia

Lactose makes up about 40% of an infant's diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world's adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people the inability to synthesize sufficient enzyme increases with age. Up to 20% of the US population suffers some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance, however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

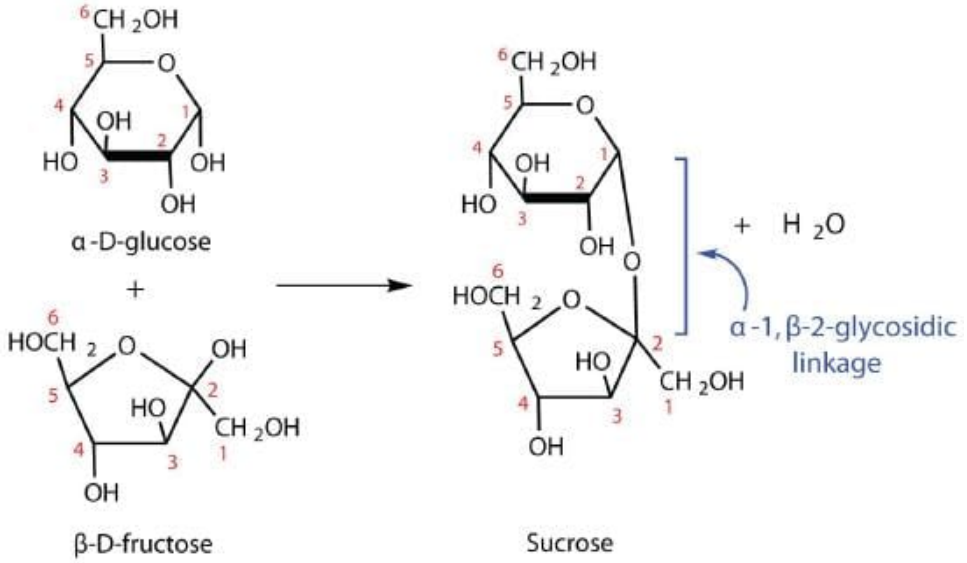
Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

Sucrose

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or

simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.



This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide "uncyclizes" to form an open-chain structure. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body's requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

Summary

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

Exercises

Exercise 25.8.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

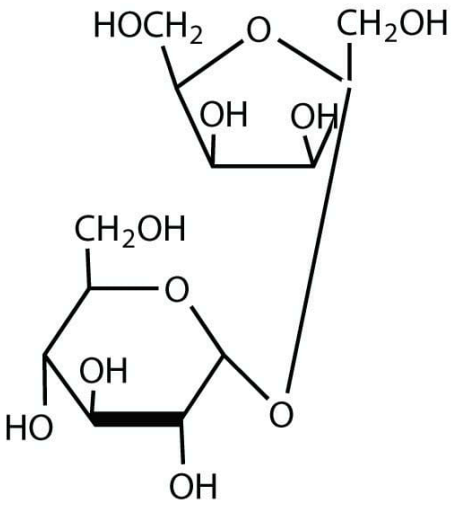
a. sucrose
b. maltose
c. lactose

Answer available at the end of this section.

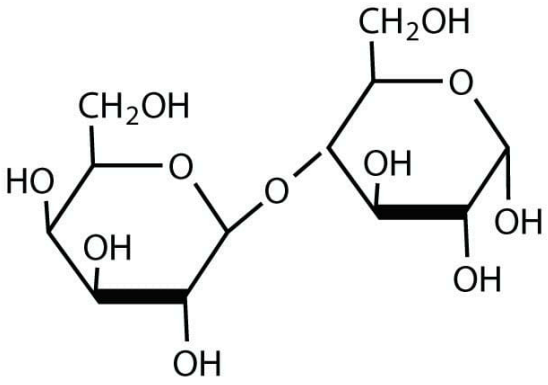
Exercise 25.8.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)



b)



Answer available at the end of this section.

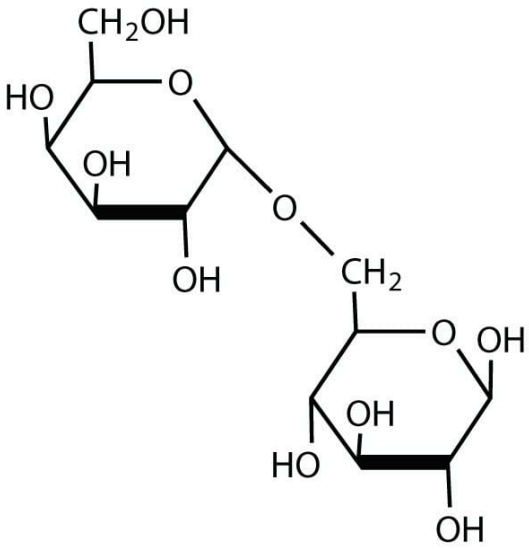
Exercise 25.8.3

Identify each disaccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position.

Answer available at the end of this section.

Exercise 25.8.4

Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



a. What monosaccharide units are incorporated into melibiose?
b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answer available at the end of this section.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

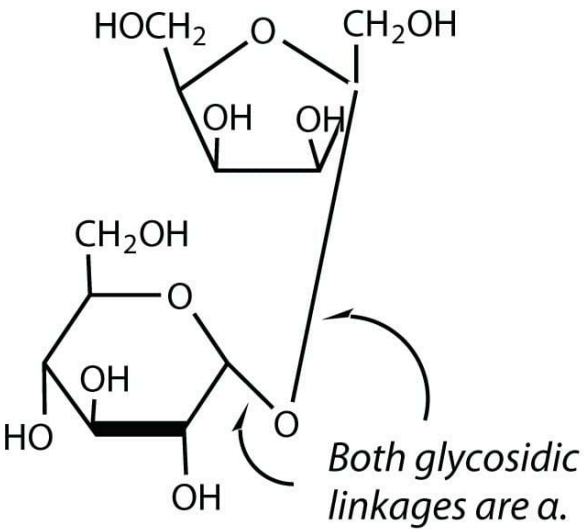
Answers

Exercise 25.8.1

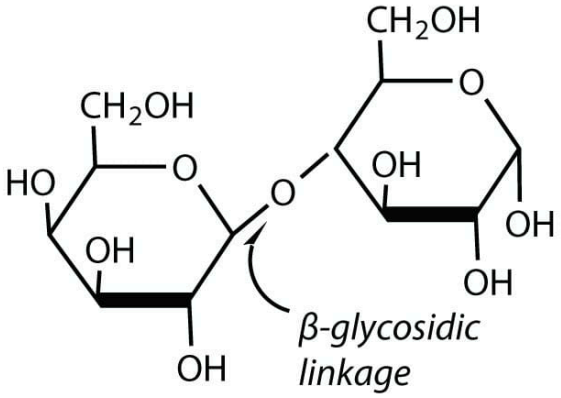
a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

Exercise 25.8.2

a)



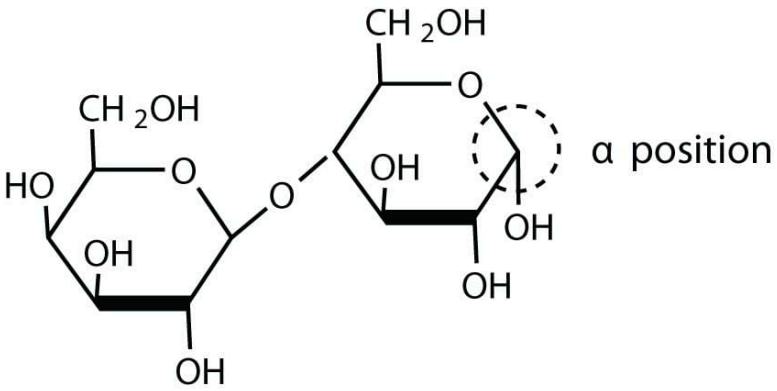
b)



Exercise 25.8.3

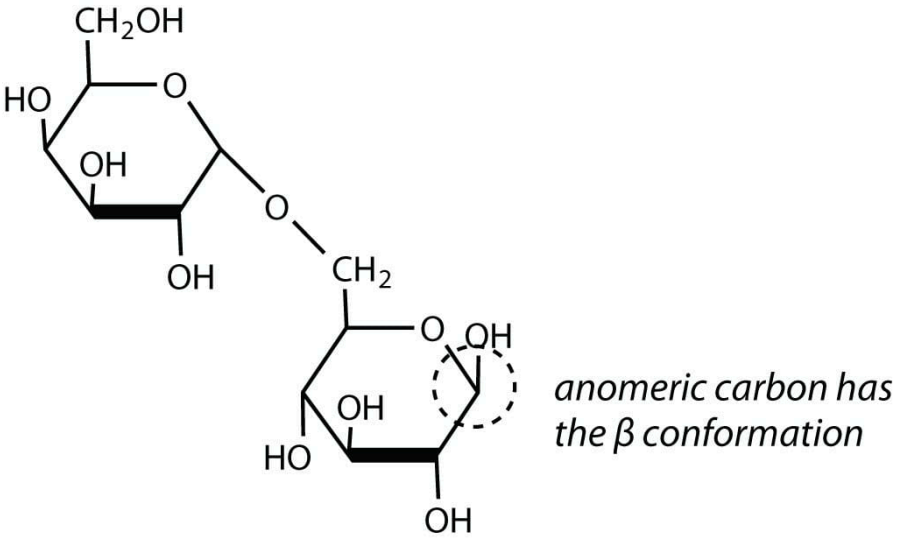
a) nonreducing

b) reducing



Exercise 25.8.4

a) galactose and glucose



b) α-glycosidic linkage
c) β.

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24.11: Complex Sugars in Nature: Disaccharides

Objectives

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amylopectin
- amylose
- polysaccharide

Learning Objectives

- To compare and contrast the structures and uses of starch, glycogen, and cellulose.

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

Starch

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure 24.11.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 24.11.1). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

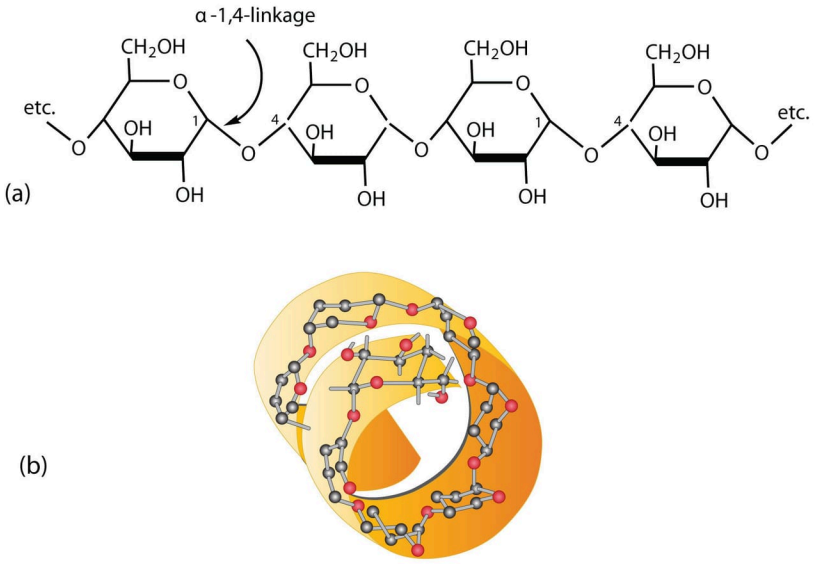


Figure 24.11.1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure 24.11.2). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

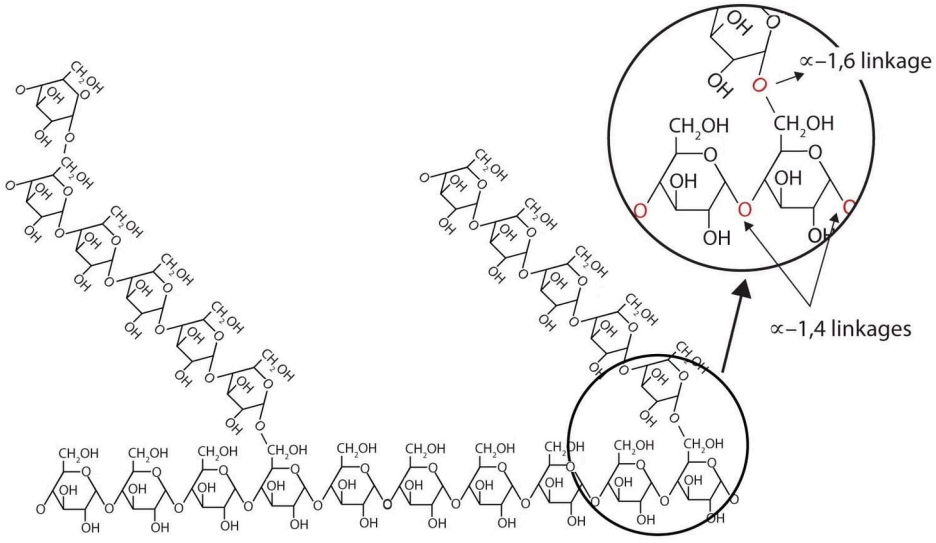


Figure 24.11.2: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

Glycogen

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

Cellulose

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of noncellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure 24.11.3). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure 24.11.3). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

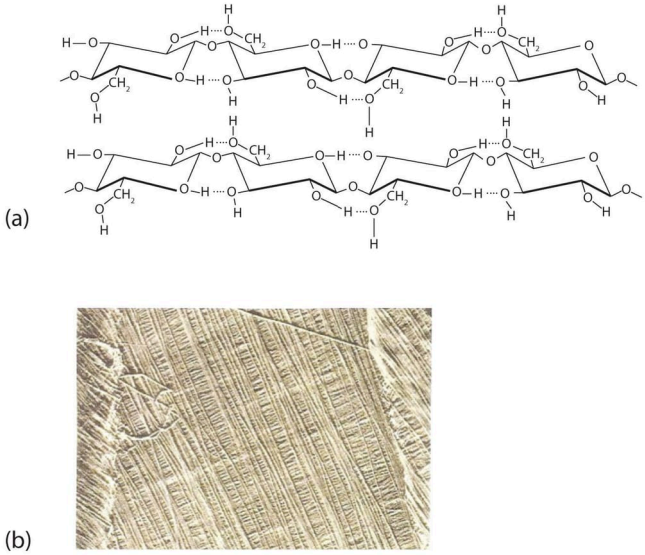


Figure 24.11.3: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes,

we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

Career Focus: Certified Diabetes Educator

Certified diabetes educators come from a variety of health professions, such as nursing and dietetics, and specialize in the education and treatment of patients with diabetes. A diabetes educator will work with patients to manage their diabetes. This involves teaching the patient to monitor blood sugar levels, make good food choices, develop and maintain an exercise program, and take medication, if required.



A certified diabetes educator at Naval Medical Center Portsmouth (left) and a registered dietician at the medical center (center), provide nutritional information to a diabetes patient and her mother at the Diabetes Boot Camp.

Diabetes educators also work with hospital or nursing home staff to improve the care of diabetic patients. Educators must be willing to spend time attending meetings and reading the current literature to maintain their knowledge of diabetes medications, nutrition, and blood monitoring devices so that they can pass this information to their patients.

Summary

Starch is a storage form of energy in plants. It contains two polymers composed of glucose units: amylose (linear) and amylopectin (branched). Glycogen is a storage form of energy in animals. It is a branched polymer composed of glucose units. It is more highly branched than amylopectin. Cellulose is a structural polymer of glucose units found in plants. It is a linear polymer with the glucose units linked through β-1,4-glycosidic bonds.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Anonymous by request
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

Objectives

You may omit Section 25.11.

Oligosaccharides

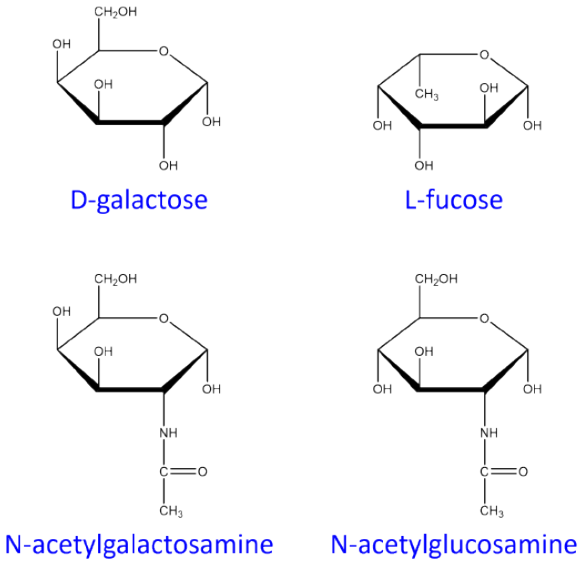
An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as a component of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

Glycoproteins

Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored by through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within the body. However, their main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell:cell, cell:protein, or protein:protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes as well, allowing for their import into the cell.

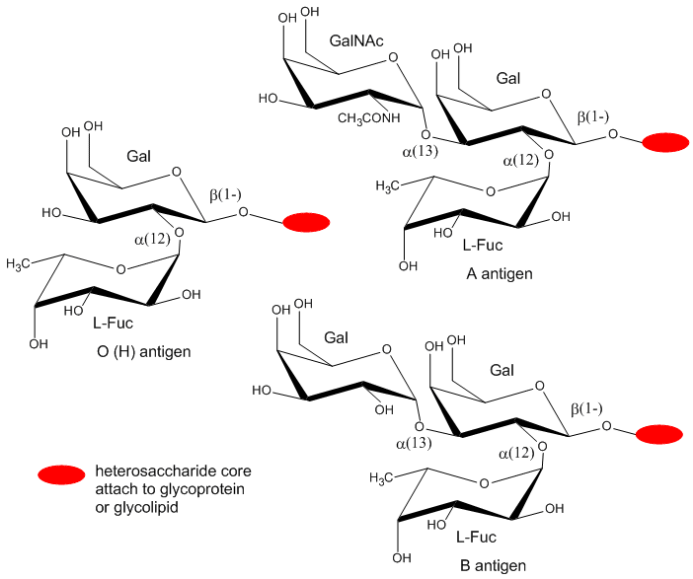
Blood Type

Cell markers are carbohydrate chains on the surface of cells where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.



Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type



ABO blood types. 6.7.2

Of the four blood types, type O has the fewest types of saccharides attached to it while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused into blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

Influenza and the Avian Flu

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is a simple yet deadly virus. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently but have low human to human transmissibility.

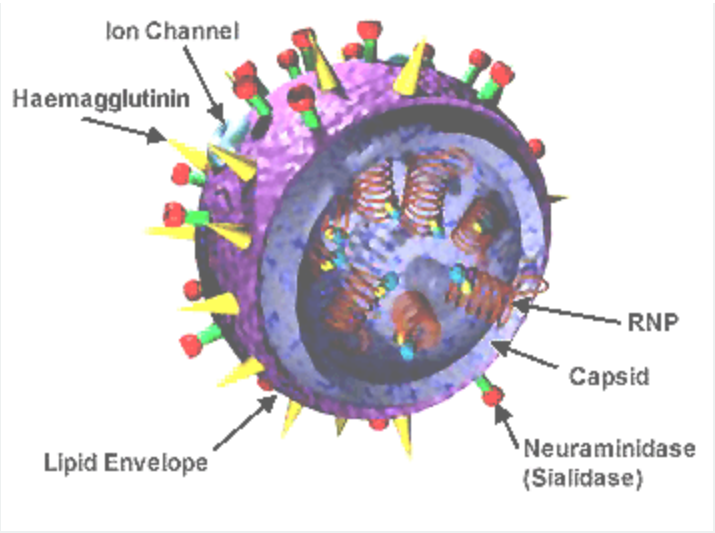
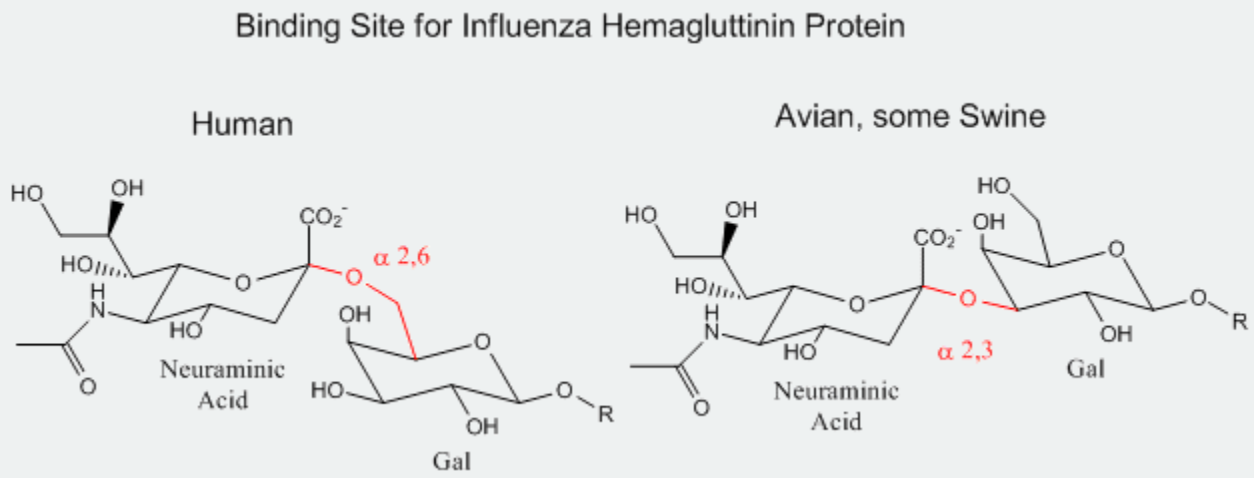
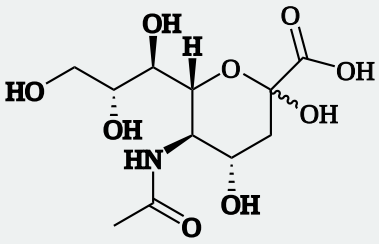


Figure 24.11.1: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Healt via Wikipedia)

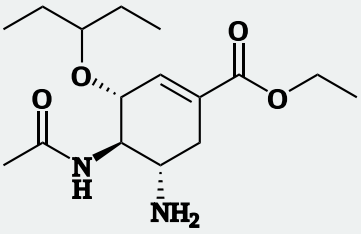
Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase whose activity is necessary for viral release from infected cells. Tamiflu appears to work against N1 of the present H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid



Tamiflu

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24.12: Polysaccharides and Other Sugars in Nature

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25: HETEROCYCLES: HETEROATOMS IN CYCLIC ORGANIC COMPOUNDS

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



-  Topic hierarchy

25.1: Naming the Heterocycles

25.2: Nonaromatic Heterocycles

25.3: Structure and Properties of Aromatic Heterocyclopentadienes

25.4: Reactions of the Aromatic Heterocyclopentadienes

25.5: Structure and Preparation of Pyridine: An Azabenzene

25.6: Reactions of Pyridine

25.7: Quinoline and Isoquinoline: The Benzopyridines

25.8: Alkaloids: Physiologically Potent Nitrogen Heterocycles in Nature

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25.1: Naming the Heterocycles

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25.2: Nonaromatic Heterocycles

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25.3: Structure and Properties of Aromatic Heterocyclopentadienes

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25.4: Reactions of the Aromatic Heterocyclopentadienes

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26: AMINO ACIDS, PEPTIDES, PROTEINS, AND NUCLEIC ACIDS: NITROGEN-CONTAINING POLYMERS IN NATURE

An organic chemistry Textmap organized around the textbook
Organic Chemistry
by Peter Vollhardt and Neil Schore



- Topic hierarchy

26.1: Structure and Properties of Amino Acids
26.2: Synthesis of Amino Acids: A Combination of Amine and Carboxylic Acid Chemistry
26.3: Synthesis of Enantiomerically Pure Amino Acids
26.4: Peptides and Proteins: Amino Acid Oligomers and Polymers
26.5: Determination of Primary Structure: Amino Acid Sequencing
26.6: Synthesis of Polypeptides: A Challenge in the Application of Protecting Groups
26.7: Merrifield Solid-Phase Peptide Synthesis
26.8: Polypeptides in Nature: Oxygen Transport by the Proteins Myoglobin and Hemoglobin
26.9: Biosynthesis of Proteins: Nucleic Acids
26.10: Protein Synthesis Through RNA
26.11: DNA Sequencing and Synthesis: Cornerstones of Gene Technology

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26.1: Structure and Properties of Amino Acids

Objectives

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: You are not expected to remember the detailed structures of all these amino acids, but you should be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: To do so, you must remember that in the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- α-amino acids
- amphoteric
- essential amino acids
- zwitterion

Study Notes

This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

Introduction to Amino Acids

Amino acids form polymers through a nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

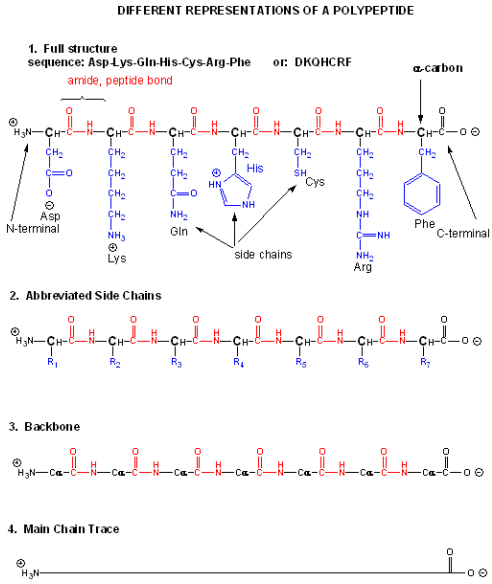
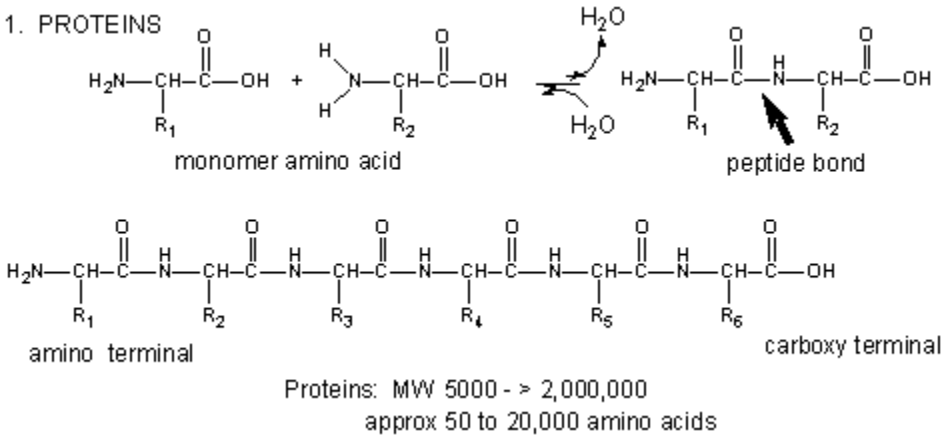


Figure: Amino Acids React to Form Proteins



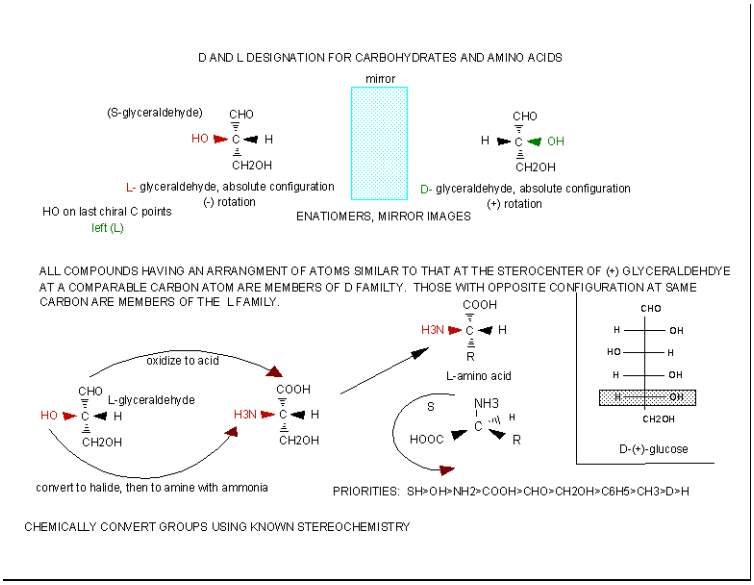
(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

Stereochemistry

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids

are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

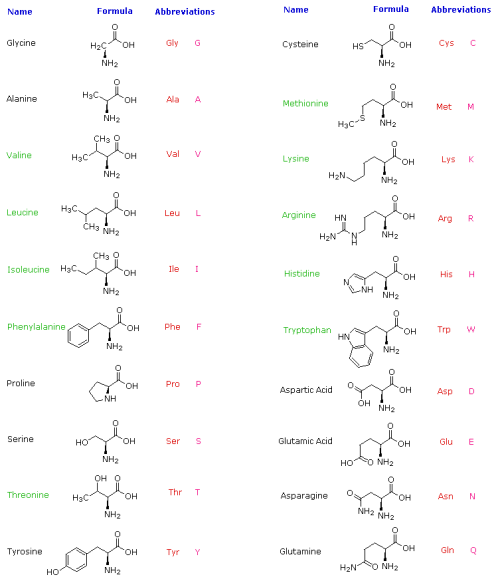
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

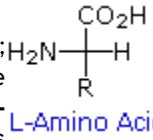
It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

Natural α-Amino Acids

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

Natural α-Amino Acids





L-Amino Acid

Some common features of these amino acids should be noted. With the exception of proline, they are all 1°-amines; and with the exception of glycine, they are all chiral. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.

The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

Physical Properties of Selected Acids and Amines

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 °C	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 °C	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 °C	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 °C	9.8

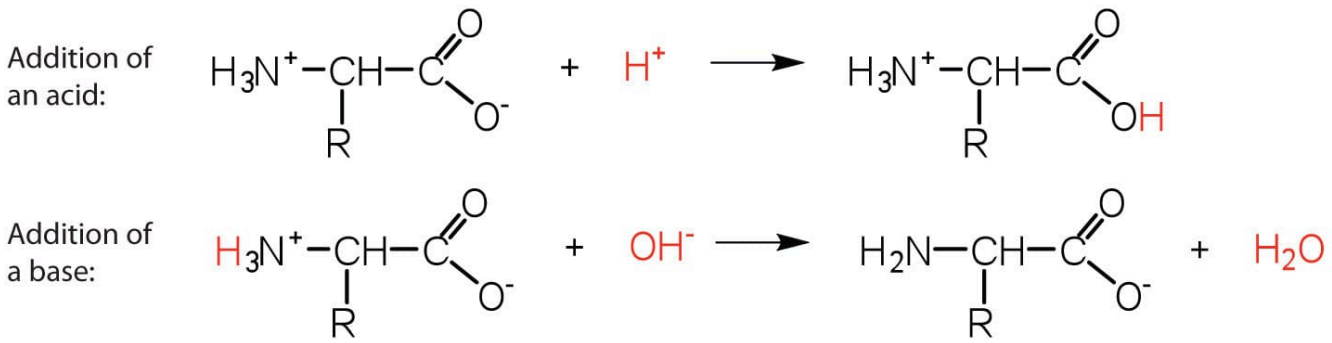
Zwitterion

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.

$CH_3CH(NH_2)CO_2H$	⇌	$CH_3CH(NH_3)^{(+)}CO_2^{(-)}$

As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1°-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

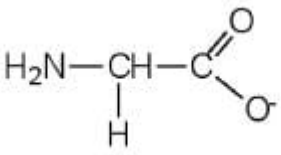


Example 26.1.1

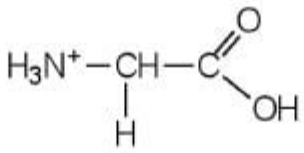
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

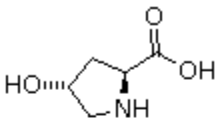


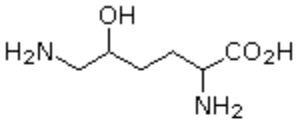
b. The acid adds H^+ to the carboxylate group.

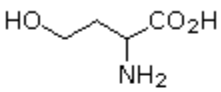


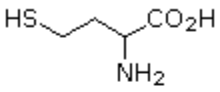
Other Natural Amino Acids

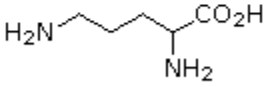
The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.


4-hydroxyproline


5-hydroxylysine

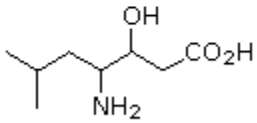

homoserine


homocysteine


ornithine


β-alanine


γ-aminobutyric acid (GABA)


statine

Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

Exercises

Exercise 26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Answer available at the end of this section.

Exercise 26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

Answer available at the end of this section.

Questions

Q26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Q26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

Solutions

S26.1.1

The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

S26.1.2

(a)

26.3 Solution A.png

(b)

26.3 Solution B 1.png

26.3 Solution B2.png

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Henry Jakubowski (College of St. Benedict/St. John's University)

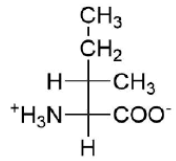
Answers

Exercise 26.1.1

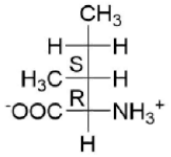
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

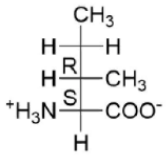
Exercise 26.1.2

(a)



(b)





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26.2: Synthesis of Amino Acids: A Combination of Amine and Carboxylic Acid Chemistry

Objectives

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

Key Terms

Make certain that you can define, and use in context, the key terms below.

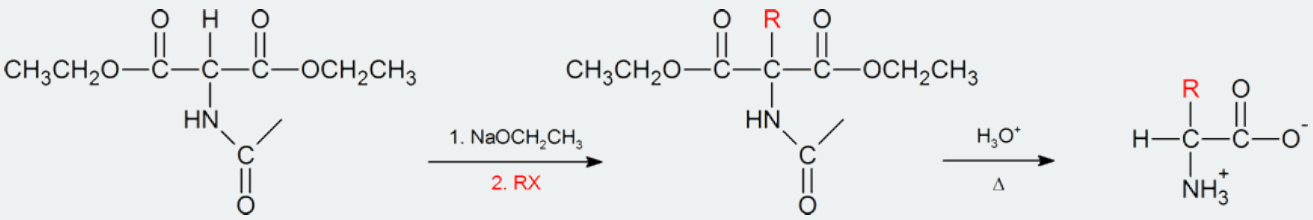
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

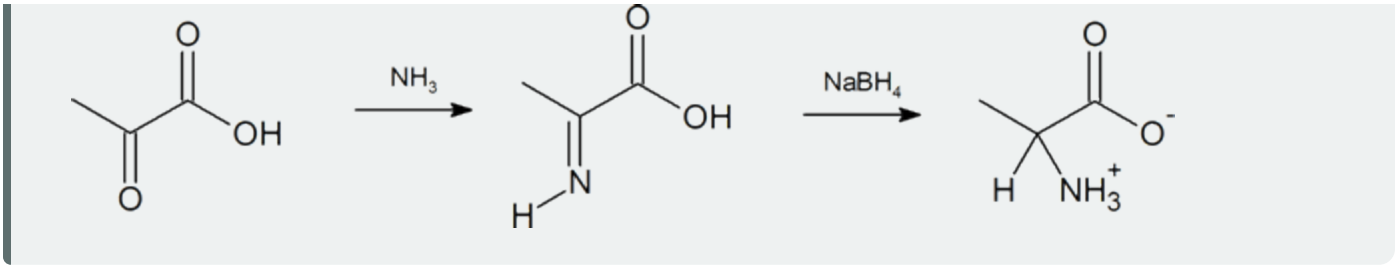
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.

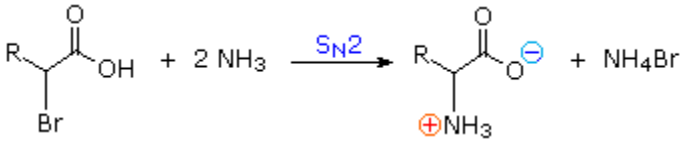


Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).

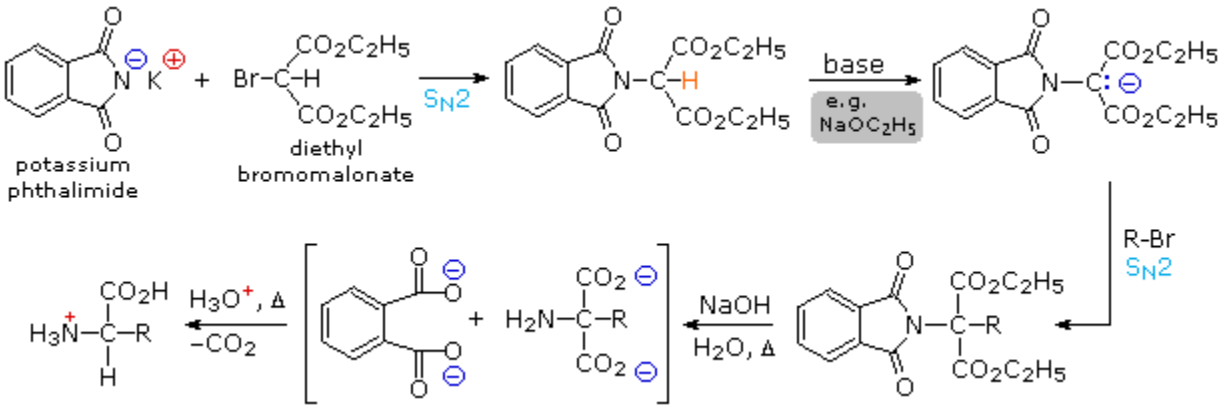


Synthesis of α-Amino AcidsEdit section

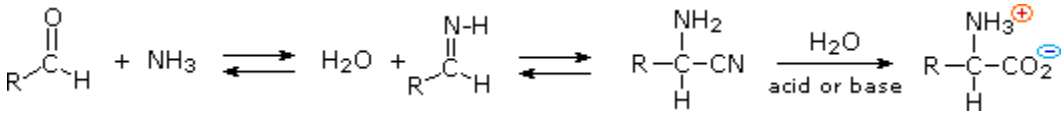
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1°- and many 2°-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).



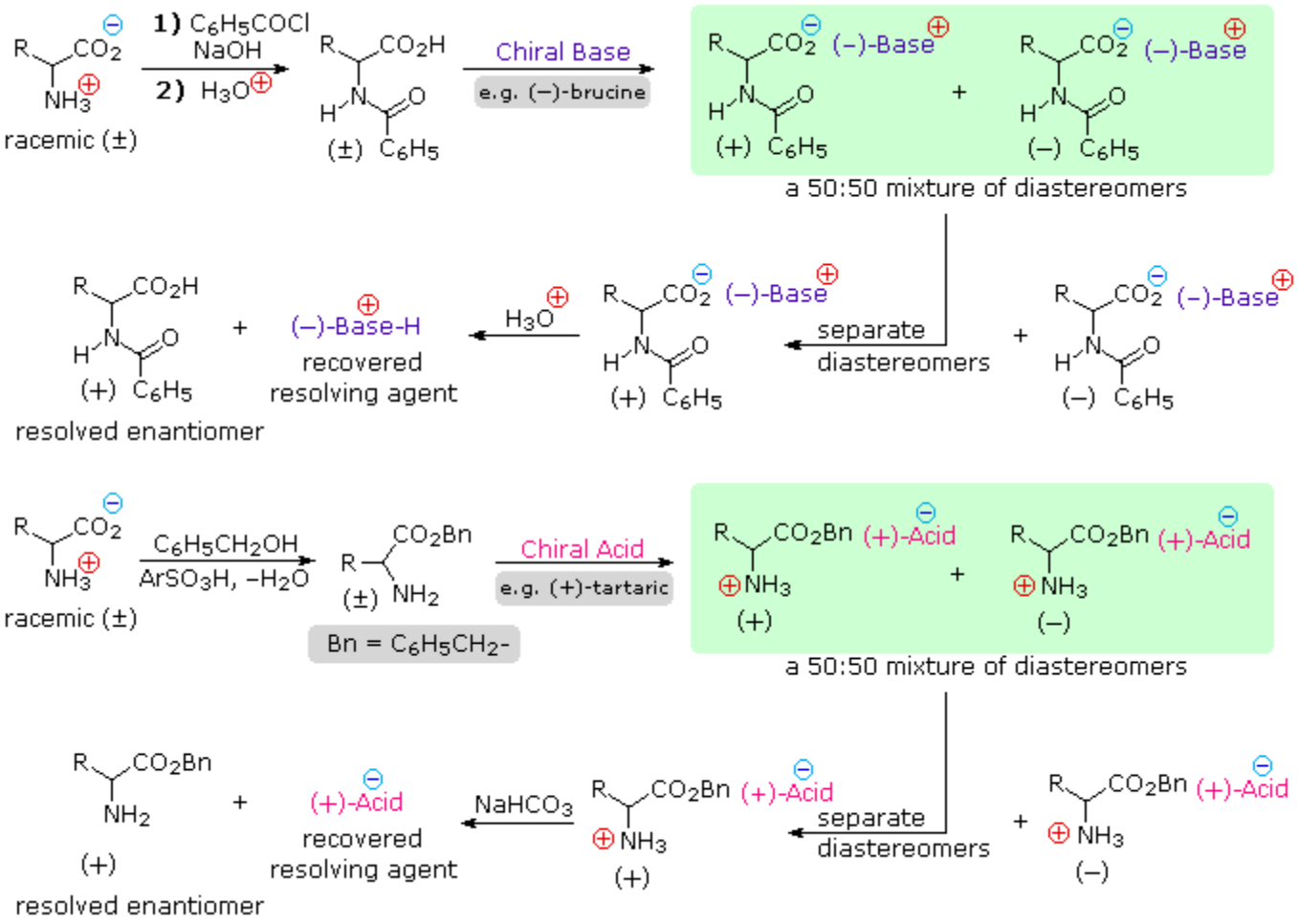
3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.



4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in

parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.



Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

Enantioselective Synthesis

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

Contributors and Attributions

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26.3: Synthesis of Enantiomerically Pure Amino Acids

Objectives

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   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
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Key Terms

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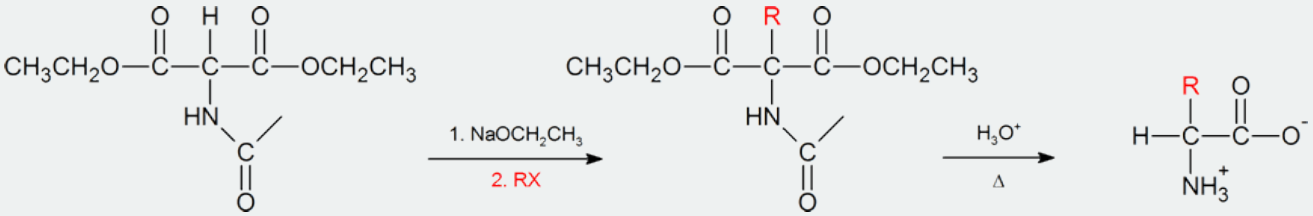
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

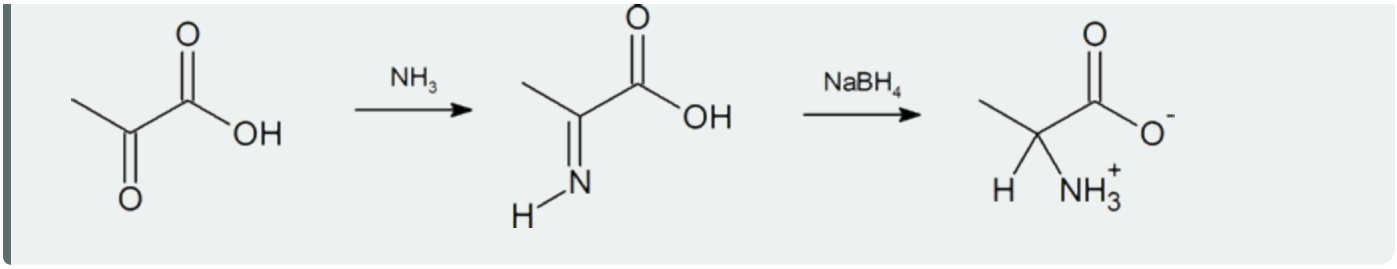
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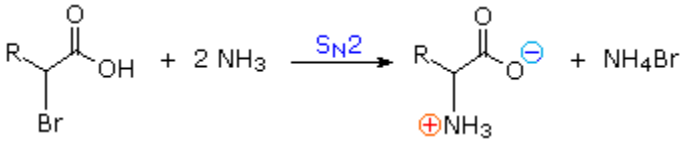


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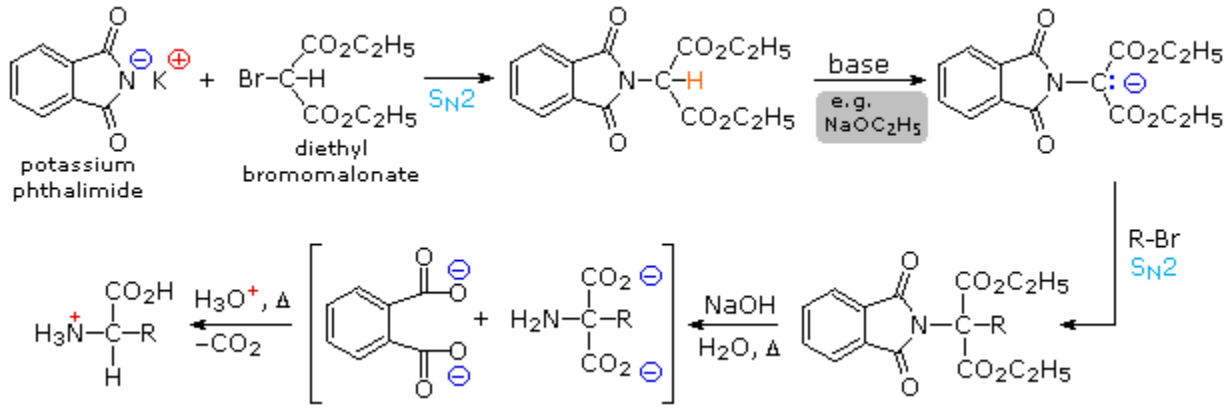


Synthesis of α-Amino AcidsEdit section

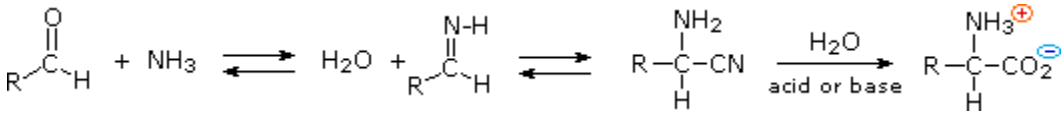
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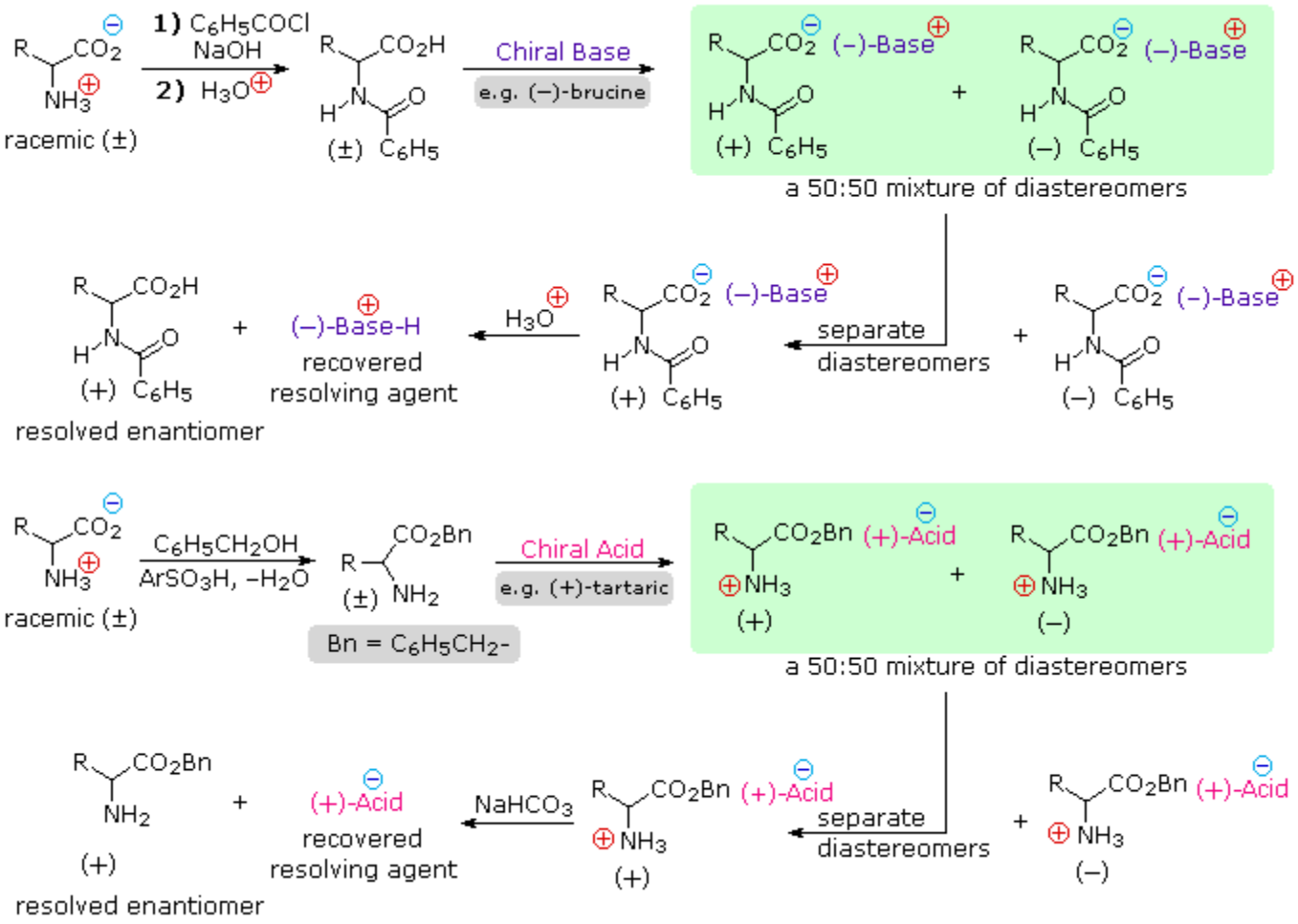
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4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in

parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.



Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

Enantioselective Synthesis

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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26.4: Peptides and Proteins: Amino Acid Oligomers and Polymers

Objectives

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C$\ce{-}$N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

Key Terms

Make certain that you can define, and use in context, the key terms below.

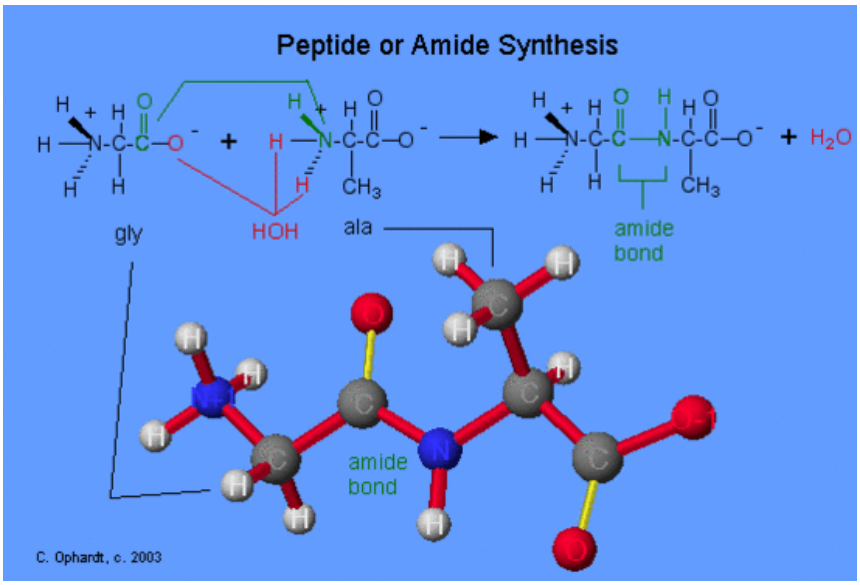
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

Study Notes

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

Peptide Bond Formation or Amide Synthesis

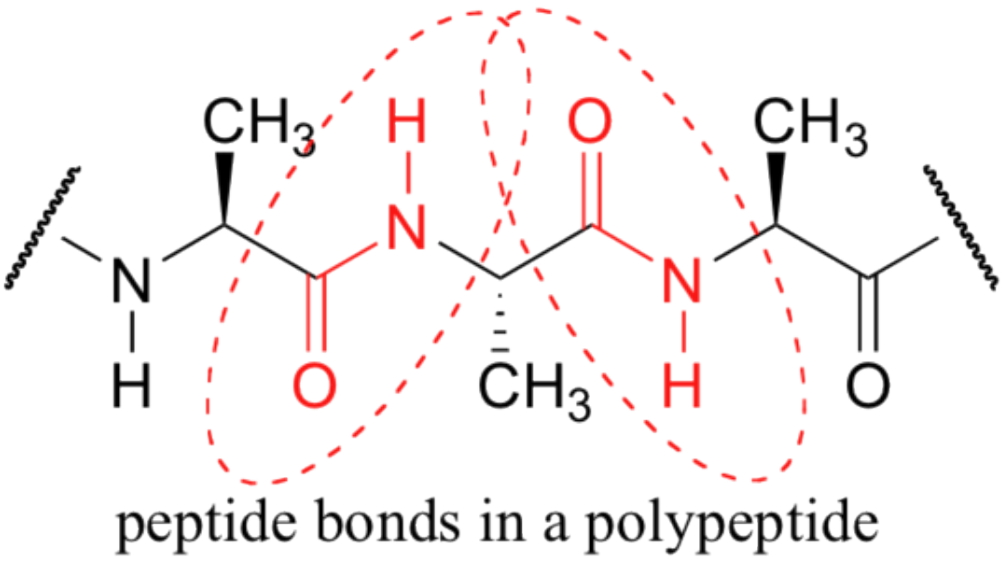
The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



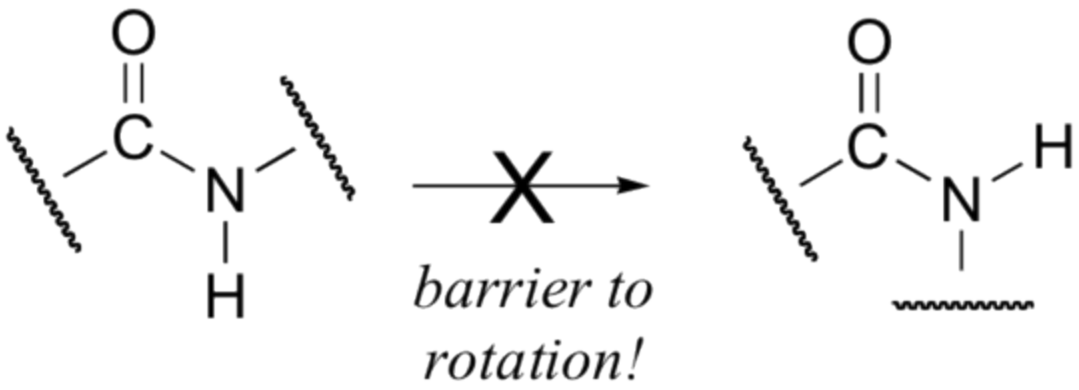
If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

Resonance contributors for the peptide bonds

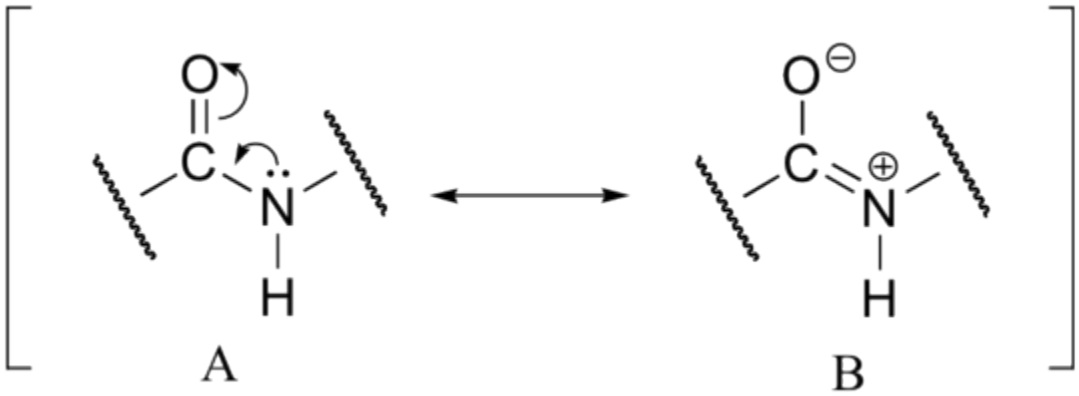
A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that the nitrogen is sp^2-hybridized. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen.



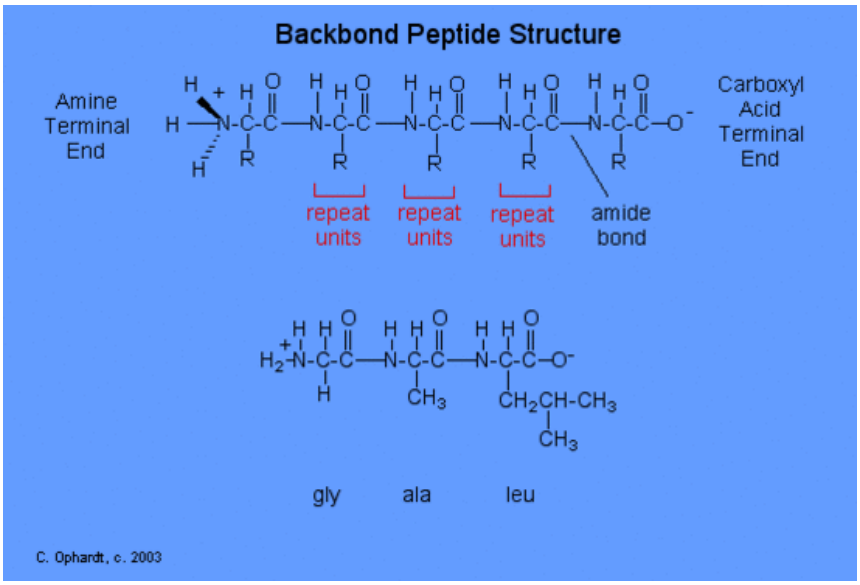
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

Backbone Peptide or Protein Structure

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.

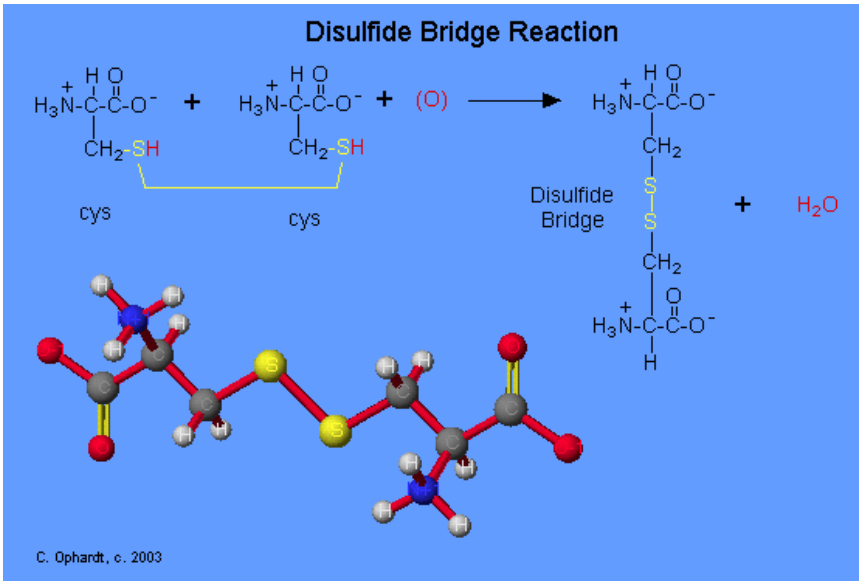
The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).

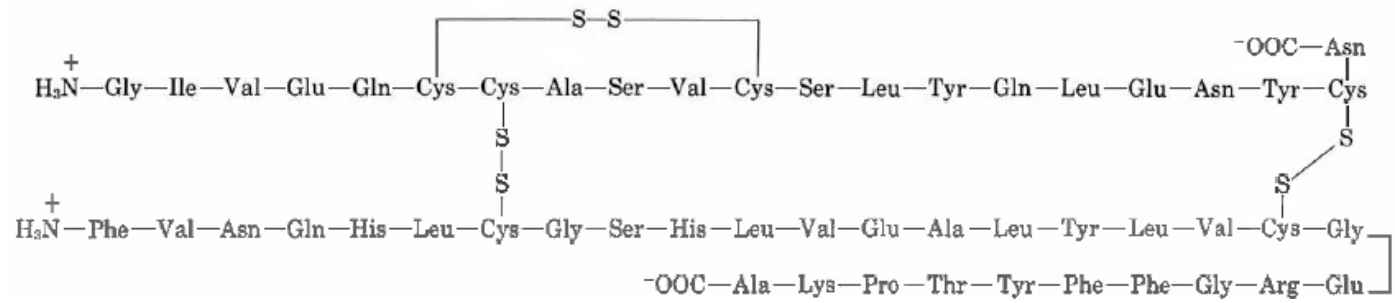


Disulfide Bridges and Oxidation-Reduction

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

Exercises

Exercise 26.4.1

Write the reaction for: ala + gly --->

Answer available at the end of this section.

Exercise 26.4.2

Write the reaction for: phe + ser --->

Answer available at the end of this section.

Exercise 26.4.3

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Answer available at the end of this section.

Exercise 26.4.4

Write the tripeptide structure for glu-cyc-gly. First write the "backbone" and then add the specific side chains.

Answer available at the end of this section.

Exercise 26.4.5

Write the tripeptide structure for phe-tyr-asn. First write the "backbone" and then add the specific side chains.

Answer available at the end of this section.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Objectives

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

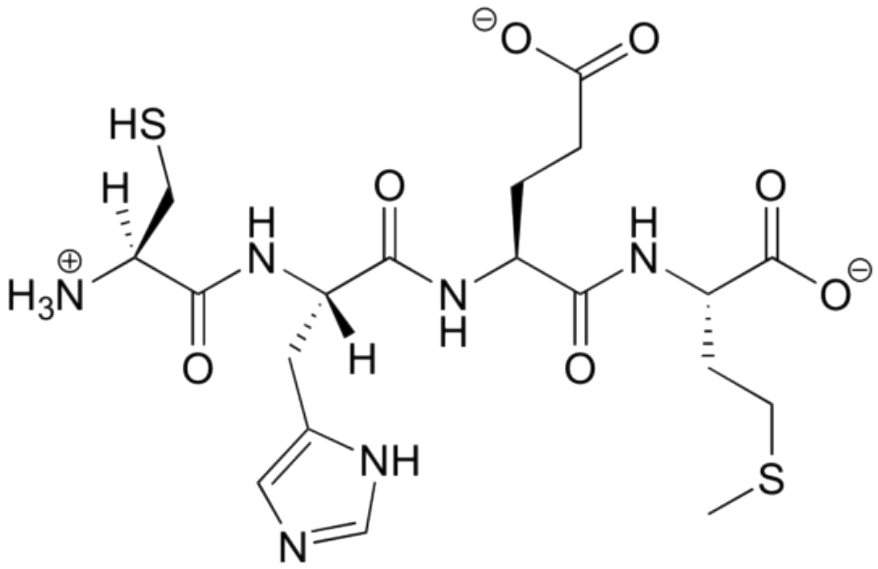
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

Study Notes

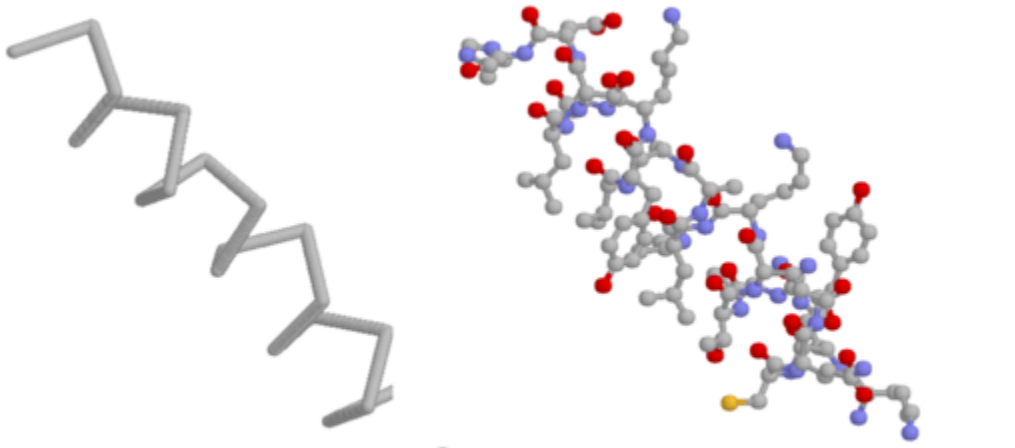
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

The four levels of protein structureEdit section

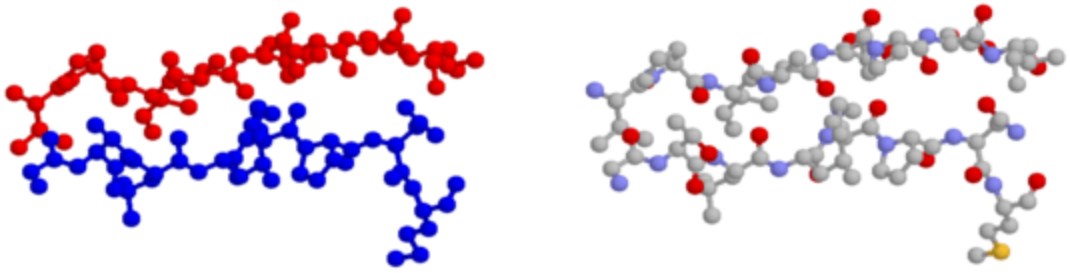
Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)



Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.

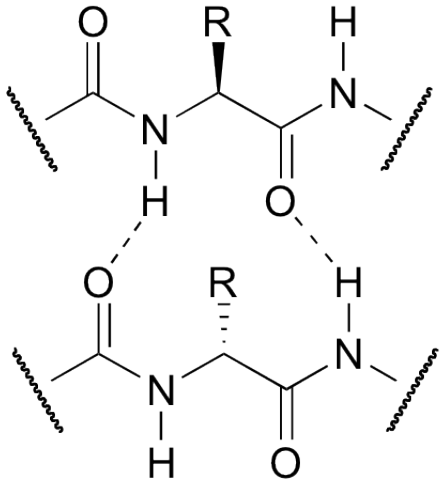


In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



hydrogen bonding in a β-strand

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

α-Helices

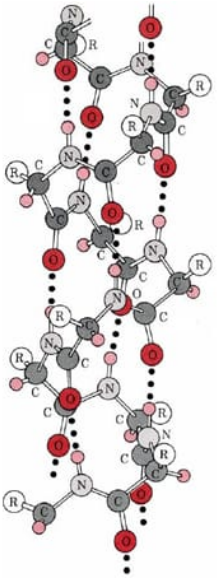


Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on top coil and the hydrogen of N-H on the bottom coil. Such a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid residues. This regular pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.

The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the entire helix due to individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.

BETA-PLEATED SHEETSEdit section

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:

Or in anti-parallel arrangement:

Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

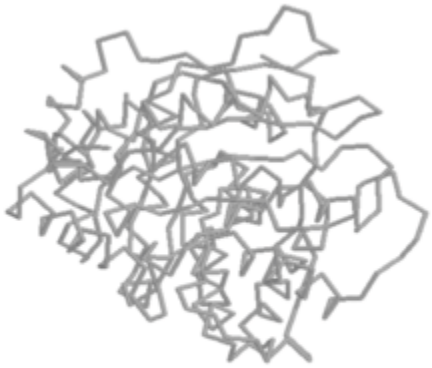
The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

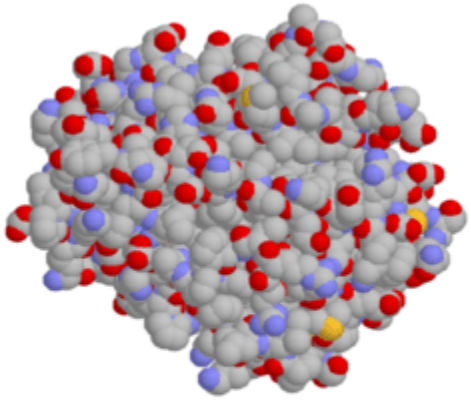
α-PLEATED SHEETSEdit section

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.

A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.

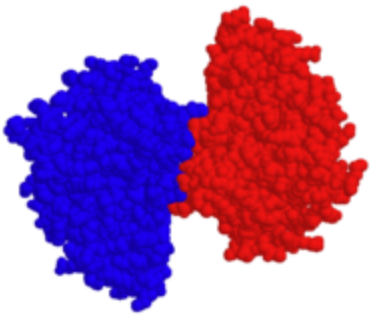


folded protein chain
(main chain view)

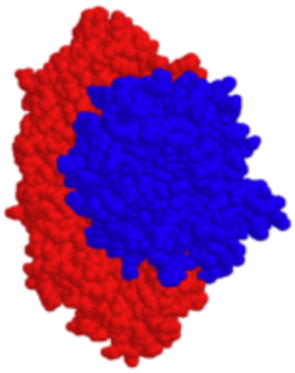


folded protein chain
('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).

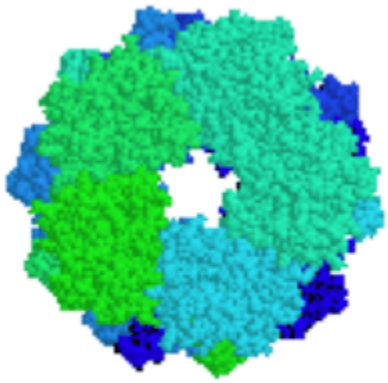


a homodimer

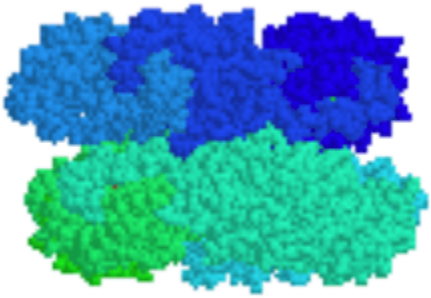


a heterodimer

Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



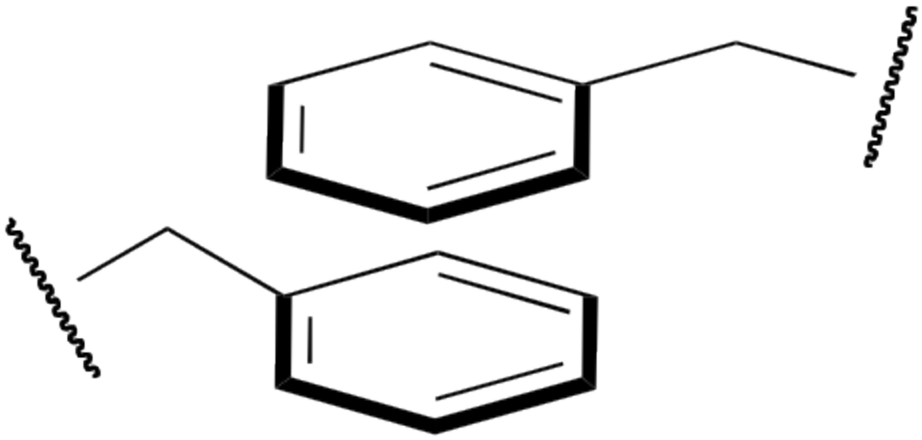
top view



side view

The molecular forces that hold proteins togetherEdit section

The question of exactly how a protein ‘finds’ its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. One interesting type of hydrophobic interaction is called ‘aromatic stacking’, and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three dimensional protein structure you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

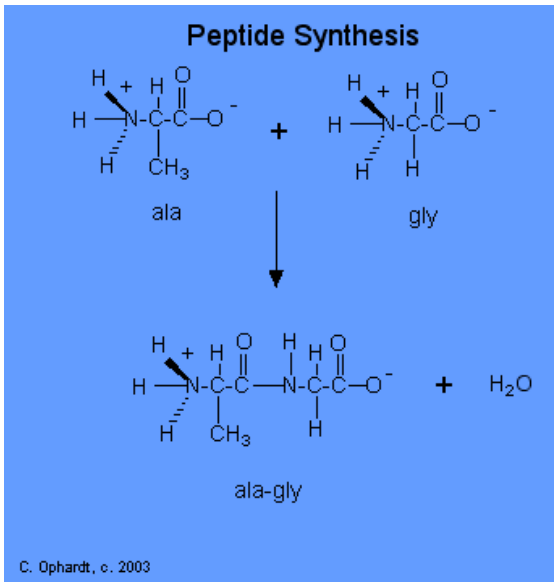
In recent years, scientists have become increasing interested in the proteins of so-called ‘thermophilic’ (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain full biological activity when in appropriately hot water - at room-temperature they act is if they are ‘frozen’. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is ‘no’: the overall three-dimensional structures of thermostable proteins look very much like those of ‘normal’ proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of ‘psychrophilic’ (cold-loving) microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

Contributors and Attributions

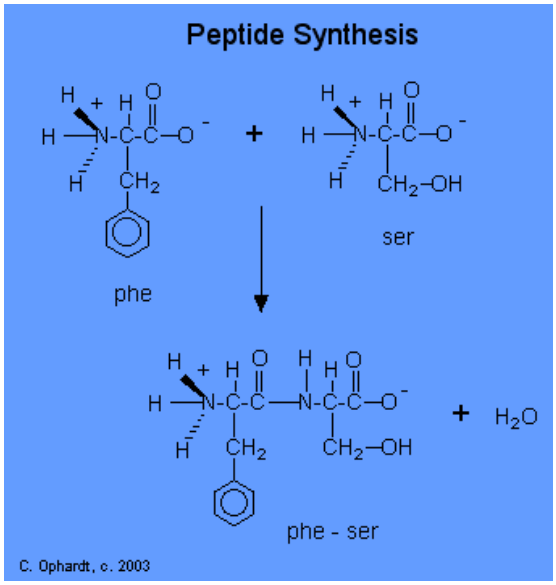
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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Ed Vitz (Kutztown University), John W. Moore (UW-Madison), Justin Shorb (Hope College), Xavier Prat-Resina (University of Minnesota Rochester), Tim Wendorff, and Adam Hahn.

Answers

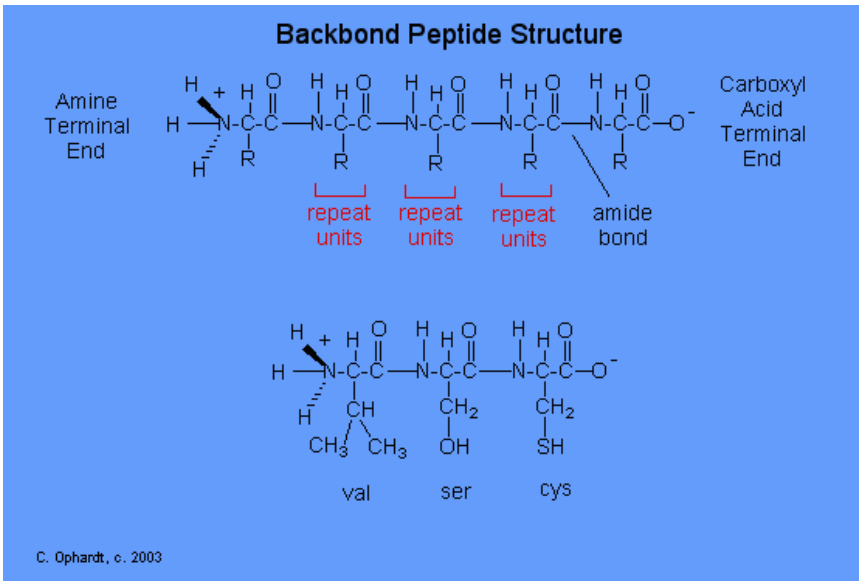
Exercise 26.4.1



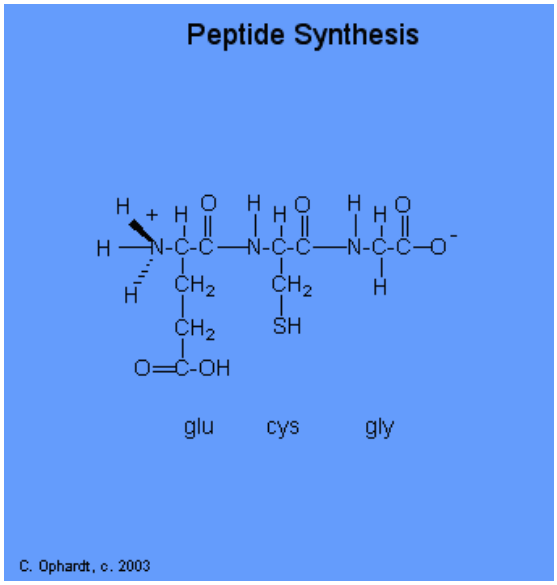
Exercise 26.4.2



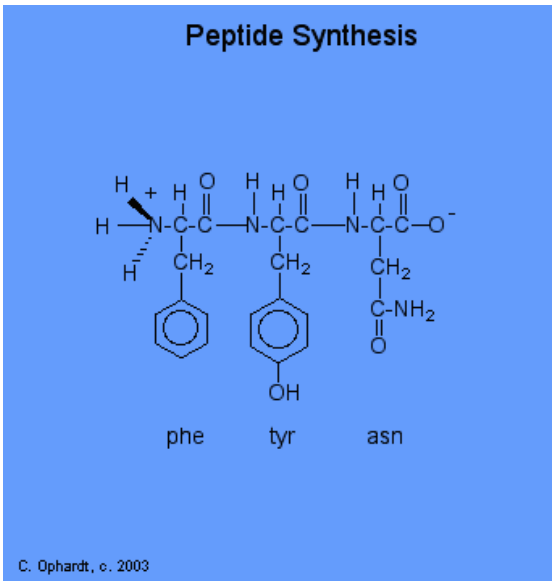
Exercise 26.4.3



Exercise 26.4.4



Exercise 26.4.5



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26.5: Determination of Primary Structure: Amino Acid Sequencing

Objectives

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

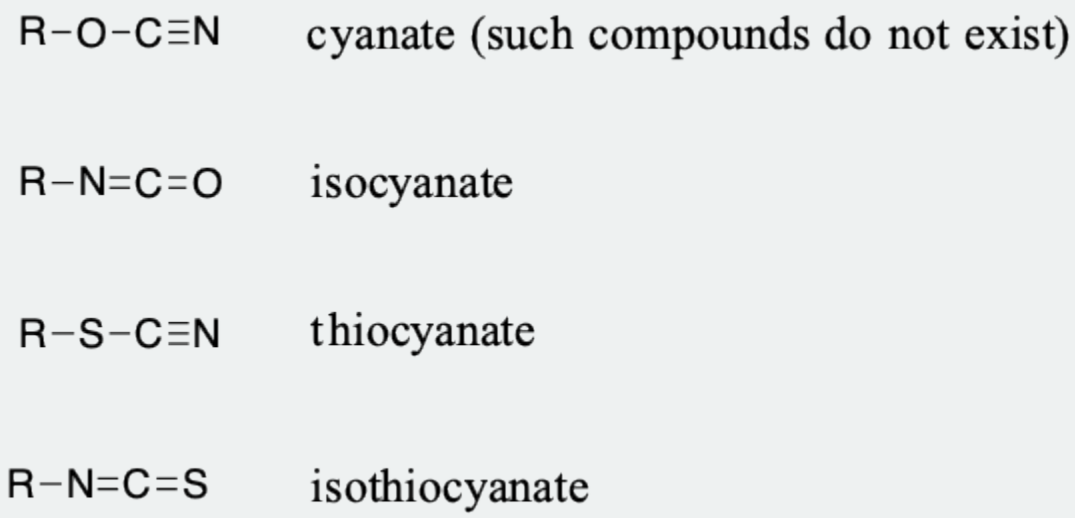
Key Terms

Make certain that you can define, and use in context, the key term below.

- Edman degradation

Study Notes

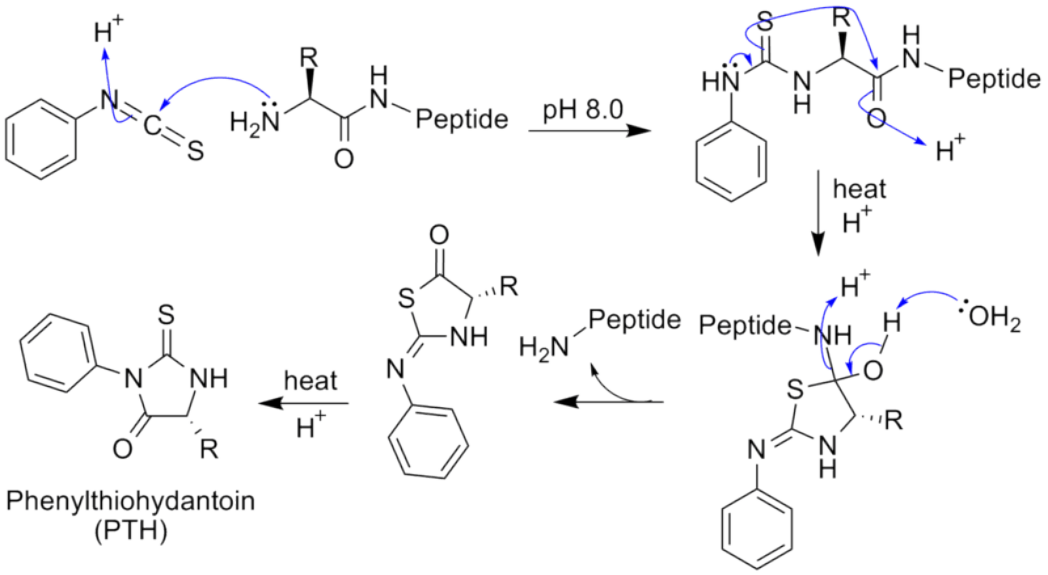
The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.



You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling

and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

Sequencing Larger Proteins

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

Contributors and Attributions

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26.6: Synthesis of Polypeptides: A Challenge in the Application of Protecting Groups

Objectives

After completing this section, you should be able to

1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. write a detailed mechanism for the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1° or 2°-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

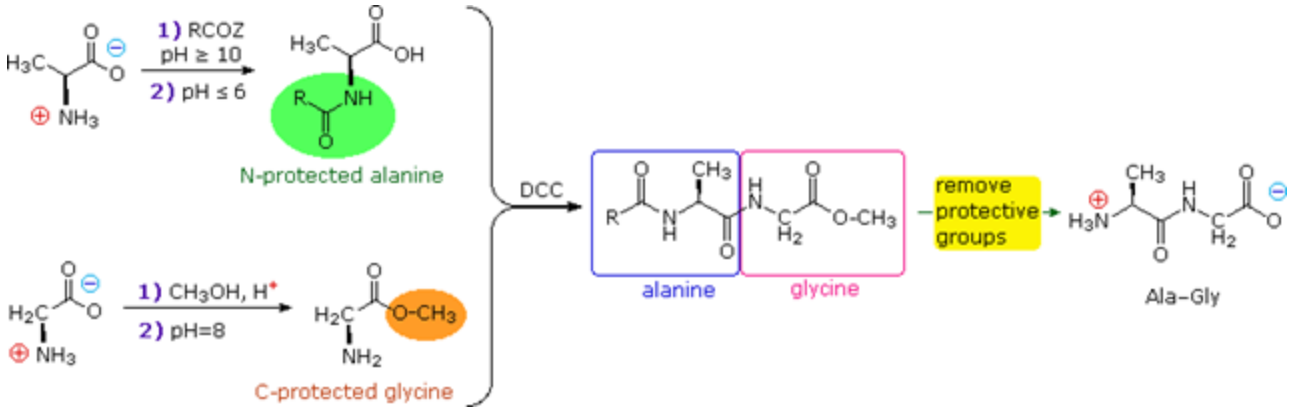
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

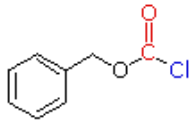
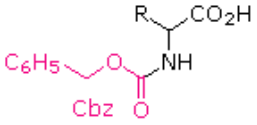
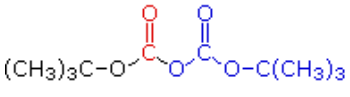
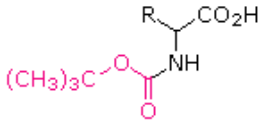
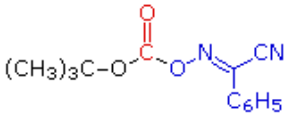
The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.

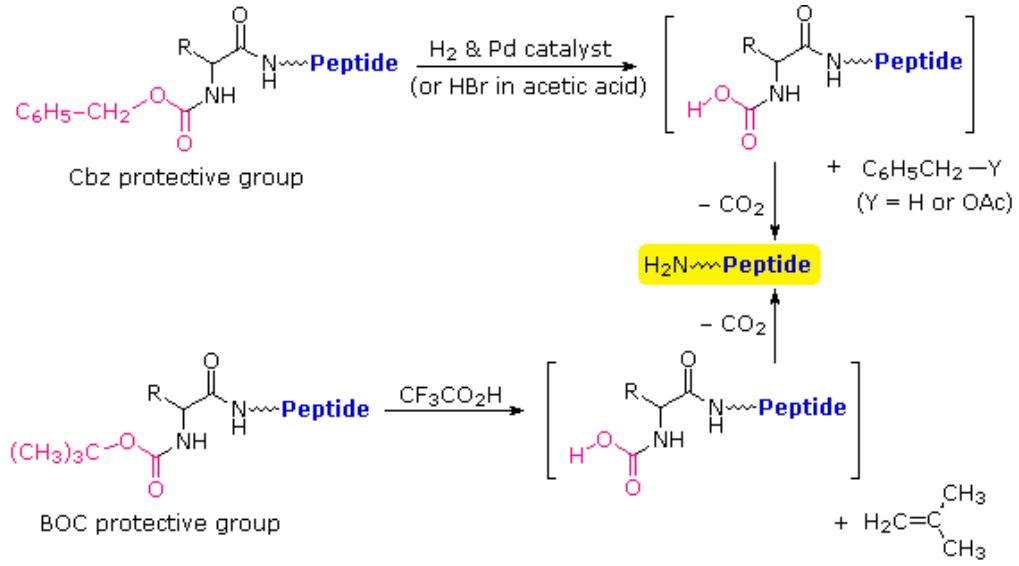


An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids.
2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.

Reagent	Protected Amino Acid	Removal Conditions
 benzyl chloroformate	 Cbz	H_2 + Pd catalyst or HBr in acetic acid
 di-t-butyl dicarbonate	 BOC or t-BOC	CF_3CO_2H
 t-butoxycarbonyloximino phenylacetonitrile BOC-ON	electrophilic carbonyl nucleophilic leaving group	



The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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26.7: Merrifield Solid-Phase Peptide Synthesis

Objectives

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

Key Terms

Make certain that you can define, and use in context, the key term below:

- solid-phase method (solid-phase synthesis)

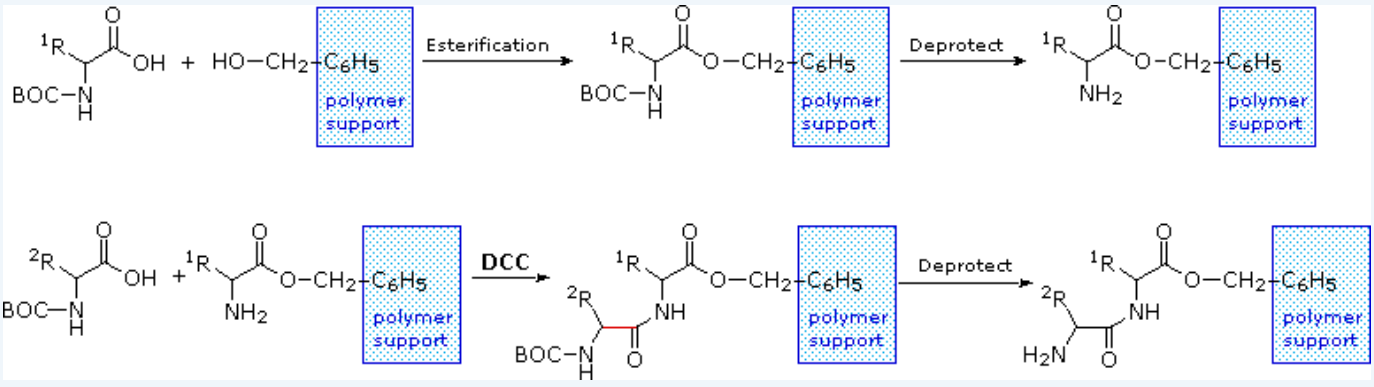
Study Notes

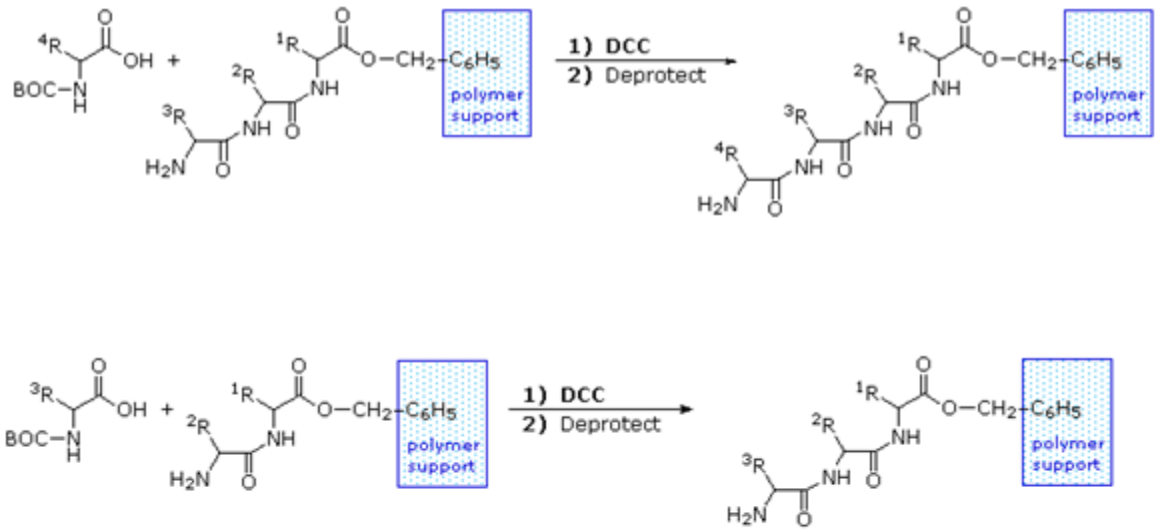
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time consuming purifications, and reduce the material losses that occur in handling, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis





Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native secondary, tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

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26.8: Polypeptides in Nature: Oxygen Transport by the Proteins Myoglobin and Hemoglobin

Oxygen Transport

Many microorganisms and most animals obtain energy by respiration, the oxidation of organic or inorganic molecules by O_2. At 25°C, however, the concentration of dissolved oxygen in water in contact with air is only about 0.25 mM. Because of their high surface area-to-volume ratio, aerobic microorganisms can obtain enough oxygen for respiration by passive diffusion of O_2 through the cell membrane. As the size of an organism increases, however, its volume increases much more rapidly than its surface area, and the need for oxygen depends on its volume. Consequently, as a multicellular organism grows larger, its need for O_2 rapidly outstrips the supply available through diffusion. Unless a transport system is available to provide an adequate supply of oxygen for the interior cells, organisms that contain more than a few cells cannot exist. In addition, O_2 is such a powerful oxidant that the oxidation reactions used to obtain metabolic energy must be carefully controlled to avoid releasing so much heat that the water in the cell boils. Consequently, in higher-level organisms, the respiratory apparatus is located in internal compartments called mitochondria, which are the power plants of a cell. Oxygen must therefore be transported not only to a cell but also to the proper compartment within a cell.

Three different chemical solutions to the problem of oxygen transport have developed independently in the course of evolution, as indicated in Table 26.8.13. Mammals, birds, reptiles, fish, and some insects use a heme protein called hemoglobin to transport oxygen from the lungs to the cells, and they use a related protein called myoglobin to temporarily store oxygen in the tissues. Several classes of invertebrates, including marine worms, use an iron-containing protein called hemerythrin to transport oxygen, whereas other classes of invertebrates (arthropods and mollusks) use a copper-containing protein called hemocyanin. Despite the presence of the hem- prefix, hemerythrin and hemocyanin do not contain a metal–porphyrin complex.

Table 26.8.13 Some Properties of the Three Classes of Oxygen-Transport Proteins

Protein	Source	M per Subunit	M per O_2 Bound	Color (deoxy form)	Color (oxy form)
hemoglobin	mammals, birds, fish, reptiles, some insects	1 Fe	1 Fe	red-purple	red
hemerythrin	marine worms	2 Fe	2 Fe	colorless	red
hemocyanin	mollusks, crustaceans, spiders	2 Cu	2 Cu	colorless	blue

Myoglobin and Hemoglobin

Myoglobin is a relatively small protein that contains 150 amino acids. The functional unit of myoglobin is an iron–porphyrin complex that is embedded in the protein (Figure 26.8.1). In myoglobin, the heme iron is five-coordinate, with only a single histidine imidazole ligand from the protein (called the proximal histidine because it is near the iron) in addition to the four nitrogen atoms of the porphyrin. A second histidine imidazole (the distal histidine because it is more distant from the iron) is located on the other side of the heme group, too far from the iron to be bonded to it. Consequently, the iron atom has a vacant coordination site, which is where O_2 binds.

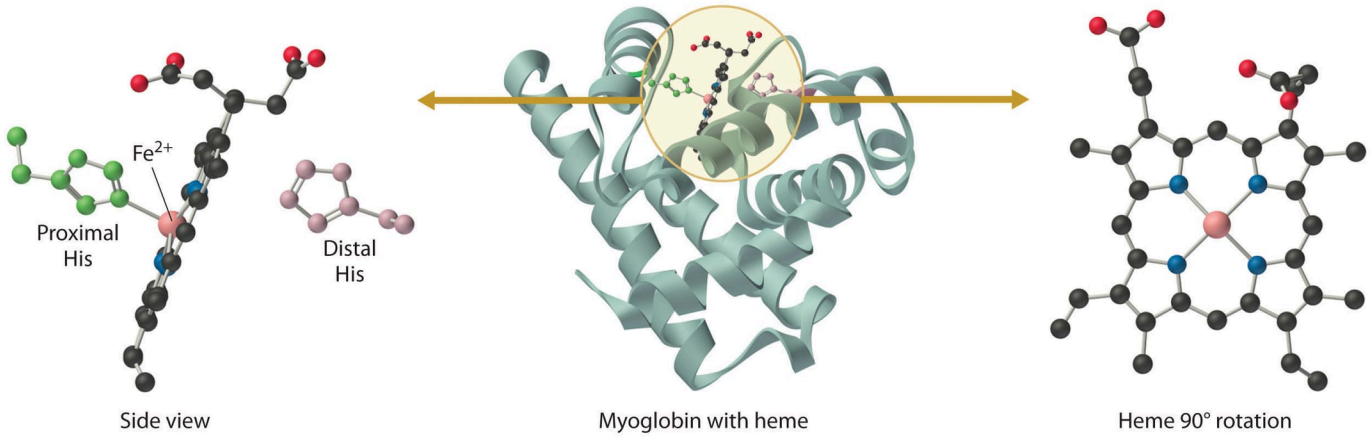


***Figure 26.8.1**: The Structure of Deoxymyoglobin, Showing the Heme Group. The iron in deoxymyoglobin is five-coordinate, with one histidine imidazole ligand from the protein. Oxygen binds at the vacant site on iron.*

In the ferrous form (deoxymyoglobin), the iron is five-coordinate and high spin. Because high-spin Fe^{2+} is too large to fit into the "hole" in the center of the porphyrin, it is about 60 pm above the plane of the porphyrin. When O_2 binds to deoxymyoglobin to form oxymyoglobin, the iron is converted from five-coordinate (high spin) to six-coordinate (low spin; Figure 26.8.2). Because low-spin Fe^{2+} and Fe^{3+} are smaller than high-spin Fe^{2+}, the iron atom moves into the plane of the porphyrin ring to form an octahedral complex. The O_2 pressure at which half of the molecules in a solution of myoglobin are bound to O_2 ($P_{1/2}$) is about 1 mm Hg (1.3×10^{-3} atm).

affinity unchanged, which is important because carbon monoxide is produced continuously in the body by degradation of the porphyrin ligand (even in nonsmokers). Under normal conditions, CO occupies approximately 1% of the heme sites in hemoglobin and myoglobin. If the affinity of hemoglobin and myoglobin for CO were 100 times greater (due to the absence of the distal histidine), essentially 100% of the heme sites would be occupied by CO, and no oxygen could be transported to the tissues. Severe carbon-monoxide poisoning, which is frequently fatal, has exactly the same effect. Thus the primary function of the distal histidine appears to be to decrease the CO affinity of hemoglobin and myoglobin to avoid self-poisoning by CO.

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26.9: Biosynthesis of Proteins: Nucleic Acids

28.01 Nucleotides and Nucleic Acids 28.02 Base Pairing in DNA: The Watson-Crick Model 28.03 Replication of DNA 28.04 Transcription of DNA

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26.10: Protein Synthesis Through RNA

28.05 Translation of RNA: Protein Biosynthesis

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26.11: DNA Sequencing and Synthesis: Cornerstones of Gene Technology

Objectives

After completing this section, you should be able to

- Describe briefly how DNA sequencing is carried out.

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

While techniques to sequence proteins have been around since the 1950s, techniques to sequence DNA were not developed until the mid-1970s, when two distinct sequencing methods were developed almost simultaneously, one by Walter Gilbert's group at Harvard University, the other by Frederick Sanger's group at Cambridge University. However, until the 1990s, the sequencing of DNA was a relatively expensive and long process. Using radiolabeled nucleotides also compounded the problem through safety concerns. With currently-available technology and automated machines, the process is cheaper, safer, and can be completed in a matter of hours. The Sanger sequencing method was used for the human genome sequencing project, which was finished its sequencing phase in 2003, but today both it and the Gilbert method have been largely replaced by better methods.

Restriction Enzymes

To be able to sequence DNA, it is first necessary to cut it into smaller fragments. What is needed is a way to cleave the DNA molecule at a few precisely-located sites so that a small set of homogeneous fragments are produced. To cut DNA at known locations, researchers use **restriction endonucleases** enzymes that have been purified from various bacterial species, and which can be purchased from various commercial sources. REs occur naturally in bacteria, where they specifically recognize short stretches of nucleotides in DNA and catalyze double-strand breaks at or near the recognition site (also known as a restriction site). These enzymes are usually named after the bacterium from which they were first isolated. For example, ***EcoRI*** and *EcoRV* are both enzymes from *E. coli*.

Restriction enzymes like EcoRI are frequently called 6-cutters, because they recognize a 6-nucleotide sequence. Assuming a random distribution of A, C, G and Ts in DNA, probability predicts that a recognition site for a 6-cutter should occur about once for every 4096 bp (4^6) in DNA. Of course, the distribution of nucleotides in DNA is not random, so the actual sizes of DNA fragments produced by EcoRI range from hundreds to many thousands of base pairs, but the mean size is close to 4000 bp. DNA fragments of this length are useful in the lab, since they long enough to contain the coding sequence for proteins and are well-resolved on agarose gels.

EcoRI recognizes the sequence G A A T T C in double stranded DNA. This recognition sequence is a palindrome with a two-fold axis of symmetry, because reading from 5' to 3' on either strand of the helix gives the same sequence. The palindromic nature of the restriction site is more obvious in the figure below. The dot in the center of the restriction site denotes the axis of symmetry. EcoRI catalyzes the hydrolysis of the phosphodiester bonds between G and A on both DNA strands. The restriction fragments generated in the reaction have short single-stranded tails at the 5'-ends. These ends are often referred to as "sticky ends," because of their ability to form hydrogen bonds with complementary DNA sequences.



Figure 26.11.1: The recognition sequence for EcoRI (blue) is cleaved by the enzyme (grey). This particular enzyme cuts DNA at a position offset from the center of the restriction site. This creates an overhanging, sticky-end. (Original-Deyholos-CC:AN)

Reading DNA Sequences

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. Sanger sequencing, also known as chain-termination sequencing, requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs - ddNTP) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated.

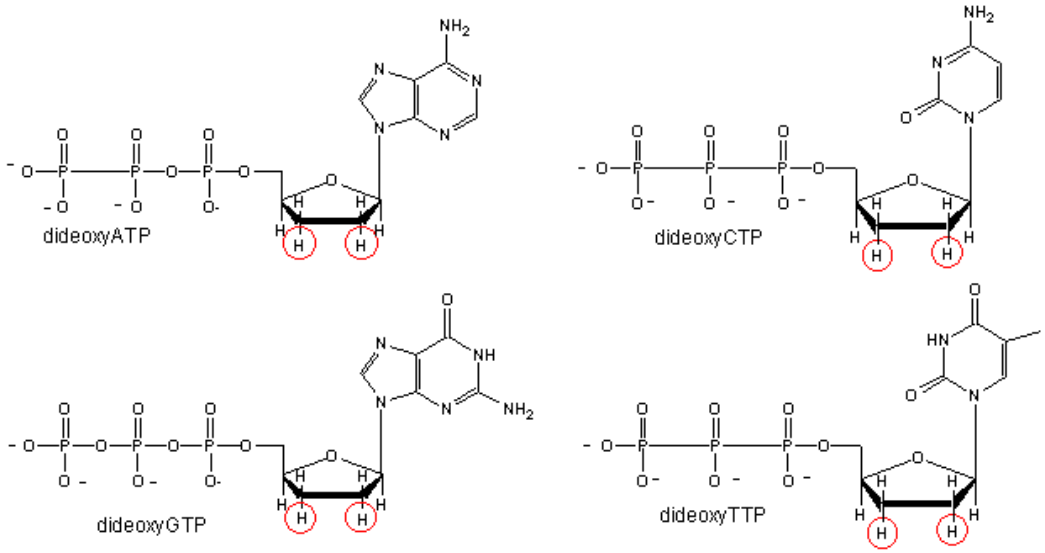


Figure 26.11.2: Didexoynucleotides

Four reaction tubes are set up, each containing the template DNA to be sequenced, a *primer* of known sequence, all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP), and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP) which has been fluorescently labeled. Most of the time in a Sanger sequencing reaction, DNA Polymerase will add a proper dNTP to the growing strand it is synthesizing in vitro. But at random locations, it will instead add a ddNTP. When it does, that strand will be terminated at the ddNTP just added. If enough template DNAs are included in the reaction mix, each one will have the labeled ddNTP inserted at a different random location, and there

will be at least one DNA terminated at each different nucleotide along its length for as long as the in vitro reaction can take place (about 900 nucleotides under optimal conditions.)

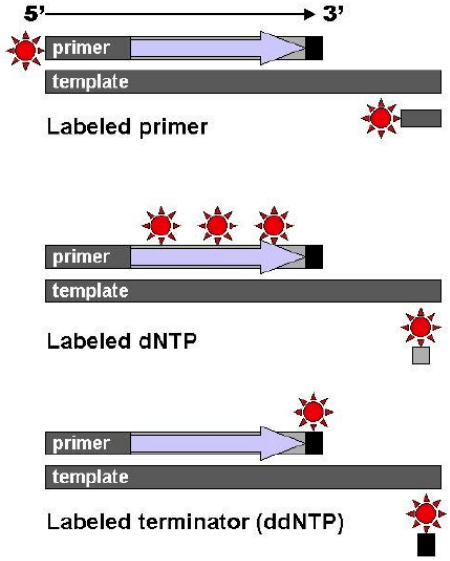


Figure 26.11.3: Sanger sequencing: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

After the reactions are over, the newly synthesized strands can be denatured from the template, and then separated by capillary electrophoresis or other equivalent methods. Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands.

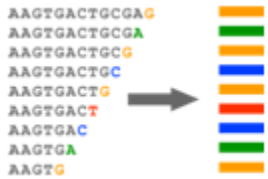


Figure 26.11.4: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

As each differently-sized fragment exits the capillary column, a laser excites the florescent tag on its terminal nucleotide. From the color of the resulting florescence, a computer can keep track of which nucleotide was present as the terminating nucleotide. The computer also keeps track of the order in which the terminating nucleotides appeared, which is the sequence of the DNA used in the original reaction. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

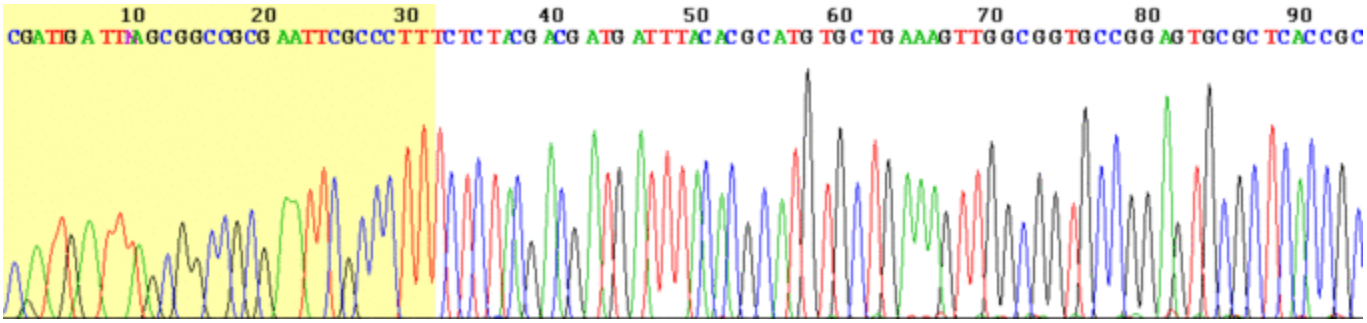


Figure 26.11.5: Chromatograph: This is an example of the output of a Sanger sequencing read using fluorescently labeled dye-terminators. The four DNA bases are represented by different colors which are interpreted by the software to give the DNA sequence above.

Scientists now know the sequence of all the 3 billion DNA base pairs in the entire human genome. This knowledge was attained by the **Human Genome Project (HGP),** a $3 billion, international scientific research project that was formally launched in 1990. The project was completed in 2003, two years ahead of its 15-year projected deadline. Determining the sequence of the billions

of base pairs that make up human DNA was the main goal of the HGP. Another goal was mapping the location and determining the function of all the genes in the human genome. There are only about 20,500 genes in human beings. If modern methods were used it might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.

Example 26.11.1

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

28.08 The Polymerase Chain Reaction

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