FUNDAMENTAL ORGANIC CHEMISTRY I



Chelsea Diane Anorma
University of Illinois Urbana-Champaign



Chem 236: Fundamental Organic Chemistry I (Chan)

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1: INTRO TO CHEMICAL STRUCTURE AND RESONANCE

1.1: Drawing Chemical Structures

1.2: Electron-Dot Model of Bonding - Lewis Structures

1.3: VSPER Theory- The Effect of Lone Pairs

1.4: Electronegativity and Bond Polarity (Review)

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1.1: Drawing Chemical Structures

Objectives

After completing this section, you should be able to

1. propose one or more acceptable Kekulé structures (structural formulas) for any given molecular formula
2. write the molecular formula of a compound, given its Kekulé structure.
3. draw the shorthand structure of a compound, given its Kekulé structure.
4. interpret shorthand structures and convert them to Kekulé structures.
5. write the molecular formula of a compound, given its shorthand structure.

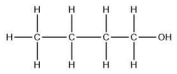
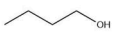
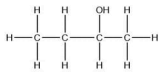
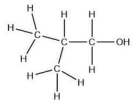
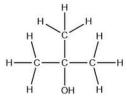
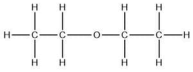
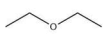
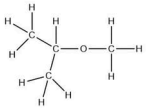
Study Notes

When drawing the structure of a neutral organic compound, you will find it helpful to remember that

- each carbon atom has four bonds.
- each nitrogen atom has three bonds.
- each oxygen atom has two bonds.
- each hydrogen atom has one bond.

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.

Table 1.1.1***:*** *Structural Formulas for $C_4H_{10}O$ isomers*

Kekulé Formula	Condensed Formula	Shorthand Formula
	$CH_3(CH_2)_3OH$	
	$C_2H_5(OH)CH_3$	
	$(CH_3)CHCH_2OH$	
	$(CH_3)_3COH$	
	$CH_3(CH_2)_2OCH_3$	
	$(CH_3)_2CHOCH_3$	

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 (unless the hydrogen is bonded to an atom other than carbon). 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 Kekulé Formula or 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.

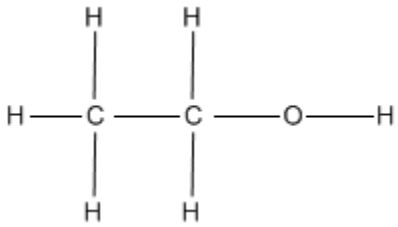


Figure 1.1.1***:*** *Kekulé Formula for Ethanol*

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.

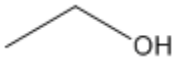


Figure 1.1.2*: Shorthand Formula for Ethanol*

Exercises

Write down the molecular formula for each of the compounds shown here.

compounds A through D for naming

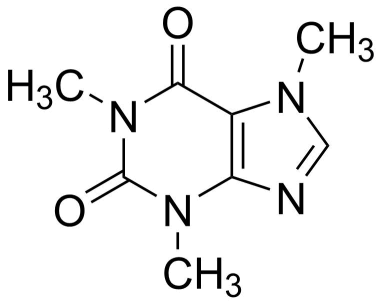
Answers:

A. C_7H_7N
B. C_5H_{10}
C. C_5H_4O
D. $C_5H_6Br_2$

Questions

Q1.12.1

Below is the molecule for caffeine. Give the molecular formula for it.



Solutions

S1.12.1

$C_8H_{10}O_2N_4$

Contributors

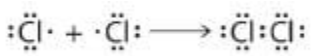
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota,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

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1.2: Electron-Dot Model of Bonding - Lewis Structures

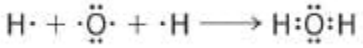
Using Lewis Dot Symbols to Describe Covalent BondingEdit section

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.Edit section

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:

Edit section



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

Edit section

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.Edit section

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

Edit section

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.

Edit section

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

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H_2OEdit section

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

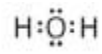
2. Each H atom (group 1) has 1 valence electron, and the O atom (group 16) has 6 valence electrons, for a total of 8 valence electrons.Edit section

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

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

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

Edit section



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.

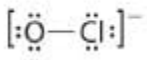
OCl^-Edit section

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

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.

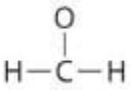
CH_2OEdit section

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:



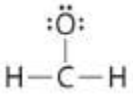
2. Each hydrogen atom (group 1) has one valence electron, carbon (group 14) has 4 valence electrons, and oxygen (group 16) has 6 valence electrons, for a total of [(2)(1) + 4 + 6] = 12 valence electrons.

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.

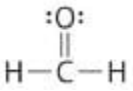
4. Adding all 6 remaining electrons to oxygen (as three lone pairs) gives the following:



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.Edit section

Example

Write the Lewis electron structure for each species.

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

Given: chemical species

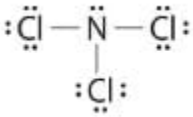
Asked for: Lewis electron structures

Strategy:

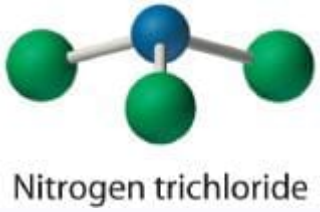
Use the six-step procedure to write the Lewis electron structure for each species.

Solution:

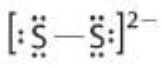
Nitrogen is less electronegative than chlorine, and halogen atoms are usually terminal, so nitrogen is the central atom. The nitrogen atom (group 15) has 5 valence electrons and each chlorine atom (group 17) has 7 valence electrons, for a total of 26 valence electrons. Using 2 electrons for each N–Cl 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:



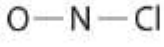
Nitrogen trichloride is an unstable oily liquid once used to bleach flour; this use is now prohibited in the United States.

1. 

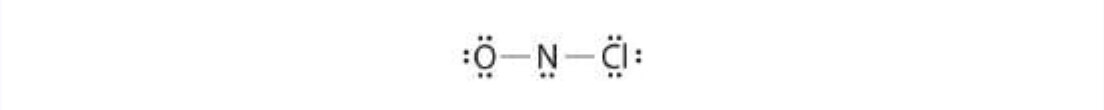
2. In a diatomic molecule or ion, we do not need to worry about a central atom. Each sulfur atom (group 16) contains 6 valence electrons, and we need to add 2 electrons for the –2 charge, giving a total of 14 valence electrons. Using 2 electrons for the S–S bond, we arrange the remaining 12 electrons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



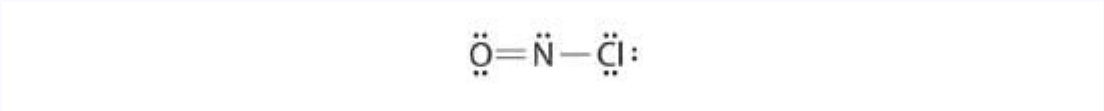
3. Because nitrogen is less electronegative than oxygen or chlorine, it is the central atom. The N atom (group 15) has 5 valence electrons, the O atom (group 16) has 6 valence electrons, and the Cl atom (group 17) has 7 valence electrons, giving a total of 18 valence electrons. Placing one bonding pair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



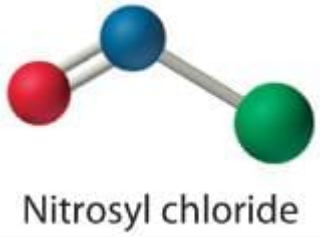
Adding three lone pairs each to oxygen and to chlorine uses 12 more electrons, leaving 2 electrons to place as a lone pair on nitrogen:



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:



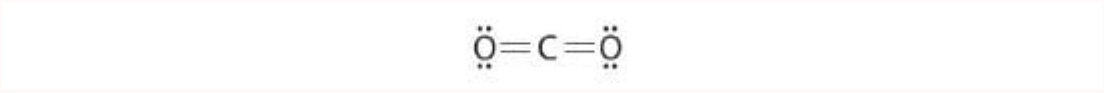
All atoms now have octet configurations. This is the Lewis electron structure of nitrosyl chloride, a highly corrosive, reddish-orange gas.



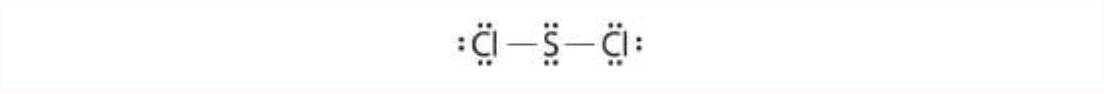
Exercise

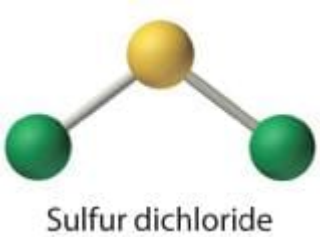
Write Lewis electron structures for CO_2 and SCl_2, a vile-smelling, unstable red liquid that is used in the manufacture of rubber.

Answer:

1. 



2. 



Formal ChargesEdit section

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:

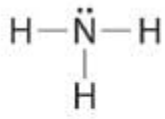
- Nonbonding electrons are assigned to the atom on which they are located.
- Bonding electrons are divided equally between the bonded atoms.

For each atom, we then compute a formal charge:

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

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

Edit section



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

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

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

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

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

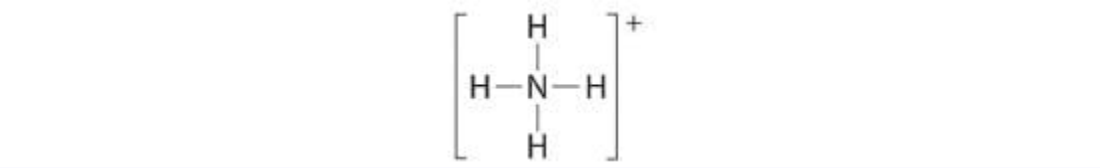
Asked for: formal charges

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:

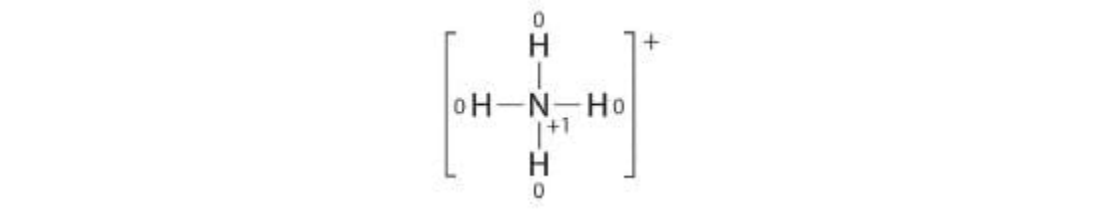
The Lewis electron structure for the NH_4^+ ion is as follows:



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

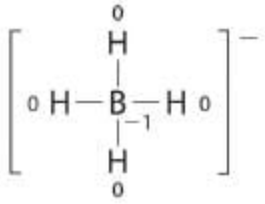


Adding together the formal charges on the atoms should give us the total charge on the molecule or ion. In this case, the sum of the formal charges is 0 + 1 + 0 + 0 + 0 = +1.

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.

Edit section

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

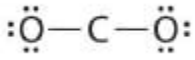
Edit section

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

Edit section

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

Edit section



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

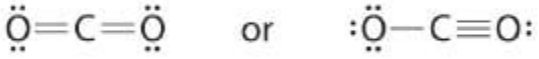
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5. No electrons are left for the central atom.

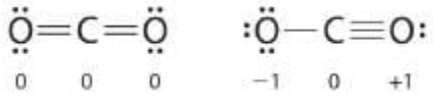
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6. To give the carbon atom an octet of electrons, we can convert two of the lone pairs on the oxygen atoms to bonding electron pairs. There are, however, two ways to do this. We can either take one electron pair from each oxygen to form a symmetrical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

Edit section



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.Edit section

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:

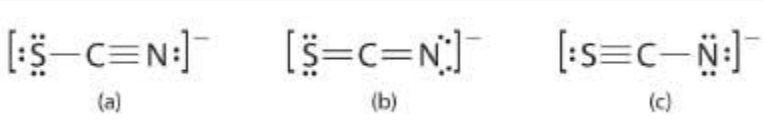
A Use the step-by-step procedure to write two plausible Lewis electron structures for SCN^-.

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:



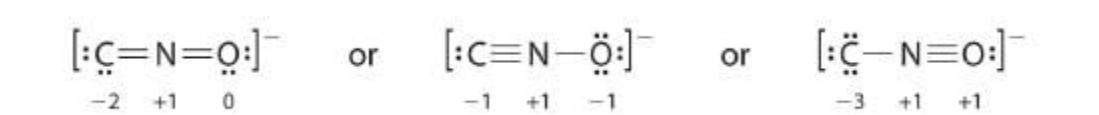
B We must calculate the formal charges on each atom to identify the more stable structure. If we begin with carbon, we notice that the carbon atom in each of these structures shares four bonding pairs, the number of bonds typical for carbon, so it has a formal charge of zero. Continuing with sulfur, 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.

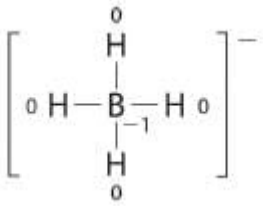
Exercise

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.



Edit section

Drawing isomers of Lewis Structures

YouTube Video

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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):

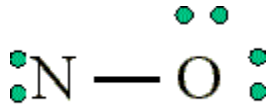


Figure 8.7.1. This is if Nitrogen monoxide has only *ten* valence electrons, which it does not.

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):

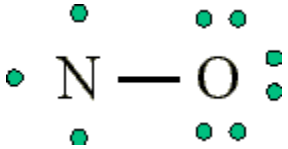


Figure 8.7.2. The proper Lewis structure for NO molecule

Free Radicals

Edit section

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):

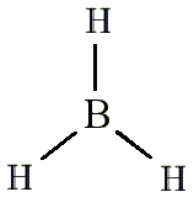


Figure 8.7.3

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).

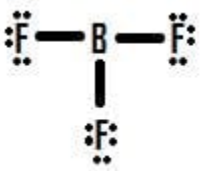


Figure 8.7.4

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):

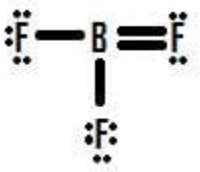


Figure 8.7.5

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:

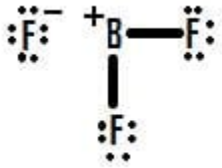


Figure 8.7.6

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 .

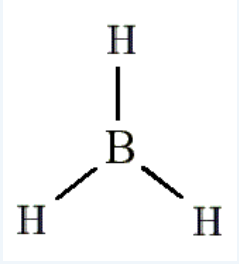
Example 8.7.1:

Draw the Lewis structure for boron trifluoride (BF_3).

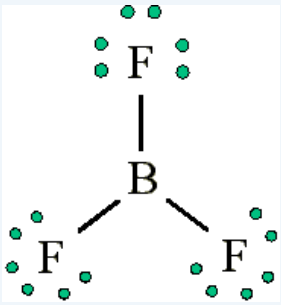
SOLUTION

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

2. Draw connectivities:



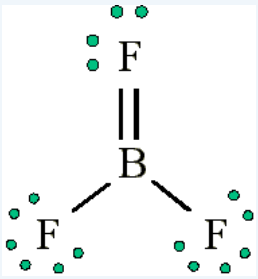
3. Add octets to outer atoms:



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:



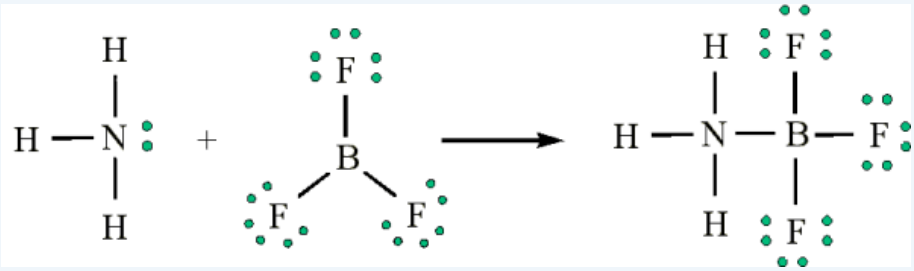
6. The central Boron now has an octet (there would be three resonance Lewis structures)

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***

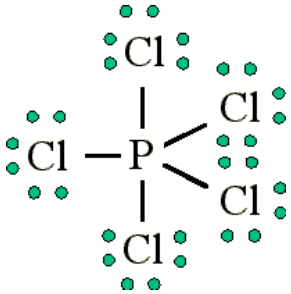
BF_3 reacts strongly with compounds which have an unshared pair of electrons which can be used to form a bond with the boron:



Exception 3: Expanded Valence Shells

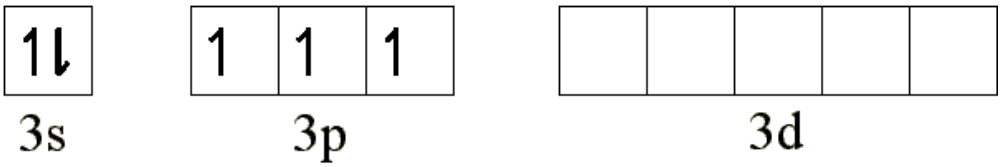
Edit section

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:

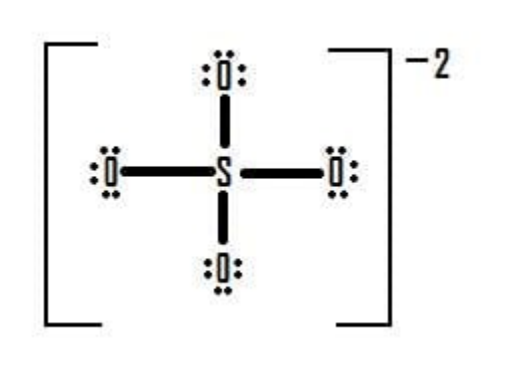


Figure 8.7.12

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:

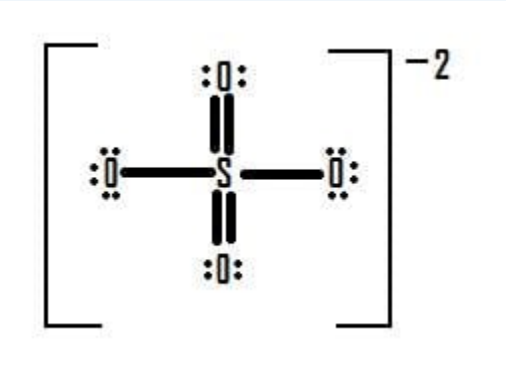


Figure 8.7.13

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.

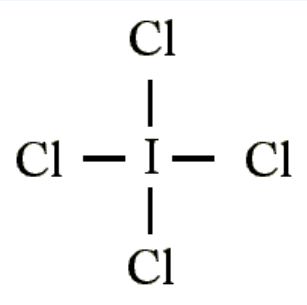
Example 8.7.3: The Ion

Draw the Lewis structure for ion.

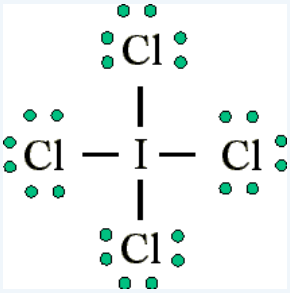
SOLUTION

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

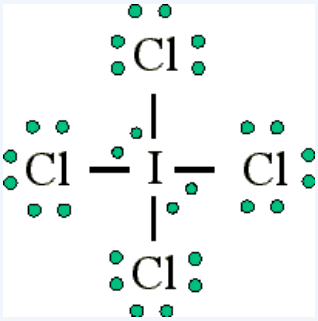
2. Draw the connectivities:



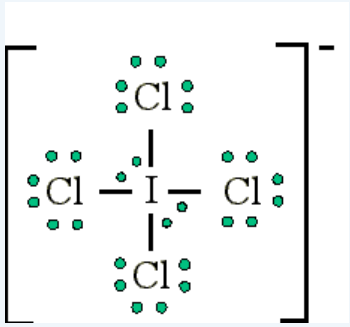
3. Add octet of electrons to outer atoms:



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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1.3: VSPER Theory- The Effect of Lone Pairs

Learning Objectives

- To use the VSEPR model to predict molecular geometries.
- To predict whether a molecule has a dipole moment.

The Lewis electron-pair approach can be used to predict the number and types of bonds between the atoms in a substance, and it indicates which atoms have lone pairs of electrons. This approach gives no information about the actual arrangement of atoms in space, however. We continue our discussion of structure and bonding by introducing the **valence-shell electron-pair repulsion** (VSEPR) model (pronounced "vesper"), which can be used to predict the shapes of many molecules and polyatomic ions. Keep in mind, however, that the VSEPR model, like any model, is a limited representation of reality; the model provides no information about bond lengths or the presence of multiple bonds.

The VSEPR Model

The VSEPR model can predict the structure of nearly any molecule or polyatomic ion in which the central atom is a nonmetal, as well as the structures of many molecules and polyatomic ions with a central metal atom. The premise of the VSEPR theory is that electron pairs located in bonds and lone pairs repel each other and will therefore adopt the geometry that places electron pairs as far apart from each other as possible. This theory is very simplistic and does not account for the subtleties of orbital interactions that influence molecular shapes; however, the simple VSEPR counting procedure accurately predicts the three-dimensional structures of a large number of compounds, which cannot be predicted using the Lewis electron-pair approach.

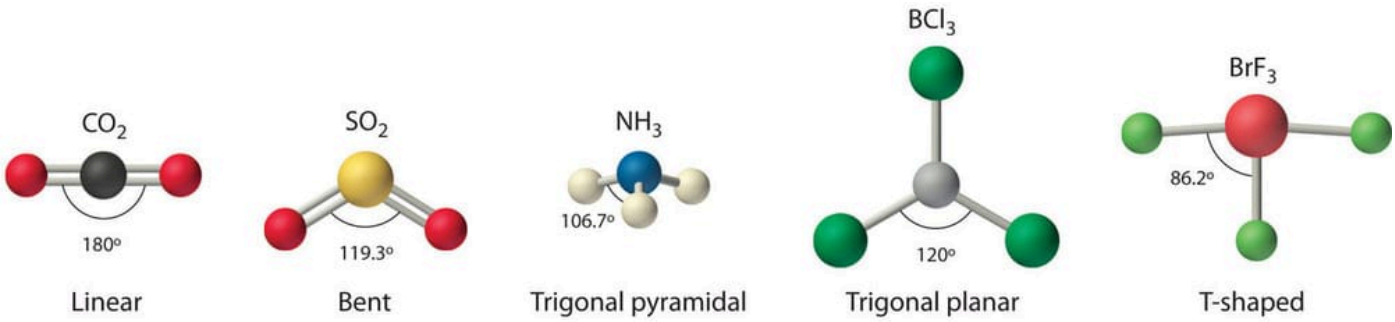


Figure 1.3.1: Common Structures for Molecules and Polyatomic Ions That Consist of a Central Atom Bonded to Two or Three Other Atoms. (CC BY-NC-SA; anonymous)

We can use the VSEPR model to predict the geometry of most polyatomic molecules and ions by focusing only on the number of electron pairs around the *central atom*, ignoring all other valence electrons present. According to this model, valence electrons in the Lewis structure form *groups*, which may consist of a single bond, a double bond, a triple bond, a lone pair of electrons, or even a single unpaired electron, which in the VSEPR model is counted as a lone pair. Because electrons repel each other electrostatically, the most stable arrangement of electron groups (i.e., the one with the lowest energy) is the one that minimizes repulsions. Groups are positioned around the central atom in a way that produces the molecular structure with the lowest energy, as illustrated in Figures 1.3.1 and 1.3.2.

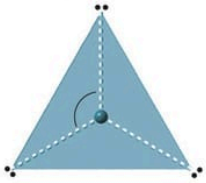
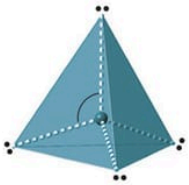
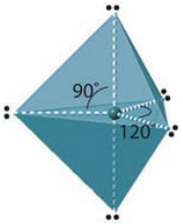
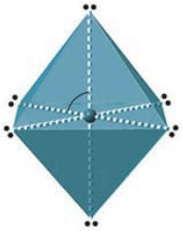
Electron Groups	2	3	4	5	6
Geometry	Linear	Trigonal planar	Tetrahedral	Trigonal bipyramidal	Octahedral
					
Predicted Bond Angles	180°	120°	109.5°	90°, 120°	90°

Figure 1.3.2: Electron Geometries for Species with Two to Six Electron Groups. Groups are placed around the central atom in a way that produces a molecular structure with the lowest energy, that is, the one that minimizes repulsions. (CC BY-NC-SA; anonymous)

In the VSEPR model, the molecule or polyatomic ion is given an AX_mE_n designation, where A is the central atom, X is a bonded atom, E is a nonbonding valence electron group (usually a lone pair of electrons), and m and n are integers. Each group around the central atom is designated as a bonding pair (BP) or lone (nonbonding) pair (LP). From the BP and LP interactions we can predict both the relative positions of the atoms and the angles between the bonds, called the bond angles. Using this information, we can describe the molecular geometry, the arrangement of the *bonded atoms* in a molecule or polyatomic ion.

VESPR Produce to predict Molecular geometry

This VESPR procedure is summarized as follows:

1. Draw the Lewis electron structure of the molecule or polyatomic ion.
2. Determine the electron group arrangement around the central atom that minimizes repulsions.
3. Assign an AX_mE_n designation; then identify the LP–LP, LP–BP, or BP–BP interactions and predict deviations from ideal bond angles.
4. Describe the molecular geometry.

We will illustrate the use of this procedure with several examples, beginning with atoms with two electron groups. In our discussion we will refer to Figure 1.3.2 and Figure 1.3.3, which summarize the common molecular geometries and idealized bond angles of molecules and ions with two to six electron groups.

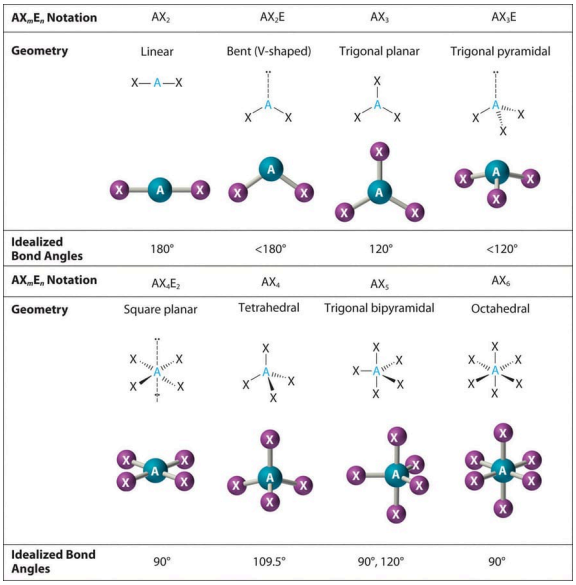


Figure 1.3.3: Common Molecular Geometries for Species with Two to Six Electron Groups. Lone pairs are shown using a dashed line. (CC BY-NC-SA; anonymous)

Linear, bent, trigonal planar, trigonal pyramidal, square planar, tetrahedral, trigonal bipyramidal, octahedral.

Two Electron Groups

Our first example is a molecule with two bonded atoms and no lone pairs of electrons, BeH_2.

AX_2 Molecules: BeH_2

1. The central atom, beryllium, contributes two valence electrons, and each hydrogen atom contributes one. The Lewis electron structure is

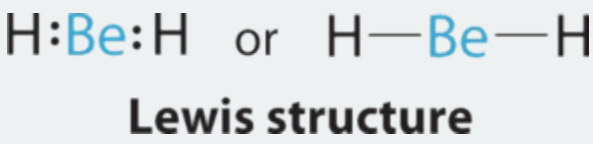


Figure 1.3.2 that the arrangement that minimizes repulsions places the groups 180° apart. (CC BY-NC-SA; anonymous)

3. Both groups around the central atom are bonding pairs (BP). Thus BeH_2 is designated as AX_2.

4. From Figure 1.3.3 we see that with two bonding pairs, the molecular geometry that minimizes repulsions in BeH_2 is *linear*.

AX_2 Molecules: CO_2

1. The central atom, carbon, contributes four valence electrons, and each oxygen atom contributes six. The Lewis electron structure is



2. The carbon atom forms two double bonds. Each double bond is a group, so there are two electron groups around the central atom. Like BeH_2, the arrangement that minimizes repulsions places the groups 180° apart.

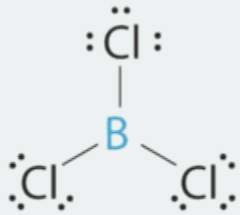
3. Once again, both groups around the central atom are bonding pairs (BP), so CO_2 is designated as AX_2.

4. VSEPR only recognizes groups around the *central* atom. Thus the lone pairs on the oxygen atoms do not influence the molecular geometry. With two bonding pairs on the central atom and no lone pairs, the molecular geometry of CO_2 is linear (Figure 1.3.3). The structure of CO_2 is shown in Figure 1.3.1.

Three Electron Groups

AX_3 Molecules: BCl_3

1. The central atom, boron, contributes three valence electrons, and each chlorine atom contributes seven valence electrons. The Lewis electron structure is



Lewis structure

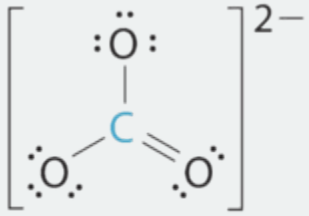
Figure 1.3.2): (CC BY-NC-SA; anonymous)

3. All electron groups are bonding pairs (BP), so the structure is designated as AX_3.

4. From Figure 1.3.3 we see that with three bonding pairs around the central atom, the molecular geometry of BCl_3 is *trigonal planar*, as shown in Figure 1.3.2.

AX_3 Molecules: CO_3^{2-}

1. The central atom, carbon, has four valence electrons, and each oxygen atom has six valence electrons. As you learned previously, the Lewis electron structure of one of three resonance forms is represented as



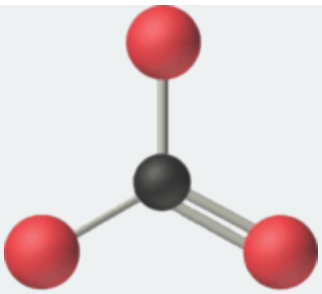
Lewis structure

Figure 1.3.2).

The three oxygens are arranged in a triangular shape with carbon at the center. Two of the oxygens have three lone pairs. One ocht oxygens has 2 lone pairs and is double bonded to the carbon. The molecule has a minus 2 charge.

3. All electron groups are bonding pairs (BP). With three bonding groups around the central atom, the structure is designated as AX_3.

4. We see from Figure 1.3.3 that the molecular geometry of CO_3^{2-} is trigonal planar with bond angles of 120°.



Molecular geometry
(trigonal planar)

In our next example we encounter the effects of lone pairs and multiple bonds on molecular geometry for the first time.

AX_2E Molecules: SO_2

1. The central atom, sulfur, has 6 valence electrons, as does each oxygen atom. With 18 valence electrons, the Lewis electron structure is shown below.

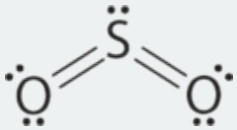


Figure 1.3.2): (CC BY-NC-SA; anonymous)

The two oxygens are double bonded to the sulfur. The oxygens have 2 lone pairs while sulfur had one lone pair.

3. There are two bonding pairs and one lone pair, so the structure is designated as AX_2E. This designation has a total of three electron pairs, two X and one E. Because a lone pair is not shared by two nuclei, it occupies more space near the central atom than a bonding pair (Figure 1.3.4). Thus bonding pairs and lone pairs repel each other electrostatically in the order BP–BP < LP–BP < LP–LP. In SO_2, we have one BP–BP interaction and two LP–BP interactions.

4. The molecular geometry is described only by the positions of the nuclei, *not* by the positions of the lone pairs. Thus with two nuclei and one lone pair the shape is *bent*, or *V shaped*, which can be viewed as a trigonal planar arrangement with a missing vertex (Figures 1.3.2 and 1.3.3). The O-S-O bond angle is expected to be *less than* 120° because of the extra space taken up by the lone pair.

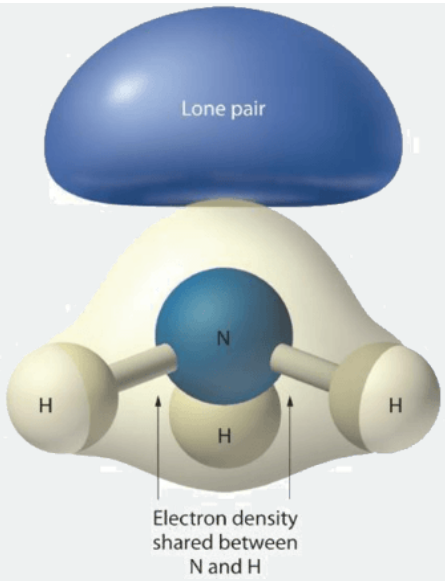
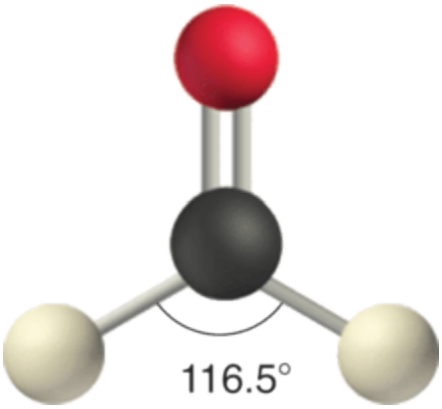


Figure 1.3.4: The Difference in the Space Occupied by a Lone Pair of Electrons and by a Bonding Pair. (CC BY-NC-SA; anonymous)

As with SO_2, this composite model of electron distribution and negative electrostatic potential in ammonia shows that a lone pair of electrons occupies a larger region of space around the nitrogen atom than does a bonding pair of electrons that is shared with a hydrogen atom.

Like lone pairs of electrons, multiple bonds occupy more space around the central atom than a single bond, which can cause other bond angles to be somewhat smaller than expected. This is because a multiple bond has a higher electron density than a single bond, so its electrons occupy more space than those of a single bond. For example, in a molecule such as CH_2O (AX_3), whose structure is shown below, the double bond repels the single bonds more strongly than the single bonds repel each other. This causes a deviation from ideal geometry (an H–C–H bond angle of 116.5° rather than 120°).

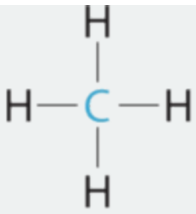


Four Electron Groups

One of the limitations of Lewis structures is that they depict molecules and ions in only two dimensions. With four electron groups, we must learn to show molecules and ions in three dimensions.

AX_4 Molecules: CH_4

1. The central atom, carbon, contributes four valence electrons, and each hydrogen atom has one valence electron, so the full Lewis electron structure is

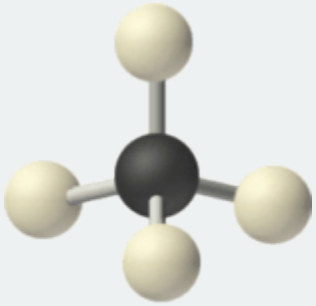


Lewis structure

2. There are four electron groups around the central atom. As shown in Figure 1.3.2, repulsions are minimized by placing the groups in the corners of a tetrahedron with bond angles of 109.5°.

3. All electron groups are bonding pairs, so the structure is designated as AX_4.

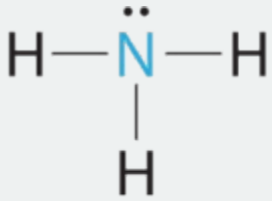
4. With four bonding pairs, the molecular geometry of methane is *tetrahedral* (Figure 1.3.3).



Molecular geometry
(tetrahedral)

AX_3E Molecules: NH_3

1. In ammonia, the central atom, nitrogen, has five valence electrons and each hydrogen donates one valence electron, producing the Lewis electron structure



Lewis structure

2. There are four electron groups around nitrogen, three bonding pairs and one lone pair. Repulsions are minimized by directing each hydrogen atom and the lone pair to the corners of a tetrahedron.

3. With three bonding pairs and one lone pair, the structure is designated as AX_3E. This designation has a total of four electron pairs, three X and one E. We expect the LP–BP interactions to cause the bonding pair angles to deviate significantly from the angles of a perfect tetrahedron.

4. There are three nuclei and one lone pair, so the molecular geometry is *trigonal pyramidal*. In essence, this is a tetrahedron with a vertex missing (Figure 1.3.3). However, the H–N–H bond angles are less than the ideal angle of 109.5° because of LP–BP repulsions (Figure 1.3.3 and Figure 1.3.4).

AX_2E_2 Molecules: H_2O

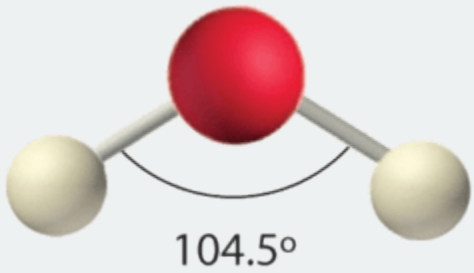
1. Oxygen has six valence electrons and each hydrogen has one valence electron, producing the Lewis electron structure



Figure 1.3.2: (CC BY-NC-SA; anonymous)

3. With two bonding pairs and two lone pairs, the structure is designated as AX_2E_2 with a total of four electron pairs. Due to LP–LP, LP–BP, and BP–BP interactions, we expect a significant deviation from idealized tetrahedral angles.

4. With two hydrogen atoms and two lone pairs of electrons, the structure has significant lone pair interactions. There are two nuclei about the central atom, so the molecular shape is *bent*, or *V shaped*, with an H–O–H angle that is even less than the H–N–H angles in NH_3, as we would expect because of the presence of two lone pairs of electrons on the central atom rather than one. This molecular shape is essentially a tetrahedron with two missing vertices.



Five Electron Groups

In previous examples it did not matter where we placed the electron groups because all positions were equivalent. In some cases, however, the positions are not equivalent. We encounter this situation for the first time with five electron groups.

AX_5 Molecules: PCl_5

1. Phosphorus has five valence electrons and each chlorine has seven valence electrons, so the Lewis electron structure of PCl_5 is

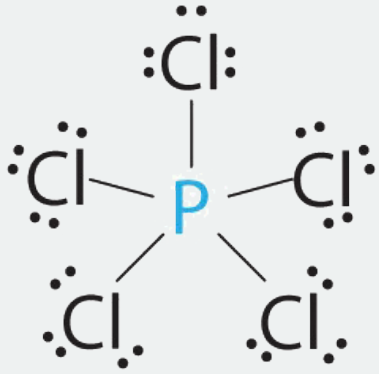
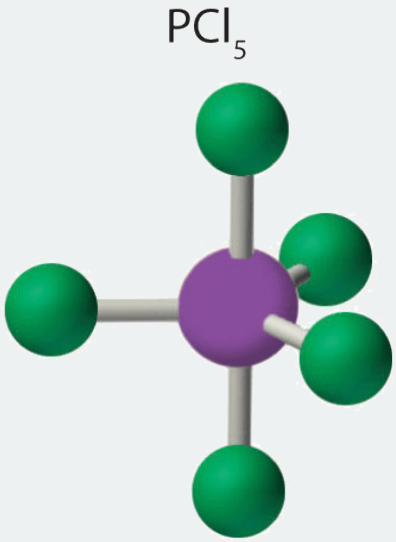


Figure 1.3.2): (CC BY-NC-SA; anonymous)

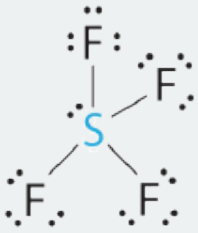
3. All electron groups are bonding pairs, so the structure is designated as AX_5. There are no lone pair interactions.

4. The molecular geometry of PCl_5 is *trigonal bipyramidal*, as shown in Figure 1.3.3. The molecule has three atoms in a plane in *equatorial* positions and two atoms above and below the plane in *axial* positions. The three equatorial positions are separated by 120° from one another, and the two axial positions are at 90° to the equatorial plane. The axial and equatorial positions are not chemically equivalent, as we will see in our next example.



AX_4E Molecules: SF_4

1. The sulfur atom has six valence electrons and each fluorine has seven valence electrons, so the Lewis electron structure is



Lewis structure

Four fluorenes are bonded to a central sulfur. Each fluorine has three lone pairs. Sulfur has one lone pair.

With an expanded valence, this species is an exception to the octet rule.

2. There are five groups around sulfur, four bonding pairs and one lone pair. With five electron groups, the lowest energy arrangement is a trigonal bipyramid, as shown in Figure 1.3.2.

3. We designate SF_4 as AX_4E; it has a total of five electron pairs. However, because the axial and equatorial positions are not chemically equivalent, where do we place the lone pair? If we place the lone pair in the axial position, we have three LP–BP repulsions at 90°. If we place it in the equatorial position, we have two 90° LP–BP repulsions at 90°. With fewer 90° LP–BP repulsions, we can predict that the structure with the lone pair of electrons in the *equatorial position is more stable than the one with the lone pair in the axial position*. We also expect a deviation from ideal geometry because a lone pair of electrons occupies more space than a bonding pair.

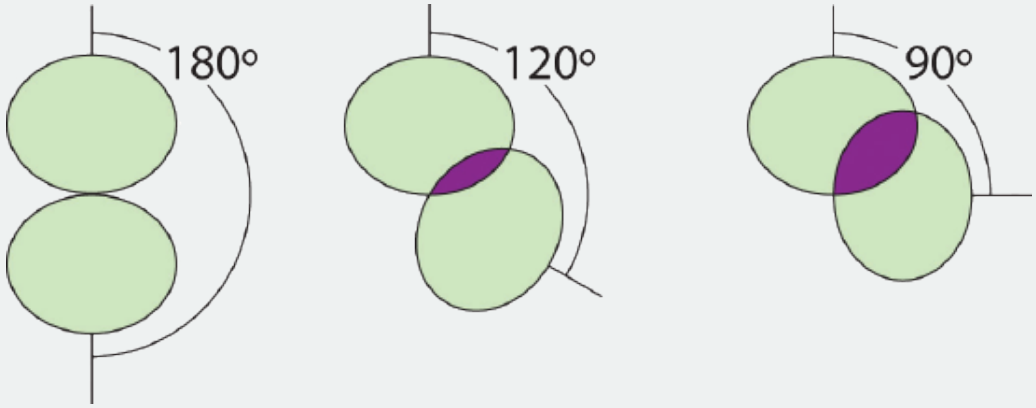
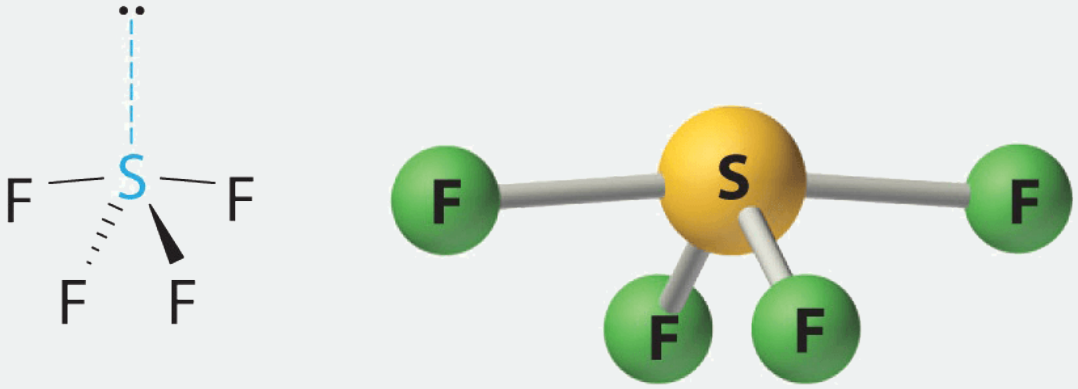


Figure 1.3.5: Illustration of the Area Shared by Two Electron Pairs versus the Angle between Them

180 degree angle has no shared space between teo electron pair, 120 degree angle has some shared area between two electron pairs. 90 degree angle has more shared space than 120.

At 90°, the two electron pairs share a relatively large region of space, which leads to strong repulsive electron–electron interactions.

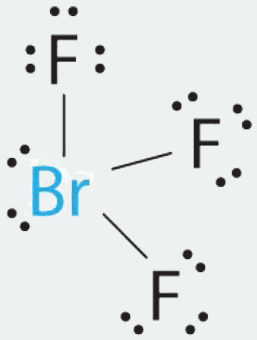
4. With four nuclei and one lone pair of electrons, the molecular structure is based on a trigonal bipyramid with a missing equatorial vertex; it is described as a *seesaw*. The F_{axial}–S–F_{axial} angle is 173° rather than 180° because of the lone pair of electrons in the equatorial plane.



Molecular geometry (seesaw)

AX_3E_2 Molecules: BrF_3

1. The bromine atom has seven valence electrons, and each fluorine has seven valence electrons, so the Lewis electron structure is



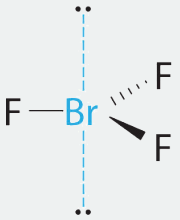
Lewis structure

Three fluorines are bonded to a central bromine. Each fluorine has three lone pairs, Bromine has two lone pairs.

Once again, we have a compound that is an exception to the octet rule.

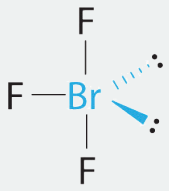
2. There are five groups around the central atom, three bonding pairs and two lone pairs. We again direct the groups toward the vertices of a trigonal bipyramid.

3. With three bonding pairs and two lone pairs, the structural designation is AX_3E_2 with a total of five electron pairs. Because the axial and equatorial positions are not equivalent, we must decide how to arrange the groups to minimize repulsions. If we place both lone pairs in the axial positions, we have six LP–BP repulsions at 90°. If both are in the equatorial positions, we have four LP–BP repulsions at 90°. If one lone pair is axial and the other equatorial, we have one LP–LP repulsion at 90° and three LP–BP repulsions at 90°:



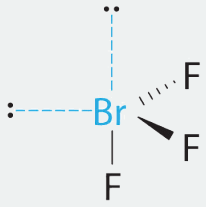
Lone pairs axial

(a)



Lone pairs equatorial

(b)



Lone pairs axial and equatorial

(c)

Interactions

90º LP–LP	0	0	1
90º LP–BP	6	4	3

If the lone pairs are axiam, the 90 degree LP-LP interactions are o and the 90 degree LP-BP interaction is zero. If the Lone pares are equatorial there are zero 90 degree LP-LP interactions and four 90 degree LP-BP intereactions. If the lone pairs are axial and equatorial there is one 90 degree LP-LP interaction and three 90 degree LP-BP interaction.

Structure (c) can be eliminated because it has a LP–LP interaction at 90°. Structure (b), with fewer LP–BP repulsions at 90° than (a), is lower in energy. However, we predict a deviation in bond angles because of the presence of the two lone pairs of electrons.

4. The three nuclei in BrF_3 determine its molecular structure, which is described as *T shaped*. This is essentially a trigonal bipyramid that is missing two equatorial vertices. The F_{axial}–Br–F_{axial} angle is 172°, less than 180° because of LP–BP repulsions (Figure 1.3.2.1).

Because lone pairs occupy more space around the central atom than bonding pairs, electrostatic repulsions are more important for lone pairs than for bonding pairs.

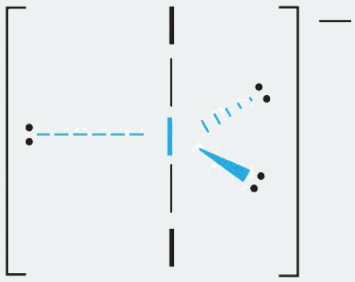
AX_2E_3 Molecules: I_3^-

1. Each iodine atom contributes seven electrons and the negative charge one, so the Lewis electron structure is



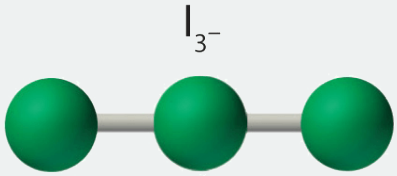
2. There are five electron groups about the central atom in I_3^-, two bonding pairs and three lone pairs. To minimize repulsions, the groups are directed to the corners of a trigonal bipyramid.

3. With two bonding pairs and three lone pairs, I_3^- has a total of five electron pairs and is designated as AX_2E_3. We must now decide how to arrange the lone pairs of electrons in a trigonal bipyramid in a way that minimizes repulsions. Placing them in the axial positions eliminates 90° LP–LP repulsions and minimizes the number of 90° LP–BP repulsions.



The three lone pairs of electrons have equivalent interactions with the three iodine atoms, so we do not expect any deviations in bonding angles.

4. With three nuclei and three lone pairs of electrons, the molecular geometry of I_3^- is linear. This can be described as a trigonal bipyramid with three equatorial vertices missing. The ion has an I–I–I angle of 180°, as expected.

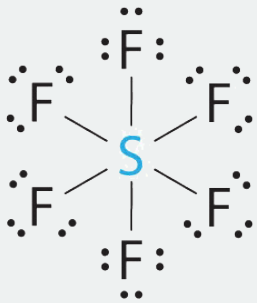


Six Electron Groups

Six electron groups form an *octahedron*, a polyhedron made of identical equilateral triangles and six identical vertices (Figure 1.3.2.)

AX_6 Molecules: SF_6

1. The central atom, sulfur, contributes six valence electrons, and each fluorine atom has seven valence electrons, so the Lewis electron structure is



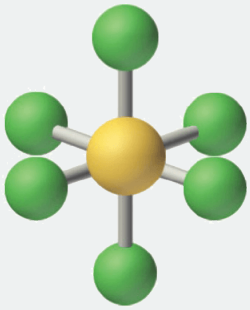
Lewis structure

With an expanded valence, this species is an exception to the octet rule.

2. There are six electron groups around the central atom, each a bonding pair. We see from Figure 1.3.2 that the geometry that minimizes repulsions is *octahedral*.

3. With only bonding pairs, SF_6 is designated as AX_6. All positions are chemically equivalent, so all electronic interactions are equivalent.

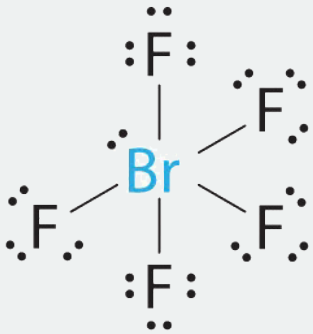
4. There are six nuclei, so the molecular geometry of SF_6 is octahedral.



Molecular geometry
(octahedral)

AX_5E Molecules: BrF_5

1. The central atom, bromine, has seven valence electrons, as does each fluorine, so the Lewis electron structure is

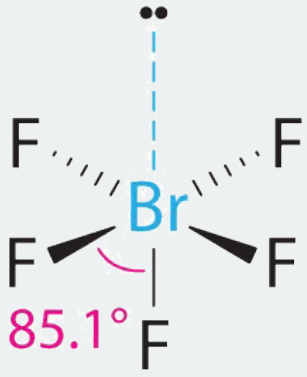


Lewis structure

Five fluorines are bonded to a central bromine. Each fluorine has three lone pairs, Bromine has one lone pair.

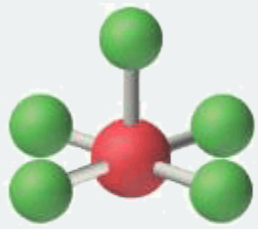
With its expanded valence, this species is an exception to the octet rule.

2. There are six electron groups around the Br, five bonding pairs and one lone pair. Placing five F atoms around Br while minimizing BP–BP and LP–BP repulsions gives the following structure:



3. With five bonding pairs and one lone pair, BrF_5 is designated as AX_5E; it has a total of six electron pairs. The BrF_5 structure has four fluorine atoms in a plane in an equatorial position and one fluorine atom and the lone pair of electrons in the axial positions. We expect all F_{axial}–Br–$F_{equatorial}$ angles to be less than 90° because of the lone pair of electrons, which occupies more space than the bonding electron pairs.

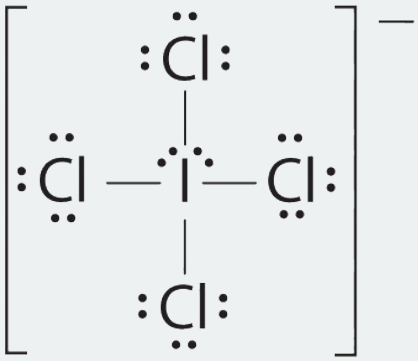
4. With five nuclei surrounding the central atom, the molecular structure is based on an octahedron with a vertex missing. This molecular structure is *square pyramidal*. The F_{axial}–B–$F_{equatorial}$ angles are 85.1°, less than 90° because of LP–BP repulsions.



Molecular geometry
(square pyramidal)

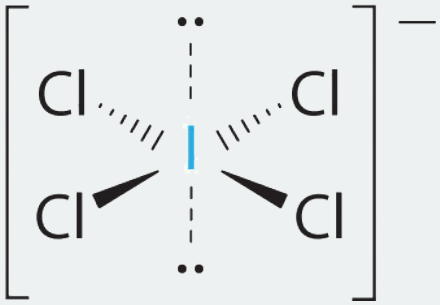
AX_4E_2 Molecules: ICl_4^-

1. The central atom, iodine, contributes seven electrons. Each chlorine contributes seven, and there is a single negative charge. The Lewis electron structure is



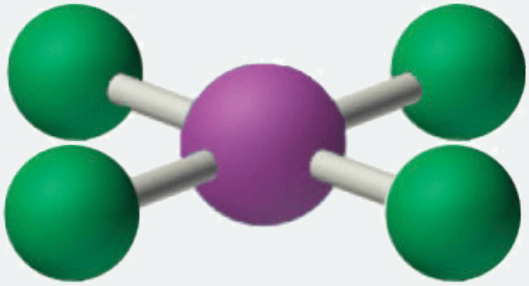
Four chlorines are bonded to a central iodine. Each chlorine has three electron pairs. The iodine has two electron pairs. The molecule is negatively charged.

2. There are six electron groups around the central atom, four bonding pairs and two lone pairs. The structure that minimizes LP–LP, LP–BP, and BP–BP repulsions is



3. ICl_4^- is designated as AX_4E_2 and has a total of six electron pairs. Although there are lone pairs of electrons, with four bonding electron pairs in the equatorial plane and the lone pairs of electrons in the axial positions, all LP–BP repulsions are the same. Therefore, we do not expect any deviation in the Cl–I–Cl bond angles.

4. With five nuclei, the ICl4– ion forms a molecular structure that is *square planar*, an octahedron with two opposite vertices missing.



The relationship between the number of electron groups around a central atom, the number of lone pairs of electrons, and the molecular geometry is summarized in Figure 1.3.6.

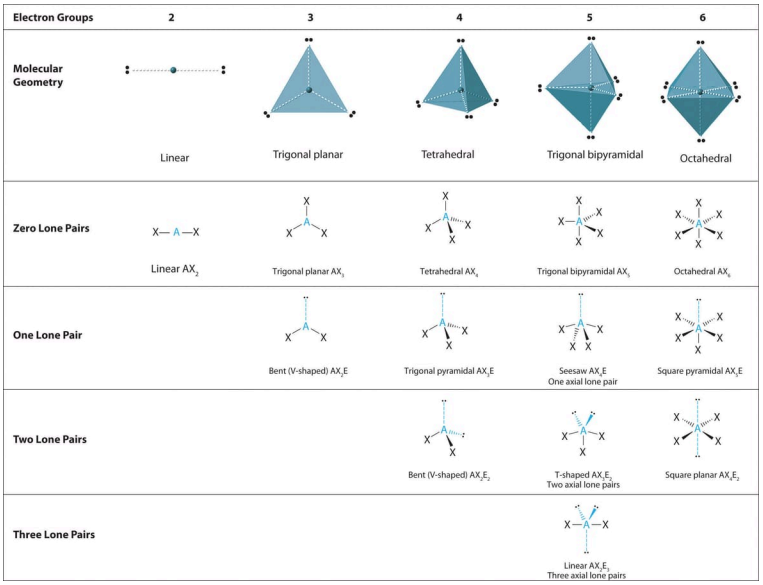


Figure 1.3.6***:*** *Overview of Molecular Geometries*

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Example 1.3.1

Using the VSEPR model, predict the molecular geometry of each molecule or ion.

1. PF_5 (phosphorus pentafluoride, a catalyst used in certain organic reactions)
2. H_3O^+ (hydronium ion)

Given: two chemical species

Asked for: molecular geometry

Strategy:

A. Draw the Lewis electron structure of the molecule or polyatomic ion.
B. Determine the electron group arrangement around the central atom that minimizes repulsions.
C. Assign an AX_mE_n designation; then identify the LP–LP, LP–BP, or BP–BP interactions and predict deviations in bond angles.
D. Describe the molecular geometry.

Solution:

1. **A** The central atom, P, has five valence electrons and each fluorine has seven valence electrons, so the Lewis structure of PF_5 is

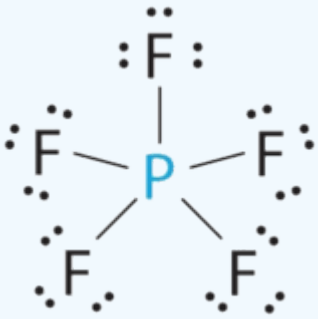


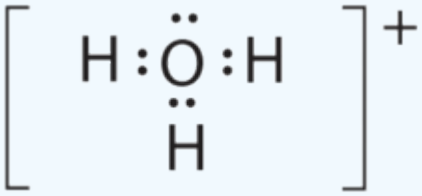
Figure 1.3.6): (CC BY-NC-SA; anonymous)

C All electron groups are bonding pairs, so PF_5 is designated as AX_5. Notice that this gives a total of five electron pairs. With no lone pair repulsions, we do not expect any bond angles to deviate from the ideal.

D The PF_5 molecule has five nuclei and no lone pairs of electrons, so its molecular geometry is trigonal bipyramidal.



2. **A** The central atom, O, has six valence electrons, and each H atom contributes one valence electron. Subtracting one electron for the positive charge gives a total of eight valence electrons, so the Lewis electron structure is

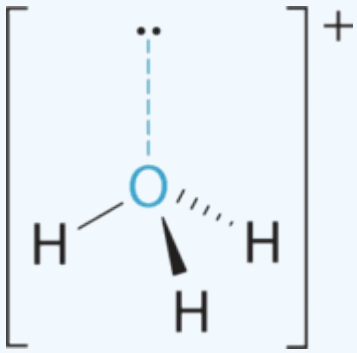


Three hydrogens are bonded to a central oxygen. The oxygen has two lone pairs. The molecule has a charge of plus one.

B There are four electron groups around oxygen, three bonding pairs and one lone pair. Like NH_3, repulsions are minimized by directing each hydrogen atom and the lone pair to the corners of a tetrahedron.

C With three bonding pairs and one lone pair, the structure is designated as AX_3E and has a total of four electron pairs (three X and one E). We expect the LP–BP interactions to cause the bonding pair angles to deviate significantly from the angles of a perfect tetrahedron.

D There are three nuclei and one lone pair, so the molecular geometry is *trigonal pyramidal*, in essence a tetrahedron missing a vertex. However, the H–O–H bond angles are less than the ideal angle of 109.5° because of LP–BP repulsions:



Exercise 1.3.1

Using the VSEPR model, predict the molecular geometry of each molecule or ion.

a. XeO_3
b. PF_6^-
c. NO_2^+

Answer a available at the end of this section.

Example 1.3.2

Predict the molecular geometry of each molecule.

1. XeF_2
2. $SnCl_2$

Given: two chemical compounds

Asked for: molecular geometry

Strategy:

Use the strategy given in Example1.3.1.

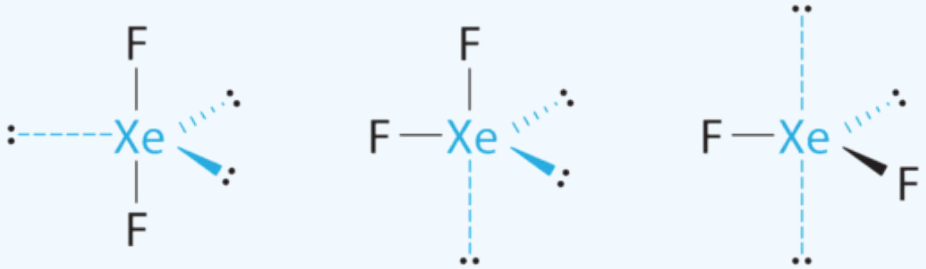
Solution:

1. **A** Xenon contributes eight electrons and each fluorine seven valence electrons, so the Lewis electron structure is



B There are five electron groups around the central atom, two bonding pairs and three lone pairs. Repulsions are minimized by placing the groups in the corners of a trigonal bipyramid.

C From B, XeF_2 is designated as AX_2E_3 and has a total of five electron pairs (two X and three E). With three lone pairs about the central atom, we can arrange the two F atoms in three possible ways: both F atoms can be axial, one can be axial and one equatorial, or both can be equatorial:



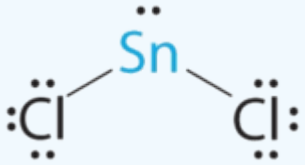
Interactions			
90 LP–LP	0	2	2

If the two F atoms are axial ther are zero 90 LP-LP interactions. If the two F atoms are axial and equatorial or just equatorial, there are 2 90 LP-LP interactions.

The structure with the lowest energy is the one that minimizes LP–LP repulsions. Both (b) and (c) have two 90° LP–LP interactions, whereas structure (a) has none. Thus both F atoms are in the axial positions, like the two iodine atoms around the central iodine in I_3^-. All LP–BP interactions are equivalent, so we do not expect a deviation from an ideal 180° in the F–Xe–F bond angle.

D With two nuclei about the central atom, the molecular geometry of XeF_2 is linear. It is a trigonal bipyramid with three missing equatorial vertices.

2. **A** The tin atom donates 4 valence electrons and each chlorine atom donates 7 valence electrons. With 18 valence electrons, the Lewis electron structure is



Two chlorines are bonded to a central tin. Each chlorine has three lone pairs. Tin has one lone pair.

B There are three electron groups around the central atom, two bonding groups and one lone pair of electrons. To minimize repulsions the three groups are initially placed at 120° angles from each other.

C From B we designate $SnCl_2$ as AX_2E. It has a total of three electron pairs, two X and one E. Because the lone pair of electrons occupies more space than the bonding pairs, we expect a decrease in the Cl–Sn–Cl bond angle due to increased LP–BP repulsions.

D With two nuclei around the central atom and one lone pair of electrons, the molecular geometry of $SnCl_2$ is bent, like SO_2, but with a Cl–Sn–Cl bond angle of 95°. The molecular geometry can be described as a trigonal planar arrangement with one vertex missing.

Exercise 1.3.2

Predict the molecular geometry of each molecule.

a. SO_3
b. XeF_4

Answer a available at the end of this section.

YouTube Video

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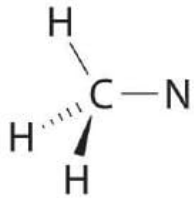
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Molecules with No Single Central Atom

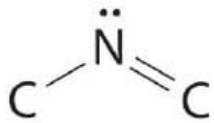
The VSEPR model can be used to predict the structure of somewhat more complex molecules with no single central atom by treating them as linked AX_mE_n fragments. We will demonstrate with methyl isocyanate (CH_3–N=C=O), a volatile and highly toxic molecule that is used to produce the pesticide Sevin. In 1984, large quantities of Sevin were accidentally released in Bhopal, India, when water leaked into storage tanks. The resulting highly exothermic reaction caused a rapid increase in pressure that ruptured the tanks, releasing large amounts of methyl isocyanate that killed approximately 3800 people and wholly or partially disabled about 50,000 others. In addition, there was significant damage to livestock and crops.

We can treat methyl isocyanate as linked AX_mE_n fragments beginning with the carbon atom at the left, which is connected to three H atoms and one N atom by single bonds. The four bonds around carbon mean that it must be surrounded by four bonding electron pairs in a configuration similar to AX_4. We can therefore predict the CH_3–N portion of the molecule to be roughly

tetrahedral, similar to methane:



The nitrogen atom is connected to one carbon by a single bond and to the other carbon by a double bond, producing a total of three bonds, C–N=C. For nitrogen to have an octet of electrons, it must also have a lone pair:



One carbon bonded to nitrogen and another carbon double bonded to the nitrogen. The nitrogen has one lone pair.

Because multiple bonds are not shown in the VSEPR model, the nitrogen is effectively surrounded by three electron pairs. Thus according to the VSEPR model, the C–N=C fragment should be bent with an angle less than 120°.

The carbon in the –N=C=O fragment is doubly bonded to both nitrogen and oxygen, which in the VSEPR model gives carbon a total of two electron pairs. The N=C=O angle should therefore be 180°, or linear. The three fragments combine to give the following structure:

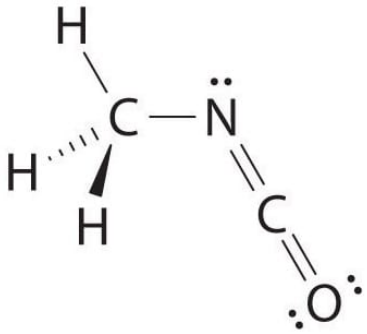


Figure 1.3.7).

Three hydrogens are bonded to a carbon. The carbon is also bonded to a nitrogen. The nitrogen is double bonded to another carbon. The second carbon is double bonded to an oxygen. The nitrogen has one lone pair. The oxygen has two lone pairs.

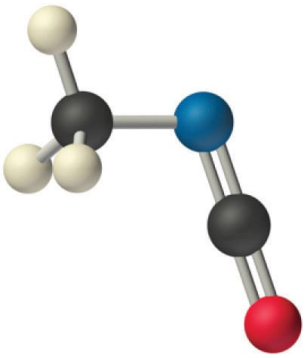


Figure 1.3.7: The Experimentally Determined Structure of Methyl Isocyanate

Certain patterns are seen in the structures of moderately complex molecules. For example, carbon atoms with four bonds (such as the carbon on the left in methyl isocyanate) are generally tetrahedral. Similarly, the carbon atom on the right has two double bonds that are similar to those in CO_2, so its geometry, like that of CO_2, is linear. Recognizing similarities to simpler molecules

will help you predict the molecular geometries of more complex molecules.

Example 1.3.3

Use the VSEPR model to predict the molecular geometry of propyne ($H_3C–C≡CH$), a gas with some anesthetic properties.

Given: chemical compound

Asked for: molecular geometry

Strategy:

Count the number of electron groups around each carbon, recognizing that in the VSEPR model, a multiple bond counts as a single group. Use Figure 1.3.3 to determine the molecular geometry around each carbon atom and then deduce the structure of the molecule as a whole.

Solution:

Because the carbon atom on the left is bonded to four other atoms, we know that it is approximately tetrahedral. The next two carbon atoms share a triple bond, and each has an additional single bond. Because a multiple bond is counted as a single bond in the VSEPR model, each carbon atom behaves as if it had two electron groups. This means that both of these carbons are linear, with C–C≡C and C≡C–H angles of 180°.

Exercise 1.3.3

Predict the geometry of allene ($H_2C=C=CH_2$), a compound with narcotic properties that is used to make more complex organic molecules.

Answer available at the end of this section.

Molecular Dipole Moments

You previously learned how to calculate the **dipole moments** of simple diatomic molecules. In more complex molecules with polar covalent bonds, the three-dimensional geometry and the compound's symmetry determine whether there is a net dipole moment. Mathematically, dipole moments are *vectors*; they possess both a *magnitude* and a *direction*. The dipole moment of a molecule is therefore the *vector sum* of the dipole moments of the individual bonds in the molecule. If the individual bond dipole moments cancel one another, there is no net dipole moment. Such is the case for CO_2, a linear molecule (Figure 1.3.8*a*). Each C–O bond in CO_2 is polar, yet experiments show that the CO_2 molecule has no dipole moment. Because the two C–O bond dipoles in CO_2 are equal in magnitude and oriented at 180° to each other, they cancel. As a result, the CO_2 molecule has no *net* dipole moment even though it has a substantial separation of charge. In contrast, the H_2O molecule is not linear (Figure 1.3.8*b*); it is bent in three-dimensional space, so the dipole moments do not cancel each other. Thus a molecule such as H_2O has a net dipole moment. We expect the concentration of negative charge to be on the oxygen, the more electronegative atom, and positive charge on the two hydrogens. This charge polarization allows H_2O to hydrogen-bond to other polarized or charged species, including other water molecules.

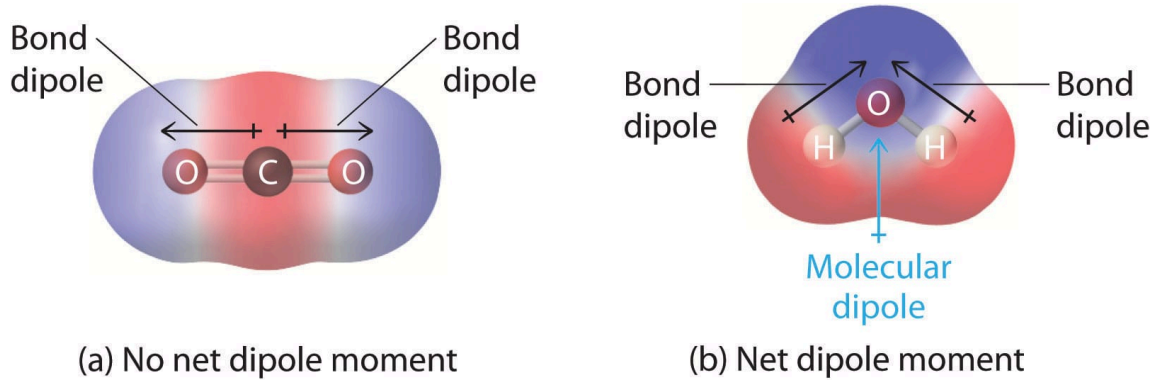


Figure 1.3.8: How Individual Bond Dipole Moments Are Added Together to Give an Overall Molecular Dipole Moment for Two Triatomic Molecules with Different Structures. (a) In CO_2, the C–O bond dipoles are equal in magnitude but oriented in opposite directions (at 180°). Their vector sum is zero, so CO_2 therefore has no net dipole. (b) In H_2O, the O–H bond dipoles are also equal in magnitude, but they are oriented at 104.5° to each other. Hence the vector sum is not zero, and H_2O has a net dipole moment.

Other examples of molecules with polar bonds are shown in Figure 1.3.9. In molecular geometries that are highly symmetrical (most notably tetrahedral and square planar, trigonal bipyramidal, and octahedral), individual bond dipole moments completely cancel, and there is no net dipole moment. Although a molecule like $CHCl_3$ is best described as tetrahedral, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments cannot cancel one another, and the molecule has a dipole moment. Due to the arrangement of the bonds in molecules that have V-shaped, trigonal pyramidal, seesaw, T-shaped, and square pyramidal geometries, the bond dipole moments cannot cancel one another. Consequently, molecules with these geometries always have a nonzero dipole moment. Molecules with asymmetrical charge distributions have a net dipole moment.

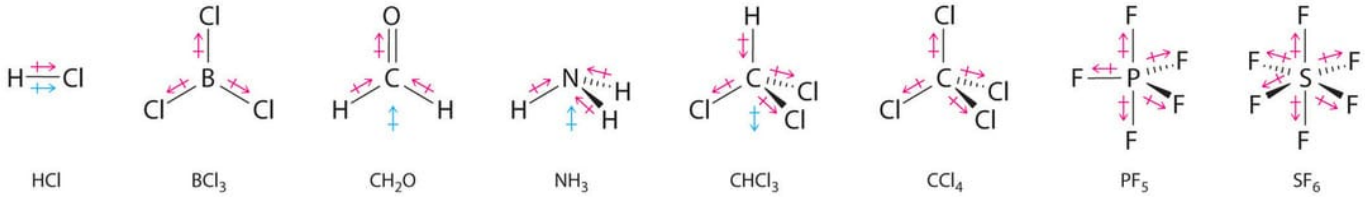


Figure 1.3.9: Molecules with Polar Bonds. Individual bond dipole moments are indicated in red. Due to their different three-dimensional structures, some molecules with polar bonds have a net dipole moment (HCl, CH_2O, NH_3, and $CHCl_3$), indicated in blue, whereas others do not because the bond dipole moments cancel (BCl_3, CCl_4, PF_5, and SF_6).

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

Example 1.3.4

Which molecule(s) has a net dipole moment?

a. H_2S
b. NHF_2
c. BF_3

Given: three chemical compounds

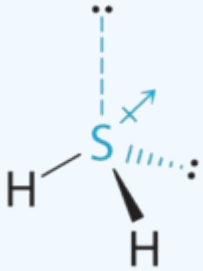
Asked for: net dipole moment

Strategy:

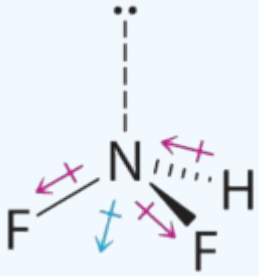
For each three-dimensional molecular geometry, predict whether the bond dipoles cancel. If they do not, then the molecule has a net dipole moment.

Solution:

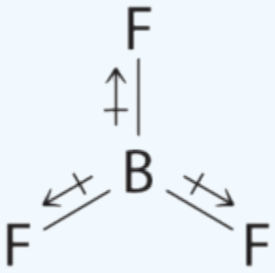
1. The total number of electrons around the central atom, S, is eight, which gives four electron pairs. Two of these electron pairs are bonding pairs and two are lone pairs, so the molecular geometry of $\mathrm{H_2S}$ is bent (Figure $1.3.6$). The bond dipoles cannot cancel one another, so the molecule has a net dipole moment.



2. Difluoroamine has a trigonal pyramidal molecular geometry. Because there is one hydrogen and two fluorines, and because of the lone pair of electrons on nitrogen, the molecule is not symmetrical, and the bond dipoles of NHF_2 cannot cancel one another. This means that NHF_2 has a net dipole moment. We expect polarization from the two fluorine atoms, the most electronegative atoms in the periodic table, to have a greater affect on the net dipole moment than polarization from the lone pair of electrons on nitrogen.



3. The molecular geometry of BF_3 is trigonal planar. Because all the B–F bonds are equal and the molecule is highly symmetrical, the dipoles cancel one another in three-dimensional space. Thus BF_3 has a net dipole moment of zero:



Exercise $1.3.4$

Which molecule(s) has a net dipole moment?

- $\mathrm{CH_3Cl}$
- $\mathrm{SO_3}$
- $\mathrm{XeO_3}$

Answer available at the end of this section.

Summary

Lewis electron structures give no information about **molecular geometry**, the arrangement of bonded atoms in a molecule or polyatomic ion, which is crucial to understanding the chemistry of a molecule. The **valence-shell electron-pair repulsion (VSEPR) model** allows us to predict which of the possible structures is actually observed in most cases. It is based on the assumption that pairs of electrons occupy space, and the lowest-energy structure is the one that minimizes electron pair–electron pair repulsions. In the VSEPR model, the molecule or polyatomic ion is given an AX_mE_n designation, where A is the central atom, X is a bonded atom, E is a nonbonding valence electron group (usually a lone pair of electrons), and m and n are integers. Each group around the central atom is designated as a bonding pair (BP) or lone (nonbonding) pair (LP). From the BP and LP interactions we can predict both the relative positions of the atoms and the angles between the bonds, called the **bond angles**. From this we can describe the **molecular geometry**. The VSEPR model can be used to predict the shapes of many molecules and polyatomic ions, but it gives no information about bond lengths and the presence of multiple bonds. A combination of VSEPR and a bonding model, such as Lewis electron structures, is necessary to understand the presence of multiple bonds.

Molecules with polar covalent bonds can have a *dipole moment*, an asymmetrical distribution of charge that results in a tendency for molecules to align themselves in an applied electric field. Any diatomic molecule with a polar covalent bond has a dipole moment, but in polyatomic molecules, the presence or absence of a net dipole moment depends on the structure. For some highly symmetrical structures, the individual bond dipole moments cancel one another, giving a dipole moment of zero.

Answers

Exercise 1.3.1

trigonal pyramidal

octahedral

linear

Exercise 1.3.2

trigonal planar

square planar

Exercise 1.3.3

The terminal carbon atoms are trigonal planar, the central carbon is linear, and the C–C–C angle is 180°.

Exercise 1.3.4

CH_3Cl and XeO_3

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1.4: Electronegativity and Bond Polarity (Review)

Learning Objective

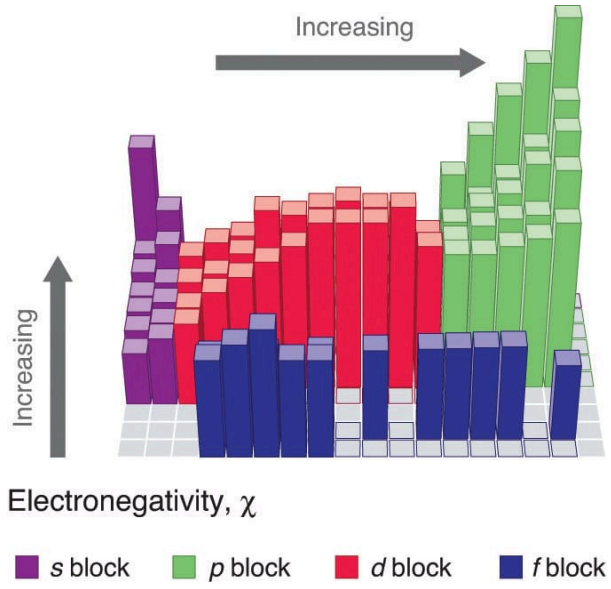
- Identify polar bonds and compounds

Electronegativity is a measure of the tendency of an atom to attract a bonding pair of electrons. The Pauling scale is the most commonly used. Fluorine (the most electronegative element) is assigned a value of 4.0, and values range down to cesium and francium which are the least electronegative at 0.7.

Patterns of electronegativity in the Periodic Table

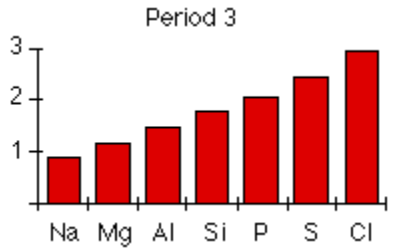
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*Electronegativity is defined as the ability of an atom in a particular molecule to attract electrons to itself. The **greater** the value, the **greater** the attractiveness for electrons.*



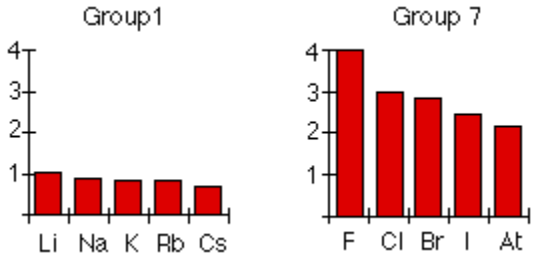
Trends in electronegativity across a period

The positively charged protons in the nucleus attract the negatively charged electrons. As the number of protons in the nucleus increases, the electronegativity or attraction will increase. Therefore electronegativity **increases** from **left to right** in a row in the periodic table. This effect only holds true for a row in the periodic table because the attraction between charges falls off rapidly with distance. The chart shows electronegativities from sodium to chlorine (ignoring argon since it does not does not form bonds).



Trends in electronegativity down a group

As you go down a group, electronegativity decreases. (If it increases up to fluorine, it must decrease as you go down.) The chart shows the patterns of electronegativity in Groups 1 and 7.



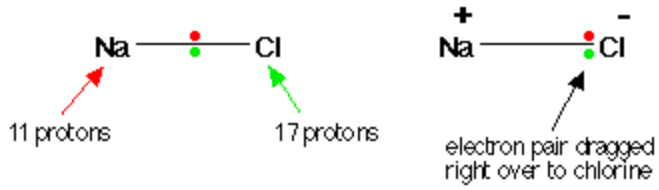
Explaining the patterns in electronegativity

The attraction that a bonding pair of electrons feels for a particular nucleus depends on:

- the number of protons in the nucleus;
- the distance from the nucleus;
- the amount of screening by inner electrons.

Why does electronegativity increase across a period?

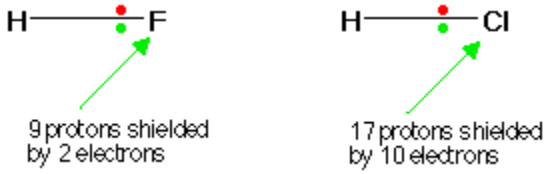
Consider sodium at the beginning of period 3 and chlorine at the end (ignoring the noble gas, argon). Think of sodium chloride as if it were covalently bonded.



Both sodium and chlorine have their bonding electrons in the 3-level. The electron pair is screened from both nuclei by the 1s, 2s and 2p electrons, but the chlorine nucleus has 6 more protons in it. It is no wonder the electron pair gets dragged so far towards the chlorine that ions are formed. Electronegativity increases across a period because the number of charges on the nucleus increases. That attracts the bonding pair of electrons more strongly.

Why does electronegativity fall as you go down a group?

As you go **down** a group, electronegativity **decreases** because the bonding pair of electrons is increasingly distant from the attraction of the nucleus. Consider the hydrogen fluoride and hydrogen chloride molecules:



The bonding pair is shielded from the fluorine's nucleus only by the $1s^2$ electrons. In the chlorine case it is shielded by all the $1s^2 2s^2 2p^6$ electrons. In each case there is a net pull from the center of the fluorine or chlorine of +7. But fluorine has the bonding pair in the 2-level rather than the 3-level as it is in chlorine. If it is closer to the nucleus, the attraction is greater.

Dipole moments occur when there is a separation of charge. They can occur between two ions in an ionic bond or between atoms in a covalent bond; dipole moments arise from differences in electronegativity. The larger the difference in electronegativity, the larger the dipole moment. The distance between the charge separation is also a deciding factor into the size of the dipole moment. The dipole moment is a measure of the polarity of the molecule.

Bond Polarity & Dipole Moment

Atoms with differences in electronegativity will share electrons unequally. The shared electrons of the covalent bond are held more tightly at the more electronegative element creating a partial negative charge, while the less electronegative element has a partial positive charge, . The larger the difference in electronegativity between the two atoms, the more polar the bond. To be considered a polar bond, the difference in electronegativity must >0.4 on the Pauling scale. Since the two electrical partial charges have opposite sign and equal magnitude and are separated by a distance, a **dipole** is established. Dipole moment is measured in debye units, which is equal to the distance between the charges multiplied by the charge (1 debye equals 3.34 x 10^{-30} coulomb-meters).

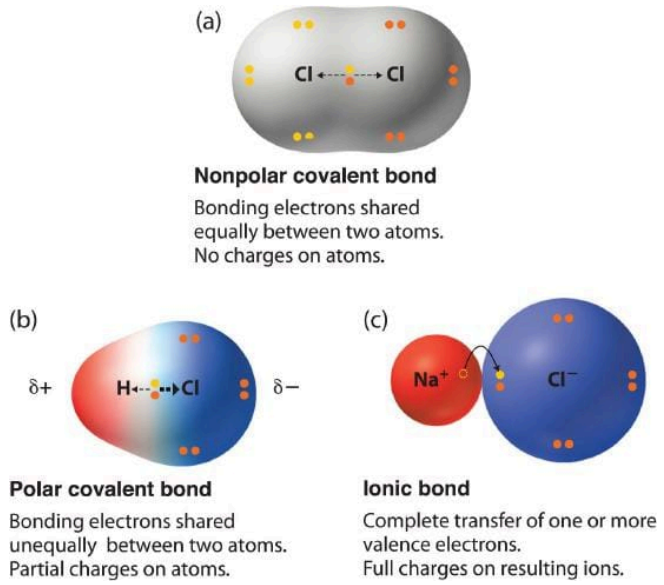


Figure 1.4.4***:*** *The Electron Distribution in a Nonpolar Covalent Bond, a Polar Covalent Bond, and an Ionic Bond Using Lewis Electron Structures. In a purely covalent bond (a), the bonding electrons are shared equally between the atoms. In a purely ionic bond (c), an electron has been transferred completely from one atom to the other. A polar covalent bond (b) is intermediate between the two extremes: the bonding electrons are shared unequally between the two atoms, and the electron distribution is asymmetrical with the electron density being greater around the more electronegative atom. Electron-rich (negatively charged) regions are shown in blue; electron-poor (positively charged) regions are shown in red.*

Polarity and Structure of Molecules

The OVERALL POLARITY of a molecule is determined by the shape of a molecule AND the polarity of its bonds. A molecule that contains polar bonds, might not have any overall polarity, depending upon its shape. The simple definition of whether a complex molecule is polar or not depends upon whether its overall centers of positive and negative charges overlap. If these centers lie at the same point in space, then the molecule has no overall polarity (and is non polar).

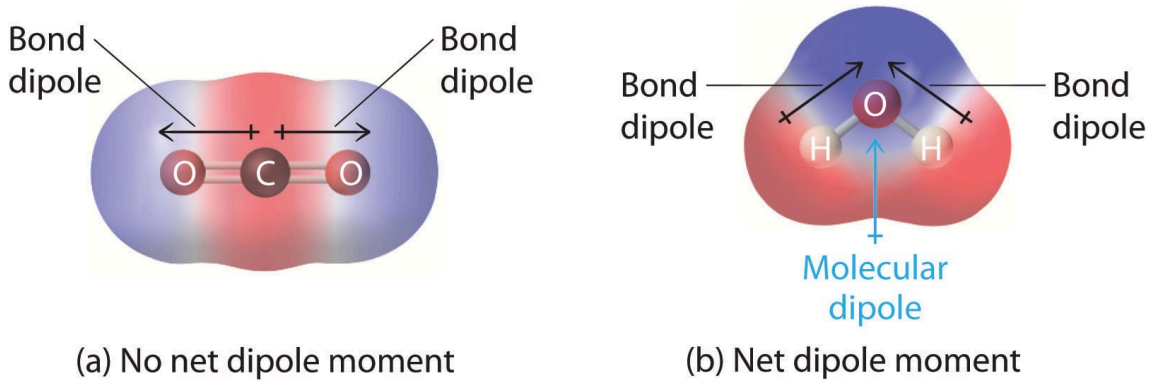


Figure 3: Charge distrubtions

If a molecule is completely symmetric, then the dipole moment vectors on each molecule will cancel each other out, making the molecule nonpolar. A molecule can only be polar if the structure of that molecule is not symmetric.

A good example of a nonpolar molecule that contains polar bonds is carbon dioxide. This is a linear molecule and the C=O bonds are, in fact, polar. The central carbon will have a net positive charge, and the two outer oxygens a net negative charge. However, since the molecule is linear, these two bond dipoles cancel each other out (i.e. vector addition of the dipoles equals zero). And the overall molecule has no dipole ($\mu = 0$.

Although a polar bond is a prerequisite for a molecule to have a dipole, not all molecules with polar bonds exhibit dipoles

Geometric Considerations

EXAMPLE 1: POLAR BONDS VS. POLAR MOLECULES

In a simple diatomic molecule like HCl, if the bond is polar, then the whole molecule is polar. What about more complicated molecules?

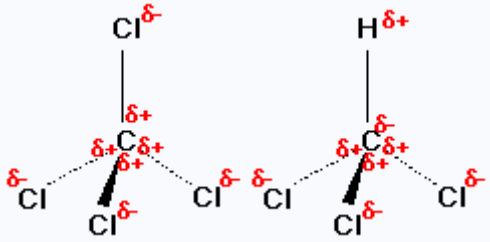


Figure: (left) CCl_4 (right) $CHCl_3$

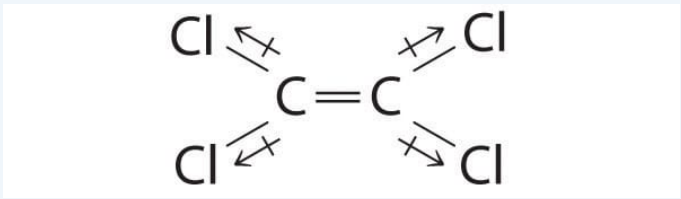
Consider CCl_4, (left panel in figure above), which as a molecule is not polar - in the sense that it doesn't have an end (or a side) which is slightly negative and one which is slightly positive. The whole of the outside of the molecule is somewhat negative, but there is no overall separation of charge from top to bottom, or from left to right.

In contrast, $CHCl_3$ is a polar molecule (right panel in figure above). The hydrogen at the top of the molecule is less electronegative than carbon and so is slightly positive. This means that the molecule now has a slightly positive "top" and a slightly negative "bottom", and so is overall a polar molecule.

A polar molecule will need to be "lop-sided" in some way.

Example 2: C_2Cl_4

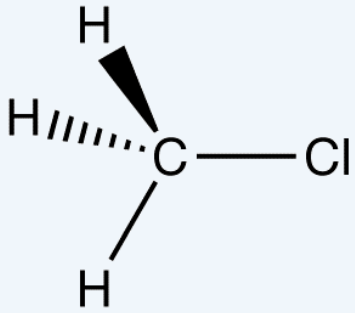
Although the C–Cl bonds are rather polar, the individual bond dipoles cancel one another in this symmetrical structure, and $Cl_2C{=}CCl_2$ does not have a net dipole moment.



Example 3: CH_3Cl

C-Cl, the key polar bond, is 178 pm. Measurement reveals 1.87 D. From this data, % ionic character can be computed. If this bor were 100% ionic (based on proton & electron),

$$\mu = \frac{178}{800}(4.80D) = 8.54D$$



Example 4: HCl

Since measurement 1.87 D,

% ionic = (1.7/8.54)x100 = 22%HCl

u = 1.03 D (measured) H-Cl bond length 127 pm

If 100% ionic,

$$\mu = \frac{127}{600}(4.80D) = 6.09D$$

ionic = (1.03/6.09)x100 = 17%

A "spectrum" of bonds

The implication of all this is that there is no clear-cut division between covalent and ionic bonds. In a pure covalent bond, the electrons are held on average exactly half way between the atoms. In a polar bond, the electrons have been dragged slightly towards one end. How far does this dragging have to go before the bond counts as ionic? There is no real answer to that. Sodium chloride is typically considered an ionic solid, but even here the sodium has not completely lost control of its electron. Because of the properties of sodium chloride, however, we tend to count it as if it were purely ionic. Lithium iodide, on the other hand, would be described as being "ionic with some covalent character". In this case, the pair of electrons has not moved entirely over to the iodine end of the bond. Lithium iodide, for example, dissolves in organic solvents like ethanol - not something which ionic substances normally do.

Summary

- No electronegativity difference between two atoms leads to a pure non-polar covalent bond.
- A small electronegativity difference leads to a polar covalent bond.
- A large electronegativity difference leads to an ionic bond.

Example 1: Polar Bonds vs. Polar Molecules

In a simple diatomic molecule like HCl, if the bond is polar, then the whole molecule is polar. What about more complicated molecules?

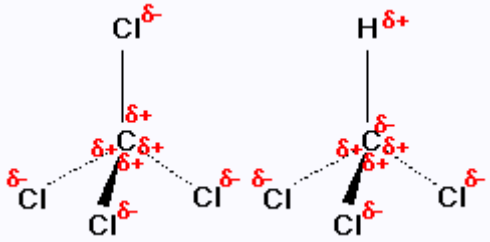


Figure: (left) CCl_4 (right) $CHCl_3$

Consider CCl_4, (left panel in figure above), which as a molecule is not polar - in the sense that it doesn't have an end (or a side) which is slightly negative and one which is slightly positive. The whole of the outside of the molecule is somewhat negative, but there is no overall separation of charge from top to bottom, or from left to right.

In contrast, $CHCl_3$ is a polar molecule (right panel in figure above). The hydrogen at the top of the molecule is less electronegative than carbon and so is slightly positive. This means that the molecule now has a slightly positive "top" and a slightly negative "bottom", and so is overall a polar molecule.

A polar molecule will need to be "lop-sided" in some way.

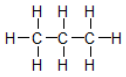
Exercises

For the following compounds,

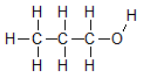
a) add lone pairs of electrons to complete octets

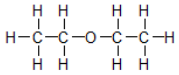
b) add dipole moment arrows or partial +/- signs to indicate polar bonds

c) predict the molecular polarity (Remember to visualize each compound in three dimensions.)

a) 

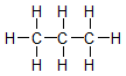
b) 

c) 

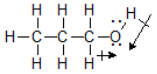
d) 

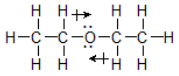
e) 

Solutions

a)  nonpolar

b)  nonpolar

c)  polar

d)  polar - molecular shape is bent around the oxygen atom

e)  polar

Contributors

- *Mike Blaber (Florida State University)*
- Jim Clark (Chemguide.co.uk)
- Prof. Richard Bank, Boise State University, Emeritus,

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1.5: Resonance

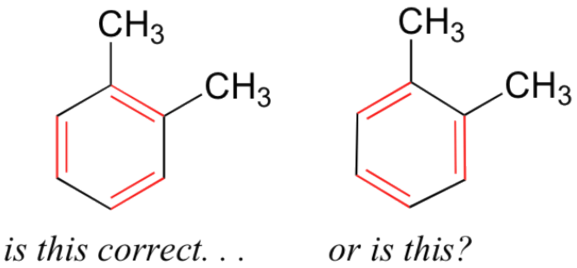
Learning Objective

- Draw resonance forms and predict the relative contribution of each resonance form to the overall structure of the compound or ion

Recognizing resonance

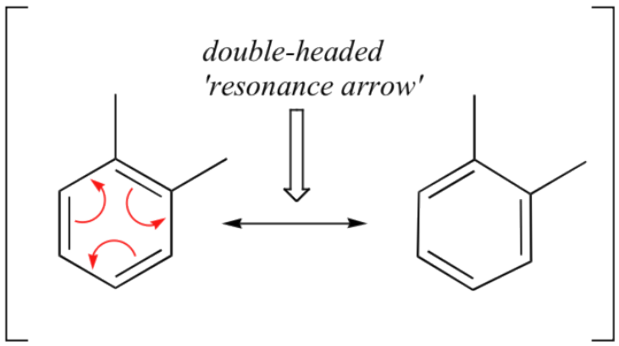
Resonance contributors involve the 'imaginary movement' of pi-bonded electrons or of lone-pair electrons that are adjacent to (i.e. conjugated to) pi bonds. You can never shift the location of electrons in sigma bonds – if you show a sigma bond forming or breaking, you are showing a chemical reaction taking place. Likewise, the positions of atoms in the molecule cannot change between two resonance contributors.

Because benzene will appear throughout this course, it is important to recognize the stability gained through the resonance delocalization of the six pi electrons throughout the six carbon atoms. Benzene also illustrates one way to recognize resonance - when it is possible to draw two or more equivalent Lewis strucutres. If we were to draw the structure of an aromatic molecule such as 1,2-dimethylbenzene, there are two ways that we could draw the double bonds:



Which way is correct? There are two simple answers to this question: 'both' and 'neither one'. Both ways of drawing the molecule are equally acceptable approximations of the bonding picture for the molecule, but neither one, by itself, is an accurate picture of the delocalized pi bonds. The two alternative drawings, however, *when considered together*, give a much more accurate picture than either one on its own. This is because they imply, together, that the carbon-carbon bonds are not double bonds, not single bonds, but about halfway in between.

When it is possible to draw more than one valid structure for a compound or ion, we have identified **resonance contributors**: two or more different Lewis structures depicting the same molecule or ion that, when considered together, do a better job of approximating delocalized pi-bonding than any single structure. By convention, resonance contributors are linked by a double-headed arrow, and are sometimes enclosed by brackets:



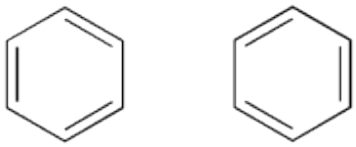
resonance contributor A resonance contributor B

In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the 'movement' of two pi electrons. A few chapters from now when we begin to study organic reactions - a process in which electron density shifts and covalent bonds between atoms break and form - this 'curved arrow notation' will become extremely important in depicting electron movement. In the drawing of resonance contributors, however, this electron 'movement' occurs only in our minds, as we try to visualize delocalized pi bonds. Nevertheless, use of the curved arrow notation is an essential skill that you will need to develop in drawing resonance contributors.

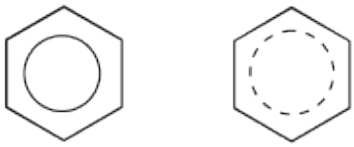
The depiction of benzene using the two resonance contributors A and B in the figure above does *not* imply that the molecule at one moment looks like structure A, then at the next moment shifts to look like structure B. Rather, at all moments, the molecule is a combination, or **resonance hybrid** of both A and B.

Caution! It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken place.

Usually, derivatives of benzene (and phenyl groups, when the benzene ring is incorporated into a larger organic structure) are depicted with only one resonance contributor, and it is assumed that the reader understands that resonance hybridization is implied. This is the convention that will be used for the most part in this book. In other books or articles, you may sometimes see benzene or a phenyl group drawn with a circle inside the hexagon, either solid or dashed, as a way of drawing a resonance hybrid.



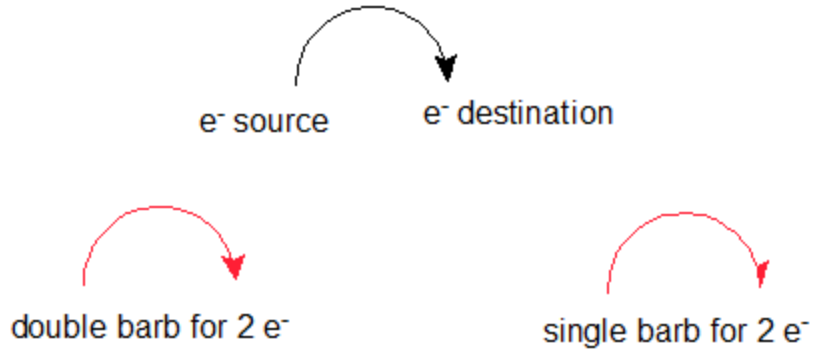
resonance contributor drawings



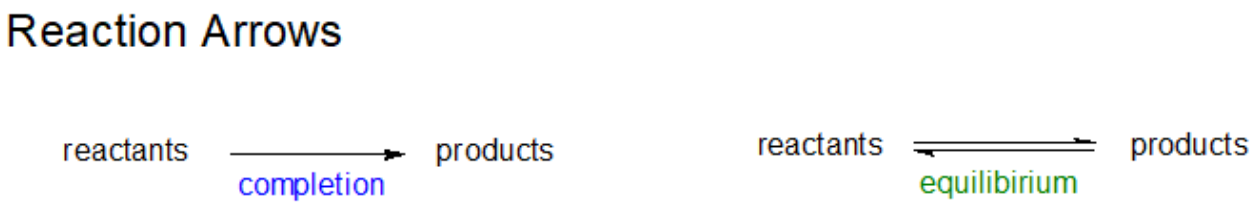
resonance hybrid drawings

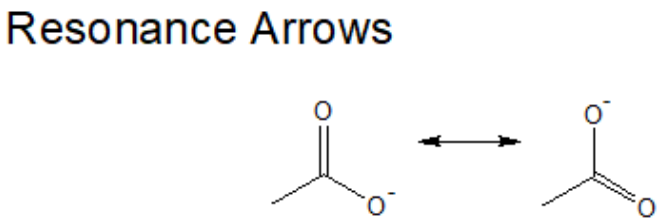
Curved arrows communicate electron flow (movement)

Curved arrows indicate electron flow. The base of the curved arrow is placed at the source of the electrons that are moving. The head of the arrow is placed at the destination of the electrons. A single barbed arrow represents one electron and a double barb represents two electrons. Electrons move from regions of relative high density to regions of low density or toward electronegative elements. It is important to use accuracy and precision when drawing curved arrows.



It is also important to consciously use the correct type of arrow. There are four primary types of arrows used by chemists to communicate one of the following: completion reaction, equilibrium reaction, electron movement, resonance forms. The three other types of arrows are shown below to build discernment between them.





Resonance Delocalizes Charge to Increase Stability

Resonance is most useful wen it delocalizes charge to stabilize reactive intermediates and products. Recognizing, drawing, and evaluating the relative stability of resonance contributors is essential to understanding organic reaction mechanisms.

Guidelines for drawing and working with resonance contributors

Learning to draw and interpret resonance structures, there are a few basic guidelines to help avoid drawing nonsensical structures. All of these guidellines make perfect sense as long as we remember that resonance contributors are merely a human-invented convention for depicting the delocalization of pi electrons in conjugated systems. When we see two different resonance contributors, we are not seeing a chemical reaction! We are seeing the exact same molecule or ion depicted in two different ways. All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron movement' arrows that would lead to a situation where a second-row element (ie. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. Sometimes, however, we will draw resonance contributors in which a carbon atom has only six electrons (ie. a carbocation). In general, all oxygen and nitrogen atoms should have a complete octet of valence electrons.

1. There is ONLY ONE STRUCTURE for each compound or ion. This structure takes its character from the sum of all the contributors, not all resonance structures contribute equally to the sum.

2. Atoms must maintain their same position.

3. Only e- move !

4. All resonance contributors for a molecule or ion must have the same net charge.

5. Recognize which electrons can participate in resonance

    a) unshared e^- pairs or radicals

    b) pi bond electrons

6. Recognize electron receptors

    a) atoms with a positive (+) charge

    b) electronegative atoms that can tolerate a negative charge

    c) atoms which possess delocalizable electrons - see #4 above

7. Common electron flow patterns

    a) move pi e^- toward positive (+) charge or other pi bonds

    b) move non-bonding e^- pairs toward pi bonds

    c) move single non-bonding e^- toward pi bonds

Evaluating Resonance Contributors

1. Identical structures are equally important.

2. Structures will a greater number of bonds are more important.

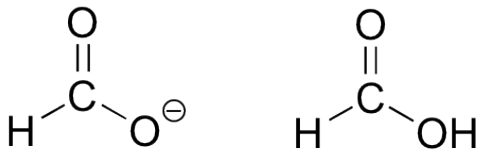
3. Structures with charge separation are less important.

4. Pay attention to electronegativities.

5. Neutral atoms need to have complete octets.

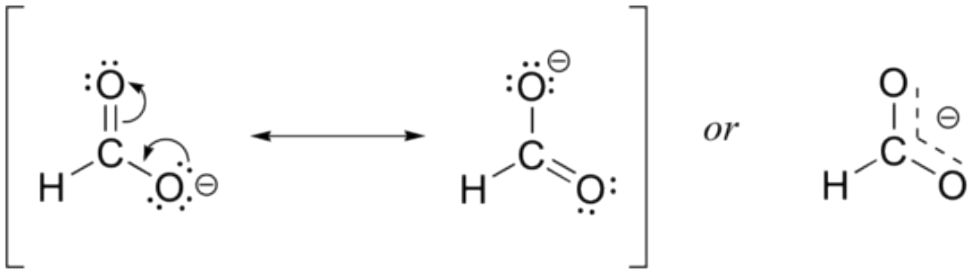
Resonance Contributors for the Carboxylate Group

The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let's next consider the carboxylate ion (the conjugate base of a carboxylic acid). As our example, we will use formate, the simplest possible carboxylate-containing molecule. The conjugate acid of formate is formic acid, which causes the painful sting you felt if you have ever been bitten by an ant.

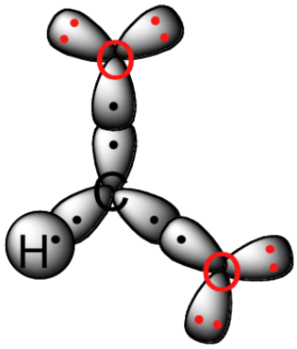


formate formic acid

Usually, you will see carboxylate groups drawn with one carbon-oxygen double bond and one carbon-oxygen single bond, with a negative formal charge located on the single-bonded oxygen. In actuality, however, the two carbon-oxygen bonds are the same length, and although there is indeed an overall negative formal charge on the group, it is shared equally between the two oxygens. Therefore, the carboxylate can be more accurately depicted by a *pair* of resonance contributors. Alternatively, a single structure can be used, with a dashed line depicting the resonance-delocalized pi bond and the negative charge located in between the two oxygens.

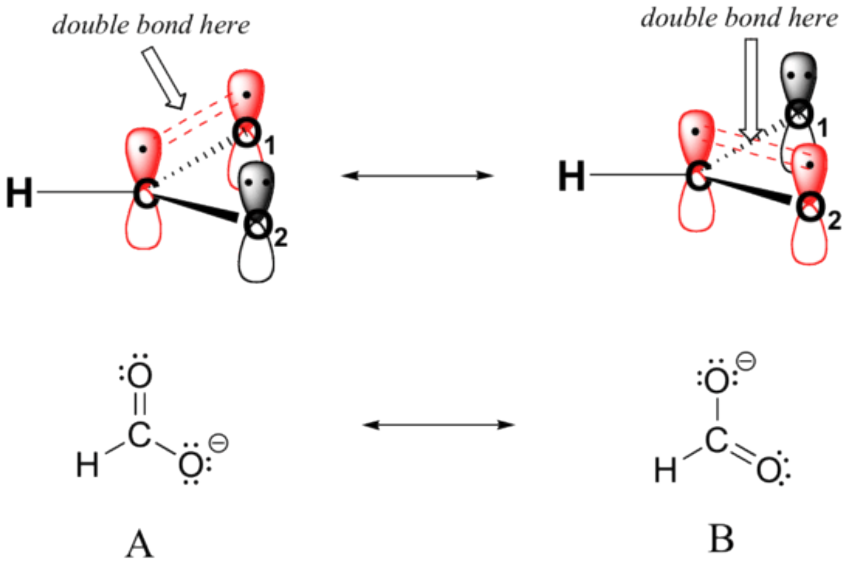


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sigma bonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

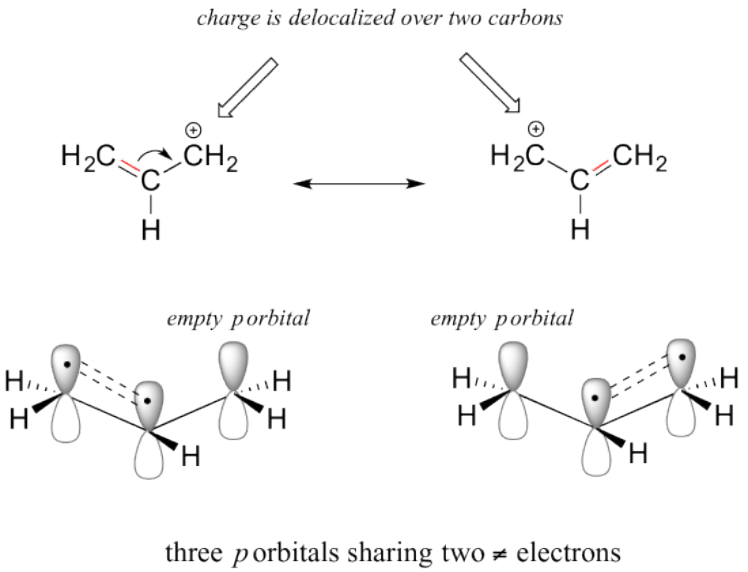
In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.



Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals sharing four delocalized pi electrons*. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of –1. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

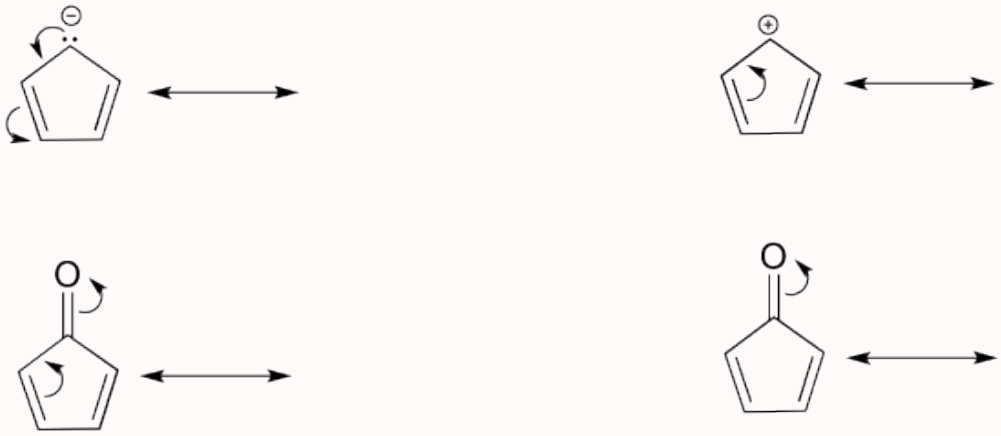
Exercise 2.13: There is a third resonance contributor for formate (which we will soon learn is considered a 'minor' contributor). Draw this resonance contributor.

Here's another example, this time with a carbocation. Recall from section 2.1 that carbocations are sp^2-hybridized, with an empty *2p* orbital oriented perpendicular to the plane formed by three sigma bonds. If a carbocation is adjacent to a double bond, then three *2p* orbitals can overlap and share the two pi electrons - another kind of conjugated pi system in which the positive charge is shared over two carbons.

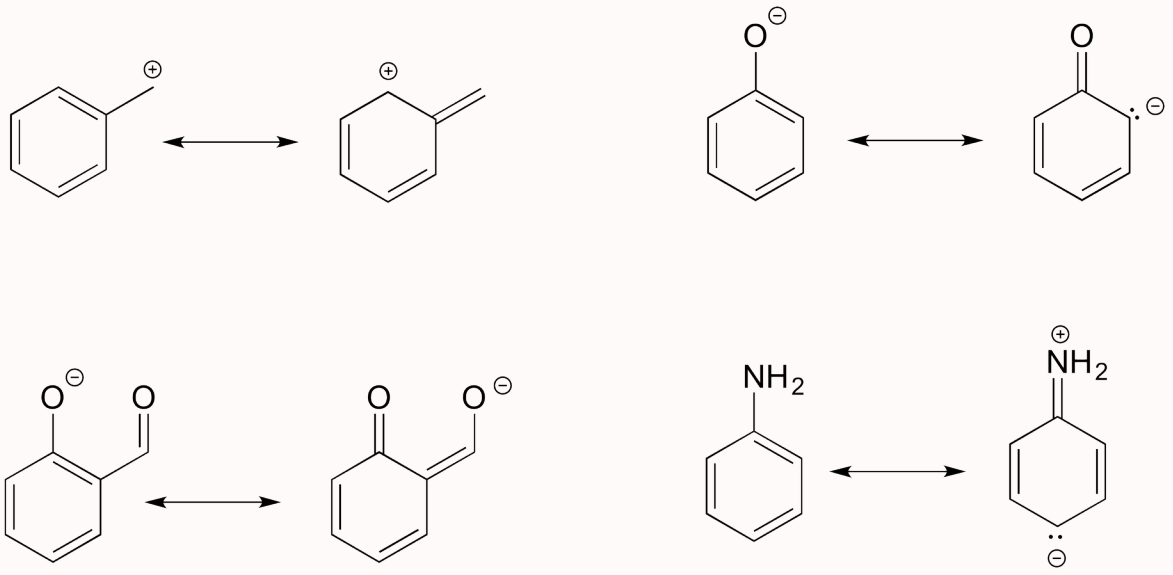


three *p* orbitals sharing two ≠ electrons

Exercise 2.14: Draw the resonance contributors that correspond to the curved, two-electron movement arrows in the resonance expressions below.



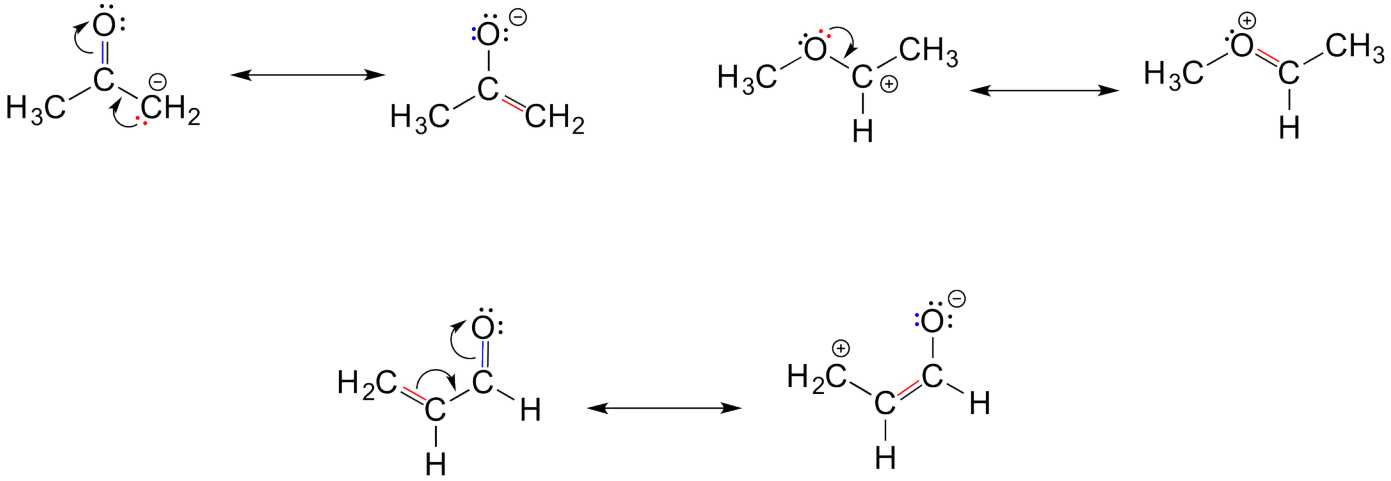
Exercise 2.15: In each resonance expression, draw curved two-electron movement arrows on the left-side contributor that shows how we get to the right-side contributor. Be sure to include formal charges.



Solutions to exercises

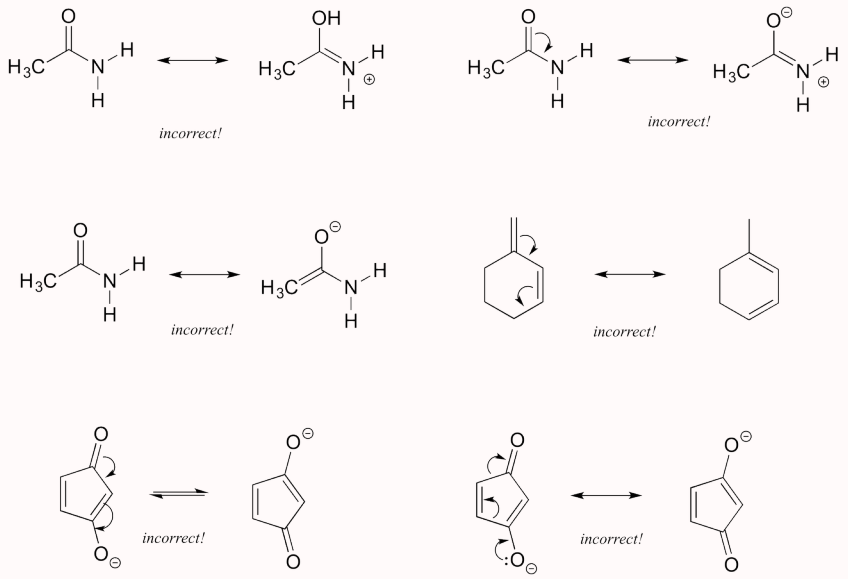
Guided Resonance Practice

Below are a few more examples of 'legal' resonance expressions. Confirm for yourself that the octet rule is not exceeded for any atoms, and that formal charges are correct.



Exercise 2.16: Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in

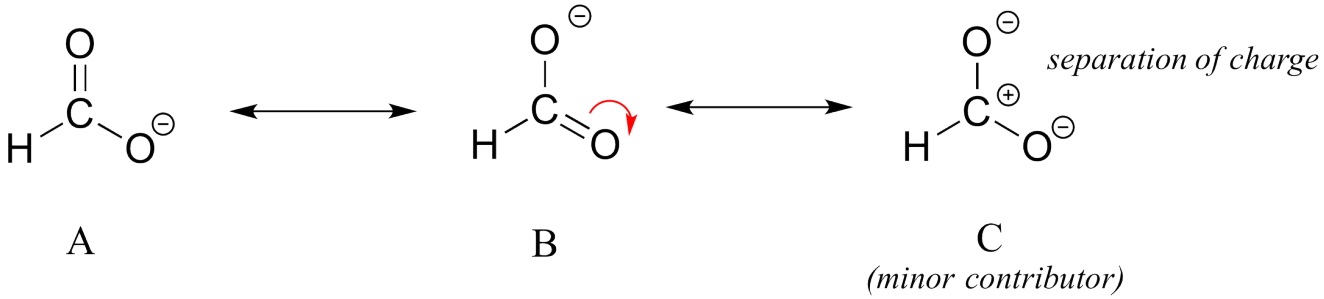
each.



Solutions to exercises

Major vs minor resonance contributors

Different resonance contributors do not always make the same contribution to the overall structure of the hybrid - rather, in many cases one contributor comes closer to depicting the actual bonding picture than another. In the case of carboxylates, contributors A and B below are equivalent in terms of their relative contribution to the hybrid structure. However, there is also a third resonance contributor ‘C, in which the carbon bears a positive formal charge and both oxygens are single-bonded and bear negative charges.



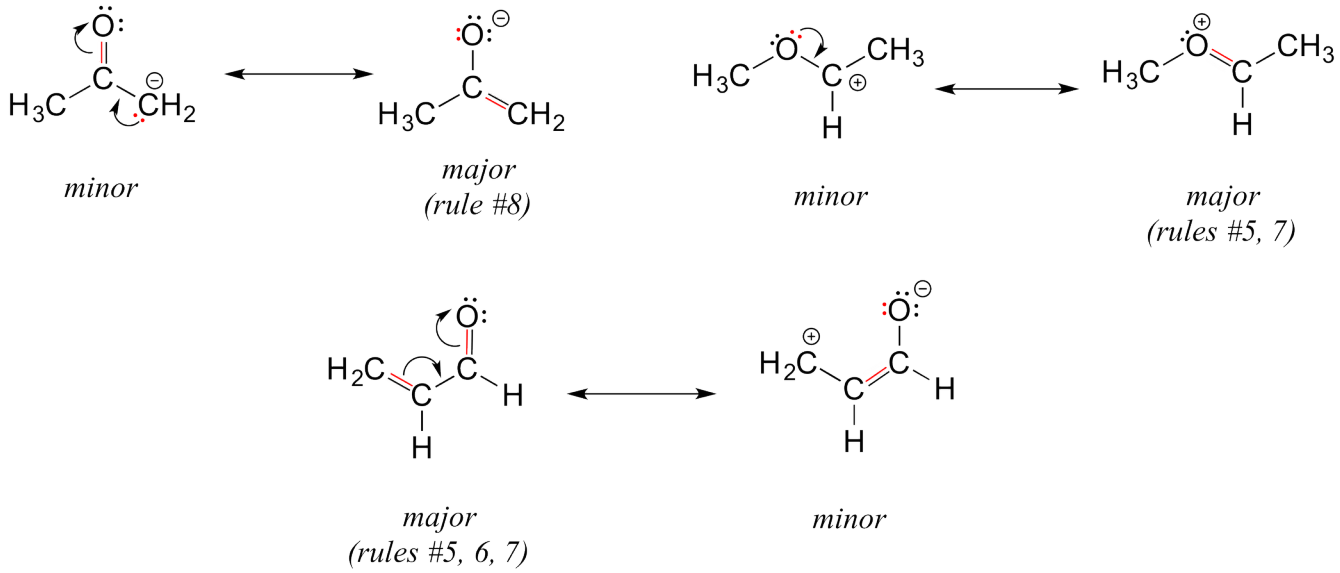
Structure C makes a less important contribution to the overall bonding picture of the group relative to A and B. How do we know that structure C is the ‘minor’ contributor? There are four basic rules which you need to learn in order to evaluate the relative importance of different resonance contributors. We will number them 5-8 so that they may be added to in the 'rules for resonance' list earlier on this page.

Rules for determining major and minor resonance contributors:

5. The carbon in contributor C does not have an octet – in general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important.
6. In structure C, a separation of charge has been introduced that is not present in A or B. In general, resonance contributors in which there is a greater separation of charge are relatively less important.
7. In structure C, there are only three bonds, compared to four in A and B. In general, a resonance structure with a lower number of total bonds is relatively less important.

8. The resonance contributor in which a negative formal charge is located on a more electronegative atom, usually oxygen or nitrogen, is more stable than one in which the negative charge is located on a less electronegative atom such as carbon. An example is in the upper left expression in the next figure.

Below are some additional examples of major and minor resonance contributors:

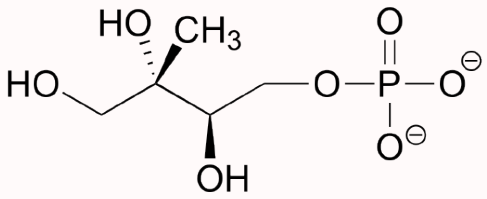


Why do we worry about a resonance contributor if it is the minor one? We will see later that very often a minor contributor can still be extremely important to our understanding of how a molecule reacts.

Exercise 2.17:

a. Draw a minor resonance structure for acetone (IUPAC name 2-propanone). Explain why it is a minor contributor.
b. Are acetone and 2-propanol resonance contributors of each other? Explain.

Exercise 2.18: Draw four additional resonance contributors for the molecule below. Label each one as major or minor (the structure below is of a major contributor).



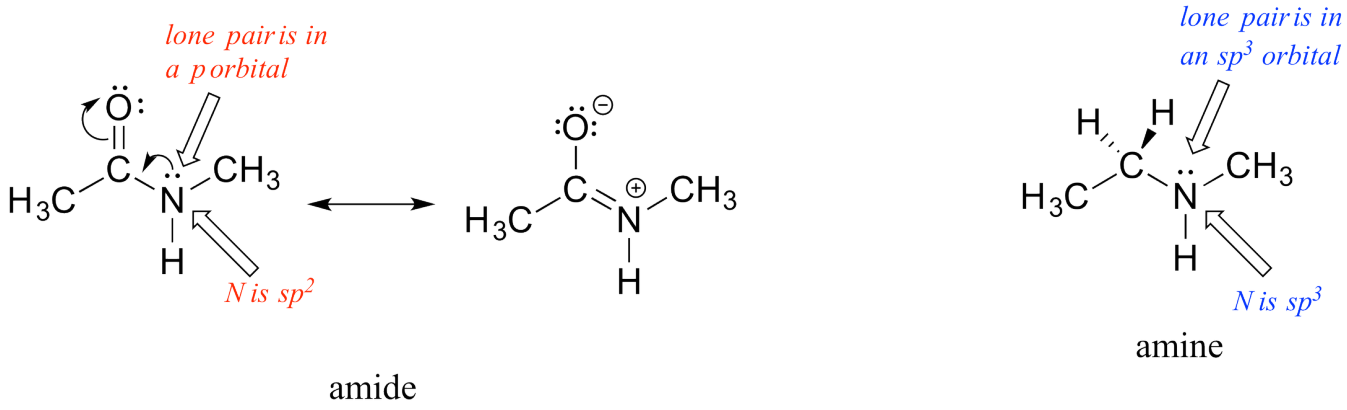
Exercise 2.19: Draw three resonance contributors of methyl acetate (IUPAC name methyl methanoate), and order them according to their relative importance to the bonding picture of the molecule. Explain your reasoning.

Solutions to exercises

Resonance and peptide bonds

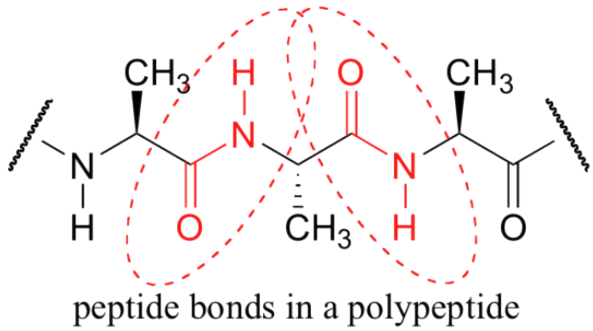
What is the hybridization state of the nitrogen atom in an amide? At first glance, it would seem logical to say that it is sp^3-hybridized, because, like the nitrogen in an amine, the Lewis structure shows three single bonds and a lone pair. The picture looks quite different, though, if we consider another resonance contributor in which the nitrogen has a double bond to the carbonyl

carbon: in this case, we would have to say that applicable hybridization is sp^2, and the bonding geometry trigonal planar rather than tetrahedral.

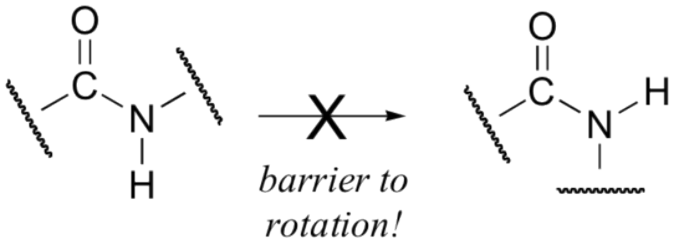


In fact, the latter picture is more accurate: the lone pair of electrons on an amide nitrogen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system, and the bonding geometry around the nitrogen is trigonal planar as expected for sp^2 hybridization. This is a good illustration of an important point: conjugation and the corresponding delocalization of electron density is stabilizing, thus if conjugation can occur, it probably will.

One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



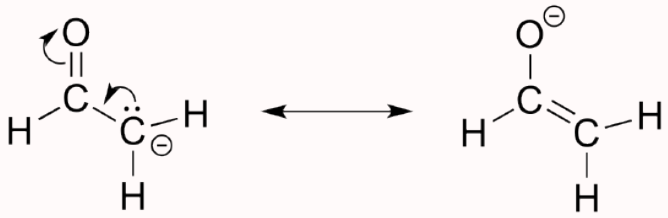
Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, *the C-N bond in a peptide linkage has a significant barrier to rotation*, indicating that to some degree, C-N pi overlap is present - in other words, there is some double bond character, and the nitrogen is sp^2 hybridized with trigonal planar geometry.



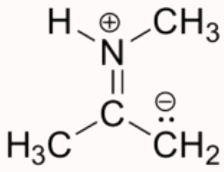
The barrier to rotation in peptide bonds is an integral part of protein structure, introducing more rigidity to the protein's backbone. If there were no barrier to rotation in a peptide bond, proteins would be much more 'floppy' and three dimensional folding would be very different.

Exercise 2.20: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in methyl amide. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping *2p* orbitals are sharing how many pi-bonded electrons?

Exercise 2.21: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in the 'enolate' anion shown below. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping *2p* orbitals are sharing how many pi-bonded electrons?

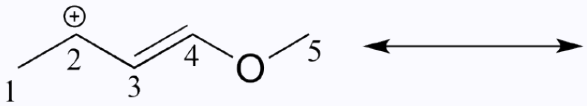


Exercise 2.22: Below is a minor resonance contributor of a species known as an 'enamine', which we will study more in chapter 12. Draw the major resonance contributor for the enamine, and explain why your contributor is the major one (refer to resonance rules #5-8 from this section).

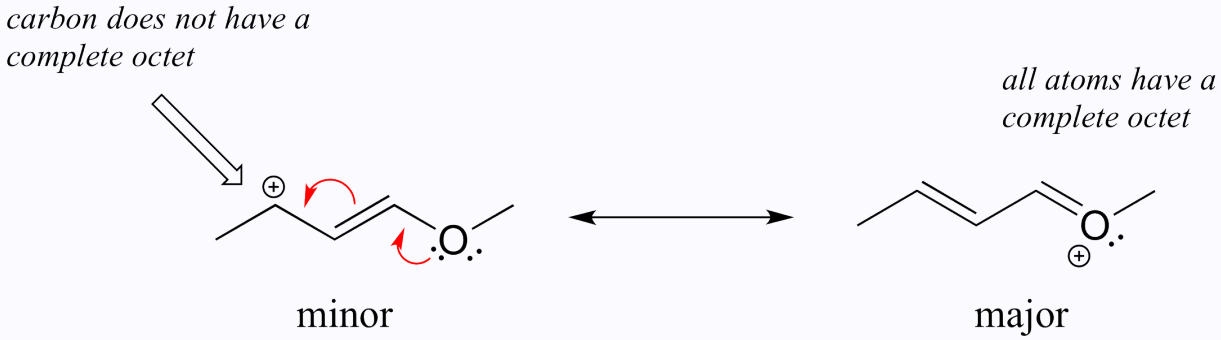


Solutions to exercises

Solved example: Draw the major resonance contributor of the structure below. Include in your figure the appropriate curved arrows showing how you got from the given structure to your structure. Explain why your contributor is the major one. In what kind of orbitals are the two lone pairs on the oxygen?

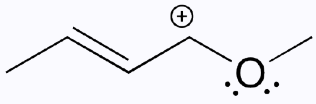


Solution: In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see the rules for drawing resonance contributors to convince yourself that these are 'legal' moves).



The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #5 and #7 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, and C_4, plus one on oxygen) sharing four pi electrons. One lone pair on the oxygen is in an unhybridized *2p* orbital and is part of the conjugated pi system, and the other is located in an sp^2 orbital.

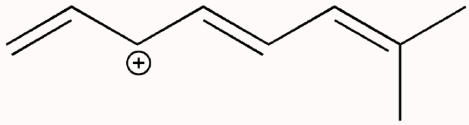
Also note that one additional contributor can be drawn, but it is also minor because it has a carbon with an incomplete octet:



minor

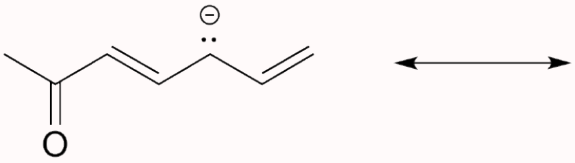
Exercise 2.23:

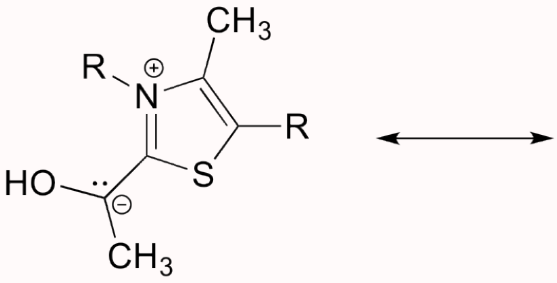
a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.



b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Exercise 2.24: Draw the major resonance contributor for each of the anions below.



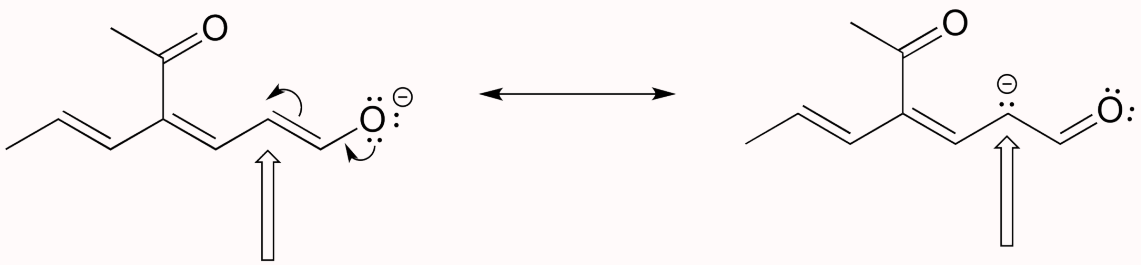


c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

Exercise 2.25: The figure below shows how the negative formal charge on the oxygen can be delocalized to the carbon indicated by an arrow. More resonance contributors can be drawn in which negative charge is delocalized to three other atoms on the molecule.

a) Circle these atoms.

b) Draw the two most important resonance contributors for the molecule.



Solutions to exercises

A word of advice

Becoming adept at drawing resonance contributors, using the curved arrow notation to show how one contributor can be converted to another, and understanding the concepts of conjugation and resonance delocalization are some of the most challenging but also most important jobs that you will have as a beginning student of organic chemistry. If you work hard now to gain a firm grasp of these ideas, you will have come a long way toward understanding much of what follows in your organic chemistry course. Conversely, if you fail to come to grips with these concepts now, a lot of what you see later in the course will seem like a bunch of mysterious and incomprehensible lines, dots, and arrows, and you will be in for a rough ride, to say the least. More so than many other topics in organic chemistry, *understanding bonding, conjugation, and resonance is something that most students really need to work on 'in person' with an instructor or tutor, preferably using a molecular modeling kit*. Keep working problems, keep asking questions, and keep at it until it all makes sense!

Kahn Academy video tutorials
- Drawing resonance structures
- More on resonance

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

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1.6: 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*:

$$\begin{aligned} MO(1) = &\quad AO(atom\ A) &+ &\quad AO(atom B) \\ MO(1) = &\quad AO(atom\ A) &- &\quad AO(atom B) \end{aligned} \tag{1.6.1}$$

The molecular orbitals created from Equation 1.6.1 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.

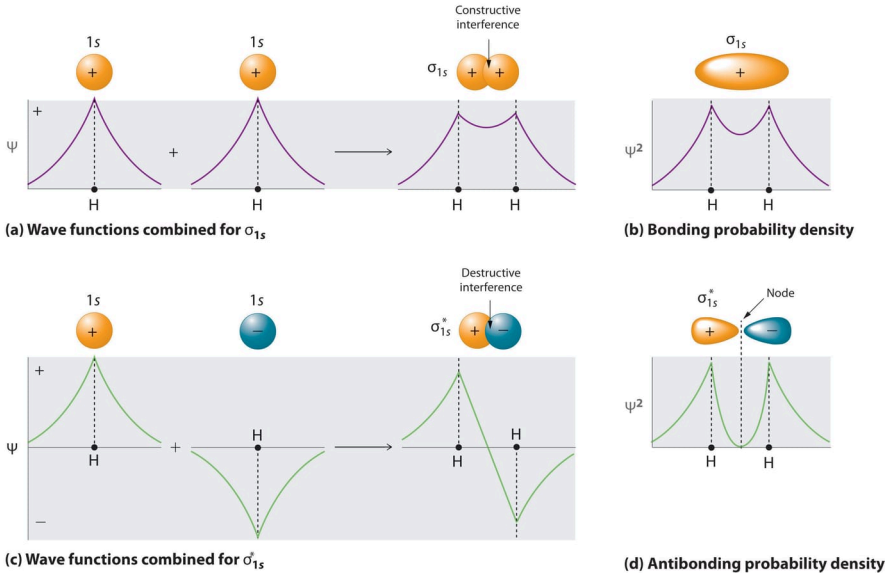


Figure 1.6.1: Molecular Orbitals for the H_2 Molecule. (a) This diagram shows the formation of a bonding σ_{1s} molecular orbital for H_2 as the sum of the wave functions (Ψ) of two H 1s atomic orbitals. (b) This plot of the square of the wave function (Ψ^2) for the bonding σ_{1s} molecular orbital illustrates 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 1.6.1). 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.

$$\sigma_{1s} \approx 1s\,(A) + 1s\,(B) \tag{1.6.2}$$

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 1.6.1). 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:

$$\sigma^\star_{1s} \approx 1s\,(A) - 1s\,(B) \tag{1.6.3}$$

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 1.6.2

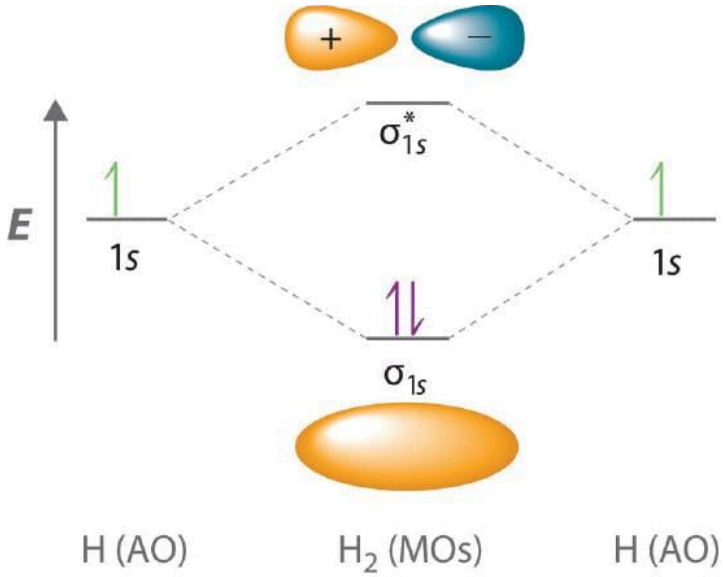


Figure 1.6.2: Molecular Orbital Energy-Level Diagram for H_2. The two available electrons (one from each H atom) in this diagram fill the bonding σ_{1s} molecular orbital. Because the energy of the σ_{1s} molecular orbital is lower than that of the two H 1s atomic orbitals, the H_2 molecule is more stable (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 1.6.2). 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:

$$bond\ order = \frac{number\ of\ bonding\ electrons - number\ of\ antibonding\ electrons}{2} \tag{1.6.4}$$

To calculate the bond order of H_2, we see from Figure 1.6.2 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

$$\frac{2-0}{2}=1 \tag{1.6.5}$$

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 1.6.2 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.

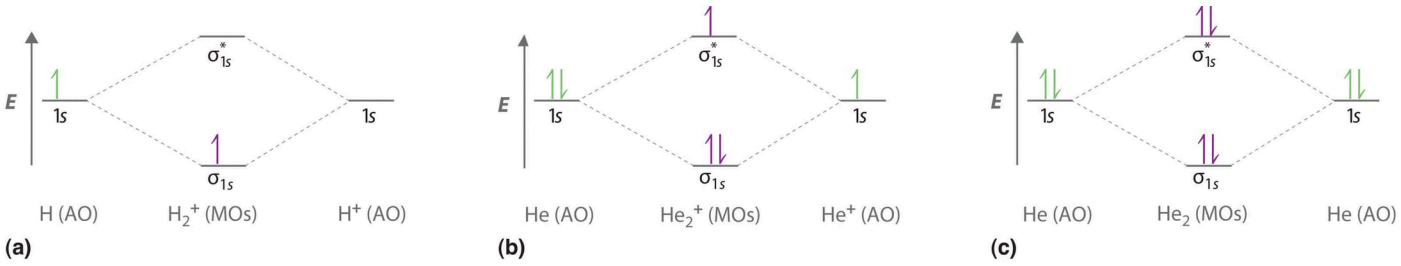


Figure 1.6.3: Molecular Orbital Energy-Level Diagrams for Diatomic Molecules with Only 1s Atomic Orbitals. (a) The H_2^+ ion, (b) the He_2^+ ion, and (c) the He_2 molecule are shown here.

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 1.6.3a 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 1.6.1, these predictions agree with the experimental data.

Figure 1.6.3b 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 1.6.1).

Table 1.6.1: 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 1.6.3*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.

YouTube Video

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Example 1.6.1

Use a molecular orbital energy-level diagram, such as those in Figure 1.6.2, to predict the bond order in the He_2^{2+} ion. Is this a stable species?

Given: chemical species

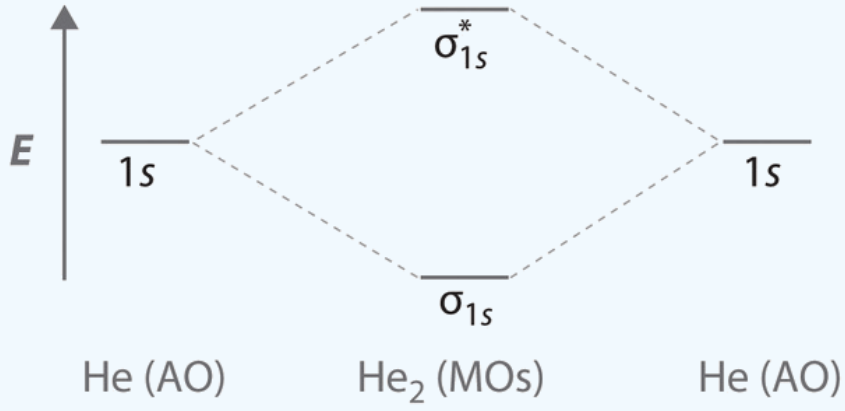
Asked for: molecular orbital energy-level diagram, bond order, and stability

Strategy:

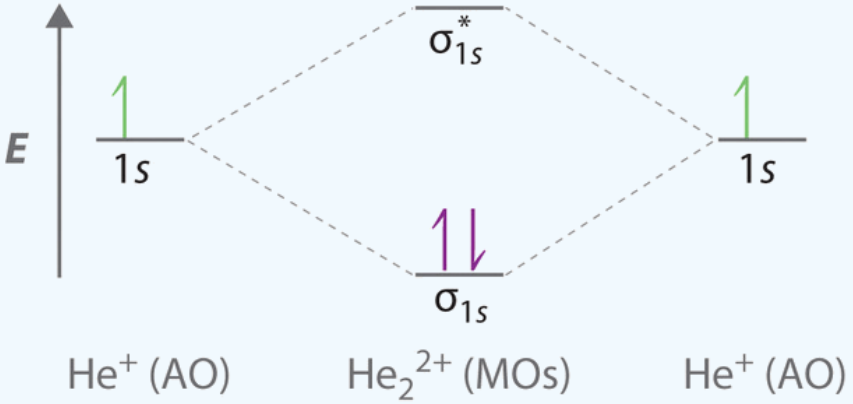
A. Combine the two He valence atomic orbitals to produce bonding and antibonding molecular orbital
B. s. Draw the molecular orbital energy-level diagram for the system.
C. Determine the total number of valence electrons in the He_2^{2+} ion. Fill the molecular orbitals in the energy-level diagram beginning 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 1.6.1

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 1.6.4, 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 1.6.4. Experimentally, all are found to be stable in the gas phase, and some are even stable in solution.

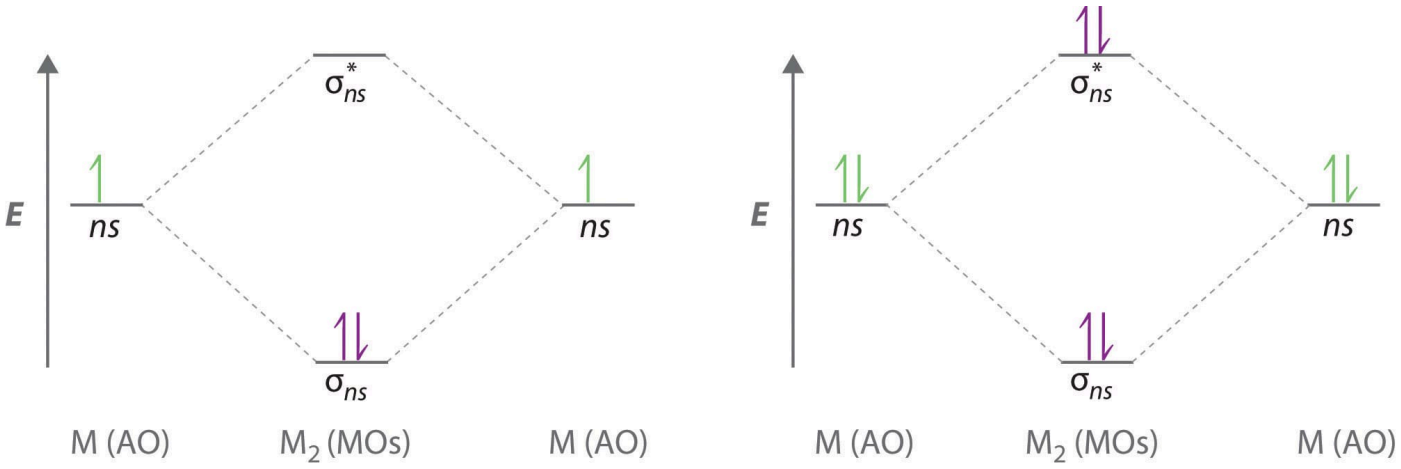


Figure 1.6.4 : Molecular Orbital Energy-Level Diagrams for Alkali Metal and Alkaline Earth Metal Diatomic (M_2) Molecules. (a) For alkali metal diatomic molecules, the two valence electrons are enough to fill the σ_{ns} (bonding) level, giving a bond order of 1. (b) For alkaline earth metal diatomic 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 1.6.2 . As shown in part (b) in Figure 1.6.4, 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 1.6.2

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

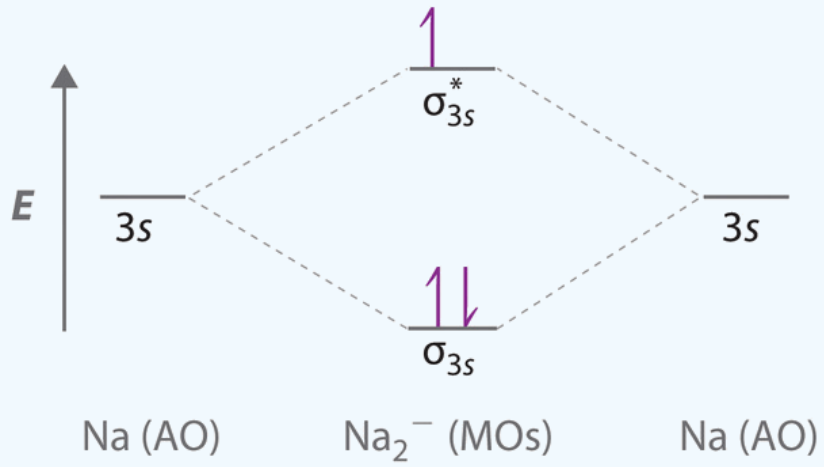
Strategy:

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 1.6.2

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.

$$\sigma_{np_z} = np_z\,(A) - np_z\,(B) \tag{1.6.6}$$

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 1.6.5, 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):

$$\sigma_{np_z} = np_z\,(A) - np_z\,(B) \tag{1.6.7}$$

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

$$\sigma_{np_z} = np_z\,(A) + np_z\,(B) \tag{1.6.8}$$

In this combination, shown in part (b) in Figure 1.6.5, 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).

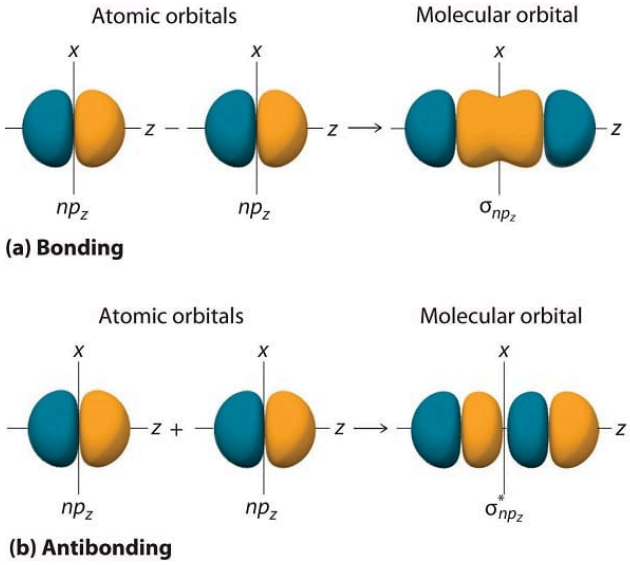


Figure 1.6.5 Formation of Molecular Orbitals from np_z Atomic Orbitals on Adjacent Atoms.(a) By convention, in a linear molecule or ion, the *z*-axis always corresponds to the internuclear axis, with +*z* to the right. As a result, the signs of the lobes of the np_z atomic orbitals on the two atoms alternate – + – +, 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 1.6.6, 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..

$$\pi_{np_x} = np_x\,(A) + np_x\,(B) \tag{1.6.9}$$

$$\pi^{\star}_{np_x} = np_x\,(A) - np_x\,(B) \tag{1.6.10}$$

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.

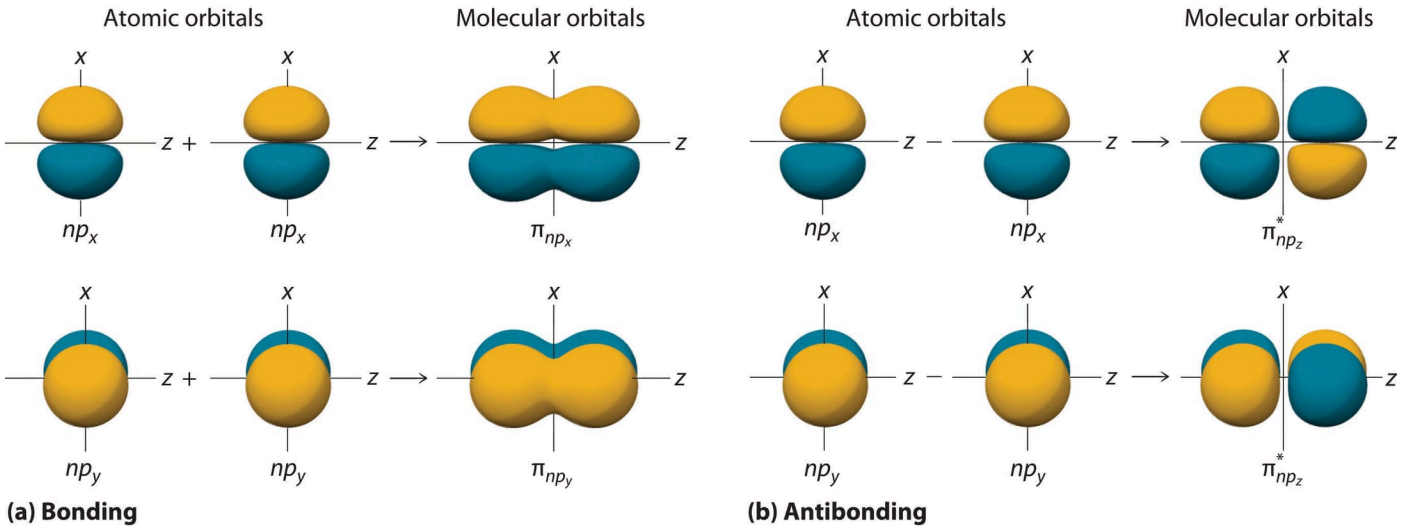


Figure 1.6.6: Formation of π Molecular Orbitals from np_x and np_y Atomic Orbitals on Adjacent Atoms.(a) Because the signs of the lobes of both the np_x and the np_y atomic orbitals on adjacent atoms are the same, in both cases the mathematical sum corresponds to a π (bonding) molecular orbital. (b) 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 1.6.7 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.

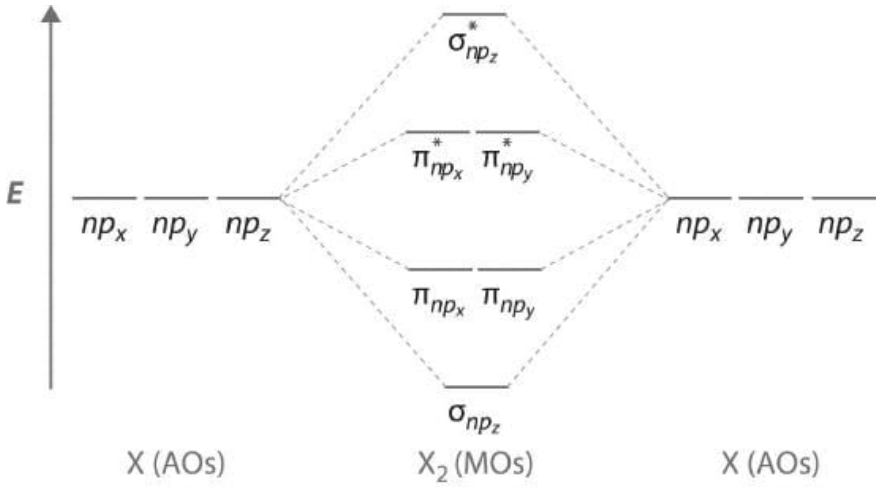


Figure 1.6.7 : The Relative Energies of the σ and π Molecular Orbitals Derived from np_x, np_y, and np_z Orbitals on Identical Adjacent Atoms. Because the two np_z orbitals point directly at each other, their orbital overlap is greater, so the difference in energy between the σ and σ* molecular orbitals 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 1.6.8, 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.

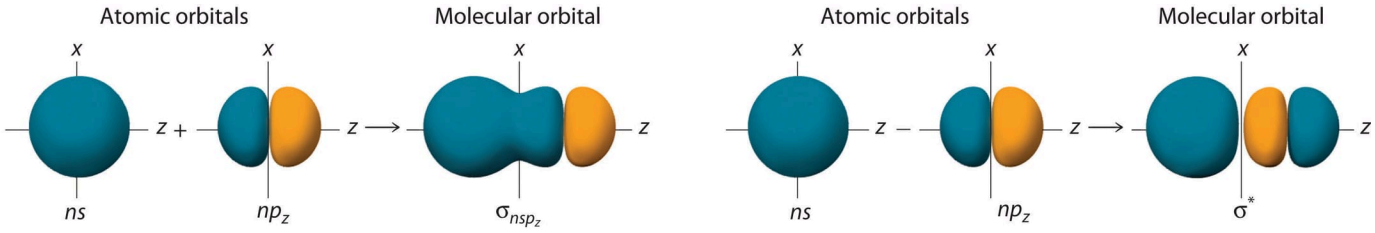


Figure 1.6.8 : Formation of Molecular Orbitals from an *ns* Atomic Orbital on One Atom and an np_z Atomic Orbital on an Adjacent Atom.(a) The mathematical sum results in a σ (bonding) molecular orbital, with increased probability density between the nuclei. (b) The mathematical difference results in 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 1.6.1

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 1.6.2

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

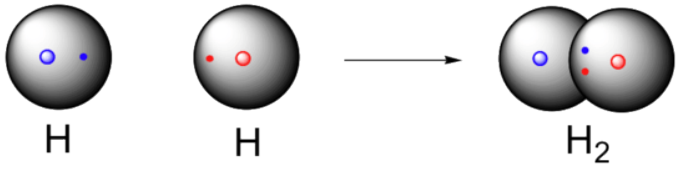
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1.7: Hybrid Orbitals- Bonding in Complex Molecules and Practice Problems

Formation of sigma bonds: the H_2 molecule

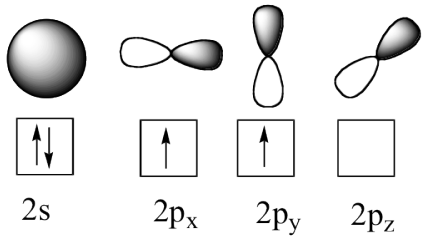
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two electrons from each of the hydrogen atoms are shared to form a covalent bond between the two atoms, what we mean in valence bond theory terms is that the two spherical 1s orbitals overlap, allowing the two electrons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



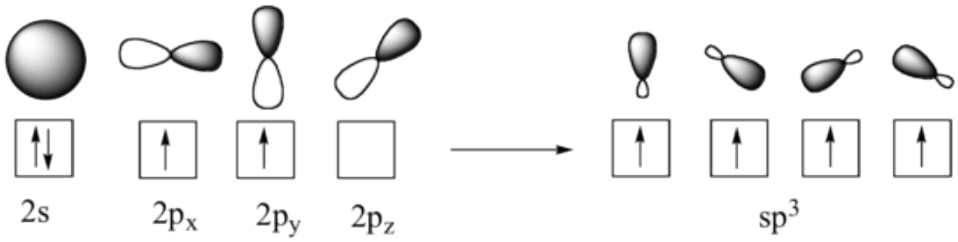
These two electrons are now attracted to the positive charge of *both* of the hydrogen nuclei, with the result that they serve as a sort of 'chemical glue' holding the two nuclei together.

Bonding in Methane

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

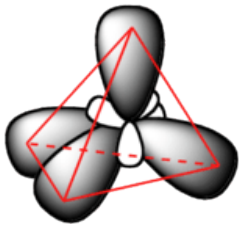


This picture, however, is problematic. How does the carbon form four bonds if it has only two half-filled *p* orbitals available for bonding? A hint comes from the experimental observation that the four C-H bonds in methane are arranged with tetrahedral geometry about the central carbon, and that each 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.



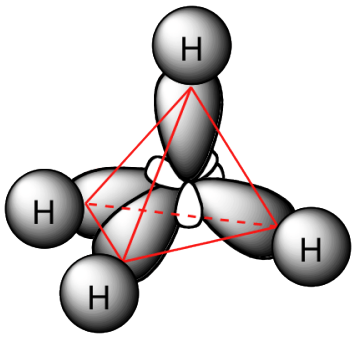
The sp^3 hybrid orbitals, like the *p* orbitals of which they are partially composed, are oblong in shape, and have two lobes of

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°.

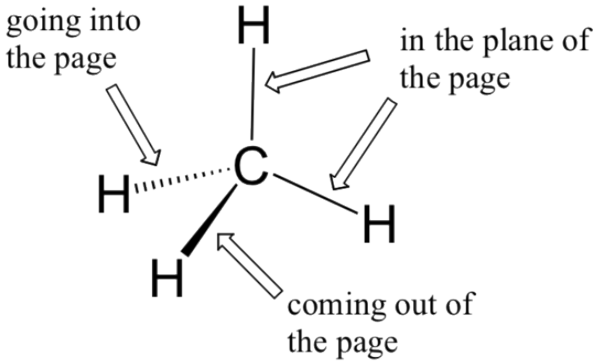


This geometric arrangement makes perfect sense if you consider that it is precisely this angle that allows the four orbitals (and the electrons in them) to be as far apart from each other as possible.This is simply a restatement of the Valence Shell Electron Pair Repulsion (VSEPR) theory that you learned 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).



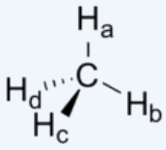
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: 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.

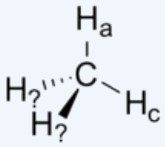


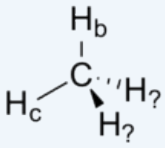
This system takes a little bit of getting used to, but with practice your eye will learn to immediately 'see' the third dimension being depicted.

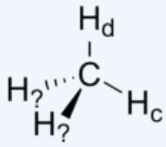
Example

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) 

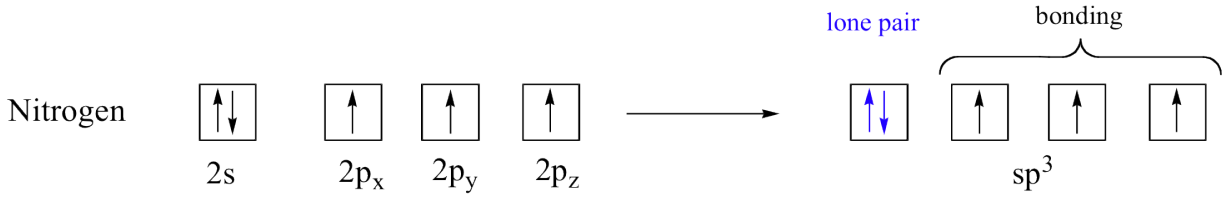
b) 

c) 

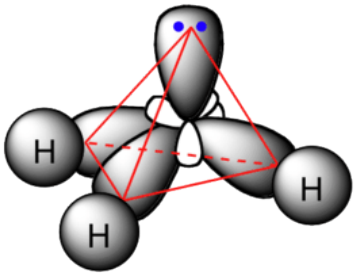
Example

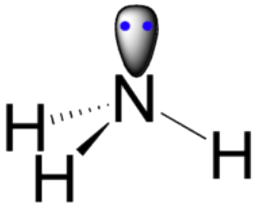
Describe, with a picture and with words, the bonding in chloroform, $CHCl_3$.

Solutions



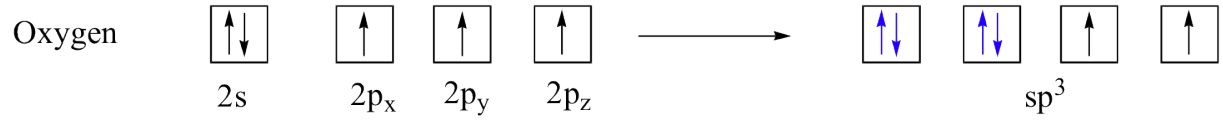
The bonding arrangement here is also tetrahedral: the three N-H bonds of ammonia can be pictured as forming the base of a trigonal pyramid, with the fourth orbital, containing the lone pair, forming the top of the pyramid.

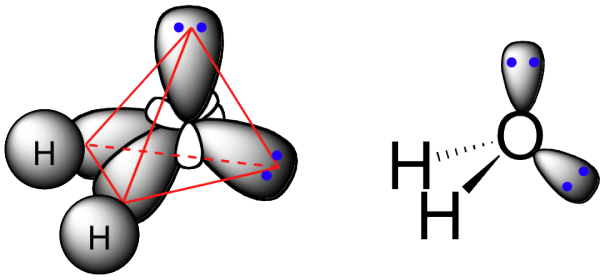




Recall from your study of VSEPR theory in General Chemistry that the lone pair, with its slightly greater repulsive effect, 'pushes' the three N-H sbonds away from the top of the pyramid, meaning that the H-N-H bond angles are slightly less than tetrahedral, at 107.3˚ rather than 109.5˚.

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

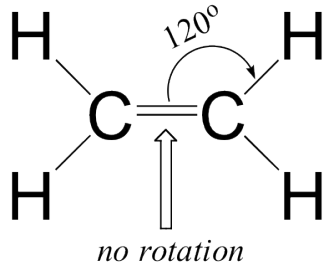
Draw, in the same style as the figures above, an orbital picture for the bonding in methylamine.

Solution

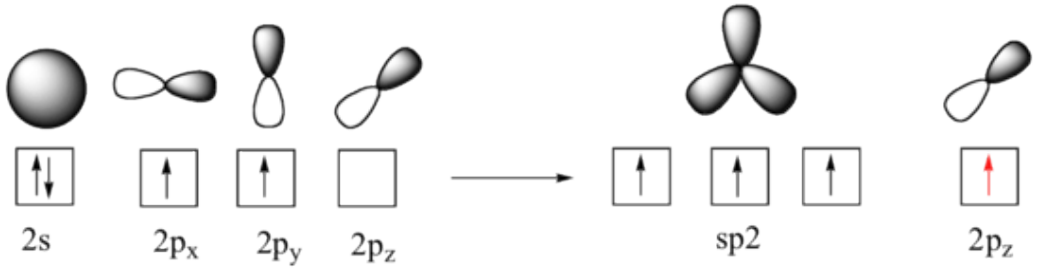
Formation of π bonds - sp^2 and sp hybridization

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:

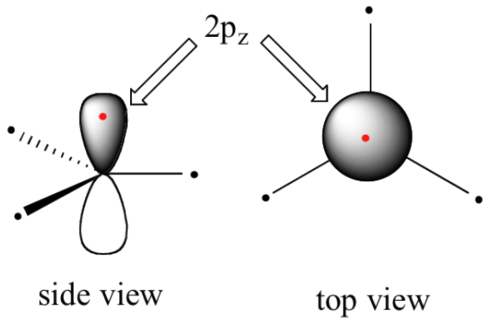
1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 1.34 Å, significantly shorter than the 1.54 Å single carbon-carbon bond in ethane.
3. There is a significant barrier to rotation about the carbon-carbon double bond.



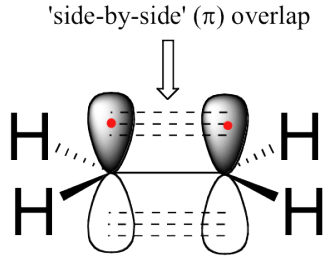
Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, 2p_x and 2p_y orbitals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

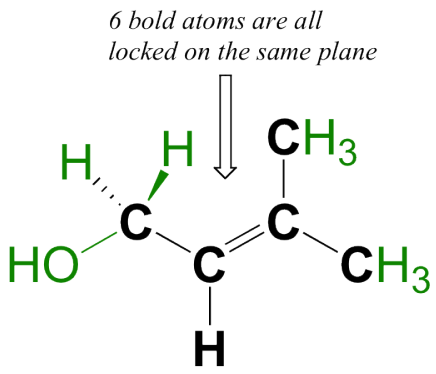


The carbon-carbon double bond in ethene consists of one sbond, formed by the overlap of two sp^2 orbitals, and a second bond, calleda **π (pi) bond**, which is formed by the *side-by-side* overlap of the two unhybridized $2p_z$ orbitals from each carbon.



spacefilling image of bonding in ethene

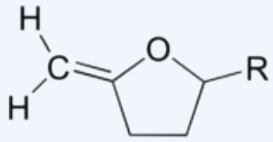
The pi bond does *not* have symmetrical symmetry. Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ 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.

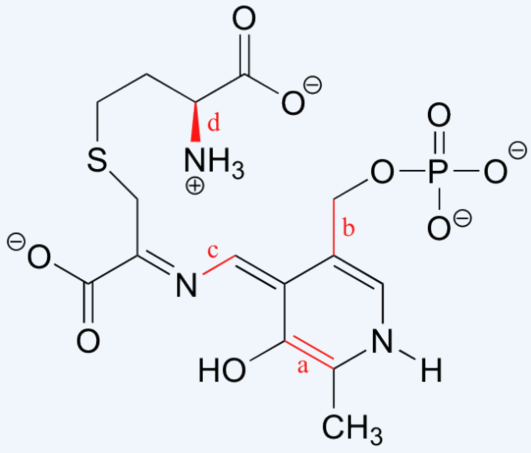
Example 1.20

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



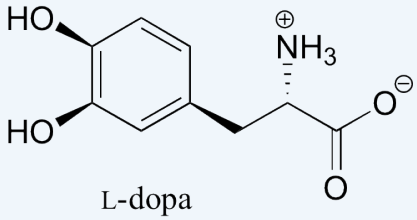
Example

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



Example

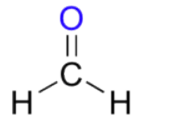
What is wrong with the way the following structure is drawn?



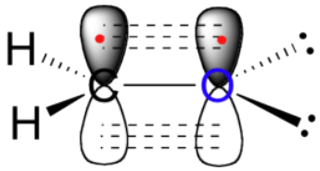
L-dopa

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.



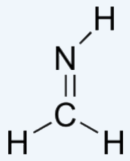
formaldehyde



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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2: ALKANES

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2.1: Chemical Properties of Alkanes

Alkanes are **not very reactive** when compared with other chemical species. This is because the backbone carbon atoms in alkanes have attained their octet of electrons through forming four covalent bonds (the maximum allowed number of bonds under the octet rule; which is why carbon's valence number is 4). These four bonds formed by carbon in alkanes are sigma bonds, which are more stable than other types of bond because of the greater overlap of carbon's atomic orbitals with neighboring atoms' atomic orbitals. To make alkanes react, the input of additional energy is needed; either through heat or radiation.

Gasoline is a mixture of the alkanes and unlike many chemicals, can be stored for long periods and transported without problem. It is only when ignited that it has enough energy to continue reacting. This property makes it difficult for alkanes to be converted into other types of organic molecules. (There are only a few ways to do this). Alkanes are also **less dense than water**, as one can observe, oil, an alkane, floats on water.

Alkanes are **non-polar solvents**. Since only C and H atoms are present, alkanes are nonpolar. Alkanes are immiscible in water but freely miscible in other non-polar solvents. Alkanes consisting of weak dipole dipole bonds can not break the strong hydrogen bond between water molecules hence it is not miscible in water. The same character is also shown by alkenes. Because alkanes contain only carbon and hydrogen, combustion produces compounds that contain only carbon, hydrogen, and/or oxygen. Like other hydrocarbons, combustion under most circumstances produces mainly carbon dioxide and water. However, alkanes require more heat to combust and do not release as much heat when they combust as other classes of hydrocarbons. Therefore, combustion of alkanes produces higher concentrations of organic compounds containing oxygen, such as aldehydes and ketones, when combusting at the same temperature as other hydrocarbons.

The general formula for alkanes is C_NH_{2N+2}; the simplest possible alkane is therefore methane, CH_4. The next simplest is ethane, C_2H_6; the series continues indefinitely. Each carbon atom in an alkane has sp^3 hybridization.

Alkanes are also known as paraffins, or collectively as the paraffin series. These terms are also used for alkanes whose carbon atoms form a single, unbranched chain. Branched-chain alkanes are called isoparaffins.

Methane through **Butane** are very flammable gases at standard temperature and pressure (STP). **Pentane** is an extremely flammable liquid boiling at 36 °C and boiling points and melting points steadily increase from there; octadecane is the first alkane which is solid at room temperature. Longer alkanes are waxy solids; candle wax generally has between C_{20} and C_{25} chains. As chain length increases ultimately we reach polyethylene, which consists of carbon chains of indefinite length, which is generally a hard white solid.

Reactions

Alkanes react only very poorly with ionic or other polar substances. The pKa values of all alkanes are above 50, and so they are practically inert to acids and bases. This inertness is the source of the term paraffins (Latin para + affinis, with the meaning here of "lacking affinity"). In crude oil the alkane molecules have remained chemically unchanged for millions of years.

However redox reactions of alkanes, in particular with oxygen and the halogens, are possible as the carbon atoms are in a strongly reduced condition; in the case of methane, the lowest possible oxidation state for carbon (−4) is reached. Reaction with oxygen leads to combustion without any smoke; with halogens, substitution. In addition, alkanes have been shown to interact with, and bind to, certain transition metal complexes.

Free radicals, molecules with unpaired electrons, play a large role in most reactions of alkanes, such as cracking and reformation where long-chain alkanes are converted into shorter-chain alkanes and straight-chain alkanes into branched-chain isomers.

In highly branched alkanes and cycloalkanes, the bond angles may differ significantly from the optimal value (109.5°) in order to allow the different groups sufficient space. This causes a tension in the molecule, known as steric hinderance, and can substantially increase the reactivity. The same is preferred for alkenes too.

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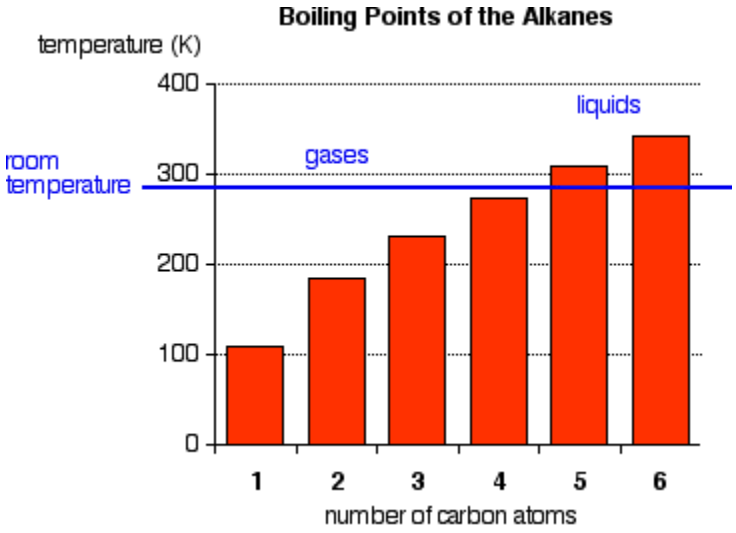
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2.2: Physical Properties of Alkanes

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 2.2.1: Structure dependent Boiling Points

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.

> The energy only description of solvation is an oversimplification because entropic effects are also 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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2.3: Nomenclature of Alkanes

The names of all alkanes end with *-ane*. Whether or not the carbons are linked together end-to-end in a ring (called *cyclic alkanes* or *cycloalkanes*) or whether they contain side chains and branches, the name of every carbon-hydrogen chain that lacks any double bonds or functional groups will end with the suffix *-ane*.

Alkanes with unbranched carbon chains are simply named by the number of carbons in the chain. The first four members of the series (in terms of number of carbon atoms) are named as follows:

1. CH_4 = **methane** = one hydrogen-saturated carbon
2. C_2H_6 = **ethane** = two hydrogen-saturated carbons
3. C_3H_8 = **propane** = three hydrogen-saturated carbons
4. C_4H_{10} = **butane** = four hydrogen-saturated carbons

Alkanes with five or more carbon atoms are named by adding the suffix *-ane* to the appropriate numerical multiplier, except the terminal *-a* is removed from the basic numerical term. Hence, C_5H_{12} is called *pentane*, C_6H_{14} is called *hexane*, C_7H_{16} is called *heptane* and so forth.

Straight-chain alkanes are sometimes indicated by the prefix *n-* (for normal) to distinguish them from branched-chain alkanes having the same number of carbon atoms. Although this is not strictly necessary, the usage is still common in cases where there is an important difference in properties between the straight-chain and branched-chain isomers: e.g. *n-hexane* is a neurotoxin while its branched-chain isomers are not.

IUPAC nomenclature

The IUPAC nomenclature is a system on which most organic chemists have agreed to provide guidelines to allow them to learn from each others' works. Nomenclature, in other words, provides a foundation of language for organic chemistry.

Number of Hydrogen to Carbons

This equation describes the relationship between the number of hydrogen and carbon atoms in alkanes:

$$\mathbf{H = 2C + 2}$$

where "C" and "H" are used to represent the number of carbon and hydrogen atoms present in one molecule. If C = 2, then H = 6.

Many textbooks put this in the following format:

$$\mathbf{C_nH_{2n+2}}$$

where "C_n" and "H_{2n+2}" represent the number of carbon and hydrogen atoms present in one molecule. If C_n = 3, then H_{2n+2} = 2(3) + 2 = 8. (For this formula look to the "n" for the number, the "C" and the "H" letters themselves do not change.)

Progressively longer hydrocarbon chains can be made and are named systematically, depending on the number of carbons in the longest chain.

The following table contains the systematic names for the first twenty straight chain alkanes. It will be important to familiarize yourself with these names because they will be the basis for naming many other organic molecules throughout your course of study.

Drawing Hydrocarbons

Recall that when carbon makes four bonds, it adopts the tetrahedral geometry. In the tetrahedral geometry, only two bonds can

occupy a plane simultaneously. The other two bonds point in back or in front of this plane. In order to represent the tetrahedral geometry in two dimensions, solid wedges are used to represent bonds pointing out of the plane of the drawing toward the viewer, and dashed wedges are used to represent bonds pointing out of the plane of the drawing away from the viewer. Consider the following representation of the molecule methane:

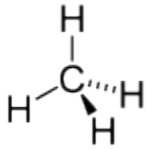


***Figure 1**: Two dimensional representation of methane*

In the above drawing, the two hydrogens connected by solid lines, as well as the carbon in the center of the molecule, exist in a plane (specifically, the plane of the computer monitor / piece of paper, etc.). The hydrogen connected by a solid wedge points out of this plane toward the viewer, and the hydrogen connected by the dashed wedge points behind this plane and away from the viewer.

In drawing hydrocarbons, it can be time-consuming to write out each atom and bond individually. In organic chemistry, hydrocarbons can be represented in a shorthand notation called a **skeletal structure**. In a skeletal structure, only the bonds between carbon atoms are represented. Individual carbon and hydrogen atoms are not drawn, and bonds to hydrogen are not drawn. In the case that the molecule contains just single bonds (sp^3 bonds), these bonds are drawn in a "zig-zag" fashion. This is because in the tetrahedral geometry all bonds point as far away from each other as possible, and the structure is not linear. Consider the following representations of the molecule propane:

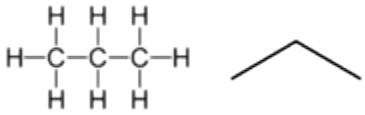
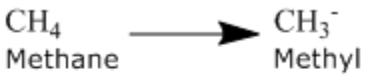


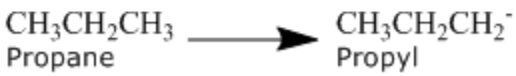
Figure 2: Full structure of propane and skeletal structure of propane

Only the bonds between carbons have been drawn, and these have been drawn in a "zig-zag" manner. Note that there is no representation of hydrogens in a skeletal structure. Since, in the absence of double or triple bonds, carbon makes four bonds total, the presence of hydrogens is implicit. Whenever an insufficient number of bonds to a carbon atom are specified in the structure, it is assumed that the rest of the bonds are made to hydrogens. For example, if the carbon atom makes only one explicit bond, there are three hydrogens implicitly attached to it. If it makes two explicit bonds, there are two hydrogens implicitly attached, etc. Note also that two lines are sufficient to represent three carbon atoms. It is the bonds only that are being drawn out, and it is understood that there are carbon atoms (with three hydrogens attached!) at the terminal ends of the structure.

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 above.

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}	$CH_3(CH_2)_7CH_3$
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	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Using Common Names with Branched Alkanes

Certain branched alkanes have common names that are still widely used today. These common names make use of prefixes, such as ***iso-***, ***sec-***, ***tert-***, and ***neo-***. The prefix ***iso-***, which stands for isomer, is commonly given to 2-methyl alkanes. In other words, if there is methyl group located on the second carbon of a carbon chain, we can use the prefix ***iso-***. The prefix will be placed in front of the alkane name that indicates the *total* number of carbons. Examples:

- isopentane which is the same as 2-methylbutane
- isobutane which is the same as 2-methylpropane

To assign the prefixes ***sec-***, which stands for secondary, and ***tert-***, for tertiary, it is important that we first learn how to classify carbon molecules. If a carbon is attached to only one other carbon, it is called a **primary** carbon. If a carbon is attached to two other carbons, it is called a **seconday** carbon. A **tertiary** carbon is attached to three other carbons and last, a **quaternary** carbon is attached to four other carbons. Examples:

- 4-*sec*-butylheptane (30g)
- 4-*tert*-butyl-5-isopropylhexane (30d); if using this example, may want to move sec/tert after iso disc

The prefix ***neo-*** refers to a substituent whose second-to-last carbon of the chain is trisubstituted (has three methyl groups attached to it). A neo-pentyl has five carbons total. Examples:

- neopentane
- neoheptane

Alkoxy Groups

Alkoxides consist of an organic group bonded to a negatively charged oxygen atom. In the general form, alkoxides are written as RO^-, where R represents the organic substituent. Similar to the alkyl groups above, the concept of naming alkoxides can be applied to any of the straight chain alkanes provided in the table above.

RO^-
Alkoxy

CH_3O^-
Methoxy

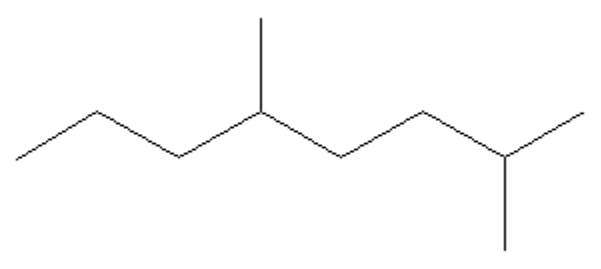
$CH_3CH_2O^-$
Ethoxy

Three Principles of Naming

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 substitute 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 substitutes and/or functional groups are written in alphabetical order.

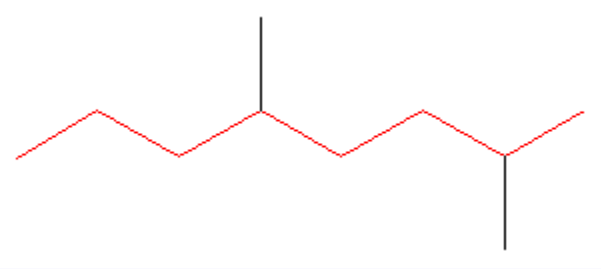
Example 1

What is the name of the following molecule?



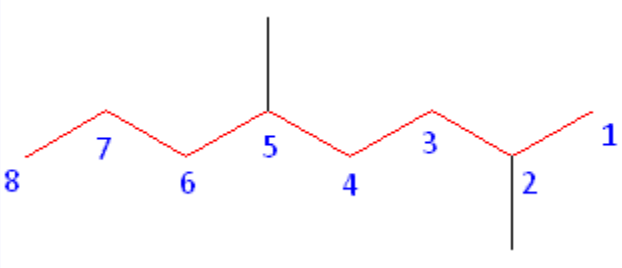
SOLUTION

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 red 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

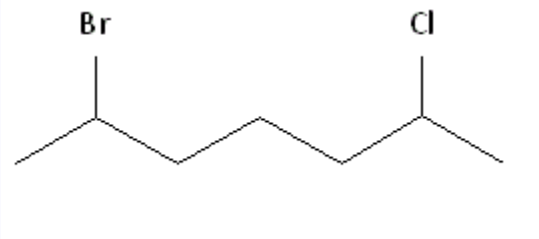
numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown 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.

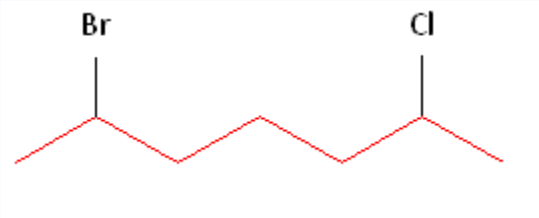
Example 2

What is the name of the following molecule?

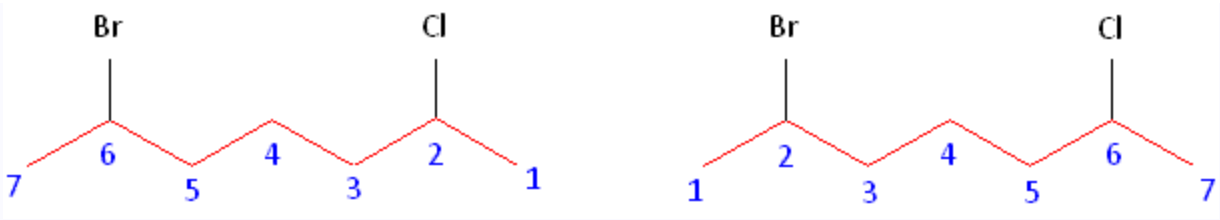


SOLUTION

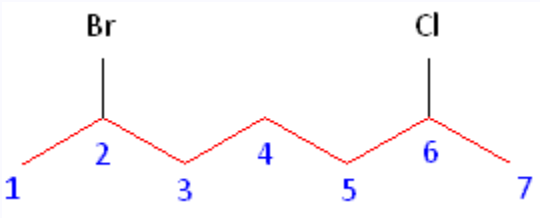
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in red and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. In this example, numbering the chain from 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.

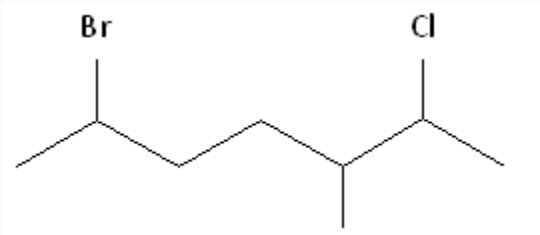


Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



Example 3

What is the name of the follow molecule?

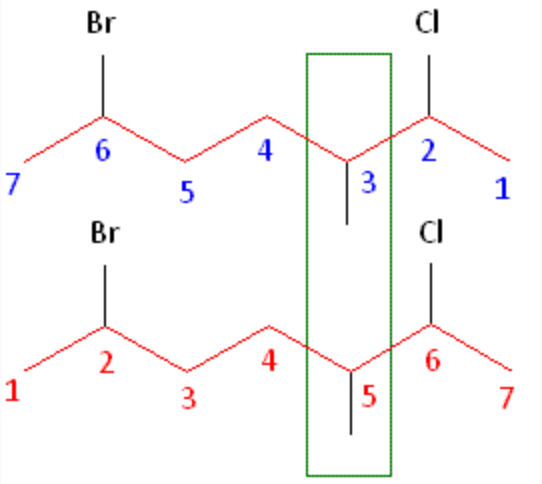


SOLUTION

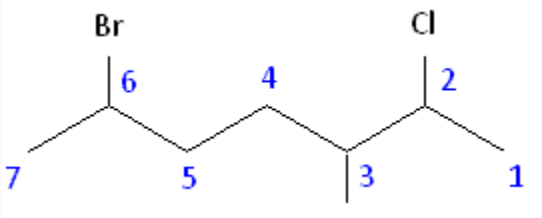
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in red and consists of seven carbons.



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.

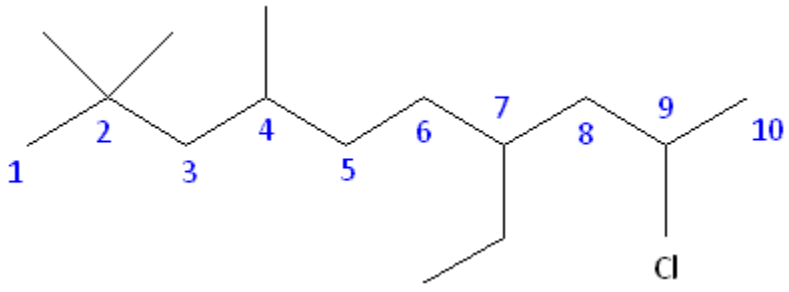
Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

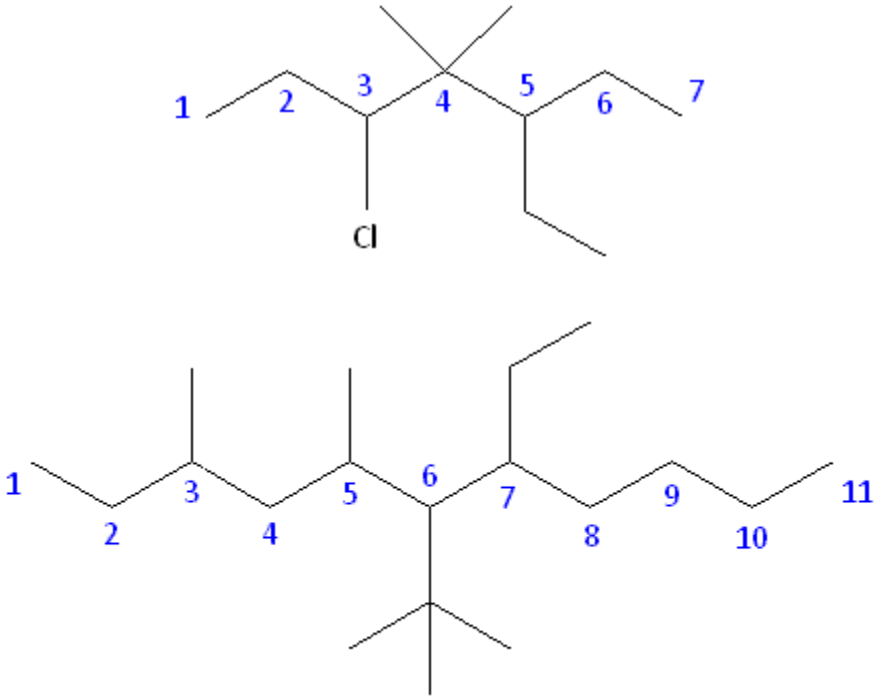
Parent chain: heptane 2-Chloro 3-Methyl 6-Bromo

6-bromo-2-chloro-3-methylheptane

Problems

What is the name of the follow molecules?





Contributors

- Jonathan Mooney (McGill University)
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2.4: Nomenclature of Cycloalkanes

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.

Introduction

Many organic compounds found in nature or created in a laboratory contain rings of carbon atoms with distinguishing chemical properties; these compounds are known as cycloalkanes. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds, but in cycloalkanes, the carbon atoms are joined in a ring. The smallest cycloalkane is cyclopropane.

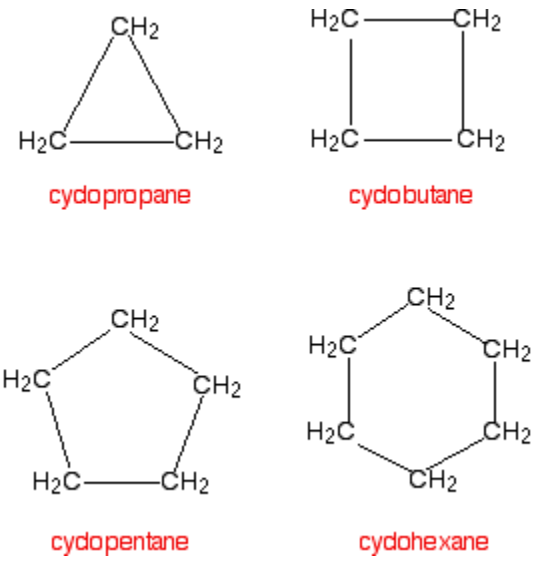


Figure 1: The first four cycloalkanes

If you count the carbons and hydrogens, you will see that they no longer fit the general formula C_nH_{2n+2}. By joining the carbon atoms in a ring,two hydrogen atoms have been lost. The general formula for a cycloalkane is C_nH_{2n}. Cyclic compounds are not all flat molecules. All of the cycloalkanes, from cyclopentane upwards, exist as "puckered rings". Cyclohexane, for example, has a ring structure that looks like this:

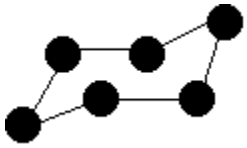
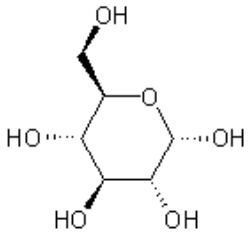
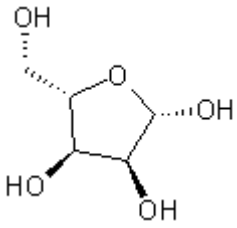
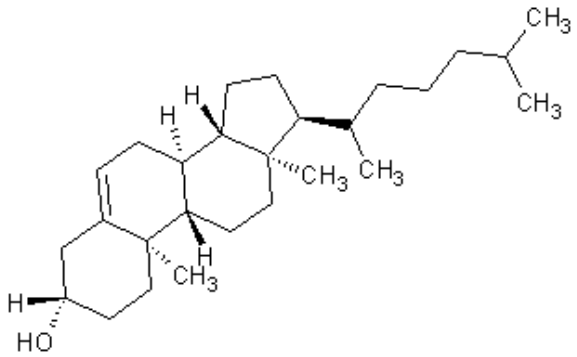


***Figure 2**: This is known as the "chair" form of cyclohexane from its shape, which vaguely resembles a chair. Note: The cyclohexane molecule is constantly changing, with the atom on the left, which is currently pointing down, flipping up, and the atom on the right flipping down. During this process, another (slightly less stable) form of cyclohexane is formed known as the "boat" form. In this arrangement, both of these atoms are either pointing up or down at the same time*

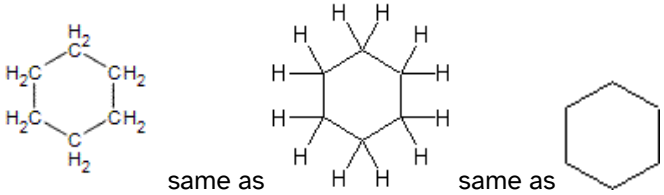
In addition to being saturated cyclic hydrocarbons, cycloalkanes may have multiple substituents or functional groups that further determine their unique chemical properties. The most common and useful cycloalkanes in organic chemistry are cyclopentane and cyclohexane, although other cycloalkanes varying in the number of carbons can be synthesized. Understanding cycloalkanes and their properties are crucial in that many of the biological processes that occur in most living things have cycloalkane-like structures.

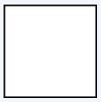
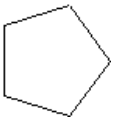
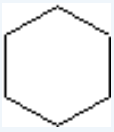
		
Glucose (6 carbon sugar)	Ribose (5 carbon sugar)	Cholesterol (polycyclic)

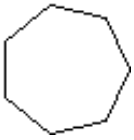
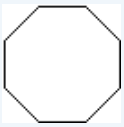
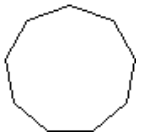
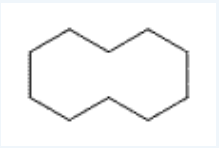
Although polycyclic compounds are important, they are highly complex and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules. The general formula of the cycloalkanes is C_nH_{2n} where n is the number of carbons. The naming of cycloalkanes follows a simple set of rules that are built upon the same basic steps in naming alkanes. Cyclic hydrocarbons have the prefix "cyclo-".

Parent Chains

For simplicity, cycloalkane molecules can be drawn in the form of skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens.



Cycloalkane	Molecular Formula	Basic Structure
Cyclopropane	\(C_3H_6\0	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	
Cyclohexane	C_6H_{12}	

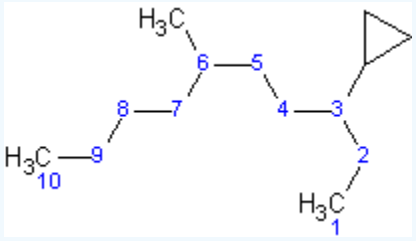
Cycloalkane	Molecular Formula	Basic Structure
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

IUPAC Rules for Nomenclature

1. Determine the cycloalkane to use as the parent chain. The parent chain is the one with the highest number of carbon atoms. If there are two cycloalkanes, use the cycloalkane with the higher number of carbons as the parent chain.
2. 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. Cycloalkane acting as a substituent to an alkyl chain has an ending "-yl" and, therefore, must be named as a cycloalkyl.

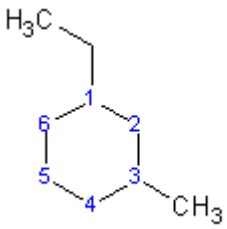
Cycloalkane	Cycloalkyl
cyclopropane	cyclopropyl
cyclobutane	cyclobutyl
cyclopentane	cyclopentyl
cyclohexane	cyclohexyl
cycloheptane	cycloheptyl
cyclooctane	cyclooctyl
cyclononane	cyclononanyl
cyclodecane	cyclodecanyl

Example 1

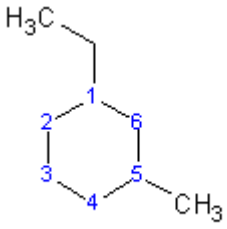


The longest straight chain contains 10 carbons, compared with cyclopropane, which only contains 3 carbons. Because cyclopropane is a substituent, it would be named a cyclopropyl-substituted alkane.

3. Determine any functional groups or other alkyl groups.
4. Number the carbons of the cycloalkane so that the carbons with functional groups or alkyl groups 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.

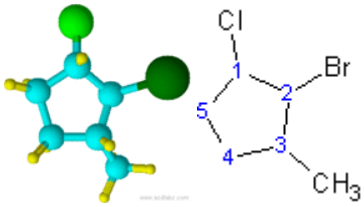


1-ethyl-3-methylcyclohexane (1+3=4) **NOT**



1-ethyl-5-methylcyclohexane (1+5=6)

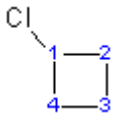
3. When naming the cycloalkane, the substituents and functional groups must be placed in alphabetical order.



(ex: 2-bromo-1-chloro-3-methylcyclopentane)

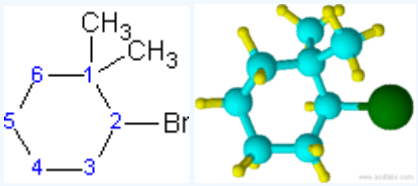
4. Indicate the carbon number with the functional group with the highest priority according to alphabetical order. A dash"-" must be placed between the numbers and the name of the substituent. After the carbon number and the dash, the name of the substituent can follow. When there is only one substituent on the parent chain, indicating the number of the carbon atoms with the substituent is not necessary.

(ex: 1-chlorocyclohexane or cholorocyclohexane is acceptable)



7. If there is more than one of the same functional group on one carbon, write the number of the carbon two, three, or four times, depending on how many of the same functional group is present on that carbon. The numbers must be separated by commas, and the name of the functional group that follows must be separated by a dash. When there are two of the same functional group, the name must have the prefix "di". When there are three of the same functional group, the name must have the prefix "tri". When there are four of the same functional group, the name must have the prefix "tetra". However, these prefixes cannot be used when determining the alphabetical priorities. There must always be commas between the numbers and the dashes that are between the numbers and the names.

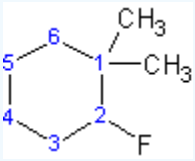
Example 2



(2-bromo-1,1-dimethylcyclohexane)

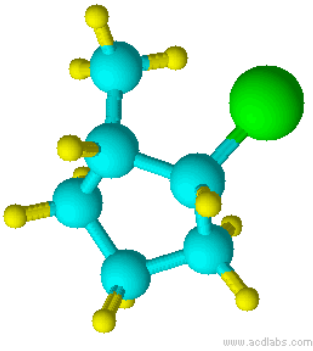
Notice that "f" of fluoro alphabetically precedes the "m" of methyl. Although "di" alphabetically precedes "f", it is not used in determining the alphabetical order.

Example 3



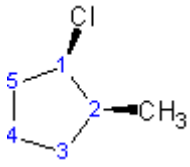
(2-fluoro-1,1,-dimethylcyclohexane **NOT** 1,1-dimethyl-2-fluorocyclohexane)

8) If the substituents of the cycloalkane are related by the cis or trans configuration, then indicate the configuration by placing "cis-" or "trans-" in front of the name of the structure.



Blue=Carbon Yellow=Hydrogen Green=Chlorine

Notice that chlorine and the methyl group are both pointed in the same direction on the axis of the molecule; therefore, they are cis.

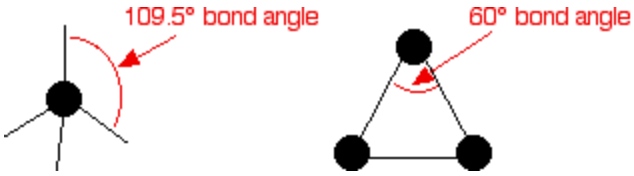


cis-1-chloro-2-methylcyclopentane

9) After all the functional groups and substituents have been mentioned with their corresponding numbers, the name of the cycloalkane can follow.

Reactivity

Cycloalkanes are very similar to the alkanes in reactivity, except for the very small ones, especially cyclopropane. Cyclopropane is significantly more reactive than what is expected because of the bond angles in the ring. Normally, when carbon forms four single bonds, the bond angles are approximately 109.5°. In cyclopropane, the bond angles are 60°.



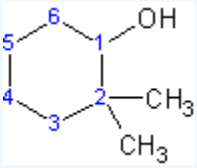
With the electron pairs this close together, there is a significant amount of repulsion between the bonding pairs joining the carbon atoms, making the bonds easier to break.

Alcohol Substituents on Cycloalkanes

Alcohol (-OH) substituents take the highest priority for carbon atom numbering in IUPAC nomenclature. The carbon atom with the alcohol substituent must be labeled as 1. Molecules containing an alcohol group have an ending "-ol", indicating the presence of an alcohol group. If there are two alcohol groups, the molecule will have a "di-" prefix before "-ol" (diol). If there are three alcohol groups, the molecule will have a "tri-" prefix before "-ol" (triol), etc.

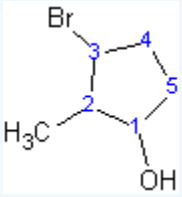
Example 4

The alcohol substituent is given the lowest number even though the two methyl groups are on the same carbon atom and labeling 1 on that carbon atom would give the lowest possible numbers. Numbering the location of the alcohol substituent is unnecessary because the ending "-ol" indicates the presence of one alcohol group on carbon atom number 1.



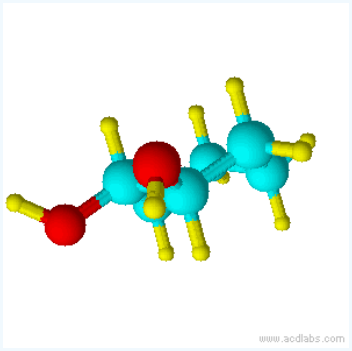
2,2-dimethylcyclohexanol **NOT** 1,1-dimethyl-cyclohexane-2-ol

Example 5

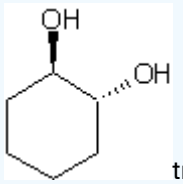


3-bromo-2-methylcyclopentanol **NOT** 1-bromo-2-methyl-cyclopentane-2-ol

Example 6



Blue=Carbon Yellow=Hydrogen Red=Oxygen



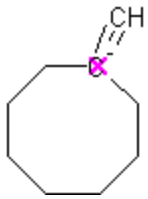
trans-cyclohexane-1,2-diol

Other Substituents on Cycloalkanes

There are many other functional groups like alcohol, which are later covered in an organic chemistry course, and they determine the ending name of a molecule. The naming of these functional groups will be explained in depth later as their chemical properties are explained.

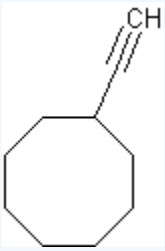
Name	Name ending
alkene	-ene
alkyne	-yne
alcohol	-ol
ether	-ether
nitrile	-nitrile
amine	-amine
aldehyde	-al
ketone	-one
carboxylic acid	-oic acid
ester	-oate
amide	-amide

Although alkynes determine the name ending of a molecule, alkyne as a substituent on a cycloalkane is not possible because alkynes are planar and would require that the carbon that is part of the ring form 5 bonds, giving the carbon atom a negative charge.



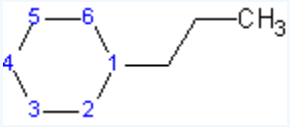
However, a cycloalkane with a triple bond-containing substituent is possible if the triple bond is not directly attached to the ring.

Example 7



ethynylcyclooctane

Example 8



1-propylcyclohexane

Summary

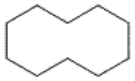
1. Determine the parent chain: the parent chain contains the most carbon atoms.
2. Number the substituents of the chain so that the sum of the numbers is the lowest possible.
3. Name the substituents and place them in alphabetical order.
4. If stereochemistry of the compound is shown, indicate the orientation as part of the nomenclature.
5. Cyclic hydrocarbons have the prefix "cyclo-" and have an "-alkane" ending unless there is an alcohol substituent present. When an alcohol substituent is present, the molecule has an "-ol" ending.

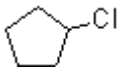
Glossary

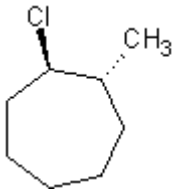
- **alcohol**: An oxygen and hydrogenOH hydroxyl group that is bonded to a substituted alkyl group.
- **alkyl:** A structure that is formed when a hydrogen atom is removed from an alkane.
- **cyclic:** Chemical compounds arranged in the form of a ring or a closed chain form.
- **cycloalkanes:** Cyclic saturated hydrocarbons with a general formula of CnH(2n). Cycloalkanes are alkanes with carbon atoms attached in the form of a closed ring.
- **functional groups:** An atom or groups of atoms that substitute for a hydrogen atom in an organic compound, giving the compound unique chemical properties and determining its reactivity.
- **hydrocarbon:** A chemical compound containing only carbon and hydrogen atoms.
- **saturated**: All of the atoms that make up a compound are single bonded to the other atoms, with no double or triple bonds.
- **skeletal structure:** A simplified structure in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens.

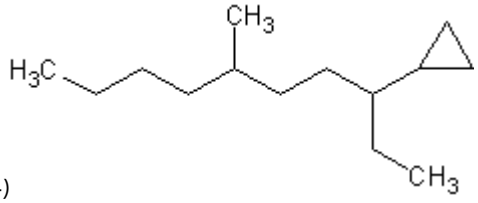
Problems

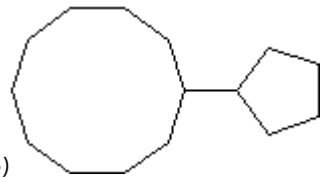
Name the following structures. (Note: The structures are complex for practice purposes and may not be found in nature.)

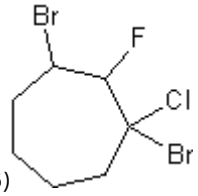
1) 

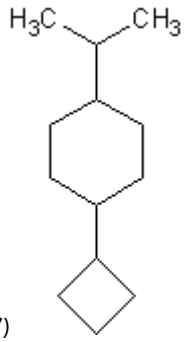
2) 

3) 

4) 

5) 

6) 

7) 

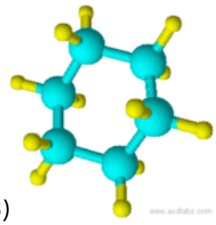
Draw the following structures.

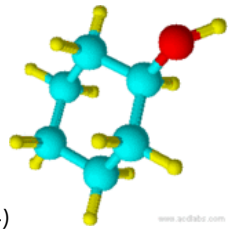
8) 1,1-dibromo-5-fluoro-3-butyl-7-methylcyclooctane 9) trans-1-bromo-2-chlorocyclopentane

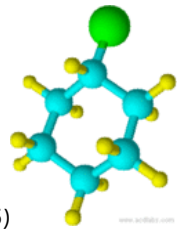
10) 1,1-dibromo-2,3-dichloro-4-propylcyclobutane 11) 2-methyl-1-ethyl-1,3-dipropylcyclopentane 12) cycloheptane-1,3,5-triol

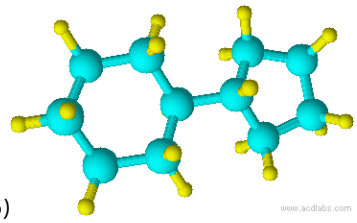
Name the following structures.

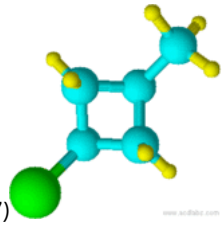
Blue=Carbon Yellow=Hydrogen Red=Oxygen Green=Chlorine

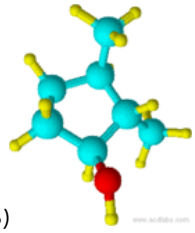
13) 

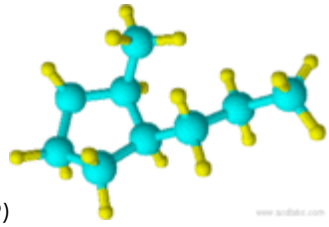
14) 

15) 

16) 

17) 

18) 

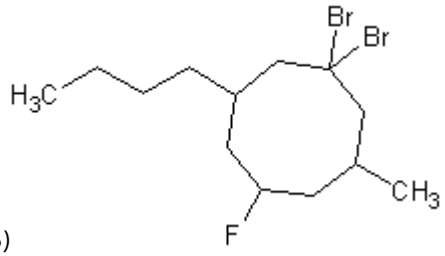
19) 

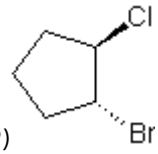
Answers to Practice Problems

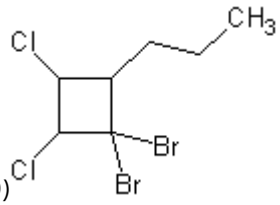
1) cyclodecane 2) chlorocyclopentane or 1-chlorocyclopentane 3) trans-1-chloro-2-methylcycloheptane

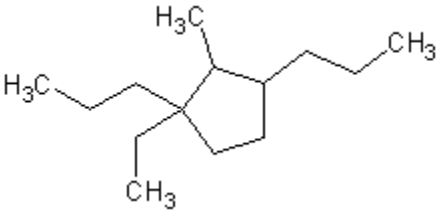
4) 3-cyclopropyl-6-methyldecane 5) cyclopentylcyclodecane or 1-cyclopentylcyclodecane 6) 1,3-dibromo-1-chloro-2-fluorocycloheptane

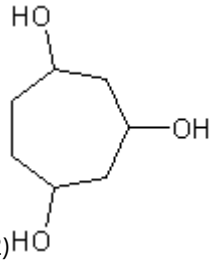
7) 1-cyclobutyl-4-isopropylcyclohexane

8) 

9) 

10) 

11) 

12) 

13) cyclohexane 14) cyclohexanol 15) chlorocyclohexane 16) cyclopentylcyclohexane 17) 1-chloro-3-methylcyclobutane

18) 2,3-dimethylcyclohexanol 19) cis-1-propyl-2-methylcyclopentane

References

1. ACD/ChemSketch Freeware, version 11.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2008.
2. Bruice, Paula Yurkanis. Oragnic Chemistry. 5th. CA. Prentice Hall, 2006.
3. Fryhle, C.B. and G. Solomons. Organic Chemistry. 9th ed. Danvers, MA: Wiley, 2008.
4. McMurry, John. Organic Chemistry. 7th ed. Belmont, California: Thomson Higher Education, 2008.
5. Sadava, Heller, Orians, Purves, Hillis. Life The Science of Biology. 8th ed. Sunderland, MA: W.H. Freeman, 2008.
6. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.

Contributors

- Pwint Zin
- Jim Clark (ChemGuide)

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2.5: Practice - Alkane Nomenclature

I. The parent compound must have the longest chain of carbon atoms

Learn: methane (1 carbon atom), ethane (2 carbon atoms), propane (3 carbon atoms), butane (4 carbon atoms), pentane (5 carbon atoms), hexane (6 carbon atoms), heptane (7 carbon atoms), octane (8 carbon atoms), nonane (9 carbon atoms) and decane (10 carbon atoms).

Try to name the following compounds:

1. CH_3-CH_2-CH_2-CH_3
2. CH_3-CH_2-CH_2-CH_2-CH_2-CH_3
3. CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3

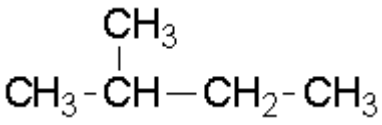
Try to draw structures for the following compounds:

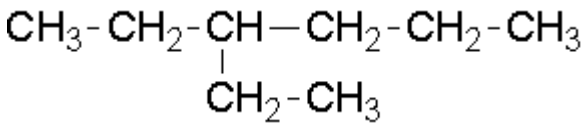
4. propane
5. pentane
6. octane

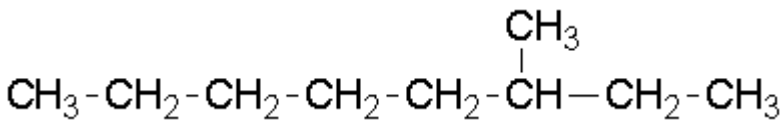
II. The parent chain is numbered to give substituents the lowest possible numbers

Substituent names are methyl, ethyl, propyl, butyl, etc. The number showing the point of attachment to the parent chain precedes the substituent name. If you have more than one substituent with the same name, a number of attachment must be given for each substituent and the number of the substituents must be designated with di-, tri-, etc.

Try to name the following compounds...

7. 

8. 

9. 

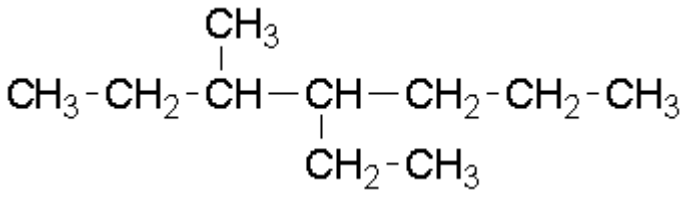
Try to draw structures for the following compounds...

10. 2,2-dimethylpropane
11. 3-methylheptane
12. 4,5-diethylnonane

III. Substituents are named in alphabetical order

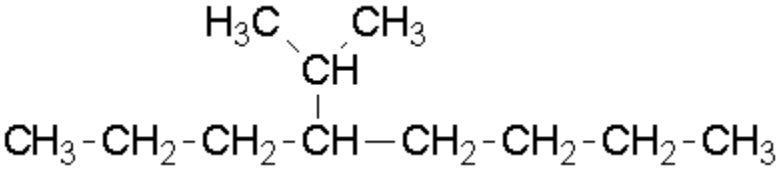
Remember that the numbering of the parent chain must give all substituents the lowest possible numbers regardless of their names.

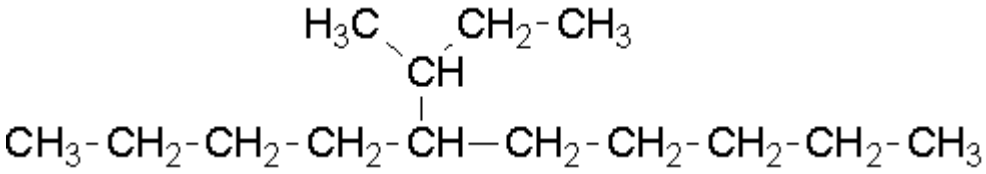
Try to name the following compound...

13. 

IV. A large substituent is numbered to give its point of attachment

The point of attachment is number one and any other smaller groups are named as substituent groups on the larger group. This numbering is independent of the numbering of the parent chain. Try to name the following compounds...

14. 

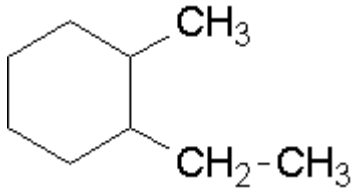
15. 

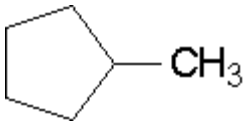
Try to draw structures for the following compounds...

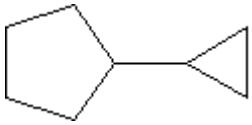
16. 4-(1-methylethyl)heptane
17. 5-(1,1-dimethylethyl)nonane

V. Ring compounds are designated with a cyclo- prefix and are numbered to give multiple substituents the lowest possible numbers

A single substituent does not need to be numbered. A ring can also be named as a substituent. Try to name the following compounds:

18. 

19. 

20. 

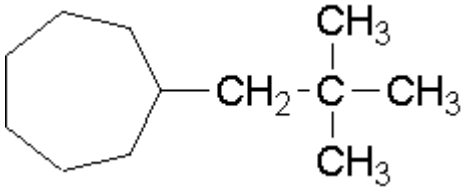
Try to draw structures for the following compounds...

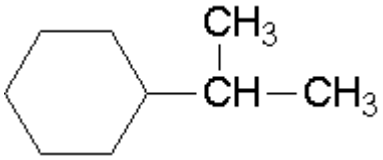
21. ethylcyclobutane
22. 1-ethyl-4-methylcyclohexane
23. cyclobutylcyclooctane

VI. Common Names

- isopropyl = 1-methylethyl
- isobutyl = 2-methylpropyl
- *sec*-butyl = 1-methylpropyl
- *tert*-butyl = 1,1-dimethylethyl
- *neo*-pentyl = 2,2-dimethylpropyl
- *iso*-pentyl = 3-methylbutyl

Try to name the following compounds using common names...

24. 

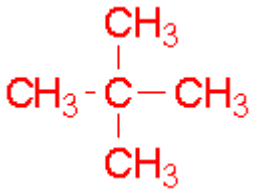
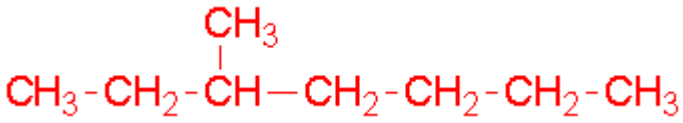
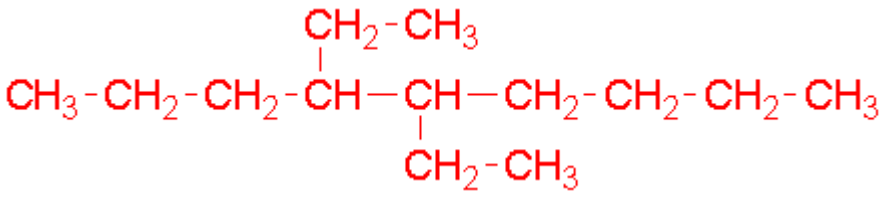
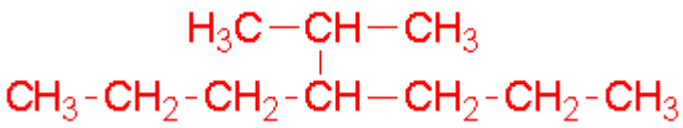
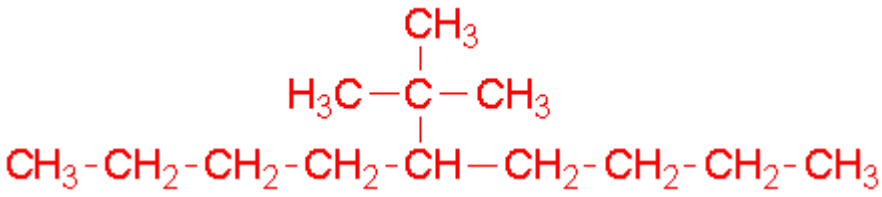
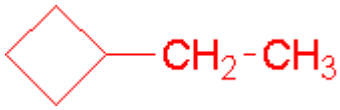
25. 

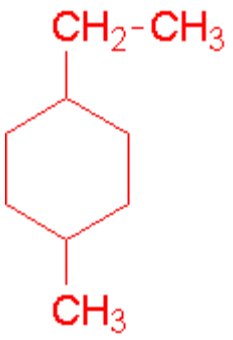
Try to draw structures for the following compounds...

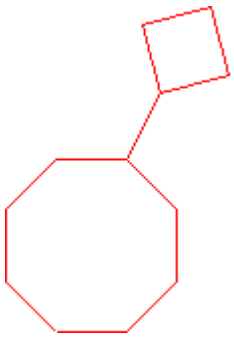
26. 4-isopropyloctane
27. isopentylcyclohexane

Answers

1. butane
2. hexane
3. nonane
4. CH_3-CH_2-CH_3
5. CH_3-CH_2-CH_2-CH2-CH_3
6. CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3
7. 2-methylbutane

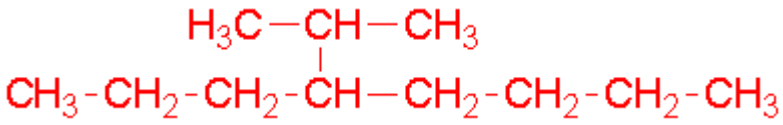
8. 3-ethylhexane
9. 3-methyloctane (Remember that you must number the parent chain to give the substituent the lowest possible number.)
10. 
11. 
12. 
13. 4-ethyl-3-methylheptane
14. 4-(1-methylethyl)octane
15. 5-(1-methylpropyl)decane
16. 
17. 
18. 1-ethyl-2-methylcyclohexane
19. methylcyclopentane (You do not need a number since there is only one substituent and it is assumed to be on the first carbon regardless of how the ring compound is drawn.)
20. cyclopropylcyclopentane
21. 

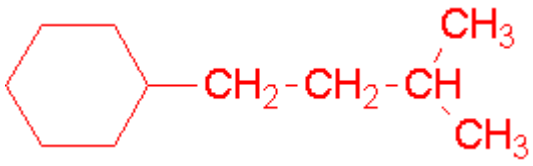
22. 

23. 

24. *neo*-pentylcycloheptane (1-(2,2-dimethyl-1-propyl)cycloheptane is the proper name.)

25. isopropylcyclohexane

26. 

27. 

Contributors

Richard Banks (Boise State University)

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2.6: Ethane Conformers

The simple alkane ethane provides a good introduction to conformational analysis. Here there is only one carbon-carbon bond, and the rotational structures (rotamers) that it may assume fall between two extremes, **staggered** and **eclipsed**. In the following description of these conformers, several structural notations are used. The first views the ethane molecule from the side, with the carbon-carbon bond being horizontal to the viewer. The hydrogens are then located in the surrounding space by **wedge** (in front of the plane) and **hatched** (behind the plane) bonds. If this structure is rotated so that carbon #1 is canted down and brought closer to the viewer, the "sawhorse" projection is presented. Finally, if the viewer looks down the carbon-carbon bond with carbon #1 in front of #2, the Newman projection is seen.

Name of Conformer Wedge-Hatched Bond Structure Sawhorse Structure Newman Projection

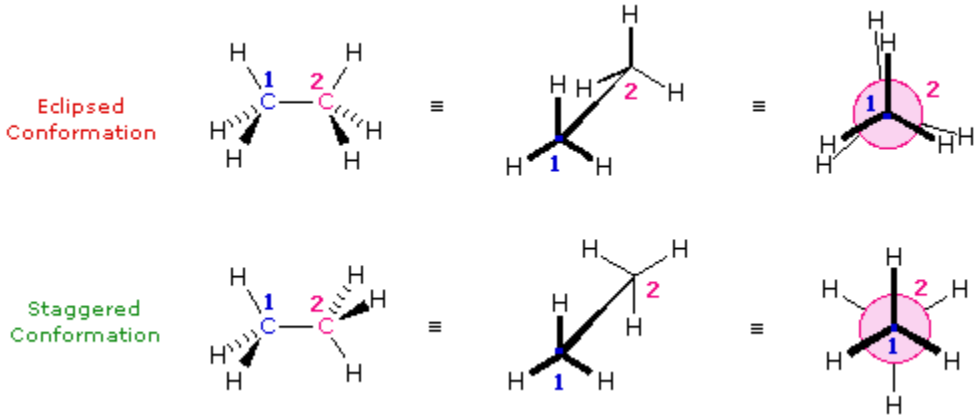


Figure 1: Extreme Conformations of Ethane

As a result of bond-electron repulsions, illustrated in Figure 2, the eclipsed conformation is less stable than the staggered conformation by roughly 3 kcal / mol (eclipsing strain). The most severe repulsions in the eclipsed conformation are depicted by the red arrows. There are six other less strong repulsions that are not shown. In the staggered conformation there are six equal bond repulsions, four of which are shown by the blue arrows, and these are all substantially less severe than the three strongest eclipsed repulsions.

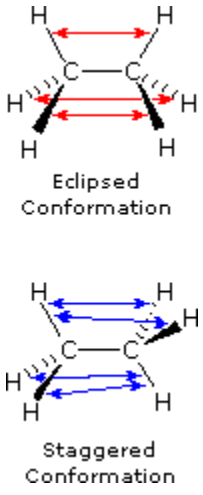
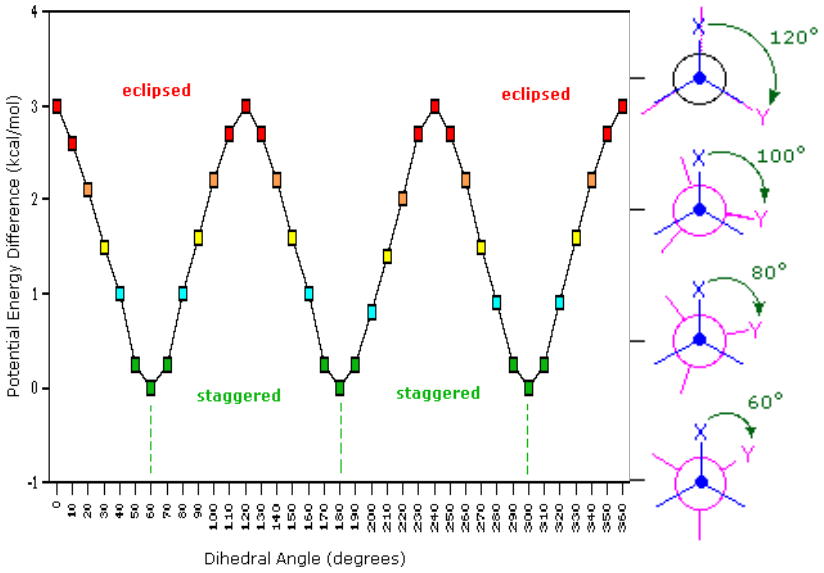
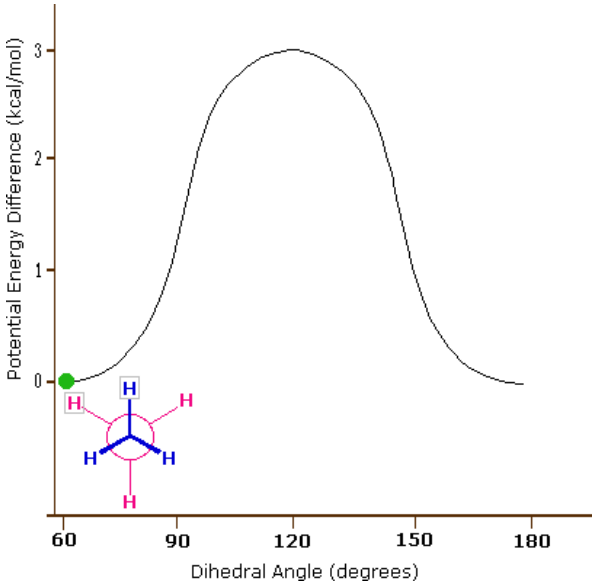


Figure 2: Bond Repulsions in Ethane

Consequently, the potential energy associated with the various conformations of ethane varies with the **dihedral angle** of the bonds, as shown below. 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.



Dihedral Angle



Potential Energy Profile for Ethane Conformers: The above animation illustrates the relationship between ethane's potential energy and its dihedral angle

Contributors

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

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2.7: Gibbs Free Energy (review)

Learning Objectives

- To understand the relationship between Gibbs free energy and work.

One of the major goals of chemical thermodynamics is to establish criteria for predicting whether a particular reaction or process will occur spontaneously. We have developed one such criterion, the change in entropy of the universe: if $\Delta S_{univ} > 0$ for a process or a reaction, then the process will occur spontaneously as written. Conversely, if $\Delta S_{univ} < 0$, a process cannot occur spontaneously; if $\Delta S_{univ} = 0$, the system is at equilibrium. The sign of ΔS_{univ} is a universally applicable and infallible indicator of the spontaneity of a reaction. Unfortunately, using ΔS_{univ} requires that we calculate ΔS for both a system and its surroundings. This is not particularly useful for two reasons: we are normally much more interested in the system than in the surroundings, and it is difficult to make quantitative measurements of the surroundings (i.e., the rest of the universe). A criterion of spontaneity that is based solely on the state functions of a system would be much more convenient and is provided by a new state function: the Gibbs free energy.

Gibbs Free Energy and the Direction of Spontaneous Reactions

The Gibbs free energy (G), often called simply free energy, was named in honor of J. Willard Gibbs (1838–1903), an American physicist who first developed the concept. It is defined in terms of three other state functions with which you are already familiar: enthalpy, temperature, and entropy:

$$G = H - TS \tag{2.7.1}$$

Because it is a combination of state functions, G is also a state function.

J. Willard Gibbs (1839–1903)

Born in Connecticut, Josiah Willard Gibbs attended Yale, as did his father, a professor of sacred literature at Yale, who was involved in the Amistad trial. In 1863, Gibbs was awarded the first engineering doctorate granted in the United States. He was appointed professor of mathematical physics at Yale in 1871, the first such professorship in the United States. His series of papers entitled “On the Equilibrium of Heterogeneous Substances” was the foundation of the field of physical chemistry and is considered one of the great achievements of the 19th century. Gibbs, whose work was translated into French by Le Chatelier, lived with his sister and brother-in-law until his death in 1903, shortly before the inauguration of the Nobel Prizes.

The criterion for predicting spontaneity is based on (ΔG), the change in G, at constant temperature and pressure. Although very few chemical reactions actually occur under conditions of constant temperature and pressure, most systems can be brought back to the initial temperature and pressure without significantly affecting the value of thermodynamic state functions such as G. At constant temperature and pressure,

$$\Delta G = \Delta H - T\Delta S \tag{2.7.2}$$

where all thermodynamic quantities are those of the system. Recall that at constant pressure, $\Delta H = q$, whether a process is reversible or irreversible, and $T\Delta S = q_{rev}$. Using these expressions, we can reduce Equation 2.7.2 to $\Delta G = q - q_{rev}$. Thus ΔG is the difference between the heat released during a process (via a reversible or an irreversible path) and the heat released for the same process occurring in a reversible manner. Under the special condition in which a process occurs reversibly, $q = q_{rev}$ and $\Delta G = 0$. As we shall soon see, if ΔG is zero, the system is at equilibrium, and there will be no net change.

What about processes for which $\Delta G \neq 0$? To understand how the sign of ΔG for a system determines the direction in which change is spontaneous, we can rewrite the relationship between ΔS and q_{rev}, discussed earlier.

$$\Delta S = \frac{q_{rev}}{T} \tag{2.7.3}$$

with the definition of ΔH in terms of q_{rev}

$$q_{rev} = \Delta H \tag{2.7.4}$$

to obtain

$$\Delta S_{\text{surr}} = -\frac{\Delta H_{\text{sys}}}{T} \tag{2.7.5}$$

Thus the entropy change of the surroundings is related to the enthalpy change of the system. We have stated that for a spontaneous reaction, $\Delta S_{univ} > 0$, so substituting we obtain

$$\Delta S_{\text{univ}} = \Delta S_{\text{sys}} + \Delta S_{\text{surr}} > 0 \tag{2.7.6}$$

$$= \Delta S_{\text{sys}} - \frac{\Delta H_{\text{sys}}}{T} > 0 \tag{2.7.7}$$

Multiplying both sides of the inequality by –T reverses the sign of the inequality; rearranging,

$$\Delta H_{sys} - T\Delta S_{sys} < 0 \tag{2.7.8}$$

which is equal to ΔG (Equation 2.7.2). We can therefore see that for a spontaneous process, $\Delta G < 0$.

The relationship between the entropy change of the surroundings and the heat gained or lost by the system provides the key connection between the thermodynamic properties of the system and the change in entropy of the universe. The relationship shown in Equation 2.7.2 allows us to predict spontaneity by focusing exclusively on the thermodynamic properties and temperature of the system. We predict that highly exothermic processes ($\Delta H \ll 0$) that increase the disorder of a system ($\Delta S_{sys} \gg 0$) would therefore occur spontaneously. An example of such a process is the decomposition of ammonium nitrate fertilizer. Ammonium nitrate was also used to destroy the Murrah Federal Building in Oklahoma City, Oklahoma, in 1995. For a system at constant temperature and pressure, we can summarize the following results:

- If $\Delta G < 0$, the process occurs spontaneously.
- If $\Delta G = 0$, the system is at equilibrium.
- If $\Delta G > 0$, the process is not spontaneous as written but occurs spontaneously in the reverse direction.

To further understand how the various components of ΔG dictate whether a process occurs spontaneously, we now look at a simple and familiar physical change: the conversion of liquid water to water vapor. If this process is carried out at 1 atm and the normal boiling point of 100.00°C (373.15 K), we can calculate ΔG from the experimentally measured value of ΔH_{vap} (40.657 kJ/mol). For vaporizing 1 mol of water, $\Delta H = 40,657; J$, so the process is highly endothermic. From the definition of ΔS (Equation 2.7.5), we know that for 1 mol of water,

$$\begin{aligned}\Delta S_{\text{vap}} &= \frac{\Delta H_{\text{vap}}}{T_{\text{b}}} \\ &= \frac{40{,}657\ \text{J}}{373.15\ \text{K}} \\ &= 108.96\ \text{J/K}\end{aligned}$$

Hence there is an increase in the disorder of the system. At the normal boiling point of water,

$$\begin{aligned}\Delta G_{100^\circ\text{C}} &= \Delta H_{100^\circ\text{C}} - T\Delta S_{100^\circ\text{C}} \\ &= 40{,}657\ \text{J} - [(373.15\ \text{K})(108.96\ \text{J/K})] \\ &= 0\ \text{J}\end{aligned}$$

The energy required for vaporization offsets the increase in disorder of the system. Thus ΔG = 0, and the liquid and vapor are in equilibrium, as is true of any liquid at its boiling point under standard conditions.

Now suppose we were to superheat 1 mol of liquid water to 110°C. The value of ΔG for the vaporization of 1 mol of water at 110°C, assuming that ΔH and ΔS do not change significantly with temperature, becomes

$$\begin{aligned}\Delta G_{110^\circ\text{C}} &= \Delta H - T\Delta S \\ &= 40{,}657\ \text{J} - [(383.15\ \text{K})(108.96\ \text{J/K})] \\ &= -1091\ \text{J}\end{aligned}$$

At 110°C, $\Delta G < 0$, and vaporization is predicted to occur spontaneously and irreversibly.

We can also calculate ΔG for the vaporization of 1 mol of water at a temperature below its normal boiling point—for example, 90°C—making the same assumptions:

$$\begin{aligned}\Delta G_{90^\circ\text{C}} &= \Delta H - T\Delta S \\ &= 40{,}657\ \text{J} - [(363.15\ \text{K})(108.96\ \text{J/K})] \\ &= 1088\ \text{J}\end{aligned}$$

At 90°C, ΔG > 0, and water does not spontaneously convert to water vapor. When using all the digits in the calculator display in carrying out our calculations, $\Delta G_{110^\circ\text{C}} = 1090\ \text{J} = -\Delta G_{90^\circ\text{C}}$, as we would predict.

Relating Enthalpy and Entropy changes under Equilibrium Conditions

$\Delta G = 0$ only if $\Delta H = T\Delta S$.

We can also calculate the temperature at which liquid water is in equilibrium with water vapor. Inserting the values of ΔH and ΔS into the definition of ΔG (Equation 2.7.2), setting $\Delta G = 0$, and solving for T,

0 J=40,657 J−T(108.96 J/K)
T=373.15 K

Thus $\Delta G = 0$ at T = 373.15 K and 1 atm, which indicates that liquid water and water vapor are in equilibrium; this temperature is called the normal boiling point of water. At temperatures greater than 373.15 K, ΔG is negative, and water evaporates spontaneously and irreversibly. Below 373.15 K, ΔG is positive, and water does not evaporate spontaneously. Instead, water vapor at a temperature less than 373.15 K and 1 atm will spontaneously and irreversibly condense to liquid water. Figure 2.7.1 shows how the ΔH and $T\Delta S$ terms vary with temperature for the vaporization of water. When the two lines cross, $\Delta G = 0$, and $\Delta H = T\Delta S$.

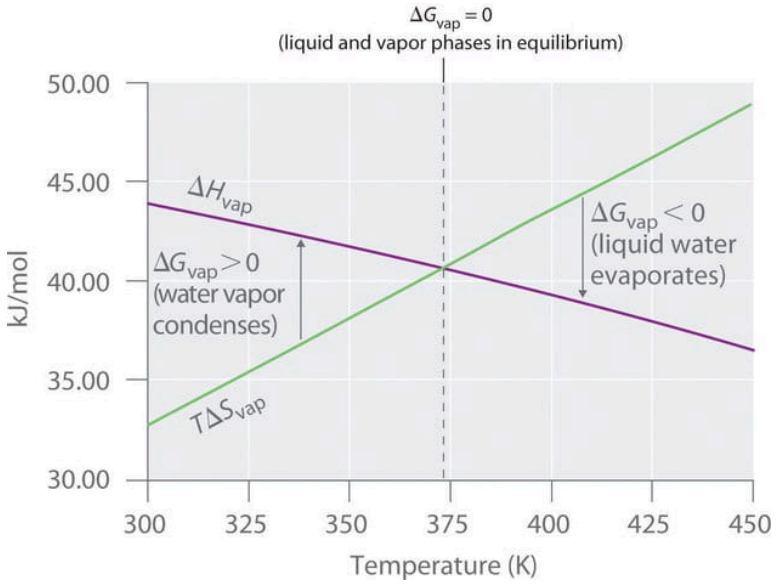


Figure 2.7.1: Temperature Dependence of ΔH and TΔS for the Vaporization of Water. Both ΔH and TΔS are temperature dependent, but the lines have opposite slopes and cross at 373.15 K at 1 atm, where ΔH = TΔS. Because ΔG = ΔH − TΔS, at this temperature ΔG = 0, indicating that the liquid and vapor phases are in equilibrium. The normal boiling point of water is therefore 373.15 K. Above the normal boiling point, the TΔS term is greater than ΔH, making ΔG < 0; hence, liquid water evaporates spontaneously. Below the normal boiling point, the ΔH term is greater than TΔS, making ΔG > 0. Thus liquid water does not evaporate spontaneously, but water vapor spontaneously condenses to liquid.

A similar situation arises in the conversion of liquid egg white to a solid when an egg is boiled. The major component of egg white is a protein called albumin, which is held in a compact, ordered structure by a large number of hydrogen bonds. Breaking them requires an input of energy ($\Delta H > 0$), which converts the albumin to a highly disordered structure in which the molecules aggregate as a disorganized solid ($\Delta S > 0$). At temperatures greater than 373 K, the $T\Delta S$ term dominates, and $\Delta G < 0$, so the conversion of a raw egg to a hard-boiled egg is an irreversible and spontaneous process above 373 K.

The Relationship between ΔG and Work

In the previous subsection, we learned that the value of ΔG allows us to predict the spontaneity of a physical or a chemical change. In addition, the magnitude of ΔG for a process provides other important information. The change in free energy (ΔG) is equal to the maximum amount of work that a system can perform on the surroundings while undergoing a spontaneous change (at constant temperature and pressure): $\Delta G = w_{max}$. To see why this is true, let's look again at the relationships among free energy, enthalpy, and entropy expressed in Equation 2.7.2. We can rearrange this equation as follows:

$$\Delta H = \Delta G + T\Delta S \tag{2.7.9}$$

This equation tells us that when energy is released during an exothermic process ($\Delta H < 0$), such as during the combustion of a fuel, some of that energy can be used to do work ($\Delta G < 0$), while some is used to increase the entropy of the universe ($T\Delta S > 0$). Only if the process occurs infinitely slowly in a perfectly reversible manner will the entropy of the universe be unchanged. (For more information on entropy and reversibility, see the previous section). Because no real system is perfectly reversible, the entropy of the universe increases during all processes that produce energy. As a result, no process that uses stored energy can ever be 100% efficient; that is, ΔH will never equal ΔG because ΔS has a positive value.

One of the major challenges facing engineers is to maximize the efficiency of converting stored energy to useful work or converting one form of energy to another. As indicated in Table 2.7.1, the efficiencies of various energy-converting devices vary widely. For example, an internal combustion engine typically uses only 25%–30% of the energy stored in the hydrocarbon fuel to perform work; the rest of the stored energy is released in an unusable form as heat. In contrast, gas–electric hybrid engines, now used in several models of automobiles, deliver approximately 50% greater fuel efficiency. A large electrical generator is highly efficient (approximately 99%) in converting mechanical to electrical energy, but a typical incandescent light bulb is one of the least efficient devices known (only approximately 5% of the electrical energy is converted to light). In contrast, a mammalian liver cell is a relatively efficient machine and can use fuels such as glucose with an efficiency of 30%–50%.

Table 2.7.1: Approximate Thermodynamic Efficiencies of Various Devices

Device	Energy Conversion	Approximate Efficiency (%)
large electrical generator	mechanical → electrical	99
chemical battery	chemical → electrical	90
home furnace	chemical → heat	65
small electric tool	electrical → mechanical	60
space shuttle engine	chemical → mechanical	50
mammalian liver cell	chemical → chemical	30–50
spinach leaf cell	light → chemical	30
internal combustion engine	chemical → mechanical	25–30
fluorescent light	electrical → light	20
solar cell	light → electricity	10-20
incandescent light bulb	electricity → light	5
yeast cell	chemical → chemical	2–4

Standard Free-Energy Change

We have seen that there is no way to measure absolute enthalpies, although we can measure changes in enthalpy (ΔH) during

a chemical reaction. Because enthalpy is one of the components of Gibbs free energy, we are consequently unable to measure absolute free energies; we can measure only changes in free energy. The standard free-energy change (ΔG°) is the change in free energy when one substance or a set of substances in their standard states is converted to one or more other substances, also in their standard states. The standard free-energy change can be calculated from the definition of free energy, if the standard enthalpy and entropy changes are known, using Equation 2.7.10:

$$\Delta G°= \Delta H°-T\Delta S° \tag{2.7.10}$$

If ΔS° and ΔH° for a reaction have the same sign, then the sign of ΔG° depends on the relative magnitudes of the ΔH° and TΔS° terms. It is important to recognize that a positive value of ΔG° for a reaction does not mean that no products will form if the reactants in their standard states are mixed; it means only that at equilibrium the concentrations of the products will be less than the concentrations of the reactants.

A positive ΔG° means that the equilibrium constant is less than 1.

Example 2.7.1

Calculate the standard free-energy change (ΔG^o) at 25°C for the reaction

$$\mathrm{H_2\,(g) + O_2\,(g)} \rightleftharpoons \mathrm{H_2O_2\,(l)} onumber \tag{2.7.11}$$

At 25°C, the standard enthalpy change (ΔH°) is –187.78 kJ/mol, and the absolute entropies of the products and reactants are:

- S°(H_2O_2) = 109.6 J/(mol•K),
- S°(O_2) = 205.2 J/(mol•K), and
- S°(H_2) = 130.7 J/(mol•K).

Is the reaction spontaneous as written?

Given: balanced chemical equation, ΔH° and S° for reactants and products

Asked for: spontaneity of reaction as written

Strategy:

A. Calculate ΔS° from the absolute molar entropy values given.
B. Use Equation 2.7.10, the calculated value of ΔS°, and other data given to calculate ΔG° for the reaction. Use the value of ΔG° to determine whether the reaction is spontaneous as written.

SOLUTION

A To calculate ΔG° for the reaction, we need to know ΔH^o, ΔS^o, and T. We are given ΔH^o, and we know that T = 298.15 K. We can calculate ΔS° from the absolute molar entropy values provided using the “products minus reactants” rule:

$$\begin{aligned}\Delta S^\circ &= S^\circ(\mathrm{H_2O_2}) - [S^\circ(\mathrm{O_2}) + S^\circ(\mathrm{H_2})] onumber \\ &= [1\ \mathrm{mol\ H_2O_2} \times 109.6\ \mathrm{J/(mol \cdot K)}] onumber \\ &\quad - \{[1\ \mathrm{mol\ H_2} \times 130.7\ \mathrm{J/(mol \cdot K)}] + [1\ \mathrm{mol\ O_2} \times 205.2\ \mathrm{J/(mol \cdot K)}]\}\ onumber \\ &= -226.3\ \mathrm{J/K\ (per\ mole\ of\ H_2O_2)}\end{aligned}$$

As we might expect for a reaction in which 2 mol of gas is converted to 1 mol of a much more ordered liquid, ΔS^o is very negative for this reaction.

B Substituting the appropriate quantities into Equation 2.7.10,

$$\begin{aligned}\Delta G^\circ &= \Delta H^\circ - T\Delta S^\circ \\ &= -187.78\ \text{kJ/mol} - (298.15\ \text{K})[-226.3\ \text{J/(mol}\cdot\text{K)} \times 1\ \text{kJ/1000 J}]onumber \\ &= -187.78\ \text{kJ/mol} + 67.47\ \text{kJ/mol} \\ &= -120.31\ \text{kJ/mol}onumber\end{aligned}$$

The negative value of ΔG^o indicates that the reaction is spontaneous as written. Because ΔS^o and ΔH^o for this reaction have the same sign, the sign of ΔG^o depends on the relative magnitudes of the ΔH^o and $T\Delta S^o$ terms. In this particular case, the enthalpy term dominates, indicating that the strength of the bonds formed in the product more than compensates for the unfavorable ΔS^o term and for the energy needed to break bonds in the reactants.

Exercise 2.7.1

Calculate the standard free-energy change (ΔG^o) at 25°C for the reaction

$$2H_2(g) + N_2(g) \rightleftharpoons N_2H_4(l)onumber. \tag{2.7.12}$$

Is the reaction spontaneous as written at 25°C?

Hint

At 25°C, the standard enthalpy change (ΔH^o) is 50.6 kJ/mol, and the absolute entropies of the products and reactants are

- S°(N_2H_4) = 121.2 J/(mol•K),
- S°(N_2) = 191.6 J/(mol•K), and
- S°(H_2) = 130.7 J/(mol•K).

Answer

149.5 kJ/mol

no, not spontaneous

Video Solution

Tabulated values of standard free energies of formation allow chemists to calculate the values of ΔG° for a wide variety of chemical reactions rather than having to measure them in the laboratory. The standard free energy of formation (ΔG_f°)of a compound is the change in free energy that occurs when 1 mol of a substance in its standard state is formed from the component elements in their standard states. By definition, the standard free energy of formation of an element in its standard state is zero at 298.15 K. One mole of Cl_2 gas at 298.15 K, for example, has $\Delta G_f^\circ = 0$. The standard free energy of formation of a compound can be calculated from the standard enthalpy of formation (ΔH°_f) and the standard entropy of formation (ΔS°_f) using the definition of free energy:

$$\Delta G_f^o = \Delta H_f^o - T\Delta S_f^o \tag{2.7.13}$$

Using standard free energies of formation to calculate the standard free energy of a reaction is analogous to calculating standard enthalpy changes from standard enthalpies of formation using the familiar “products minus reactants” rule:

$$\Delta G_{rxn}^o = \sum m\Delta G_f^o(products) - \sum n\Delta_f^o(reactants) \tag{2.7.14}$$

where m and n are the stoichiometric coefficients of each product and reactant in the balanced chemical equation. A very large negative ΔG° indicates a strong tendency for products to form spontaneously from reactants; it does not, however, necessarily indicate that the reaction will occur rapidly. To make this determination, we need to evaluate the kinetics of the reaction.

The "Products minus Reactants" Rule

The ΔG^o of a reaction can be calculated from tabulated ΔG°_f values (Table T1) using the “products minus reactants” rule.

Example 2.7.2

Calculate ΔG° for the reaction of isooctane with oxygen gas to give carbon dioxide and water (described in Example 7). Use the following data:

- $\Delta G°_f$(isooctane) = –353.2 kJ/mol,
- $\Delta G°_f(CO_2)$ = –394.4 kJ/mol, and
- $\Delta G°_f(H_2O)$ = –237.1 kJ/mol. Is the reaction spontaneous as written?

Given: balanced chemical equation and values of $\Delta G°_f$ for isooctane, CO_2, and H_2O

Asked for: spontaneity of reaction as written

Strategy:

Use the “products minus reactants” rule to obtain ΔG°_{rxn}, remembering that $\Delta G°_f$ for an element in its standard state is zero. From the calculated value, determine whether the reaction is spontaneous as written.

SOLUTION

The balanced chemical equation for the reaction is as follows:

$$\mathrm{C_8H_{18}\,(l)} + \tfrac{25}{2}\,\mathrm{O_2\,(g)} \;\rightarrow 8\,\mathrm{CO_2\,(g)} + 9\,\mathrm{H_2O\,(l)} onumber \tag{2.7.15}$$

We are given ΔG°_f values for all the products and reactants except O_2(g). Because oxygen gas is an element in its standard state, ΔG°_f (O_2) is zero. Using the “products minus reactants” rule,

$$\begin{aligned}\Delta G^\circ &= [8\Delta G^\circ_f(\mathrm{CO_2}) + 9\Delta G^\circ_f(\mathrm{H_2O})] - \left[1\Delta G^\circ_f(\mathrm{C_8H_{18}}) + \frac{25}{2}\Delta G^\circ_f(\mathrm{O_2})\right] onumber \\ &= [(8\text{ mol})(-394.4\text{ kJ/mol}) + (9\text{ mol})(-237.1\text{ kJ/mol})] onumber \\ &\quad - \left[(1\text{ mol})(-353.2\text{ kJ/mol}) + \left(\frac{25}{2}\text{ mol}\right)(0\text{ kJ/mol})\right] onumber \\ &= -4935.9\text{ kJ (per mol of }\mathrm{C_8H_{18}}) onumber\end{aligned}$$

Because ΔG° is a large negative number, there is a strong tendency for the spontaneous formation of products from reactants (though not necessarily at a rapid rate). Also notice that the magnitude of ΔG° is largely determined by the ΔG°_f of the stable products: water and carbon dioxide.

Exercise 2.7.2

Calculate ΔG° for the reaction of benzene with hydrogen gas to give cyclohexane using the following data

- ΔG°_f(benzene) = 124.5 kJ/mol
- ΔG°_f (cyclohexane) = 217.3 kJ/mol.

Is the reaction spontaneous as written?

Answer

92.8 kJ; no

Video Solution

Calculated values of ΔG° are extremely useful in predicting whether a reaction will occur spontaneously if the reactants and products are mixed under standard conditions. We should note, however, that very few reactions are actually carried out under standard conditions, and calculated values of ΔG° may not tell us whether a given reaction will occur spontaneously under nonstandard conditions. What determines whether a reaction will occur spontaneously is the free-energy change (ΔG) under the actual experimental conditions, which are usually different from ΔG°. If the ΔH and TΔS terms for a reaction have the same sign, for example, then it may be possible to reverse the sign of ΔG by changing the temperature, thereby converting a reaction that is not thermodynamically spontaneous, having $K_{eq} < 1$, to one that is, having a $K_{eq} > 1$, or vice versa. Because ΔH and ΔS usually do not vary greatly with temperature in the absence of a phase change, we can use tabulated values of ΔH° and ΔS° to calculate ΔG° at various temperatures, as long as no phase change occurs over the temperature range being considered.

In the absence of a phase change, neither ΔH nor ΔS vary greatly with temperature.

Example 2.7.3

Calculate (a) ΔG° and (b) $\Delta G_{300°C}$ for the reaction $N_2(g)+3H_2(g)⇌2NH_3(g)$, assuming that ΔH and ΔS do not change between 25°C and 300°C. Use these data:

- $S°(N_2)$ = 191.6 J/(mol•K),
- $S°(H_2)$ = 130.7 J/(mol•K),
- $S°(NH_3)$ = 192.8 J/(mol•K), and
- ΔH°_f (NH_3) = −45.9 kJ/mol.

Given: balanced chemical equation, temperatures, S° values, and ΔH°_f for NH_3

Asked for: ΔG° and ΔG at 300°C

Strategy:

A. Convert each temperature to kelvins. Then calculate ΔS° for the reaction. Calculate ΔH° for the reaction, recalling that ΔH°_f for any element in its standard state is zero.
B. Substitute the appropriate values into Equation 2.7.10 to obtain ΔG° for the reaction.
C. Assuming that ΔH and ΔS are independent of temperature, substitute values into Equation 2.7.2 to obtain ΔG for the reaction at 300°C.

SOLUTION

A To calculate ΔG° for the reaction using Equation 2.7.10, we must know the temperature as well as the values of ΔS° and ΔH°. At standard conditions, the temperature is 25°C, or 298 K. We can calculate ΔS° for the reaction from the absolute molar entropy values given for the reactants and the products using the “products minus reactants” rule:

$$\Delta S^\circ_{rxn} = 2S^\circ(NH_3) - [S^\circ(N_2) + 3S^\circ(H_2)] onumber \tag{2.7.16}$$
$$= [2 \text{ mol } NH_3 \times 192.8 \text{ J}/(\text{mol} \cdot \text{K})] onumber \tag{2.7.17}$$
$$- \{[1 \text{ mol } N_2 \times 191.6 \text{ J}/(\text{mol} \cdot \text{K})] + [3 \text{ mol } H_2 \times 130.7 \text{ J}/(\text{mol} \cdot \text{K})]\} onumber \tag{2.7.18}$$
$$= -198.1 \text{ J/K (per mole of } N_2) \tag{2.7.19}$$

We can also calculate ΔH° for the reaction using the “products minus reactants” rule. The value of ΔH°_f (NH_3) is given, and ΔH°_f is zero for both N_2 and H_2:

$$\Delta H^\circ_{\text{rxn}} = 2\Delta H^\circ_f(\text{NH}_3) - [\Delta H^\circ_f(\text{N}_2) + 3\Delta H^\circ_f(\text{H}_2)] onumber \quad (2.7.20)$$
$$= [2 \times (-45.9 \text{ kJ/mol})] - [(1 \times 0 \text{ kJ/mol}) + (3 \times 0 \text{ kJ/mol})] onumber \quad (2.7.21)$$
$$= -91.8 \text{ kJ(per mole of } \text{N}_2) onumber \quad (2.7.22)$$

B Inserting the appropriate values into Equation 2.7.10

$$\Delta G^\circ_{\text{rxn}} = \Delta H^\circ - T\Delta S^\circ = (-91.8 \text{ kJ}) - (298 \text{ K})(-198.1 \text{ J/K})(1 \text{ kJ}/1000 \text{ J}) = -32.7 \text{ kJ (per mole of } \text{N}_2) onumber \quad (2.7.23)$$

C To calculate ΔG for this reaction at 300°C, we assume that ΔH and ΔS are independent of temperature (i.e., $\Delta H_{300°C}$ = H° and $\Delta S_{300°C}$ = ΔS°) and insert the appropriate temperature (573 K) into Equation 2.7.2:

$$\begin{aligned} \Delta G_{300^\circ\text{C}} &= \Delta H_{300^\circ\text{C}} - (573 \text{ K})(\Delta S_{300^\circ\text{C}}) \\ &= \Delta H^\circ - (573 \text{ K})\Delta S^\circ onumber \\ &= (-91.8 \text{ kJ}) - (573 \text{ K})(-198.1 \text{ J/K})(1 \text{ kJ}/1000 \text{ J}) \\ &= 21.7 \text{ kJ (per mole of } \text{N}_2) \end{aligned}$$

In this example, changing the temperature has a major effect on the thermodynamic spontaneity of the reaction. Under standard conditions, the reaction of nitrogen and hydrogen gas to produce ammonia is thermodynamically spontaneous, but in practice, it is too slow to be useful industrially. Increasing the temperature in an attempt to make this reaction occur more rapidly also changes the thermodynamics by causing the –TΔS° term to dominate, and the reaction is no longer spontaneous at high temperatures; that is, its K_{eq} is less than one. This is a classic example of the conflict encountered in real systems between thermodynamics and kinetics, which is often unavoidable.

Exercise 2.7.3

Calculate

a. ΔG ° and
b. $\Delta G_{750°C}$

for the following reaction

$$2\,\text{NO}\,(\text{g}) + \text{O}_2\,(\text{g}) \rightleftharpoons 2\,\text{NO}_2\,(\text{g}) onumber \quad (2.7.24)$$

which is important in the formation of urban smog. Assume that ΔH and ΔS do not change between 25.0°C and 750°C and use these data:

- S°(NO) = 210.8 J/(mol•K),
- S°(O_2) = 205.2 J/(mol•K),
- S°(NO_2) = 240.1 J/(mol•K),
- ΔH°_f(NO_2) = 33.2 kJ/mol, and
- ΔH°_f (NO) = 91.3 kJ/mol.

Answer a

–72.5 kJ/mol of O_2

Answer b

33.8 kJ/mol of O_2

The effect of temperature on the spontaneity of a reaction, which is an important factor in the design of an experiment or an industrial process, depends on the sign and magnitude of both ΔH° and ΔS°. The temperature at which a given reaction is at equilibrium can be calculated by setting ΔG° = 0 in Equation 2.7.10, as illustrated in Example 2.7.4.

Example 2.7.4

As you saw in Example 2.7.3, the reaction of nitrogen and hydrogen gas to produce ammonia is one in which ΔH° and ΔS° are both negative. Such reactions are predicted to be thermodynamically spontaneous at low temperatures but nonspontaneous at high temperatures. Use the data in Example 9.5.3 to calculate the temperature at which this reaction changes from spontaneous to nonspontaneous, assuming that ΔH° and ΔS° are independent of temperature.

Given: ΔH° and ΔS°

Asked for: temperature at which reaction changes from spontaneous to nonspontaneous

Strategy:

Set ΔG° equal to zero in Equation 2.7.10 and solve for T, the temperature at which the reaction becomes nonspontaneous.

SOLUTION

In Example 2.7.3, we calculated that ΔH° is –91.8 kJ/mol of N_2 and ΔS° is –198.1 J/K per mole of N_2, corresponding to ΔG° = –32.7 kJ/mol of N_2 at 25°C. Thus the reaction is indeed spontaneous at low temperatures, as expected based on the signs of ΔH° and ΔS°. The temperature at which the reaction becomes nonspontaneous is found by setting ΔG° equal to zero and rearranging Equation 2.7.10 to solve for T:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = 0$$

$$\Delta H^\circ = T\Delta S^\circ$$

$$T = \frac{\Delta H^\circ}{\Delta S^\circ} = \frac{(-91.8\ \text{kJ})(1000\ \text{J/kJ})}{-198.1\ \text{J/K}} = 463\ \text{K}$$

This is a case in which a chemical engineer is severely limited by thermodynamics. Any attempt to increase the rate of reaction of nitrogen with hydrogen by increasing the temperature will cause reactants to be favored over products above 463 K.

Exercise 2.7.4

As you found in the exercise in Example 2.7.3, ΔH° and ΔS° are both negative for the reaction of nitric oxide and oxygen to form nitrogen dioxide. Use those data to calculate the temperature at which this reaction changes from spontaneous to nonspontaneous.

Answer

792.6 K

Video Solution

Summary

- The change in Gibbs free energy, which is based solely on changes in state functions, is the criterion for predicting the spontaneity of a reaction.
- Free-energy change:

$$\Delta G = \Delta H - T\Delta Sonumber \tag{2.7.25}$$

- Standard free-energy change:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ onumber \tag{2.7.26}$$

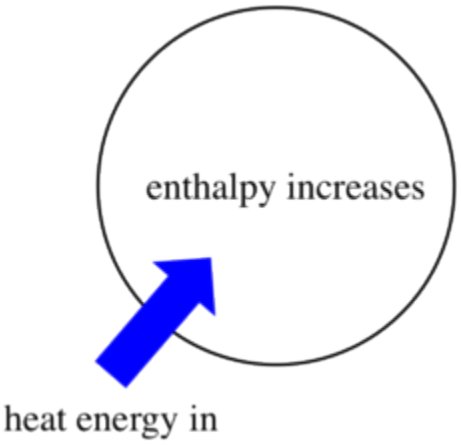
We can predict whether a reaction will occur spontaneously by combining the entropy, enthalpy, and temperature of a system in

a new state function called Gibbs free energy (G). The change in free energy (ΔG) is the difference between the heat released during a process and the heat released for the same process occurring in a reversible manner. If a system is at equilibrium, $\Delta G = 0$. If the process is spontaneous, $\Delta G < 0$. If the process is not spontaneous as written but is spontaneous in the reverse direction, $\Delta G > 0$. At constant temperature and pressure, ΔG is equal to the maximum amount of work a system can perform on its surroundings while undergoing a spontaneous change. The standard free-energy change (ΔG°) is the change in free energy when one substance or a set of substances in their standard states is converted to one or more other substances, also in their standard states. The standard free energy of formation (ΔG°_f), is the change in free energy that occurs when 1 mol of a substance in its standard state is formed from the component elements in their standard states. Tabulated values of standard free energies of formation are used to calculate ΔG° for a reaction.

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2.8: Enthalpy Changes in Reactions

Thermodynamics is the study of the relationship between heat (or energy) and work. Enthalpy is a central factor in thermodynamics. It is the heat content of a system. The heat that passes into or out of the system during a reaction is the enthalpy change. Whether the enthalpy of the system increases (i.e. when energy is added) or decreases (because energy is given off) is a crucial factor that determines whether a reaction can happen.





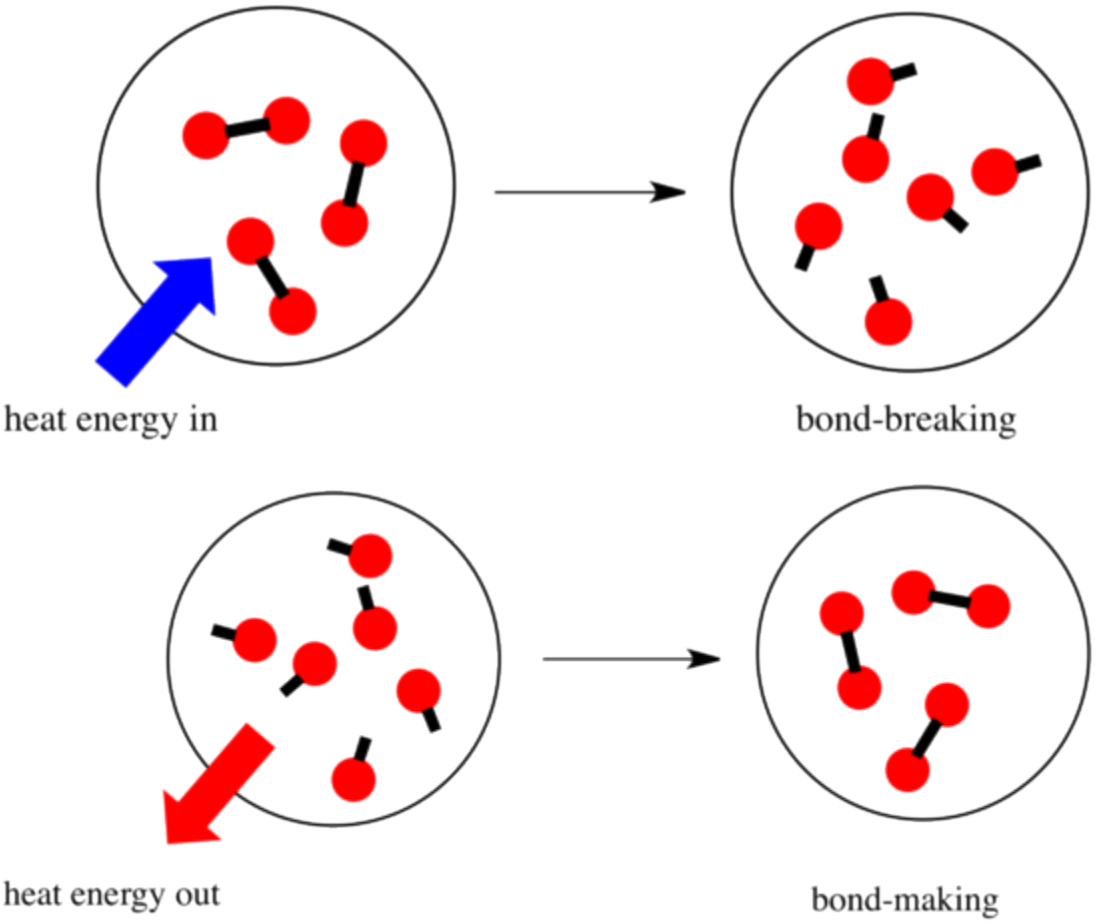
Sometimes, we call the energy of the molecules undergoing change the "internal enthalpy". Sometimes, we call it the "enthalpy of the system." These two phrases refer to the same thing. Similarly, the energy of the molecules that do not take part in the reaction is called the "*external enthalpy*" or the "*enthalpy of the surroundings*".

Roughly speaking, the energy changes that we looked at in the introduction to thermodynamics were changes in enthalpy. We will see in the next section that there is another energetic factor, entropy, that we also need to consider in reactions. For now, we will just look at enthalpy.

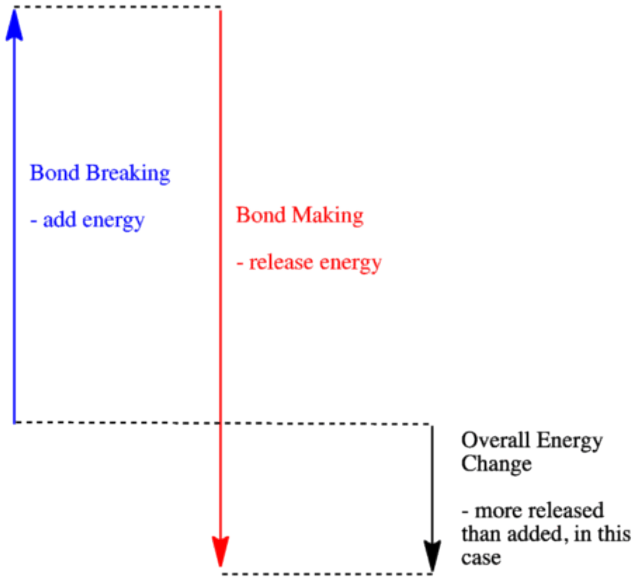
- Enthalpy is the heat content of a system.
- The enthalpy change of a reaction is roughly equivalent to the amount of energy lost or gained during the reaction.
- A reaction is favored if the enthalpy of the system decreases over the reaction.

That last statement is a lot like the description of energetics on the previous page. If a system undergoes a reaction and gives off energy, its own energy content decreases. It has less energy left over if it gave some away. Why does the energy of a set of molecules change when a reaction occurs? To answer that, we need to think about what happens in a chemical reaction.

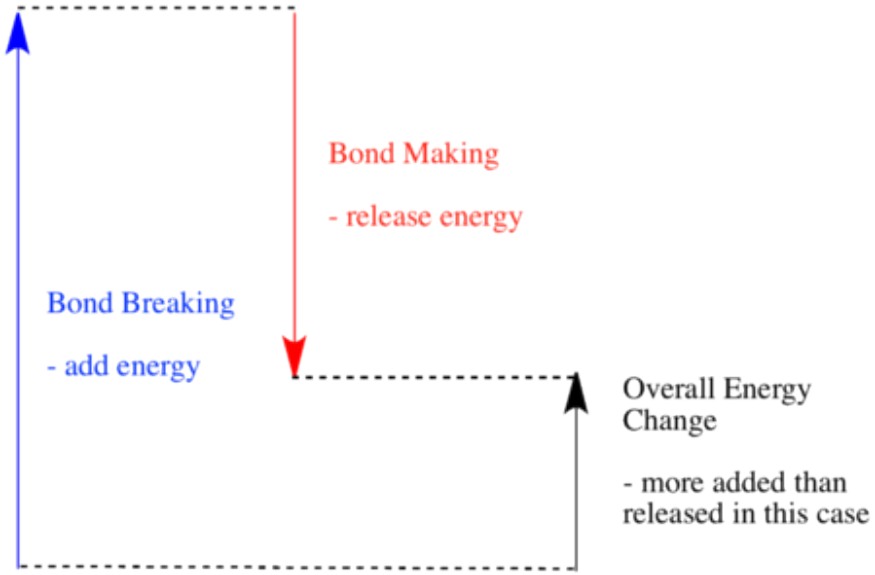
In a reaction, there is a change in chemical bonding. Some of the bonds in the reactants are broken, and new bonds are made to form the products. It costs energy to break bonds, but energy is released when new bonds are made.



Whether a reaction is able to go forward may depend on the balance between these bond-making and bond-breaking steps.



- A reaction is exothermic if more energy is released by formation of new bonds than is consumed by breaking old bonds.
- A reaction is exothermic if weaker bonds are traded for stronger ones.
- A reaction is endothermic if bond-breaking costs more energy than what is provided in bond-making.



Bond energies (the amount of energy that must be added in order to break a bond) are an important factor in determining whether a reaction will occur. Bond strengths are not always easy to predict, because the strength of a bond depends on a number of factors. However, lots of people have done lots of work measuring bond strengths, and they have collected the information in tables, so if you need to know how strong a bond is, you can just look up the information you need.

Bond	Bond Energy (kcal/mol)	Bond	Bond Energy (kcal/mol)
H-H	104	O-H	111
C-C	83	C-H	99
O=O	119	N-H	93
N=N	226	C=O	180

For example, suppose you wanted to know whether the combustion of methane were an exothermic or endothermic reaction. I am going to guess that it's exothermic, because this reaction (and others like it) is used to provide heat for lots of homes by burning natural gas in furnaces.

The "combustion" of methane means that it is burned in air, so that it reacts with oxygen. The products of burning hydrocarbons are mostly carbon dioxide and water. The carbon atom in methane (CH_4) gets incorporated into a carbon dioxide molecule. The hydrogen atoms get incorporated into water molecules. There are four hydrogen atoms in methane, so that's enough to make two molecules of H_2O.

- Four C-H bonds must be broken in the combustion of methane.
- Four new O-H bonds are made when the hydrogens from methane are added into new water molecules.
- Two new C=O bonds are made when the carbon from methane is added into a CO_2 molecule.

The other piece of the puzzle is the oxygen source for the reaction. Oxygen is present in the atmosphere mostly as O_2. Because we need two oxygen atoms in the CO_2 molecule and two more oxygen atoms for the two water molecules, we need a total of four oxygen atoms for the reaction, which could be provided by two O_2 molecules.

- Two O=O bonds must be broken to provide the oxygen atoms for the products.

Altogether, that's four C-H and two O=O bonds broken, plus two C=O and four O-H bonds made. That's 4 x 99 kcal/mol for the C-H bonds and 2 x 119 kcal/mol for the O=O bonds, a total of 634 kJ/mol added. The reaction releases 2 x 180 kcal/mol for the C=O bonds and 4 x 111 kcla/mol for the OH bonds, totaling 804 kcal/mol. Overall, there is 170 kcal/mol more released than is consumed.

That means the reaction is exothermic, so it produces heat. It's probably a good way to heat your home.

Problem TD2.1.

Compare the combustion of ethane to the combustion of methane.

1. Write a reaction for the combustion of ethane, CH_3CH_3, to carbon dioxide and water.
2. How many carbon dioxide molecules would be produced from one molecule of ethane?
3. How many water molecules would be produced from one molecule of ethane?
4. How many oxygen molecules would be needed to provide oxygen atoms to accomplish the steps in questions (b) and (c)?
5. How much energy is consumed / produced by the reaction? Compare this result to the one for methane.

Problem TD2.2.

The Haber-Bosch process is used to make ammonia for fertilizer. It employs the reaction of hydrogen gas (H_2) with atmospheric nitrogen (N_2) in a 3:1 ratio to produce ammonia (NH_3).

1. Write a reaction for the Haber-Bosch process.
2. How many ammonia molecules would be produced from one molecule of nitrogen?
3. How much energy is consumed / produced by the reaction?

Contributors

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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2.9: Entropy Changes in Chemical Reactions

Learning Objectives

- To calculate entropy changes for a chemical reaction

We have seen that the energy given off (or absorbed) by a reaction, and monitored by noting the change in temperature of the surroundings, can be used to determine the enthalpy of a reaction (e.g. by using a calorimeter). Tragically, there is no comparable easy way to experimentally measure the change in entropy for a reaction. Suppose we know that energy is going into a system (or coming out of it), and yet we do not observe any change in temperature. What is going on in such a situation? Changes in internal energy, that are not accompanied by a temperature change, might reflect changes in the entropy of the system.

For example, consider water at °0C at 1 atm pressure

- This is the temperature and pressure condition where liquid and solid phases of water are in equilibrium (also known as the melting point of ice)

$$\mathrm{H_2O\,(s)\ \rightarrow H_2O\,(l)} \tag{2.9.1}$$

- At such a temperature and pressure we have a situation (by definition) where we have some ice and some liquid water
- If a small amount of energy is input into the system the equilibrium will shift slightly to the right (i.e. in favor of the liquid state)
- Likewise if a small amount of energy is withdrawn from the system, the equilibrium will shift to the left (more ice)

> However, in both of the above situations, the energy change is not accompanied by a change in temperature (the temperature will not change until we no longer have an equilibrium condition; i.e. all the ice has melted or all the liquid has frozen)

Since the quantitative term that relates the amount of heat energy input vs. the rise in temperature is the heat capacity, it would seem that in some way, information about the heat capacity (and how it changes with temperature) would allow us to determine the entropy change in a system. In fact, values for the "standard molar entropy" of a substance have units of J/mol K, the same units as for molar heat capacity.

Standard Molar Entropy, S^0

The entropy of a substance has an absolute value of 0 entropy at 0 K.

- **Standard molar entropies** are listed for a reference temperature (like 298 K) and 1 atm pressure (i.e. the entropy of a pure substance at 298 K and 1 atm pressure). A table of standard molar entropies at 0K would be pretty useless because it would be 0 for every substance (duh!) Standard molar entropy values are listed for a variety of substances in Table T2.
- When comparing standard molar entropies for a substance that is either a solid, liquid or gas at 298 K and 1 atm pressure, the gas will have more entropy than the liquid, and the liquid will have more entropy than the solid
- Unlike *enthalpies of formation*, standard molar entropies of elements are not 0.

The entropy change in a chemical reaction is given by the sum of the entropies of the products minus the sum of the entropies of the reactants. As with other calculations related to balanced equations, the coefficients of each component must be taken into account in the entropy calculation (the *n*, and *m*, terms below are there to indicate that the coefficients must be accounted for):

$$\Delta S^0 = \sum_n nS^0(products) - \sum_m mS^0(reactants) \tag{2.9.2}$$

Example 2.9.1: Haber Process

Calculate the change in entropy associated with the Haber process for the production of ammonia from nitrogen and hydrogen gas.

$$\mathrm{N_2\,(g) + 3\,H_2\,(g)\ \rightleftharpoons\ 2\,NH_3\,(g)}$$

At 298K as a standard temperature:

- $S^0(NH_3)$ = 192.5 J/mol K
- $S^0(H_2)$ = 130.6 J/mol K
- $S^0(N_2)$ = 191.5 J/mol K

Solution

From the balanced equation we can write the equation for ΔS^0 (the change in the standard molar entropy for the reaction):

$$\Delta S^0 = 2*S^0(NH_3) - [S^0(N_2) + (3*S^0(H_2))]$$

$$\Delta S^0 = 2*192.5 - [191.5 + (3*130.6)]$$

$$\Delta S^0 = -198.3 \text{ J/mol K}$$

It would appear that the process results in a ***decrease*** in entropy - i.e. a decrease in disorder. This is expected because we are decreasing the number of gas molecules. In other words the $N_2(g)$ used to float around independently of the H_2 gas molecules. After the reaction, the two are bonded together and can't float around freely from one another. (I guess you can consider marriage as a negative entropy process!)

To calculate ΔS° for a chemical reaction from standard molar entropies, we use the familiar “products minus reactants” rule, in which the absolute entropy of each reactant and product is multiplied by its stoichiometric coefficient in the balanced chemical equation. Example 2.9.2 illustrates this procedure for the combustion of the liquid hydrocarbon isooctane (C_8H_{18}; 2,2,4-trimethylpentane).

ΔS° for a reaction can be calculated from absolute entropy values using the same “products minus reactants” rule used to calculate ΔH°.

Example 2.9.2: Combustion of Octane

Use the data in Table T2 to calculate ΔS° for the combustion reaction of liquid isooctane with O_2(g) to give CO_2(g) and H_2O(g) at 298 K.

Given: standard molar entropies, reactants, and products

Asked for: ΔS°

Strategy:

Write the balanced chemical equation for the reaction and identify the appropriate quantities in Table T2. Subtract the sum of the absolute entropies of the reactants from the sum of the absolute entropies of the products, each multiplied by their appropriate stoichiometric coefficients, to obtain ΔS° for the reaction.

Solution:

The balanced chemical equation for the complete combustion of isooctane (C_8H_{18}) is as follows:

$$\mathrm{C_8H_{18}\,(l) + \tfrac{25}{2}\,O_2\,(g) \;\rightarrow 8\,CO_2\,(g) + 9\,H_2O\,(g)}$$

We calculate ΔS° for the reaction using the "products minus reactants" rule, where m and n are the stoichiometric coefficients of each product and each reactant:

$$\begin{aligned}\Delta S^\circ_{\text{rxn}} &= \sum mS^\circ(\text{products}) - \sum nS^\circ(\text{reactants})\\ &= [8S^\circ(\mathrm{CO_2}) + 9S^\circ(\mathrm{H_2O})] - [S^\circ(\mathrm{C_8H_{18}}) + \frac{25}{2}S^\circ(\mathrm{O_2})]\\ &= \{[8\text{ mol }\mathrm{CO_2} \times 213.8\text{ J/(mol}\cdot\text{K)}] + [9\text{ mol }\mathrm{H_2O} \times 188.8\text{ J/(mol}\cdot\text{K)}]\}\\ &- \left\{[1\text{ mol }\mathrm{C_8H_{18}} \times 329.3\text{ J/(mol}\cdot\text{K)}] + \left[\frac{25}{2}\text{ mol }\mathrm{O_2} \times 205.2\text{ J/(mol}\cdot\text{K)}\right]\right\}\\ &= 515.3\text{ J/K}\end{aligned}$$

ΔS° is positive, as expected for a combustion reaction in which one large hydrocarbon molecule is converted to many molecules of gaseous products.

Exercise 2.9.2

Use the data in Table T2 to calculate ΔS° for the reaction of H_2(g) with liquid benzene (C_6H_6) to give cyclohexane (C_6H_{12}).

Answer

–361.1 J/K

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2.10: Activation Energy and Rate

Learning Objectives

- To understand why and how chemical reactions occur.

It is possible to use kinetics studies of a chemical system, such as the effect of changes in reactant concentrations, to deduce events that occur on a microscopic scale, such as collisions between individual particles. Such studies have led to the collision model of chemical kinetics, which is a useful tool for understanding the behavior of reacting chemical species. The collision model explains why chemical reactions often occur more rapidly at higher temperatures. For example, the reaction rates of many reactions that occur at room temperature approximately double with a temperature increase of only 10°C. In this section, we will use the collision model to analyze this relationship between temperature and reaction rates. Before delving into the relationship between temperature and reaction rate, we must discuss three microscopic factors that influence the observed macroscopic reaction rates.

Microscopic Factor 1: Collisional Frequency

Central to collision model is that a chemical reaction can occur only when the reactant molecules, atoms, or ions collide. Hence, the observed rate is influence by the frequency of collisions between the reactants. The **collisional frequency** is the average rate in which two reactants collide for a given system and is used to express the average number of collisions per unit of time in a defined system. While deriving the collisional frequency (Z_{AB}) between two species in a gas is straightforward, it is beyond the scope of this text and the equation for collisional frequency of A and B is the following:

$$Z_{AB} = N_A N_B \left(r_A + r_B\right)^2 \sqrt{\frac{8\pi k_B T}{\mu_{AB}}} \tag{2.10.1}$$

with

- N_A and N_B are the numbers of A and B molecules in the system, respectively
- r_a and r_b are the radii of molecule A and B, respectively
- k_B is the Boltzmann constant k_B = 1.380 x 10^{-23} Joules Kelvin
- T is the temperature in Kelvin
- μ_{AB} is calculated via $\mu_{AB} = \frac{m_A m_B}{m_A + m_B}$

The specifics of Equation 2.10.1 are not important for this conversation, but it is important to identify that Z_{AB} increases with increasing density (i.e., increasing N_A and N_B), with increasing reactant size (r_a and r_b), with increasing velocities (predicted via Kinetic Molecular Theory), and with increasing temperature (although weakly because of the square root function).

YouTube Video

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A Video Discussing Collision Theory of Kinetics: Collusion Theory of Kinetics (opens in new window) [youtu.be]

Microscopic Factor 2: Activation Energy

Previously, we discussed the kinetic molecular theory of gases, which showed that the average kinetic energy of the particles of a gas increases with increasing temperature. Because the speed of a particle is proportional to the square root of its kinetic energy, increasing the temperature will also increase the number of collisions between molecules per unit time. What the kinetic molecular theory of gases does not explain is why the reaction rate of most reactions approximately doubles with a 10°C temperature increase. This result is surprisingly large considering that a 10°C increase in the temperature of a gas from 300 K to 310 K increases the kinetic energy of the particles by only about 4%, leading to an increase in molecular speed of only about 2% and a correspondingly small increase in the number of bimolecular collisions per unit time.

The collision model of chemical kinetics explains this behavior by introducing the concept of **activation energy** (E_a). We will define this concept using the reaction of NO with ozone, which plays an important role in the depletion of ozone in the ozone layer:

$$\mathrm{NO\,(g) + O_3\,(g) \ \rightarrow NO_2\,(g) + O_2\,(g)}$$

Increasing the temperature from 200 K to 350 K causes the rate constant for this particular reaction to increase by a factor of more than 10, whereas the increase in the frequency of bimolecular collisions over this temperature range is only 30%. Thus something other than an increase in the collision rate must be affecting the reaction rate.

Experimental rate law for this reaction is

$$\mathrm{rate} = k[\mathrm{NO}][\mathrm{O_3}]$$

and is used to identify how the reaction rate (not the rate constant) vares with concentration. The rate constant, however, does vary with temperature. Figure $2.10.1$ shows a plot of the rate constant of the reaction of NO with $\mathrm{O_3}$ at various temperatures. The relationship is not linear but instead resembles the relationships seen in graphs of vapor pressure versus temperature (e.g, the Clausius-Claperyon equation). In all three cases, the shape of the plots results from a distribution of kinetic energy over a population of particles (electrons in the case of conductivity; molecules in the case of vapor pressure; and molecules, atoms, or ions in the case of reaction rates). Only a fraction of the particles have sufficient energy to overcome an energy barrier.

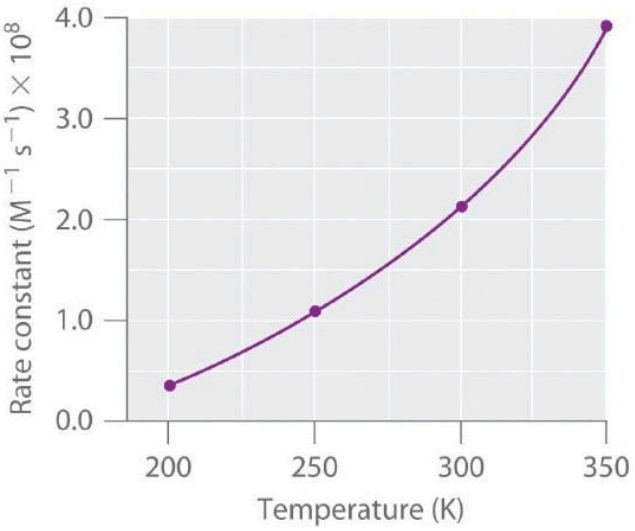


Figure $2.10.1$: Rate Constant versus Temperature for the Reaction of NO with $\mathrm{O_3}$The nonlinear shape of the curve is caused by a distribution of kinetic energy over a population of molecules. Only a fraction of the particles have enough energy to overcome an energy barrier, but as the temperature is increased, the size of that fraction increases. (CC BY-SA-NC; anonymous)

In the case of vapor pressure, particles must overcome an energy barrier to escape from the liquid phase to the gas phase. This barrier corresponds to the energy of the intermolecular forces that hold the molecules together in the liquid. In conductivity, the barrier is the energy gap between the filled and empty bands. In chemical reactions, the energy barrier corresponds to the amount of energy the particles must have to react when they collide. This energy threshold, called the **activation energy**, was first postulated in 1888 by the Swedish chemist Svante Arrhenius (1859–1927; Nobel Prize in Chemistry 1903). It is the minimum amount of energy needed for a reaction to occur. Reacting molecules must have enough energy to overcome electrostatic

repulsion, and a minimum amount of energy is required to break chemical bonds so that new ones may be formed. Molecules that collide with less than the threshold energy bounce off one another chemically unchanged, with only their direction of travel and their speed altered by the collision. Molecules that are able to overcome the energy barrier are able to react and form an arrangement of atoms called the **activated complex** or the **transition state** of the reaction. The activated complex is not a reaction intermediate; it does not last long enough to be detected readily.

> Any phenomenon that depends on the distribution of thermal energy in a population of particles has a nonlinear temperature dependence.

We can graph the energy of a reaction by plotting the potential energy of the system as the reaction progresses. Figure $2.10.2$ shows a plot for the $NO–O_3$ system, in which the vertical axis is potential energy and the horizontal axis is the reaction coordinate, which indicates the progress of the reaction with time. The activated complex is shown in brackets with an asterisk. The overall change in potential energy for the reaction (ΔE) is negative, which means that the reaction releases energy. (In this case, ΔE is –200.8 kJ/mol.) To react, however, the molecules must overcome the energy barrier to reaction (E_a is 9.6 kJ/mol). That is, 9.6 kJ/mol must be put into the system as the activation energy. Below this threshold, the particles do not have enough energy for the reaction to occur.

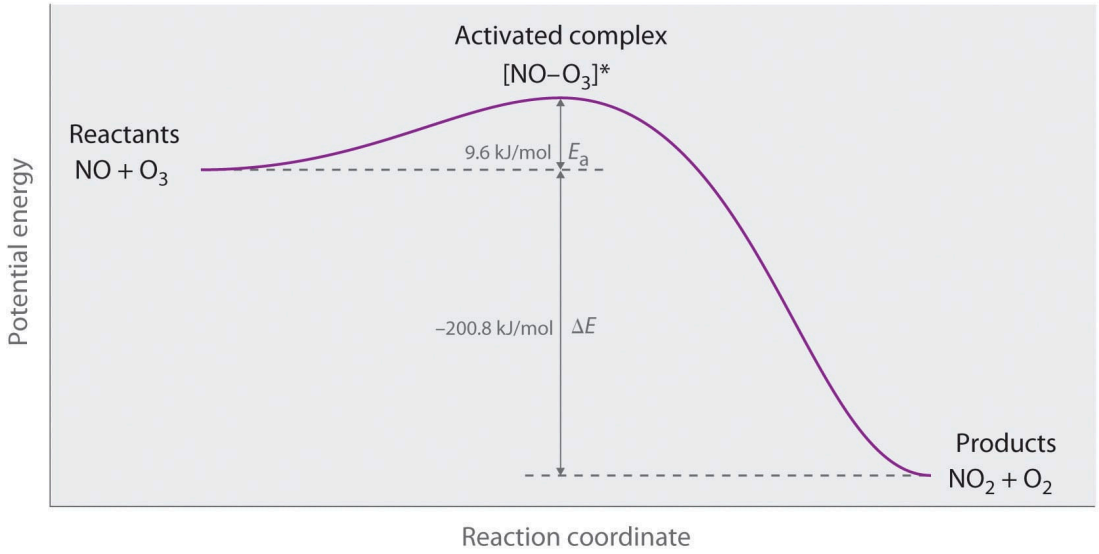


Figure $2.10.2$: Energy of the Activated Complex for the $NO–O_3$ System. The diagram shows how the energy of this system varies as the reaction proceeds from reactants to products. Note the initial increase in energy required to form the activated complex. (CC BY-SA-NC; anonymous)

Figure $2.10.3a$ illustrates the general situation in which the products have a lower potential energy than the reactants. In contrast, Figure $2.10.3b$ illustrates the case in which the products have a higher potential energy than the reactants, so the overall reaction requires an input of energy; that is, it is energetically uphill, and \(\Delta E > 0\). Although the energy changes that result from a reaction can be positive, negative, or even zero, in most cases an energy barrier must be overcome before a reaction can occur. This means that the activation energy is almost always positive; there is a class of reactions called barrierless reactions, but those are discussed elsewhere.

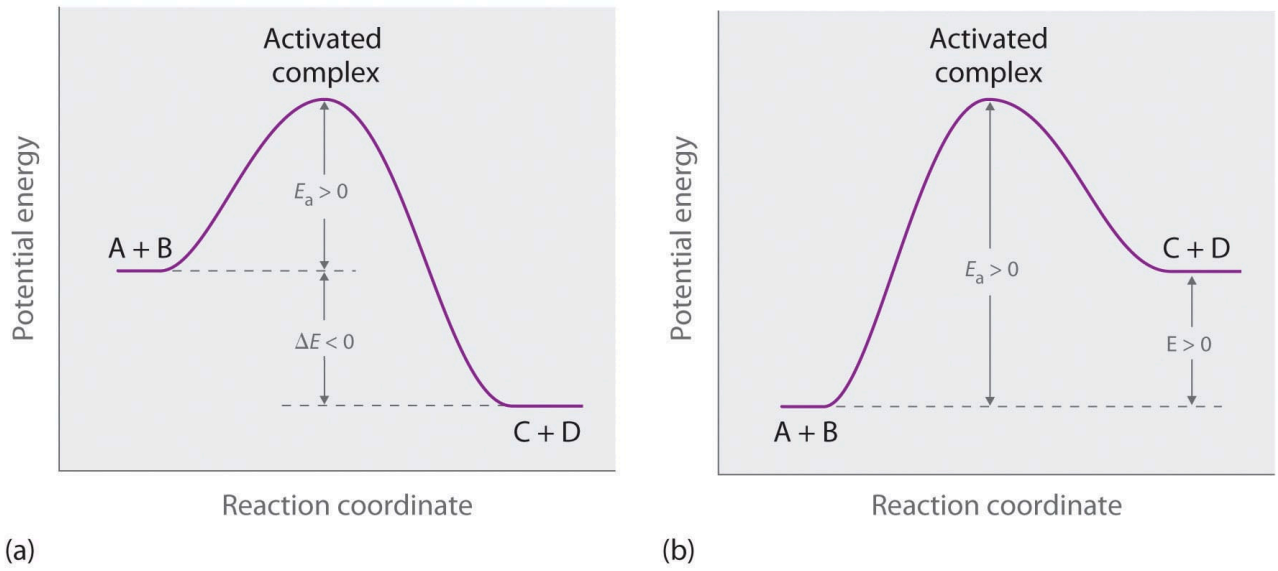


Figure 2.10.3: Differentiating between E_a and ΔE. The potential energy diagrams for a reaction with (a) ΔE < 0 and (b) ΔE > 0 illustrate the change in the potential energy of the system as reactants are converted to products. In both cases, E_a is positive. For a reaction such as the one shown in (b), E_a must be greater than ΔE. (CC BY-SA-NC; anonymous)

For similar reactions under comparable conditions, the one with the smallest E_a will occur most rapidly.

Whereas ΔE is related to the tendency of a reaction to occur spontaneously, E_a gives us information about the reaction rate and how rapidly the reaction rate changes with temperature. For two similar reactions under comparable conditions, the reaction with the smallest E_a will occur more rapidly.

Figure 2.10.4 shows both the kinetic energy distributions and a potential energy diagram for a reaction. The shaded areas show that at the lower temperature (300 K), only a small fraction of molecules collide with kinetic energy greater than E_a; however, at the higher temperature (500 K) a much larger fraction of molecules collide with kinetic energy greater than E_a. Consequently, the reaction rate is much slower at the lower temperature because only a relatively few molecules collide with enough energy to overcome the potential energy barrier.

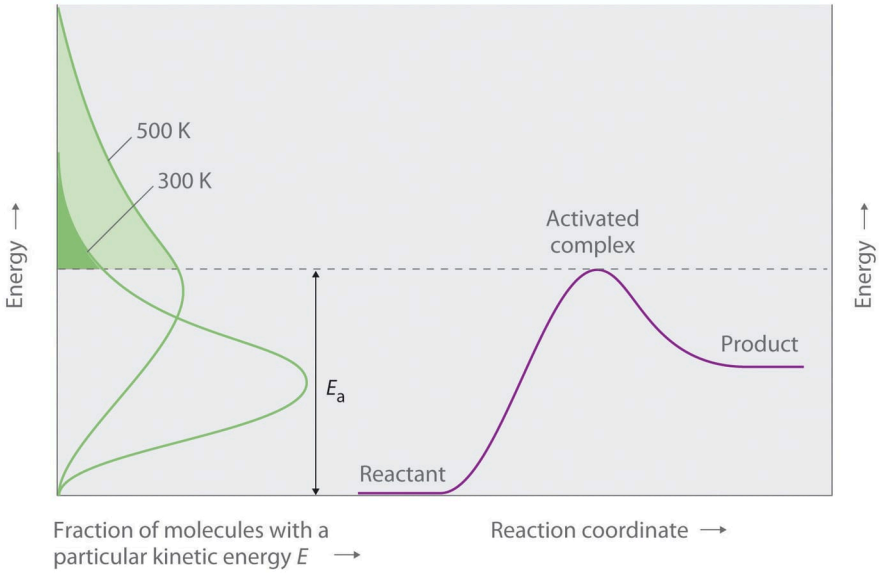


Figure 2.10.4: Surmounting the Energy Barrier to a Reaction. This chart juxtaposes the energy distributions of lower-temperature (300 K) and higher-temperature (500 K) samples of a gas against the potential energy diagram for a reaction. Only those molecules in the shaded region of the energy distribution curve have E > E_a and are therefore able to cross the energy barrier separating reactants and products. The fraction of molecules with $E > E_a$ is much greater at 500 K than at 300 K, so the reaction will occur much more rapidly at 500 K. (CC BY-SA-NC; anonymous)

Energy is on the y axis while reaction coordinate and fraction of molecules with a particular kinetic energy E are on the x axis.

YouTube Video

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Video Discussing Transition State Theory: Transition State Theory(opens in new window) [youtu.be]

Microscopic Factor 3: Sterics

Even when the energy of collisions between two reactant species is greater than E_a, most collisions do not produce a reaction. The probability of a reaction occurring depends not only on the collision energy but also on the spatial orientation of the molecules when they collide. For NO and O_3 to produce NO_2 and O_2, a terminal oxygen atom of O_3 must collide with the nitrogen atom of NO at an angle that allows O_3 to transfer an oxygen atom to NO to produce NO_2 (Figure 2.10.4). All other collisions produce no reaction. Because fewer than 1% of all possible orientations of NO and O_3 result in a reaction at kinetic energies greater than E_a, most collisions of NO and O_3 are unproductive. The fraction of orientations that result in a reaction is called the **steric factor** (ρ) and its value can range from $\rho = 0$ (no orientations of molecules result in reaction) to $\rho = 1$ (all orientations result in reaction).

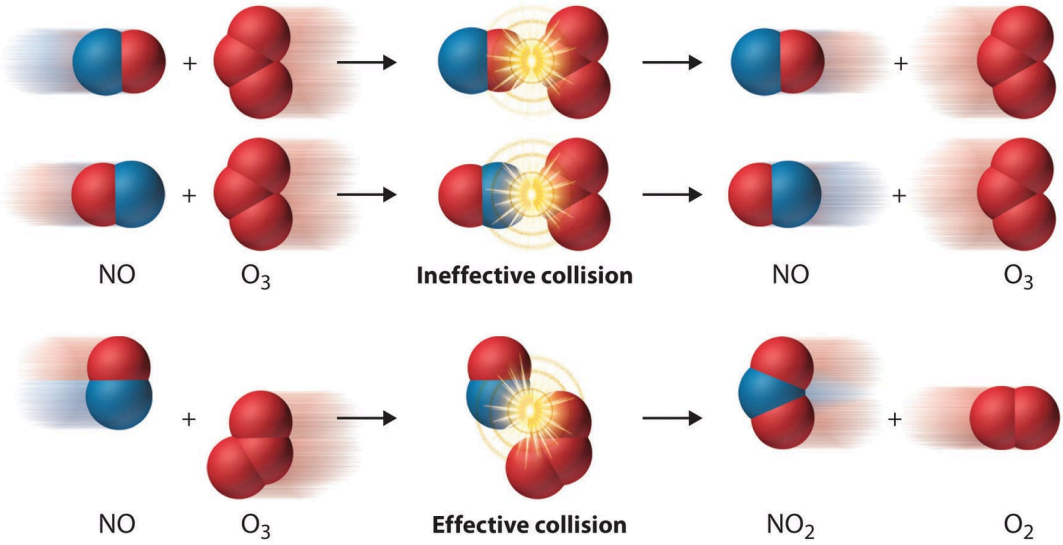


Figure 2.10.4: The Effect of Molecular Orientation on the Reaction of NO and $\mathrm{O_3}$. Most collisions of NO and $\mathrm{O_3}$ molecules occur with an incorrect orientation for a reaction to occur. Only those collisions in which the N atom of NO collides with one of the terminal O atoms of $\mathrm{O_3}$ are likely to produce $\mathrm{NO_2}$ and $\mathrm{O_2}$, even if the molecules collide with $E > E_a$. (CC BY-SA-NC; anonymous)

Macroscopic Behavior: The Arrhenius Equation

The collision model explains why most collisions between molecules do not result in a chemical reaction. For example, nitrogen and oxygen molecules in a single liter of air at room temperature and 1 atm of pressure collide about 10^{30} times per second. If every collision produced two molecules of NO, the atmosphere would have been converted to NO and then $\mathrm{NO_2}$ a long time ago. Instead, in most collisions, the molecules simply bounce off one another without reacting, much as marbles bounce off each other when they collide.

For an $A + B$ elementary reaction, all three microscopic factors discussed above that affect the reaction rate can be summarized in a single relationship:

$$\text{rate} = (\text{collision frequency}) \times (\text{steric factor}) \times (\text{fraction of collisions with } E > E_a)$$

where

$$\text{rate} = k[A][B] \tag{2.10.2}$$

Arrhenius used these relationships to arrive at an equation that relates the magnitude of the rate constant for a reaction to the temperature, the activation energy, and the constant, A, called the **frequency factor**:

$$k = Ae^{-E_a/RT} \tag{2.10.3}$$

The frequency factor is used to convert concentrations to collisions per second (scaled by the steric factor). Because the frequency of collisions depends on the temperature, A is actually not constant (Equation 2.10.1). Instead, A increases slightly with temperature as the increased kinetic energy of molecules at higher temperatures causes them to move slightly faster and thus undergo more collisions per unit time.

Equation 2.10.3 is known as the **Arrhenius equation** and summarizes the collision model of chemical kinetics, where T is the absolute temperature (in K) and R is the ideal gas constant [8.314 J/(K·mol)]. E_a indicates the sensitivity of the reaction to changes in temperature. The reaction rate with a large E_a increases rapidly with increasing temperature, whereas the reaction rate with a smaller E_a increases much more slowly with increasing temperature.

If we know the reaction rate at various temperatures, we can use the Arrhenius equation to calculate the activation energy. Taking the natural logarithm of both sides of Equation 2.10.3,

$$\ln k = \ln A + \left(-\frac{E_a}{RT}\right) \tag{2.10.4}$$

$$= \ln A + \left[\left(-\frac{E_a}{R}\right)\left(\frac{1}{T}\right)\right] \tag{2.10.5}$$

Equation 2.10.5 is the equation of a straight line,

$$y = mx + b$$

where $y = \ln k$ and $x = 1/T$. This means that a plot of $\ln k$ versus $1/T$ is a straight line with a slope of $-E_a/R$ and an intercept of $\ln A$. In fact, we need to measure the reaction rate at only two temperatures to estimate E_a.

Knowing the E_a at one temperature allows us to predict the reaction rate at other temperatures. This is important in cooking and food preservation, for example, as well as in controlling industrial reactions to prevent potential disasters. The procedure for determining E_a from reaction rates measured at several temperatures is illustrated in Example 2.10.1.

YouTube Video

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A Video Discussing The Arrhenius Equation: The Arrhenius Equation(opens in new window) [youtu.be]

Example 2.10.1: Chirping Tree Crickets

Many people believe that the rate of a tree cricket's chirping is related to temperature. To see whether this is true, biologists have carried out accurate measurements of the rate of tree cricket chirping (f) as a function of temperature (T). Use the data in the following table, along with the graph of ln[chirping rate] versus $1/T$ to calculate E_a for the biochemical reaction that controls cricket chirping. Then predict the chirping rate on a very hot evening, when the temperature is 308 K (35°C, or 95°F).

Chirping Tree Crickets Frequency Table

Frequency (f; chirps/min)	ln f	T (K)	1/T (K)
200	5.30	299	3.34×10^{-3}
179	5.19	298	3.36×10^{-3}
158	5.06	296	3.38×10^{-3}
141	4.95	294	3.40×10^{-3}
126	4.84	293	3.41×10^{-3}
112	4.72	292	3.42×10^{-3}
100	4.61	290	3.45×10^{-3}
89	4.49	289	3.46×10^{-3}
79	4.37	287	3.48×10^{-3}

Given: chirping rate at various temperatures

Asked for: activation energy and chirping rate at specified temperature

Strategy:

A. From the plot of $\ln f$ versus $1/T$, calculate the slope of the line ($-E_a/R$) and then solve for the activation energy.
B. Express Equation 2.10.5 in terms of k_1 and T_1 and then in terms of k_2 and T_2.
C. Subtract the two equations; rearrange the result to describe k_2/k_1 in terms of T_2 and T_1.
D. Using measured data from the table, solve the equation to obtain the ratio k_2/k_1. Using the value listed in the table for k_1, solve for k_2.

Solution

A If cricket chirping is controlled by a reaction that obeys the Arrhenius equation, then a plot of $\ln f$ versus $1/T$ should give a straight line (Figure 2.10.6).

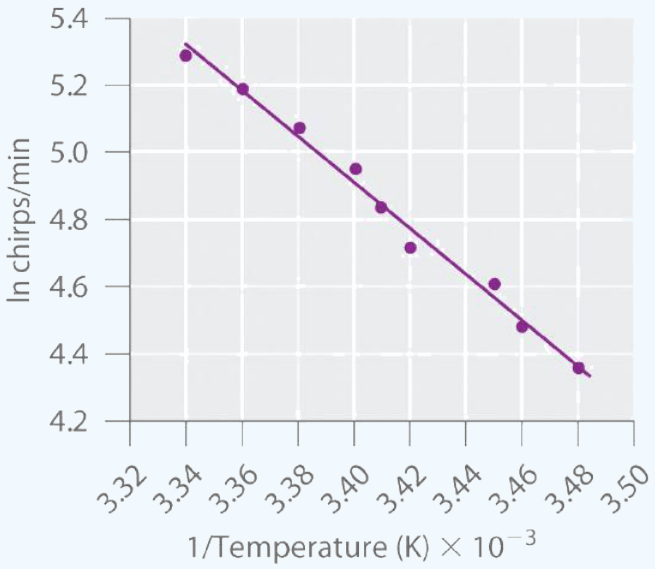


Figure 2.10.6: Graphical Determination of E_a for Tree Cricket Chirping. When the natural logarithm of the rate of tree cricket chirping is plotted versus 1/T, a straight line results. The slope of the line suggests that the chirping rate is controlled by a single reaction with an E_a of 55 kJ/mol. (CC BY-SA-NC; anonymous)

Also, the slope of the plot of $\ln f$ versus $1/T$ should be equal to $-E_a/R$. We can use the two endpoints in Figure 2.10.6 to estimate the slope:

$$\begin{aligned}\text{slope} &= \frac{\Delta \ln f}{\Delta(1/T)} \\ &= \frac{5.30 - 4.37}{3.34 \times 10^{-3}\ \text{K}^{-1} - 3.48 \times 10^{-3}\ \text{K}^{-1}} \\ &= \frac{0.93}{-0.14 \times 10^{-3}\ \text{K}^{-1}} \\ &= -6.6 \times 10^{3}\ \text{K}\end{aligned}$$

A computer best-fit line through all the points has a slope of –6.67 × 10^3 K, so our estimate is very close. We now use it to solve for the activation energy:

$$\begin{aligned}E_\text{a} &= -(\text{slope})(R) \\ &= -(-6.6 \times 10^{3}\ \text{K})\left(\frac{8.314\ \text{J}}{\text{K} \cdot \text{mol}}\right)\left(\frac{1\ \text{KJ}}{1000\ \text{J}}\right) \\ &= \frac{55\ \text{kJ}}{\text{mol}}\end{aligned}$$

B If the activation energy of a reaction and the rate constant at one temperature are known, then we can calculate the reaction rate at any other temperature. We can use Equation 2.10.5 to express the known rate constant (k_1) at the first temperature (T_1) as follows:

$$\ln k_1 = \ln A - \frac{E_a}{RT_1}$$

Similarly, we can express the unknown rate constant (k_2) at the second temperature (T_2) as follows:

$$\ln k_2 = \ln A - \frac{E_a}{RT_2}$$

C These two equations contain four known quantities (E_a, T_1, T_2, and k_1) and two unknowns (A and k_2). We can eliminate A by subtracting the first equation from the second:

$$\begin{aligned} \ln k_2 - \ln k_1 &= \left(\ln A - \frac{E_a}{RT_2}\right) - \left(\ln A - \frac{E_a}{RT_1}\right) \\ &= -\frac{E_a}{RT_2} + \frac{E_a}{RT_1} \end{aligned}$$

Then

$$\ln \frac{k_2}{k_1} = \frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

D To obtain the best prediction of chirping rate at 308 K (T_2), we try to choose for T_1 and k_1 the measured rate constant and corresponding temperature in the data table that is closest to the best-fit line in the graph. Choosing data for T_1 = 296 K, where f = 158, and using the E_a calculated previously,

$$\begin{aligned} \ln \frac{k_{T_2}}{k_{T_1}} &= \frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \\ &= \frac{55\ \text{kJ/mol}}{8.314\ \text{J/(K}\cdot\text{mol)}}\left(\frac{1000\ \text{J}}{1\ \text{kJ}}\right)\left(\frac{1}{296\ \text{K}} - \frac{1}{308\ \text{K}}\right) \\ &= 0.87 \end{aligned}$$

Thus k_{308}/k_{296} = 2.4 and k_{308} = (2.4)(158) = 380, and the chirping rate on a night when the temperature is 308 K is predicted to be 380 chirps per minute.

Exercise 2.10.1A

The equation for the decomposition of NO_2 to NO and O_2 is second order in NO_2:

$$2\,NO_2\,(g) \longrightarrow 2\,NO\,(g) + O_2\,(g)$$

Data for the reaction rate as a function of temperature are listed in the following table. Calculate E_a for the reaction and the rate constant at 700 K.

Data for the reaction rate as a function of temperature

T (K)	k ($M^{-1}\cdot s^{-1}$)
592	522
603	755
627	1700
652	4020
656	5030

Answer available at the end of this section.

Exercise $2.10.1B$

What E_a results in a doubling of the reaction rate with a 10°C increase in temperature from 20° to 30°C?

Answer available at the end of this section.

YouTube Video

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Summary

For a chemical reaction to occur, an energy threshold must be overcome, and the reacting species must also have the correct spatial orientation. The Arrhenius equation is $k = Ae^{-E_a/RT}$. A minimum energy (activation energy,vE_a) is required for a collision between molecules to result in a chemical reaction. Plots of potential energy for a system versus the reaction coordinate show an energy barrier that must be overcome for the reaction to occur. The arrangement of atoms at the highest point of this barrier is the activated complex, or transition state, of the reaction. At a given temperature, the higher the E_a, the slower the reaction. The fraction of orientations that result in a reaction is the steric factor. The frequency factor, steric factor, and activation energy are related to the rate constant in the Arrhenius equation: $k = Ae^{-E_a/RT}$. A plot of the natural logarithm of k versus $1/T$ is a straight line with a slope of $-E_a/R$.

Answers

Exercise $2.10.1A$

E_a = 114 kJ/mol; k_{700}= 18,600 $M^{-1}{\cdot}s^{-1}$ = 1.86 × 10^4 $M^{-1}{\cdot}s^{-1}$.

Exercise $2.10.1B$

about 51 kJ/mol

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3: ACIDS, BASES, AND ARROW PUSHING

3.1: Acids and Bases - The Brønsted-Lowry Definition

3.2: Acids and Bases - The Lewis Definition

3.3: Classification of Reagents as Electrophiles and Nucleophiles. Acids and Bases

3.4: Using Curved Arrows in Polar Reaction Mechanisms

3.5: Acid Strength and pK_a

3.6: A Summary of the Factors that Determine Acid Strength

3.7: Organic Acids and Bases

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3.1: Acids and Bases - The Brønsted-Lowry Definition

Objectives

After completing this section, you should be able to

1. state the Brønsted-Lowry definition of an acid and a base.
2. identify the Brønsted-Lowry acid and base in a given acid-base reaction.
3. identify the conjugate base of an acid and identify the conjugate acid of a base.

Key Terms

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

- Brønsted-Lowry acid
- Brønsted-Lowry base
- conjugate acid
- conjugate base

Study Notes

You should already be familiar with the Brønsted-Lowry concept of acidity and the differences between strong and weak acids. You may wish to review this topic before proceeding.

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-Lowry Definition

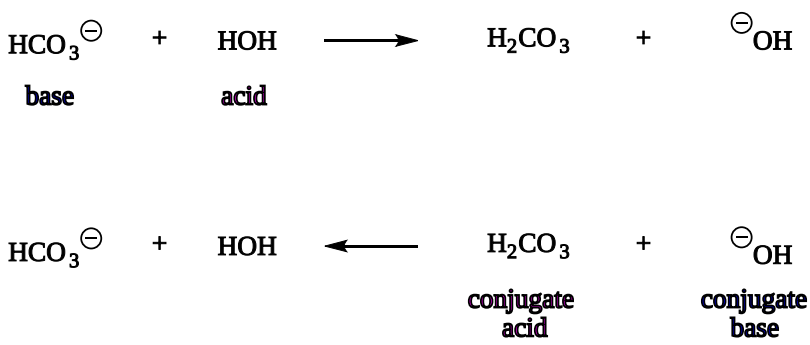
J.N. Brønsted and T.M. Lowry independently developed the theory of proton donors and proton acceptors in acid-base reactions, coincidentally in the same region and during the same year. The Arrhenius theory where acids and bases are defined by whether the molecule produces hydrogen ion or hydroxide ion when dissolved in water was too limiting, because not all chemical reactions, especially organic reactions, occur in water. The Brønsted-Lowry Theory defines an acid a proton donor, while a base is a proton acceptor. This is illustrated in the following reactions:

$$HCl + HOH \rightarrow H_3O^+ + Cl^-$$

$$HOH + NH_3 \rightarrow NH_4^+ + OH^-$$

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

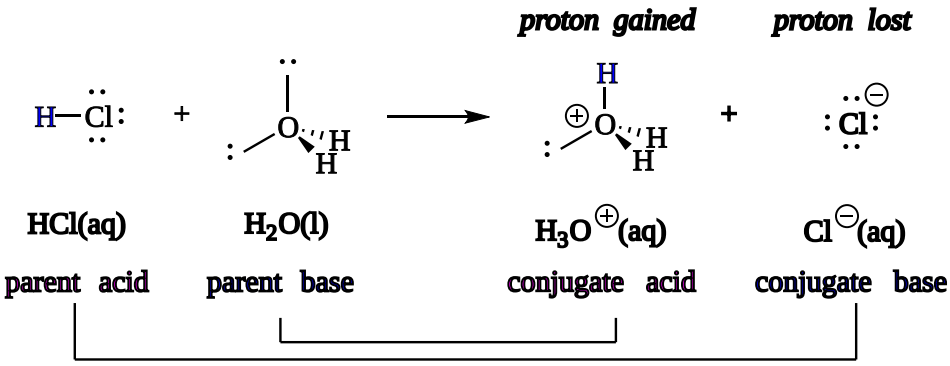
The determination of a substance as a Brønsted-Lowry acid or base can only be done by examining the reaction, since many chemicals can be either an acid or a base. For example, HOH is a base in the first reaction and an acid in the second reaction.



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, then that substance is the acid (donates hydrogen ions). If the number of hydrogens has increased, then 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 the conjugate acid and conjugate base compared to those on the left. Also note that an acid turns into a conjugate base, and the base turns into the conjugate acid after the reaction is over.

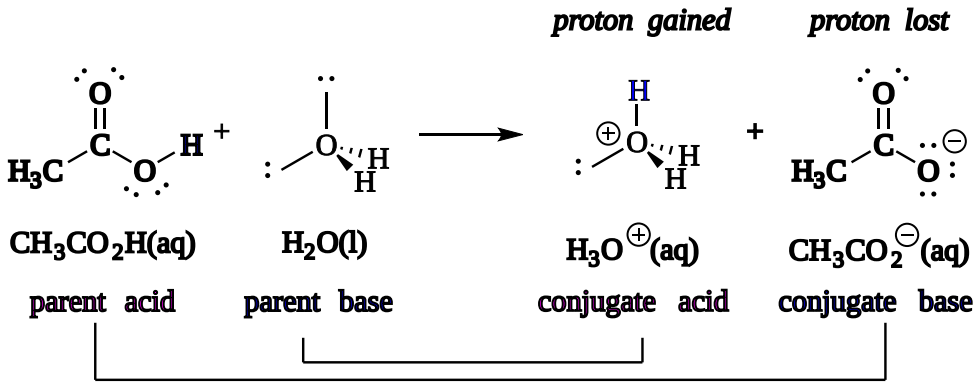
Conjugate Acid–Base PairsEdit section

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. For example, in the reaction of HCl with water shown below, 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_3O^+, forming 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.

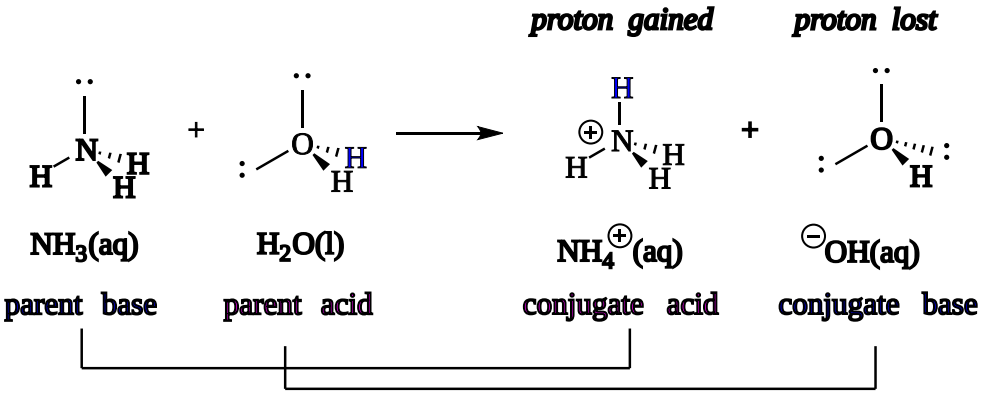


All acid–base reactions contain two conjugate acid–base pairs.

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).



In the reaction of ammonia with water to give ammonium ions and hydroxide ions, 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^-.



Example 3.1.1

Aniline ($C_6H_5NH_2$) is slightly soluble in water. It has a nitrogen atom that can accept a hydrogen ion from a water molecule just like the nitrogen atom in ammonia does. Write the chemical equation for this reaction and identify the Brønsted-Lowry acid and base.

Solution

$C_6H_5NH_2$ and H_2O are the reactants. When $C_6H_5NH_2$ accepts a proton from H_2O, it gains an extra H and a positive charge and leaves an OH^- ion behind. The reaction is as follows:

$$C_6H_5NH_2\,(aq) + H_2O(\ell) \rightleftharpoons C_6H_5NH_3{}^+\,(aq) + OH^-\,(aq)$$

Because $C_6H_5NH_2$ accepts a proton, it is the Brønsted-Lowry base. The H_2O molecule, because it donates a proton, is the Brønsted-Lowry acid.

Example 3.1.1

Identify the conjugate acid-base pairs in this equilibrium.

$$(CH_3)_3N + H_2O \rightleftharpoons (CH_3)_3NH^+ + OH^-$$

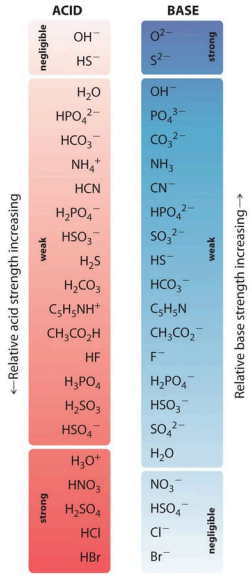
Solution

One pair is H_2O and OH^-, where H_2O has one more H^+ and is the conjugate acid, while OH^- has one less H^+ and is the conjugate base.

The other pair consists of $(CH_3)_3N$ and $(CH_3)_3NH^+$, where $(CH_3)_3NH^+$ is the conjugate acid (it has an additional proton) and $(CH_3)_3N$ is the conjugate base.

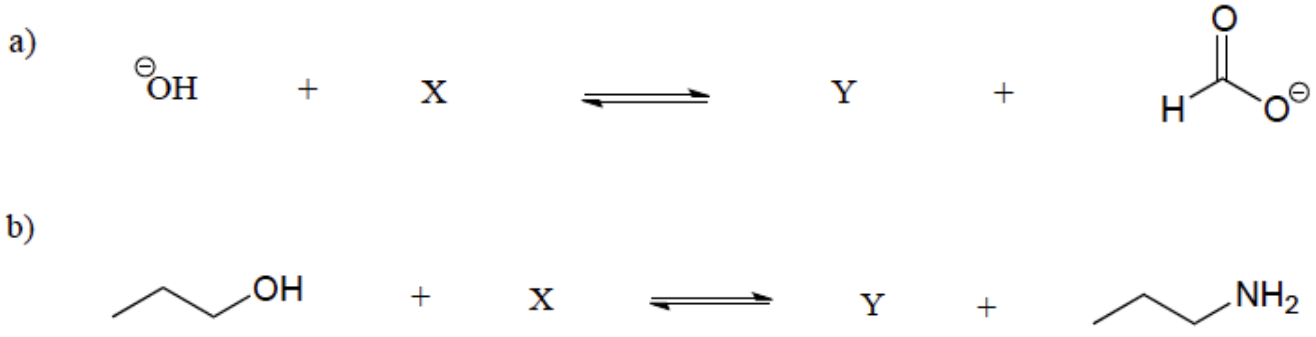
Some common conjugate acid–base pairs are shown in Figure 2.7.1. The strongest acids are at the bottom left, and the strongest bases are at the top right. The conjugate base of a strong acid is a very weak base, and, conversely, the conjugate acid of a strong base is a very weak acid.

Figure 2.7.1 *The Relative Strengths of Some Common Conjugate Acid–Base Pairs*



Exercises

1. Identify the Brønsted-Lowry acids and bases in the reactions given below.
   a. $CH3CH2O^- + H2O <=> CH3CH2OH + OH^-$
   b. $CH3CH2OH + H2SO4 <=> CH3CH2OH2 + +HSO4-$
2. Show the structures of species X and Y in the following acid-base reactions:



Answer:

1. a. acids and bases identified in ethoxide reaction with water

b. acids and bases identified in ethanol reaction with sulfuric acid

2. a)



b)



Questions

Q2.7.1

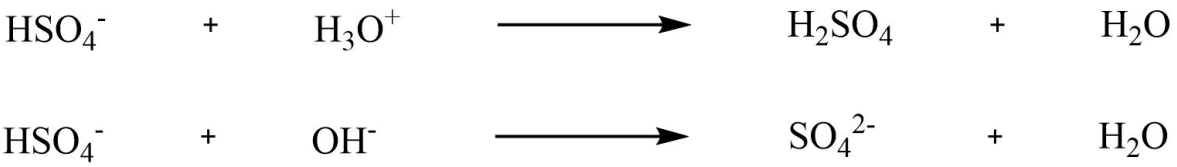
Is the following molecule a Brønsted acid or base?

HSO_4^-

Solutions

S2.7.1

It can be both, consider the following schemes:



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3.2: Acids and Bases - The Lewis Definition

Objectives

After completing this section, you should be able to

1. state the Lewis definition of an acid and a base.
2. identify a given compound as being a Lewis acid or Lewis base, given its Lewis structure or its Kekulé structure.
3. identify an organic molecule or ion in a reaction as either an electrophile or nucleophile.

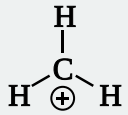
Key Terms

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

- Lewis acid
- Lewis base
- Electrophile
- Nucleophile

Study Notes

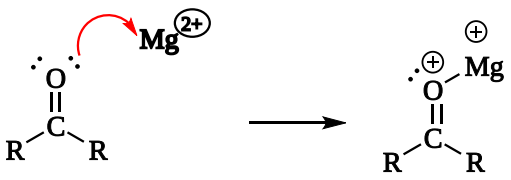
The Lewis concept of acidity and basicity will be of great use to you when you study reaction mechanisms. The realization that an ion such as



is electron deficient, and is therefore a Lewis acid, should help you understand why this ion reacts with substances which are Lewis bases (e.g., H_2O).

Introduction to Lewis Acid-Base Theory

The Brønsted acid-base theory has been used throughout the history of acid and base chemistry. However, this theory is very restrictive and focuses primarily on acids and bases acting as proton donors and acceptors. Sometimes conditions arise where the theory doesn't necessarily fit, such as in solids and gases. In 1923, G.N. Lewis from UC Berkeley proposed an alternate theory to describe acids and bases. His theory gave a generalized explanation of acids and bases based on structure and bonding. Through the use of the Lewis definition of acids and bases, chemists are now able to predict a wider variety of acid-base reactions. Lewis' theory used electrons instead of proton transfer and specifically stated that an acid is a species that accepts an electron pair while a base donates an electron pair.



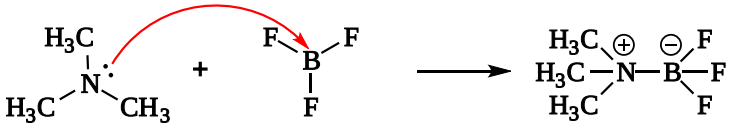
Example of Lewis base (oxygen atom from carbonyl) reacting with Lewis Acid (Mg^{2+} ion).

The reaction of a Lewis acid and a Lewis base will produce a coordinate covalent bond. A coordinate covalent bond is just a type of covalent bond in which one reactant donates both electrons to form the bond. In this case the Lewis base donates its electrons to form a bond to the Lewis acid. The resulting product is called an addition compound, or more commonly a complex. The electron-pair flow from Lewis base to Lewis acid is shown using curved arrows much like those used for resonance structures in Section 2.5. Curved arrows always mean that an electron pair moves from the atom at the tail of the arrow to the atom at the head of the arrow. In this case the lone pair on the Lewis base attacks the Lewis acid forming a bond. This new type of electron pair movement, along with those described in Section 2.5 will be used throughout this text to describe electron flow during reactions.

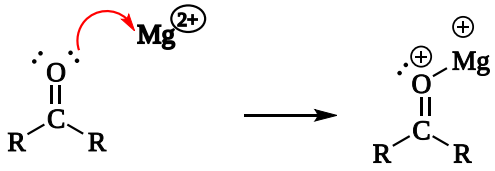
- Lewis Acid: a species that accepts an electron pair and will typically either have vacant orbitals or a polar bond involving hydrogen such that it can donate H^+ (which has an empty 1s orbital)
- Lewis Base: a species that donates an electron pair and will have lone-pair electrons of pi bonding electrons.

Lewis Acids

Neutral compounds of boron, aluminum, and the other Group 13 elements, (BF_3, $AlCl_3$), which possess only six valence electrons, have a very strong tendency to gain an additional electron pair. Because these compounds are only surrounded by three electron groups, they are sp^2 hybridized, contained a vacant p orbital, and are potent Lewis acids. Trimethylamine's lone pair elections are contained in an sp^3 hybrid orbital making it a Lewis base. These two orbitals overlap, creating a covalent bond in a boron trifluoride-trimethylamine complex. The movement of electrons during this interaction is show by by an arrow.



Positive ions are often Lewis acids because they have an electrostatic attraction for electron donors. Examples include alkali and alkaline earth metals in the group IA and IIA columns. K^+, Mg^{2+} and Ca^{2+} are sometimes seen as Lewis acidic sites in biology, for example. These ions are very stable forms of these elements because of their low electron ionization potentials. However, their positive charges do attract electron donors.The interaction between a magnesium cation (Mg^{+2}) and a carbonyl oxygen is a common example of a Lewis acid-base reaction. The carbonyl oxygen (the Lewis base) donates a pair of electrons to the magnesium cation (the Lewis acid). As we will see in Chapter 19 when we begin the study of reactions involving carbonyl groups, this interaction has the very important effect of increasing the polarity of the carbon-oxygen double bond.



The eight-electron rule does not hold throughout the periodic table. In order to obtain noble gas configurations, some atoms may need eighteen electrons in their valence shell. Transition metals such as titanium, iron and nickel may have up to eighteen electrons and can frequently accept electron pairs from Lewis bases. Transition metals are often Lewis acids. For example, titanium has four valence electrons and can form four bonds in compounds such as titanium tetrakis (isopropoxide), below, or titanium tetrachloride, $TiCl_4$. However, the titanium atom in that compound has only eight valence electrons, not eighteen. It can easily accept electrons from donors.

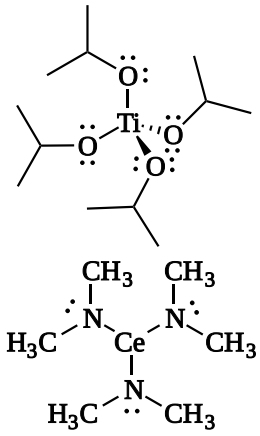


Figure 3.2.1: *Although titanium has eight electrons in this molecule, titanium tetrakis(isopropoxide), it can accommodate up to eighteen. It is a Lewis acid. The cerium atom in cerium tris(dimethylamide) comes from a similar part of the periodic table and is also a Lewis acid.*

For example, when THF and $TiCl_4$ are combined, a Lewis acid-base complex is formed, $TiCl_4(THF)_2$. $TiCl_4(THF)_2$ is a yellow solid at room temperature.

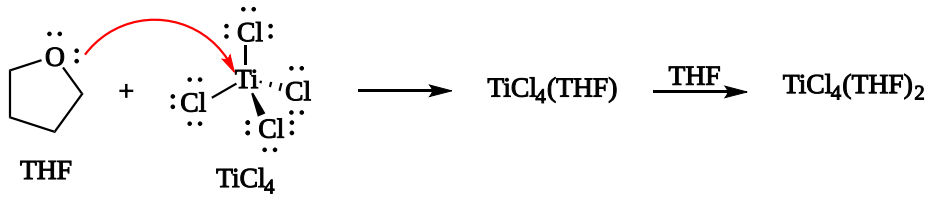


Figure 3.2.2: *A Lewis acid-base complex between tetrahydrofuran (THF) and titanium tetrachloride.*

The Proton as a Common Lewis Acid

Perhaps the most common example of a Lewis acid is also the simplest. It is the hydrogen cation (H^+) or proton. It is called a proton because, in most hydrogen atoms, the only particle in the nucleus is a proton. If an electron is removed to make a cation, a proton is all that is left. A proton is a Lewis acid for a number of reasons. It has a positive charge, and so it will attract electrons, which are negative. Also, it lacks the electron configuration of its noble gas neighbor, helium. Helium has two electrons. If a Lewis base or nucleophile donates a pair of electrons to a proton, the proton will obtain a helium noble gas configuration.

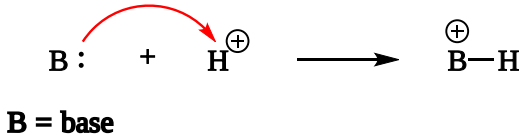


Figure 3.2.3: *Proton reacting as a Lewis acid.*

There is something about hydrogen cations that is not so simple, however. They are actually not so common. Instead, protons are generally always bound to a Lewis base. Hydrogen is almost always covalently (or coordinately) bonded to another atom. Many of the other elements commonly found in compounds with hydrogen are more electronegative than hydrogen. As a result, hydrogen often has a partial positive charge making is still act as a Lewis Acid.

A acid-base reaction involving protons might better be expressed as:

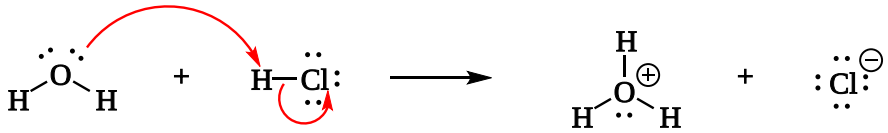


Figure 3.2.4: *Proton transfer from one site to another.*

The Lewis acid-base interactions we have looked at so far are slightly different here. Instead of two compounds coming together and forming a bond, we have one Lewis base replacing another at a proton. Two specific movements of electrons are shown in the reaction both of which are show by arrows. Lone pair electrons on oxygen attack the hydrogen to form an O-H bond in the product. Also, the electrons of the H-Cl bond move to become a lone pair on chlorine as the H-Cl bond breaks. These two arrows together are said to represent the mechanism of this acid-base reaction.

Lewis Bases

What makes a molecule (or an atom or ion) a Lewis base? It must have a pair of electrons available to share with another atom to form a bond. The most readily available electrons are those that are not already in bonds. Bonding electrons are low in energy. Non-bonding electrons are higher in energy and may be stabilized when they are delocalized in a new bond. Lewis bases usually have non-bonding electrons or lone pairs this makes oxygen and nitrogen compounds common Lewis bases. Lewis bases may be anionic or neutral. The basic requirement is that they have a pair of electrons to donate.

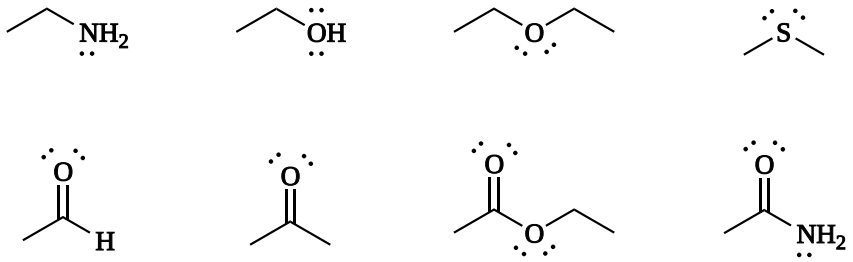


Figure 3.2.5: Some common organic examples of Lewis bases. Most oxygen, nitrogen and sulfur containing compounds can act as Lewis Bases.

Note 1: Ammonia

Ammonia, NH_3, has a lone pair and is a Lewis base. It can donate to compounds that will accept electrons.



Ammonia donating to an electron acceptor or Lewis acid.

Not all compounds can act as a Lewis base. For example, methane, CH_4, has all of its valence electrons in bonding pairs. These bonding pairs are too stable to donate under normal conditions therefore methane is not a Lewis base. Neutral boron compounds also have all electrons in bonding pairs. For example, borane, BH_3 has no lone pairs; all its valence electrons are in bonds. Boron compounds are not typically Lewis bases.

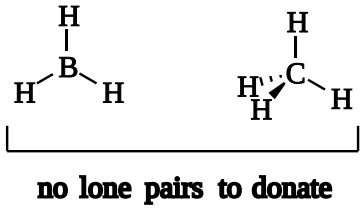


Figure 3.2.6: *Carbon and boron compounds with all sigma bonds do not have lone pairs, and do not act as Lewis bases.*

Exercise 3.2.1

Which of the following compounds would you expect to be Lewis bases?

a) SiH_4 b) AlH_3 c) PH_3 d) SH_2 e) ^-SH

Answer available at the end of this section.

Lewis Acid-Base Complexes

What happens when a Lewis base donates a pair of electrons to a Lewis acid? The electron pushing formalism (arrows) we have been using to illustrate the behavior of Lewis acids and Lewis bases is meant to show the direction of electron movement from the donor to the acceptor. However, given that a bond can be thought of as a pair of electrons that are shared between two atoms (in this case, between the donor and the acceptor), these arrows also show where bonds are forming.

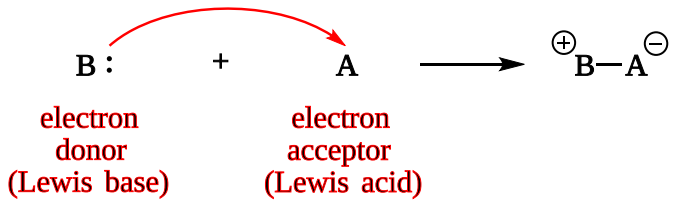


Figure 3.2.7: Donation of electrons from a Lewis base to a Lewis acid.

The electrons donated from a Lewis base to a Lewis acid form a new bond. A new, larger compound is formed from the smaller Lewis acid and Lewis base. This compound is called a Lewis acid-base complex. A simple example of Lewis acid-base complexation involves ammonia and boron trifluoride. The nitrogen atom has a lone pair and is an electron donor. The boron has no octet and is an electron acceptor. The two compounds can form a Lewis acid-base complex or a coordination complex together.

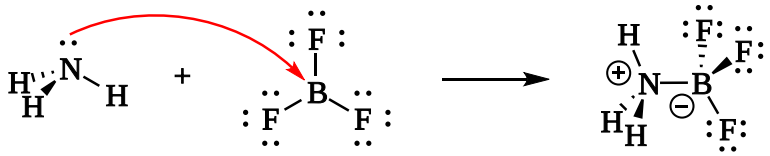


Figure 3.2.8: *Formation of a Lewis acid-base complex from ammonia and boron trifluoride.*

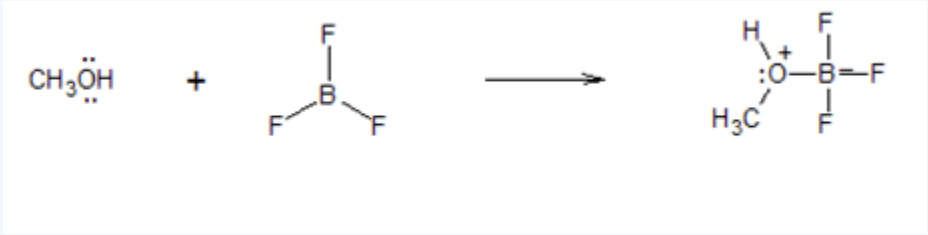
When the nitrogen donates a pair of electrons to share with the boron, the bond that forms is sometimes called a coordinate bond. A coordinate bond is any covalent bond that arose because one atom brought a pair of its electrons and donated them to another.

In organic chemistry terminology, the electron donor is called a **nucleophile** and the electron acceptor is called an **electrophile**. Ammonia is a nucleophile and boron trifluoride is an electrophile.

- Because Lewis bases are attracted to electron-deficient atoms, and because positive charge is generally associated with the nucleus of an atom, Lewis bases are sometimes refered to as "nucleophiles". Nucleophile means nucleus-loving.
- Because Lewis acids attract electron pairs, Lewis acids are sometimes called "electrophiles". Electrophile means electron-loving.

Exercise 3.2.2

For the following reaction, add curved arrows (electron pushing formalism) to indicate the electron flow.



Answer available at the end of this section.

Exercise 3.2.3

A Lewis acid-base complex is formed between THF (tetrahyrofuran) and borane, BH_3.

a) Which compound is the Lewis acid? Which one is the Lewis base?

b) Which atom in the Lewis acid is the acidic site? Why?

c) Which atom in the Lewis base is the basic site? Why?

d) How many donors would be needed to satisfy the acidic site?

e) Show, using arrow notation, the reaction to form a Lewis acid-base complex.

f) Borane is highly pyrophoric; it reacts violently with air, bursting into flames. Show, using arrow notation, what might be happening when borane contacts the air.

g) Borane-THF complex is much less pyrophoric than borane. Why do you suppose that is so?

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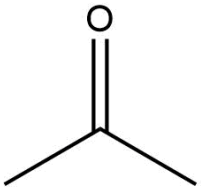
Answer available at the end of this section.

Exercises

Questions

Q2.11.1

For the following molecules state wither they are Lewis acid or base and wither or not they are a Brønsted acid or base.



NH_4^+

Solutions

S2.11.1

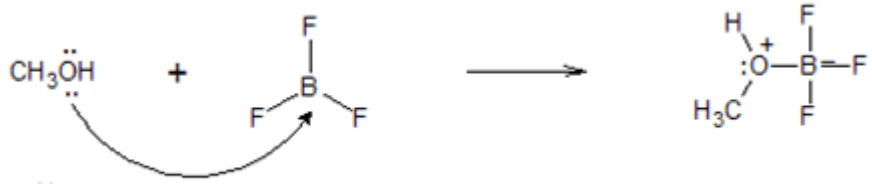
Acetone is a Lewis base and a Brønsted base. Ammonium cation is both a Lewis acid and a weak Brønsted acid.

Answers

Exercise 3.2.1

a) No, silicon has 4 valence electrons (like carbon) and all 4 are involved in sigma bonds
b) No, aluminum has 3 valence electrons and all 3 are involved in sigma bonds
c) Yes, phosphorus has 5 valence electrons, so there is one lone pair available
d) Yes, sulfur has 6 valence electrons, so there are two lone pairs available
e) Yes, this ion has 3 lone pairs available

Exercise 3.2.2



Exercise 3.2.3

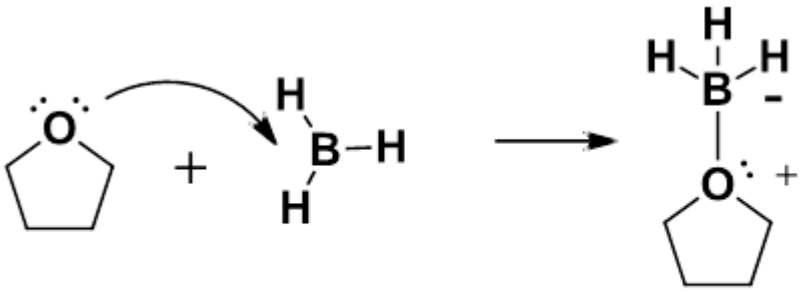
a) Borane is the Lewis acid. THF has lone pair electrons so it is the Lewis base.

b) The Boron atom has an unfilled octet so it has an empty p orbital that can accept electrons.

c) The oxygen atom in THF has lone pair electrons contained in a sp^3 hybridized orbital.

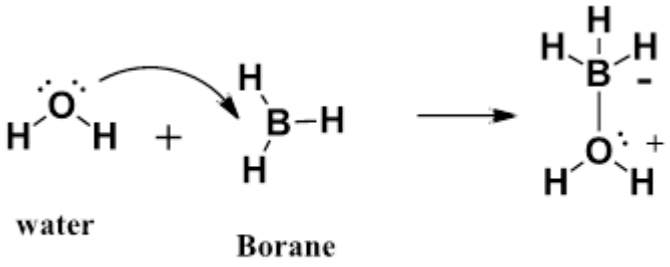
d) The boron in borane has six electrons around it so it would only need one lone pair donor to reach an octet.

e) Show, using arrow notation, the reaction to form a Lewis acid-base complex.



Acid-Base Complex

f) The Borane initially reacts with water in air.



water Borane

Acid-Base Complex

g) After the Borane-THF complex is formed, the boron atom has a complete octet making it less reactive.

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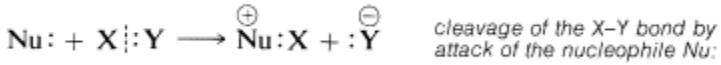
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3.3: Classification of Reagents as Electrophiles and Nucleophiles. Acids and Bases

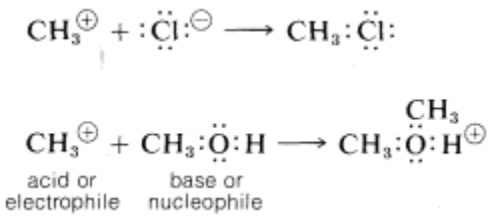
To understand ionic reactions, we need to be able to recognize whether a particular reagent will act to *acquire an electron pair* or to *donate an electron pair*. Reagents that acquire an electron pair in chemical reactions are said to be **electrophilic** ("electron-loving"). We can picture this in a general way as a heterolytic bond breaking of compound $X:Y$ by an electrophile E such that E becomes bonded to Y by the electron pair of the XY bond. Thus



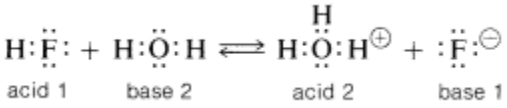
Reagents that donate an electron pair in chemical reactions are said to be **nucleophilic** ("nucleus loving"). Thus the $X:Y$ bond also can be considered to be broken by the nucleophile $Nu:$, which donates its electron pair to X while Y leaves as $Y:^{\ominus}$ with the electrons of the $X:Y$ bond:



Thus, by definition, electrophiles are electron-pair acceptors and nucleophiles are electron-pair donors. These definitions correspond closely to definitions used in the generalized theory of acids and bases proposed by G. N. Lewis (1923). According to Lewis, an acid is any substance that can accept an electron pair, and a base is any substance that can donated an electron pair to form a covalent bond. Therefore acids must be electrophiles and bases must be nucleophiles. For example, the methyl cation may be regarded as a **Lewis acid**, or an electrophile, because it *accepts* electrons from reagents such as chloride ion or methanol. In turn, because chloride ion and methanol donate electrons to the methyl cation they are classified as **Lewis bases**, or nucleophiles:

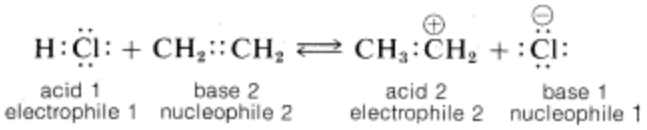


The generalized Lewis concept of acids and bases also includes common proton-transfer reactions.[1] Thus water acts as a base because one of the electron pairs on oxygen can abstract a proton from a reagent such as hydrogen fluoride:



Alternatively, the hydronium ion ($H_3O^{\oplus}$) is an acid because it can accept electrons from another reagent (e.g., fluoride ion) by donating a proton.

A proton donor can be classified as an electrophile and a proton acceptor as a nucleophile. For example, hydrogen chloride can transfer a proton to ethene to form the ethyl cation. Therefore hydrogen chloride functions as the electrophile, or acid, and ethene functions as the nucleophile, or base:



What then is the difference between an acid and an electrophile, or between a base and nucleophile? No great difference until we try to use the terms in a *quantitative* sense. For example, if we refer to acid strength, or acidity, this means the position of *equilibrium* in an acid-base reaction. The equilibrium constant K_a for the dissociation of an acid HA, or the pK_a, is a quantitative measure of acid strength. The larger the value of K_a or the smaller the pK_a, the stronger the acid.

A summary of the relationships between K_a and pK_a follow, where the quantities in brackets are concentrations:

$$HA + H_2O \rightleftharpoons H_3O^{\oplus} + A^{\ominus}$$

$$K_a = \frac{[H_3O^{\oplus}][A^{\ominus}]}{[HA]}$$

(Notice that the concentration of water does not appear in this expression; it is the solvent and its concentration is large and constant.)

or

$$-\log K_a = -\log [H_3O^{\oplus}] + \log \frac{[HA]}{[A^{\ominus}]}$$

By definition, $-\log\ K_a = pK_a$ and $-\log\ [H_3O^{\oplus}] = pH$; hence

$$pK_a = pH + \log \frac{[HA]}{[A^{\ominus}]}$$

or

$$pK_a = pH + \log \frac{[\text{undissociated acid}]}{[\text{anion of the acid}]}$$

(This sometimes is referred to as the Henderson-Hasselbalch equation.)

However, in referring to the strength of reagents as electrophiles or nucleophiles we usually are not referring to chemical equilibria but to *reaction rates*. A good nucleophile is a reagent that reacts rapidly with a particular electrophile. In contrast, a poor nucleophile reacts only slowly with the same electrophile. Consequently, it should not then be taken for granted that there is a parallel between the acidity or basicity of a reagent and its reactivity as an electrophile or nucleophile. For instance, it is incorrect to assume that the strengths of a series of bases, $B:$, in aqueous solution will *necessarily* parallel their nucleophilicities toward a carbon electrophile, such as methyl chloride:

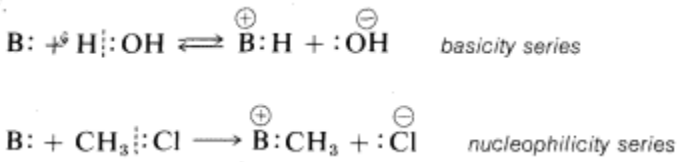
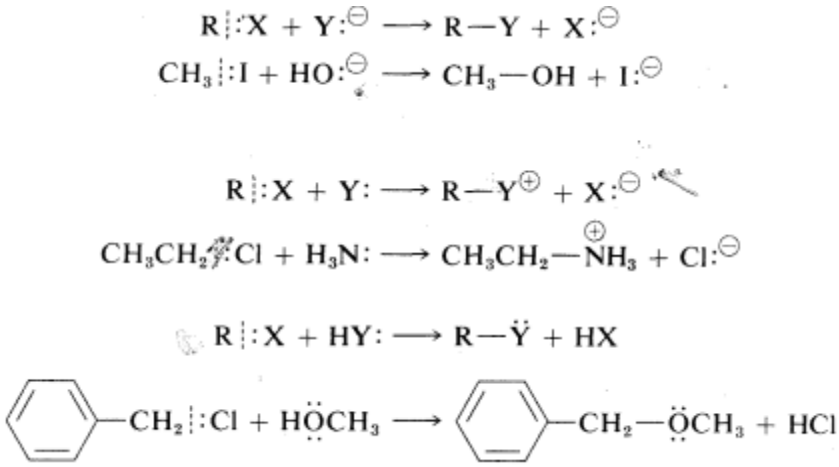


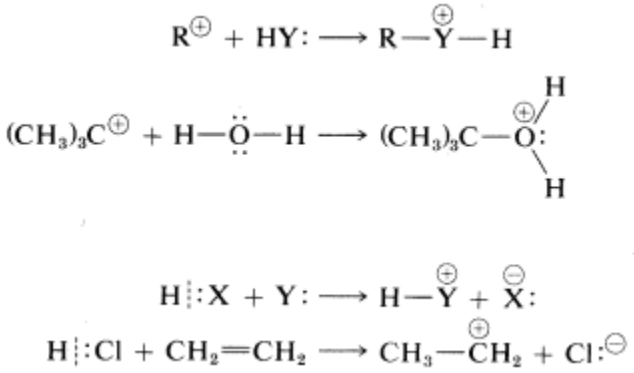
Figure 4-4). Even so, it turns out that most strong bases are good nucleophiles and that most strong proton acids are good electrophiles. We will see that the converse may not be true. Good nucleophiles are not always strong bases [examples are $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and $(CH_3)_2S$] and good electrophiles are not always strong acids by either the Bronsted-Lowry or Lewis definitions (examples are $HOBr$, Br_2, Cl_2, I_2).

In what follows we will be concerned with the rates of ionic reactions under *nonequilibrium* conditions. We shall use the term *nucleophilic* repeatedly and we want you to understand that a nucleophile is any neutral or charged reagent that supplies a pair

of electrons, either bonding or nonbonding, to form a new covalent bond. In substitution reactions the nucleophile usually is an anion, $Y:^{\ominus}$, or a neutral molecule, $Y:$ or $HY:$. The operation of each of these is illustrated in the following equations for reactions of the general compound RX and some specific examples:



An *electrophile* is any neutral or charged reagent that accepts an electron pair (from a nucleophile) to form a new bond. In the preceding substitution reactions, the electrophile is RX. The electrophile in other reactions may be a carbon cation or a proton donor, as in the following examples:



[1]The concept of an acid as a **proton donor** and a base as a **proton acceptor** is due to Bronsted and Lowry (1923). Previous to this time, acids and bases generally were defined as substances that functioned by forming $H^{\oplus}$ or $OH^{\ominus}$ in water solutions. The Bronsted-Lowry concept was important because it liberated acid-base phenomena from the confines of water-containing solvents by focusing attention on *proton transfers* rather than the formation of $H^{\oplus}$ or $OH^{\ominus}$. The Lewis concept of generalized acids and bases further broadened the picture by showing the relationship between proton transfers and reactions where an electron-pair acceptor is transferred from one electron-pair donor to another.

Contributors and Attributions

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3.4: Using Curved Arrows in Polar Reaction Mechanisms

Objective

After completing this section, you should be able to use curved (curly) arrows, in conjunction with a chemical equation, to show the movement of electron pairs in a simple polar reaction, such as electrophilic addition.

Key Terms

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

- electrophlic
- nucleophlic

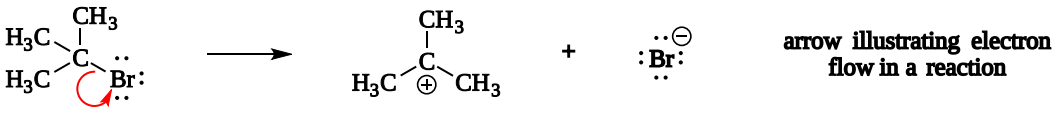
Pushing Electrons and Curved Arrows

Understanding the location of electrons and being able to draw the curved arrows that depict the mechanisms by which the reactions occur is one of the most critical tools for learning organic chemistry since they allow you to understand what controls reactions, and how reactions proceed.

Before you can do this you need to understand that a **bond** is due to a pair of electrons shared between atoms. When asked to draw a mechanism, curved arrows should be used to show all the bonding changes that occur. A few simple lessons that illustrate these concepts can be found below.

Lesson 1

If we remove the pair of electrons in a bond, then we BREAK that bond. This is true for single and multiple bonds as shown below:



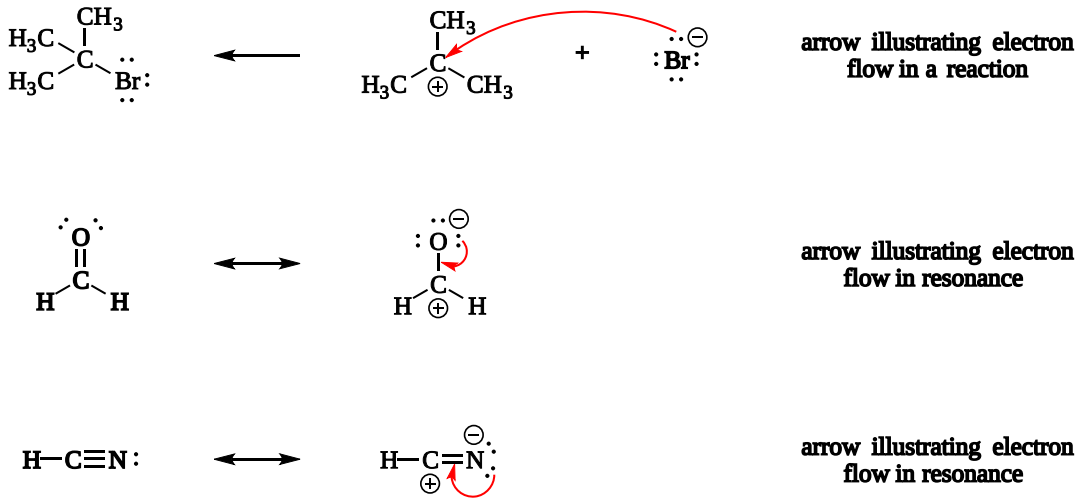




Notice that since the starting materials were *neutral*, the products are also *neutral*. In general terms, the *sum of the charges* on the starting materials MUST equal the *sum of the charges* on the products since we have the **same number of electrons**.

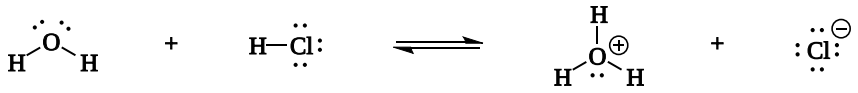
The first example is a REACTION since we broke a sigma bond. In the second two examples, we moved pi electrons into long pairs. This is RESONANCE.

If we move electrons between two atoms, then we MAKE a new bond:

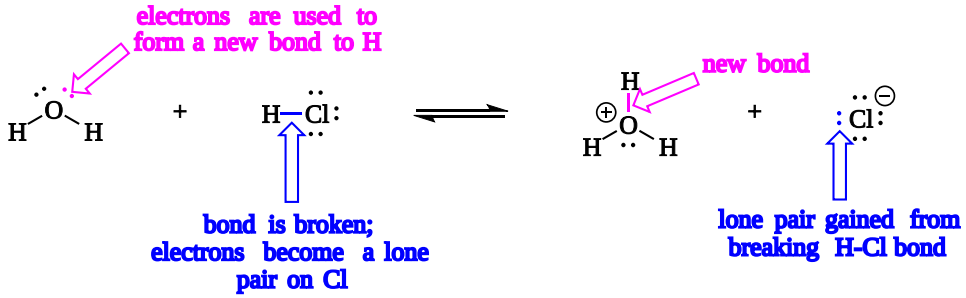


We always show electrons moving from **electron rich** to **electron poor**.

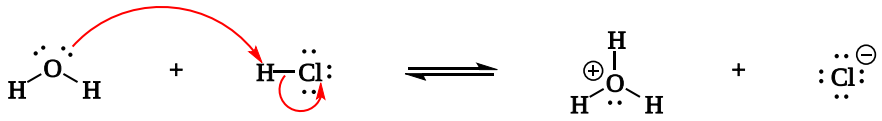
Lesson 2



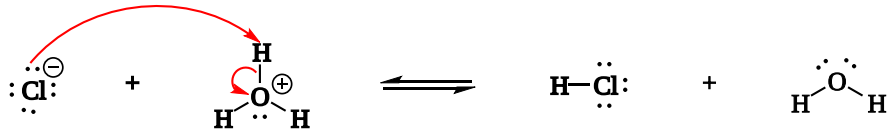
This is a simple acid/base reaction, showing the formation of the hydronium ion produced when hydrochloric acid is dissolved in water. It is useful to analyze the bond changes that are occurring. Water is functioning as a **base** and hydrochloric acid as an **acid**. Consider the differences in bonding between the starting materials and the products:



One of the lone pairs on the oxygen atom of water was used to form a bond to a hydrogen atom, creating the hydronium ion (H_3O^+) seen in the products. The hydrogen-chlorine bond of HCl was broken, and the electrons in this bond became a lone pair on the chlorine atom, thus generating a chloride ion. We can illustrate these changes in bonding using the curved arrows shown below.



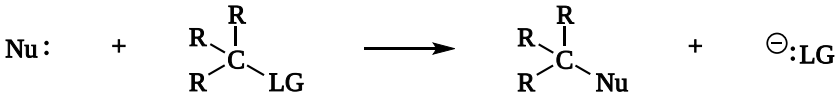
Note that in this diagram, the overall charge of the reactants is the same as the overall charge of the products. We can also show the curved arrows for the reverse reaction:



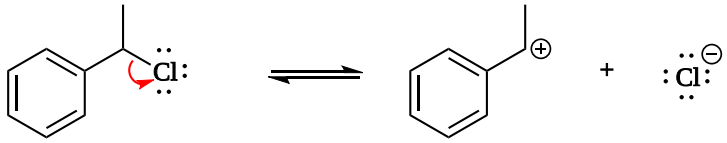
This shows the formation of the new H-Cl bond by using a lone pair of electrons from the electron-rich chloride ion to form a bond to an electron poor hydrogen atom of the hydronium ion. Because hydrogen can only form one bond, the oxygen-hydrogen bond is broken and its electrons become a lone pair on the electron-poor oxygen atom. Notice that the charges balance!

Lesson 3

In this section, we will look at the curved arrows for some nucleophilic substitution reactions. Overall, the processes involved are similar to those for the acid/base reactions described above. In a nucleophilic substitution reaction, an electron-rich nucleophile (Nu) becomes bonded to an electron-poor carbon atom, and a leaving group (LG) is displaced. In bonding terms, we must *make* a Nu-C bond and *break* a C-LG bond.

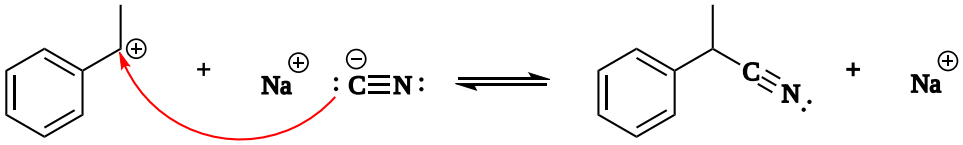


Let's consider the stepwise S_N1 reaction between (1-chloroethyl)benzene and sodium cyanide. The first step of this process is breaking the C-Cl bond, where the electrons in that bond become a lone pair on the chlorine atom. The carbon atom has lost electrons and therefore becomes positive, generating a secondary carbocation. Because the chlorine atom gained an additional lone pair of electrons, it becomes a negatively charged chloride ion.

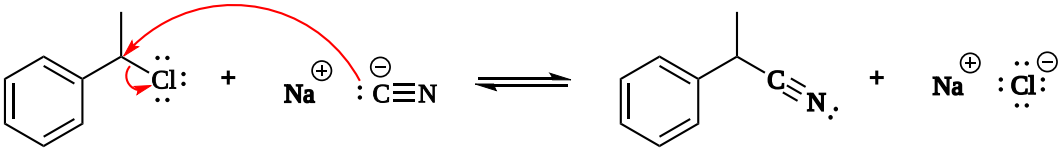


(1-chloroethyl)benzene

In the second step, the electron-rich nucleophile donates electrons to form a new C-C bond with the electron-poor secondary carbocation.



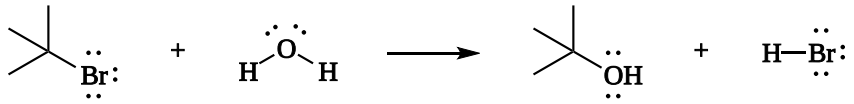
In an S_N2 reaction, the bond forming and breaking processes occur simultaneously. The scheme below shows the Nu donating electrons to form a new C-C bond at the same time that the C-Cl bond is breaking. The electrons in the C-Cl bond become a long pair on the chlorine atom, generating a chloride ion. Forming and breaking the bonds simultaneously allows carbon to obey the octet rule throughout this process.



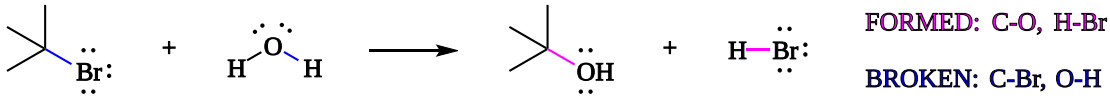
Notice that in all steps for the processes above, the overall charges of the starting materials match those of the products.

Lesson 4

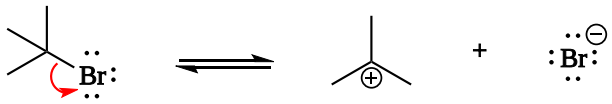
This section will dissect another substitution reaction, although it is more involved. Let's consider the S_N1 reaction of *tert*-butyl bromide with water.



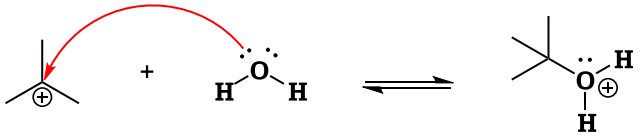
It can be helpful to take inventory of which bonds have been formed, and which bonds have been broken.



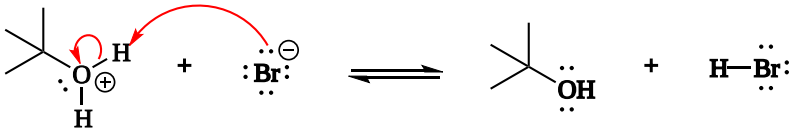
The curved arrows we draw must account for ALL of these bonding changes. Since we are dealing with an S_N1 reaction process, the first step will be cleavage of the C-Br bond to give a carbocation and and a bromide anion.



Water then acts as a nucleophile, using one of its lone pairs to form a bond to the electron-poor *t*-butyl cation. This generates an oxonium ion, where oxygen has three bonds and a positive formal charge.

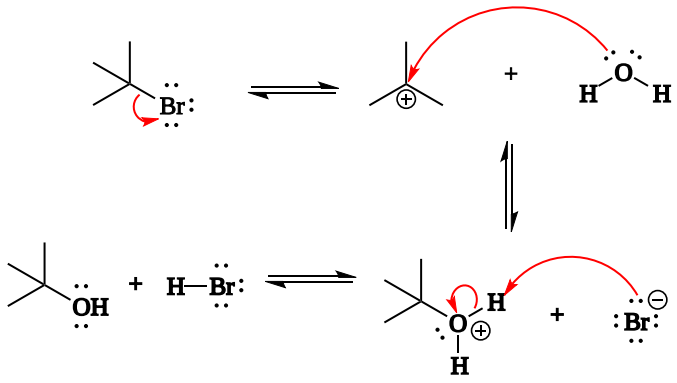


The final step is an acid/base reaction between the bromide anion generated in step 1 and the oxonium product of step 2. The bromide anion acts as a base, using a lone pair to form a bond to one of the hydrogen atoms. The O-H bond then breaks, and its electrons become a lone pair on oxygen. This gives the final products of HBr and *t*-butyl alcohol.

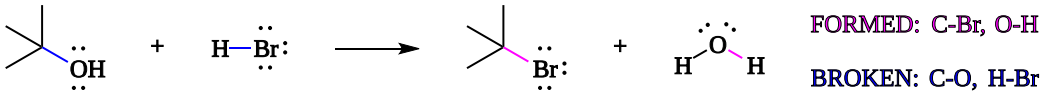


Notice that in each of the mechanistic steps above, the overall charge of the reactant side balances with the overall charge of the product side.

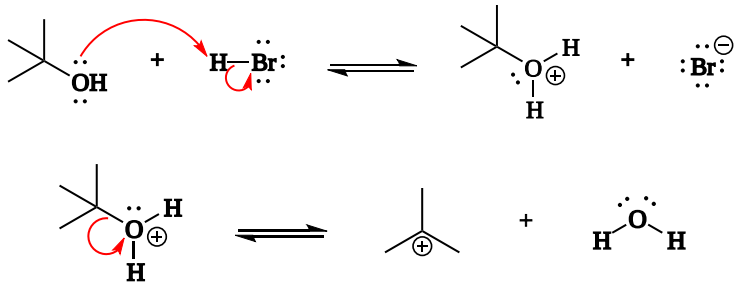
While the above process was broken down into distinct steps, however it is important to note that mechanisms are almost always shown as a continuous process. The overall mechanism for this processes can be found below:



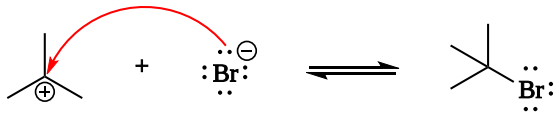
Now consider the reverse reaction, i.e. the reaction of *t*-butyl alcohol with hydrobromic acid to generate *t*-butyl bromide and water. The scheme is shown below, along with an analysis of the bonds formed and broken in this process:



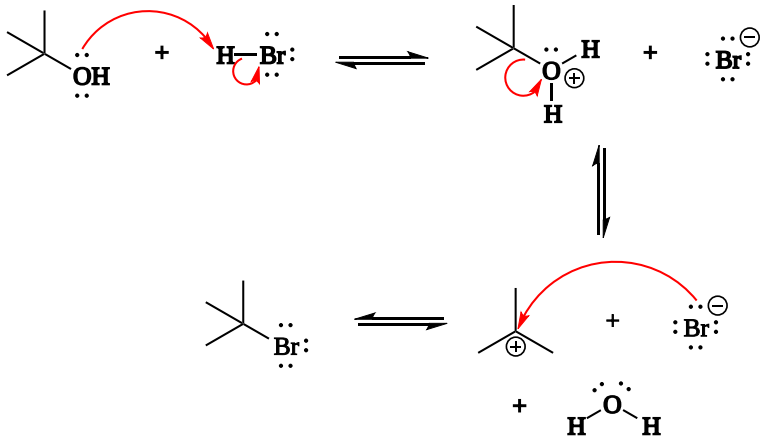
The mechanism must occur via the same pathway as shown above (Law of Macroscopic Reversibility), however this mechanism can still be deduced without knowing that. First, it is known that HBr is a strong acid and can donate a proton to a base. The most basic sites in the whole system are the lone pairs on the oxygen atom of *t*-butanol. Since the lone pairs are the electron-rich area of the molecule, the arrow starts at a lone pair and ends at the proton of HBr. The H-Br bond breaks, pushing its electrons onto the bromine atom and generating a bromide ion.



The bromide ion generated in the first step can then react with the *t*-butyl cation to generate *t*-butyl bromide.



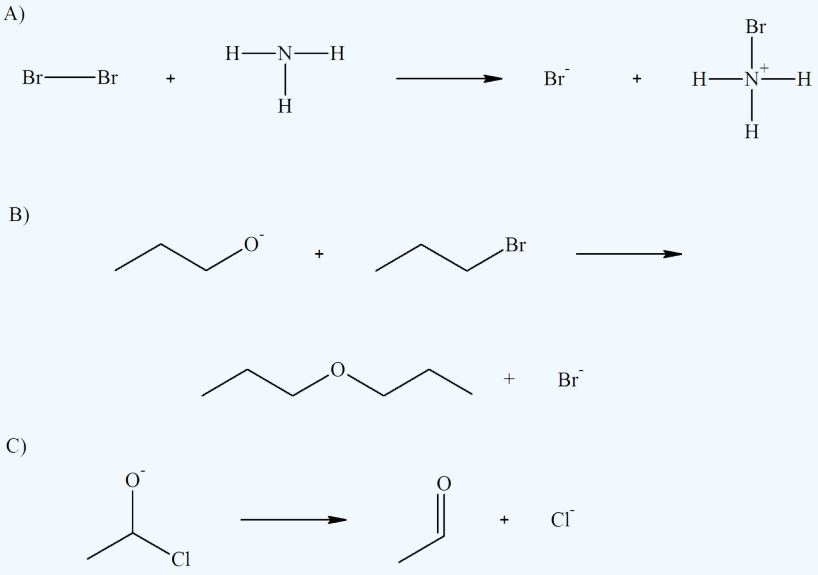
Once again, the above the overall process is broken down into individual steps, however it is more common to illustrate this as one overall process:



Curved Arrow Summary

- Curved arrows flow from electron rich to electron poor.
- Therefore they start from lone pairs or bonds.
- The charges in any particular step should always be balanced.
- Remember to obey the rules of valence (*eg*. octet rule for C,N,O,F *etc*.)
- If electrons are taken out of a bond, then that bond is broken.
- If electrons are placed between two atoms then it implies a bond is being made.

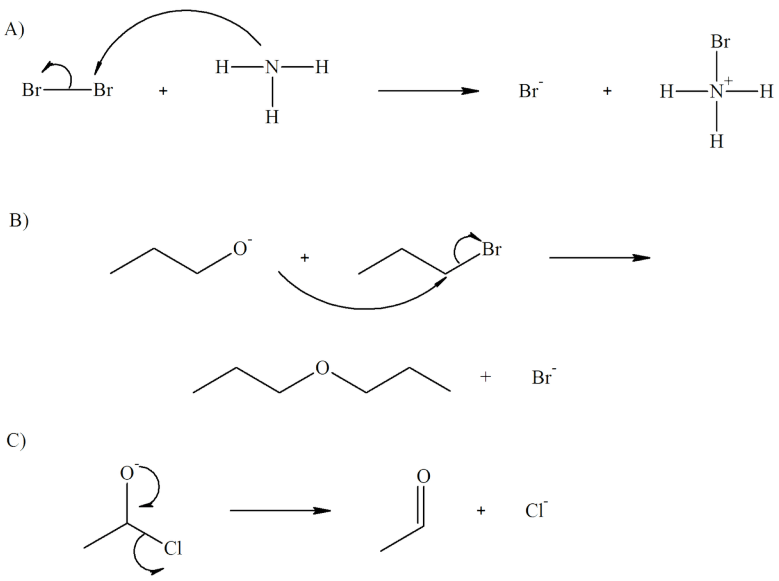
Exercise 3.4.1



Answer available at the end of this section.

Answers

Exercise 3.4.1

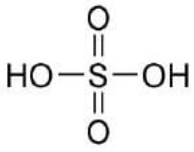


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3.5: Acid Strength and pK_a

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.

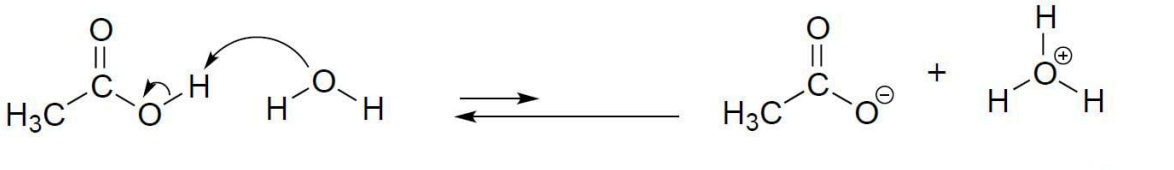


sulfuric acid

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 **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.



H-A
acetic acid

:B
water

A^-
acetate ion

$H\text{-}B^+$
hydronium ion

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 s*olvent* 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 s*olutes,* and so their activities are approximated with molarities. The acid dissociation constant, or K_a, for acetic acid is therefore defined as:

$$K_{eq} = \frac{a_{CH_3COO^-} \cdot a_{H_3O^+}}{a_{CH_3COOH} \cdot a_{H_2O}} \approx \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][1]} \tag{3.5.1}$$

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

$$K_{eq} = K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.75 \times 10^{-5} \tag{3.5.2}$$

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

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{3.5.3}$$

or

$$K_a = \frac{[A][H_3O^+]}{[HA^+]} \tag{3.5.4}$$

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 x 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.*

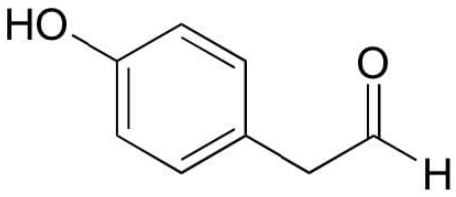
It is important to realize that pK_a is not at all the same thing as pH: the former is an inherent property of a compound or functional group, while the latter is the measure of the hydronium ion concentration in a particular aqueous solution:

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

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.

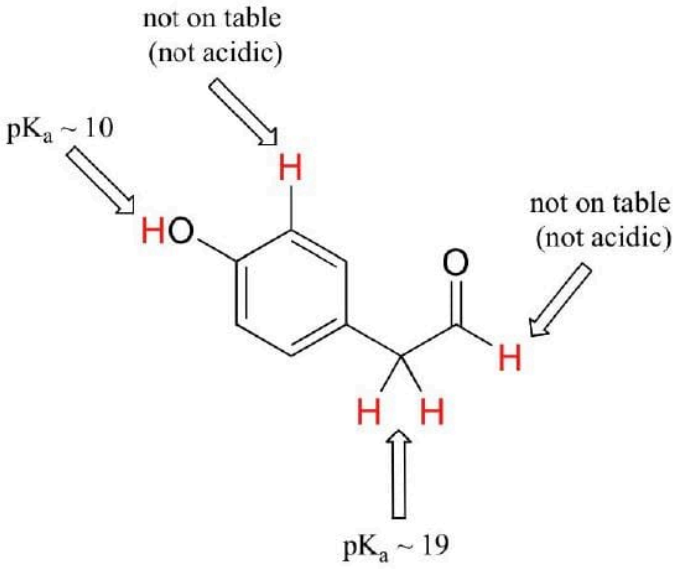
Our table of pK_a values will also allow us to compare the strengths of different bases by comparing the pK_avalues of their conjugate acids. The key idea to remember is this: *the stronger the conjugate acid, the weaker the conjugate base*. Sulfuric acid is the strongest acid on our list with a pK_a 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

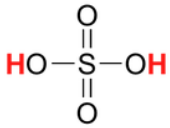
Notice in this example that we need to evaluate the potential acidity at *four* different locations on the molecule.



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!)



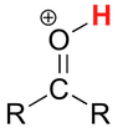
sulfuric acid
pK_a -10, 2.0



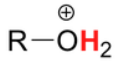
hydrochloric acid
pK_a -7



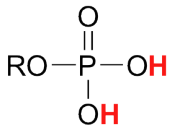
hydronium
pK_a 0.00



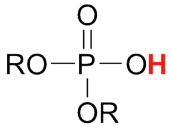
protonated ketone
pK_a ~ -7



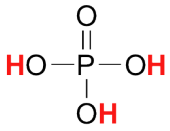
protonated alcohol
pK_a ~ -3



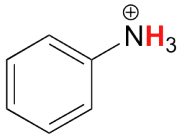
phosphate monoester [1]
pK_a ~ 1, 6.5



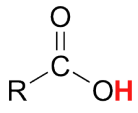
phosphate diester [1]
pK_a ~ 1.5



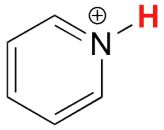
phosphoric acid
pK_a = 2.2, 7.2, 12.3



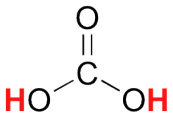
aniline
pK_a = 4.6



carboxylic acid
pK_a ~ 4-5



pyridinium
pK_a 5.3

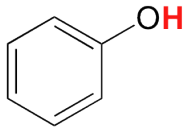


carbonic acid
pK_a 6.4, 10.3

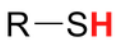
hydrogen cyanide
pK_a 9.2



ammonium
pK_a 9.2



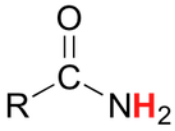
phenol
pK_a 9.9



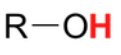
thiol
pK_a ~ 10-11



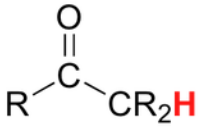
water
pK_a **14.0**



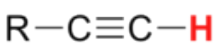
amide
pK_a ~ 17



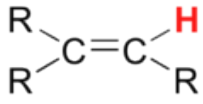
alcohol
pK_a ~ 16-18



α-proton
pK_a ~18-20



terminal alkyne
pK_a ~ 25



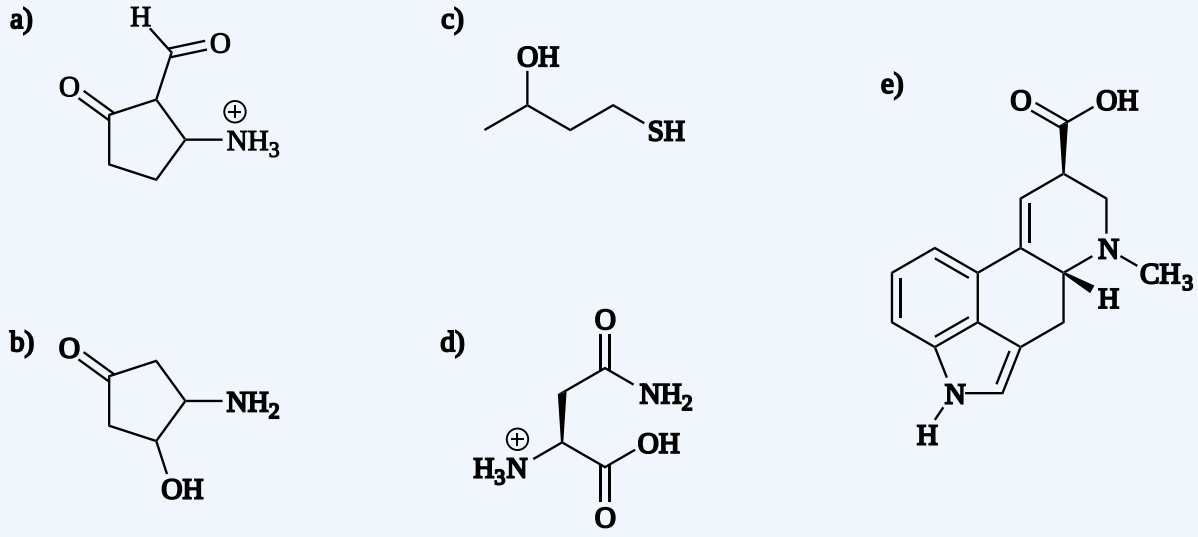
terminal alkene
pK_a ~ 35



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.



Solution

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

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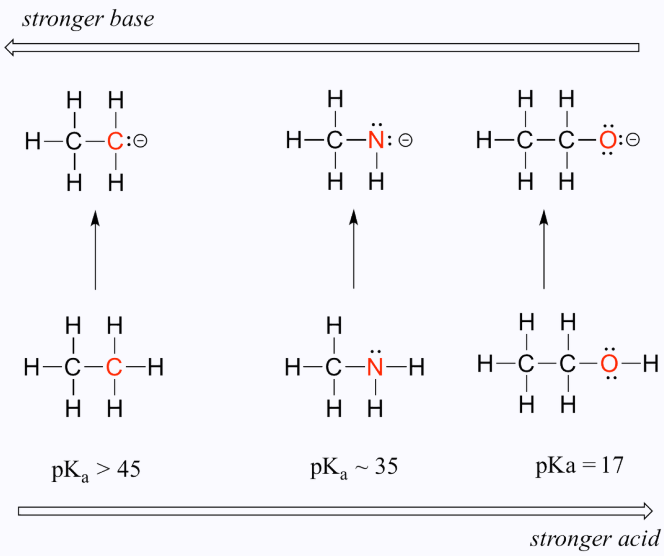
3.6: A Summary of the Factors that Determine Acid Strength

Now that we know how to quantify the strength of an acid or base, our next job is to gain an understanding of the fundamental reasons behind *why* one compound is more acidic or more basic than another. This is a big step: we are, for the first time, taking our knowledge of organic s*tructure* and applying it to a question of organic *reactivity*. Many of the ideas that we'll see for the first here will continue to apply throughout the book as we tackle many other organic reaction types.

A: Periodic trends

First, we will focus on individual atoms, and think about trends associated with the position of an element on the periodic table. We'll use as our first models the simple organic compounds ethane, methylamine, and ethanol, but the concepts apply equally to more complex biomolecules with the same functionalities, for example the side chains of the amino acids alanine (alkane), lysine (amine), and serine (alcohol).

Horizontal periodic trend in acidity and basicity



We can see a clear trend in acidity as we move from left to right along the second row of the periodic table from carbon to nitrogen to oxygen. The key to understanding this trend is to consider the hypothetical conjugate base in each case*: the more stable (weaker) the conjugate base, the stronger the acid*. Look at where the negative charge ends up in each conjugate base. In the conjugate base of ethane, the negative charge is borne by a carbon atom, while on the conjugate base of methylamine and ethanol the negative charge is located on a nitrogen and an oxygen, respectively. Remember that electronegativity also increases as we move from left to right along a row of the periodic table, meaning that oxygen is the most electronegative of the three atoms, and carbon the least.

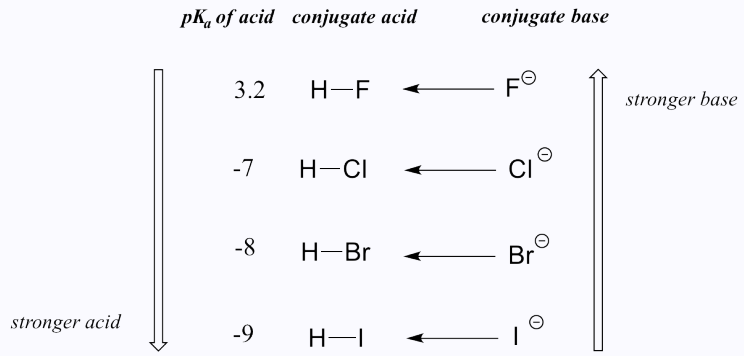
The more electronegative an atom, the better able it is to bear a negative charge. Weaker bases have negative charges on more electronegative atoms; stronger bases have negative charges on less electronegative atoms.

Thus, the methoxide anion is the most stable (lowest energy, least basic) of the three conjugate bases, and the ethyl carbanion anion is the least stable (highest energy, most basic). Conversely, ethanol is the strongest acid, and ethane the weakest acid.

When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best

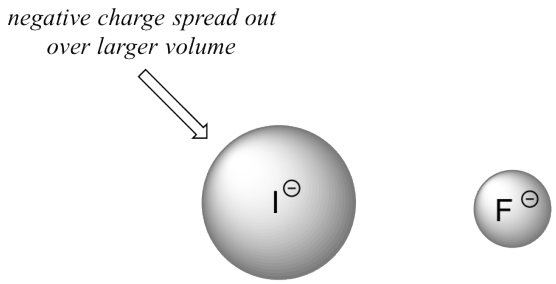
illustrated with the haloacids and halides: basicity, like electronegativity, increases as we move up the column.

Vertical periodic trend in acidity and basicity



Conversely, acidity in the haloacids increases as we move *down* the column.

In order to make sense of this trend, we will once again consider the stability of the conjugate bases. Because fluorine is the most electronegative halogen element, we might expect fluoride to also be the least basic halogen ion. But in fact, it is the *least* stable, and the most basic! It turns out that when moving vertically in the periodic table, the *size* of the atom trumps its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodide ion, the negative charge is spread out over a significantly larger volume:



This illustrates a fundamental concept in organic chemistry:

Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' over a larger area.

We will see this idea expressed again and again throughout our study of organic reactivity, in many different contexts. For now, we are applying the concept only to the influence of atomic radius on base strength. Because fluoride is the least stable (most basic) of the halide conjugate bases, HF is the least acidic of the haloacids, only slightly stronger than a carboxylic acid. HI, with a pK_a of about -9, is almost as strong as sulfuric acid.

More importantly to the study of biological organic chemistry, this trend tells us that ***thiols are more acidic than alcohols***. The pK_a of the thiol group on the cysteine side chain, for example, is approximately 8.3, while the pK_a for the alcohol group on the serine side chain is on the order of 17.

Remember the concept of 'driving force' that we learned about in chapter 6? Recall that the driving force for a reaction is usually based on two factors: relative charge stability, and relative total bond energy. Let's see how this applies to a simple acid-base reaction between hydrochloric acid and fluoride ion:

$$HCl + F^- \rightarrow HF + Cl^-$$

We know that HCl (pK_a -7) is a stronger acid than HF (pK_a 3.2), so the equilibrium for the reaction lies on the product side: the reaction is exergonic, and a 'driving force' pushes reactant to product.

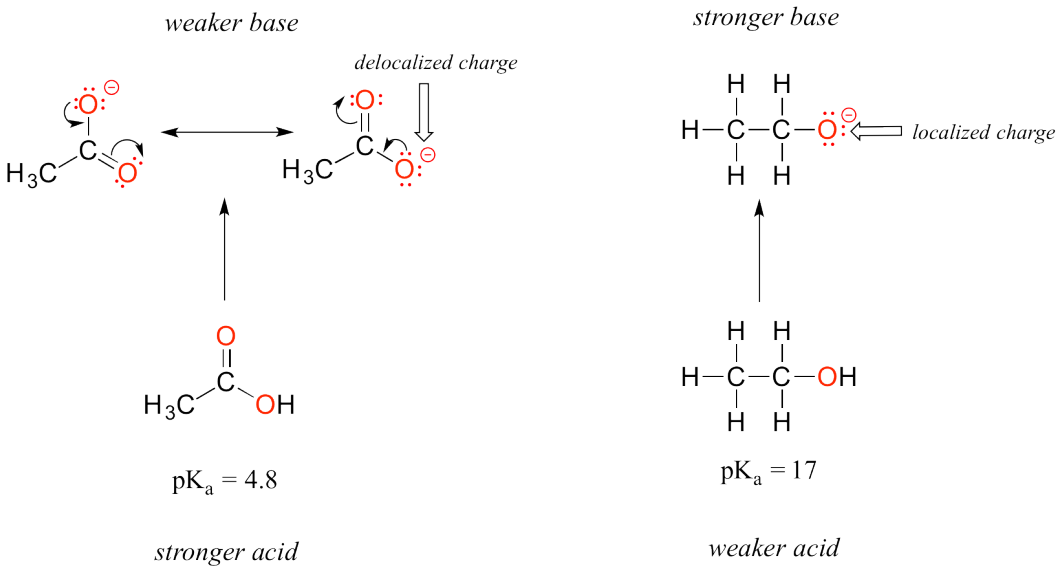
What explains this driving force? Consider first the charge factor: as we just learned, chloride ion (on the product side) is more stable than fluoride ion (on the reactant side). This partially accounts for the driving force going from reactant to product in this reaction: we are going from less stable ion to a more stable ion.

What about total bond energy, the other factor in driving force? If you consult a table of bond energies, you will see that the H-F bond on the product side is more energetic (stronger) than the H-Cl bond on the reactant side: 565 kJ/mol *vs* 427 kJ/mol, respectively). This also contributes to the driving force: we are moving from a weaker (less stable) bond to a stronger (more stable) bond.

B: Resonance effects

In the previous section we focused our attention on periodic trends - the differences in acidity and basicity between groups where the exchangeable proton was bound to different elements. Now, it is time to think about how the structure of different organic groups contributes to their relative acidity or basicity, even when we are talking about *the same element acting as the proton donor/acceptor*. The first model pair we will consider is ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups.

Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are strikingly different. What makes a carboxylic acid so much more acidic than an alcohol? As before, we begin by considering the stability of the conjugate bases, remembering that a more stable (weaker) conjugate base corresponds to a stronger acid.

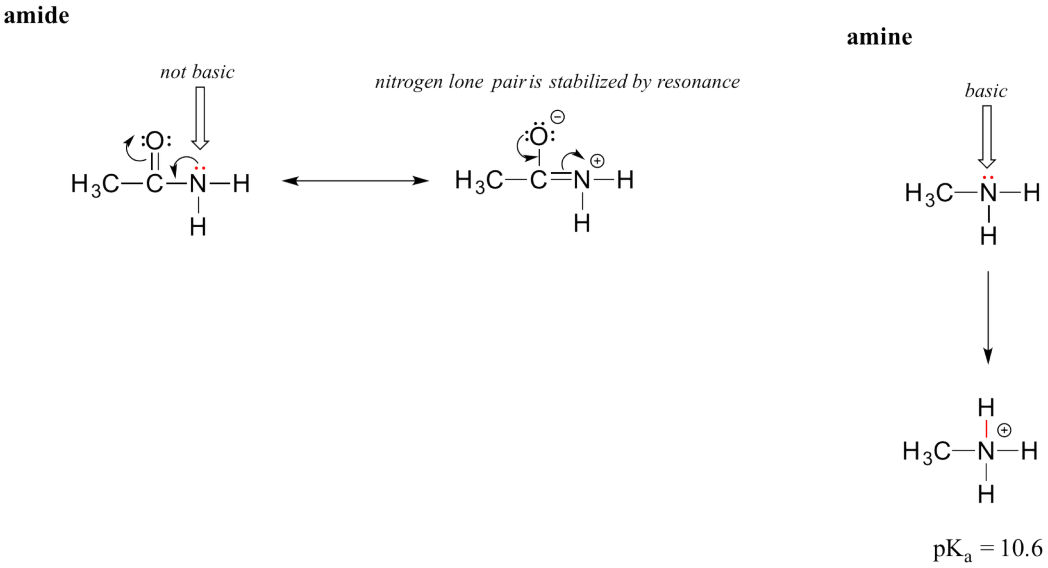


In both species, the negative charge on the conjugate base is located on oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: two resonance contributors can be drawn for the conjugate base, and the negative charge can be delocalized (shared) over two oxygen atoms. In the ethoxide ion, by contrast, the negative charge is localized, or 'locked' on the single oxygen – it has nowhere else to go. This makes the ethoxide ion much less stable.

Recall the important general statement that we made a little earlier: 'Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one location.' Now, we are seeing this concept in another context, where a charge is being 'spread out' (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 12 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so we are talking about a fator of 10^{12} between the K_a values for the two molecules!)

The resonance effect also nicely explains why a nitrogen atom is basic when it is in an amine, but *not* basic when it is part of an amide group. Recall that in an amide, there is significant double-bond character to the carbon-nitrogen bond, due to a minor but still important resonance contributor in which the nitrogen lone pair is part of a pi bond.



Whereas the lone pair of an amine nitrogen is 'stuck' in one place, the lone pair on an amide nitrogen is delocalized by resonance. Notice that in this case, we are extending our central statement to say that *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 available for bonding with a proton – these two electrons are too 'comfortable' being part of the delocalized pi bonding system. The lone pair on an amine nitrogen, by contrast, is not so comfortable - it is *not* part of a delocalized pi system, and is available to form a bond with any acidic proton that might be nearby.

If an amide group is protonated, it will be at the oxygen rather than the nitrogen.

Exercise 7.3.1

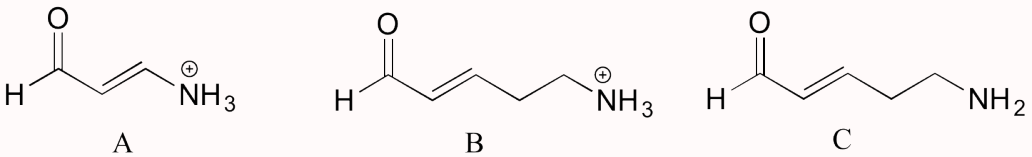
a) Draw the Lewis structure of nitric acid, HNO_3.

b) Nitric acid is a strong acid - it has a pK$_a$ of -1.4. Make a structural argument to account for its strength. Your answer should involve the structure of nitrate, the conjugate base of nitric acid.

Solution

Exercise 7.3.2

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

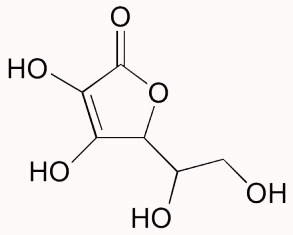


Solution

Exercise 7.3.3

(challenging!) Often it requires some careful thought to predict the most acidic proton on a molecule. Ascorbic acid, also

known as Vitamin C, has a pK_a of 4.1 - the fact that this is in the range of carboxylic acids suggest to us that the negative charge on the conjugate base can be delocalized by resonance to *two* oxygen atoms. Which if the four OH protons on the molecule is most acidic? Draw the structure of ascorbate, the conjugate base of ascorbic acid, then draw a second resonance contributor showing how the negative charge is delocalized to a second oxygen atom. *Hint* - try removing each OH group in turn, then use your resonance drawing skills to figure out whether or not delocalization of charge can occur.

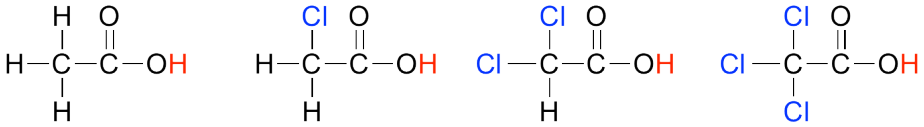


ascorbic acid
(Vitamin C)

Solution

C: Inductive effects

Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:



$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 1.3$ $pK_a = 0.64$

The presence of the chlorine atoms clearly increases the acidity of the carboxylic acid group, but the argument here does not have to do with resonance delocalization, because no additional resonance contributors can be drawn for the chlorinated molecules. Rather, the explanation for this phenomenon involves something called the **inductive effect**. A chlorine atom is more electronegative than a hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. In effect, the chlorine atoms are helping to further spread out the electron density of the conjugate base, which as we know has a stabilizing effect. In this context, the chlorine substituent can be referred to as an **electron-withdrawing group**. Notice that the pKa-lowering effect of each chlorine atom, while significant, is not as dramatic as the delocalizing resonance effect illustrated by the difference in pK_a values between an alcohol and a carboxylic acid. In general, *resonance effects are more powerful than inductive effects*.

Because the inductive effect depends on electronegativity, fluorine substituents have a more pronounced pKa-lowered effect than chlorine substituents.

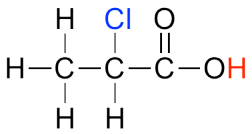


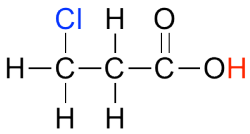
trichloroacetic acid
$pK_a = 0.64$

trifluoroacetic acid
$pK_a = -0.25$

In addition, the inductive takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away.

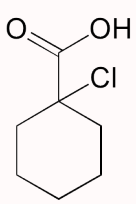
stronger acid



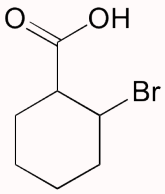


Exercise 7.3.4

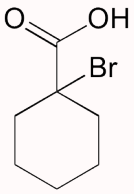
Rank the compounds below from most acidic to least acidic, and explain your reasoning.



A



B



C

Solution

Next section⇒

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

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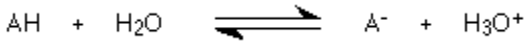
3.7: Organic Acids and Bases

This page explains the acidity of simple organic acids and looks at the factors which affect their relative strengths.

Organic acids as weak acids

For the purposes of this topic, we are going to take the definition of an acid as "a substance which donates hydrogen ions (protons) to other things". We are going to get a measure of this by looking at how easily the acids release hydrogen ions to water molecules when they are in solution in water.

An acid in solution sets up this equilibrium:



A hydroxonium ion is formed together with the anion (negative ion) from the acid.

This equilibrium is sometimes simplified by leaving out the water to emphasise the ionisation of the acid.



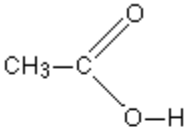
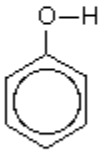
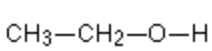
If you write it like this, you must include the state symbols - "(aq)". Writing $H^+_{(aq)}$ implies that the hydrogen ion is attached to a water molecule as H_3O^+. Hydrogen ions are always attached to something during chemical reactions.

The organic acids are weak in the sense that this ionisation is very incomplete. At any one time, most of the acid will be present in the solution as un-ionised molecules. For example, in the case of dilute ethanoic acid, the solution contains about 99% of ethanoic acid molecules - at any instant, only about 1% have actually ionised. The position of equilibrium therefore lies well to the left.

Comparing the strengths of weak acids

The strengths of weak acids are measured on the pK_a scale. The smaller the number on this scale, the stronger the acid is.

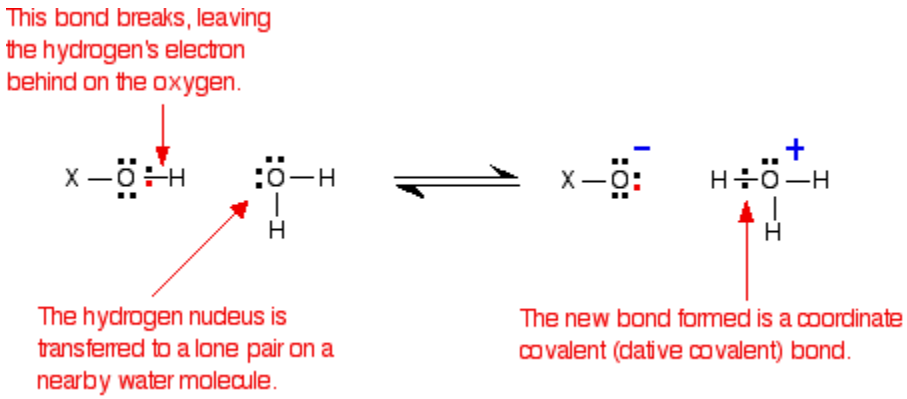
Three of the compounds we shall be looking at, together with their pK_a values are:

		pK_a
ethanoic acid		4.76
phenol		10.00
ethanol		about 16

Remember - the smaller the number the stronger the acid. Comparing the other two to ethanoic acid, you will see that phenol is very much weaker with a pK_a of 10.00, and ethanol is so weak with a pK_a of about 16 that it hardly counts as acidic at all!

Why are these acids acidic?

In each case, the same bond gets broken - the bond between the hydrogen and oxygen in an -OH group. Writing the rest of the molecule as "X":



So . . . if the same bond is being broken in each case, why do these three compounds have such widely different acid strengths?

Differences in acid strengths between carboxylic acids, phenols and alcohols

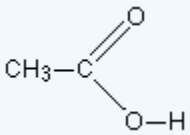
Two of the factors which influence the ionization of an acid are:

- the strength of the bond being broken,
- the stability of the ions being formed.

In these cases, you seem to be breaking the same oxygen-hydrogen bond each time, and so you might expect the strengths to be similar. The most important factor in determining the relative acid strengths of these molecules is the nature of the ions formed. You always get a hydroxonium ion - so that's constant - but the nature of the anion (the negative ion) varies markedly from case to case.

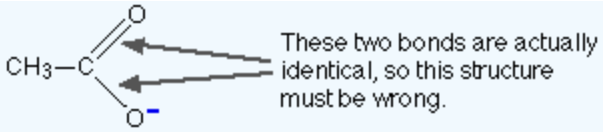
Example 3.7.1: Ethanoic Acid

Ethanoic acid has the structure:



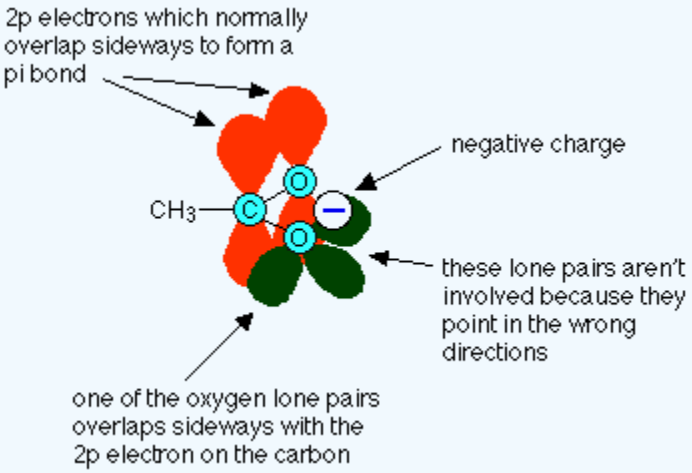
The acidic hydrogen is the one attached to the oxygen. When ethanoic acid ionises it forms the ethanoate ion, CH_3COO^-.

You might reasonably suppose that the structure of the ethanoate ion was as below, but measurements of bond lengths show that the two carbon-oxygen bonds are identical and somewhere in length between a single and a double bond.

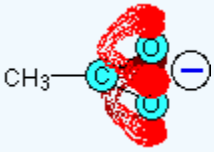


To understand why this is, you have to look in some detail at the bonding in the ethanoate ion. Like any other double bond, a carbon-oxygen double bond is made up of two different parts. One electron pair is found on the line between the two nuclei - this is known as a sigma bond. The other electron pair is found above and below the plane of the molecule in a pi bond. Pi bonds are made by sideways overlap between p orbitals on the carbon and the oxygen.

In an ethanoate ion, one of the lone pairs on the negative oxygen ends up almost parallel to these p orbitals, and overlaps with them

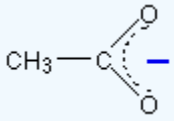


This leads to a delocalised pi system over the whole of the -COO^- group, rather like that in benzene.



All the oxygen lone pairs have been left out of this diagram to avoid confusion. Because the oxygens are more electronegative than the carbon, the delocalised system is heavily distorted so that the electrons spend much more time in the region of the oxygen atoms.

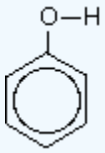
So where is the negative charge in all this? It has been spread around over the whole of the -COO^- group, but with the greatest chance of finding it in the region of the two oxygen atoms. Ethanoate ions can be drawn simply as:



The dotted line represents the delocalisation. The negative charge is written centrally on that end of the molecule to show that it isn't localised on one of the oxygen atoms. The more you can spread charge around, the more stable an ion becomes. In this case, if you delocalise the negative charge over several atoms, it is going to be much less attractive to hydrogen ions - and so you are less likely to re-form the ethanoic acid.

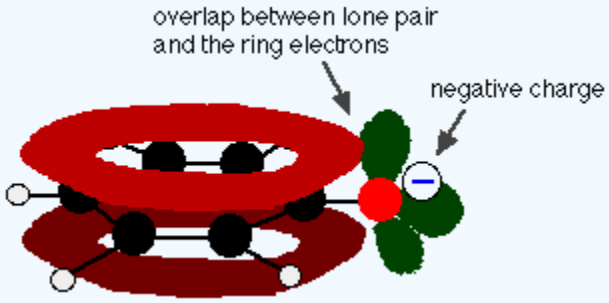
Example 3.7.2: Phenol

Phenols have an -OH group attached directly to a benzene ring. Phenol itself is the simplest of these with nothing else attached to the ring apart from the -OH group.

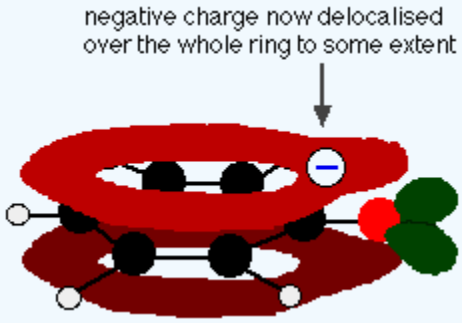


When the hydrogen-oxygen bond in phenol breaks, you get a phenoxide ion, $C_6H_5O^-$.

Delocalisation also occurs in this ion. This time, one of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.

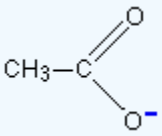


This overlap leads to a delocalisation which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localised on the oxygen, but is spread out around the whole ion.

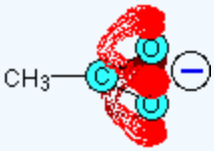


Why then is phenol a much weaker acid than ethanoic acid?

Think about the ethanoate ion again. If there wasn't any delocalisation, the charge would all be on one of the oxygen atoms, like this:



But the delocalisation spreads this charge over the whole of the COO group. Because oxygen is more electronegative than carbon, you can think of most of the charge being shared between the two oxygens (shown by the heavy red shading in this diagram).



If there wasn't any delocalisation, one of the oxygens would have a full charge which would be very attractive towards hydrogen ions. With delocalisation, that charge is spread over two oxygen atoms, and neither will be as attractive to a hydrogen ion as if one of the oxygens carried the whole charge.

That means that the ethanoate ion won't take up a hydrogen ion as easily as it would if there wasn't any delocalisation. Because some of it stays ionised, the formation of the hydrogen ions means that it is acidic.

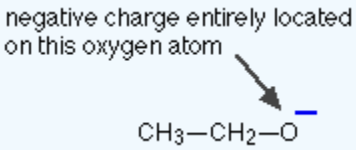
In the phenoxide ion, the single oxygen atom is still the most electronegative thing present, and the delocalised system will be heavily distorted towards it. That still leaves the oxygen atom with most of its negative charge.

What delocalisation there is makes the phenoxide ion more stable than it would otherwise be, and so phenol is acidic to an extent.

However, the delocalisation hasn't shared the charge around very effectively. There is still lots of negative charge around the oxygen to which hydrogen ions will be attracted - and so the phenol will readily re-form. Phenol is therefore only very weakly acidic.

Example 3.7.3: Ethanol

Ethanol, CH_3CH_2OH, is so weakly acidic that you would hardly count it as acidic at all. If the hydrogen-oxygen bond breaks to release a hydrogen ion, an ethoxide ion is formed:



This has nothing at all going for it. There is no way of delocalising the negative charge, which remains firmly on the oxygen atom. That intense negative charge will be highly attractive towards hydrogen ions, and so the ethanol will instantly re-form.

Since ethanol is very poor at losing hydrogen ions, it is hardly acidic at all.

Variations in acid strengths between different carboxylic acids

You might think that all carboxylic acids would have the same strength because each depends on the delocalization of the negative charge around the $-COO^-$ group to make the anion more stable, and so more reluctant to re-combine with a hydrogen ion.

In fact, the carboxylic acids have widely different acidities. One obvious difference is between methanoic acid, HCOOH, and the other simple carboxylic acids:

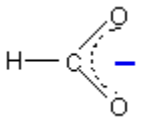
	pK_a
HCOOH	3.75
CH_3COOH	4.76
CH_3CH_2COOH	4.87

$CH_3CH_2CH_2COOH$	4.82

Remember that the higher the value for pK_a, the weaker the acid is.

Why is ethanoic acid weaker than methanoic acid? It again depends on the stability of the anions formed - on how much it is possible to delocalise the negative charge. The less the charge is delocalised, the less stable the ion, and the weaker the acid.

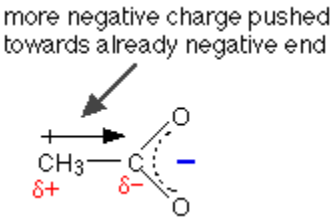
The methanoate ion (from methanoic acid) is:



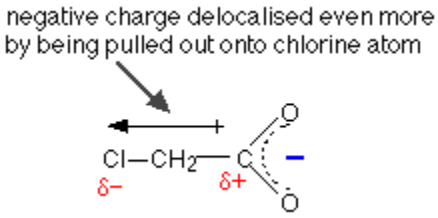
The only difference between this and the ethanoate ion is the presence of the CH_3 group in the ethanoate.

But that's important! Alkyl groups have a tendency to "push" electrons away from themselves. That means that there will be a small amount of extra negative charge built up on the $-COO^-$ group. Any build-up of charge will make the ion less stable, and more attractive to hydrogen ions.

Ethanoic acid is therefore weaker than methanoic acid, because it will re-form more easily from its ions.



The other alkyl groups have "electron-pushing" effects very similar to the methyl group, and so the strengths of propanoic acid and butanoic acid are very similar to ethanoic acid. The acids can be strengthened by pulling charge away from the $-COO^-$ end. You can do this by attaching electronegative atoms like chlorine to the chain.



As the next table shows, the more chlorines you can attach the better:

	pK_a
CH_3COOH	4.76
$CH_2ClCOOH$	2.86
$CHCl_2COOH$	1.29
CCl_3COOH	0.65

Trichloroethanoic acid is quite a strong acid.

Attaching different halogens also makes a difference. Fluorine is the most electronegative and so you would expect it to be most successful at pulling charge away from the $-COO^-$ end and so strengthening the acid.

	pK_a
CH_2FCOOH	2.66
$CH_2ClCOOH$	2.86
$CH_2BrCOOH$	2.90
CH_2ICOOH	3.17

The effect is there, but isn't as great as you might expect.

Finally, notice that the effect falls off quite quickly as the attached halogen gets further away from the $-COO^-$ end. Here is what happens if you move a chlorine atom along the chain in butanoic acid.

	pK_a
$CH_3CH_2CH_2COOH$	4.82
$CH_3CH_2CHClCOOH$	2.84
$CH_3CHClCH_2COOH$	4.06
$CH_2ClCH_2CH_2COOH$	4.52

The chlorine is effective at withdrawing charge when it is next-door to the $-COO^-$ group, and much less so as it gets even one carbon further away.

This page explains why simple organic bases are basic and looks at the factors which affect their relative strengths. For A'level purposes, all the bases we are concerned with are primary amines - compounds in which one of the hydrogens in an ammonia molecule, NH_3, is replaced either by an alkyl group or a benzene ring.

Ammonia as a weak base

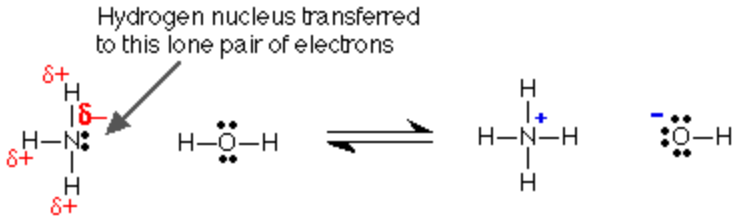
All of the compounds we are concerned with are derived from ammonia and so we'll start by looking at the reason for its basic properties. For the purposes of this topic, we are going to take the definition of a base as "a substance which combines with hydrogen ions (protons)". We are going to get a measure of this by looking at how easily the bases take hydrogen ions from water molecules when they are in solution in water.

Ammonia in solution sets up this equilibrium:

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

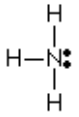
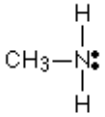
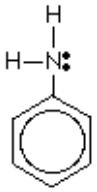
An ammonium ion is formed together with hydroxide ions. Because the ammonia is only a weak base, it doesn't hang on to the extra hydrogen ion very effectively and so the reaction is reversible. At any one time, about 99% of the ammonia is present as unreacted molecules. The position of equilibrium lies well to the left.

The ammonia reacts as a base because of the active lone pair on the nitrogen. Nitrogen is more electronegative than hydrogen and so attracts the bonding electrons in the ammonia molecule towards itself. That means that in addition to the lone pair, there is a build-up of negative charge around the nitrogen atom. That combination of extra negativity and active lone pair attracts the new hydrogen from the water.



Comparing the strengths of weak bases

The strengths of weak bases are measured on the pK_b scale. The smaller the number on this scale, the stronger the base is. Three of the compounds we shall be looking at, together with their pK_b values are:

		pK_b
ammonia		4.75
methylamine		3.36
phenylamine		9.38

Remember - the smaller the number the stronger the base. Comparing the other two to ammonia, you will see that methylamine is a stronger base, whereas phenylamine is very much weaker.

- Methylamine is typical of aliphatic primary amines - where the $-NH_2$ group is attached to a carbon chain. All aliphatic primary amines are stronger bases than ammonia.
- Phenylamine is typical of aromatic primary amines - where the $-NH_2$ group is attached directly to a benzene ring. These are very much weaker bases than ammonia.

Explaining the differences in base strengths

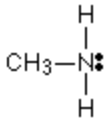
Two of the factors which influence the strength of a base are:

- the ease with which the lone pair picks up a hydrogen ion,
- the stability of the ions being formed.

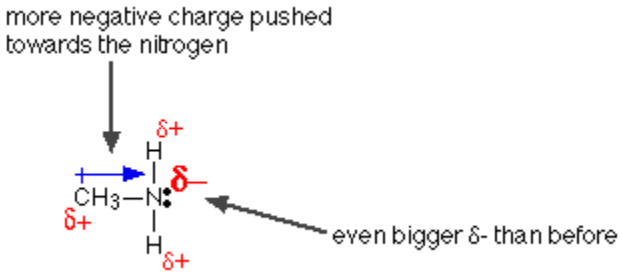
Why are aliphatic primary amines stronger bases than ammonia?

Methylamine

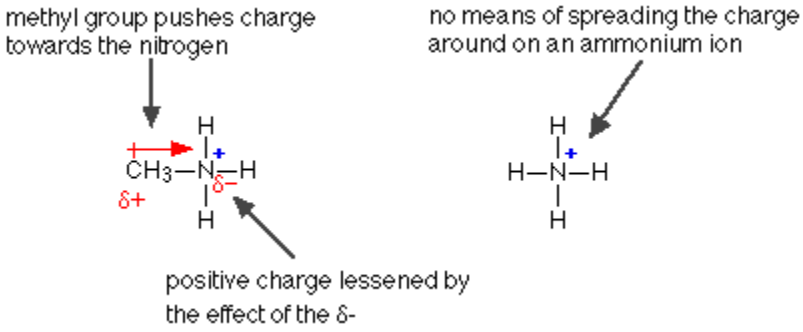
Methylamine has the structure:



The only difference between this and ammonia is the presence of the CH_3 group in the methylamine. But that's important! Alkyl groups have a tendency to "push" electrons away from themselves. That means that there will be a small amount of extra negative charge built up on the nitrogen atom. That extra negativity around the nitrogen makes the lone pair even more attractive towards hydrogen ions.



Making the nitrogen more negative helps the lone pair to pick up a hydrogen ion. What about the effect on the positive methylammonium ion formed? Is this more stable than a simple ammonium ion? Compare the methylammonium ion with an ammonium ion:



In the methylammonium ion, the positive charge is spread around the ion by the "electron-pushing" effect of the methyl group. The more you can spread charge around, the more stable an ion becomes. In the ammonium ion there isn't any way of spreading the charge.

To summarize:

- The nitrogen is more negative in methylamine than in ammonia, and so it picks up a hydrogen ion more readily.
- The ion formed from methylamine is more stable than the one formed from ammonia, and so is less likely to shed the hydrogen ion again.

Taken together, these mean that methylamine is a stronger base than ammonia.

The other aliphatic primary amines

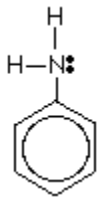
The other alkyl groups have "electron-pushing" effects very similar to the methyl group, and so the strengths of the other aliphatic primary amines are very similar to methylamine. For example:

	pK_b
CH_3NH_2	3.36
$CH_3CH_2NH_2$	3.27

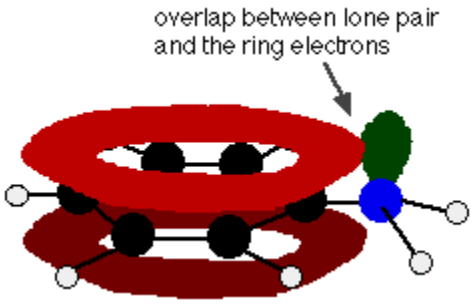
$CH_3CH_2CH_2NH_2$	3.16
$CH_3CH_2CH_2CH_2NH_2$	3.39

Why are aromatic primary amines much weaker bases than ammonia?

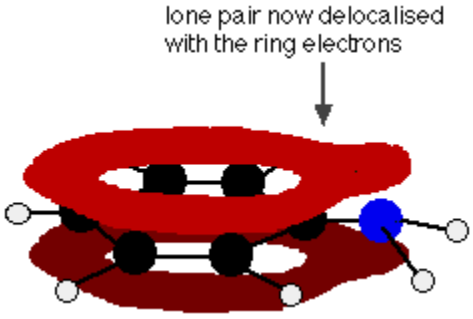
An aromatic primary amine is one in which the $-NH_2$ group is attached directly to a benzene ring. The only one you are likely to come across is phenylamine. Phenylamine has the structure:



The lone pair on the nitrogen touches the delocalized ring electrons . . .



. . . and becomes delocalized with them:



That means that the lone pair is no longer fully available to combine with hydrogen ions. The nitrogen is still the most electronegative atom in the molecule, and so the delocalized electrons will be attracted towards it, but the intensity of charge around the nitrogen is nothing like what it is in, say, an ammonia molecule.

The other problem is that if the lone pair is used to join to a hydrogen ion, it is no longer available to contribute to the delocalisation. That means that the delocalization would have to be disrupted if the phenylamine acts as a base. Delocalization makes molecules more stable, and so disrupting the delocalization costs energy and will not happen easily.

Taken together - the lack of intense charge around the nitrogen, and the need to break some delocalization - this means that phenylamine is a very weak base indeed.

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4: INTRODUCTION TO ALKENES

4.1: The π Bond
4.2: Nomenclature of Alkenes
4.3: Degree of Unsaturation
4.4: Electrophilic Addition Reactions of Alkenes
4.5: Carbocation Structure and Stability
4.6: Carbocation Rearrangements
4.7: Markovnikov Addition

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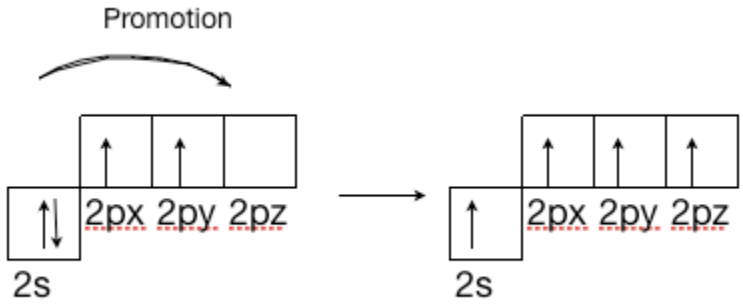
4.1: The π Bond

Ethene is the formal IUPAC name for $H_2C=CH_2$, but it also goes by a common name: Ethylene. The name Ethylene is used because it is like an ethyl group (CH_2CH_3) but there is a double bond between the two carbon atoms in it. Ethene has the formula C_2H_4 and is the simplest alkene because it has the fewest carbons (two) necessary for a carbon-carbon double bond.

Introduction

Bonding in carbon is covalent, containing either sigma or π bonds. Carbon can make single, double, or triple bonds. The number of bonds it makes determines the structure. With four single bonds, carbon has a tetrahedral structure, while with one double bond it's structure is trigonal planar, and with a triple bond it has a linear structure.

A solitary carbon atom has four electrons, two in the 2s orbital, and one in each of the $2p_x$ and $2p_y$ orbitals, leaving the $2p_z$ orbital empty. A single carbon atom can make up to four bonds, but by looking at its electron configuration this would not be possible because there are only two electrons available to bond with. The other two are in a lone pair state, making them much less reactive to another electron that is by itself. Well it is, in order to make the four bonds, the carbon atom promotes one of the 2s electrons into the empty $2p_z$ orbital, leaving the carbon with four unpaired electrons allowing it to now form four bonds. The electron is not promoted spontaneously. It becomes promoted when a photon of light with the correct wavelength hits the carbon atom. When this photon hits the carbon atom it gives the atom enough energy to promote one of the lone pair electrons to the $2p_z$ orbital.



Sigma and Pi Bonds

All the bonds in Ethene are covalent, meaning that they are all formed by two adjacent atoms sharing their valence electrons. As opposed to ionic bonds which hold atoms together through the attraction of two ions of opposite charges.

Sigma bonds are created when there is overlap of similar orbitals, orbitals that are aligned along the inter-nuclear axis. Common sigma bonds are $s+s$, p_z+p_z and $s+p_z$, z is the axis of the bond on the xyz-plane of the atom.

π bonds are created when there is adequate overlap of similar, adjacent p orbitals, such as p_x+p_x and p_y+p_y. Each p orbital has two lobes, one usually indicated by a + and the other indicated by a - (sometimes one may be shaded while the other is not). This + and - (shaded, not shaded) are only meant to indicate the opposite phase ϕ the wave functions, they **do not** indicate any type of electrical charge. For a π bond to form both lobes of the p orbital must overlap, + with + and - with -. When a + lobe overlaps with a - lobe this creates an anti-bonding orbital interaction which is much higher in energy, and therefore not a desirable interaction.

Usually there can be no π bonds between two atoms without having at least one sigma bond present first. But there are special cases such as dicarbon (C_2) where the central bond is a π bond not a sigma bond, but in cases like these the two atoms want to have as much orbital overlap as possible so the bond lengths between the atoms are smaller than what is normally expected.

The π bond in ethene is weak compared to the sigma bond between the two carbons. This weakness makes the π bond and the overall molecule a site of comparatively high chemical reactivity to an array of different substances. This is due to the high electron density in the π bond, and because it is a weak bond with high electron density the π bond will easily break in order to form two separate sigma bonds. Sites such as these are referred to as functional groups or functionalities. These groups

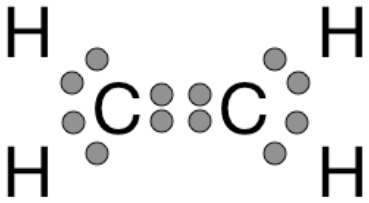
have characteristic properties and they control the reactivity of the molecule as a whole. How these functional groups and other reactants form various products are an important concept in organic chemistry.

Orbital Bonding in Ethene

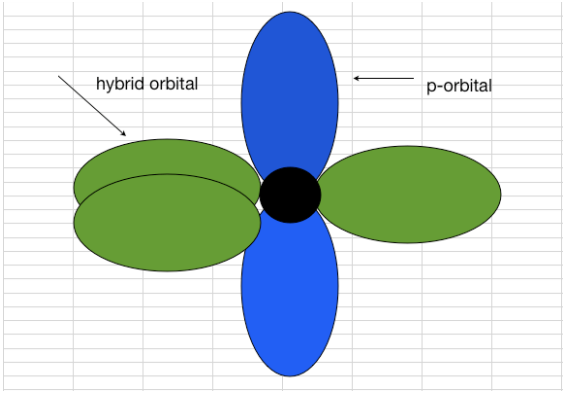
Ethene is made up of four $1s^1$ Hydrogen atoms and two $2s^2\ 2p_x^1\ 2p_y^2$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight in the valence shell. Having eight valence electrons around carbon gives the atom itself the same electron configuration as neon, a noble gas. Carbon wants to have the same configuration as Neon because when it has eight valence electrons carbon is at its most stable, lowest energy state, it has all of the electrons that it wants, so it is no longer reactive.

Structure of Ethene

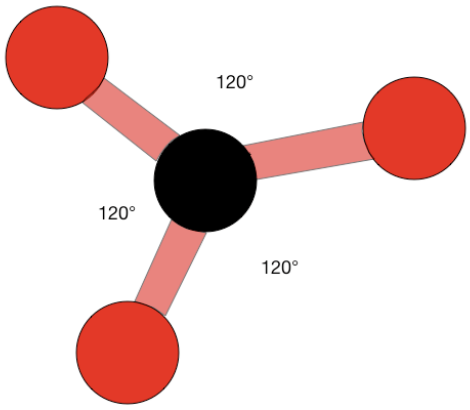
Ethene is not a very complicated molecule. It contains two carbon atoms that are double bonded to each other, with each of these atoms also bonded to two Hydrogen atoms.



This forms a total of three bonds to each carbon atom, giving them an sp^2 hybridization. Since the carbon atom is forming three sigma bonds instead of the four that it can, it only needs to hybridize three of its outer orbitals, instead of four. It does this by using the $2s$ electron and two of the $2p$ electrons, leaving the other unchanged. This new orbital is called an sp^2 hybrid because that's exactly what it is, it is made from one s orbital and two p orbitals.



When atoms are an sp^2 hybrid they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



The H-C-H bond angle is 117°, which is very close to the ideal 120° of a carbon with sp^2 hybridization. The other two angles (H-C=C) are both 121.5°.

Rigidity in Ethene

There is rigidity in the Ethene molecule due to the double-bonded carbons. In Ethane there are two carbons that share a single bond, this allows the two Methyl groups to rotate with respect to each other. These different conformations result in higher and lower energy forms of Ethane. In Ethene there is no free rotation about the carbon-carbon sigma bond. There is no rotation because there is also a π bond along with the sigma bond between the two carbons. A π bond is only formed when there is adequate overlap between both top and bottom p-orbitals. In order for there to be free rotation the p-orbitals would have to go through a phase where they are 90° from each other, which would break the π bond because there would be no overlap. Since the π bond is essential to the structure of Ethene it must not break, so there can be not free rotation about the carbon-carbon sigma bond.

References

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5th Ed.). New York: W. H. Freeman.

Outside Links

- Sigma Bond: http://en.Wikipedia.org/wiki/Sigma_bond
- Pi Bond: http://en.Wikipedia.org/wiki/Pi_bond
- Ethene (Ethylene): http://en.Wikipedia.org/wiki/Ethene
- Trigonal Planar Structure & Picture: http://en.Wikipedia.org/wiki/Trigonal_planar
- http://bcs.whfreeman.com/vollhardtsc...5e/default.asp

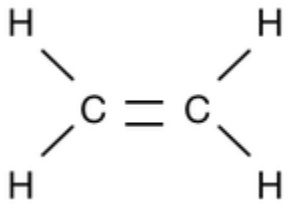
Problems

1. Write out the condensed formula for ethene.
2. Write out the Kekulé formula for ethene.
3. Write out the bond-line formula for ethene.
4. What are the distances between carbon and hydrogen atoms when they are bonded? Carbon-carbon single bond? Carbon-carbon double bond?
5. Why is it that the carbons in ethene cannot freely rotate around the carbon-carbon double bond?

Answers

1. H_2CCH_2

2.



3. –

4. C-H: 1.076 angstroms, C-C: 1.54 angstroms, C=C: 1.330 angstroms

5. the carbons cannot freely rotate about the carbon-carbon double bond because in order to rotate the p-orbitals would have to pass through a 90° point where there would no longer be any overlap, so the π bond would have to break for there to be free rotation.

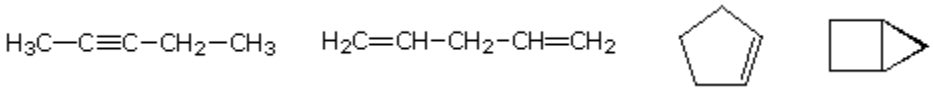
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- Structure and Bonding in Ethene: The \(\pi\) Bond is licensed CC BY-NC-SA 4.0.

4.2: Nomenclature of Alkenes

The molecular formula of a hydrocarbon provides information about the possible structural types it may represent. For example, consider compounds having the formula C_5H_8. The formula of the five-carbon alkane pentane is C_5H_{12} so the difference in hydrogen content is 4. This difference suggests such compounds may have a triple bond, two double bonds, a ring plus a double bond, or two rings. Some examples are shown here, and there are at least fourteen others!



Hence, as with alkanes, a consistent nomenclature system needs to be adopted that can separate the nature of these unsaturated chemicals. The simplest are the alkenes, which are hydrocarbons which have *carbon-carbon double bond* functional groups and are unsaturated hydrocarbons with the molecular formula is CnH_2n, which is also the same molecular formula as cycloalkanes.

IUPAC Rules for Alkene Nomenclature

1. The **ene** suffix (ending) indicates an alkene or cycloalkene.
2. The longest chain chosen for the root name must include both carbon atoms of the double bond.
3. The root chain must be numbered from the end nearest a double bond carbon atom. If the double bond is in the center of the chain, the nearest substituent rule is used to determine the end where numbering starts.
4. The smaller of the two numbers designating the carbon atoms of the double bond is used as the double bond locator.
5. If more than one double bond is present the compound is named as a diene, triene or equivalent prefix indicating the number of double bonds, and each double bond is assigned a locator number.
6. Substituent groups containing double bonds are:
    - **H_2C=CH–** Vinyl group
    - **H_2C=CH–CH_2–** Allyl group

Rule 1

Alkenes are named using the same general naming rules for alkanes, except that the suffix is now -ene. Here is a chart containing the systemic name for the first twenty straight chain alkenes.

Name	Molecular formula		Name	Molecular formula
Ethene	C_2H_4		Undecene	$C_{11}H_{22}$
Propene	C_3H_6		Dodecene	$C_{12}H_{24}$
Butene	C_4H_8		Tridecene	$C_{13}H_{26}$
Pentene	C_5H_{10}		Tetradecene	$C_{14}H_{28}$
Hexene	C_6H_{12}		Pentadecene	$C_{15}H_{30}$

Name	Molecular formula		Name	Molecular formula
Heptene	C_7H_{14}		Hexadecene	$C_{16}H_{32}$
Octene	C_8H_{16}		Heptadecene	$C_{17}H_{34}$
Nonene	C_9H_{18}		Octadecene	$C_{18}H_{36}$
Decene	$C_{10}H_{20}$		Nonadecene	$C_{19}H_{38}$

Did you notice how there is no methene? Because it is impossible for a carbon to have a double bond with nothing.

Rule 2

The parent structure is the longest chain containing both carbon atoms of the double bond. If the alkene contains only one double bond and that double bond is terminal (the double bond is at one end of the molecule or another) then it is not necessary to place any number in front of the name.

- **butane:** C_4H_{10} ($CH_3CH_2CH_2CH_3$)
- **butene:** C_4H_8 ($CH_2{=}CHCH_2CH_3$)

If the double bond is not terminal (if it is on a carbon somewhere in the center of the chain) then the carbons should be numbered in such a way as to give the first of the two double-bonded carbons the lowest possible number, and that number should precede the "ene" suffix with a dash, as shown below.

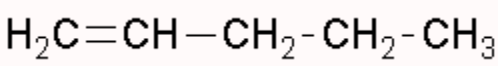
- **correct:** pent-2-ene ($CH_3CH{=}CHCH_2CH_3$)
- **incorrect:** pent-3-ene ($CH_3CH_2CH{=}CHCH_3$)

The second one is incorrect because flipping the formula horizontally results in a lower number for the alkene.

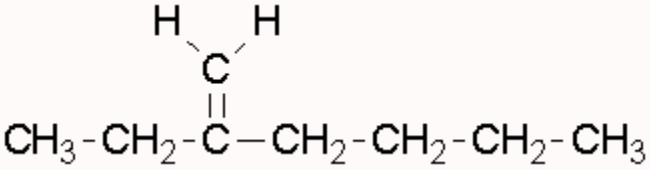
Exercise $4.2.1$

Name the following compounds:

a:



b.



Answer a

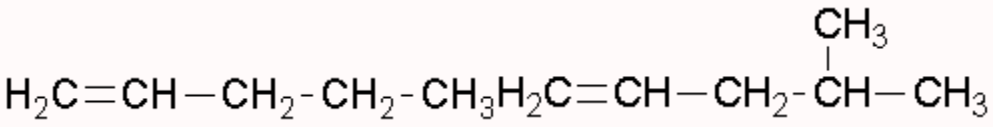
1-pentene or pent-1-ene

Answer b

2-ethyl-1-hexene or 2-ethylhex-1-ene

Exercise 4.2.2

a: Name the following compound (hint: give the double bond the lowest possible numbers regardless of substituent placement).

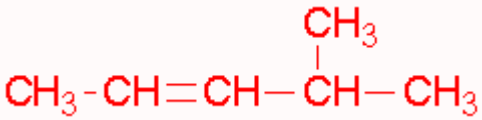


b. Draw a structure for 4-methyl-2-pentene.

Answer a

4-methylpent-1-ene

Answer b



Rule 4

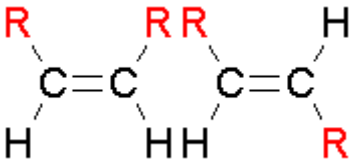
If there is more than one double bond in an alkene, all of the bonds should be numbered in the name of the molecule - even terminal double bonds. The numbers should go from lowest to highest, and be separated from one another by a comma. The IUPAC numerical prefixes are used to indicate the number of double bonds.

- **octa-2,4-diene:** $CH_3CH{=}CHCH{=}CHCH_2CH_2CH_3$
- **deca-1,5-diene:** $CH_2{=}CHCH_2CH_2CH{=}CHCH_2CH_2CH_2CH_3$

Note that the numbering of "2-4" above yields a molecule with two double bonds separated by just one single bond. Double bonds in such a condition are called "conjugated", and they represent an enhanced stability of conformation, so they are energetically favored as reactants in many situations and combinations.

Rule 4: Geometric Isomers

Double bonds can exist as geometric isomers and these isomers are designated by using either the cis / trans designation or the more flexible E / Z designation.



cis Isomers have the two largest groups are on the same side of the double bond (left structure above) and trans Isomers have the two largest groups are on opposite sides of the double bond (right structure above).E/Z nomenclature

If there are 3 or 4 non-hydrogen different atoms attached to the alkene then use the E, Z system.

- E (entgegen) means the higher priority groups are opposite one another relative to the double bond.
- Z (zusammen) means the higher priority groups are on the same side relative to the double bond.

E = entgegan ("trans") Z = zusamen ("cis")

Priority of groups is based on the atomic mass of attached atoms (not the size of the group). An atom attached by a multiple bond is counted once for each bond.

fluorine atom > isopropyl group > n-hexyl group

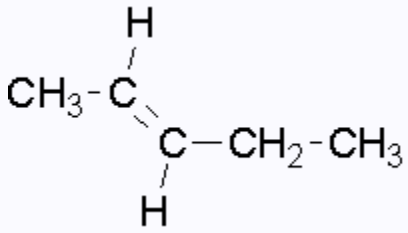
deuterium atom > hydrogen atom

$$-CH_2-CH=CH_2 > -CH_2CH_2CH_3$$

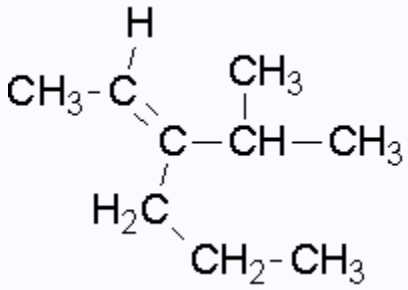
Example 4.2.5

Try to name the following compounds using both cis-trans and E/Z conventions:

a:



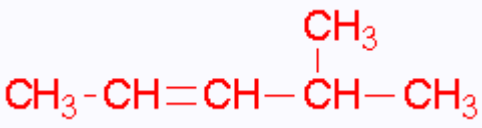
b:



Answer a

4-methylpent-1-ene

Answer b



Example 4.2.3

What is the name of this molecule?



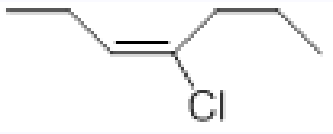
Solution

In this diagram this is a cis conformation. It has both the substituents going upward. This molecule would be called (cis) 5-chloro-3-heptene.)

Trans would look like this

Example 4.2.4

What is the name of this molecule?



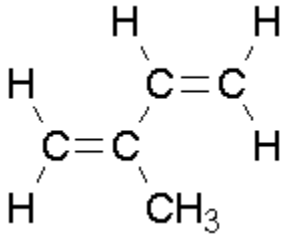
Solution

In this example it is E-4-chloro-3-heptene. It is E because the Chlorine and the CH_2CH_3 are the two higher priorities and they are on opposite sides.

Common names

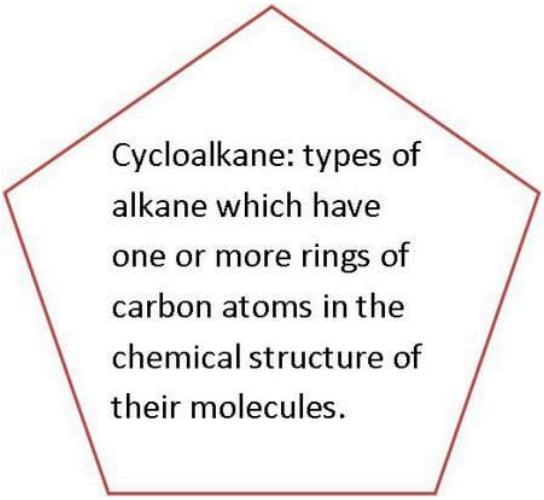
Remove the -ane suffix and add -ylene. There are a couple of unique ones like ethenyl's common name is vinyl and 2-propenyl's common name is allyl. That you should know are...

- vinyl substituent $H_2C=CH-$
- allyl substituent $H_2C=CH-CH_2-$
- allene molecule $H_2C=C=CH_2$
- isoprene

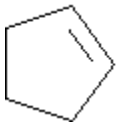


Endocyclic Alkenes

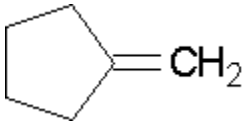
Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.



Cyclopentene is an example of an endocyclic double bond.



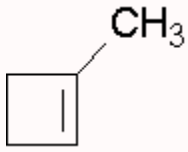
Methylenecylopentane is an example of an exocyclic double bond.



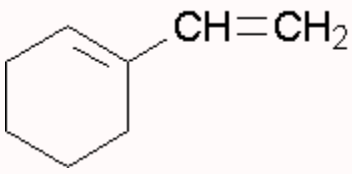
Exercise 4.2.1

Name the following compounds:

a:



b:



Answer a

1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.

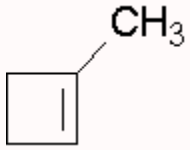
Answer b

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.

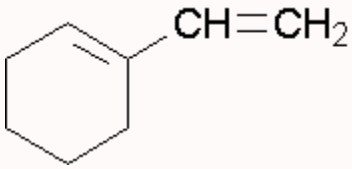
Exercise 4.2.1

Name the following compounds:

a:



b:



Answer a

1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.

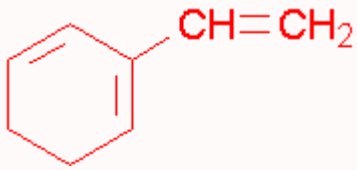
Answer b

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.

Exercise 4.2.1

Draw structures for the following 2-vinyl-1,3-cyclohexadiene

Answer



References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Problems

Try to name the following compounds...

1-pentene or pent-1-ene

2-ethyl-1-hexene or 2-ethylhex-1-ene

Try to draw structures for the following compounds...

- 2-pentene

$CH_3–CH=CH–CH_2–CH_3$

- 3-heptene

$CH_3–CH_2–CH=CH–CH_2–CH_2–CH_3$

b. Give the double bond the lowest possible numbers regardless of substituent placement.

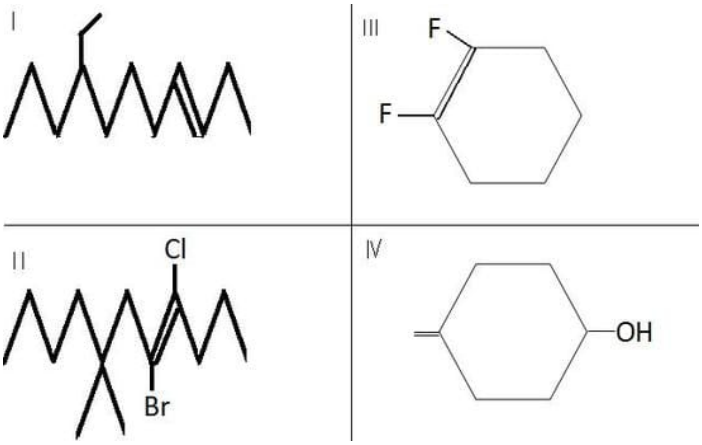
• Try to name the following compound...

J

• Try to draw a structure for the following compound...

4-methyl-2-pentene J

Name the following structures:



v. Draw (Z)-5-Chloro-3-ethly-4-hexen-2-ol.

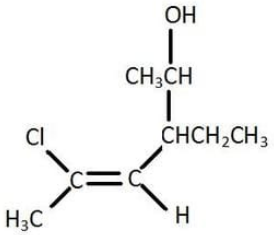
Answers

I. trans-8-ethyl-3-undecene

II. E-5-bromo-4-chloro-7,7-dimethyl-4-undecene

III. Z-1,2-difluoro-cyclohexene

IV. 4-ethenylcyclohexanol.



V.

Contributors

- S. Devarajan (UCD)
- Richard Banks (Boise State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jonathan Mooney (McGill University)

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4.3: Degree of Unsaturation

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 since knowing the degrees of unsaturation make it easier for one to figure out the molecular structure; it helps one double-check the number of π bonds and/or cyclic rings.

Saturated vs. Unsaturated Molecules

In the lab, saturation may be thought of as the point when a solution cannot dissolve anymore of a substance added to it. In terms of degrees of unsaturation, a molecule only containing single bonds with no rings is considered saturated.

$CH_3CH_2CH_3$	chewiki_sat.bmp	chewiki_sat2 (3).bmp	1-methyoxypentane

Unlike saturated molecules, unsaturated molecules contain double bond(s), triple bond(s) and/or ring(s).

$CH_3CH{=}CHCH_3$	chewiki_unsat1.bmp	chewiki_unsat2.bmp	chewiki_unsat3.bmp	3-chloro-5-octyne

Calculating Degrees of Unsaturation (DoU)

Degree of Unsaturation (DoU) is also known as **Double Bond Equivalent**. If the molecular formula is given, plug in the numbers into this formula:

$$DoU = \frac{2C + 2 + N - X - H}{2} \tag{4.3.1}$$

- 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

As stated before, a saturated molecule contains only single bonds and no rings. Another way of interpreting this is that a saturated molecule has the maximum number of hydrogen atoms possible to be an acyclic alkane. Thus, the number of hydrogens can be represented by 2C+2, which is the general molecular representation of an alkane. 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]*. The compound needs 4 more hydrogens in order to be fully saturated *(expected number of hydrogens-observed number of hydrogens=8-4=4)*. Degrees of unsaturation is equal to 2, or half the number of hydrogens the molecule needs to be classified as saturated. Hence, the DoB formula divides by 2. The formula subtracts the number of X's because a halogen (X) replaces a hydrogen in a compound. For instance, in chloroethane, C_2H_5Cl, there is one less hydrogen compared to ethane, C_2H_6.

For a compound to be saturated, there is one more hydrogen in a molecule when nitrogen is present. Therefore, we add the number of nitrogens (N). This can be seen with C_3H_9N compared to C_3H_8. Oxygen and sulfur are not included in the formula

because saturation is unaffected by these elements. As seen in alcohols, the same number of hydrogens in ethanol, C_2H_5OH, matches the number of hydrogens in ethane, C_2H_6.

The following chart illustrates the possible combinations of the number of double bond(s), triple bond(s), and/or ring(s) for a given degree of unsaturation. Each row corresponds to a different combination.

- 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).

DoU	Possible combinations of rings/ bonds		
	# of rings	# of double bonds	# of triple bonds
1	1	0	0
	0	1	0
2	2	0	0
	0	2	0
	0	0	1
	1	1	0
3	3	0	0
	2	1	0
	1	2	0
	0	1	1
	0	3	0
	1	0	1

Remember, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or rings. For instance, a degree of unsaturation of 3 can contain 3 rings, 2 rings+1 double bond, 1 ring+2 double bonds, 1 ring+1 triple bond, 1 double bond+1 triple bond, *or* 3 double bonds.

Example: 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.

chewiki_unsat1.bmp

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.

4 DoB_2.bmp 4 DoB_3.bmp 4DoB_1.bmp

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)

Problems

1. Are the following molecules saturated or unsaturated:
    1. chewiki_prob1a.bmp (b.)chewiki_prob2b.bmp (c.) chewiki_prob1c.bmp (d.) $C_{10}H_6N_4$
2. Using the molecules from 1., give the degrees of unsaturation for each.
3. Calculate the degrees of unsaturation for the following molecular formulas:
    1. (a.) C_9H_{20} (b.) C_7H_8 (c.) C_5H_7Cl (d.) $C_9H_9NO_4$
4. Using the molecular formulas from 3, are the molecules unsaturated or saturated.
5. Using the molecular formulas from 3, if the molecules are unsaturated, how many rings/double bonds/triple bonds are predicted?

Answers

1.

(a.) **unsaturated** (E*ven though rings only contain single bonds, rings are considered unsaturated.)*

(b.) **unsaturated**

(c.) **saturated**

(d.) **unsaturated**

2. *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**

(b.) **2** *(one double bond and the double bond from the carbonyl)*

(c.) **0**

(d.) **10**

3. *Use the formula to solve*

(a.) **0**

(b.) **4**

(c.) **2**

(d.) **6**

4.

(a.) **saturated**

(b.) **unsaturated**

(c.) **unsaturated**

(d.) **unsaturated**

5.

(a.) **0** (Remember-a saturated molecule only contains single bonds)

(b.) *The molecule can contain any of these combinations* **(i) 4 double bonds (ii) 4 rings (iii) 2 double bonds+2 rings (iv) 1 double bond+3 rings (v) 3 double bonds+1 ring (vi) 1 triple bond+2 rings (vii) 2 triple bonds (viii) 1 triple bond+1 double bond+1 ring (ix) 1 triple bond+2 double bonds**

(c.) (**i) 1 triple bond (ii) 1 ring+1 double bond (iii) 2 rings (iv) 2 double bonds**

(d.) **(i) 3 triple bonds (ii) 2 triple bonds+2 double bonds (iii) 2 triple bonds+1 double bond+1 ring (iv)...** *(As you can see, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or ring. Thus, the formula may give numerous possible structures for a given molecular formula.)*

Contributors

- Kim Quach (UCD)

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4.4: Electrophilic Addition Reactions of Alkenes

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

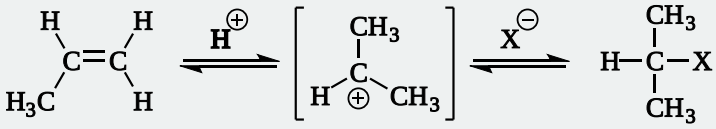
Make certain that you can define, and use in context, the key terms below.

- 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.

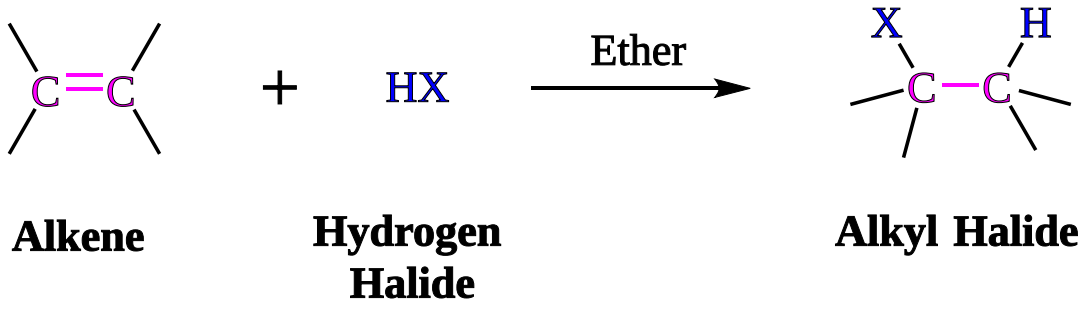
Introduction

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.

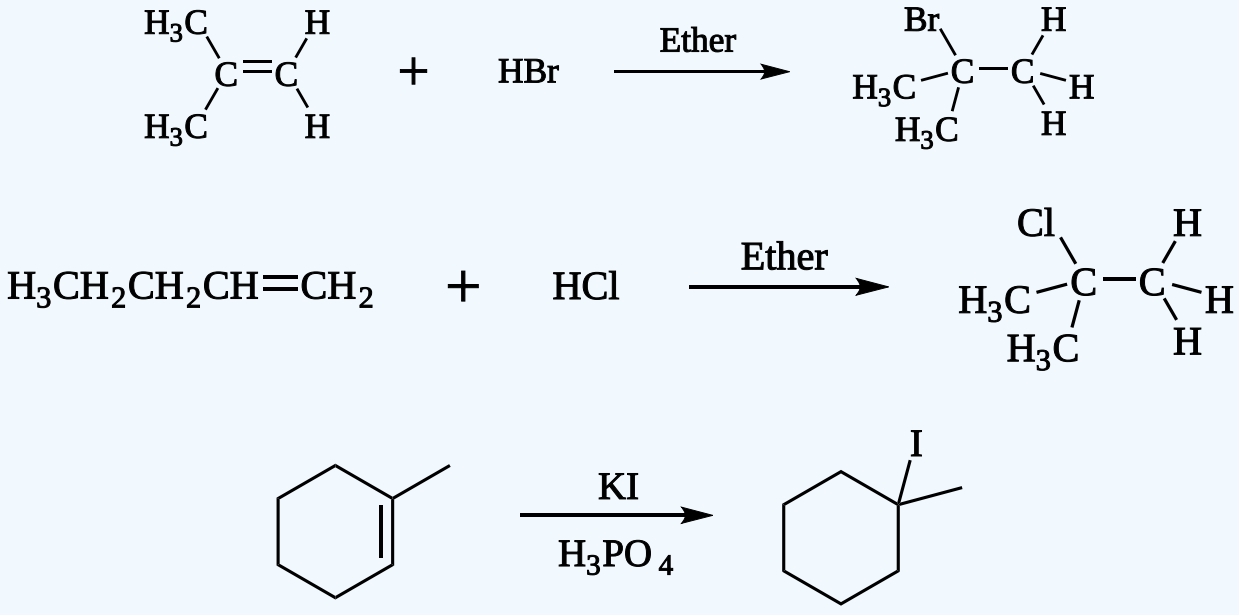
As discussed in Section 6-5, the double bond in alkenes is electron rich due to the prescience of 4 electrons instead of the two in a single bond. Also, the pi electrons are positioned above and below the double bond making them more accessibly for reactions. Overall, double bonds can easily donate lone 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 4.4.1



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 4.4.1 Electrophilic addition of HCl to ethene.

With but-2-ene you get 2-chlorobutane:

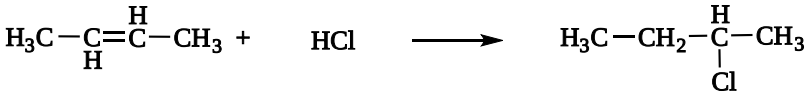


Figure 4.4.2 Electrophilic addition of HCl to but-2-ene.

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.

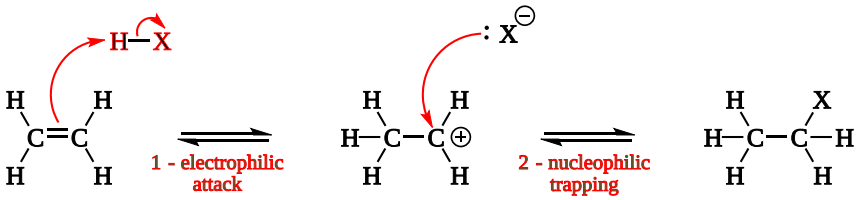


Figure 4.4.3*Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene*

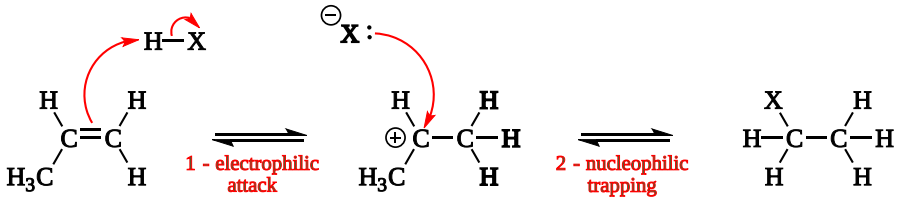
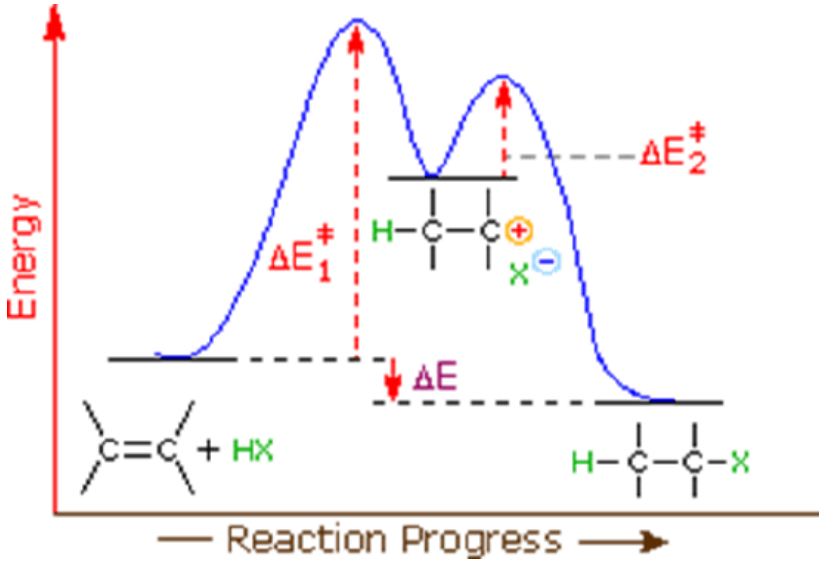


Figure 4.4.4 *Mechanism of Electrophilic Addition of Hydrogen Halide to Propene*

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.

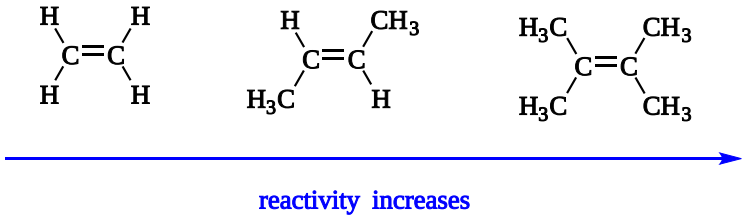
When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound 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:

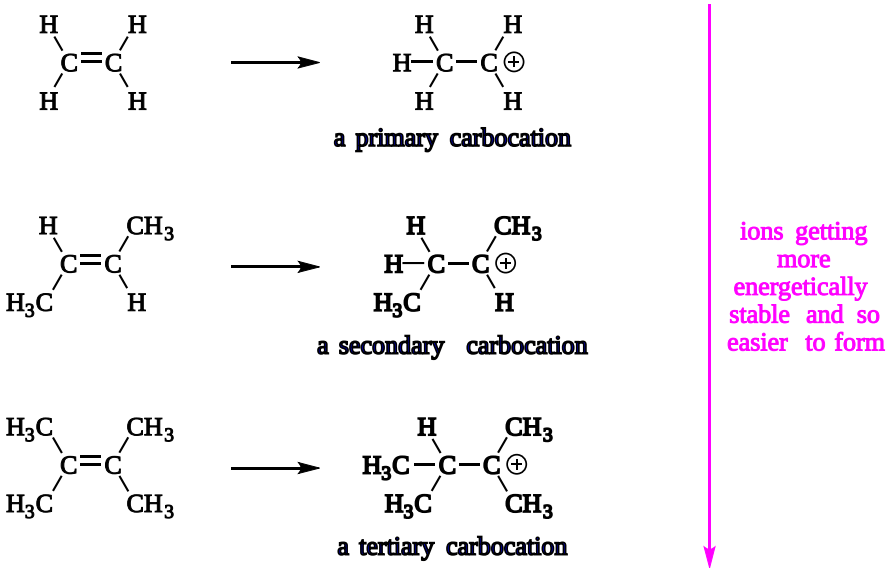


There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

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.

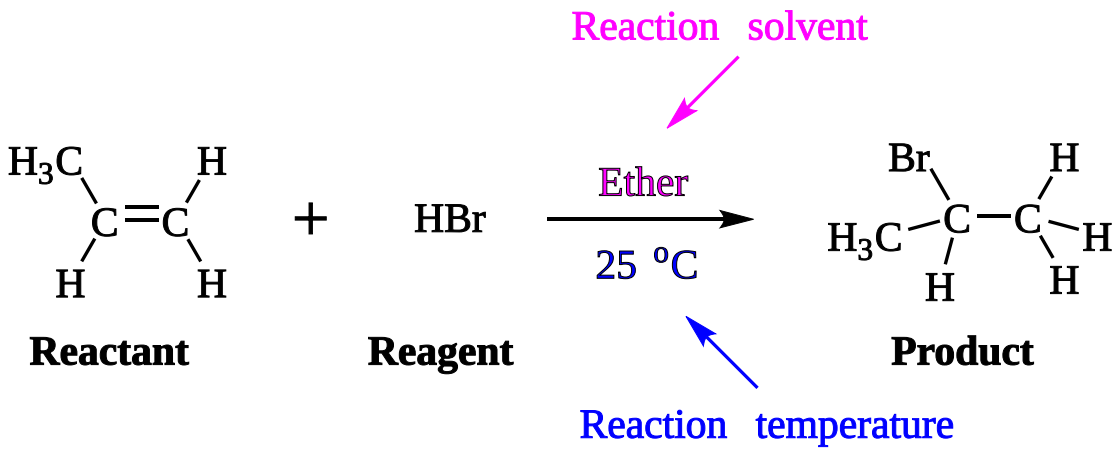
The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



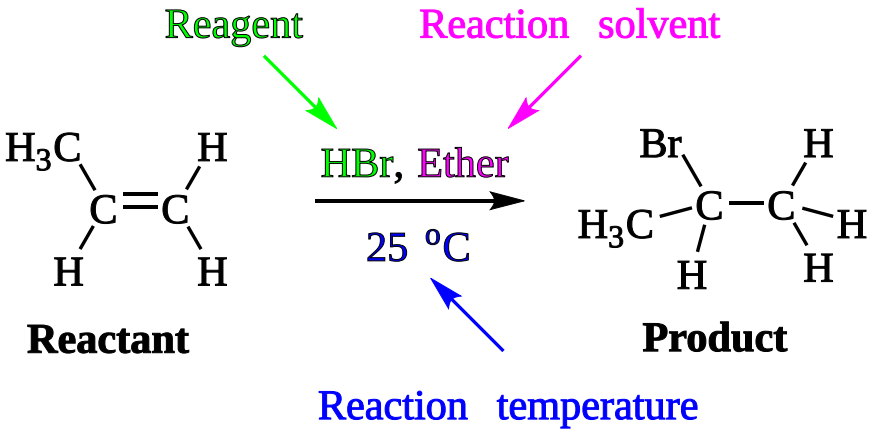
The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

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.



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4.5: Carbocation Structure and Stability

Objectives

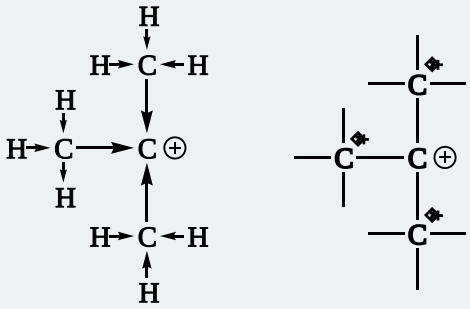
After completing this section, you should be able to

- describe the geometry of a given carbocation.
- arrange a given series of carbocations in order of increasing or decreasing stability.
- explain the relative stability of methyl, primary, secondary and tertiary carbocations in terms of hyperconjugation and inductive effects.

Study Notes

Although hyperconjugation can be used to explain the relative stabilities of carbocations, this explanation is certainly not the only one, and is by no means universally accepted. A more common explanation, involving the concept of an inductive effect, is given below.

It is a general principle in chemistry that the more a charge is dispersed, the more stable is the species carrying the charge. Put simply, a species in which a positive charge is shared between two atoms would be more stable than a similar species in which the charge is borne wholly by a single atom. In a tertiary carbocation, the positively charged carbon atom attracts the bonding electrons in the three carbon-carbon sigma (σ) bonds, and thus creates slight positive charges on the carbon atoms of the three surrounding alkyl groups (and, indeed, on the hydrogen atoms attached to them). Chemists sometimes use an arrow to represent this inductive release:



Note: These diagrams do not reflect the geometry of the carbocation. The overall charge on the carbocation remains unchanged, but some of the charge is now carried by the alkyl groups attached to the central carbon atom; that is, the charge has been dispersed.

In the tertiary carbocation shown above, the three alkyl groups help to stabilize the positive charge. In a secondary carbocation, only two alkyl groups would be available for this purpose, while a primary carbocation has only one alkyl group available. Thus the observed order of stability for carbocations is as follows:

tertiary > secondary > primary > methyl.

Stability of carbocation intermediates

The next step in understanding why Markovnikov's rule is often followed in electrophilic additions, involves understanding the structure and stability of the carboncation intermediate formed during the mechanism.

Carbocation Structure

Carbocations typically have three substituents which makes the carbon sp^2 hybridized and gives the overall molecule a trigonal planar geometry (Figure 4.5.1). The carbocation's substituents are all in the same plane and have a bond angle of 120° between them. The carbon atom in the carbocation is electron deficient; it only has six valence electrons which are used to form three sigma covalent bonds with the substituents. The carbocation carbon has an unoccupied p orbital which is perpendicular to the plane created by the substituents. The p orbital can easily accept electron pairs during reactions making carbocations excellent Lewis acids.

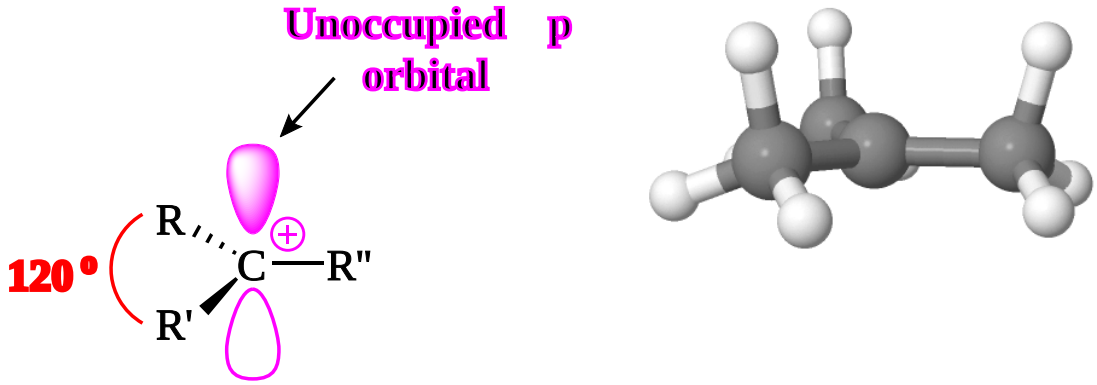
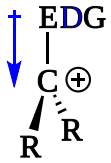


Figure 4.5.1: (1) Hybridization of a generic carbocation and (2) the structure of the tert-butyl cation ($C_4H_9^+$).

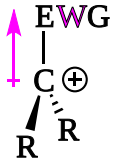
Stability of Carbocation Intermediates

By being a reactive intermediate of the electrophilic addition mechanism, the stability of a carbocation has a direct effect on the reaction. The critical question now becomes, *what stabilizes a carbocation*?

A positively charged species such as a carbocation is very electron-poor, and thus anything which donates electron density will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.



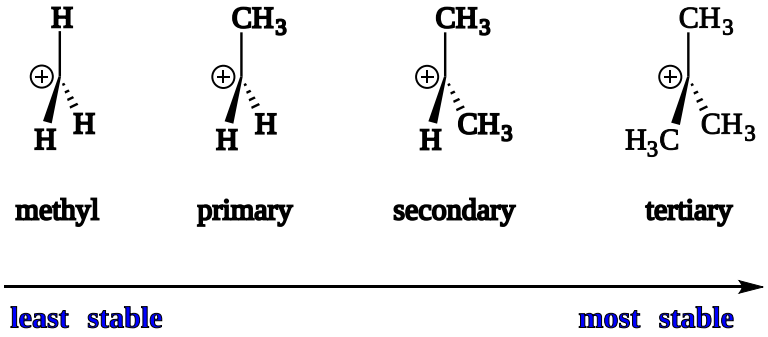
electron donating group *stabilizes* a carbocation



electron withdrawing group *destabilizes* a carbocation

Extensive experimental evidence has shown that a carbocation becomes more stable as the number of alkyl substituents increases. Carbocations can be given a designation based on the number of alkyl groups attached to the carbocation carbon. Three alkyl groups is called a tertiary (3°) carbocation, 2 alkyl groups is called secondary (2°), and 1 alkyl group is called primary (1°). No alkyl groups are attached (3 hydrogen substituents) is called a methyl carbocation.

The overall order of stability is as follows:

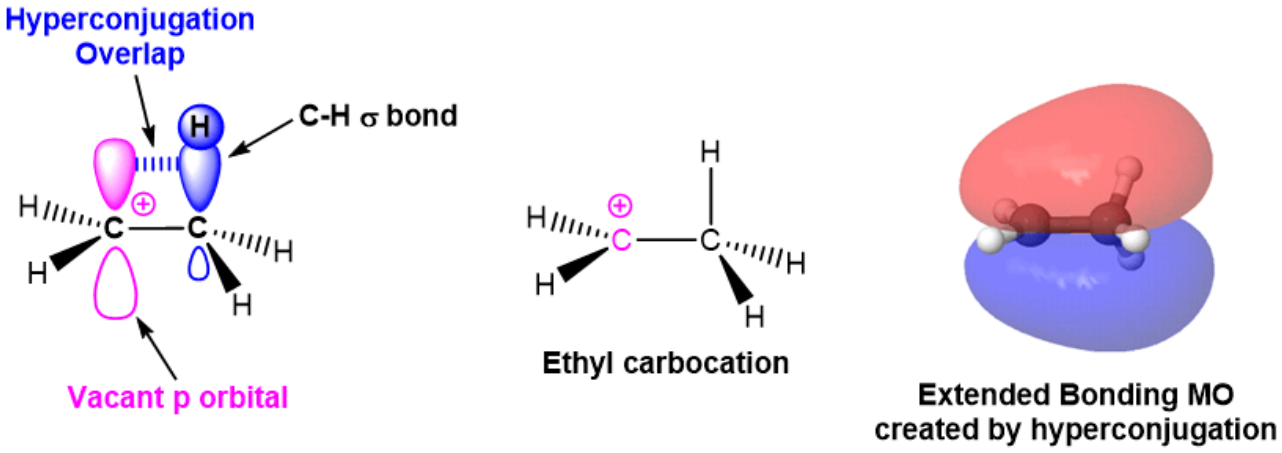


Alkyl groups stabilized carbocations for two reasons. The first is through inductive effects. As discussed in **Section 2-1**, inductive effects occur when the electrons in covalent bonds are shifted towards an nearby atom with a higher electronegativity. In this case, the positively charged carbocation draws in electron density from the surrounding substituents thereby gaining stabilization by slightly reducing its positive charge. Alkyl groups are more effective at inductively donating electron density than a hydrogen because they are larger, more polarizable, and contain more bonding electrons. As more alkyl groups are attached to the carbocation more inductive electron donation occurs and the carbocation becomes more stable.

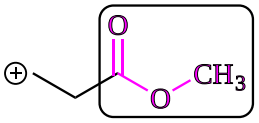
The second reason alkyl groups stabilize carbocations is through hyperconjugation. As previously discussed in **Section 7.6**, hyperconjugation is an electron donation that occurs from the parallel overlap of p orbitals with adjacent hybridized orbitals participating in sigma bonds. This electron donation serves to stabilize the carbocation. As the number of alkyl substituents increases, the number of sigma bonds available for hyperconjugation increases, and the carbocation tends to become more stabilized.

In the example of ethyl carbocation shown below, the p orbital from a sp^2 hybridized carbocation carbon involved interacts with a sp^3 hybridized orbital participating in an adjacent C-H sigma bond. Electron density from the C-H sigma bond is donated into carbocation's p orbital providing stabilization.

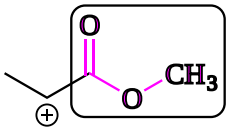
The molecular orbital of the ethyl carbocation shows the interaction of electrons in methyl group's C-H sigma bonds with the adjacent empty p orbital from the carbocation. The interaction creates a bonding molecular orbital which extends over the three atom chain (C-C-H) involved in hyperconjugation. The expanded molecular orbital helps to stabilize the carbocation.



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 that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.



A: more stable

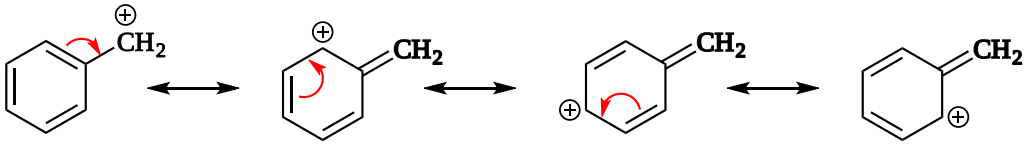


B: less stable

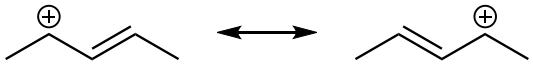
The difference in stability can be explained by considering the electron-withdrawing inductive effect of the ester carbonyl. Recall that inductive effects - whether electron-withdrawing or donating - are relayed through covalent bonds and that the strength of the effect decreases rapidly as the number 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.

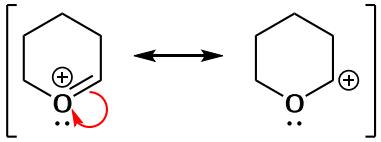
Stabilization of a carbocation can also occur through resonance effects, and as we have already discussed in the acid-base chapter, resonance effects as a rule are more powerful than inductive effects. Consider the simple case of a **benzylic** carbocation:



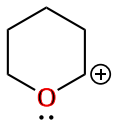
This carbocation is comparatively stable. In this case, electron donation is a resonance effect. Three additional resonance structures can be drawn for this carbocation in which the positive charge is located on one of three aromatic carbons. The positive charge is not isolated on the benzylic carbon, 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.



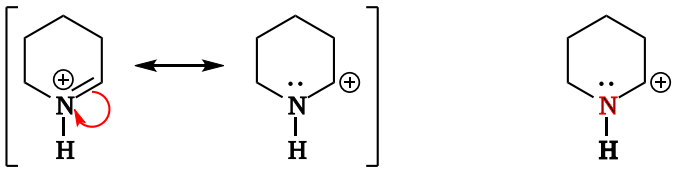
Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall 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)

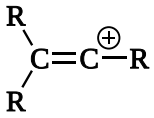


more stable

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.

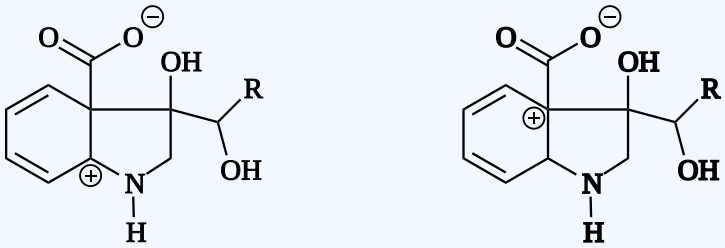
Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.



a vinylic carbocation (very unstable)

Example 4.5.1

In which of the structures below is the carbocation expected to be more stable? Explain.



Answer available at the end of this section.

Example 4.5.2

Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.

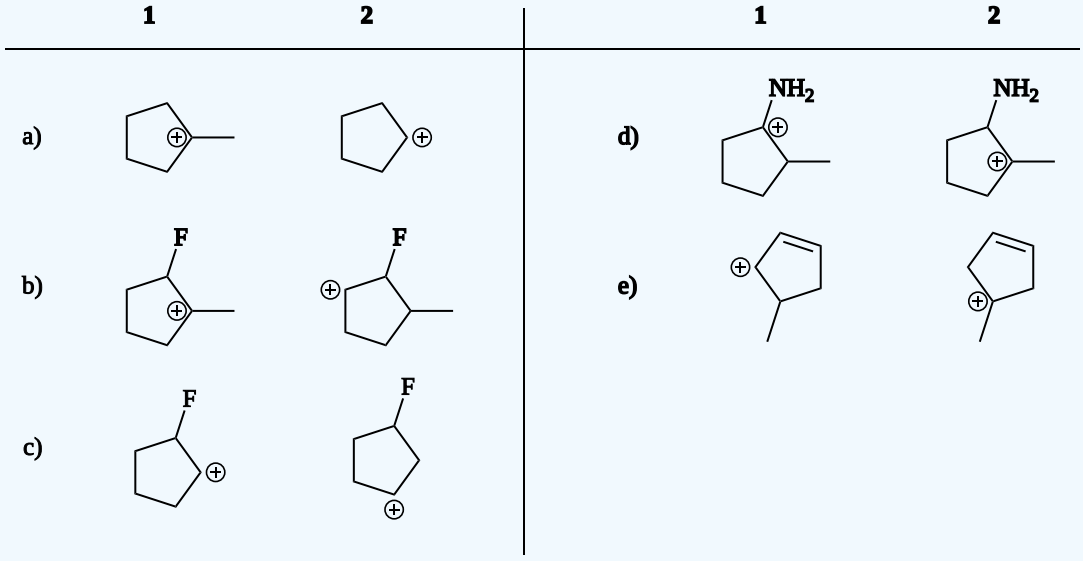
Answer available at the end of this section.

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 4.5.3

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.

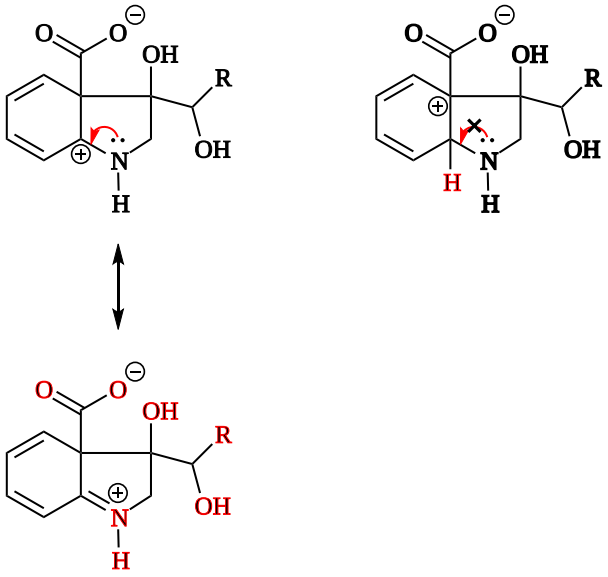


Answer available at the end of this section.

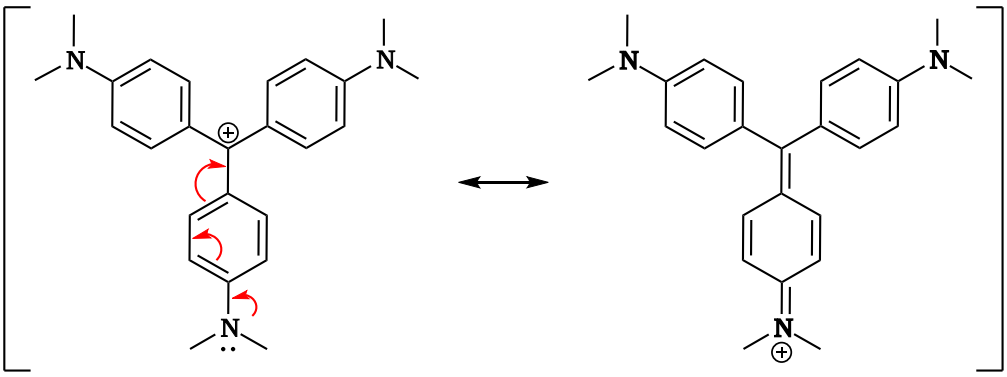
Answers

Example 4.5.1

In the carbocation on the left, the positive charge is located in a position relative to the nitrogen such that the lone pair of electrons on the nitrogen can be donated to fill the empty orbital. This is not possible for the carbocation species on the right.



Example 4.5.2



Example 4.5.3

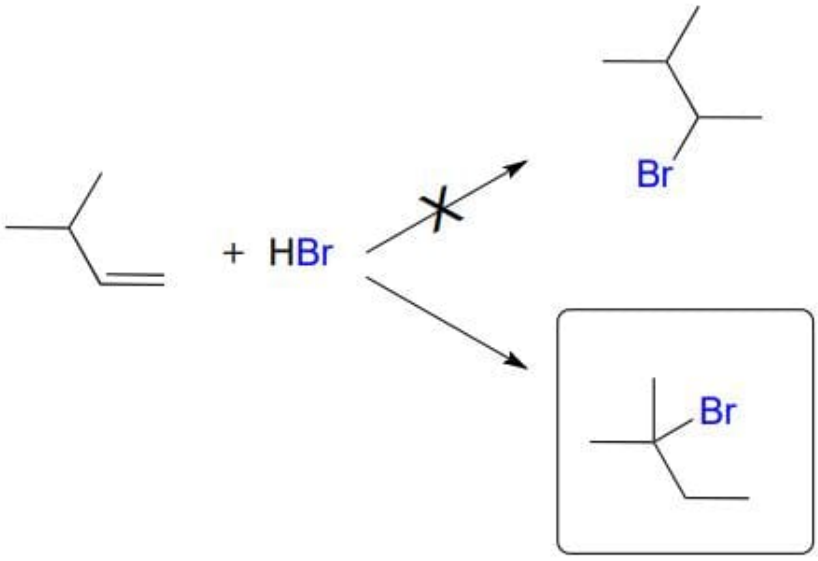
a. 1 (tertiary vs. secondary carbocation)
b. 1 (tertiary vs. secondary carbocation)
c. 2 (positive charge is further from electron-withdrawing fluorine)
d. 1 (lone pair on nitrogen can donate electrons by resonance)
e. 1 (allylic carbocation – positive charge can be delocalized to a second carbon)

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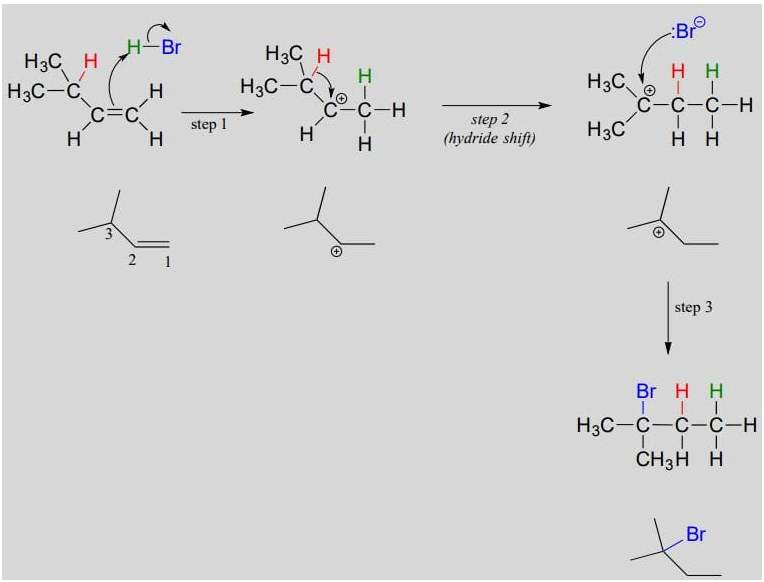
4.6: Carbocation Rearrangements

Earlier in this chapter we introduced the so-called 'Markovnikov rule', which can be used to predict the favored regiochemical outcome of electrophilic additions to asymmetric alkenes. According to what we have learned, addition of HBr to 3-methyl-1-butene should result in a secondary bromoalkane. However, the predominant product that is actually be observed in this reaction is a tertiary alkyl bromide! Little or no secondary alkyl bromide forms.



To explain this result, let's take a look at the mechanism for the reaction:

Electrophilic addition with a hydride shift:

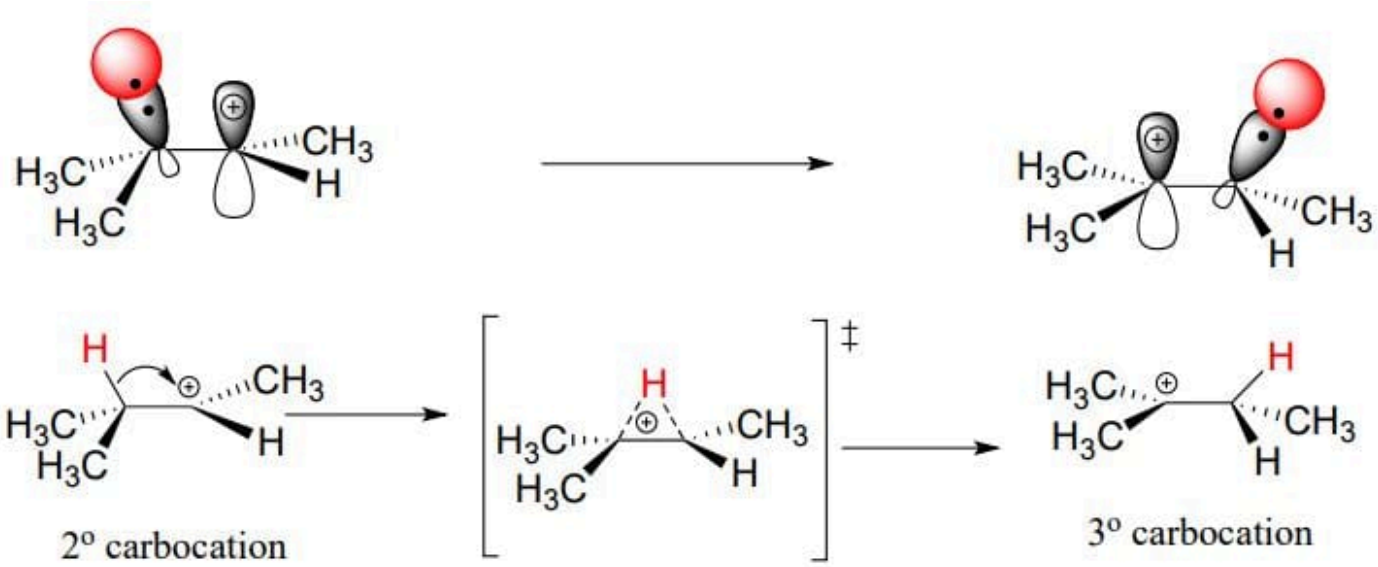


Protonation of the double bond results in a secondary carbocation (step 1). What happens next (step 2 above) is a process called a carbocation rearrangement, and more specifically, a hydride shift. The electrons in the bond between carbon #3 and a hydrogen are attracted by the positive charge on carbon #2, and they simply shift over to fill the empty p orbital, pulling the proton over with them. Notice that the hydride, in shifting, is not acting as an actual leaving group - a hydride ion is a very strong base and a very poor leaving group.

An important reminder

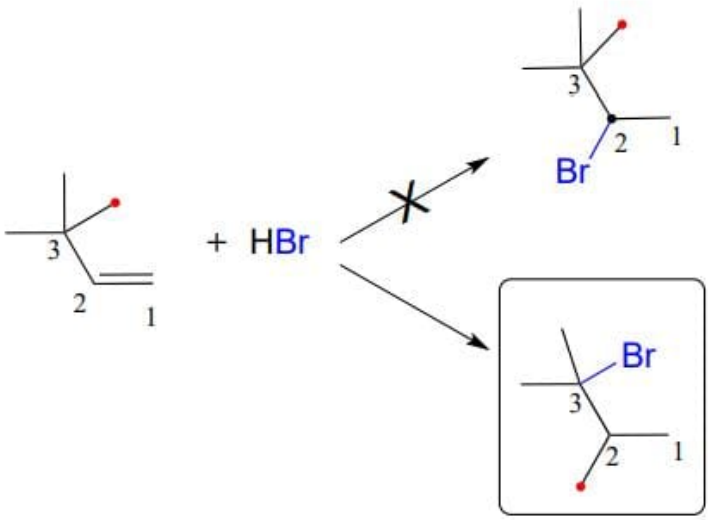
A hydride ion (H^-) is a proton plus two electrons. Be sure not to confuse a hydride ion with H^+, which is just a proton without any electrons.

As the shift proceeds, a new $C-H$ σ bond is formed at carbon #2, and carbon #3 is left with an empty p orbital and a positive charge.



What is the thermodynamic driving force for this process? Notice that the hydride shift results in the conversion of a secondary carbocation to a (more stable) tertiary carbocation - a thermodynamically downhill step. As it turns out, the shift occurs so quickly that it is accomplished before the bromide nucleophile has time to attack at carbon #2. Rather, the bromide will attack (step 3) at carbon #3 to complete the addition.

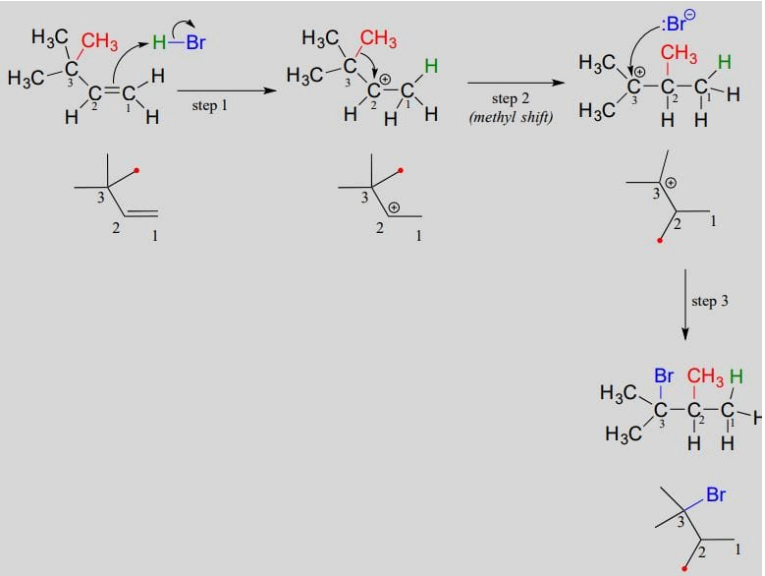
Consider another example. When HBr is added to 3,3-dimethyl-1-butene, the product is a tertiary - rather than a secondary - alkyl bromide.



Notice that in the observed product, the carbon framework has been rearranged: the methyl carbon indicated by a red dot has shifted from carbon #3 to carbon #2. This is an example of another type of carbocation rearrangement, called a methyl shift.

Below is the mechanism for the reaction. Once again a secondary carbocation intermediate is formed in step 1. In this case, there is no hydrogen on carbon #3 available to shift over create a more stable tertiary carbocation. Instead, it is a methyl group that does the shifting, as the electrons in the carbon-carbon σ bond move over to fill the empty orbital on carbon #2 (step 2 below).

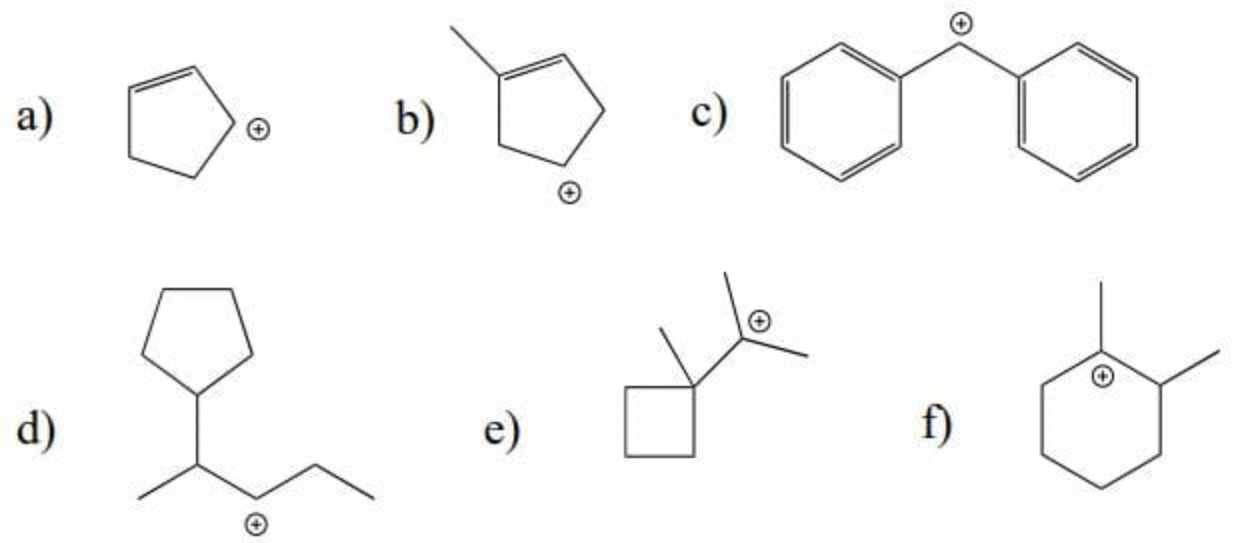
Electrophilic addition with methyl shift:



The methyl shift results in the conversion of a secondary carbocation to a more stable tertiary carbocation. The end result is a rearrangement of the carbon framework of the molecule.

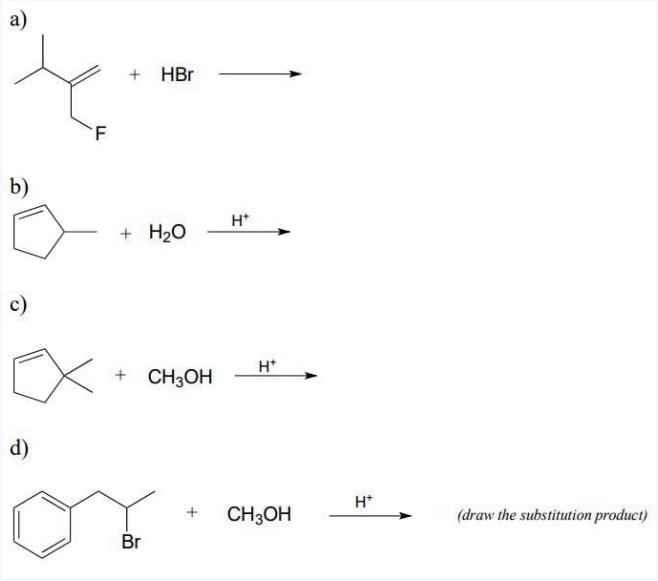
Exercise 14.6.1

Which of the following carbocations are likely to undergo a shift? If a shift is likely, draw the new carbocation that would result.



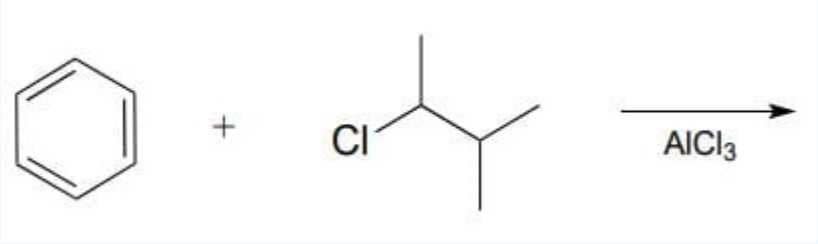
Exercise 14.6.2

In the (non-biochemcial) reactions below, the major product forms as the result of a hydride or methyl shift from a carbocation intermediate. Predict the structure of the major product for each reaction, disregarding stereochemistry.

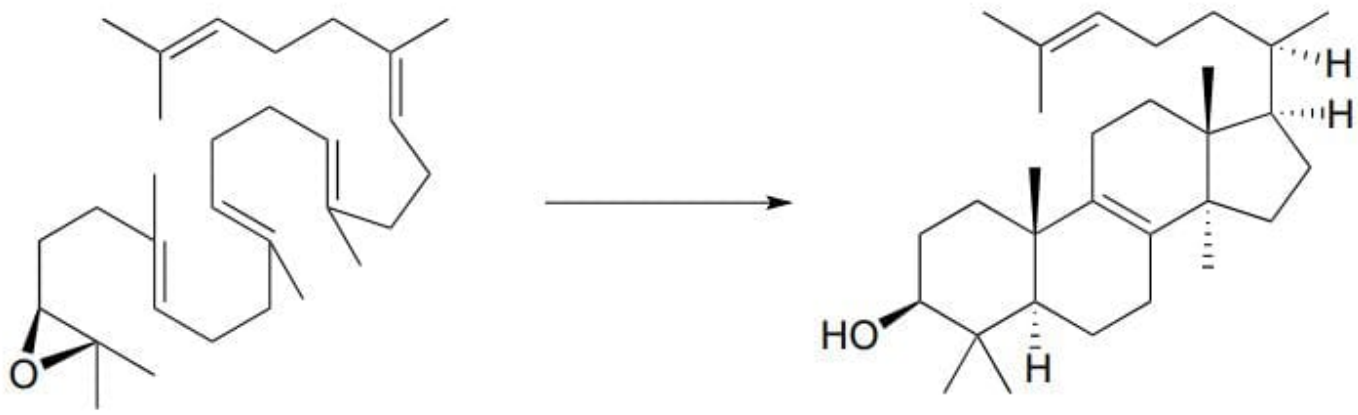


Exercise 14.6.3

Draw the most abundant product of this laboratory Friedel-Crafts reaction:



Carbocation rearrangements are involved in many known biochemical reactions. Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. For example, one of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol (E.C. 5.4.99.7).



(3S)-2,3-oxidosqualene lanosterol

This complex but fascinating reaction has two phases. The first phase is where the actual cyclization takes place, with the formation of four new carbon-carbon bonds and a carbocation intermediate. This phase is a 'cascade' of electrophilic alkene addition steps, beginning with addition of an electrophilic functional group called an 'epoxide'.

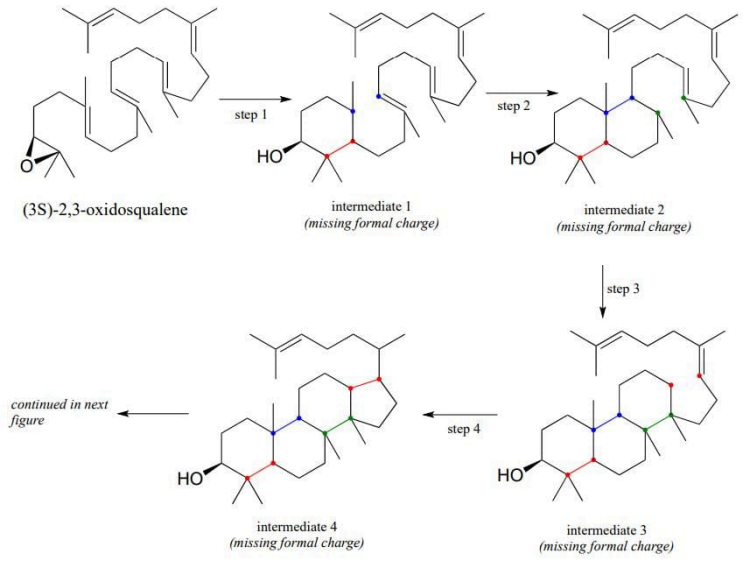
The epoxide functional group - composed of a three membered ring with two carbons and an oxygen - is relatively rare in biomolecules and biochemical reactions, and for this reason it is not discussed in detail in this book. However, epoxides are an important and versatile intermediate in laboratory organic synthesis, so you will learn much more about how they are made and how they react if you take a course in chemical synthesis. For now, it is sufficient to recognize that the carbon atoms of an epoxide are potent electrophiles, due to both the carbon-oxygen bond dipoles and the inherent strain of the three membered ring.

The second phase involves a series of hydride and methyl shifts culminating in a deprotonation. In the exercise below, you will have the opportunity to work through the entire cyclase reaction mechanism. In section 15.7, we will take a look at how the epoxide group of oxidosqualene is formed. Trends Pharm. Sci. 2005, 26, 335; J. Phys Chem B., 2012, 116, 13857.

Exercise 14.6.4

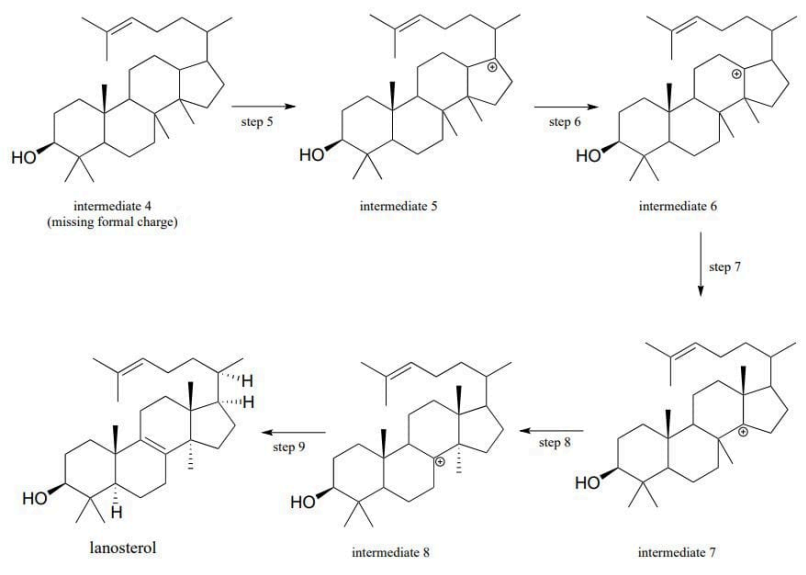
a. The figure below outlines the first, cyclizing phase of the reaction that converts oxidosqualene to lanosterol. However, the diagram is missing electron movement arrows, and intermediates 1-4 are all missing formal charges - fill these in.

First phase (ring formation):



b. Next comes the 'shifting' phase of the reaction. Once again, supply the missing mechanistic arrows.

Second phase: rearrangement and deprotonation



c. Look at the first and last steps of the entire process: overall, would you describe this as an electrophilic addition or substitution?

The oxidosqualene cyclization reaction and others like it are truly remarkable examples of the exquisite control exerted by enzymes over the course of a chemical reaction. Consider: an open-chain starting molecule is converted, by a single enzyme, into a complex multiple fused-ring structure with seven chiral centers. Oxidosqualene could potentially cyclize in many different ways, resulting in a great variety of different products. In order for the enzyme to catalyze the formation of a single product with the correct connectivity and stereochemistry, the enzyme must be able to maintain precise control of the conformation of the starting compound and all reactive intermediates in the active site, while also excluding water molecules which could attack at any of the positively charged carbons.

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4.7: Markovnikov Addition

Markovnikov addition, also called Markovnikov's rule, states that a protic acid (HX) will add to an alkene such that the proton will bond to the less substituted carbon.

Introduction

During this addition, the carbocation intermediate bares a positive charge on the most substituted carbon. The more substituted carbon, the more stable (tertiary > secondar > primary > methyl). If the reverse occurs, that is the more electronegative atom (X) ends up bonding to the least substituted carbon, it is termed anti-Markovnikov addition. The figure below shows a figure of both additions:

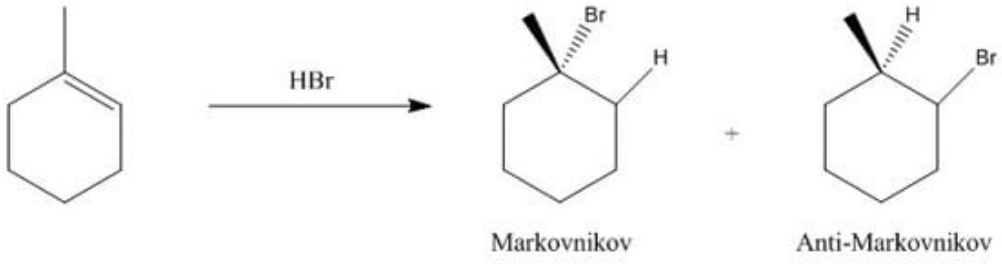


Fig. 1. *Markovnikov and anti-Markovnikov additions of HBr to 1-methylcyclohexene.*

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5: ADDITION REACTIONS OF ALKENES

5.1: Electrophilic Addition of Hydrogen Halides

5.2: Addition of Strong Brønsted Acids

5.3: Electrophilic Addition of Halogens to Alkenes

5.4: Hydration of Alkenes

5.5: Formation of alcohols from alkenes

5.6: Catalytic Hydrogenation

5.7: Hydration- Oxymercuration-Demercuration

5.8: Hydration- Hydroboration-Oxidation

5.9: Oxidative Cleavage of Alkenes

5.10: Free Radicals

5.11: Addition of Radicals to Alkenes

5.12: Anti-Markovnikov Product Formation

5.13: Homolytic Cleavage and Bond Dissociation Energies

5.14: Polymerization of Alkenes

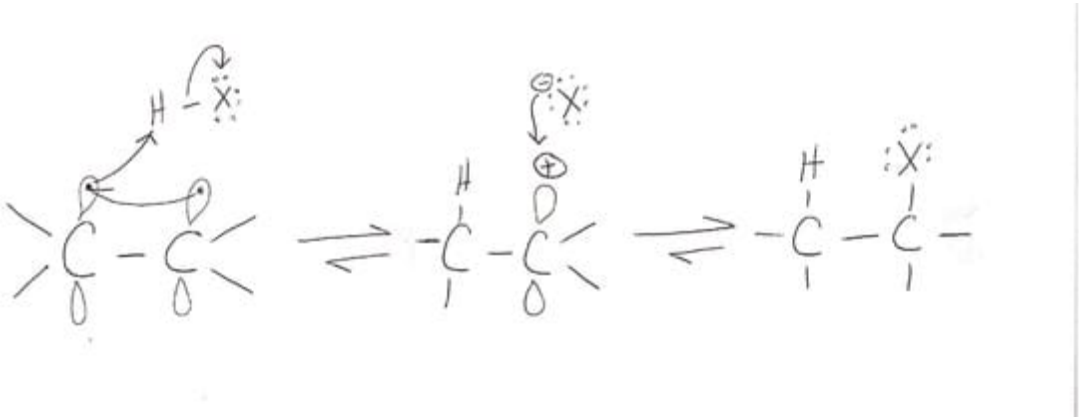
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5.1: Electrophilic Addition of Hydrogen Halides

Due to the nature of the π bond, π bonds can act like a nucleophile and undergo addition of electrophiles. The π electrons have a high electron density in the π electron cloud which can be easily polarized (give up the electrons) and can act like a nucleophile (nucleus-loving due to too many electrons; wants to give them away to electrophile). This behavior is very similar to the behavior that the lone pair electrons have on a Lewis base.

Introduction

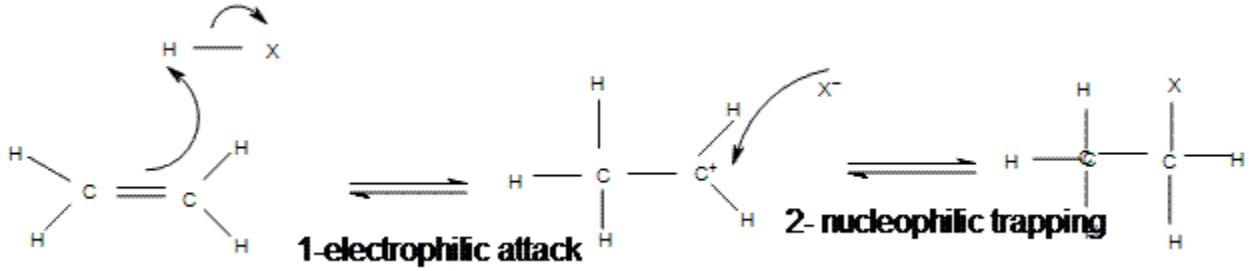
There are many types of electrophilic addition, but this section will focus on the addition of hydrogen halides.



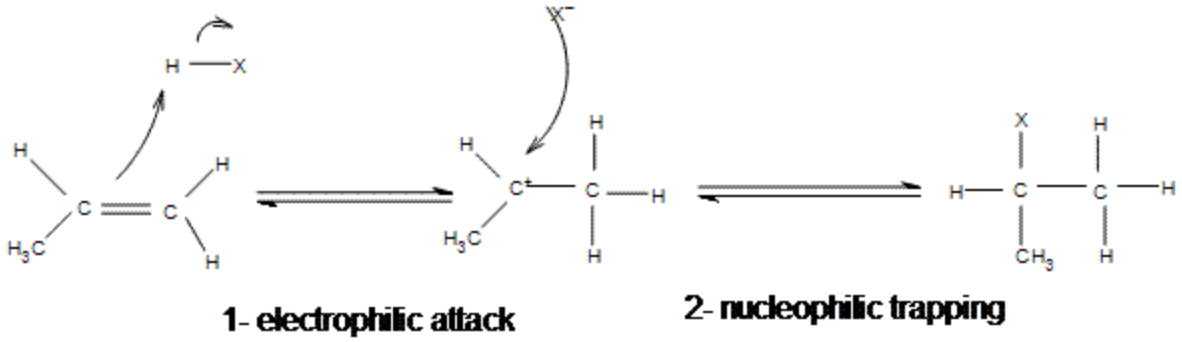
Reaction

The addition of hydrogen halides is one of the easiest electrophilic addition reactions because it uses the simplest electrophile: the proton. Hydrogen halides provide both a electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of π electrons, attaching it to the molecule (1). This is basically the reverse of the last step in the E1 reaction (deprotonation step). The resulting molecule will have a single carbon- carbon bond with a positive charge on one of them (carbocation). The next step is when the nucleophile (halide) bonds to the carbocation, producing a new molecule with both the original hydrogen and halide attached to the organic reactant (2). The second step will only occur if a good nucleophile is used.

Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene



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).

Relative Rates of Addition of HX and their causes

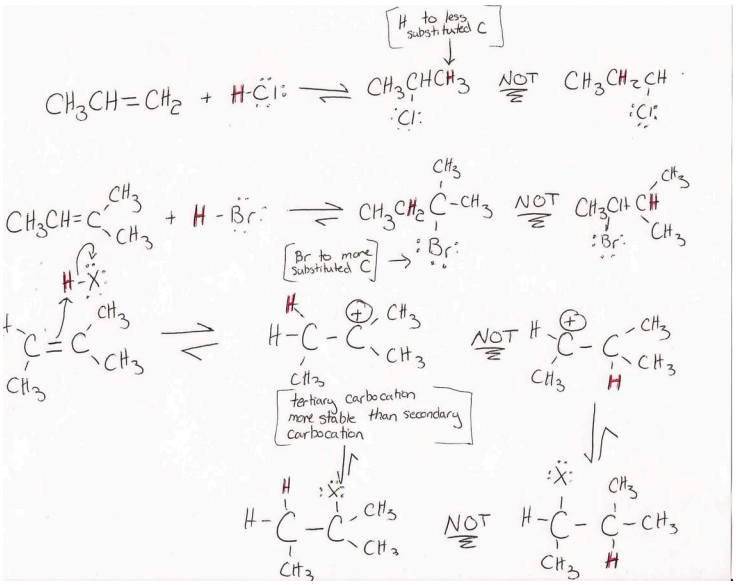
Name	Rate	Size of "X"	Overlap of Orbitals
HF	slowest	smallest	good
HCl	slow	small	okay
HBr	fast	large	bad
HI	fastest	largest	horrifically bad

- *Gaseous hydrogen halides are used and bubbled through the reactant or the hydrogen halide is added in a solvent such as acetic acid to produce decent amounts of the product. It also helps to do a aqueous work up afterward to get a good yield of product. This reaction is usually carried out at lower temperatures.*

Regiochemistry

The regiochemistry of this reaction can be explained through Markovnikov's Rule. The basics of this rule states that the proton will add to the less substituted carbon and the halogen goes to the more substituted carbon. This may seem odd that the larger atom is going to the more sterically hindered spot, but this rule is more about the stability of the intermediate. The addition will occur in a way that produces the most stable carbocation after the initial protonation (the intermediate needs to have a stable carbocation). Tertiary and secondary carbocations are the most stable due to hyperconjugation, so the more substituted the carbon is the more stable the carbocation will be.

Examples of regioselective behavior in Electrophilic Addition: Markovnikov's Rule



Since the intermediate of this reaction is a carbocation the carbocation wants to be the most stable it can be. In some case this will mean that the carbocation will rearrange. This is very likely when there are no good nucleophiles present to trap the carbocation in a certain position. The rearrangement of the carbocation depends on many things but generally rearrangements will occur when there are no good nucleophiles present such as in a strong acid.

Stereochemistry

The stereochemistry for this reaction is random. The important thing to understand is the regiochemistry and the Markovnikov's Rule (this will come up a lot!).

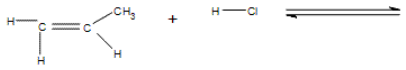
References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W.H. Freeman and Company, 2007.
2. Francis A. Coreg, Richard J. Sundberg. Advanced Organic Chemistry: Part B: Reactions and Synthesis. Springer, 2007.

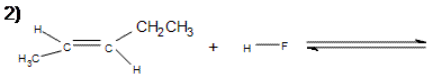
Problems

Write out the following reactions and think about the rate of the reaction:

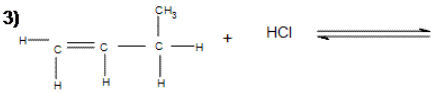
1)



2)



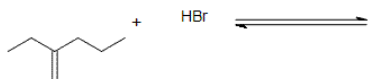
3)



4)



5)



Contributors

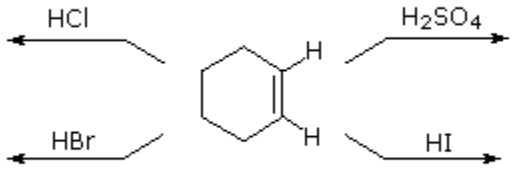
- Ivy Gardner

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5.2: Addition of Strong Brønsted Acids

Strong Brønsted acids such as HCl, HBr, HI & H_2SO_4, rapidly add to the C=C functional group of alkenes to give products in which new covalent bonds are formed to hydrogen and to the conjugate base of the acid. Using the above equation as a guide, write the addition products expected on reacting each of these reagents with cyclohexene.



Weak Brønsted acids such as water (pK_a = 15.7) and acetic acid (pK_a = 4.75) do not normally add to alkenes. However, the addition of a strong acid serves to catalyze the addition of water, and in this way alcohols may be prepared from alkenes. For example, if sulfuric acid is dissolved in water it is completely ionized to the hydronium ion, $H_3O^{(+)}$, and this strongly acidic (pK_a = -1.74) species effects hydration of ethene and other alkenes.

$$CH_2{=}CH_2 + H_3O^{(+)} \longrightarrow HCH_2{-}CH_2OH + H^{(+)}$$

The importance of choosing an appropriate solvent for these addition reactions should now be clear. If the addition of HCl, HBr or HI is desired, water and alcohols should not be used. These strong acids will ionize in such solvents to give $ROH_2^{(+)}$ and the nucleophilic oxygen of the solvent will compete with the halide anions in the final step, giving alcohol and ether products. By using inert solvents such as hexane, benzene and methylene chloride, these competing solvent additions are avoided. Because these additions proceed by way of polar or ionic intermediates, the rate of reaction is greater in polar solvents, such as nitromethane and acetonitrile, than in non-polar solvents, such as cyclohexane and carbon tetrachloride.

Regioselectivity and the Markovnikov Rule

Only one product is possible from the addition of these strong acids to symmetrical alkenes such as ethene and cyclohexene. However, if the double bond carbon atoms are not structurally equivalent, as in molecules of 1-butene, 2-methyl-2-butene and 1-methylcyclohexene, the reagent conceivably may add in two different ways. This is shown for 2-methyl-2-butene in the following equation.

$(CH_3)_2C{=}CHCH_3$ + H-Cl	⟶	$(CH_3)_2CH{-}CHClCH_3$	or	$(CH_3)_2CCl{-}CHHCH_3$
2-methyl-2-butene		2-chloro-3-methylbutane		2-chloro-2-methylbutane

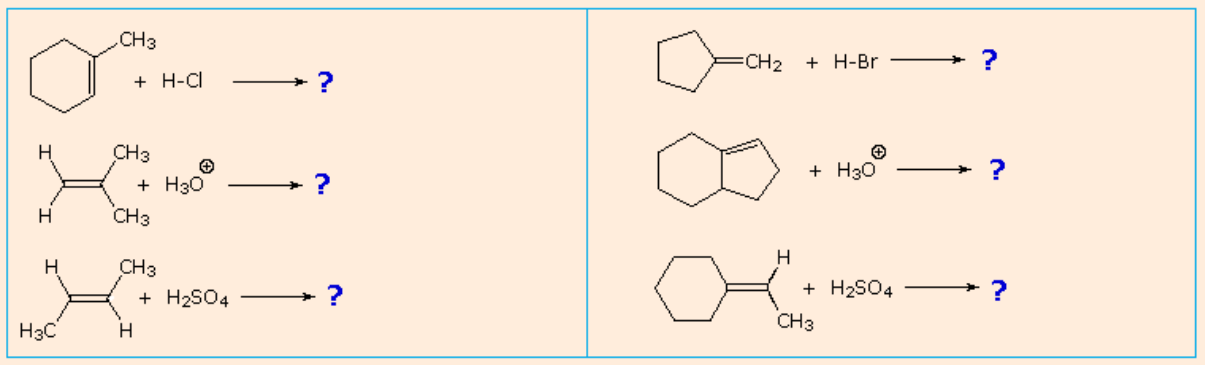
When addition reactions to such unsymmetrical alkenes are carried out, we find that one of the two possible constitutionally isomeric products is formed preferentially. Selectivity of this sort is termed **regioselectivity**. In the above example, 2-chloro-2-methylbutane is nearly the exclusive product. Similarly, 1-butene forms 2-bromobutane as the predominant product on treatment with HBr.

$$CH_3CH_2CH{=}CH_2 + HBr \xrightarrow[\text{addition}]{\text{regioselective}} CH_3CH_2CHBrCH_3 \quad \text{not} \quad CH_3CH_2CH_2CH_2Br$$

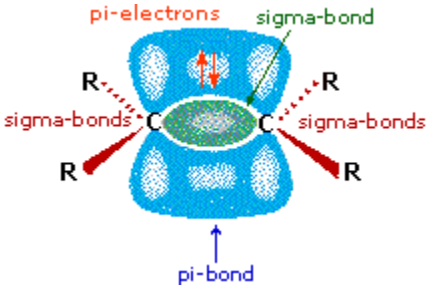
After studying many addition reactions of this kind, the Russian chemist Vladimir Markovnikov noticed a trend in the structure of the favored addition product. He formulated this trend as an empirical rule we now ca**ll The Markovnikov Rule:** When a Brønsted

acid, HX, adds to an unsymmetrically substituted double bond, the acidic hydrogen of the acid bonds to that carbon of the double bond that has the greater number of hydrogen atoms already attached to it.
In more homelier vernacular this rule may be restated as, "**Them that has gits.**"

It is a helpful exercise to predict the favored product in examples such as those shown below:

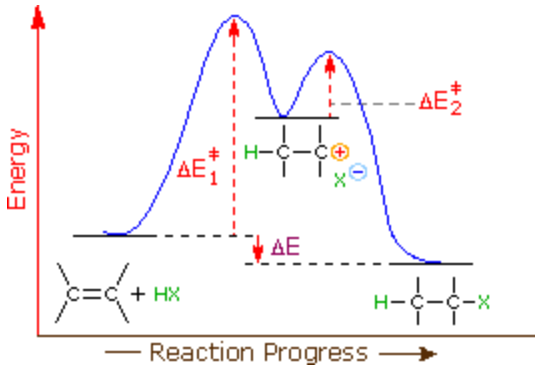


Empirical rules like the Markovnikov Rule are useful aids for remembering and predicting experimental results. Indeed, empirical rules are often the first step toward practical mastery of a subject, but they seldom constitute true understanding. The Markovnikov Rule, for example, suggests there are common and important principles at work in these addition reactions, but it does not tell us what they are. The next step in achieving an understanding of this reaction must be to construct a rational mechanistic model that can be tested by experiment.



All the reagents discussed here are strong Brønsted acids so, as a first step, it seems sensible to find a base with which the acid can react. Since we know that these acids do not react with alkanes, it must be the pi-electrons of the alkene double bond that serve as the base. As shown in the diagram on the right, the pi-orbital extends into the space immediately above and below the plane of the double bond, and the electrons occupying this orbital may be attracted to the proton of a Brønsted acid. The resulting acid-base equilibrium generates a carbocation intermediate (the conjugate acid of the alkene) which then combines rapidly with the anionic conjugate base of the Brønsted acid. This two-step mechanism is illustrated for the reaction of ethene with hydrogen chloride by the following equations.

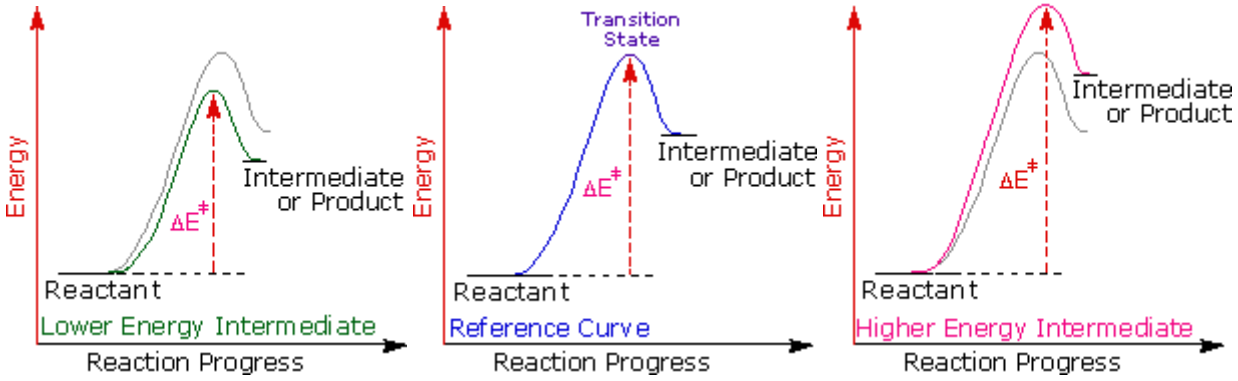
First Step: $H_2C{=}CH_2 + HCl$	$\rightleftharpoons$	$HH_2C{-}CH_2^{(+)} + Cl^{(-)}$
Second Step: $HH_2C{-}CH_2^{(+)} + Cl^{(-)}$	$\longrightarrow$	$HH_2C{-}CH_2Cl$



An energy diagram for this two-step addition mechanism is shown to the left. From this diagram we see that the slow or rate-determining step (the first step) is also the product determining step (the anion will necessarily bond to the carbocation site). Electron donating double bond substituents increase the reactivity of an alkene, as evidenced by the increased rate of hydration of 2-methylpropene (two alkyl groups) compared with 1-butene (one alkyl group). Evidently, alkyl substituents act to increase the rate of addition by lowering the activation energy, $\Delta E^{\ddagger}_1$ of the rate determining step, and it is here we should look for a rationalization of Markovnikov's rule.

As expected, electron withdrawing substituents, such as fluorine or chlorine, reduce the reactivity of an alkene to addition by acids (vinyl chloride is less reactive than ethene).

George Hammond formulated a useful principle that relates the nature of a transition state to its location on the reaction path. This **Hammond Postulate** states that **a transition state will be structurally and energetically similar to the species (reactant, intermediate or product) nearest to it on the reaction path**. In strongly exothermic reactions the transition state will resemble the reactant species. In strongly endothermic conversions, such as that shown to the right, the transition state will resemble the high-energy intermediate or product, and will track the energy of this intermediate if it changes. This change in transition state energy and activation energy as the stability of the intermediate changes may be observed by clicking the higher or lower buttons to the right of the energy diagram. Three examples may be examined, and the reference curve is changed to gray in the diagrams for higher (magenta) and lower (green) energy intermediates.

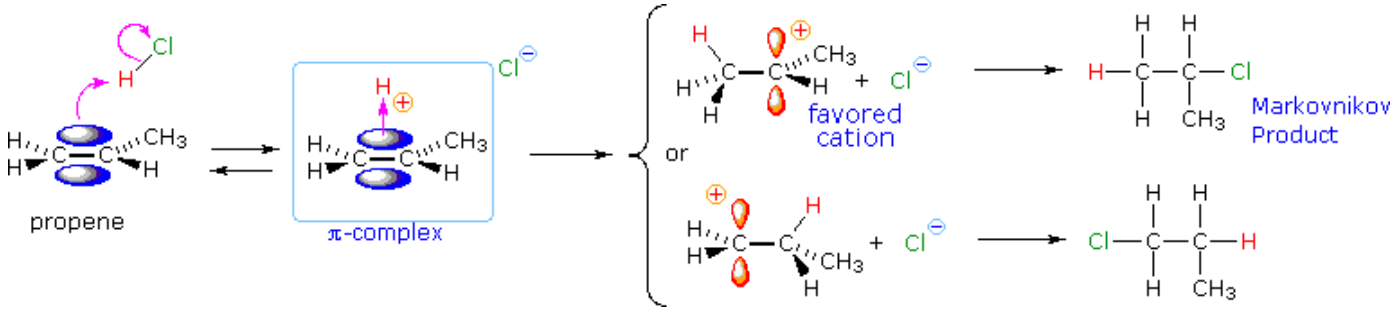


The carbocation intermediate formed in the first step of the addition reaction now assumes a key role, in that it directly influences the activation energy for this step. Independent research shows that the stability of carbocations varies with the nature of substituents, in a manner similar to that seen for alkyl radicals. The exceptional stability of allyl and benzyl cations is the result of charge delocalization, and the stabilizing influence of alkyl substituents, although less pronounced, has been interpreted in a similar fashion.

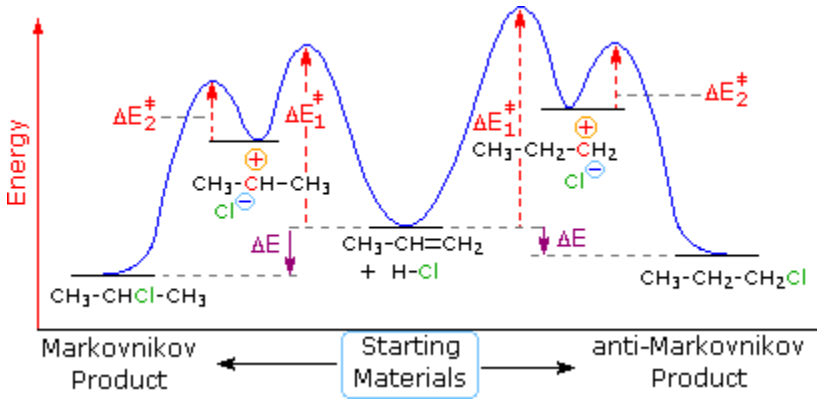
Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	CH_2=CH-$CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

From this information, applying the Hammond Postulate, we arrive at a plausible rationalization of Markovnikov's rule. **When an**

unsymmetrically substituted double bond is protonated, we expect the more stable carbocation intermediate to be formed faster than the less stable alternative, because the activation energy of the path to the former is the lower of the two possibilities. This is illustrated by the following equation for the addition of hydrogen chloride to propene. Note that the initial acid-base equilibrium leads to a pi-complex which immediately reorganizes to a sigma-bonded carbocation intermediate. The more stable 2°-carbocation is formed preferentially, and the conjugate base of the Brønsted acid (chloride anion in the example shown below) then rapidly bonds to this electrophilic intermediate to form the final product.



The following energy diagram summarizes these features. Note that the pi-complex is not shown, since this rapidly and reversibly formed species is common to both possible reaction paths.



A more extensive discussion of the factors that influence carbocation stability may be accessed by Clicking Here.

Contributors

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

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5.3: Electrophilic Addition of Halogens to Alkenes

Halogens can act as electrophiles to attack a double bond in alkene. Double bond represents a region of electron density and therefore functions as a nucleophile. How is it possible for a halogen to obtain positive charge to be an electrophile?

Introduction

As halogen molecule, for example Br_2, approaches a double bond of the alkene, electrons in the double bond repel electrons in bromine molecule causing polarization of the halogen bond. This creates a dipolar moment in the halogen molecule bond. Heterolytic bond cleavage occurs and one of the halogens obtains positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but stereoselective.Stereochemistry of this addition can be explained by the mechanism of the reaction.In the first step electrophilic halogen with a positive charge approaches the double carbon bond and 2 p orbitals of the halogen, bond with two carbon atoms and create a cyclic ion with a halogen as the intermediate step. In the second step, halogen with the negative charge attacks any 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 **vicinial dihalides through anti** addition.

$$\mathrm{R_2C{=}CR_2 + X_2 \ \rightarrow R_2CX{-}CR_2X} \tag{5.3.1}$$

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.

Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl_4) can be used in this reaction.

Because halogen with negative charge can attack any carbon from the opposite side of the cycle 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**

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 intermediate cycle with the double bond.

Mechanism1.bmp

Step 2: In the second step, bromide anion attacks any carbon of the bridged bromonium ion from the back side of the cycle. Cycle opens up and two halogens are in the position **anti**.

Mechanism 2 a.bmp

Summary

Halogens can act as electrophiles due to polarizability of their covalent bond.Addition of halogens is stereospecific and produces vicinial dihalides with anti addition.Cis starting material will give mixture of enantiomers and trans produces a meso compound.

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1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function.New Yourk: W.H.Freeman and Company 2007
2. Chemestry-A Europian Journal 9 (2003) :1036-1044

Problems

1.What is the mechanism of adding Cl_2 to the cyclohexene?

Chem2.bmp

2.A reaction of Br_2 molecule in an inert solvent with alkene follows?

a) syn addition

b) anti addition

c) Morkovnikov rule

3)Chem5 Q.bmp

4)Chem 5 Q.bmp

Key:

1.

Choloro problem 2.bmp

2. b

3.Chem exampl 4.bmp enantiomer

4.Chemestry problem 4.bmp

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5.4: Hydration of Alkenes

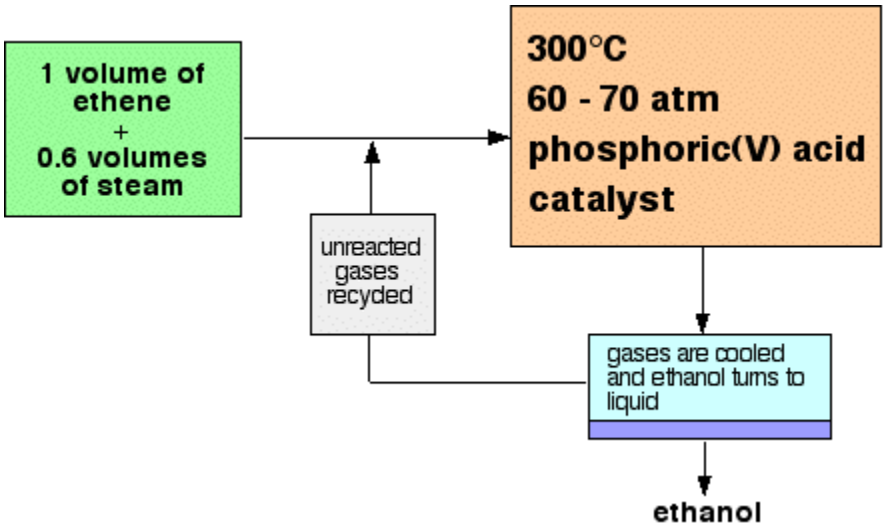
This page looks at the production of alcohols by the direct hydration of alkenes - adding water directly to the carbon-carbon double bond.

Manufacturing ethanol

Ethanol is manufactured by reacting ethene with steam. The reaction is reversible.

$$CH_2{=}CH_{2(g)} + H_2O_{(g)} \rightleftharpoons CH_3CH_2OH_{(g)}$$

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:



Manufacturing other alcohols

If you start from an unsymmetrical alkene like propene, you have to be careful to think about which way around the water adds across the carbon-carbon double bond. Markovnikov's Rule says that when you add a molecule HX across a carbon-carbon double bond, the hydrogen joins to the carbon atom which already has the more hydrogen atoms attached to it.

Thinking of water as H-OH, the hydrogen will add to the carbon with the more hydrogens already attached. That means that in the propene case, you will get propan-2-ol rather than propan-1-ol.

$$CH_3\text{-}CH{=}CH_2 + H_2O \rightleftharpoons CH_3\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_3$$

propan-2-ol

The conditions used during manufacture vary from alcohol to alcohol.

Contributors

Jim Clark (Chemguide.co.uk)

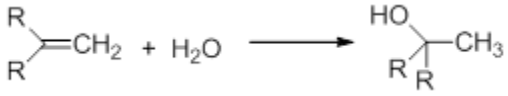
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5.5: Formation of alcohols from alkenes

Alkenes can be converted to alcohols by the net addition of water across the double bond. There are multiple ways that are commonly used to do this transformation.

Hydration of Alkenes

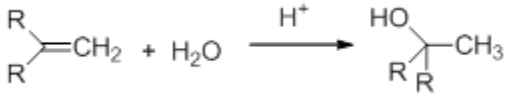
The net addition of water to alkenes is known as hydration.



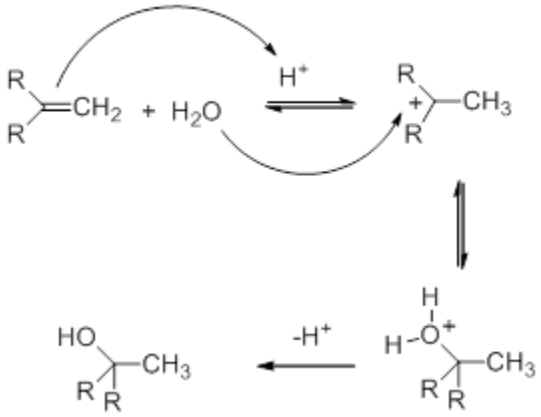
The result involves breaking the pi bond in the alkene and an OH bond in water and the formation of a C-H bond and a C-OH bond. The reaction is typically exothermic by 10 - 15 kcal/mol,[1] but has an entropy change of -35 - -40 cal/mol K. Consequently, the net free energy change for the process tends to close to 0, and the equilibrium constant for the direct addition is close to 1. Nonetheless, there are multiple approaches that allow this transformation to be carried out to completion.

Acid-Catalyzed Hydration

The direct addtion of water to an alkene is too slow to be of any significance. However, the addition can be catayzed by Lewis or Bronsted acids.



The mechanism of hydration involves electrophlic addition of the proton (or acid) to the double bond to form a carbocation intermediate. Addition of water in the second step results in formation of an oxonium ion, which, upon deprotonation, gives the alcohol.



The proton in the oxonium intermediate can be deprotonated by any base present, including the conjugate base of the acid used as a catalyst, or even by another alkene molecule, which would generate another carbocation intermediate and propagate the chain mechanism.

Using Le Châtelier's Principle to get the product

The extent of reaction of the acid catalyzed hydration of alkenes is determined by the equilibrium constant, which, as noted

above, is near unity. Consequently, the reaction can be carried out by adding excess water to increase the yield of products, an application of Le Châtelier's Principle. Alternatively, the reverse reaction, acid-catalyzed dehydration of the alcohol to form the alkene can promoted by removing water from the reaction by using a Dean-Stark trap.

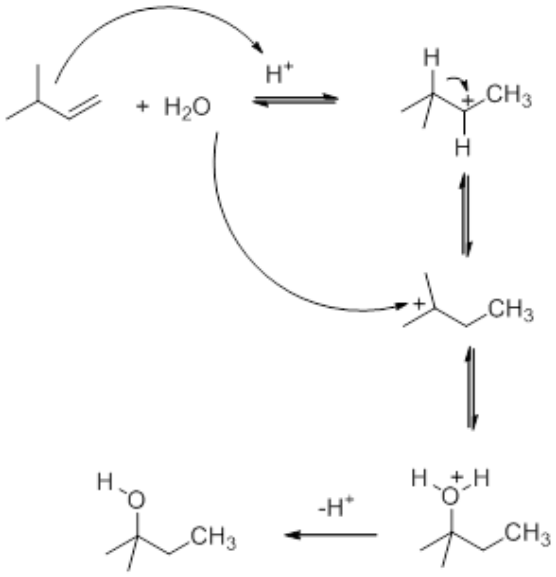
Regioselectivity of addition

Protonation of the alkene in the first step of the reaction can occur at either carbon. However, the more stable carbocation is preferably formed. The order of stability of alkyl cations is

$$3^o > 2^o > 1^o$$

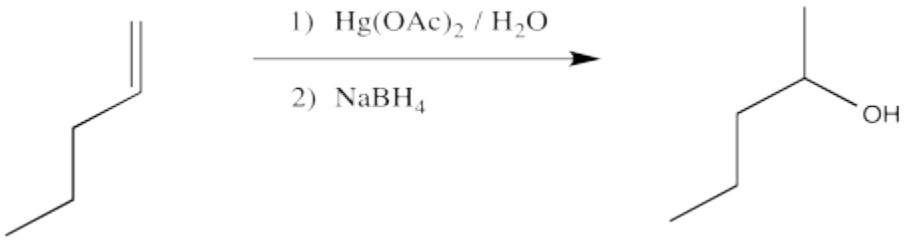
Therefore, protonation will occur at the *less substituted carbon*, to create the more substituted carbocation, where the water adds. The addition of a proton at the less substituted carbon and the -OH to the more substituted carbon is known as Markovnikov's Rule.

The carbocation formed in the reaction is prone to rearrangement, if possible. Therefore, hydration of an olefiin next to a branched aliphatic center will result in the alcohol forming in a position that was not part of the original double bond.



Oxymercuration

Transition metals can also be used as the acids for hydration reactions. In some cases, coordination of the alkene to a metal leaves it susceptible to reaction with a nucleophile such as water. The classic case of nucleophilic donation to a coordinated alkene occurs with mercury (II) salts such as mercuric chloride, $HgCl_2$, or mercuric acetate, $Hg(OAc)_2$. The reaction, or rather the sequence of reactions, is called oxymercuration - demercuration or oxymercuration - reduction.

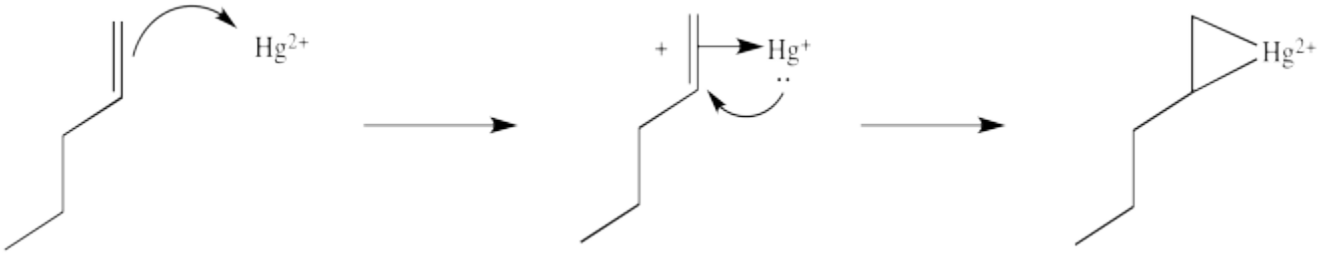


We will break the two different reactions in this sequence apart and focus only on the first one: oxymercuration. This reaction qualifies as an electrophilic addition because, as in the previous cases, it begins with donation of a π-bonding pair to an electrophile. In this case, we will consider the electrophile to be aqueous Hg^{2+} ion.

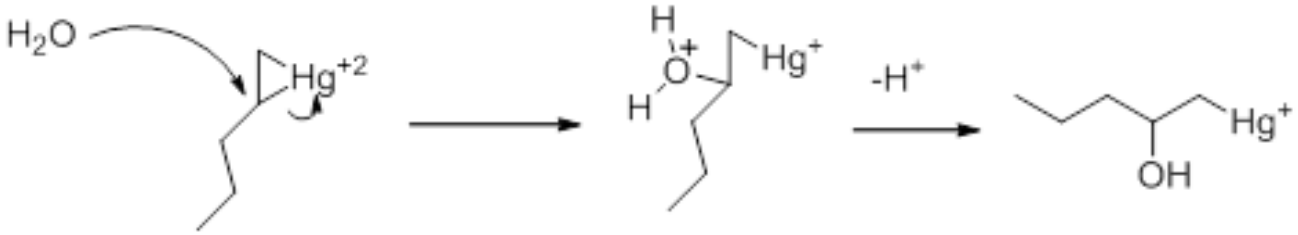


That electrophilic addition (from the alkene's perspective) results in the formation of an alkene complex. In reality, the mercury ion is also coordinated by several water molecules, but we will ignore them for simplicity.

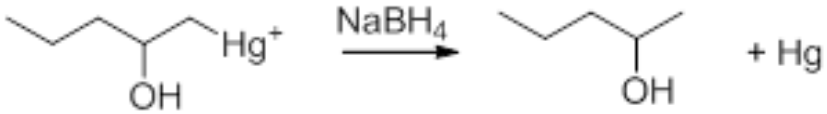
The complex formed by addition of mercury is not a localized carbocation, as is formed by protonation, but is better considered a bridged or cyclic structure, which results from addition of d electrons to the empty orbital in the cation.



This situation is something like formation of a cyclic bromonium ion formed in the bromination of alkenes. As with bromination, the cyclic intermediate can be opened by attack of a nucleophile, in this case, water.

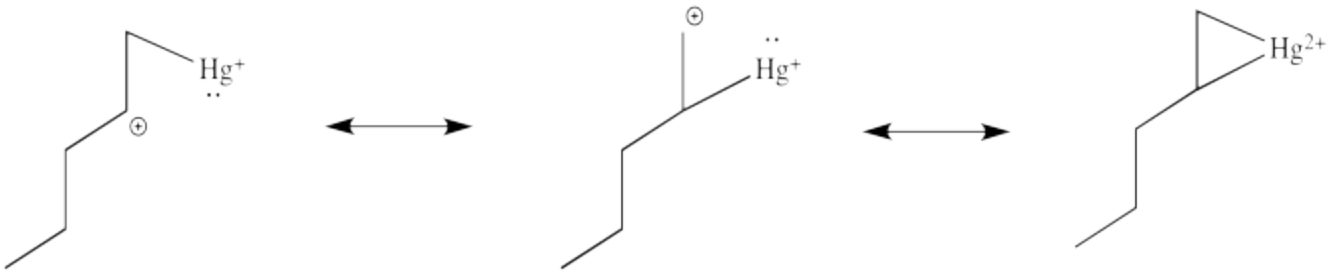


The final part of the reaction sequence is displacement of mercury from the hydroxyalkylmercury complex, effected through addition of sodium borohydride. The details of the reaction are usually dismissed in textbooks because they have little to do with electrophilic addition, the topic we are focusing on. However, the result is that the mercury is replaced by a hydrogen atom. The metal is converted to silvery, liquid, elemental mercury.



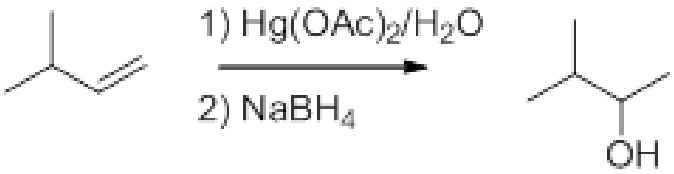
Regioselectivy of hydration by oxymercuration

As shown above, oxymercuration leads to Markovnikov addition of water to the double bond. The reason for this can be seen by considering the electronic structure of the cyclic cation. The electronic structure of the cyclic intermediate can be deduced by using resonance structures as shown below.



By considering these resonance structures, it can be seen that the postive charge is distributed over both of the carbons of the olefin. However, because the resonance structure on the left has the positive charge on a secondary carbon, it is energetically more favorable than the structure in the middle, where the charge is a primary cation. Consequently, although the charge is distributed over both carbons, the more substituted carbon has more positive charge density in the overall resonance hybrid. Therefore, it is more electrophilic, and is more susceptibleable to nucleophlic attack.

An important advantage of oxymercuration over simple acid catalysis is that the cyclic structure is not prone to rearrangement, and can therefore is amenable to hydration of alkenes with branched substituents.



Hydroboration-Oxidation

Hydroboration Oxidation

References

1. http://webbook.nist.gov/chemistry/

Contributors

- Prof. Paul G. Wenthold (Purdue University)

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5.6: 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

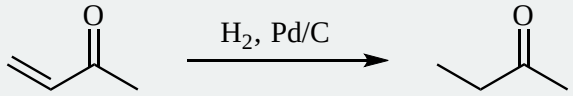
Study Notes

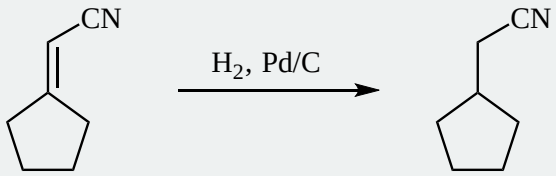
Chemical reactions that are heterogeneous have reactants that are in at least two different phases (e.g. gas with a solid), whereas homogeneous reactions occur in a single phase (e.g. gas with another gas).

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.

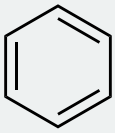




Aromatic rings are also not reduced under the conditions used to reduce alkenes, although these rings appear to contain three carbon-carbon double bonds. As you will see later, aromatic rings do not really contain any double bonds, and many chemists prefer to represent the benzene ring as a hexagon with a circle inside it

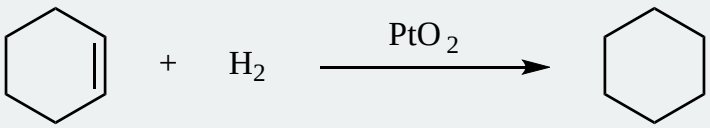


rather than as a hexagon with three alternating double bonds.

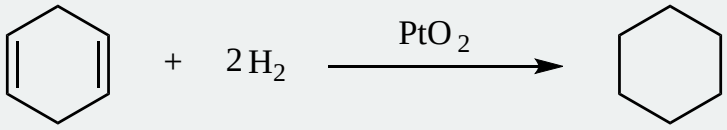


The representation of the benzene ring will be discussed further in Section 15.2.

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:

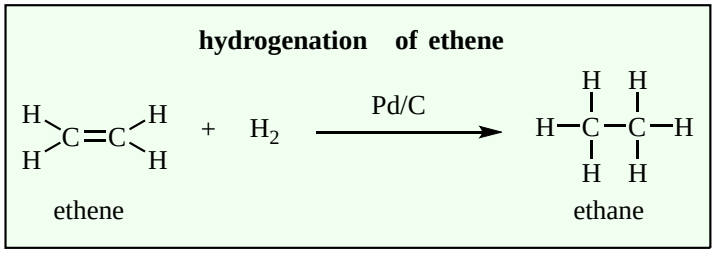


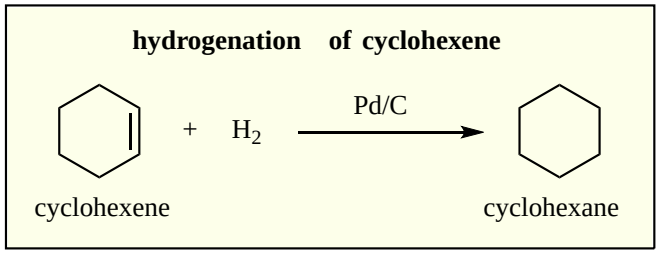
A chemist would say that cyclohexene reacts with one equivalent of hydrogen, and 1,4-cyclohexadiene reacts with two equivalents of hydrogen. If you take a known amount of an unknown, unsaturated hydrocarbon and determine how much hydrogen it will absorb, you can readily determine the number of double 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)

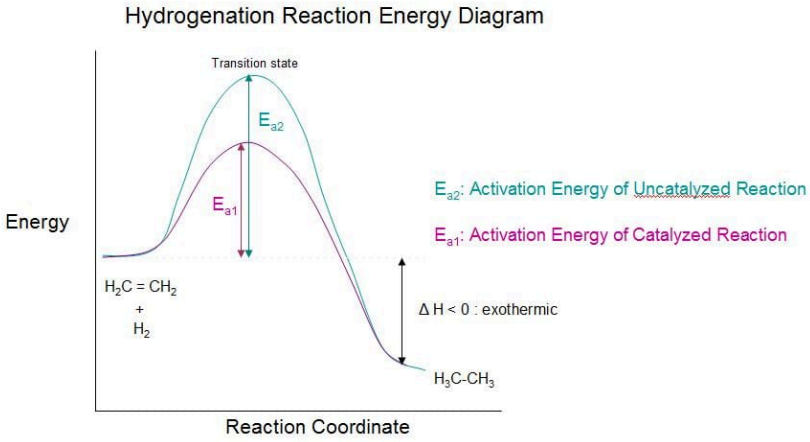
is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking 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.



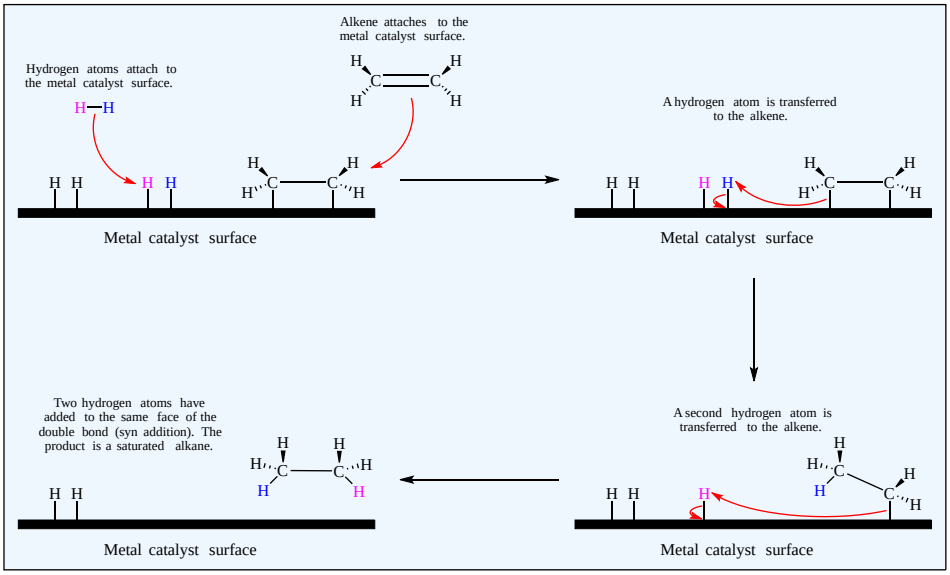
A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

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.

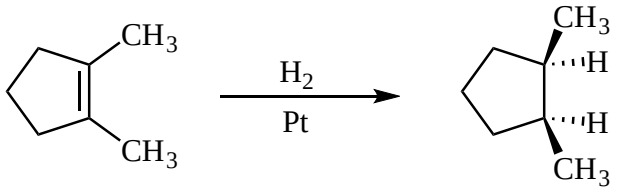
Alkene Isomer	$(CH_3)_2CHCH=CH_2$ 3-methyl-1-butene	$CH_2=C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C=CHCH_3$ 2-methyl-2-butene

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 5.6.1

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.

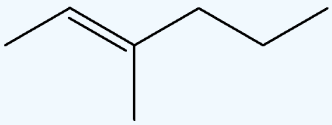
Exercise 5.6.2

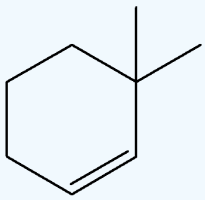
When 1.000 g of a certain triglyceride (fat) is treated with hydrogen gas in the presence of Adams' catalyst, it is found that the volume of hydrogen gas consumed at 99.8 kPa and 25.0°C is 162 mL. A separate experiment indicates that the molar mass of the fat is 914 g mol^{-1}. How many carbon-carbon double bonds does the compound contain?

Answer available at the end of this section.

Exercise 5.6.3

Predict the products if the following alkenes were reacted with catalytic hydrogen.





Answer available at the end of this section.

Answers

Exercise 5.6.1

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 5.6.2

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

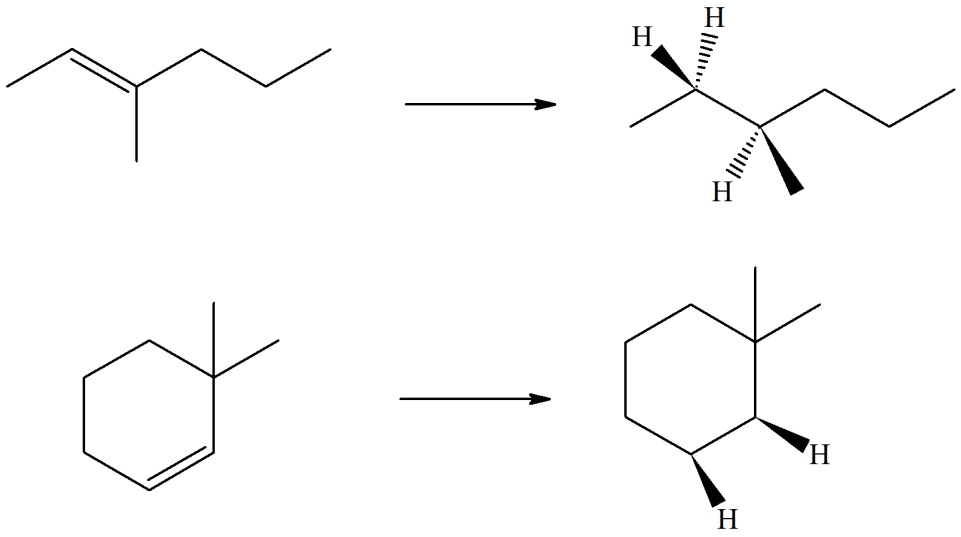
Math input error

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 5.6.3



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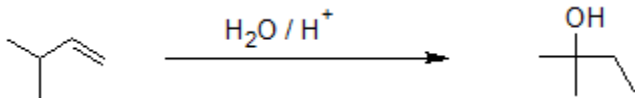
5.7: Hydration- Oxymercuration-Demercuration

Learning Objective

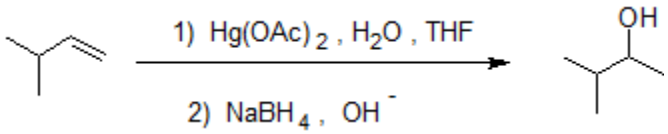
- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation)

Introduction

Acid-catalyzed hydration of alkenes is limited by carbocation stability. Carbocation rearrangement can occur to form a more stable ion as shown in the example below.



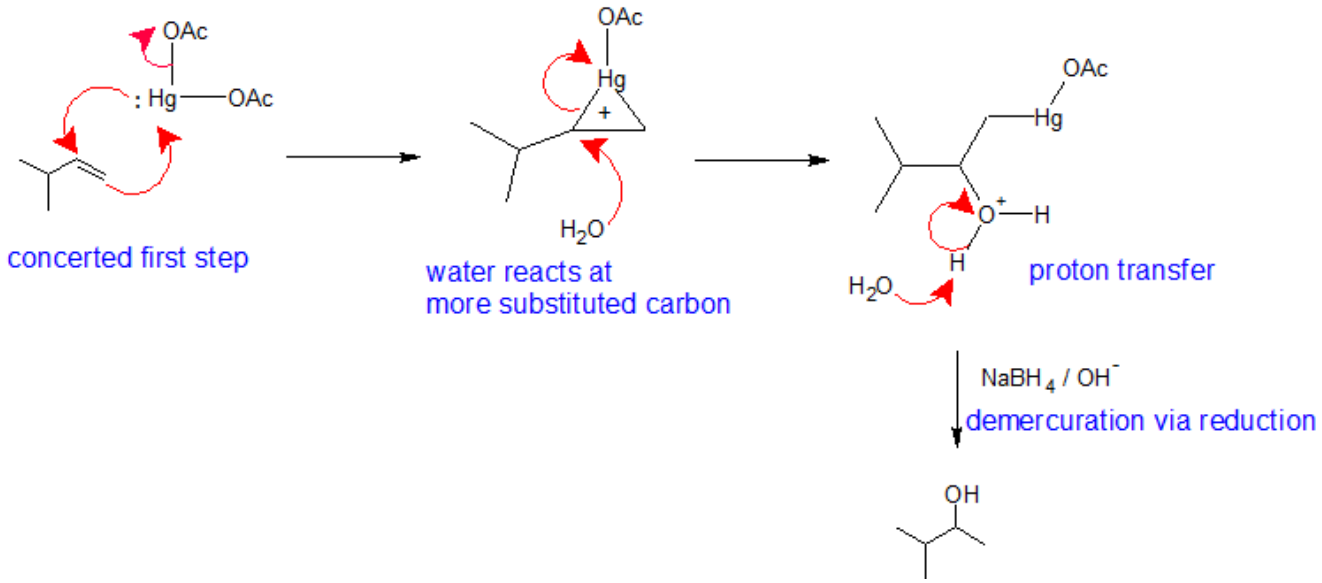
Alkene hydration using the oxymercuration-demercuration reaction pathway reliably produces the Markovnikov product without carbocation rearrangment as shown in the example below.



Oxymercuration-Demercuration is a two step pathway used to produce alcohols.

Oxymercuration-Demercuration Mechanism

This mechanism is similar to the previous electrophilic addition reactions. The major difference is that a mercurium ion bridge stabilizes the carbocation intermediate so that it cannot rearrange. Metals are electropositive. Mercury carries a partial positive charge in the acetate complex and is the electrophile. During the first step of this mechanism, the pi electrons form a bond to mercury while the lone pair on the mercury simultaneously bonds to the other vinyl carbon creating a mercurium ion bridge. The mercurium ion forms in conjunction with the loss of an acetate ion. The mercurium ion stabilizes the carbocation so that it does not rearrange. In the second step of this mechanism, a water molecule reacts with the most substituted carbon to open the mercurium ion bridge. The third step of this mechanism is a proton transfer to a solvent water molecule to neutralize the addition product. The fourth step of the reaction pathway is the reduction of the organomercury intermediate with sodium borohydride under basic conditions. The mechanism of the fourth step is beyond the scope of first year organic chemistry.



Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's Regioselectivity with the OH group attached to the most substituted carbon and the H attached to the least substituted carbon. The reaction is useful, because strong acids are not required and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

Exercise

1. Show how to prepare 3-methyl2-pentanol from 3-methyl-1-pentene.

Note: Questions 2-5 have not shown the water present in the sulfuric acid solution and have indicated a second neutralization step. Some authors simply write H^+/H_2O as a single step.

2. Draw the bond-line structure for the product.

PP1 Q (1).bmp

3. Draw the bond-line structure for the product. How does the cyclopropane group affect the reaction?

PP2 Q.bmp

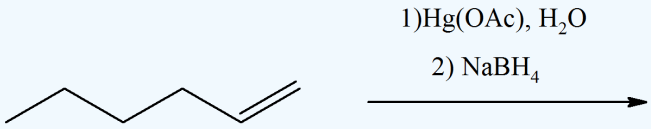
4. Draw the bond-line structure for the product. (Hint: What is different about this problem?)

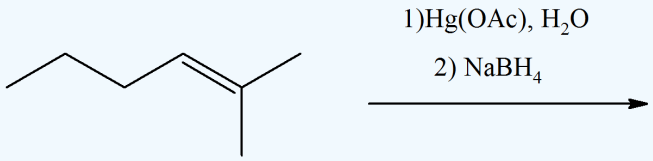
PP3 Q.bmp

5. Draw the bond-line structure for the product(s). Indicate any shifts as well as the major product:

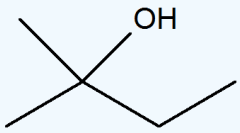
PP5 Q.bmp

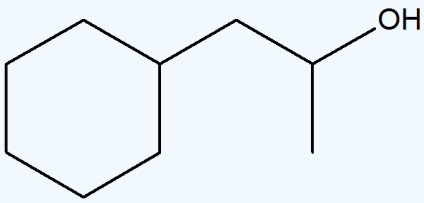
6. In each case, predict the product(s) of these reactants of oxymercuration.





7. Propose the alkene that was the reactant for each of these products of oxymercuration.





Answer available at the end of this section.

References

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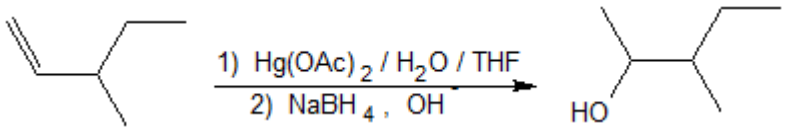
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Lance Peery (UCD), Duyen Dao-Tran (UCD)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)
- Prof. Steven Farmer (Sonoma State University)

Answers

Exercise

1.



2. This reaction is electrophilic hydration.

PP1 A.bmp

3. 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

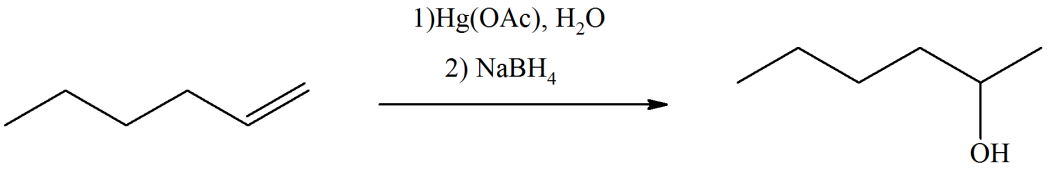
4. A hydride shift actually occurs from the top of the 1-methylcyclopentane to where the carbocation had formed.

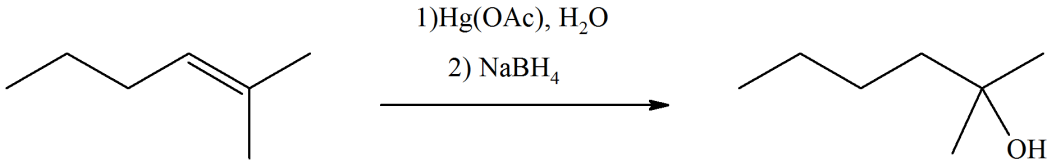
PP3 A (1).bmp

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.

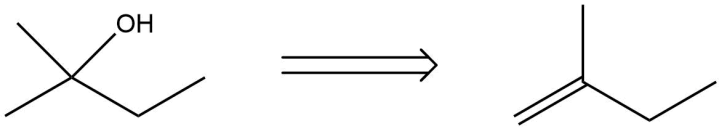
PP5 A.bmp

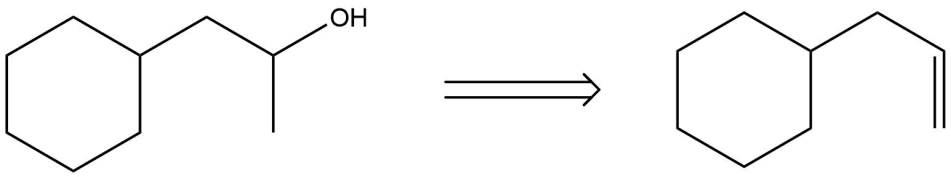
6.





7.





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5.8: Hydration- Hydroboration-Oxidation

Learning Objectives

- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation)

Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an anti-Markovnikov manner, where the hydrogen (from $\mathrm{BH_3}$ or $\mathrm{BHR_2}$) 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 the electrophile 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.

The Borane Complex

It is very important to understand the structure and properties of the borane molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula $\mathrm{B_2H_6}$ (diborane).

$$\mathrm{BH_3} \longrightarrow \mathrm{B_2H_6}$$

Since diborane dimer ignites spontaneously in air, it commercially distributed in ether or tetrahydrofuran (THF) solutions. In these solutions, the borane can exist as a Lewis acid-base complex which allows boron to have an octet of electrons.

THF.bmp

The Mechanism

Step #1: Hydroboration of the alkene

The addition of the borane to the alkene is initiated and proceeds as a concerted reaction because bond breaking and bond formation occur at the same time. The vacant 2p orbital of the boron takes the role of electrophile and accepts the pi electrons from the nucleophilic alkene. 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). With a concerted mechanism, there is no carbocation formation.

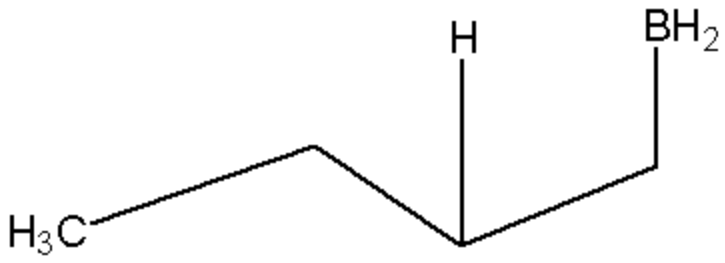
concerted reaction 1.bmp

Transition state

TRANSITION STATE FINAL 2 (2).bmp

* Note that a carbocation is not formed. Therefore, no rearrangement takes place.





It is important to note that reaction continues two more times until all three hydrogens on the borane have reacted with alkenes to create the trialkylborane intermediate R3B.

Step #2: Oxidation of the Trialkylborane by Hydrogen Peroxide

The hydrogen peroxide (HOOH) is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from the previous hydroboration.

$$\mathrm{HOOH + OH^- \longrightarrow HOO^- + HOH} \tag{5.8.1}$$

oxidation part 1 (1).bmp

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 loss of a hydroxide ion.

1,2, SHIFT.bmp

Two more of these reactions with hydroperoxide will occur in order give a trialkylborate

trialkylborate.bmp

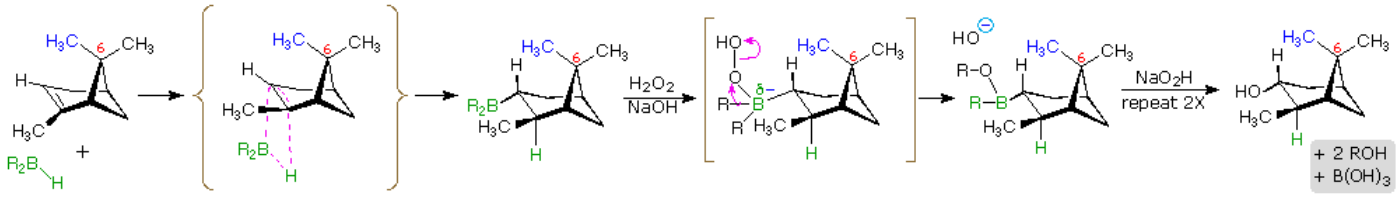
In the final step of the oxidation process, the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate (\ce{Na3BO3}\).

$$\mathrm{(RO_3)B + 3\,NaOH \longrightarrow 3\,OH + Na_3BO_3} \tag{5.8.2}$$

If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided at the end of this section.

Stereochemistry of the Hydroboration Step

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 blue 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.

Exercises

1. Draw the bond-line structure of the product(s) for these following reactions?

a)

PROBLEM 1.bmp

b)

PROBLEM #2.bmp

c)

PROBELM #3.bmp

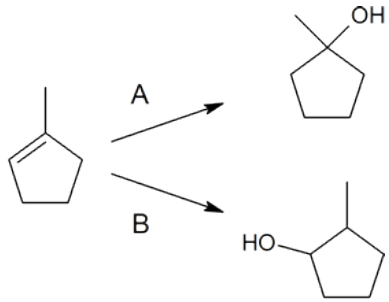
2. Draw the structural formulas for the alcohols that result from hydroboration-oxidation of the alkenes shown.

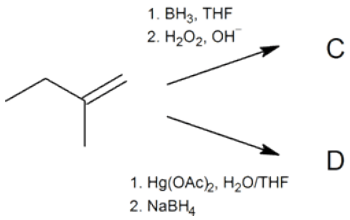
a)

problem 4.bmp

b) (E)-3-methyl-2-pentene

3. Write out the reagents or products (A–D) shown in the following reaction schemes.

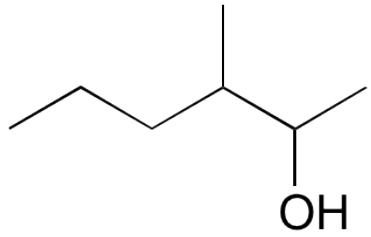




Answer

1.

a) answer #1.bmp

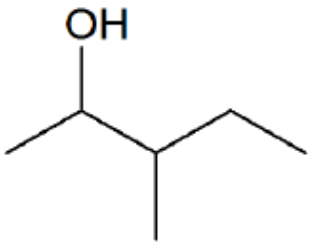


b)

c) Answer #3.bmp

2.

a) Answer #4.bmp



b)

3.

alkene hydration reaction answers

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1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
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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

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- Jim Clark (Chemguide.co.uk)
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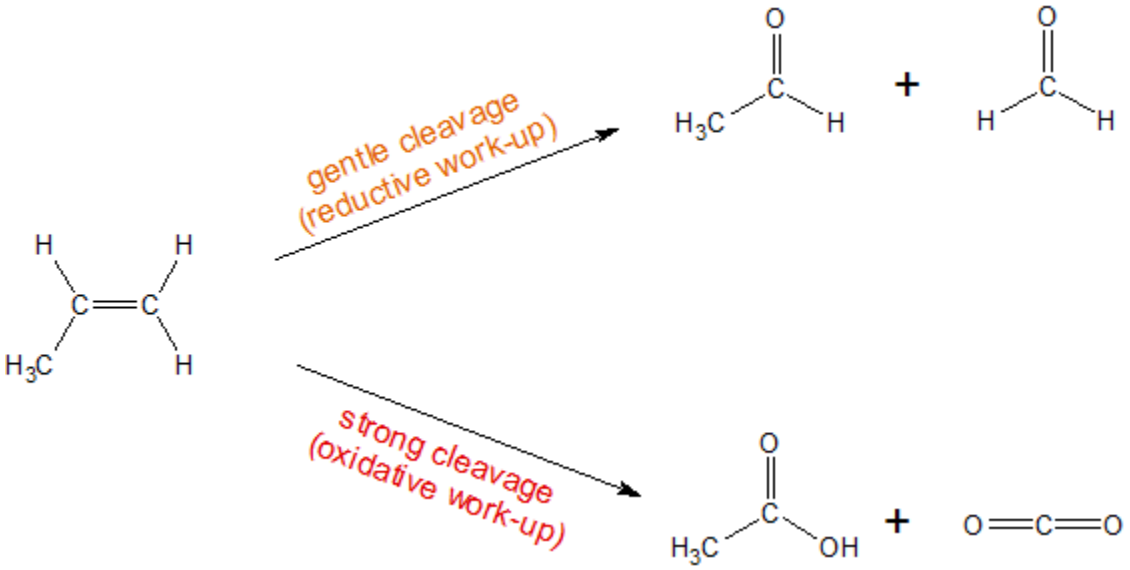
5.9: Oxidative Cleavage of Alkenes

Learning Objective

- predict the products/specify the reagents for oxidative cleavage of alkenes

Overview

Oxidative cleavage can occur by several different reaction pathways. The cleavage can be strong or gentle depending on the reaction conditions and/or the work-up of the initial reaction product. Both alkenes and alkynes can undergo cleavage reactions. This section will focus on alkenes.



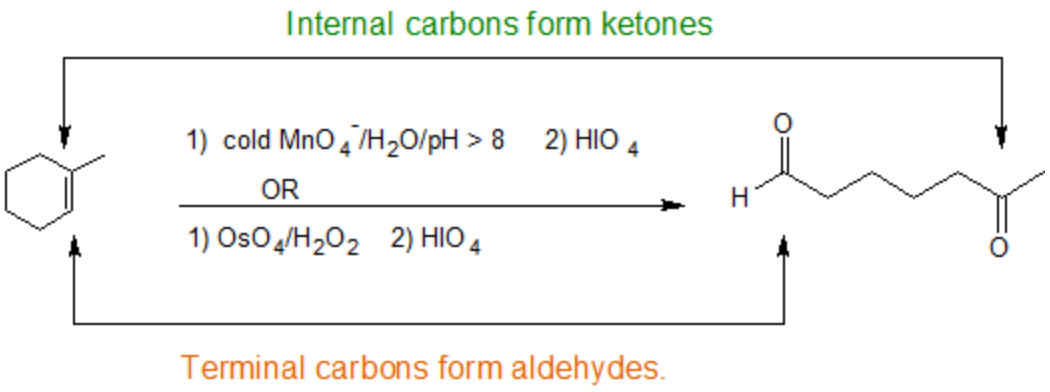
Gentle cleavage of alkenes occurs by two primary reaction pathways: ozolysis with a reductive work-up or syn-dihydroxylation followed by oxidation with perioidc acid. Gentle cleavage will leave terminal carbons partially oxidized to aldehydes. Strong cleavage of alkenes will fully oxidize terminal carbons to carboxylic acids. Internal carbons become ketones by either reaction pathway.

Why so many reactions?

At first glance, it may seem silly to have more than more reaction pathway for the same functional group conversion. As this course proceeds, it will become necessary to target reactions to a single functional group of an organic compound with multiple functional groups. A particular reaction pathway can be advantageous when the reactivity of the entire molecule is considered, not just a single functional group.

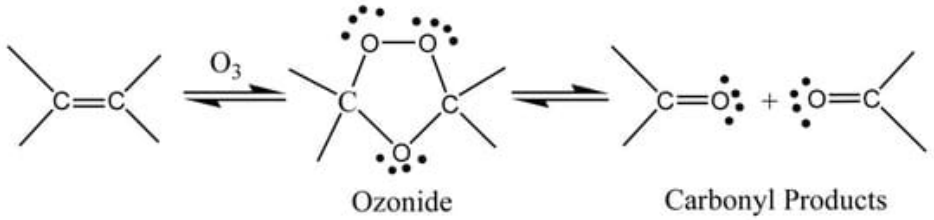
Gentle Cleavage: Syn-Dihydroxylation followed by Periodic Acid

Alkenes can also be gently cleavage in a two-step reaction sequence in which the alkene first undergoes syn-dihydroxylation using cold, slightly basic $KMnO_4$ or OsO_4/H_2O_2 followed by oxidation with periodic acid (HIO_4). Both reaction sequences are shown below using 1-methylcyclohexene as an example.



Gentle Cleavage: Ozonolysis with a Reduction Work-up

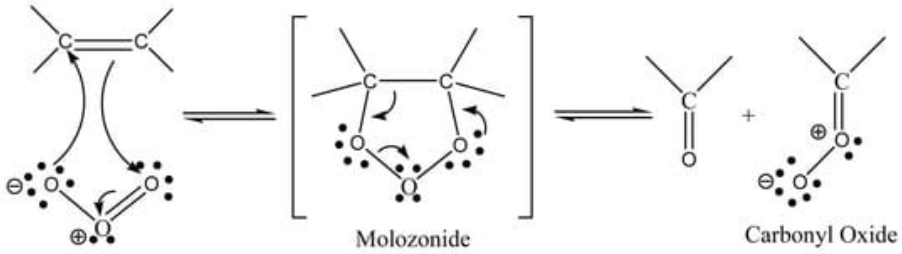
Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes by breaking 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.



Ozonolysis Reaction Mechanism

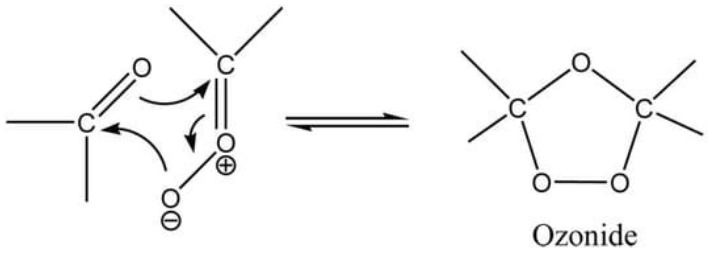
The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the carbon-carbon double bond and is replaced by a carbon-oxygen double bond instead.

Step 1:



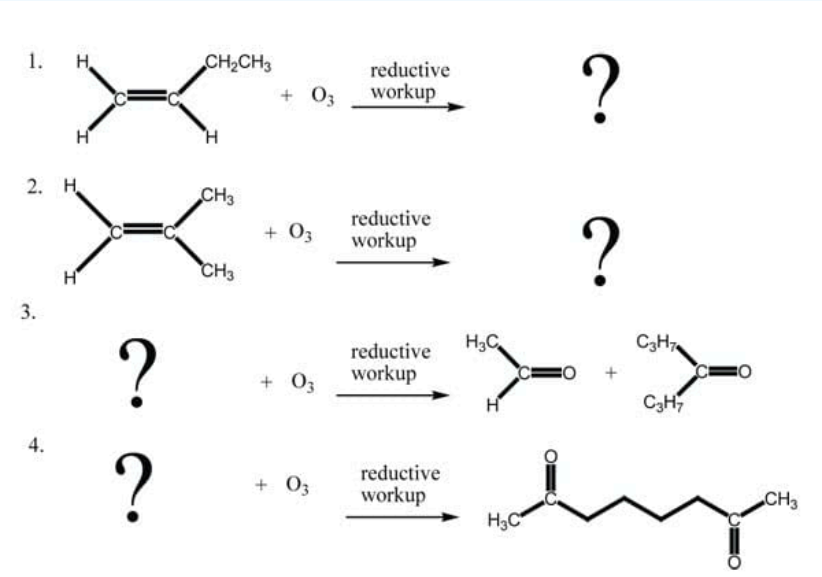
The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the carbon-carbon double bond to form the molozonide intermediate. Due to low stablility of molozonide, it continues reacting and breaks apart to form a carbonyl and a carbonyl oxide molecule.

Step 2:



The electrons of the carbonyl and the carbonyl oxide form the stable ozonide intermediate which can then undergo an oxidative or reductive work-up to form the products of interest. A reductive workup converts the ozonide molecule into the desired carbonyl products with aldehyde on terminal carbons. An oxidative workup converts the ozonide molecule into the desired carbonyl products with carboxylic acids on terminal carbons. The two reaction workup conditions are summarized below.

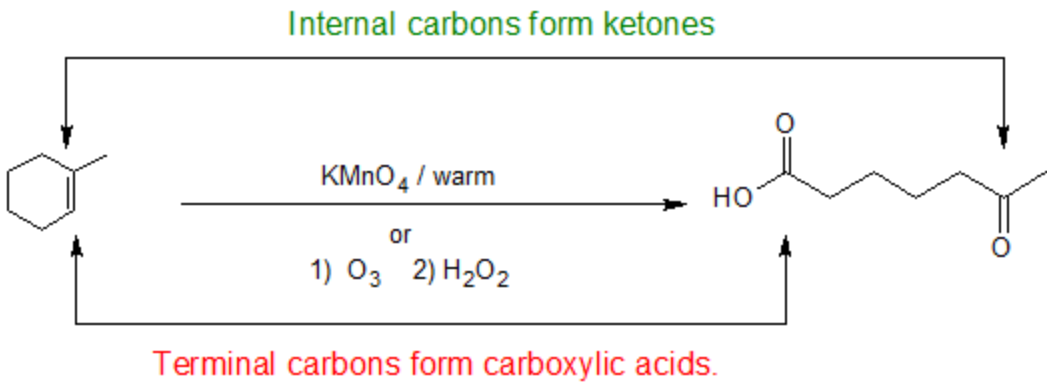
Exercises



Answers available at the end of this section.

Strong Cleavage from Strong Oxidative Reactions

When the reaction conditions for potassium permanganate are warm, then the oxidation reaction is stronger and cleavage occurs at the alkene with any terminal carbons fully oxidizing to carboxylic acids. When the ozonolysis reaction is followed by an oxidative work-up, then any terminal carbons will oxidize fully to the carboxylic acid as shown in the example below. The example for 1-methylcycohexene is shown below.

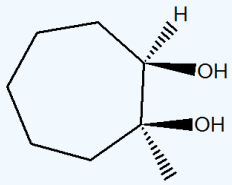


Exercise

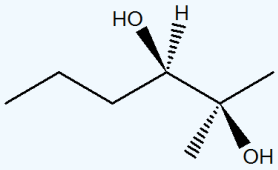
5. What would you expect the products to be from the reaction of *cis*-2-pentene with *m*-chloro-peroxybenzoic acid? Show the stereochemistry of the final product.

6. Give a reaction scheme with starting alkenes and required reagents to produce the following compounds.

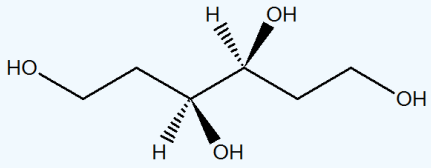
(a)



(b)



(c)



Answer available at the end of this section.

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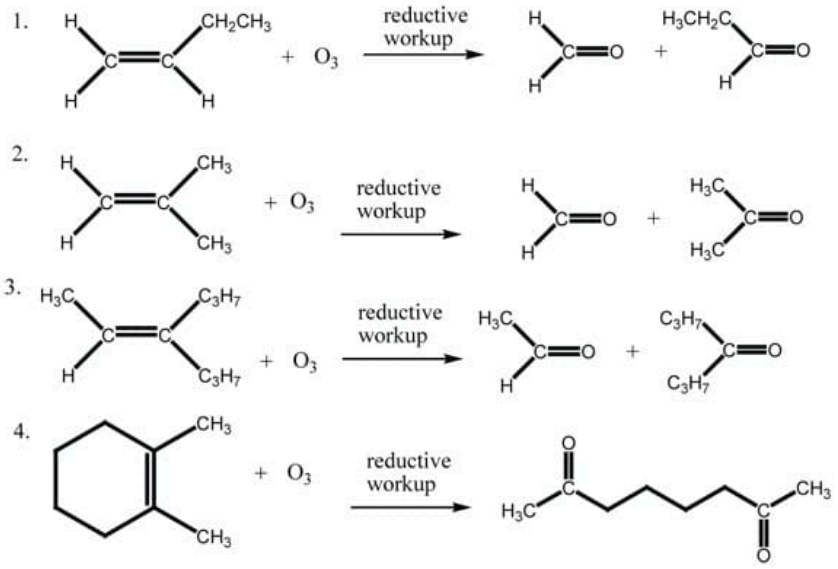
Contributors and Attributions

- 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)

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."

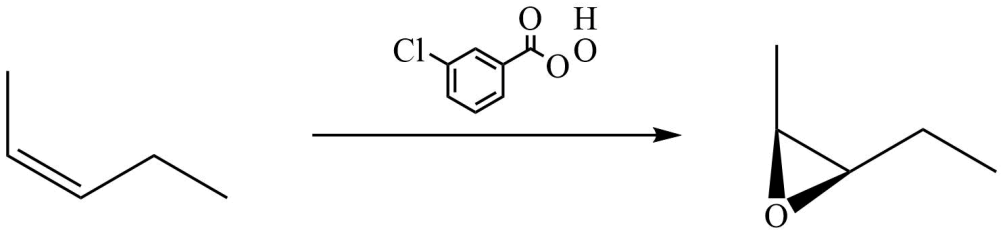
Answers

Exercises

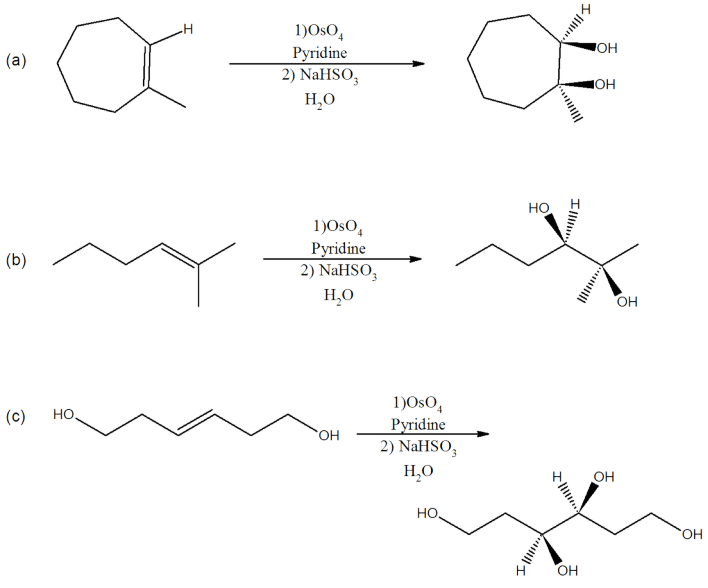


Exercise

5.



6.



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5.10: Free 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.

A notable example of a free radical is the hydroxyl radical (HO•), a molecule that is one hydrogen atom short of a water molecule and thus has one bond "dangling" from the oxygen. Two other examples are the carbene molecule (**:**CH2), which has two dangling bonds; and the superoxide anion (•O–2), the oxygen molecule O2 with one extra electron, which has one dangling bond. In contrast, the hydroxyl anion (HO–), the oxide anion (O2–) and thecarbenium cation (CH+3) are not radicals, since the bonds that may appear to be dangling are in fact resolved by the addition or removal of electrons.

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.

Free radicals play an important role in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes. In living organisms, the free radicals superoxide and nitric oxideand their reaction products regulate many processes, such as control of vascular tone and thus blood pressure. They also play a key role in the intermediary metabolism of various biological compounds. Such radicals can even be messengers in a process dubbed redox signaling. A radical may be trapped within a *solvent cage* or be otherwise bound.

Until late in the 20th century the word "radical" was used in chemistry to indicate any connected group of atoms, such as a methyl group or a carboxyl, whether it was part of a larger molecule or a molecule on its own. The qualifier "free" was then needed to specify the unbound case. Following recent nomenclature revisions, a part of a larger molecule is now called a functional group or substituent, and "radical" now implies "free". However, the old nomenclature may still occur in the literature.

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 chemical equations, free radicals are frequently denoted by a dot placed immediately to the right of the atomic symbol or molecular formula as follows:

$$\mathrm{Cl_2} \xrightarrow{UV} \mathrm{Cl\cdot} + \mathrm{Cl\cdot}$$

Chlorine gas can be broken down by ultraviolet light to form atomic chlorine radicals.

Radical reaction mechanisms use single-headed arrows to depict the movement of single electrons:

Radical.svg

The homolytic cleavage of the breaking bond is drawn with a 'fish-hook' arrow to distinguish from the usual movement of two

electrons depicted by a standard curly arrow. It should be noted that the second electron of the breaking bond also moves to pair up with the attacking radical electron; this is not explicitly indicated in this case.

Free radicals also take part in radical addition and radical substitution as reactive intermediates. Chain reactions involving free radicals can usually be divided into three distinct processes. These are *initiation*, *propagation*, and *termination*.

- **Initiation** reactions are those that result in a net increase in the number of free radicals. They may involve the formation of free radicals from stable species as in Reaction 1 above or they may involve reactions of free radicals with stable species to form more free radicals.
- **Propagation** reactions are those reactions involving free radicals in which the total number of free radicals remains the same.
- **Termination** reactions are those reactions resulting in a net decrease in the number of free radicals. Typically two free radicals combine to form a more stable species, for example: $2Cl\bullet \rightarrow Cl_2$

Formation

The formation of radicals may involve breaking of covalent bonds homolytically, a process that requires significant amounts of energy. For example, splitting H_2 into $2H\bullet$ has a $\Delta H°$ of +435 kJ/mol, and Cl_2 into $2Cl\bullet$ has a $\Delta H°$ of +243 kJ/mol. This is known as the homolytic bond dissociation energy, and is usually abbreviated as the symbol $\Delta H°$. The bond energy between two covalently bonded atoms is affected by the structure of the molecule as a whole, not just the identity of the two atoms. Likewise, radicals requiring more energy to form are less stable than those requiring less energy. Homolytic bond cleavage most often happens between two atoms of similar electronegativity. In organic chemistry this is often the O-O bond in peroxide species or O-N bonds. Sometimes radical formation is spin-forbidden, presenting an additional barrier. However, propagation is a very exothermic reaction. Likewise, although radical ions do exist, most species are electrically neutral. Radicals may also be formed by single electron oxidation or reduction of an atom or molecule. An example is the production of superoxide by the electron transport chain. Early studies of organometallic chemistry, especially tetra-alkyl lead species by F.A. Paneth and K. Hahnfeld in the 1930s supported heterolytic fission of bonds and a radical based mechanism.

Persistence and stability

The radical derived from *α-tocopherol*

Although radicals are generally short-lived due to their reactivity, there are long-lived radicals. These are categorized as follows:

Stable radicals

The prime example of a stable radical is molecular dioxygen (O_2). Another common example is nitric oxide (NO). Organic radicals can be long lived if they occur in a conjugated π system, such as the radical derived from α-tocopherol (vitamin E). There are also hundreds of examples of thiazyl radicals, which show low reactivity and remarkable thermodynamic stability with only a very limited extent of π resonance stabilization.[1][2]

Persistent radicals

Persistent radical compounds are those whose longevity is due to steric crowding around the radical center, which makes it physically difficult for the radical to react with another molecule.[3] Examples of these include Gomberg's triphenylmethyl radical, Fremy's salt(Potassium nitrosodisulfonate, $(KSO_3)_2NO\cdot$), nitroxides, (general formula $R_2NO\cdot$) such as TEMPO, TEMPOL, nitronyl nitroxides, and azephenylenyls and radicals derived from PTM (perchlorophenylmethyl radical) and TTM (tris(2,4,6-trichlorophenyl)methyl radical). Persistent radicals are generated in great quantity during combustion, and "may be responsible for the oxidative stress resulting in cardiopulmonary disease and probably cancer that has been attributed to exposure to airborne fine particles."[4]

Diradicals

Diradicals are molecules containing two radical centers. Multiple radical centers can exist in a molecule. Atmospheric oxygen

naturally exists as a diradical in its ground state as triplet oxygen. The low reactivity of atmospheric oxygen is due to its diradical state. Non-radical states of dioxygen are actually less stable than the diradical. The relative stability of the oxygen diradical is primarily due to the spin-forbidden nature of the triplet-singlet transition required for it to grab electrons, i.e., "oxidize". The diradical state of oxygen also results in its paramagnetic character, which is demonstrated by its attraction to an external magnet.[5]

Reactivity

Radical alkyl intermediates are stabilized by similar physical processes to carbocations: as a general rule, the more substituted the radical center is, the more stable it is. This directs their reactions. Thus, formation of a tertiary radical ($R_3C\cdot$) is favored over secondary ($R_2HC\cdot$), which is favored over primary ($RH_2C\cdot$). Likewise, radicals next to functional groups such as carbonyl, nitrile, and ether are more stable than tertiary alkyl radicals.

Radicals attack double bonds. However, unlike similar ions, such radical reactions are not as much directed by electrostatic interactions. For example, the reactivity of nucleophilic ions with α,β-unsaturated compounds (C=C–C=O) is directed by the electron-withdrawing effect of the oxygen, resulting in a partial positive charge on the carbonyl carbon. There are two reactions that are observed in the ionic case: the carbonyl is attacked in a direct addition to carbonyl, or the vinyl is attacked in conjugate addition, and in either case, the charge on the nucleophile is taken by the oxygen. Radicals add rapidly to the double bond, and the resulting α-radical carbonyl is relatively stable; it can couple with another molecule or be oxidized. Nonetheless, the electrophilic/neutrophilic character of radicals has been shown in a variety of instances. One example is the alternating tendency of the copolymerization of maleic anhydride (electrophilic) and styrene (slightly nucleophilic).

In intramolecular reactions, precise control can be achieved despite the extreme reactivity of radicals. In general, radicals attack the closest reactive site the most readily. Therefore, when there is a choice, a preference for five-membered rings is observed: four-membered rings are too strained, and collisions with carbons six or more atoms away in the chain are infrequent.

Carbenes and nitrenes, which are diradicals, have distinctive chemistry.

Combustion

Spectrum of the blue flame from a butane torch showing excited molecular radical band emission and Swan bands

A familiar free-radical reaction is combustion. The oxygen molecule is a stable diradical, best represented by ·O-O·. Because spins of the electrons are parallel, this molecule is stable. While the ground stateof oxygen is this unreactive spin-unpaired (triplet) diradical, an extremely reactive spin-paired (singlet) state is available. For combustion to occur, the energy barrier between these must be overcome. This barrier can be overcome by heat, requiring high temperatures. The triplet-singlet transition is also "forbidden". This presents an additional barrier to the reaction. It also means molecular oxygen is relatively unreactive at room temperature except in the presence of a catalytic heavy atom such as iron or copper.

Combustion consists of various radical chain reactions that the singlet radical can initiate. The flammability of a given material strongly depends on the concentration of free radicals that must be obtained before initiation and propagation reactions dominate leading to combustion of the material. Once the combustible material has been consumed, termination reactions again dominate and the flame dies out. As indicated, promotion of propagation or termination reactions alters flammability. For example, because lead itself deactivates free radicals in the gasoline-air mixture, tetraethyl lead was once commonly added to gasoline. This prevents the combustion from initiating in an uncontrolled manner or in unburnt residues (engine knocking) or premature ignition (preignition).

When a hydrocarbon is burned, a large number of different oxygen radicals are involved. Initially, hydroperoxyl radical (HOO·) are formed. These then react further to give organic hydroperoxides that break up into hydroxyl radicals (HO·).

Polymerization

In addition to combustion, many polymerization reactions involve free radicals. As a result many plastics, enamels, and other polymers are formed through radical polymerization. For instance, drying oils and alkyd paints harden due to radical crosslinking by oxygen from the atmosphere.

Recent advances in radical polymerization methods, known as living radical polymerization, include:

- Reversible addition-fragmentation chain transfer (RAFT)
- Atom transfer radical polymerization (ATRP)
- Nitroxide mediated polymerization (NMP)

These methods produce polymers with a much narrower distribution of molecular weights.

Atmospheric radicals

The most common radical in the lower atmosphere is molecular dioxygen. Photodissociation of source molecules produces other free radicals. In the lower atmosphere, the most important examples of free radical production are the photodissociation of nitrogen dioxide to give an oxygen atom and nitric oxide (see eq. 1 below), which plays a key role in smog formation—and the photodissociation of ozone to give the excited oxygen atom O(1D) (see eq. 2 below). The net and return reactions are also shown (eq. 3 and 4, respectively).

1. $\mathrm{NO_2} \xrightarrow{h\nu} \mathrm{NO} + \mathrm{O}$
2. $\mathrm{O} + \mathrm{O_2} \rightarrow \mathrm{O_3}$
3. $\mathrm{NO_2} + \mathrm{O_2} \xrightarrow{h\nu} \mathrm{NO} + \mathrm{O_3}$
4. $\mathrm{NO} + \mathrm{O_3} \rightarrow \mathrm{NO_2} + \mathrm{O_2}$

In the upper atmosphere, a particularly important source of radicals is the photodissociation of normally unreactive chlorofluorocarbons (CFCs) by solar ultraviolet radiation, or by reactions with other stratospheric constituents (see eq. 1 below). These reactions give off the chlorine radical, Cl•, which reacts with ozone in a catalytic chain reaction ending in Ozone depletion and regeneration of the chlorine radical, allowing it to reparticipate in the reaction (see eq. 2–4 below). Such reactions are believed to be the primary cause of depletion of the ozone layer (the net result is shown in eq. 5 below), and this is why the use of chlorofluorocarbons as refrigerants has been restricted.

1. $\mathrm{CFCS} \xrightarrow{h\nu} \mathrm{Cl\cdot}$
2. $\mathrm{Cl\cdot} + \mathrm{O_3} \rightarrow \mathrm{ClO\cdot} + \mathrm{O_2}$
3. $\mathrm{O_3} \xrightarrow{h\nu} \mathrm{O} + \mathrm{O_2}$
4. $\mathrm{O} + \mathrm{ClO\cdot} \rightarrow \mathrm{Cl\cdot} + \mathrm{O_2}$
5. $2\mathrm{O_3} \xrightarrow{h\nu} 3\mathrm{O_2}$

In biology

Free radicals play an important role in a number of biological processes. Many of these are necessary for life, such as the intracellular killing of bacteria by phagocytic cells such as granulocytes and macrophages. Researchers have also implicated free radicals in certain cell signalling processes,[6] known as redox signaling.

The two most important oxygen-centered free radicals are superoxide and hydroxyl radical. They derive from molecular oxygen under reducing conditions. However, because of their reactivity, these same free radicals can participate in unwanted side reactions resulting in cell damage. Excessive amounts of these free radicals can lead to cell injury and death, which may contribute to many diseases such as cancer, stroke, myocardial infarction, diabetes and major disorders.[7] Many forms of cancer are thought to be the result of reactions between free radicals and DNA, potentially resulting in mutations that can adversely affect the cell cycle and potentially lead to malignancy.[8] Some of the symptoms of aging such as atherosclerosis are also attributed to free-radical induced oxidation of cholesterol to 7-ketocholesterol.[9] In addition free radicals contribute to alcohol-induced liver damage, perhaps more than alcohol itself. Free radicals produced by cigarette smoke are implicated in inactivation of alpha 1-antitrypsin in the lung. This process promotes the development of emphysema.

Free radicals may also be involved in Parkinson's disease, senile and drug-induced deafness, schizophrenia, and Alzheimer's.[10] The classic free-radical syndrome, the iron-storage disease hemochromatosis, is typically associated with a constellation of free-radical-related symptoms including movement disorder, psychosis, skin pigmentary melanin abnormalities, deafness, arthritis, and diabetes mellitus. The free-radical theory of aging proposes that free radicals underlie the aging process itself. Similarly, the process of mitohormesis suggests that repeated exposure to free radicals may extend life span.

Because free radicals are necessary for life, the body has a number of mechanisms to minimize free-radical-induced damage and to repair damage that occurs, such as the enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. In addition, antioxidants play a key role in these defense mechanisms. These are often the three vitamins, vitamin A, vitamin C and vitamin E and polyphenol antioxidants. Furthermore, there is good evidence indicating that bilirubin and uric acid can act as antioxidants to help neutralize certain free radicals. Bilirubin comes from the breakdown of red blood cells' contents, while uric acid is a breakdown product of purines. Too much bilirubin, though, can lead to jaundice, which could eventually damage the central nervous system, while too much uric acid causes gout.[11]

Reactive oxygen species

Reactive oxygen species or ROS are species such as superoxide, hydrogen peroxide, and hydroxyl radical and are associated with cell damage. ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling.

Oxybenzone has been found to form free radicals in sunlight, and therefore may be associated with cell damage as well. This only occurred when it was combined with other ingredients commonly found in sunscreens, like titanium oxide and octyl methoxycinnamate.[12]

Loose definition of radicals

In most fields of chemistry, the historical definition of radicals contends that the molecules have nonzero spin. However in fields including spectroscopy, chemical reaction, and astrochemistry, the definition is slightly different. Gerhard Herzberg, who won the Nobel prize for his research into the electron structure and geometry of radicals, suggested a looser definition of free radicals: "any transient (chemically unstable) species (atom, molecule, or ion)".[13] The main point of his suggestion is that there are many chemically unstable molecules that have zero spin, such as C_2, C_3, CH_2 and so on. This definition is more convenient for discussions of transient chemical processes and astrochemistry; therefore researchers in these fields prefer to use this loose definition.[14]

Diagnostics

Free radical diagnostic techniques include:

- Electron spin resonance

  A widely used technique for studying free radicals, and other paramagnetic species, is electron spin resonance spectroscopy (ESR). This is alternately referred to as "electron paramagnetic resonance" (EPR) spectroscopy. It is conceptually related to nuclear magnetic resonance, though electrons resonate with higher-frequency fields at a given fixed magnetic field than do most nuclei.

- Nuclear magnetic resonance using a phenomenon called CIDNP
- Chemical labelling

  Chemical labelling by quenching with free radicals, e.g. with nitric oxide (NO) or DPPH (2,2-diphenyl-1-picrylhydrazyl), followed by spectroscopic methods like X-ray photoelectron spectroscopy (XPS) or absorption spectroscopy, respectively.

- Use of free radical markers

  Stable, specific or non-specific derivates of physiological substances can be measured e.g. lipid peroxidation products (isoprostanes, TBARS), amino acid oxidation products (meta-tyrosine, ortho-tyrosine, hydroxy-Leu, dityrosine etc.), peptide oxidation products (oxidized glutathione – GSSG)

  2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) is a chemical compound used to study the chemistry of the oxidation of drugs.[15] It is a free radical-generating azo compound. It is gaining prominence as a model oxidant in small molecule and proteintherapeutics for its ability to initiate oxidation reactions via both nucleophilic and free radical mechanisms.[16]

- Indirect method

  Measurement of the decrease in the amount of antioxidants (e.g. TAS, reduced glutathione – GSH)

- Trapping agents

  Using a chemical species that reacts with free radicals to form a stable product that can then be readily measured (Hydroxyl radical and salicylic acid)

See also

- -yl
- Electron pair
- Globally Harmonized System of Classification and Labelling of Chemicals
- Hofmann–Löffler reaction

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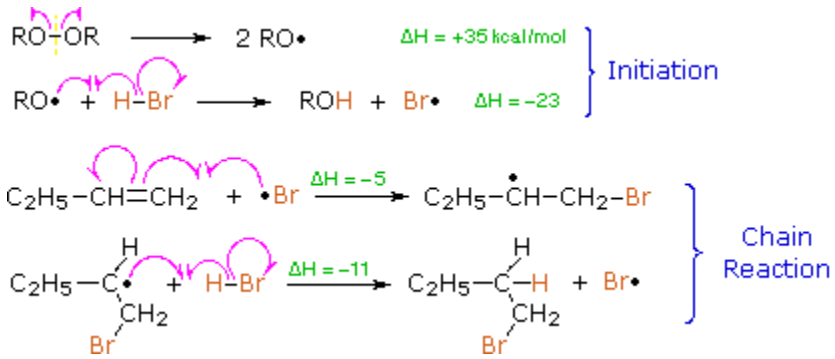
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5.11: Addition of Radicals to Alkenes

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

$RCH{=}CH_2 + CCl_4$ (peroxide initiator) —> $RCHClCH_2CCl_3$

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.

$RCH_2(CH_3)CH\bullet + CH_3CH{=}CH_2$ —> $RCH_2(CH_3)CH\text{-}CH_2(CH_3)CH\bullet + CH_3CH{=}CH_2$ —> $RCH_2(CH_3)CHCH_2(CH_3)CH\text{-}CH_2(CH_3)CH\bullet$

—> **etc.**

Contributors

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

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5.12: Anti-Markovnikov Product Formation

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.

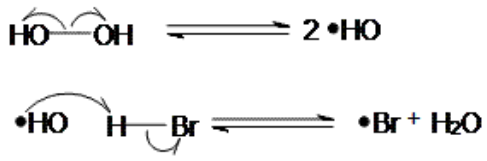
Introduction

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

The 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.

dd.bmp

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

Problems

Please give the product(s) of the reactions below:

1. $CH_3{-}C(CH_3){=}CH{-}CH_3 + HBr + H_2O_2 \rightarrow$
2. $CH_3C(CH_3){=}CH{-}CH_3 + HI + H_2O_2 \rightarrow$
3. $CH_3C(CH_3){=}CH{-}CH_3 + HCl + H_2O_2 \rightarrow$
4. $CH_3CH{=}CH{-}CH_3 + HBr + H_2O_2 \rightarrow$
5. $CH_3C(CH_3){=}CH{-}CH_3 + HBr \rightarrow$

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)

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5.13: Homolytic Cleavage and Bond Dissociation Energies

Learning Objective

- calculate reaction enthalpies from bond dissociation energies

Introduction

The homolytic bond dissociation energy is the amount of energy needed to break apart one mole of covalently bonded gases into a pair of radicals. The SI units used to describe bond energy are kiloJoules per mole of bonds (kJ/Mol). It indicates how strongly the atoms are bonded to each other. *Solvation* is the interaction between solvent molecules and the ions or molecules dissolved in that solvent.

Breaking a covalent bond between two partners, A-B, can occur either heterolytically, where the shared pair of electron goes with one partner or another

$$A - B \rightarrow A^{+} + B:^{-} \tag{5.13.1}$$

or

$$A - B \rightarrow A:^{-} + B^{+} \tag{5.13.2}$$

or homolytically, where one electron stays with each partner.

$$A - B \rightarrow A^{\bullet} + B^{\bullet} \tag{5.13.3}$$

The products of homolytic cleavage are radicals and the energy that is required to break the bond homolytically is called the *Bond Dissociation Energy* (BDE) and is a measure of the strength of the bond.

Calculation of the BDE

The BDE for a molecule A-B is calculated as the difference in the enthalpies of formation of the products and reactants for homolysis

$$BDE = \Delta_f H(A^{\bullet}) + \Delta_f H(B^{\bullet}) - \Delta_f H(A - B) \tag{5.13.4}$$

Officially, the IUPAC definition of bond dissociation energy refers to the energy change that occurs at 0 K, and the symbol is D_o. However, it is commonly referred to as BDE, the bond dissociation energy, and it is generally used, albeit imprecisely, interchangeably with the bond dissociation *enthalpy*, which generally refers to the enthalpy change at room temperature (298K). Although there are technically differences between BDEs at 0 K and 298 K, those difference are not large and generally do not affect interpretations of chemical processes.

Bond Breakage/Formation

Bond dissociation energy (or enthalpy) is a state function and consequently does not depend on the path by which it occurs. Therefore, the specific mechanism in how a bond breaks or is formed does not affect the BDE. Bond dissociation energies are useful in assessing the energetics of chemical processes. For chemical reactions, combining bond dissociation energies for bonds formed and bonds broken in a chemical reaction using Hess's Law can be used to estimate reaction enthalpies.

Example: Chlorination of Methane

Consider the chlorination of methane

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{5.13.5}$$

the overall reaction thermochemistry can be calculated exactly by combining the BDEs for the bonds broken and bonds formed

CH_4 → CH_3• + H• BDE(CH_3-H)

Cl_2 → 2Cl• BDE(Cl_2)\]

H• + Cl• → HCl -BDE(HCl)

CH_3• + Cl• → CH_3Cl -BDE(CH_3-Cl)

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{5.13.6}$$

$$\Delta H = BDE(R-H) + BDE(Cl_2) - BDE(HCl) - BDE(CH_3 - Cl) \tag{5.13.7}$$

Because reaction enthalpy is a state function, it does not matter what reactions are combined to make up the overall process using Hess's Law. However, BDEs are convenient to use because they are readily available.

Alternatively, BDEs can be used to assess individual steps of a mechanism. For example, an important step in free radical chlorination of alkanes is the abstraction of hydrogen from the alkane to form a free radical.

RH + Cl• → R• + HCl

The energy change for this step is equal to the difference in the BDEs in RH and HCl

$$\Delta H = BDE(R-H) - BDE(HCl) \tag{5.13.8}$$

This relationship shows that the hydrogen abstraction step is more favorable when BDE(R-H) is smaller. The difference in energies accounts for the selectivity in the halogenation of hydrocarbons with different types of C-H bonds.

Table 6.8.1: Representative C-H BDEs in Organic Molecules

R-H	D_o, kJ/mol	D_{298}, kJ/mol	R-H	D_o, kJ/mol	D_{298}, kJ/mol
CH_3-H	432.7±0.1	439.3±0.4	H_2C=CH-H	456.7±2.7	463.2±2.9
CH_3CH_2-H		423.0±1.7	C_6H_5-H	465.8±1.9	472.4±2.5
$(CH_3)_2$CH-H		412.5±1.7	HCCH	551.2±0.1	557.8±0.3
$(CH_3)_3$C-H		403.8±1.7			
			H_2C=CHCH_2-H		371.5±1.7
HC(O)-H		368.6±0.8	$C_6H_5CH_2$-H		375.3±2.5
CH_3C(O)-H		374.0±1.2			

Trends in C-H BDEs

It is important to remember that C-H BDEs refer to the energy it takes to break the bond, and is the difference in energy between the reactants and the products. Therefore, it is not appropriate to interpret BDEs solely in terms of the "stability of the radical

products" as is often done.

Analysis of the BDEs shown in the table above shows that there are some systematic trends:

1. **BDEs vary with hybridization:** Bonds with sp^3 hybridized carbons are weakest and bonds with sp hybridized carbons are much stronger. The vinyl and phenyl C-H bonds are similar, reflecting their sp^2 hybridization. The correlation with hybridization can be viewed as a reflection of the C-H bond lengths. Longer bonds formed with sp^3 orbitals are consequently weaker. Shorter bonds formed with orbitals that have more s-character are similarly stronger.
2. **C-H BDEs vary with substitution:** Among sp^3 hybridized systems, methane has the strongest C-H bond. C-H bonds on primary carbons are stronger than those on secondary carbons, which are stronger than those on tertiary carbons.

Interpretation of C-H BDEs for sp^3 Hybridized Carbons

The interpretation of the BDEs in saturated molecules has been subject of recent controversy. As indicated above, the variation in BDEs with substitution has traditionally been interpreted as reflecting the stabilities of the alkyl radicals, with the assessment that more highly substituted radicals are more stable, as with carbocations. Although this is a popular explanation, it fails to account fo the fact the bonds to groups other than H do not show the same types of variation.

R	BDE(R-CH3)	BDE(R-Cl)	BDE(R-Br)	BDE(R-OH)
CH_3-	377.0±0.4	350.2±0.4	301.7±1.3	385.3±0.4
CH_3CH_2-	372.4±1.7	354.8±2.1	302.9±2.5	393.3±1.7
$(CH_3)_2CH$-	370.7±1.7	356.5±2.1	309.2±2.9	399.6±1.7
$(CH_3)_3C$-	366.1±1.7	355.2±2.9	303.8±2.5	400.8±1.7

Therefore, although C-CH_3 bonds get weaker with more substitution, the effect is not nearly as large as that observed with C-H bonds. The strengths of C-Cl and C-Br bonds are not affected by substitution, despite the fact that the same radicals are formed as when breaking C-H bonds, and the C-OH bonds in alcohols actually *increase* with more substitution.

Gronert has proposed that the variation in BDEs is alternately explained as resulting from destabilization of the reactants due to steric repulsion of the substituents, which is released in the nearly planar radicals.[1] Considering that BDEs reflect the relative energies of reactants and products, either explanation can account for the trend in BDEs.

Another factor that needs to be considered is the electronegativity. The Pauling definition of electronegativity says that the bond dissociation energy between unequal partners is going to be dependent on the difference in electrongativities, according to the expression

$$D_o(A-B) = \frac{D_o(A-A) + D_o(B-B)}{2} + (X_A - X_B)^2 \tag{5.13.9}$$

where X_A and X_B are the electronegativities and the bond energies are in eV. Therefore, the variation in BDEs can be interpreted as reflecting variation in the electronegativities of the different types of alkyl fragments.

There is likely some merit in all three interpretations. Since Gronert's original publication of his alternate explanation, there have been many desperate attempts to defend the radical stability explanation.

Exercise

1. Given that $\Delta H°$ for the reaction

   $CH_{4(g)} + 4F_{2(g)} \rightarrow CF_{4(g)} + 4HF_{(g)}$

is –1936 kJ, use the following data to calculate the average bond energy of the \(\ce{{\sf{C-F}}$ bonds in CF_4.

Bond	Average Bond Energy
C — H	413 kJ · mol^{-1}
F — F	155 kJ · mol^{-1}
H — F	567 kJ · mol^{-1}

2. Calculate $\Delta H°$ for the reactions given below.
   a. $CH_3CH_2OCH_3$ + HI -> CH_3CH_2OH + CH_3I
   b. CH_3Cl + NH_3 -> CH_3NH_2 + HCl

Answer available at the end of this section.

References

1. Gronert, S. *J. Org. Chem.* **2006**, *13*, 1209

Further Reading

MasterOrganicChemistry

Bond Strengths And Radical Stability

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Prof. Paul G. Wenthold (Purdue University)

Answers

Exercise

[redacted]$CH_{4(g)}$ + 4 $F_{2(g)}$ → $CF_{4(g)}$ + 4$HF_{(g)}$ ΔH°=–416 kcal

Bonds broken:

4 mol C-H bonds $\times \frac{(413\ \text{kJ})}{(1\ \text{mol})} = 1652\ \text{kJ}$

4 mol F-F bonds $\times \frac{(155\ \text{kJ})}{(1\ \text{mol})} = 620\ \text{kJ}$

Bonds formed:

4 mol C-F bonds $\times \frac{(x\ \text{kJ})}{(1\ \text{mol})} = 4x\ \text{kJ}$

(where *x* = the average energy of one mole of C-F bonds in CF_4, expressed in kJ)

4 mol H-F bonds $\times \frac{(567\ \text{kJ})}{(1\ \text{mol})} = 2268\ \text{kJ}$

$$\begin{aligned}\Delta H° &= \Delta H°(\text{bonds broken}) - \Delta H°(\text{bonds formed}) \\ &= (1652\ \text{kJ} + 620\ \text{kJ}) - (4x + 2268\ \text{kJ}) \\ &= 1652\ \text{kJ} + 620\ \text{kJ} - 4x - 2268\ \text{kJ} \\ &= -1936\ \text{kJ}\end{aligned}$$

Thus,

$$\begin{aligned}4x &= 1936\ \text{kJ} - 2268\ \text{kJ} + 620\ \text{kJ} + 1652\ \text{kJ} \\ &= 1940\ \text{kJ}\end{aligned}$$

and

$$x = \frac{1940\ \text{kJ}}{4\ \text{mol}}$$
$$= 385\ \text{kJ} \cdot \text{mol}^{-1}$$

The average energy of a C-F bond in CF_4 is 385 kJ · mol^{-1}

2. $CH_3Cl + NH_3 \rightarrow CH_3NH_2 + HCl$

Reactant bonds broken	D
CH_3-Cl	351 kJ/mol
NH_2-H	449 kJ/mol
	800 kJ/mol

Product bonds formed	D
CH_3-NH_2	335 kJ/mol
$H-Cl$	432 kJ/mol
	767 kJ/mol

$$\Delta H^\circ = D_{\text{bonds broken}} + D_{\text{bonds formed}}$$
$$= 800\ \text{kJ/mol} - 767\ \text{kJ/mol}$$
$$= +33\ \text{kJ/mol}$$

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5.14: Polymerization of Alkenes

One of the most important technical reactions of alkenes is their conversion to higher-molecular-weight compounds or **polymers** (Table 10-4). A polymer is defined as a *long-chain molecule with recurring structural units*. Thus polymerization of propene gives a long-chain hydrocarbon with recurring $-\mathrm{CH}(\mathrm{CH_3})-\mathrm{CH_2}-$ units:

$$n \times \mathrm{CH_3CH{=}CH_2} \longrightarrow \left[\mathrm{CH}(\mathrm{CH_3})-\mathrm{CH_2}\right]_n \qquad \Delta H^0 = -n \times 20 \text{ kcal}$$

propene (propylene) → polypropene (polypropylene)

Table 10-4: *Alkene Monomers and Their Polymers*

Monomer	Formula	Type of addition polymerization	Polymer or Trade Name	Uses
ethene	$CH_2{=}CH_2$	radical (high pressure), coordination	polyethene	film, containers, piping
chloroethene (vinyl chloride)	$CH_2{=}CHCl$	radical	polyvinyl chloride (PVC)	film, insulation, piping, leatherette
fluoroethene	$CH_2{=}CHF$	radical	Tedlar	coatings
chlorotrifluoroethene	$CF_2{=}CFCl$	radical	Kel-F	gaskets, insulation
tetrafluoroethene	$CF_2{=}CF_2$	radical	Teflon	gaskets, valves, insulation, coatings
propene	$CH_3CH{=}CH_2$	coordination	polypropene, Herculon	fibers, molded articles
2-methylpropene	$(CH_3)_2C{=}CH_2$	cationic	Vistanex, Oppanol, butyl rubber	pressure-sensitive adhesives
styrene	$C_6H_5CH{=}CH_2$	radical	polystyrene	molded articles
propenenitrile (acrylonitrile)	$CH_2{=}CHCN$	radical	Orlon, Acrilan	acrylic fibers
methyl 2-methyl-propenoate (methyl methacrylate)	$CH_2{=}C(CH_3)CO_2CH_3$	radical anionic	Lucite, Plexiglas	coatings, molded articles

Most technically important polymerizations of alkenes occur by chain mechanisms and may be classed as anion, cation, or radical reactions, depending upon the character of the chain-carrying species. In each case, the key steps involve successive additions to molecules of the alkene, the differences being in the number of electrons that are supplied by the attacking agent for formation of the new carbon-carbon bond. For simplicity, these steps will be illustrated by using ethene, even though it does not polymerize very easily by any of them:

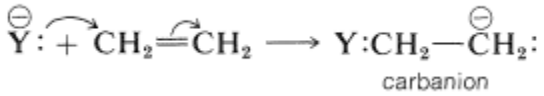
$$\mathrm{R{-}CH_2{-}\overset{\ominus}{C}H_2{:} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\ominus}{C}H_2{:}}, \text{ etc.}$$

$$\mathrm{R{-}CH_2{-}\overset{\oplus}{C}H_2 + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\oplus}{C}H_2}, \text{ etc.}$$

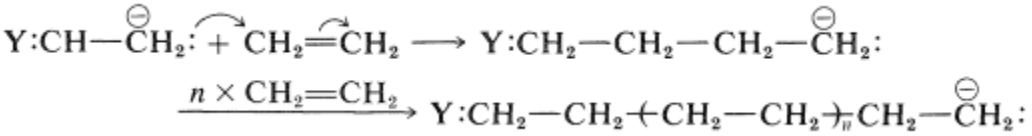
$$\mathrm{R{-}CH_2{-}CH_2{\cdot} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{\cdot}}, \text{ etc.}$$

Anionic Polymerization

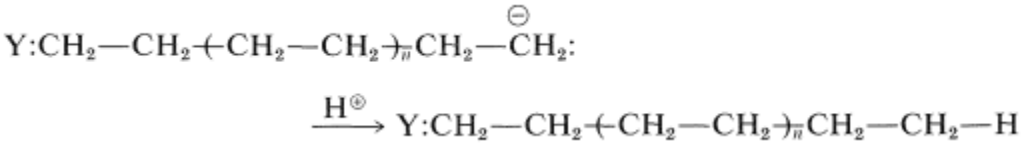
Initiation of alkene polymerization by the anion-chain mechanism may be formulated as involving an attack by a nucleophilic reagent $Y^{\ominus}$ on one end of the double bond and formation of a carbanion:



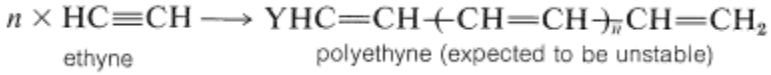
Attack by the carbanion on another alkene molecule would give a four-carbon carbanion, and subsequent additions to further alkene molecules would lead to a high-molecular-weight anion:



The growing chain can be terminated by any reaction (such as the addition of a proton) that would destroy the carbanion on the end of the chain:

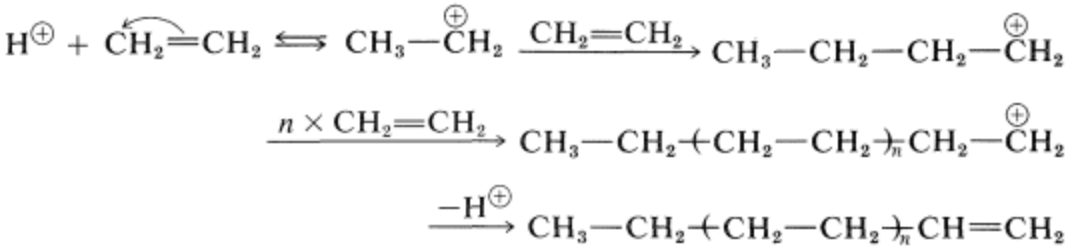


Anionic polymerization of alkenes is quite difficult to achieve because few anions (or nucleophiles) are able to add readily to alkene double bonds (see Section 10-6). Anionic polymerization occurs readily only with alkenes substituted with sufficiently powerful electron-attracting groups to expedite nucleophilic attack. By this reasoning, alkynes should polymerize more readily than alkenes under anionic conditions, but there appear to be no technically important alkyne polymerizations in operation by this or any other mechanism. Perhaps this is because the resultant polymer would be highly conjugated, and therefore highly reactive, and may not survive the experimental conditions:

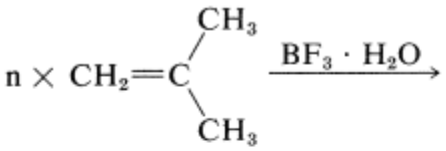


Cationic Polymerization

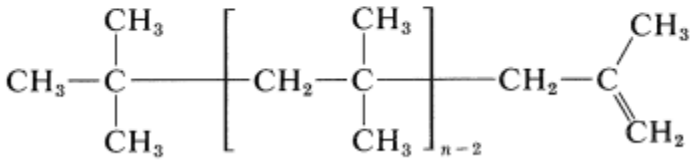
Polymerization of an alkene by acidic reagents can be formulated by a mechanism similar to the addition of hydrogen halides to alkene linkages. First, a proton from a suitable acid adds to an alkene to yield a carbocation. Then, in the absence of any other reasonably strong nucleophilic reagent, another alkene molecule donates an electron pair and forms a longer-chain cation. Continuation of this process can lead to a high-molecular-weight cation. Termination can occur by loss of a proton. The following equations represent the overall reaction sequence:



Ethene does not polymerize by the cationic mechanism because it does not have sufficiently electron-donating groups to permit easy formation of the intermediate growing-chain cation. 2-Methylpropene has electron-donating alkyl groups and polymerizes much more easily than ethene by this type of mechanism. The usual catalysts for cationic polymerization of 2-methylpropene are sulfuric acid, hydrogen fluoride, or a complex of boron trifluoride and water. Under nearly anhydrous conditions a very long chain polymer called polyisobutylene is formed.



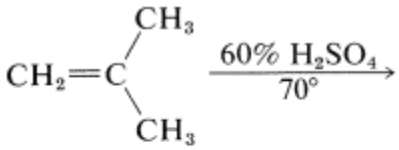
2-methylpropene
(isobutylene)

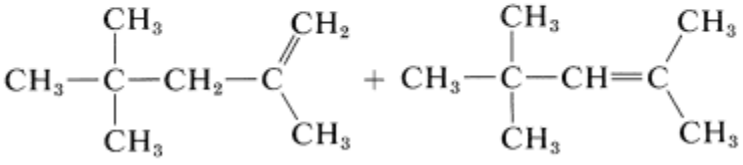


poly-2-methylpropene
(polyisobutylene)

Polyisobutylene fractions of particular molecular weights are very tacky and are used as adhesives for pressure-sealing tapes.

In the presence of 60% sulfuric acid, 2-methylpropene is *not* converted to a long-chain polymer, but to a mixture of eight-carbon alkenes. The mechanism is like that of the polymerization of 2-methylpropene under nearly anhydrous conditions, except that chain termination occurs after only one 2-methylpropene molecule has been added:

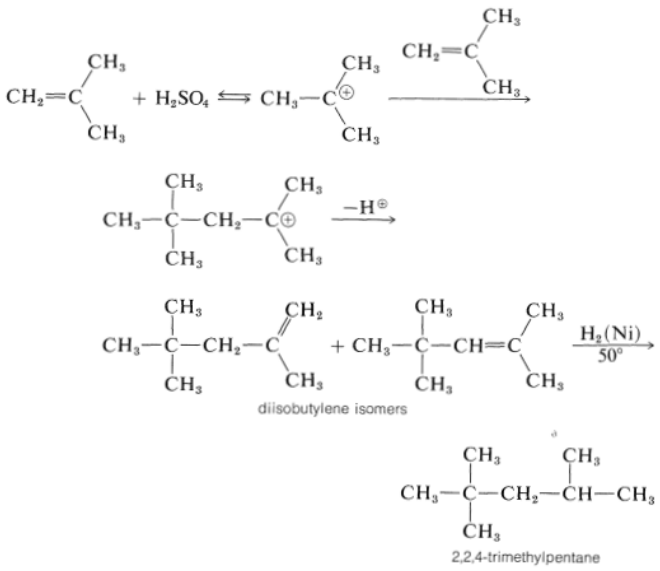




"diisobutylene"

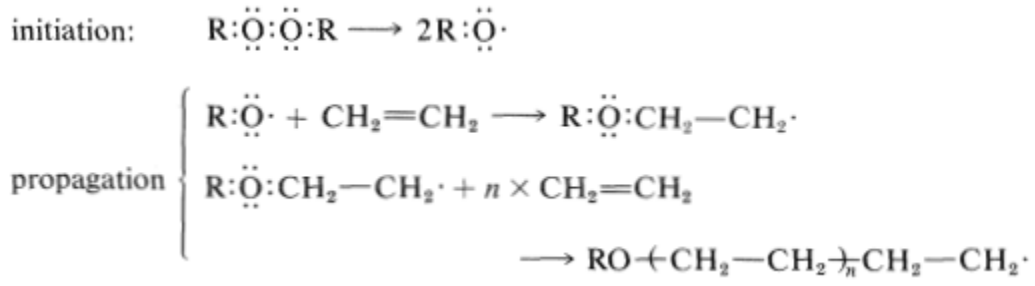
The short chain length is due to the *high water concentration*; the intermediate carbocation loses a proton to water *before* it can react with another alkene molecule.

The proton can be lost in two different ways, and a mixture of alkene isomers is obtained. The alkene mixture is known as "diisobutylene" and has a number of commercial uses. Hydrogenation yields 2,2,4-trimethylpentane (often erroneously called "isooctane"), which is used as the standard "100 antiknock rating" fuel for internal-combustion gasoline engines:

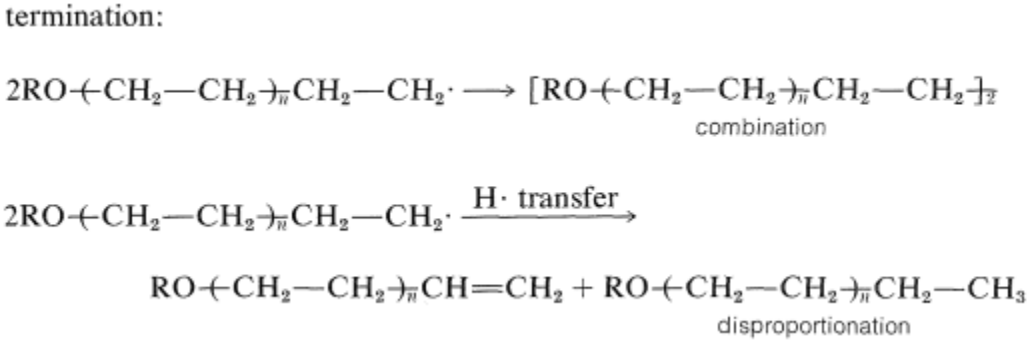


Radical Polymerization

Ethene can be polymerized with peroxide catalysts under high pressure ($1000\ \text{atm}$ or more, literally in a cannon barrel) at temperatures in excess of $100°$. The initiation step involves formation of radicals, and chain propagation entails stepwise addition of radicals to ethene molecules.



Chain termination can occur by any reaction resulting in combination or disproportionation of free radicals.



The polyethene produced in this way has from 100 to 1000 ethene units in the hydrocarbon chain. The polymer possesses a number of desirable properties as a plastic and is used widely for electrical insulation, packaging films, piping, and a variety of molded articles. Propene and 2-methylpropene do not polymerize satisfactorily by radical mechanisms.

Coordination Polymerization

A relatively low-pressure, low-temperature ethene polymerization has been achieved with an aluminum-molybdenum oxide catalyst, which requires occasional activation with hydrogen (Phillips Petroleum process). Ethene also polymerizes quite rapidly at atmospheric pressure and room temperature in an alkane solvent containing a suspension of the insoluble reaction product from triethylaluminum and titanium tetrachloride (Ziegler process). Both the Phillips and Ziegler processes produce very high-molecular-weight polyethene with exceptional physical properties. The unusual characteristics of these reactions indicate that no simple anion, cation, or radical mechanism can be involved. It is believed that the catalysts act by coordinating with the alkene molecules in somewhat the same way that hydrogenation catalysts combine with alkenes (Section 11-2A).

Polymerization of propene by the Ziegler process gives a very useful plastic material. It can be made into durable fibers or molded into a variety of shapes. Copolymers (polymers with more than one kind of monomer unit in the polymer chains) of ethene and propene made by the Ziegler process have highly desirable rubberlike properties and are potentially the cheapest useful elastomers (elastic polymers). A Nobel Prize was shared in 1963 by K. Ziegler and G. Natta for their work on alkene polymerization.

The properties and uses of polymers are discussed in greater detail in Chapters 13 and 29. The most important alkene monomers used in addition polymerizations are listed in Table 10-4 along with some names and uses of the corresponding polymers.

References

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6: PRINCIPLES OF STEREOCHEMISTRY

6.1: Chirality and Stereoisomers

6.2: R-S Sequence Rules

6.3: Optical Activity

6.4: Optical Activity - more detail

6.5: Racemic Mixtures and the Resolution of Enantiomers

6.6: Diastereomers

6.7: Diastereomers - more detail

6.8: Meso Compounds

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6.1: Chirality and Stereoisomers

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.

Introduction

Organic compounds, molecules created around a chain of carbon atom (more commonly known as carbon backbone), play an essential role in the chemistry of life. These molecules derive their importance from the energy they carry, mainly in a form of potential energy between atomic molecules. Since such potential force can be widely affected due to changes in atomic placement, it is important to understand the concept of an isomer, a molecule sharing same atomic make up as another but differing in structural arrangements. This article will be devoted to a specific isomers called stereoisomers and its property of chirality (Figure 1).

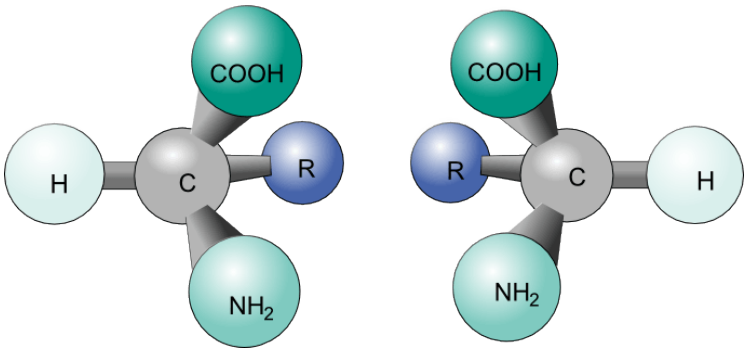


Figure 1: Two enantiomers of a tetrahedral complex.

The concepts of steroisomerism and chirality command great deal of importance in modern organic chemistry, as these ideas helps to understand the physical and theoretical reasons behind the formation and structures of numerous organic molecules, the main reason behind the energy embedded in these essential chemicals. In contrast to more well-known constitutional isomerism, which develops isotopic compounds simply by different atomic connectivity, stereoisomerism generally maintains equal atomic connections and orders of building blocks as well as having same numbers of atoms and types of elements.

What, then, makes stereoisomers so unique? To answer this question, the learner must be able to think and imagine in not just two-dimensional images, but also three-dimensional space. This is due to the fact that stereoisomers are isomers because their atoms are different from others in terms of spatial arrangement.

Spatial Arrangement

First and foremost, one must understand the concept of spatial arrangement in order to understand stereoisomerism and chirality. Spatial arrangement of atoms concern how different atomic particles and molecules are situated about in the space around the organic compound, namely its carbon chain. In this sense, spatial arrangement of an organic molecule are different another if an atom is shifted in any three-dimensional direction by even one degree. This opens up a very broad possibility of different molecules, each with their unique placement of atoms in three-dimensional space .

Stereoisomers

Stereoisomers are, as mentioned above, different types of isomers within themselves, each with distinct characteristics that further separate them as different chemical entities having different properties. Types called enantiomers are the previously-mentioned mirror-image stereoisomers, and will be explained in detail in this article. Another type, a diastereomer, has different properties and will be introduced afterward.

Enantiomers

This type of stereoisomer is the essential mirror-image, non-superimposable type of stereoisomer introduced at the beginning of the article. Figure 2 provides a perfect example; note that the blue plane in the middle denotes the mirror plane.

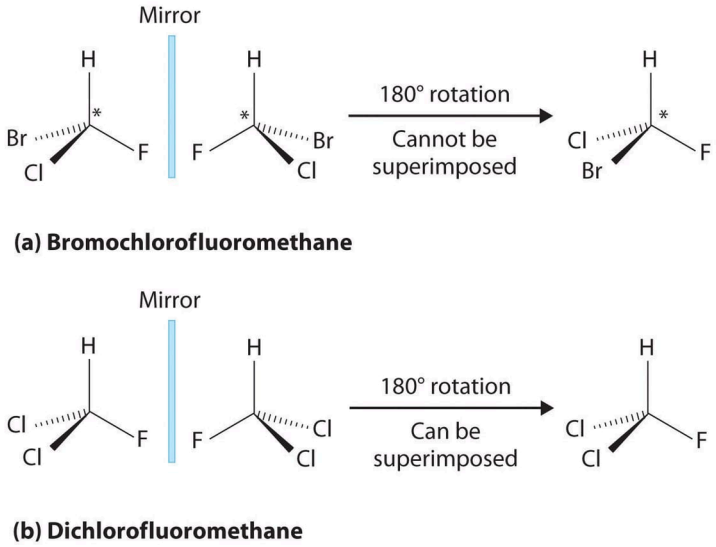


Figure 2: Comparison of Chiral and Achiral Molecules. (a) Bromochlorofluoromethane is a chiral molecule whose stereocenter is designated with an asterisk. Rotation of its mirror image does not generate the original structure. To superimpose the mirror images, bonds must be broken and reformed. (b) In contrast, dichlorofluoromethane and its mirror image can be rotated so they are superimposable.

Note that even if one were to flip the left molecule over to the right, the atomic spatial arrangement will not be equal. This is equivalent to the left hand - right hand relationship, and is aptly referred to as 'handedness' in molecules. This can be somewhat counterintuitive, so this article recommends the reader try the 'hand' example. Place both palms facing up, and hands next to each other. Now flip either side over to the other. One hand should be showing the back of the hand, while the other shows the palm. They are not the same and non-superimposable.

This is where the concept of chirality comes in as one of the most essential and defining ideas of stereoisomerism.

Chirality

Chirality essentially means 'mirror-image, non-superimposable molecules', and to say that a molecule is chiral is to say that its mirror image (it must have one) is not the same as itself. Whether a molecule is chiral or achiral depends upon a certain set of overlapping conditions. Figure 2 shows examples of chiral and achiral molecules. Notice the distinct characteristic of the achiral molecule: it possesses two atoms of the same element. In theory and reality, if one were to create a plane that runs through the other two atoms, they will be able to create what is known as a bisecting plane: The images on either side of the plane are the same as the other (Figure 3).

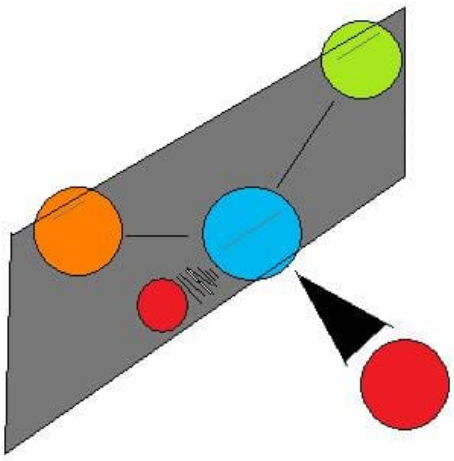


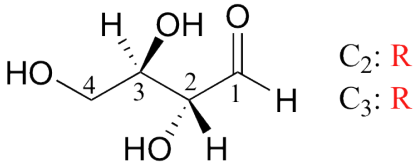
Figure 3.

In this case, the molecule is considered 'achiral'. In other words, to distinguish a chiral molecule from an achiral molecule, one must search for the existence of the bisecting plane in a molecule. All chiral molecules are deprived of a bisecting plane, whether simple or complex.

In general, no molecule with different surrounding atoms is achiral. Chirality is a simple but essential concept that supports the concept of stereoisomerism, used to explain one type of stereoisomer. The chemical properties of a chiral molecule differ from those of its mirror image, and this is the significance of chirality in modern organic chemistry.

Compounds with Multiple Chiral Centers

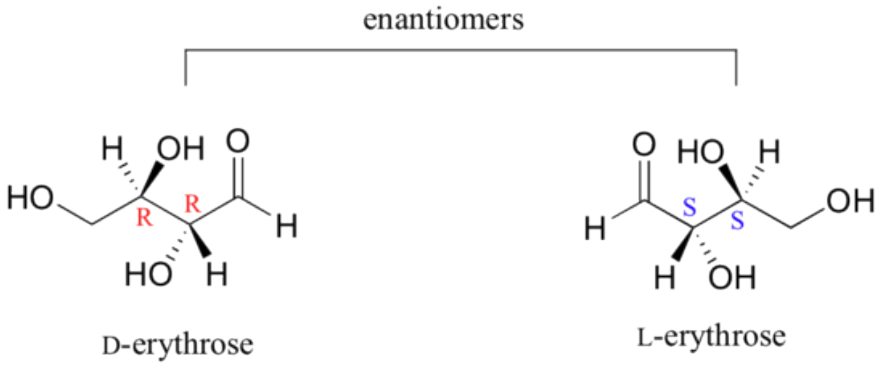
We turn our attention next to molecules which have more than one stereocenter. We will start with a common four-carbon sugar called D-erythrose.



D-erythrose

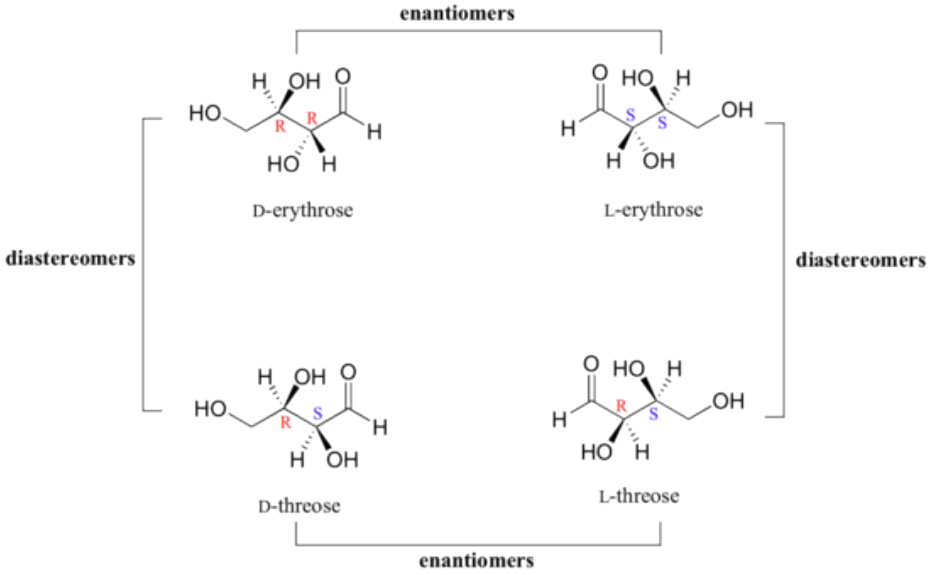
A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry class. We will use the *D/L* designations 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. *In a pair of enantiomers, **all** of the chiral centers are of the opposite configuration.*

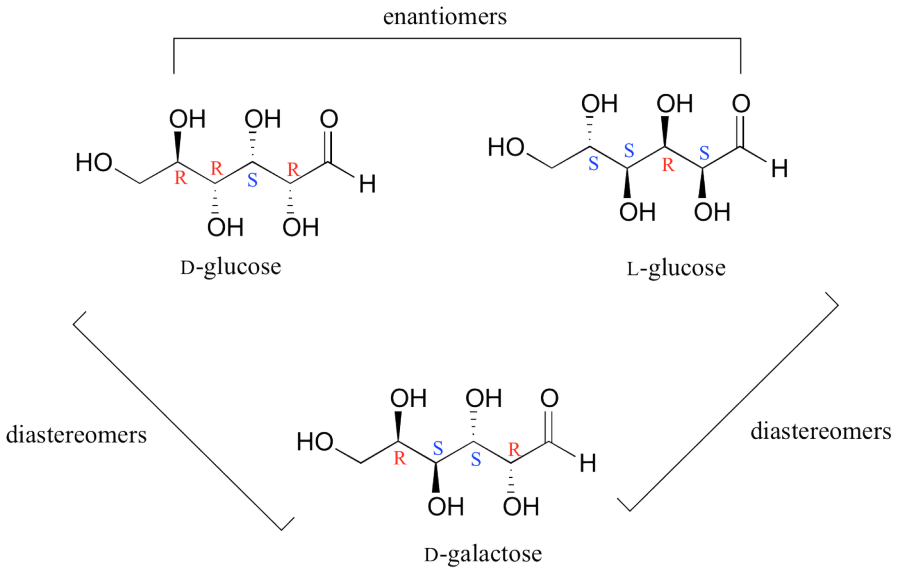
What happens if we draw a stereoisomer of erythrose in which the configuration is S at C_2 and *R* at C_3? This stereoisomer, which is a sugar called D-threose, is *not* a mirror image of erythrose. D-threose is a **diastereomer** of both D-erythrose and L-erythrose.



The definition of diastereomers is simple: if two molecules are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers, then they are diastereomers by default. *In practical terms, this means that at least one - but not all - of the chiral centers are opposite in a pair of diastereomers*. By definition, two molecules that are diastereomers are *not* mirror images of each other.

L-threose, the enantiomer of D-threose, has the *R* configuration at C_2 and the S configuration at C_3. L-threose is a diastereomer of both erythrose enantiomers.

In general, a structure with *n* stereocenters will have 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 3.10

Draw the structure of L-galactose, the enantiomer of D-galactose.

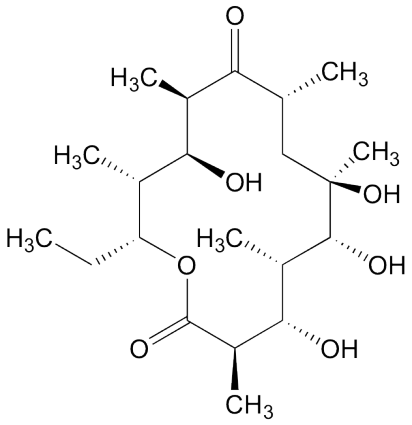
Solution

Example 3.11

Draw the structure of two more diastereomers of D-glucose. One should be an epimer.

Solution

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.

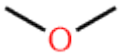
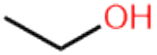
We know that enantiomers have identical physical properties and equal but opposite degrees of specific rotation. Diastereomers, in theory at least, have different physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that 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.

Constitutional isomers

Constitutional isomers, or **structural isomers,** are molecules with the same chemical formula but different atom and bond orientations. For example, both 3-methylpentane and hexane have the same chemical formula, C_6H_{14}, yet they clearly have different structures:

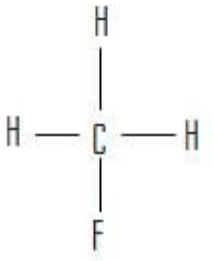
	
3-methylpentane	hexane

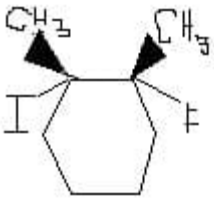
Another example involves functional groups. Methoxy methane, an ether, and ethanol, an alcohol, both have the chemical formula C_2H_6O:

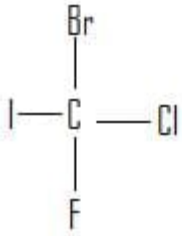
	
Methoxy methane	Ethanol

Exercise 6.1.1

Identify the following as either a constitutional isomer or stereoisomer. If stereoisomer, determine if it is an enantiomer or diastereomer. Explain the reason behind the answer. Also mark chirality for each molecule.

1. 

2. 

3. 

References

1. Anslyn, Eric V. and Dougherty, Dennis A. Modern Physical Organic Chemistry. Chicago, IL.: University Science. 2005
2. Hick, Janice M. The Physical Chemistry of Chirality. New York, N.Y.: An American Chemical Society Publication. 2001.
3. Vollhardt, K. Peter C. and Schore, Neil E. Organic Chemistry: Structure and Function. Fifth Edition. New York, N.Y.: W. H. Freeman Company, 2007.

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6.2: R-S Sequence Rules

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

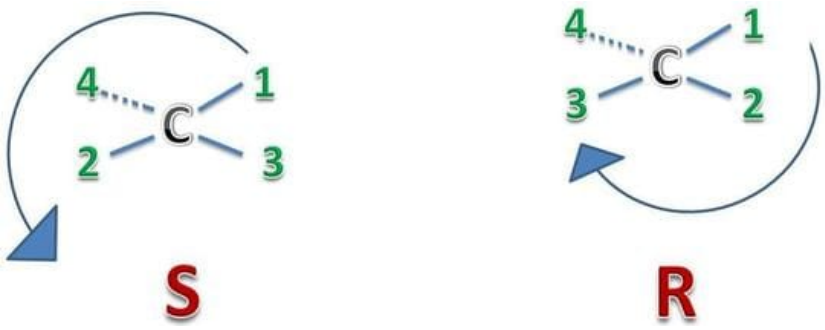
The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and is also often called the **Cahn-Ingold-Prelog rules**. In addition to the Cahn-Ingold system, there are two ways of experimentally determining the absolute configuration 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.



Consider the first picture: a curved arrow is drawn from the highest priority (*1*) substituent to the lowest priority *(4)* substituent. If the arrow points in a counterclockwise direction (**left** when leaving the 12 o' clock position), the configuration at stereocenter is considered **S** ("Sinister" → Latin= "left"). If, however, the arrow points clockwise,(**Right** when leaving the 12 o' clock position) then the stereocenter is labeled ***R*** ("Rectus" → Latin= "right"). The ***R*** *or* **S** is then added as a prefix, in parenthesis, to the name of the enantiomer of interest. For example: (*R*)-2-Bromobutane and (*S*)-2,3- Dihydroxypropanal.

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 substituent with a higher atomic number takes precedence over a substituent with a lower atomic number. Hydrogen is the lowest possible priority substituent, because it has the lowest atomic number.

1. When dealing with isotopes, the atom with the higher atomic mass receives higher priority.

2. When visualizing the molecule, the lowest priority substituent should always point away from the viewer (a dashed line indicates this). To understand how this works or looks, imagine that a clock and a pole. Attach the pole to the back of the clock, so that when when looking at the face of the clock the pole points away from the viewer in the same way the lowest priority substituent should point away.
3. Then, draw an arrow from the highest priority atom to the 2nd highest priority atom to the 3rd highest priority atom. Because the 4th highest priority atom is placed in the back, the arrow should appear like it is going across the face of a clock. If it is going clockwise, then it is an R-enantiomer; If it is going counterclockwise, it is an S-enantiomer.

When looking at a problem with wedges and dashes, if the lowest priority atom is not on the dashed line pointing away, the molecule must be rotated.
Remember that

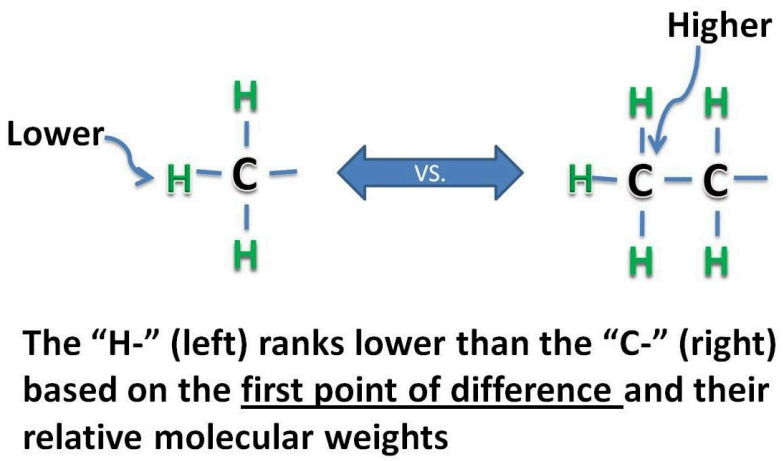
- Wedges indicate coming towards the viewer.
- Dashes indicate pointing away from the viewer.

Rule 2

If there are two substituents with equal rank, proceed along the two substituent chains until there is a point of difference. First, 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.

If the chains are similar, proceed down the chain, until a point of difference.

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 another 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.



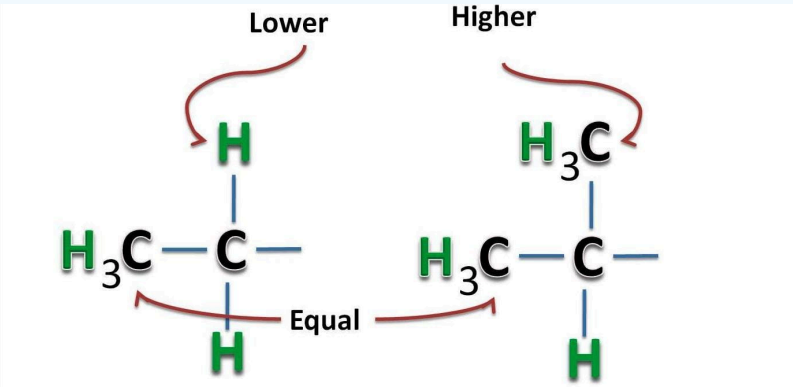
Rule 3

If a chain is connected to the same kind of atom twice or three times, check to see if the atom it is connected to has a greater atomic number than any of the atoms that the competing chain is connected to.

- If none of the atoms connected to the competing chain(s) at the same point has a greater atomic number: the chain bonded to the same atom multiple times has the greater priority
- If however, one of the atoms connected to the competing chain has a higher atomic number: that chain has the higher priority.

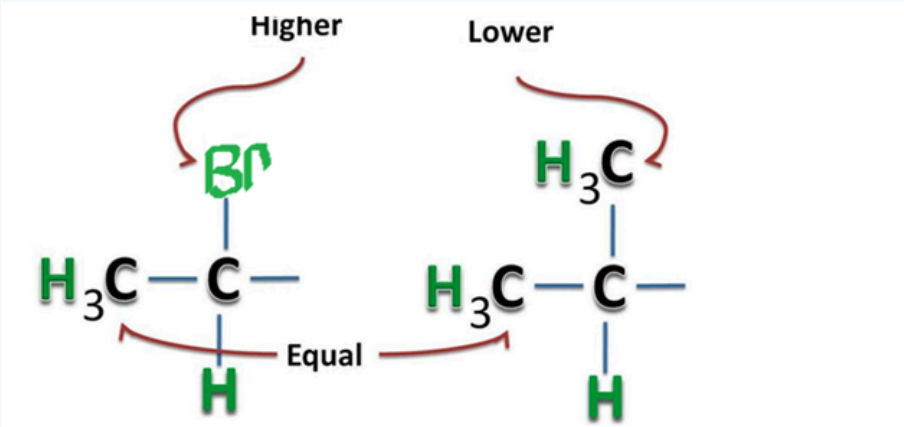
Example 2

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:



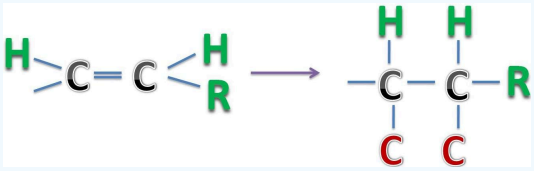
The "C-" (right) ranks higher than the "H-" (left) based on the first point of difference and their relative molecular weights.

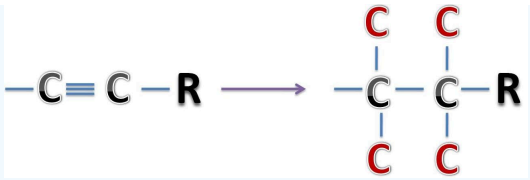
However:



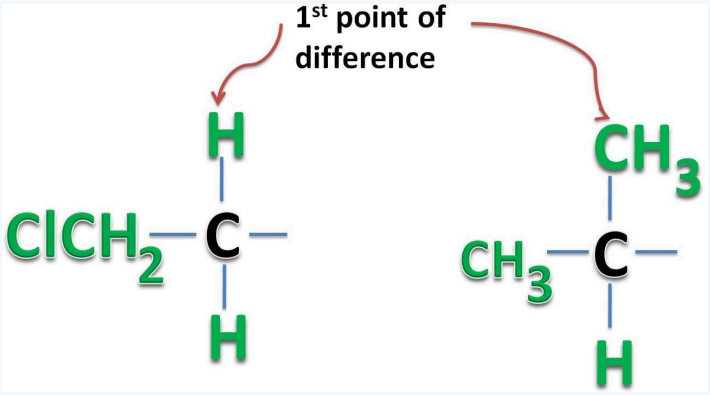
In this case, even though the one on the right has 2 connections to an atom (C), it is the lower priority. This is because one of the atoms on the left molecule(Br) ranks higher(it has a bigger atomic number)than any of the atoms on the right.

Remember that being double or triple bonded to an atom means that the atom is connected to the same atom twice. In such a case, follow the same method as above.

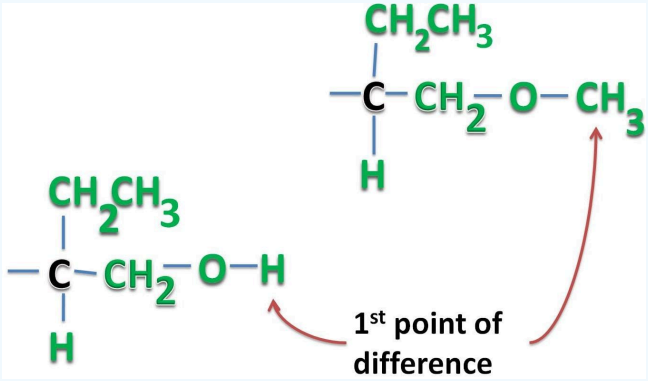




Caution!!
Keep in mind that priority is determined by the **first** point of difference along the two similar substituent chains. After the first point of difference, the rest of the chain is irrelevant.



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.



After all your substituents have been prioritized in the correct manner, you can now name/label the molecule **R** or **S.**

1. Put the lowest priority substituent in the back (dashed line).
2. Proceed from 1 to 2 to 3. (it is helpful to draw or imagine an arcing arrow that goes from 1--> 2-->3)
3. Determine if the direction from 1 to 2 to 3 clockwise or counterclockwise.

i) If it is **clockwise** it is **R.**
ii) if it is **counterclockwise** it is **S**.

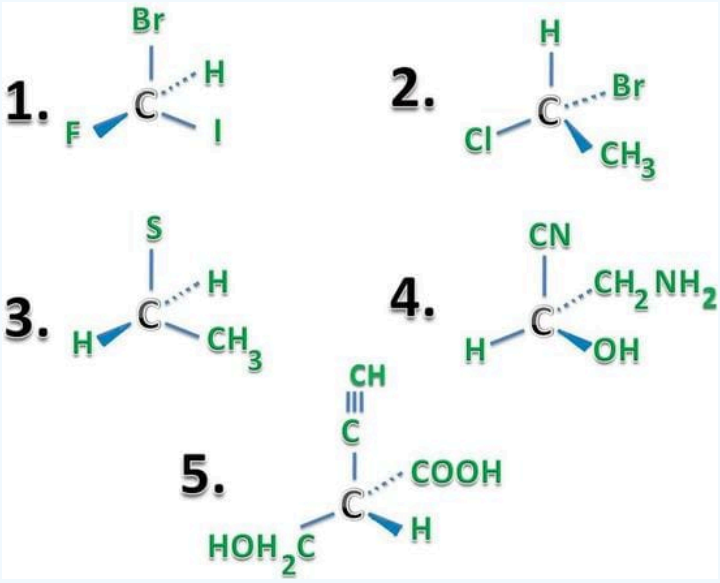
USE YOUR MODELING KIT: Models assist in visualizing the structure. When using a model, make sure the lowest priority is pointing away from you. Then determine the direction from the highest priority substituent to the lowest: clockwise (R) or counterclockwise (S).

IF YOU DO NOT HAVE A MODELING KIT: remember that the dashes mean the bond is going into the screen and the wedges means that bond is coming out of the screen. If the lowest priority bond is not pointing to the back, mentally rotate it so that it is. However, it is very useful when learning organic chemistry to use models.

If you have a modeling kit use it to help you solve the following practice problems.

Exercise 6.2.1

Are the following R or S?



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

Exercise 6.2.1

1. **S:** I > Br > F > H. The lowest priority substituent, H, is already going towards the back. It turns left going from I to Br to F, so it's a S.
2. **R:** Br > Cl > CH_3 > H. You have to switch the H and Br in order to place the H, the lowest priority, in the back. Then, going from Br to Cl, CH_3 is turning to the right, giving you a R.
3. **Neither R or S**: This molecule is achiral. Only chiral molecules can be named R or S.
4. **R:** OH > CN > CH_2NH_2 > H. The H, the lowest priority, has to be switched to the back. Then, going from OH to CN to CH_2NH_2, you are turning right, giving you a R. **(5)**
5. **S:** $-COOH$ > $-CH_2OH$ > $C{\equiv}CH$ > H. Then, going from $-COOH$ to $-CH_2OH$ to $-C{\equiv}CH$ you are turning left, giving you a S configuration.

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6.3: Optical Activity

Optical activity is an effect of an optical isomer's interaction with plane-polarized light.

Introduction

Optical isomers, or enantiomers, have the same sequence of atoms and bonds but are different in their 3D shape. Two enantiomers are nonsuperimposible mirror images of one another (i.e., chiral), with the most common cited example being our hands. Our left hand is a mirror image of our right, yet there is no way our left thumb can be over our right thumb if our palms are facing the same way and placed over one another. Optical isomers also have no axis of symmetry, which means that there is no line that bisects the compound such that the left half is a mirror image of the right half.

Optical isomers have basically the same properties (melting points, boiling points, etc.) but there are a few exceptions (uses in biological mechanisms and optical activity). There are drugs, called enantiopure drugs, that have different effects based on whether the drug is a racemic mixture or purely one enantiomer. For example, d-ethambutol treats tuberculosis, while l-ethambutol causes blindness. Optical activity is the interaction of these enantiomers with plane-polarized light.

A Brief History

Optical activity was first observed by the French physicist Jean-Baptiste Biot. He concluded that the change in direction of plane-polarized light when it passed through certain substances was actually a rotation of light, and that it had a molecular basis. His work was supported by the experimentation of Louis Pasteur. Pasteur observed the existence of two crystals that were mirror images in tartaric acid, an acid found in wine. Through meticulous experimentation, he found that one set of molecules rotated polarized light clockwise while the other rotated light counterclockwise to the same extent. He also observed that a mixture of both, a *racemic mixture* (or *racemic modification*), did not rotate light because the optical activity of one molecule canceled the effects of the other molecule. Pasteur was the first to show the existence of chiral molecules.

Rotation of Light

An enantiomer that rotates plane-polarized light in the positive direction, or clockwise, is called dextrorotary [(+), or d-], while the enantiomer that rotates the light in the negative direction, or counterclockwise, is called levorotary [(-), or l-]. When both d- and l-isomers are present in equal amounts, the mixture is called a racemic mixture.

plane of polarization of plane polarized Light

image source

In the picture above, you can see that unpolarized light passes through a filter so that only waves that oscillate in a certain direction can pass through. When these waves interact with an optically active material, they are rotated either clockwise or counterclockwise, depending on the enantiomer. In the case of the image above, the light is rotated clockwise so the substance is the dextrorotary enantiomer.

Measuring Optical Activity

Optical activity is measured by a polarimeter, and is dependent on several factors: concentration of the sample, temperature, length of the sample tube or cell, and wavelength of the light passing through the sample. Rotation is given in +/- degrees, depending on whether the sample has d- (positive) or l- (negative) enantiomers. The standard measurement for rotation for a specific chemical compound is called the specific rotation, defined as an angle measured at a path length of 1 decimeter and a concentration of 1g/ml. The specific rotation of a pure substance is an intrinsic property. In solution, the formula for specific rotation is:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \cdot c} \tag{6.3.1}$$

where

- [α] is the specific rotation in degrees cm^3 dm^{-1} g^{-1}.
- λ is the wavelength in nanometers,
- α is the measured angle of rotation of a substance,
- T is the temperature in degrees,
- l is the path length in decimeters,
- c is the concentration in g/ml, and

References

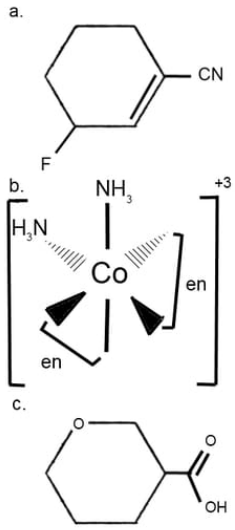
1. Pettrucci, Ralph H., Harwood, Herring, Madura. General Chemistry: Principles and Modern Applications. 9th. Upper Saddle River: Pearson Prentice Hall, 2007.
2. Raymond, Kenneth W. General Organic and Biological Chemistry. 3rd. Hoboken: John Wiley & Sons, Inc. 2010.

Practice Questions

1. Why doesn't a racemic mixture show optical activity?
2. Does the following image show optically active molecules (image source)?

3. What would happen if your feet were not optical isomers of each other?
4. Your friend has tuberculosis. Assuming you like your friend and you want him to live, which isomer of ethambutol do you give him and why?
5. Draw each compound's enantiomer.

Answers



1. In a racemic mixture, both dextrorotary and levorotary enantiomers are present in equal amounts, so the overall rotation of polarized light is zero. The clockwise rotation is canceled by the counterclockwise rotation.
2. Yes, because the molecules are mirror images of one another.
3. You'd be a terrible dancer. (Get it? Two left feet? Haha.)
4. Dextrorotary ethambutol, because l-ethambutol would not only fail to cure him, but it would also leave him blind.
5. Enantiomers

http://en.Wikipedia.org/wiki/Enantiopure_drug

Contributors

- Nanki J Natt (UCD), Anna Zhu (UCD)

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6.4: Optical Activity - more detail

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

6.4.1).

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.

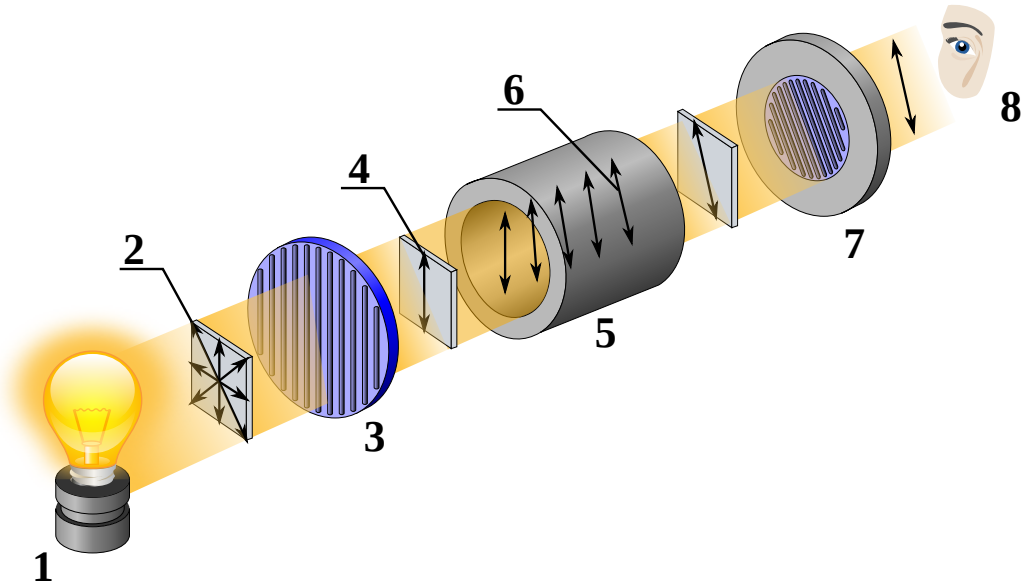


Figure 6.4.1: Operating principle of an optical polarimeter. 1. Light source 2. Unpolarized light 3. Linear polarizer 4. Linearly polarized light 5. Sample tube containing molecules under study 6. Optical rotation due to molecules 7. Rotatable linear analyzer 8. Detector. (CC BY-SA 3.0 Unported; Kaidor 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 6.4.1

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 6.4.2

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 6.4.3

Is the morphine in the previous excercise dextrorotatory or levorotatory?

Answer available at the end of this section.

Exercise 6.4.4

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 6.4.5a

The specific rotation of (S)-carvone is (+) 61° 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 6.4.5b

b) What are the percentages of (S)- and (*R*)- carvone in the sample mixture?

Answer available at the end of this section.

Exercise 6.4.5c

c) What is the ee (enantiomeric excess)?

Answer available at the end of this section.

Exercise 6.4.6a

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 6.4.6b

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 6.4.6c

Determine the ee's of the following from the percentages

- 85 % (*R*) cysteine

Answer available at the end of this section.

Exercise 6.4.6d

Determine the ee's of the following from the percentages

- 50 % (S) alanine

Answer available at the end of this section.

Answers

Exercise 6.4.1

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 6.4.2

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 6.4.3

Since morphine has a (-) rotation, it indicates that it rotates light to the left (counterclockwise) and morphine is levorotatory.

Exercise 6.4.4

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 6.4.5*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 6.4.5*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 6.4.5*c*

ee = [(% more abundant isomer – 50) x 100]/50 = [(68.9 – 50) x100]/50 = 37.8 % ee

Exercise 6.4.6*a*

[(95 – 50) x 100] / 50 = 90 % ee (*R*)-tartaric acid

Exercise 6.4.6*b*

[(75 – 50) x 100] / 50 = 50 % ee (S)- limonene

Exercise 6.4.6*c*

(85 – 50) x 100] / 50 = 70 % ee (*R*)-cysteine

Exercise 6.4.6*d*

(50 – 50) x 100] / 50 = 0 % ee, racemic mixture

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6.5: Racemic Mixtures and the Resolution 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.

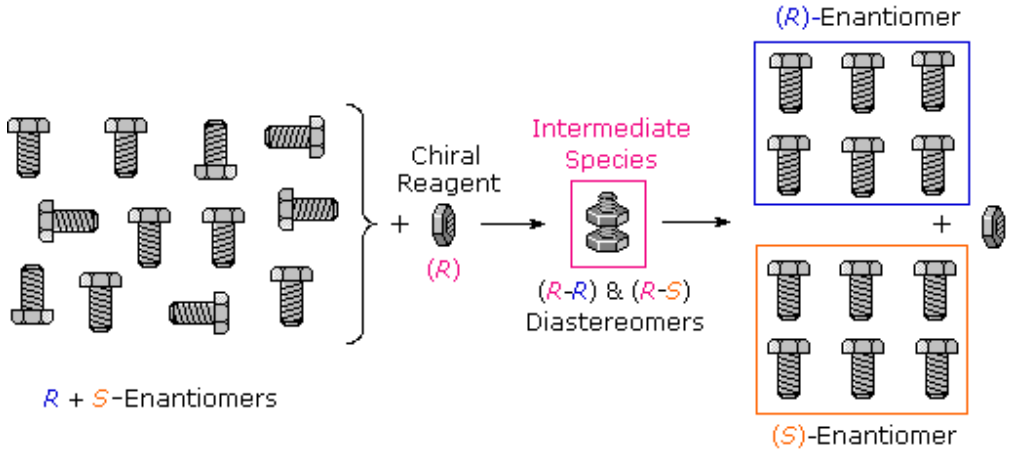


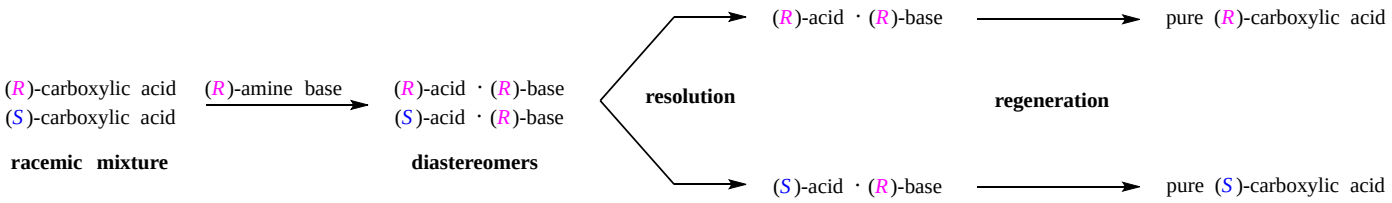
Figure 5.8.1:

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.

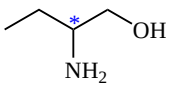
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution 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

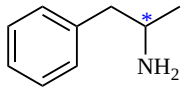
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or (*R*)/(S) mixture of enantiomers of a carboxylic 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.



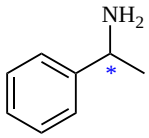
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino-1-butanol, amphetamine, and 1-phenylethanamine, also can be used, but first they must be resolved themselves.



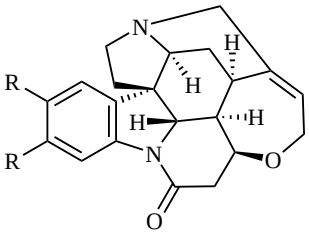
2-amino-1-butanol



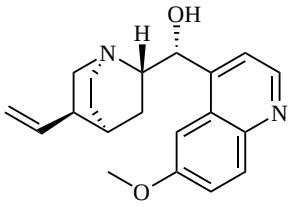
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



R = H,strychnine
R = OCH_3, brucine



quinine
(antimicrobial)
(antimalarial)

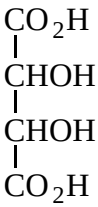
Worked Example 6.5.1

Show how (S)-1-phenylethylamine can be used to resolve a racemic mixture of lactic acid. Please draw all the structures involved.

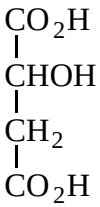
Answer available at the end of this section.

Resolution of Racemic Bases

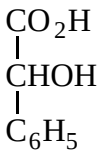
Chiral acids, such as (+)-tartaric acid, (-)-malic acid, (-)-mandelic acid, and (+)-camphor- 10-sulfonic acid, are used for the resolution of a racemic base.



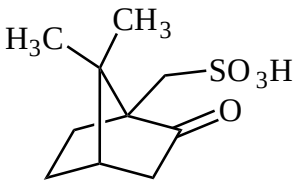
tartaric acid
(2,3-dihydroxy-
butanedioic acid)



malic acid
(2-hydroxybutane-
dioic acid)



mandelic acid
(2-hydroxy-2-
phenylethanoic acid)

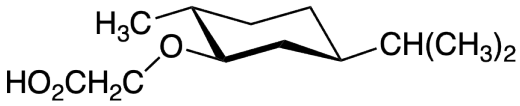


camphor-10-
sulfonic acid

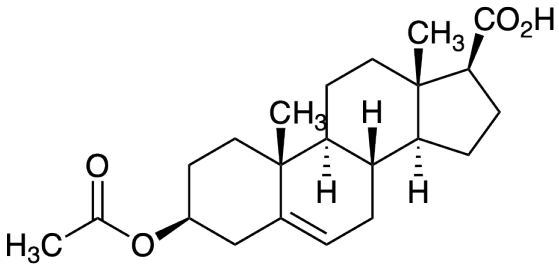
The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind 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:

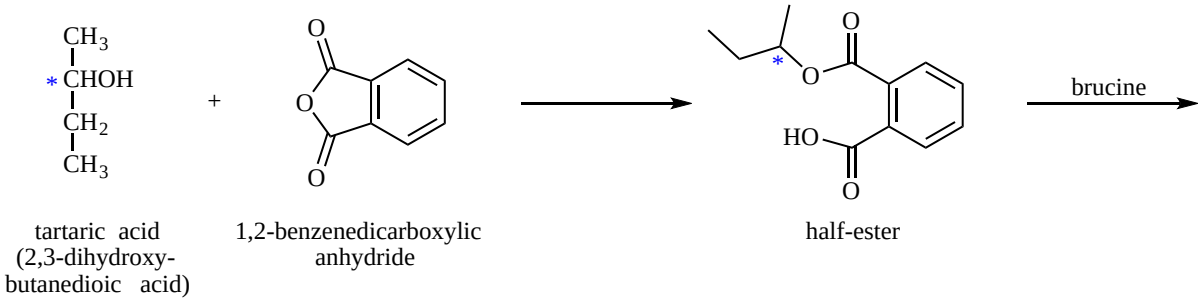


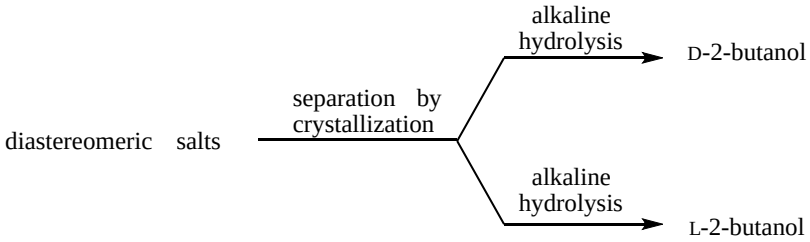
menthoxyethanoic acid



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

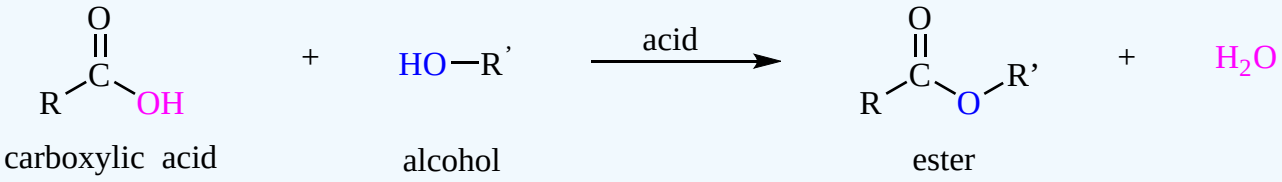
It important to understand the changes in chirality which occur during the formation of product during a reaction. A chiral reaction product, has the possibility of forming multiple stereoisomers which all need to be considered. Changes in chirality, if possible, will be discussed with each individual 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 6.5.2

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?



carboxylic acid alcohol ester

Answer available at the end of this section.

Exercise 6.5.1

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 6.5.2

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.

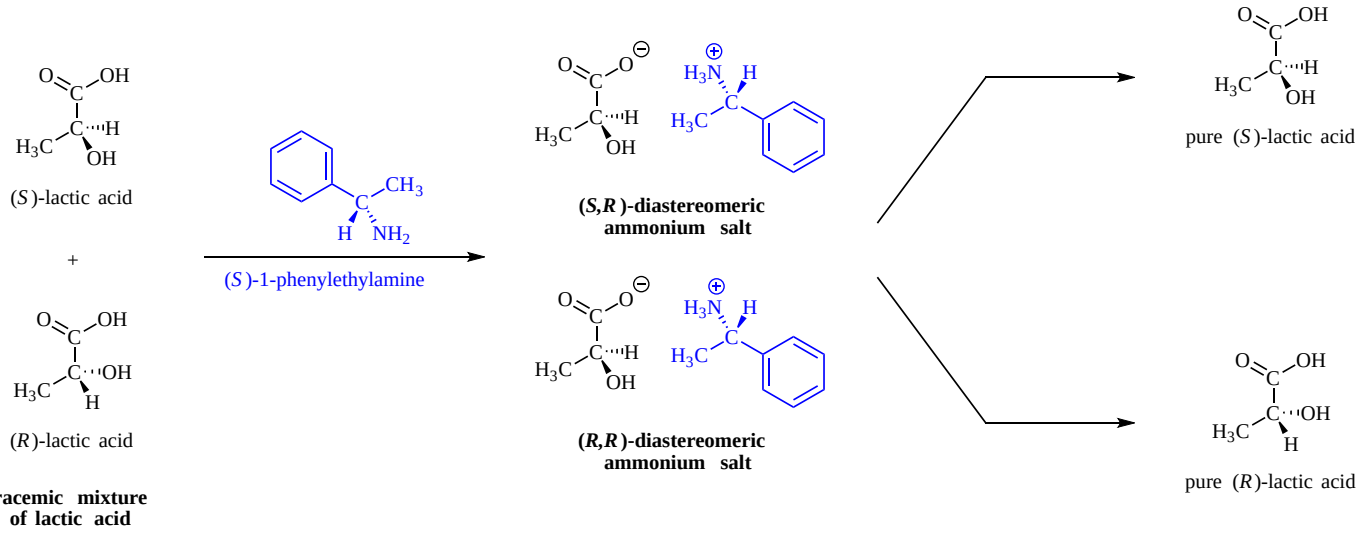
Exercise 6.5.3

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.

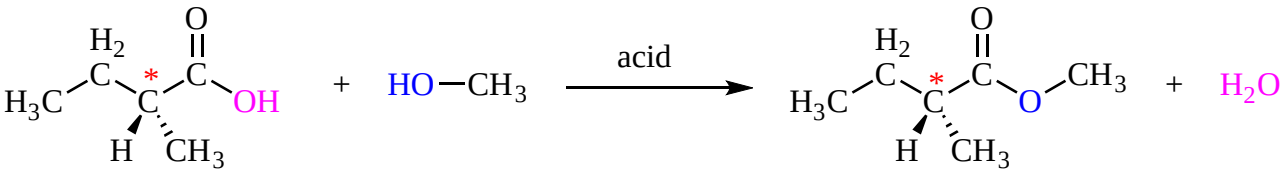
Answers

Worked Example 6.5.1



Worked Example 6.5.2

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 6.5.1

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 6.5.2

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 6.5.3

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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6.6: Diastereomers

Diastereomers are stereoisomers that are not related as object and mirror image and are not enantiomers. Unlike enatiomers which **are mirror images** of each other and **non-sumperimposable**, 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. They have **two or more** stereocenters.

Introduction

It is easy to mistake between diasteromers and enantiomers. For example, we have four steroisomers of 3-bromo-2-butanol. The four possible combination are SS, RR, SR and RS (Figure 1). One of the molecule is the enantiomer of its mirror image molecule and diasteromer of each of the other two molecule (SS is enantiomer of RR and diasteromer of RS and SR). SS's mirror image is RR and they are not superimposable, so they are enantiomers. RS and SR are not mirror image of SS and are not superimposable to each other, so they are diasteromers.

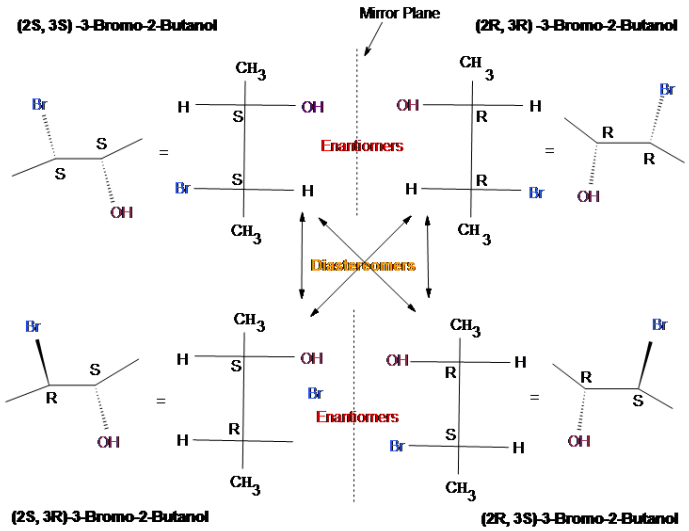


Figure 1

Diastereomers vs. Enantiomers vs. Meso Compounds

Tartaric acid, $C_4H_6O_6$, is an organic compound that can be found in grape, bananas, and in wine. The structures of tartaric acid itself is really interesting. Naturally, it is in the form of (R,R) stereocenters. Artificially, it can be in the meso form (R,S), which is achiral. R,R tartaric acid is enantiomer to is mirror image which is S,S tartaric acid and diasteromers to meso-tartaric acid (figure 2).

(R,R) and (S,S) tartaric acid have similar physical properties and reactivity. However, meso-tartaric acid have different physical properties and reactivity. For example, melting point of (R,R) & (S,S) tartaric is about 170 degree Celsius, and melting point of meso-tartaric acid is about 145 degree Celsius.

chem1 (1).bmp

Figure 2

To identify meso, meso compound is superimposed on its mirror image, and has an internal plane that is symmetry (figure 3). Meso-tartaric acid is achiral and optically unactive.

meso.bmp

Problems

Identify which of the following pair is enantiomers, diastereomers or meso compounds.

practice.bmp

Answer

a. Diasteromers
b. Identical
c. Meso
d. Enantiomers

Outside Links

- http://www.sparknotes.com/chemistry/...section2.rhtml
- http://en.Wikipedia.org/wiki/Diastereomer
- http://en.Wikipedia.org/wiki/Tartaric_acid

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6.7: Diastereomers - more detail

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

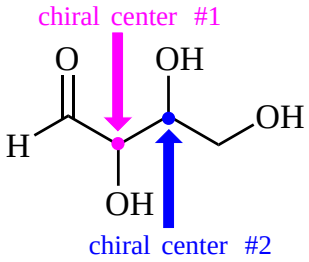
Make certain that you can define, and use in context, the key term below.

- diastereomer

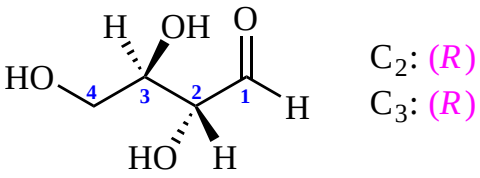
Diastereomers are two molecules which are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers. Unlike enantiomers which **are mirror images** of each other and **non-superimposable**, diastereomers are **not mirror images** of each 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.



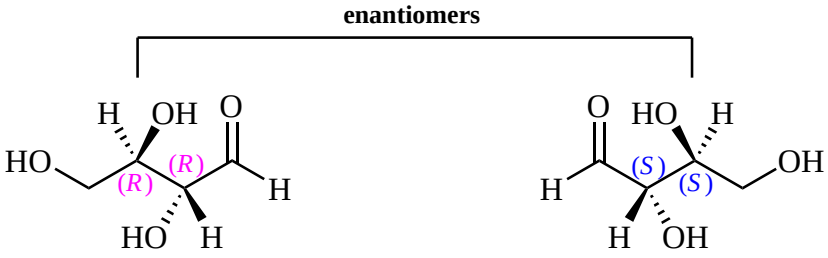
We will start with a common four-carbon sugar called D-erythrose.



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).

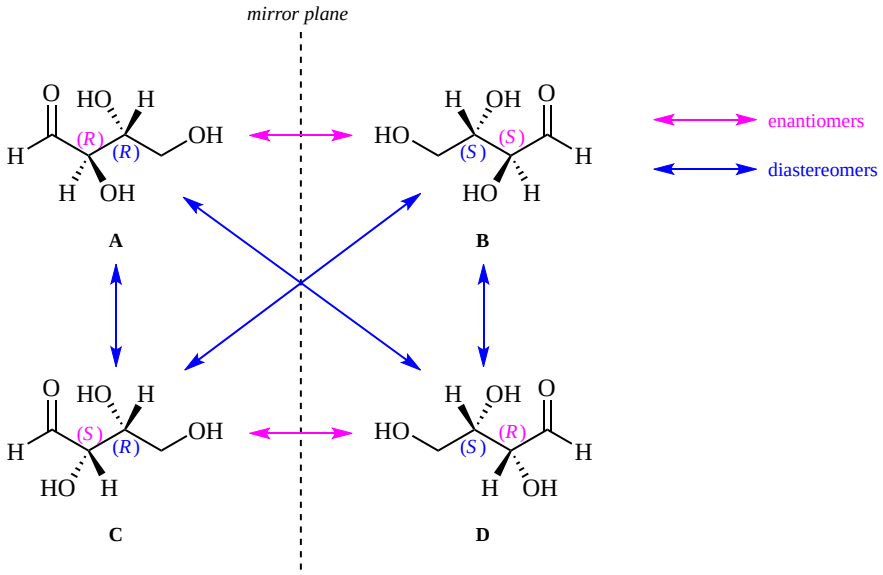


D-erythrose L-erythrose

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:

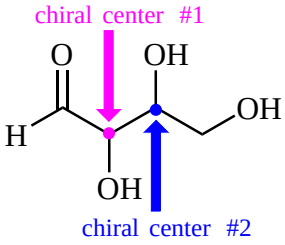
Stereoisomer Shortcuts

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.



possible configurations:

(*R*,*R*) (*R*,*S*)

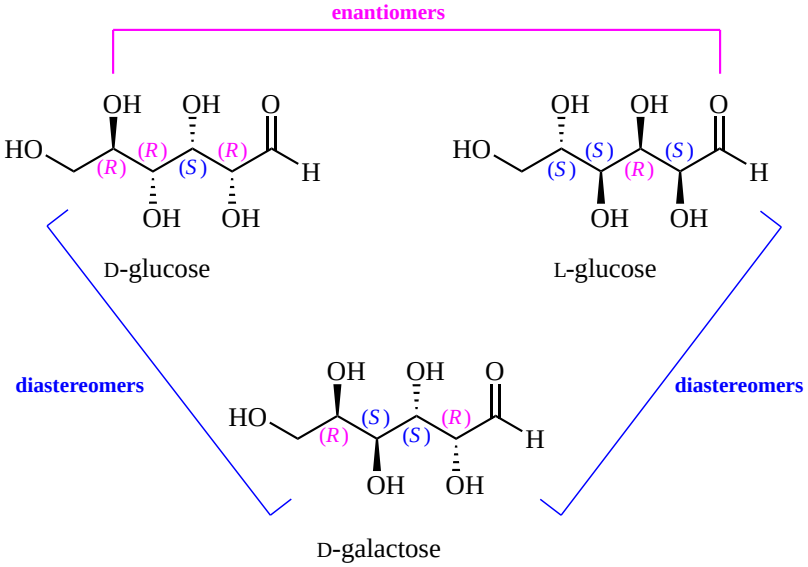
(*S*,*S*) (*S*,*R*)

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).



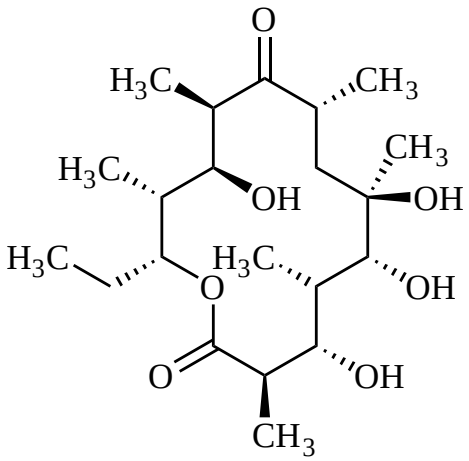
In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown 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 6.7.1

- 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 6.7.1

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 6.7.2*a*

What is the relationship between enantiomers?

Answer available at the end of this section.

Exercise 6.7.2*b*

How does the stereochemistry in diastereomers differ from each other?

Answer available at the end of this section.

Exercise 6.7.2*c*

What are epimers?

Answer available at the end of this section.

Exercise 6.7.3a

Draw the structure of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

Exercise 6.7.3b

Draw both diastereomers of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

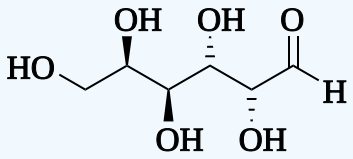
Exercise 6.7.3c

Draw the enantiomer of (2R,3R) 2-fluoro-3-methylhexane.

Answer available at the end of this section.

Exercise 6.7.4a

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.

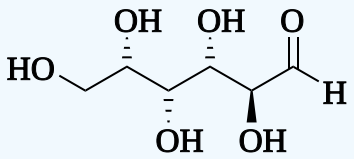
Exercise 6.7.4b

Draw a diastereomer of D-galactose that is an epimer.

Answer available at the end of this section.

Exercise 6.7.4c

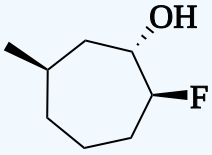
Identify if the following diastereomer of galactose is an epimer of D- galactose or L- galactose.



Answer available at the end of this section.

Exercise 6.7.5a

For the compound shown below, label each chiral center as R or S.



Answer available at the end of this section.

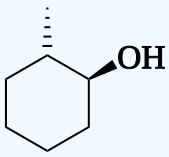
Exercise 6.7.5b

How many stereoisomers are possible for the compound in part a)?

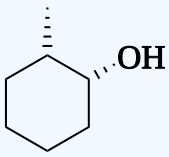
Answer available at the end of this section.

Exercise 6.7.6

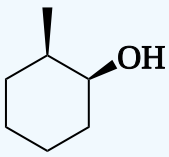
Consider the stereoisomers below.



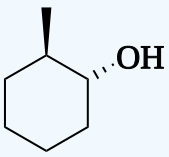
i



ii



iii



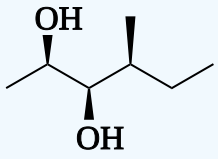
iv

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of ii?
c. Which is/are an epimer of i?

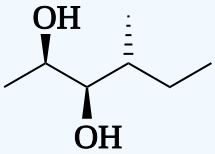
Answer available at the end of this section.

Exercise 6.7.7

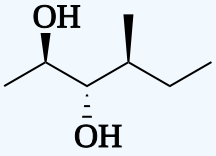
Consider the 8 stereoisomers below.



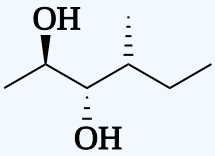
i



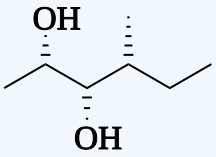
ii



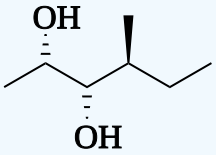
iii



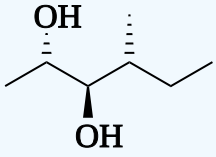
iv



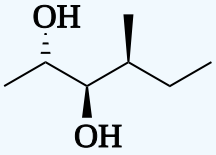
v



vi



vii



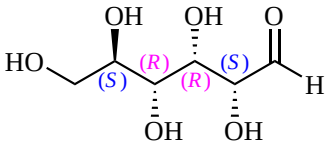
viii

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of i?
c. Which is/are an epimer of i?

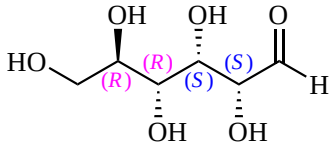
Answer available at the end of this section.

Answers

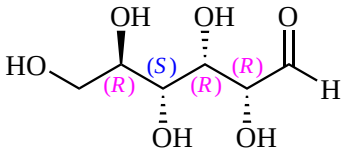
Example 6.7.1



L-galactose



L-mannose
(epimer of D-glucose)



L-gulose
(diasteromer of D-glucose)

Exercise 6.7.1

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 6.7.2*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.

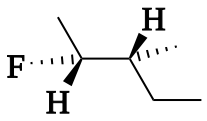
Exercise 6.7.2*b*

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 6.7.2*c*

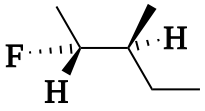
Epimers are when **only one** chiral center is the opposite (in molecules with 2 or more chiral centers) in its diastereomer.

Exercise 6.7.3*a*

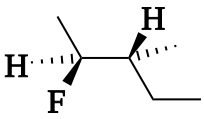


2R,3R

Exercise $6.7.3b$

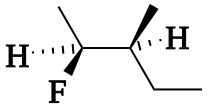


2R,3S



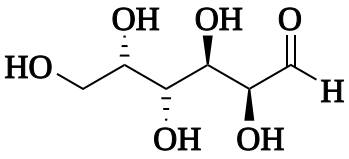
2S,3R

Exercise $6.7.3c$



2S,3S

Exercise $6.7.4a$

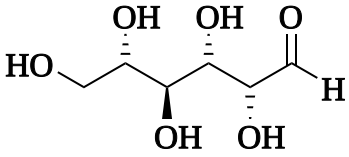


S, *R*, *R*, *S*

L-galactose

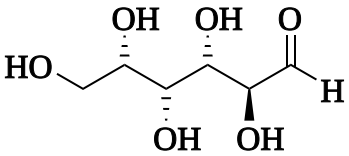
Exercise $6.7.4b$

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*

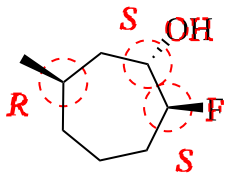
Exercise $6.7.4c$



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 $6.7.5a$



Exercise $6.7.5b$

Since there are 3 chiral centers, 2^3 = 8 possible stereoisomers.

Exercise $6.7.6$

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 $6.7.7$

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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6.8: Meso Compounds

Meso compounds are achiral compounds that has multiple chiral centers. It is superimposed on its mirror image and is optically **inactive** despite its stereocenters.

Introduction

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 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, result in **optically inactive**. Cyclic compounds may also be meso.

Identification

If A is a meso compound, it should have two or more stereocenters, an internal plane, and the stereochemistry should be R and S.

1. Look for an internal plane, or internal mirror, that lies in between the compound.
2. The stereochemistry (e.g. R or S) is very crucial in determining whether it is a meso compound or not. As mentioned above, a meso compound is optically inactive, so their stereochemistry should cancel out. For instance, R cancels S out in a meso compound with two stereocenters.

Meso1 (1).bmp

***trans*-1,2-dichloro-1,2-ethanediol**

Meso2 (5).bmp

***(meso)*-2,3-dibromobutane**

Tips: An interesting thing about single bonds or sp^3-orbitals is that we can rotate the substituted groups that attached to a stereocenter around to recognize the internal plane. As the molecule is rotated, its stereochemistry does not change. For example:

rotated (1).bmp

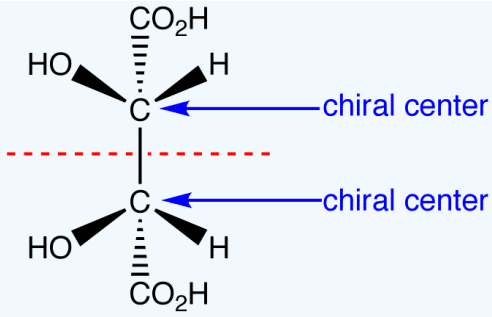
Another case is when we rotate the whole molecule by 180 degree. Both molecules below are still meso.

rotated180.bmp

Remember the internal plane here is depicted on two dimensions. However, in reality, it is three dimensions, so be aware of it when we identify the internal mirror.

Example

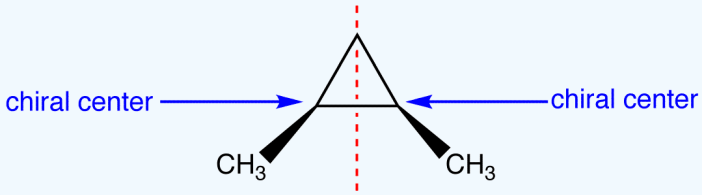
This molecule has a plane of symmetry (the horizontal plane going through the red broken line) and, therefore, is achiral; However, it has two chiral carbons and is consequentially a meso compound.



1

Example 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.



2

Other Examples of meso compounds

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cyclobutane. They do not necessarily have to be two stereocenters, but can have more.

Meso3 (1).bmp

Cyclic.bmp

Optical Activity Analysis

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 (+).

Problems

Beside meso, there are also other types of molecules: enantiomer, diastereomer, and identical. Determine if the following molecules are meso.

Mesopracticeprob.bmp

Answer key: A C, D, E are meso compounds.

References

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5thEd.). New York: W. H. Freeman. (190-192)
2. Shore, N. (2007). *Study Guide and Solutions Manual for Organic Chemistry* (5th Ed.). New York: W.H. Freeman. (70-80)

Contributors

- Duy Dang
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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7: CYCLIC COMPOUNDS - STEREOCHEMISTRY OF REACTIONS

7.1: Ring Strain and the Structure of Cycloalkanes

7.2: Cycloalkanes and Ring Strain

7.3: Cyclohexane Conformations

7.4: Conformations of Monosubstituted Cyclohexanes

7.5: Conformations of Disubstituted Cyclohexanes

7.6: Polycyclic Alkanes

7.7: Carbocyclic Products in Nature

7.8: Steroids

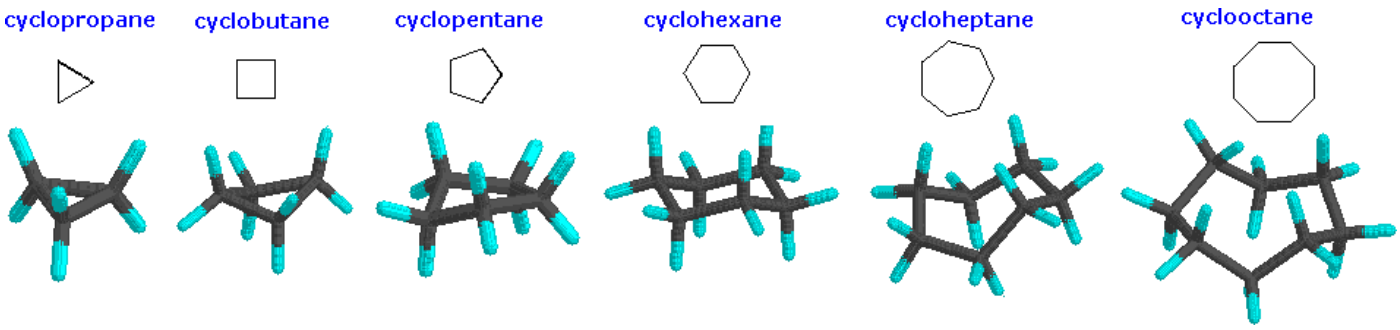
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7.1: Ring Strain and the Structure of Cycloalkanes

Cycloalkanes are very important in components of food, pharmaceutical drugs, and much more. However, to use cycloalkanes in such applications, we must know the effects, functions, properties, and structures of cycloalkanes. Cycloalkanes are alkanes that are in the form of a ring; hence, the prefix cyclo-. Stable cycloalkanes cannot be formed with carbon chains of just any length. Recall that in alkanes, carbon adopts the sp^3 tetrahedral geometry in which the angles between bonds are 109.5°. For some cycloalkanes to form, the angle between bonds must deviate from this ideal angle, an effect known as **angle strain**. Additionally, some hydrogen atoms may come into closer proximity with each other than is desirable (become eclipsed), an effect called **torsional strain**. These destabilizing effects, angle strain and torsional strain are known together as **ring strain**. The smaller cycloalkanes, cyclopropane and cyclobutane, have particularly high ring strains because their bond angles deviate substantially from 109.5° and their hydrogens eclipse each other. Cyclopentane is a more stable molecule with a small amount of ring strain, while **cyclohexane** is able to adopt the perfect geometry of a cycloalkane in which all angles are the ideal 109.5° and no hydrogens are eclipsed; it has no ring strain at all. Cycloalkanes larger than cyclohexane have ring strain and are not commonly encountered in organic chemistry.

Ring Strain and the Structures of Cycloalkanes

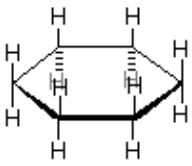
There are many forms of cycloalkanes, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, among others. The process of naming cycloalkanes is the same as naming alkanes but the addition of the prefix cyclo- is required. Cyclobutane is in a form of a square, which is highly unfavorable and unstable (this will be explained soon). There are different drawings for cyclobutane, but they are equivalent to each other. Cyclobutane can reduce the ring string by puckering the square cyclobutane. Cyclopentane takes the shape of a pentagon and cyclohexane is in the shape of a hexagon.



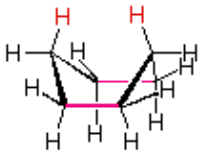
Chair Conformation of Cyclohexane - Equitorial and Axial

There are two ways to draw cyclohexane because it can be in a hexagon shape or in a different conformational form called the **chair** conformation and the **boat** conformation.

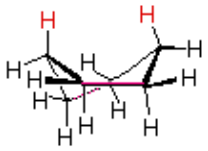
- The chair conformation drawing is more favored than the boat because of the energy, the steric hindrance, and a new strain called the **transannular strain**.
- The boat conformation is not the favored conformation because it is less stable and has a steric repulsion between the two H's, shown with the pink curve. This is known as the transannular strain, which means that the strain results from steric crowding of two groups across a ring. The boat is less stable than the chair by 6.9 kcal/mol. The boat conformation, however, is flexible, and when we twist one of the C-C bonds, it reduces the transannular strain.
- When we twist the C-C bond in a boat, it becomes a twisted boat.



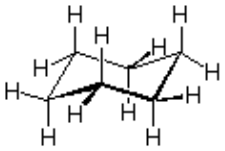
Planar Structure
severe angle strain (120°)
severe eclipsing strain (all bonds)
small steric strain



Boat Conformation
slight angle strain
eclipsing strain at two bonds
steric crowding of two hydrogens



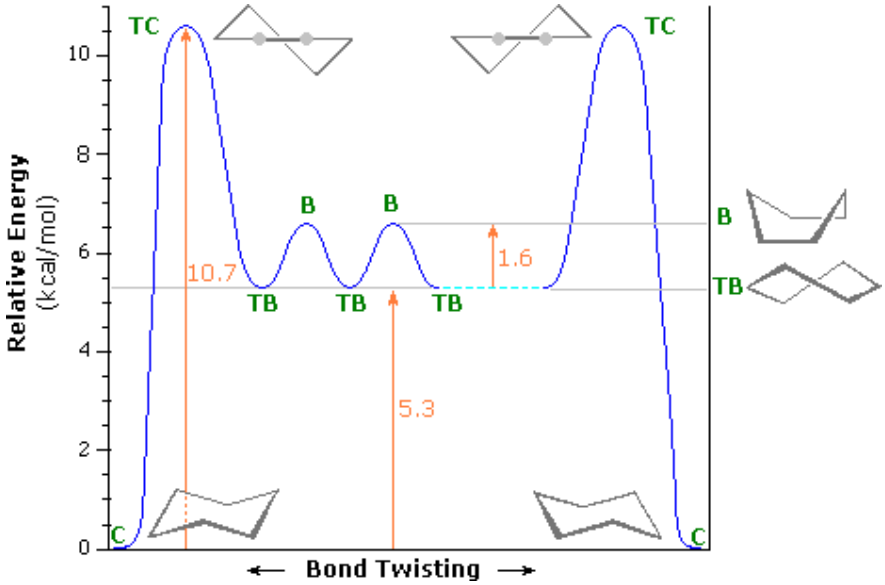
Twist Boat Conformation
slight angle strain
small eclipsing strain
small steric strain



Chair Conformation
no angle strain
no eclipsing strain
small steric strain

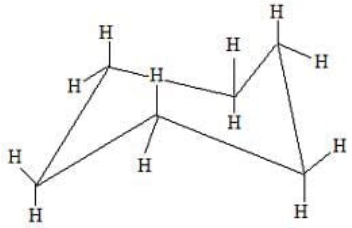
Some Conformations of Cyclohexane Rings. (William Reusch, MSU)

Although there are multiple ways to draw cyclohexane, the most stable and major conformer is the chair because is has a lower activation barrier from the energy diagram.

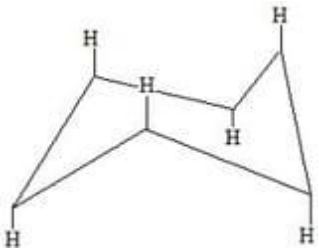


Conformational Energy Profile of Cyclohexane. (William Reusch, MSU).

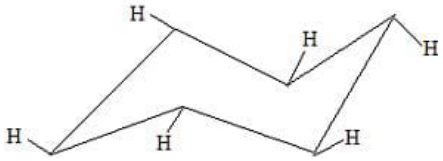
The transition state structure is called a **half chair**. This energy diagram shows that the chair conformation is lower in energy; therefore, it is more stable. The chair conformation is more stable because it does not have any steric hindrance or steric repulsion between the hydrogen bonds. By drawing cyclohexane in a chair conformation, we can see how the H's are positioned. There are two positions for the H's in the chair conformation, which are in an axial or an equitorial formation.



This is how a chair conformation looks, but you're probably wondering which H's are in the equitorial and axial form. Here are more pictures to help.



These are hydrogens in the axial form.



These hydrogens are in an equitorial form. Of these two positions of the H's, the equitorial form will be the most stable because the hydrogen atoms, or perhaps the other substituents, will not be touching each other. This is the best time to build a chair conformation in an equitorial and an axial form to demonstrate the stability of the equitorial form.

Ring Strain

Cycloalkanes tend to give off a very high and non-favorable energy, and the spatial orientation of the atoms is called the ring strain. When atoms are close together, their proximity is highly unfavorable and causes steric hindrance. The reason we do not want ring strain and steric hindrance is because heat will be released due to an increase in energy; therefore, a lot of that energy is stored in the bonds and molecules, causing the ring to be unstable and reactive. Another reason we try to avoid ring strain is because it will affect the structures and the conformational function of the smaller cycloalkanes. One way to determine the presence of ring strain is by its heat of combustion. By comparing the heat of combustion with the value measured for the straight chain molecule, we can determine the stability of the ring. There are two types of strain, which are eclipsing/torsional strain and bond angle strain. Bond angle strain causes a ring to have a poor overlap between the atoms, resulting in weak and reactive C-C bonds. An eclipsed spatial arrangement of the atoms on the cycloalkanes results in high energy.

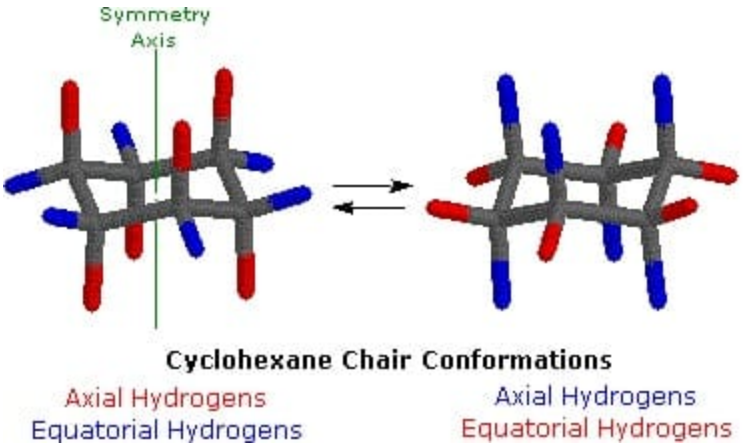
With so many cycloalkanes, which ones have the highest ring strain and are very unlikely to stay in its current form? The figures below show cyclopropane, cyclobutane, and cyclopentane, respectively. Cyclopropane is one of the cycloalkanes that has an incredibly high and unfavorable energy, followed by cyclobutane as the next strained cycloalkane. Any ring that is small (with three to four carbons) has a significant amount of ring strain; cyclopropane and cyclobutane are in the category of small rings. A ring with five to seven carbons is considered to have minimal to zero strain, and typical examples are cyclopentane, cyclohexane, and cycloheptane. However, a ring with eight to twelve carbons is considered to have a moderate strain, and if a ring has beyond twelve carbons, it has minimal strain.

There are different types of ring strain:

- **Transannular strain** isdefined as the crowding of the two groups in a ring.
- **Eclipsing strain,** also known as torsional strain, is intramolecular strain due to the bonding interaction between two eclipsed atoms or groups.
- **Bond angle strain** is present when there is a poor overlap between the atoms. There must be an ideal bond angle to achieve the maximum bond strength and that will allow the overlapping of the atomic/hybrid orbitals.

Cyclohexane

Most of the time, cyclohexane adopts the fully staggered, ideal angle **chair conformation**. In the chair conformation, if any carbon-carbon bond were examined, it would be found to exist with its substituents in the staggered conformation and all bonds would be found to possess an angle of 109.5°.



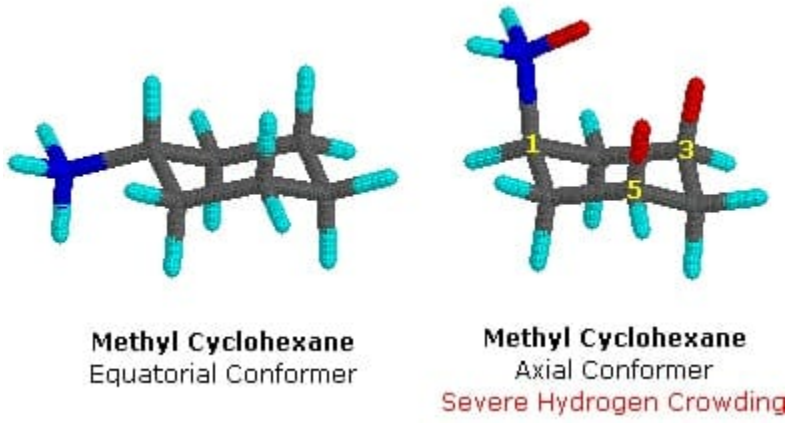
Cyclohexane in the chair conformation. (William Reusch, MSU).

In the chair conformation, hydrogen atoms are labeled according to their location. Those hydrogens which exist above or below the plane of the molecule (shown with red bonds above) are called **axial**. Those hydrogens which exist in the plane of the molecule (shown with blue bonds above) are called **equatorial**.

Although the chair conformation is the most stable conformation that cyclohexane can adopt, there is enough thermal energy for it to also pass through less favorable conformations before returning to a different chair conformation. When it does so, the axial and equatorial substituents change places. The passage of cyclohexane from one chair conformation to another, during which the axial substituents switch places with the equatorial substituents, is called a **ring flip**.

Methylcyclohexane

Methylcyclohexane is cyclohexane in which one hydrogen atom is replaced with a methyl group substituent. Methylcyclohexane can adopt two basic chair conformations: one in which the methyl group is axial, and one in which it is equatorial. Methylcyclohexane strongly prefers the equatorial conformation. In the axial conformation, the methyl group comes in close proximity to the axial hydrogens, an energetically unfavorable effect known as a **1,3-diaxial interaction** (Figure 3). Thus, the equatorial conformation is preferred for the methyl group. In most cases, if the cyclohexane ring contains a substituent, the substituent will prefer the equatorial conformation.



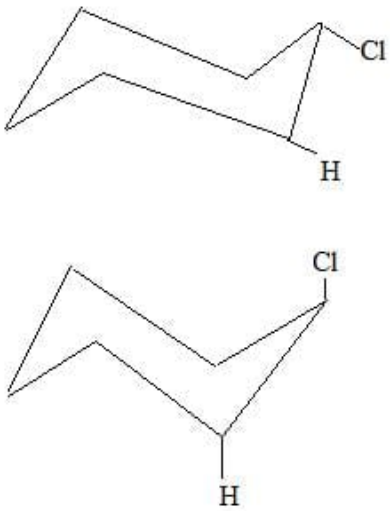
Methylcyclohexane in the chair conformation. (William Reusch, MSU).

References

1. Bachrach, Steven M. Computational Organic Chemistry. Wiley- Interscience. (2007).
2. McMurray, John E. Organic Chemistry Sixth Edition. Brooks Cole. (2003).
3. Vollhardt and Schore. Organic Chemistry Structure and Function Fifth Edition. New York. (2007).

Problems

1. Trans- 1,2-dimethylcyclopropane is more stable than cis-1,2-dimethylcyclopropane. Why? Drawing a picture of the two will help your explanation.
2. Out of all the cycloalkanes, which one has the most ring strain and which one is strain free? Explain.
3. Which of these chair conformations are the most stable and why?



3.

4. What does it mean when people say "increase in heat leads to increase in energy" and how does that statement relate to ring strains?
5. Why is that the bigger rings have lesser strains compared to smaller rings?

Answers

1. The cis isomer suffers from steric hindrance and has a larger heat of combustion.
2. Cyclopropane- ring strain. Cyclohexane chair conformation- ring strain free.
3. Top one is more stable because it is in an equitorial conformation. When assembling it with the OChem Molecular Structure Tool Kit, equitorial formation is more spread out.
4. When there is an increase in heat there will be an increase of energy released therefore there will be a lot of energy stored in the bond and molecule making it unstable.
5. Smaller rings are more compacts, which leads to steric hindrance and the angles for these smaller rings are harder to get ends to meet. Bigger rings tend to have more space and that the atoms attached to the ring won't be touching each other as much as atoms attached to the smaller ring.

Contributors

- Jonathan Mooney (McGill University)

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7.2: Cycloalkanes and Ring Strain

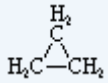
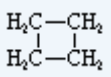
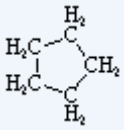
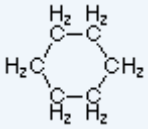
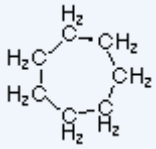
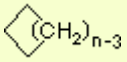
Learning Objective

- explain the partial rotation of carbon-carbon single bonds in rings
- explain ring strain and its relationship to cycloalkane stability

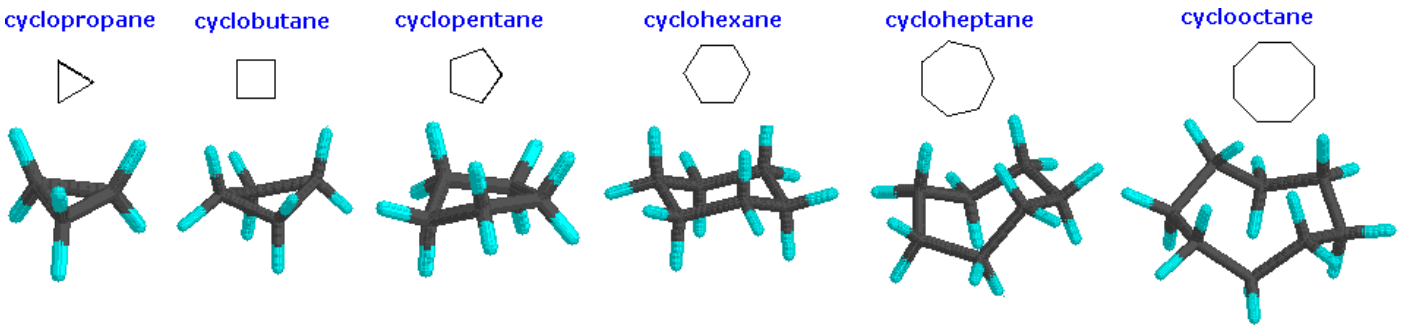
Cycloalkanes (aka Rings)

Cycloalkanes have one or more rings of carbon atoms. The simplest examples of this class consist of a single, unsubstituted carbon ring, and these form a homologous series similar to the unbranched alkanes. The IUPAC names of the first five members of this series are given in the following table. The last column gives the general formula for a cycloalkane of any size. If a simple unbranched alkane is converted to a cycloalkane two hydrogen atoms, one from each end of the chain, must be lost. Hence the general formula for a cycloalkane composed of **n** carbons is $\mathbf{C_nH_{2n}}$. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so such compounds are still considered to be **saturated** with hydrogen.

Table: Examples of Simple Cycloalkanes

Name	Cyclopropane	Cyclobutane	Cyclopentane	Cyclohexane	Cycloheptane	Cycloalkane
Molecular Formula	C_3H_6	C_4H_8	C_5H_{10}	C_6H_{12}	C_7H_{14}	C_nH_{2n}
Structural Formula						$(CH_2)_n$
Line Formula						

Although the customary line drawings of simple cycloalkanes are geometrical polygons, the actual shape of these compounds in most cases is very different. Cyclic systems are a little different from open-chain systems. In an open chain, any bond can be rotated 360 degrees, going through many different conformations. Complete rotation isn't possible in a cyclic system, because the parts that you would be trying to twist away from each other would still be connected together. 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.



The Baeyer Theory and the Experimental Evidence of Ring Strain

Many of the properties of cyclopropane and its derivatives are similar to the properties of alkenes. In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane derivatives are different from cyclopentane and cyclohexane, because their C—C—C angles cannot have the tetrahedral value of 109.5°. At the same time, Baeyer hypothesized that the difficulties encountered in synthesizing cycloalkane rings from C7 upward was the result of the angle strain that would be expected if the large rings were regular planar polygons (see Table 12-3). Baeyer also believed that cyclohexane had a planar structure like that shown in Figure 12-2, which would mean that the bond angles would have to deviate 10.5° from the tetrahedral value. However, in 1895, the then unknown chemist H. Sachse suggested that cyclohexane exists in the strain-free chair and boat forms discussed in Section 12-3. This suggestion was not accepted at the time because it led to the prediction of several possible isomers for compounds such as chlorocyclohexane (cf. Exercise 12-4). The idea that such isomers might act as a single substance, as the result of rapid equilibration, seemed like a needless complication, and it was not until 1918 that E. Mohr proposed a definitive way to distinguish between the Baeyer and Sachse cyclohexanes. As will be discussed in Section 12-9, the result, now known as the Sachse-Mohr theory, was complete confirmation of the idea of nonplanar large rings.

Table: Strain in Cycloalkane Rings and Heats of Combustion of Cycloalkanes

Compound	n	Angle Strain at each CH2	Heat of Combustion ΔHo (kcal/mol)	Heat of Combustion ΔHo per CH2/N (kcal/mol)	Total Strain (kcal/mol)
ethene	2	109.5	337.2	168.6	22.4
cyclopropane	3	49.5	499.9	166.6	27.7
cyclobutane	4	19.5	655.9	164.0	26.3
cyclopentane	5	1.5	793.4	158.7	6.5
cyclohexane	6	10.5	944.8	157.5	0.4
cycloheptane	7	19.1	1108.1	158.4	6.3
cyclooctane	8	25.5	1268.9	158.6	9.7
cyclononane	9	30.5	1429.5	158.8	12.9
cyclodecane	10	34.5	1586.1	158.6	12.1
cyclopentadecane	15	46.5	2362.5	157.5	1.5
open chain alkane				157.4	-

Ring Strain in Cycloalkanes

Ring Strain occurs because the carbons in cycloalkanes are sp^3 hybridized, which means that they do not have the expected ideal bond angle of 109.5^{o} ; this causes an increase in the potential energy because of the desire for the carbons to be at an ideal 109.5^{o}. An example of ring strain can be seen in the diagram of cyclopropane below in which the bond angle is 60° between the carbons.

cyclopropane.bmp

The reason for ring strain can be seen through the tetrahedral carbon model. The C-C-C bond angles in cyclopropane (diagram above) (60°) and cyclobutane (90°) are much different than the ideal bond angle of 109.5^{o}. This bond angle causes cyclopropane and cyclobutane to have a high ring strain. However, molecules, such as cyclohexane and cyclopentane, would have a much lower ring strain because the bond angle between the carbons is much closer to 109.5^{o}.

Below are some examples of cycloalkanes. Ring strain can be seen more prevalently in the cyclopropane and cyclobutane models

3d cycloalkanes.bmp

Below is a chart of cycloalkanes and their respective heats of combustion (ΔH_{comb}). The ΔH_{comb} value increases as the number

of carbons in the cycloalkane increases (higher membered ring), and the $\Delta H_{comb}/CH_2$ ratio decreases. The increase in ΔH_{comb} can be attributed to the greater amount of London Dispersion forces. However, the decrease in $\Delta H_{comb}/CH_2$can be attributed to a decrease in the ring strain.

energy table.bmp

Certain cycloalkanes, such as cyclohexane, deal with ring strain by forming conformers. 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.

Other Types of StrainEdit section

There are many different types of strain that occur with cycloalkanes. In addition to ring strain, there is also transannular strain, eclipsing, or torsional strain and bond angle strain.Transannular strain exists when there is steric repulsion between atoms. Eclipsing (torsional) strain exists when a cycloalkane is unable to adopt a staggered conformation around a C-C bond, and bond angle strain is the energy needed to distort the tetrahedral carbons enough to close the ring. The presence of angle strain in a molecule indicates that there are bond angles in that particular molecule that deviate from the ideal bond angles required (i.e., that molecule has conformers).

transannular strain.bmp

pentane.bmp text2.bmp

conformer.bmp

Cyclopropane

A three membered ring has no rotational freedom whatsoever, so the three carbon atoms in cyclopropane are all constrained to lie in the same plane 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.



cyclopropane

Furthermore, if you look at a model you will find that the neighboring C-H bonds (C-C bonds, too) are all held in eclipsed conformations.

Cyclopropane is always at maximum torsional strain. This strain can be illustrated in a line drawing of cyclopropane as shown from the side. In this oblique view, the dark lines mean that those sides of the ring are closer to you.



However, the ring isn't big enough to introduce any steric strain, which does not become a factor until we reach six membered rings. Until that point, rings are not flexible enough for two atoms to reach around and bump into each other.

The really big problem with cyclopropane is that the C-C-C bond angles are all too small.

- All the carbon atoms in cyclopropane appear to be tetrahedral.
- These bond angles ought to be 109 degrees.
- The angles in an equilateral triangle are actually 60 degrees, about half as large as the optimum angle.
- This factor introduces a huge amount of strain in the molecule, called ring strain.

Cyclobutane

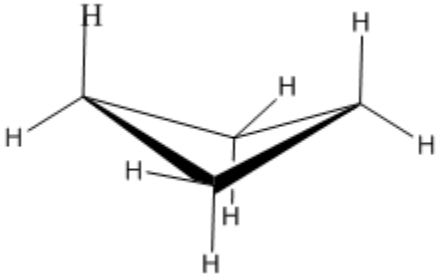
Cyclobutane is a four membered ring. In two dimensions, it is a square, with 90 degree angles at each corner. Cyclobutane reduces some bond-eclipsing strain by folding (the out-of-plane dihedral angle is about 25°), but the total eclipsing and angle strain remains high. Cyclopentane has very little angle strain (the angles of a pentagon are 108°), but its eclipsing strain would be large (about 10 kcal/mol) if it remained planar. Consequently, the five-membered ring adopts non-planar puckered conformations whenever possible.



cyclobutane

However, in three dimensions, cyclobutane is flexible enough to buckle into a "butterfly" shape, relieving torsional strain a little bit. When it does that, the bond angles get a little worse, going from 90 degrees to 88 degrees.

In a line drawing, this butterfly shape is usually shown from the side, with the near edges drawn using darker lines.



- With bond angles of 88 rather than 109 degrees, cyclobutane has a lot of ring strain, but less than in cyclopropane.
- Torsional strain is still present, but the neighbouring bonds are not exactly eclipsed in the butterfly.
- Cyclobutane is still not large enough that the molecule can reach around to cause crowding. Steric strain is very low.
- Cyclobutanes are a little more stable than cyclopropanes and are also a little more common in nature.

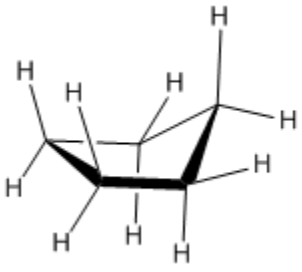
Cyclopentane

Cyclopentanes are even more stable than cyclobutanes, and they are the second-most common paraffinic ring in nature, after cyclohexanes. In two dimensions, a cyclopentane appears to be a regular pentagon.



cyclopentane

In three dimensions, there is enough freedom of rotation to allow a slight twist out of this planar shape. In a line drawing, this three-dimensional shape is drawn from an oblique view, just like cyclobutane.



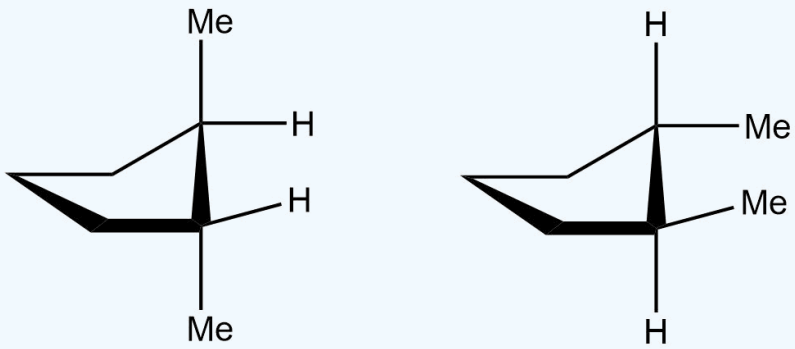
- The ideal angle in a regular pentagon is about 107 degrees, very close to a tetrahedral bond angle.
- Cyclopentane distorts only very slightly into an "envelope" shape in which one corner of the pentagon is lifted up above the plane of the other four, and as a result, ring strain is entirely removed.
- The envelope removes torsional strain along the sides and flap of the envelope. However, the neighbouring carbons are eclipsed along the "bottom" of the envelope, away from the flap. There is still some torsional strain in cyclopentane.
- Again, there is no steric strain in this system.

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).

Exercise 7.2.1

1. 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?

2. In the two conformations of *cis*-cyclopentane one is more stable than the other. Explain why this is.



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)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

Exercise 7.2.1

1. There are 8 eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

2. The first conformation is more stable. Even though the methyl groups are *cis* in the model on the left, they are eclipsing due the conformation, therefore increasing the strain within the molecule.

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7.3: Cyclohexane Conformations

Learning Objective

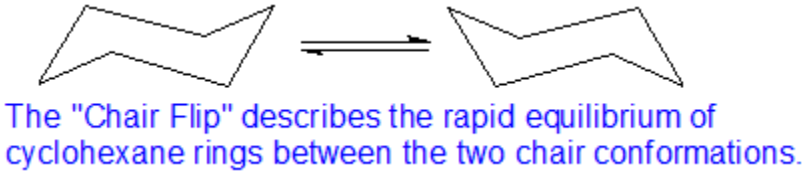
- draw cyclohexane conformations (chair & boat)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for cyclohexane

Introduction

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).

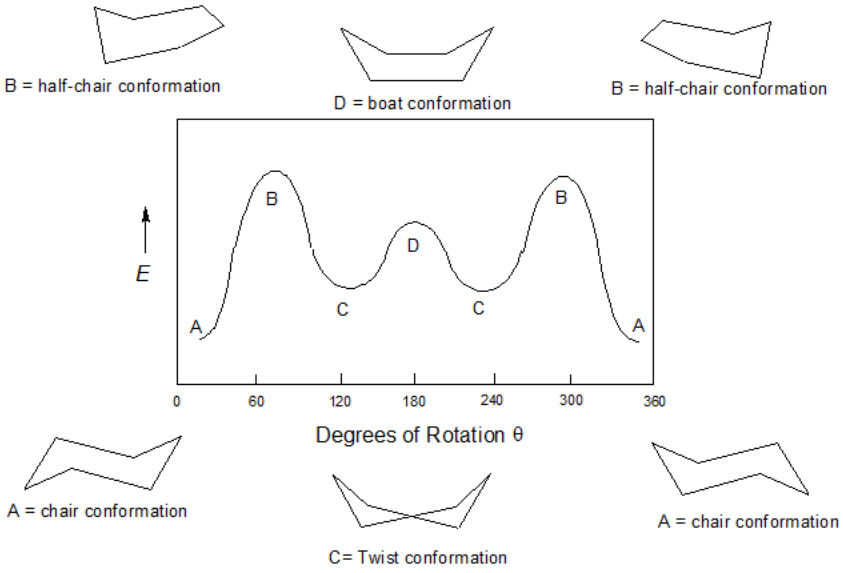
Cyclohexane Conformations (aka Chair Flips)

Cyclohexane is rapidly rotating between the two most stable conformations known as the chair conformations in what is called the "Chair Flip" shown below.



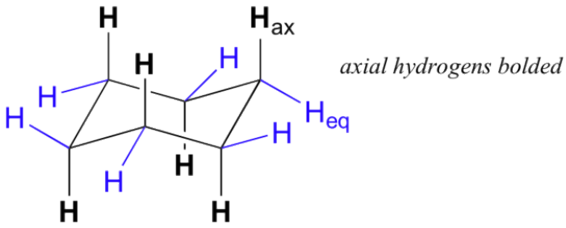
The "Chair Flip" describes the rapid equilibrium of cyclohexane rings between the two chair conformations.

Several other notable cyclohexane conformations occur during the transition from one chair conformer to the other - the boat, the twist, and the half-chair. The relative energies of the conformations is a direct reflection of their relative stabilities. These structural and energetic relationships are summarized in the conformational energy diagram for cyclohexane below.

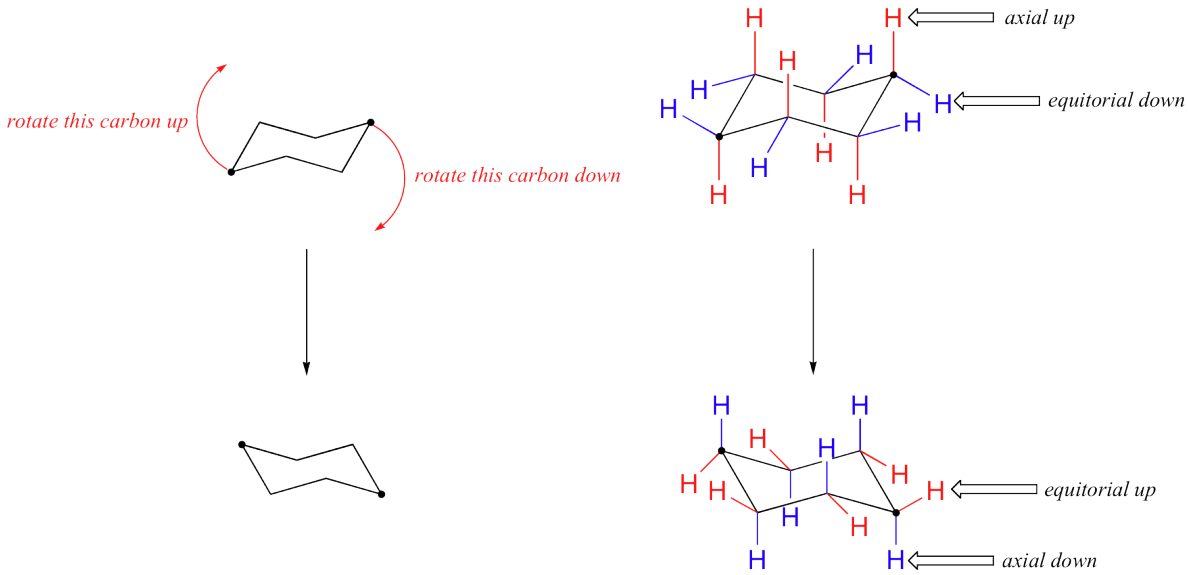


The Chair Conformation - a closer look

Since the chair conformation has the lowest potential energy, it is the most relevant to the conformation of cyclohexane. On careful examination of a chair conformation of cyclohexane, we find 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 in bold. Since there are two equivalent chair conformations of cyclohexane in rapid equilibrium, all twelve hydrogens have 50% equatorial and 50% axial character. 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 hydrogens to become axial, and vice-versa.



How to draw stereo bonds ("up" and "down" bonds)Edit section

There are various ways to show these orientations. The solid (dark) "up wedge" I used is certainly common. Some people use an analogous "down wedge", which is light, to indicate a down bond; unfortunately, there is no agreement as to which way the wedge should point, and you are left relying on the lightness of the wedge to know it is "down". The "down bond" avoids this wedge ambiguity, and just uses some kind of light line. The down bond I used (e.g., in Figure 5B) is a dashed line; IUPAC encourages a series of parallel lines, something like ||||||| What I did is a variation of what is recommended by IUPAC:

- In **ISIS/Draw**, the "up wedge" and "down bond" that I used, along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the tool button for ordinary C-C bonds.
- In **Symyx Draw**, the "up wedge" and "down bond", along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the "Chain" tool button.
- **ChemSketch** provides up and down wedges, but not the simple up and down bonds discussed above. The wedges are

available from the second toolbar across the top. For an expanded discussion of using these wedges, see the section of my ChemSketch Guide on Stereochemistry: Wedge bonds.

As always, the information provided on these pages in intended to help you get started. Each program has more options for drawing bonds than discussed here. When you feel the need, look around!

How to Draw chairsEdit section

Most of the structures shown on this page were drawn with the free program **ISIS/Draw**. I have posted a guide to help you get started with ISIS/Draw. ISIS/Draw provides a simple cyclohexane (6-ring) hexagon template on the toolbar across the top. It provides templates for various 6-ring chair structures from the Templates menu; choose Rings. There are templates for simple chairs, without substituents (e.g., Fig 1B), and for chairs showing all the substituents (e.g., Fig 2B). In either case, you can add, delete, or change things as you wish. Various kinds of stereo bonds (wedges and bars) are available by clicking the left-side tool button that is just below the regular C-C single bond button. It may have a wedge shown on it, but this will vary depending on how it has been used. To choose a type of stereo bond, click on the button and hold the mouse click; a new menu will appear to the right of the button.

The free drawing program **Symyx Draw**, the successor to ISIS/Draw, provides similar templates and tools. A basic chair structure is provided on the default template bar that is shown. More options are available by choosing the Rings template. See my page Symyx Draw for a general guide for getting started with this program.

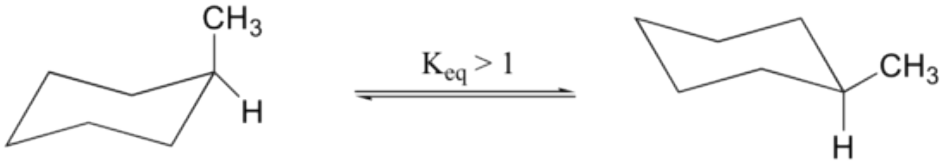
The free drawing program **ChemSketch** provides similar templates and tools. To find the special templates for chairs, go to the **Templates** menu, choose **Template Window**, and then choose "Rings" from the drop-down menu near upper left. See my page ChemSketch for a general guide for getting started with this program.

If you want to draw chair structures by hand (and if you are going on in organic chemistry, you should)... Be careful. The precise zigs and zags, and the angles of substituents are all important. Your textbook may offer you some hints for how to draw chairs. A short item in the Journal of Chemical Education offers a nice trick, showing how the chair can be thought of as consisting of an M and a W. The article is V Dragojlovic, A method for drawing the cyclohexane ring and its substituents. J Chem Educ 78:923, 7/01. (I thank M Farooq Wahab, Chemistry, Univ Karachi, for suggesting that this article be noted here.)

Aside from drawing the basic chair, the key points in adding substituents are:

- Axial groups alternate up and down, and are shown "vertical".
- Equatorial groups are approximately horizontal, but actually somewhat distorted from that, so that the angle from the axial group is a bit more than a right angle -- reflecting the common 109 degree bond angle.
- As cautioned before, it is usually easier to draw and see what is happening at the four corners of the chair than at the two middle positions. Try to use the corners as much as possible.

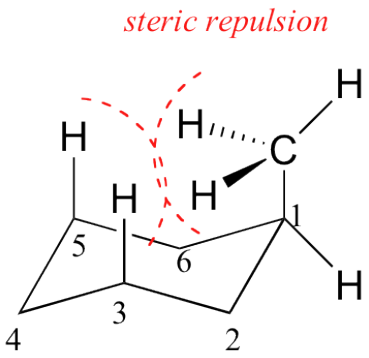
Because axial bonds are parallel to each other, substituents larger than hydrogen generally suffer greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents assume equatorial orientation***.



methyl group axial

methyl group equitorial
(more stable)

When the methyl group in the structure above occupies an axial position it suffers steric crowding by the two axial hydrogens located on the same side of the ring.



The conformation in which the methyl group is equatorial is more stable, and thus the equilibrium lies in this direction

Exercise

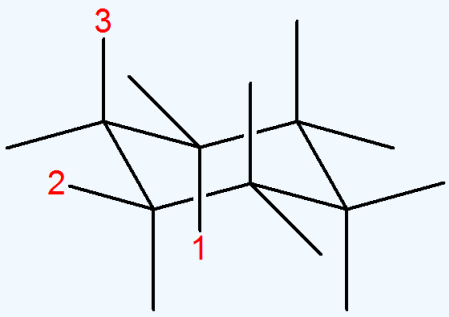
Questions

1. Consider the conformations of cyclohexane, chair, boat, twist boat. Order them in increasing strain in the molecule.

2. Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

3. Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

4. In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).



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)

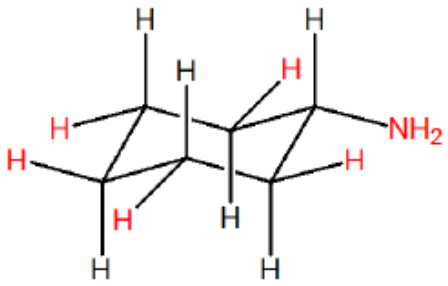
>Robert Bruner (http://bbruner.org)

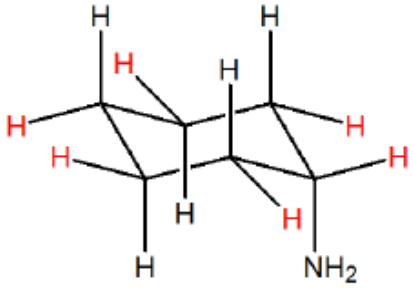
Answers

Exercise

1. Chair < Twist Boat < Boat (most strain)

2.

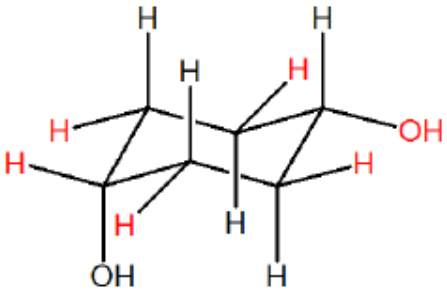


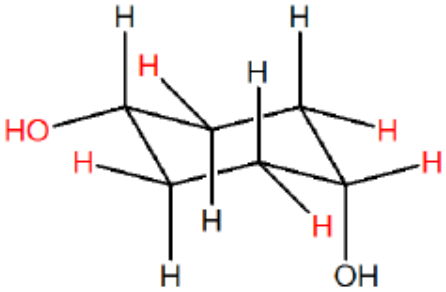


Axial

Equatorial

3.

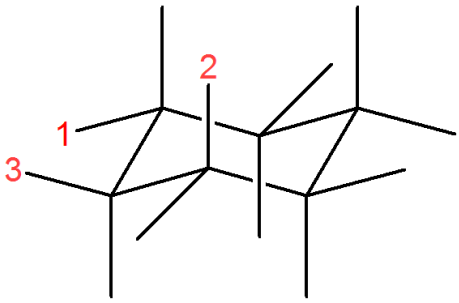




Axial

Equatorial

4. Original conformation: 1 = axial, 2 = equatorial, 3 = axial
Flipped chair now looks like this.



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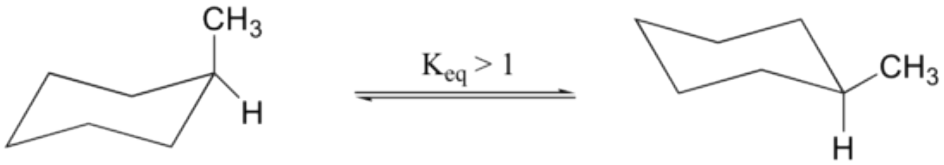
7.4: Conformations of Monosubstituted Cyclohexanes

Learning Objective

- draw mono-substituted cyclohexane conformers (chair only)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for butane, higher alkanes, cyclohexane, mono-substituted cyclohexanes, and disubstituted cyclohexanes

Introduction

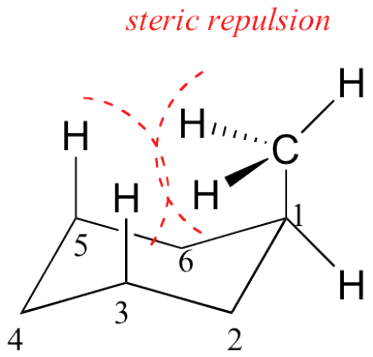
Because axial bonds are parallel to each other, substituents larger than hydrogen generally suffer greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents assume equatorial orientation***.



methyl group axial

methyl group equitorial
(more stable)

When the methyl group in the structure above occupies an axial position it suffers steric crowding by the two axial hydrogens located on the same side of the ring. The conformation in which the methyl group is equatorial is more stable, and thus the equilibrium lies in this direction.



In examining possible structures for monosubstituted cyclohexanes, it is useful to follow two principles:

i. Chair conformations are generally more stable than other possibilities.
ii. Substituents on chair conformers prefer to occupy equatorial positions due to the increased steric hindrance of axial locations.

Experimental Measurements of Steric Hindrance

The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane may be determined by the conformational equilibrium of the compound. The corresponding equilibrium constant is related to the energy difference between the conformers and collecting such data allows us to evaluate the relative tendency of

substituents to exist in an equatorial or axial location.

Looking at the energy values the table, it is clear that the apparent "size" of a substituent (in terms of its preference for equatorial over axial orientation) is influenced by its width and bond length to cyclohexane, as evidenced by the fact that an axial vinyl group is less hindered than ethyl, and iodine slightly less than chlorine.

A Selection of AG° Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes

Substituent	$-\Delta G^o$ kcal/mol	Substituent	$-\Delta G^o$ 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	$(CH_3)_3C-$	0.7
$F-$	0.3	F-	1.3
$Cl-$	0.5	C_6H_5-	3.0
$Br-$	0.5		
$I-$	0.5		

Exercise

1. In the molecule, cyclohexyl ethyne there is little steric strain, why?

Answer available at the end of this section.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

>Robert Bruner (http://bbruner.org)

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

Answers

Exercise

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.



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7.5: Conformations of Disubstituted Cyclohexanes

Learning Objective

- draw di-substituted cyclohexane conformers (chair only)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for disubstituted cyclohexanes

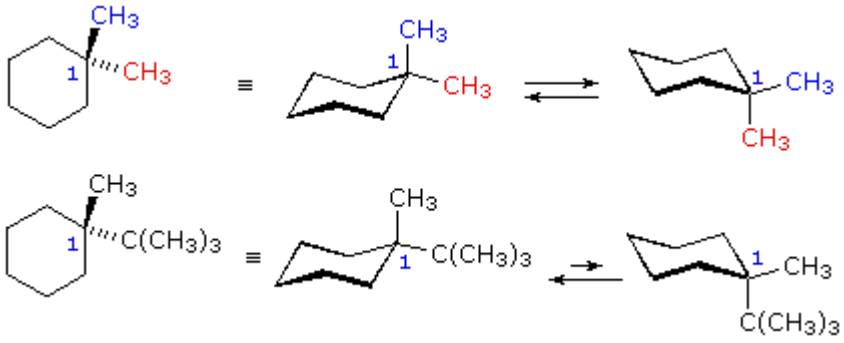
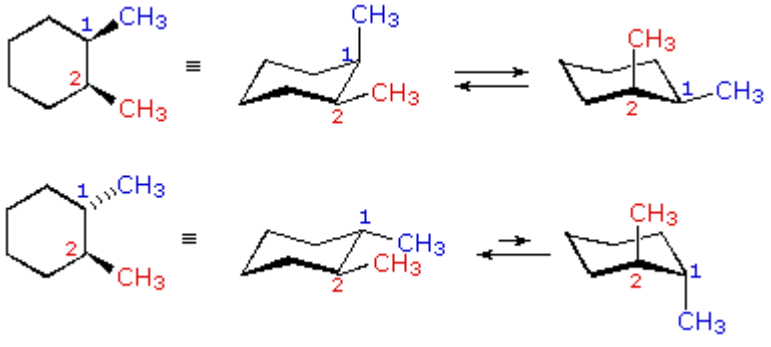
Conformational Structures of Disubstituted Cyclohexanes

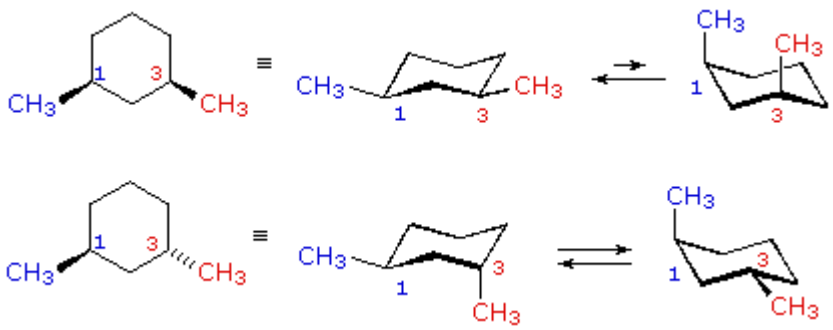
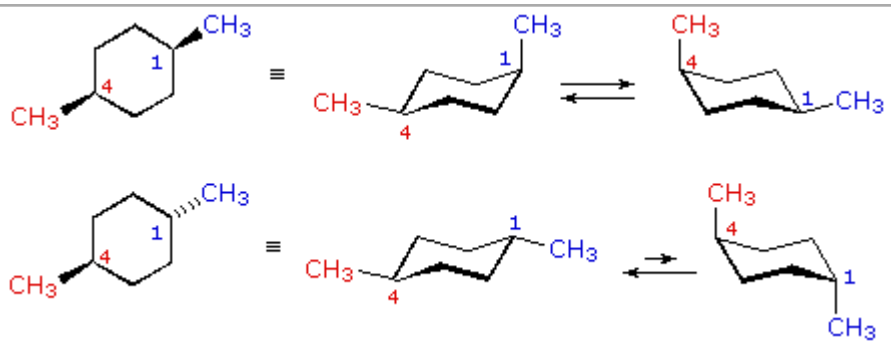
In a sample of cyclohexane, the two identical chair conformers are present in equal concentration, and the hydrogens are all equivalent (50% equatorial & 50% axial) due to rapid interconversion of the conformers. When the cyclohexane ring bears a substituent, the two chair conformers are not the same. In one conformer the substituent is axial, in the other it is equatorial. Due to steric hindrance in the axial location, substituent groups prefer to be equatorial and that chair conformer predominates in the equilibrium.

When cycloalkanes have two substituents on different ring carbon atoms, then a pair of configurational stereoisomers exist. Now we must examine the way in which favorable ring conformations influence the properties of the configurational isomers. Remember, configurational stereoisomers are stable, unique chemical compounds, whereas, conformational isomers are different rotations of the same compound. In examining possible structures for disubstituted cyclohexane, it is useful to follow two principles:

1. Substituents on chair conformers prefer to occupy equatorial positions due to the increased steric hindrance of axial locations.

The following equations and formulas illustrate how the presence of two or more substituent on a cyclohexane ring perturbs the interconversion of the two chair conformers in ways that can be predicted. When there is a potential energy difference between the conformers, then the lower energy conformation is favored as indicated by the equilibrium reaction arrows.

1,1-dimethylcyclohexane **1-t-butyl-1-methylcyclohexane**	
cis-1,2-dimethylcyclohexane **trans-1,2-dimethylcyclohexane**	

cis-1,3-dimethylcyclohexane **trans-1,3-dimethylcyclohexane**	
cis-1,4-dimethylcyclohexane **trans-1,4-dimethylcyclohexane**	

In the case of 1,1-disubstituted cyclohexanes, one of the substituents must necessarily be axial and the other equatorial, regardless of which chair conformer is considered. Since the substituents are the same in 1,1-dimethylcyclohexane, the two conformers are identical and present in equal concentration. In 1-t-butyl-1-methylcyclohexane the t-butyl group is much larger than the methyl, and that chair conformer in which the larger group is equatorial will be favored in the equilibrium(> 99%). Consequently, the methyl group in this compound is almost exclusively axial in its orientation.

In the cases of 1,2-, 1,3- and 1,4-disubstituted compounds the analysis is a bit more complex. It is always possible to have both groups equatorial, but whether this requires a cis-relationship or a trans-relationship depends on the relative location of the substituents. As we count around the ring from carbon #1 to #6, the uppermost bond on each carbon changes its orientation from equatorial (or axial) to axial (or equatorial) and back. It is important to remember that the **bonds on a given side of a chair ring-conformation always alternate in this fashion**. Therefore, it should be clear that for cis-1,2-disubstitution, one of the substituents must be equatorial and the other axial; in the trans-isomer both may be equatorial. Because of the alternating nature of equatorial and axial bonds, the opposite relationship is true for 1,3-disubstitution (cis is all equatorial, trans is equatorial/axial). Finally, 1,4-disubstitution reverts to the 1,2-pattern.

The conformations of some substituted cyclohexanes may be examined as interactive models by Clicking Here.

It can be helpful to add the hydrogen atoms at the axial positions to help recognize the equatorial position.

Exercise

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.

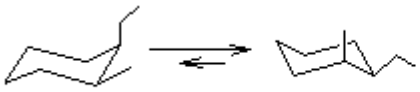
Answer available at the end of this section.

Contributors

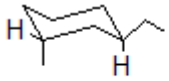
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Answers

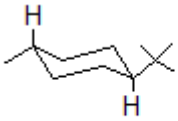
Exercise

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

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7.6: 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

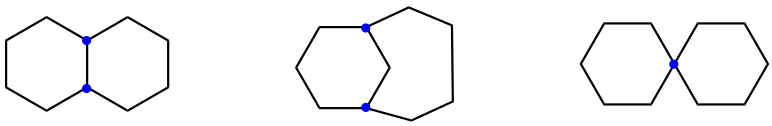
Study Notes

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.



fused bridged spiro

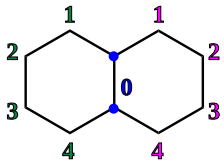
• = bridgehead carbons

Bicyclic Isomers of $C_{10}H_{18}$

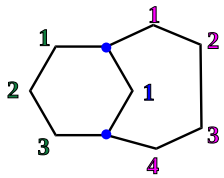
Naming Fused and Bridged Compounds

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.

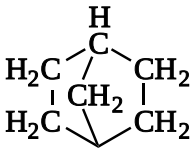


bicyclo[4.4.0]decane

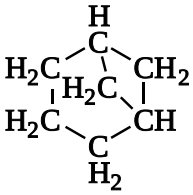


bicyclo[4.3.1]decane

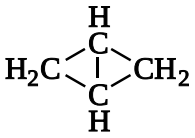
Examples with carbons and hydrogens explicitly shown:



bicyclo[2.2.1]heptane



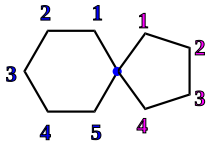
bicyclo[3.1.1]heptane



bicyclo[1.1.0]butane

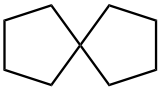
Naming Spiro Compounds

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.

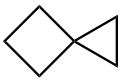


spiro[5.4]decane

Examples



spiro[4.4]nonane



spiro[3.2]hexane

Conformations in Bicyclic Ring SystemsEdit section

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.



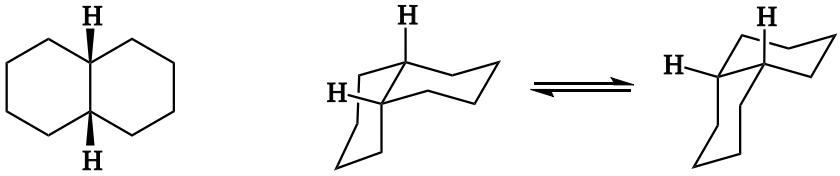
***trans* -decalin**
(rigid)

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.

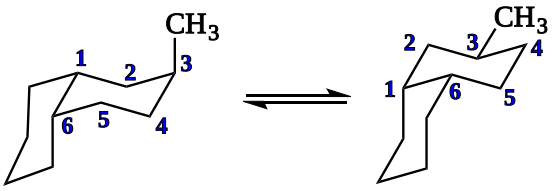


***cis* -decalin**
(more flexible)

Interactive Element

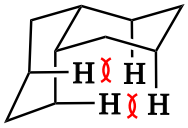
The 3D Structure of *Cis*-Decalin

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.

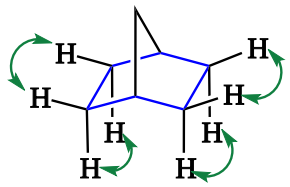


norbornane, or
bicyclo[2.2.1]heptane

Interactive Element

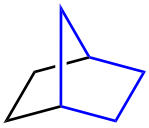
The 3D Structure of Norbornane

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.



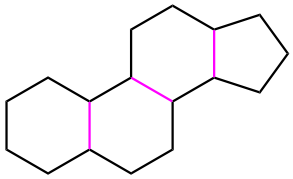
(green arrows used to illustrate
eclipsing hydrogens)

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.

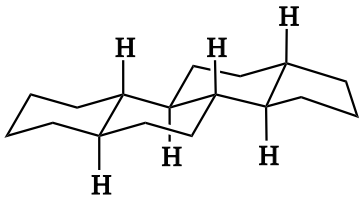


Polycyclic Systems in Nature

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.

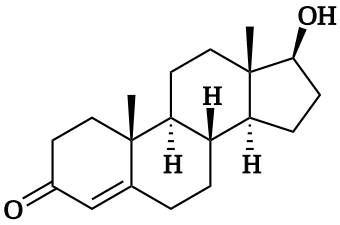


basic steroid ring confguration
(fused bonds highlighted in purple)

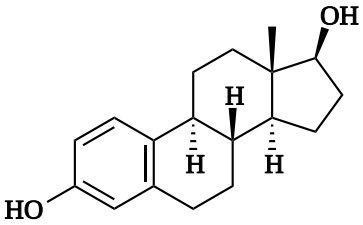


trans-trans-trans

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

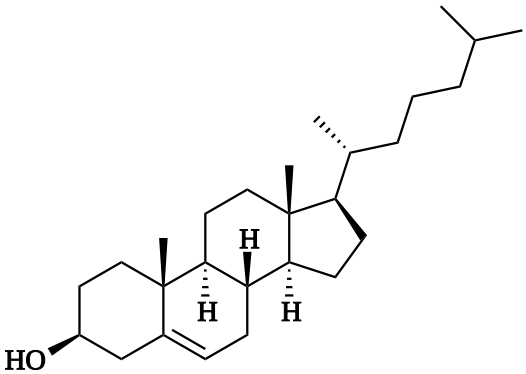


estradiol

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

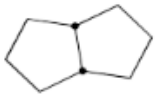
1)

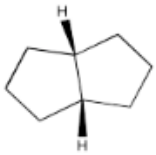
a) 

b) 

c) 

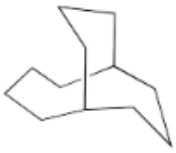
d) 

e) 

= 

f) 

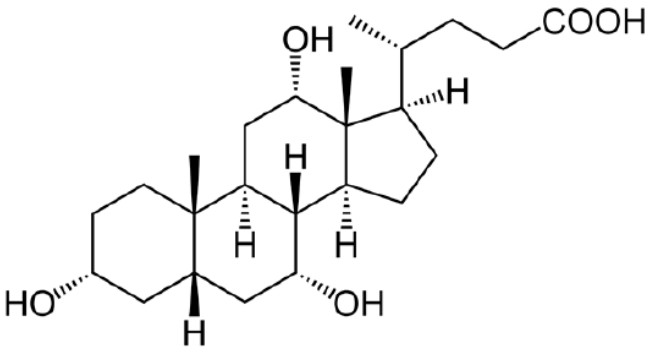
g) 

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

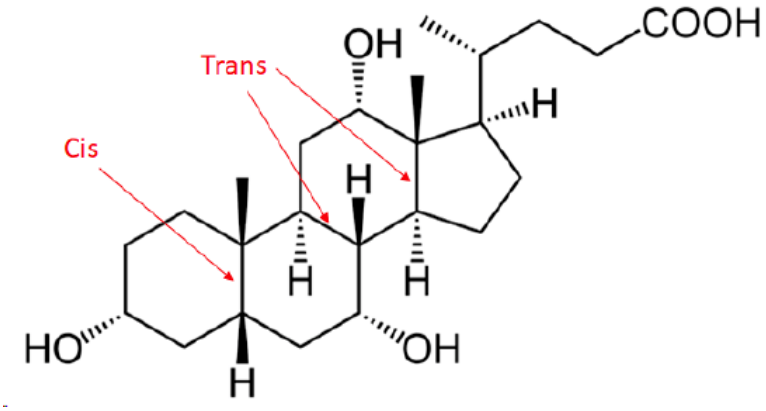
g) Bicyclo[1.1.1]pentane

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

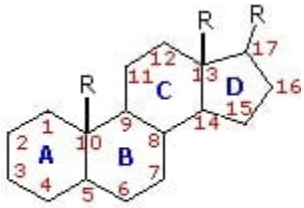
Cis-decalin has fewer steric interactions than *trans*-decalin.

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7.7: Carbocyclic Products in Nature

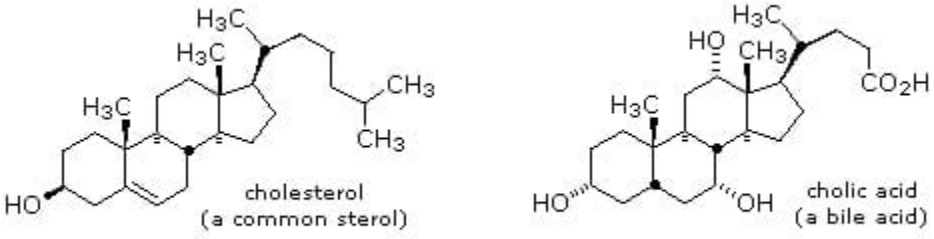
The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram 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.



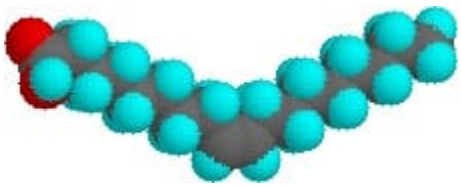
The Steroid
Carbon Skeleton

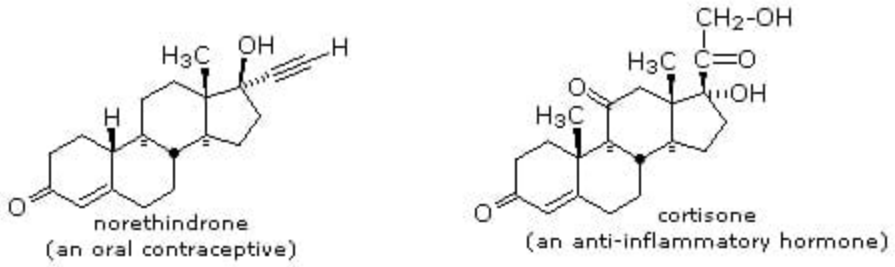
Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry 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.

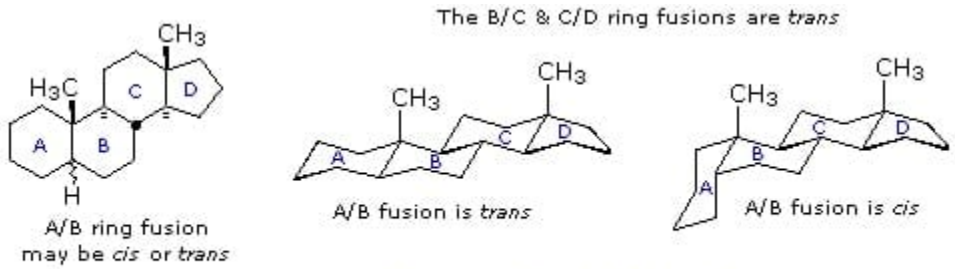


Typical Animal Steroids





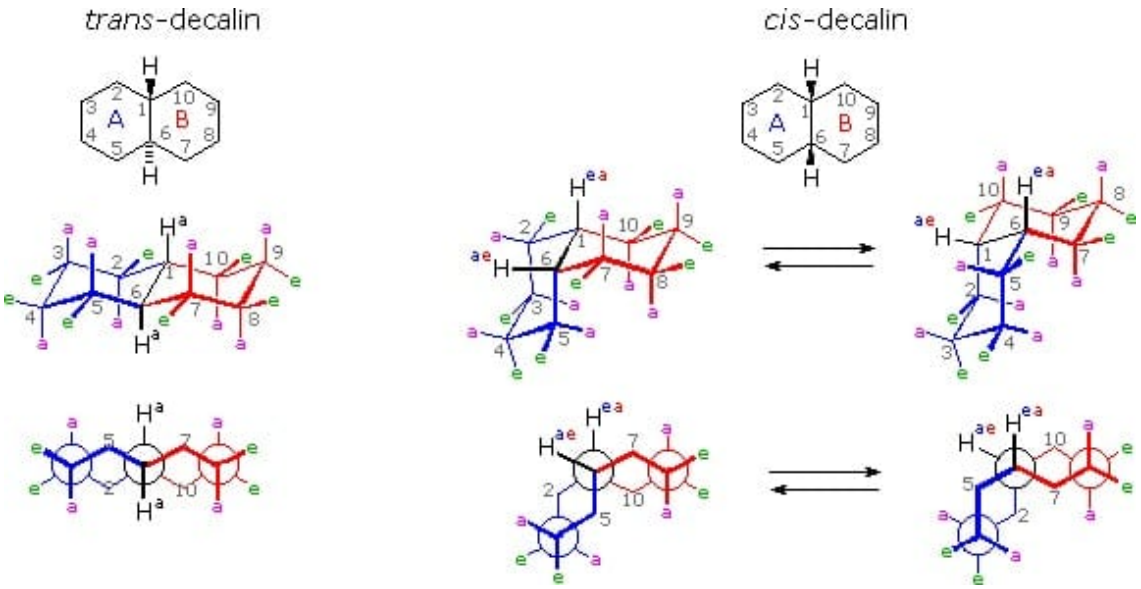
Medicinally Useful Steroids

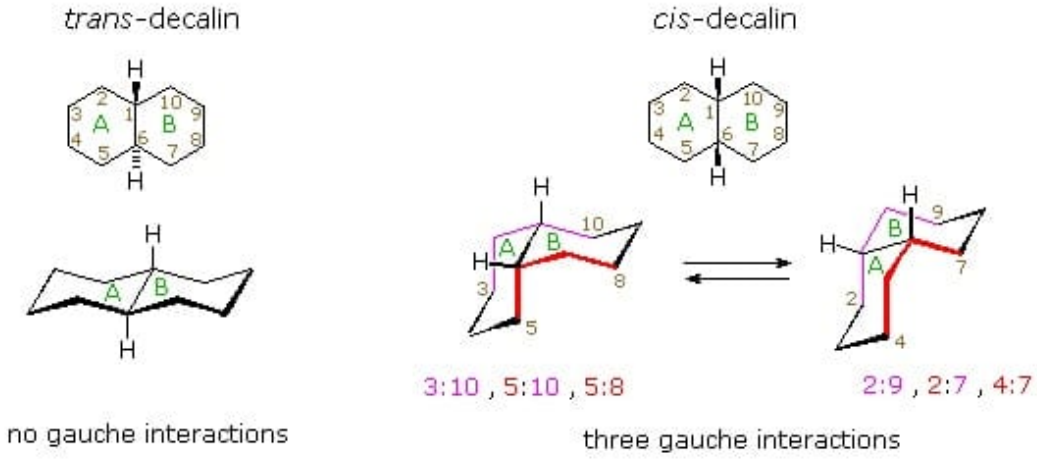


Common Steroid Conformations

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.



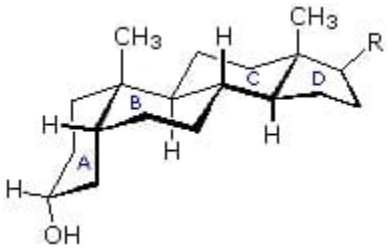


The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (H^a) axial to both rings. Note that the bonds directed 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.

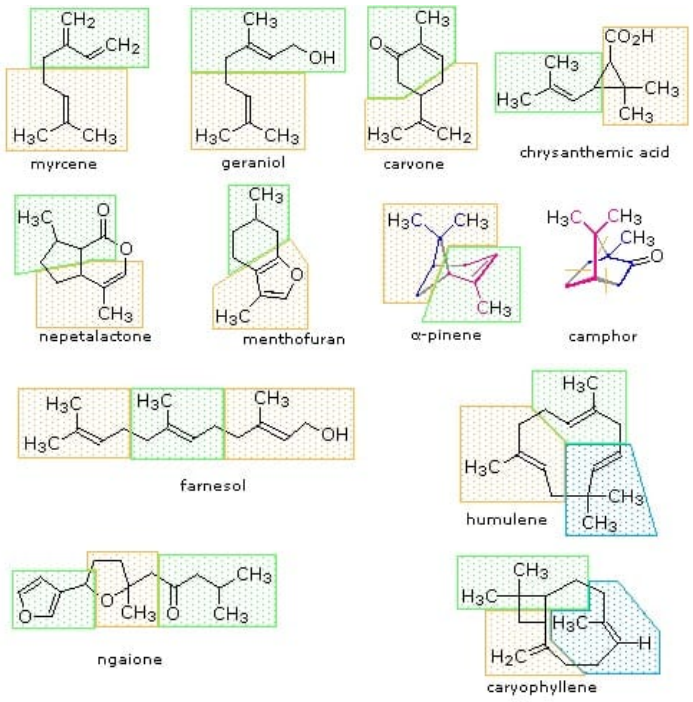


Figure: Monoterpenes and diterpenes

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.

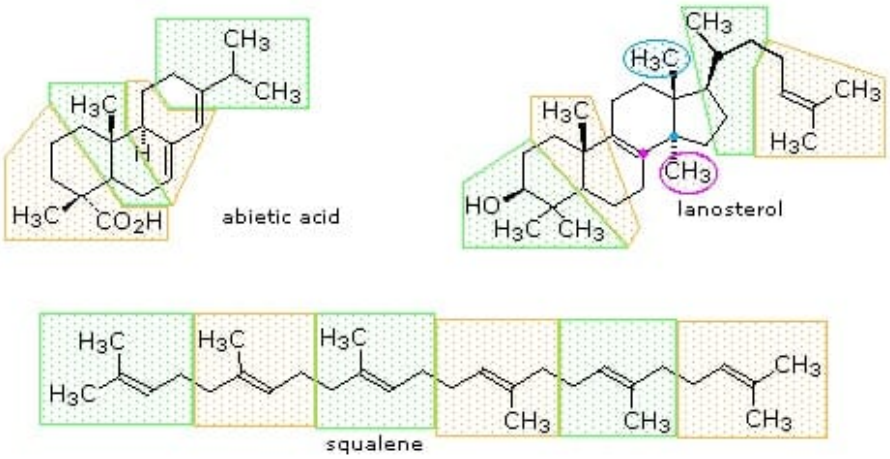
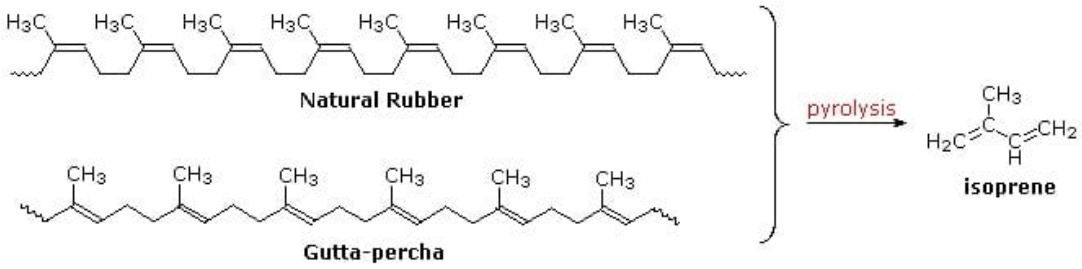


Figure: Triterpenes

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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7.8: Steroids

Objectives

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge and dash structure from which to work.

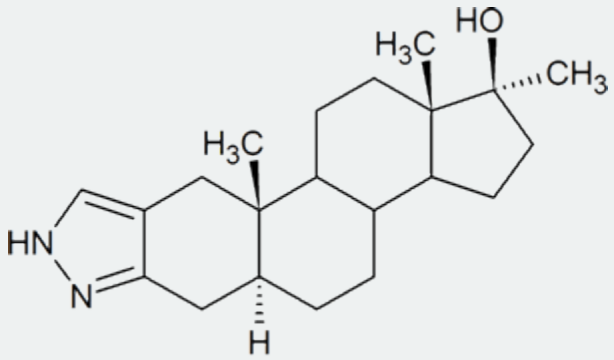
Key Terms

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

- steroid

Study Notes

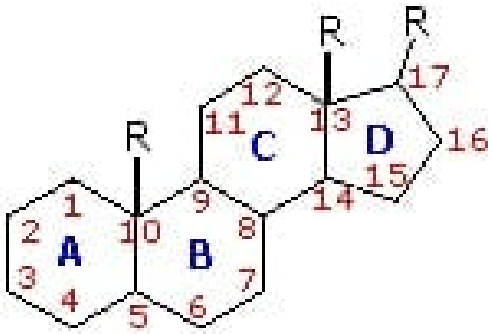
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word “steroid” and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

General Steroid Structure

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 below. 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. 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.

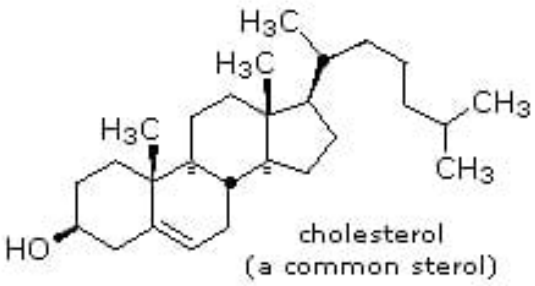


The Steroid
Carbon Skeleton

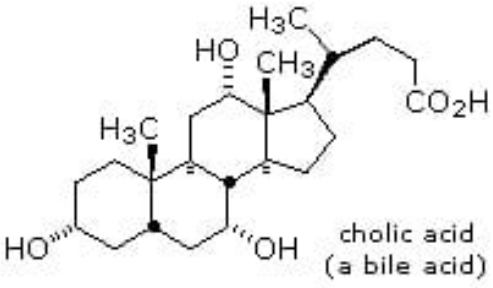
Common Steroids

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.

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.



cholesterol
(a common sterol)



cholic acid
(a bile acid)

Typical Animal Steroids

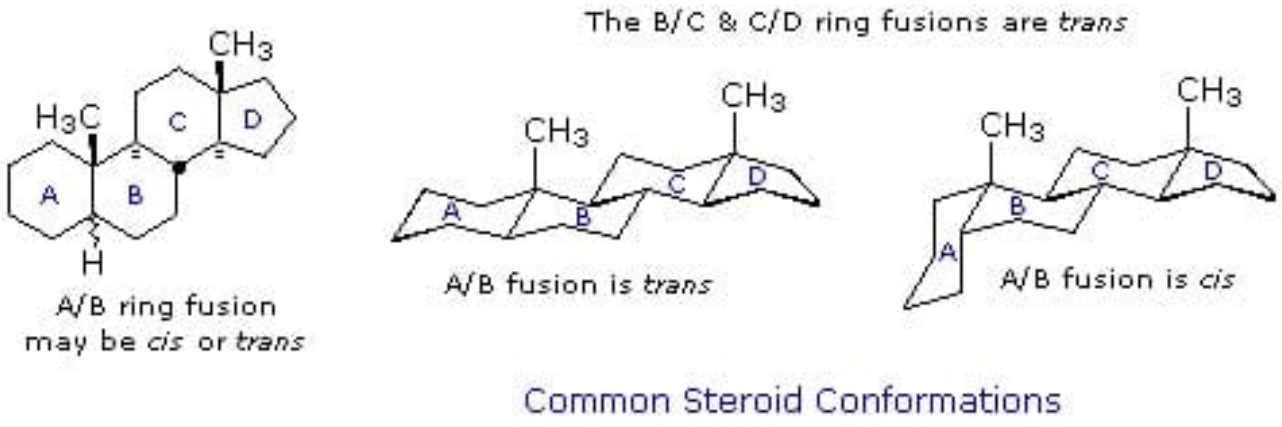


norethindrone
(an oral contraceptive)



cortisone
(an anti-inflammatory hormone)

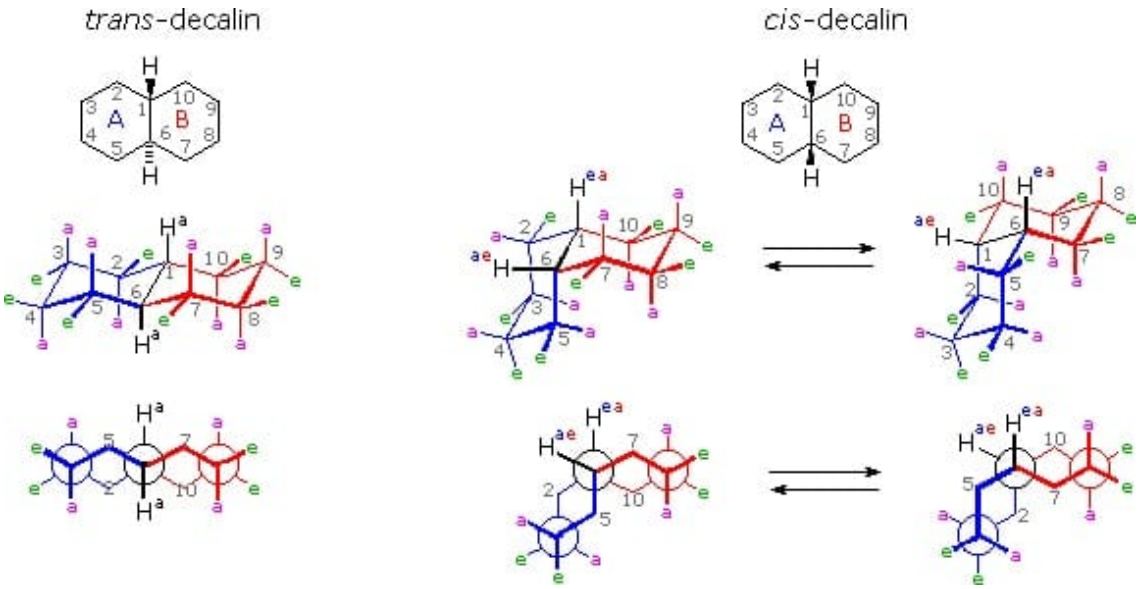
Medicinally Useful Steroids

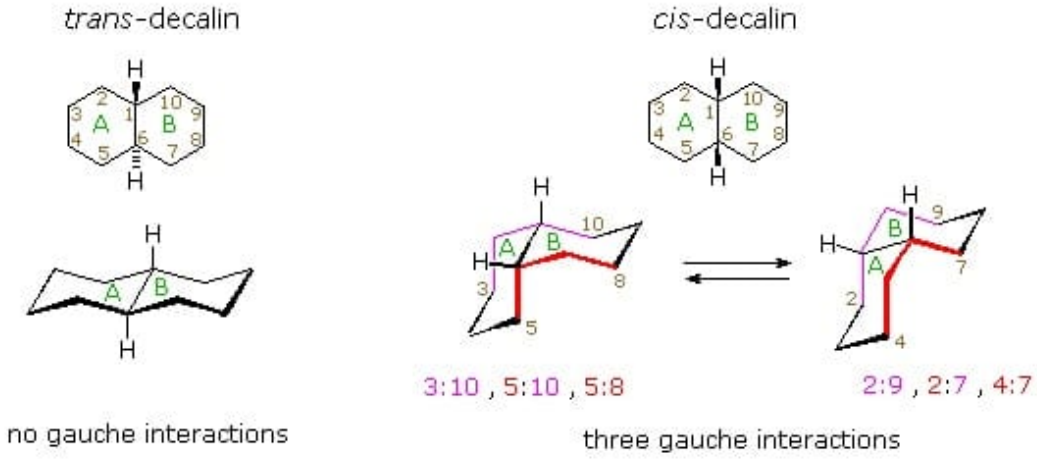


Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of 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.

Decalin as a model system

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.





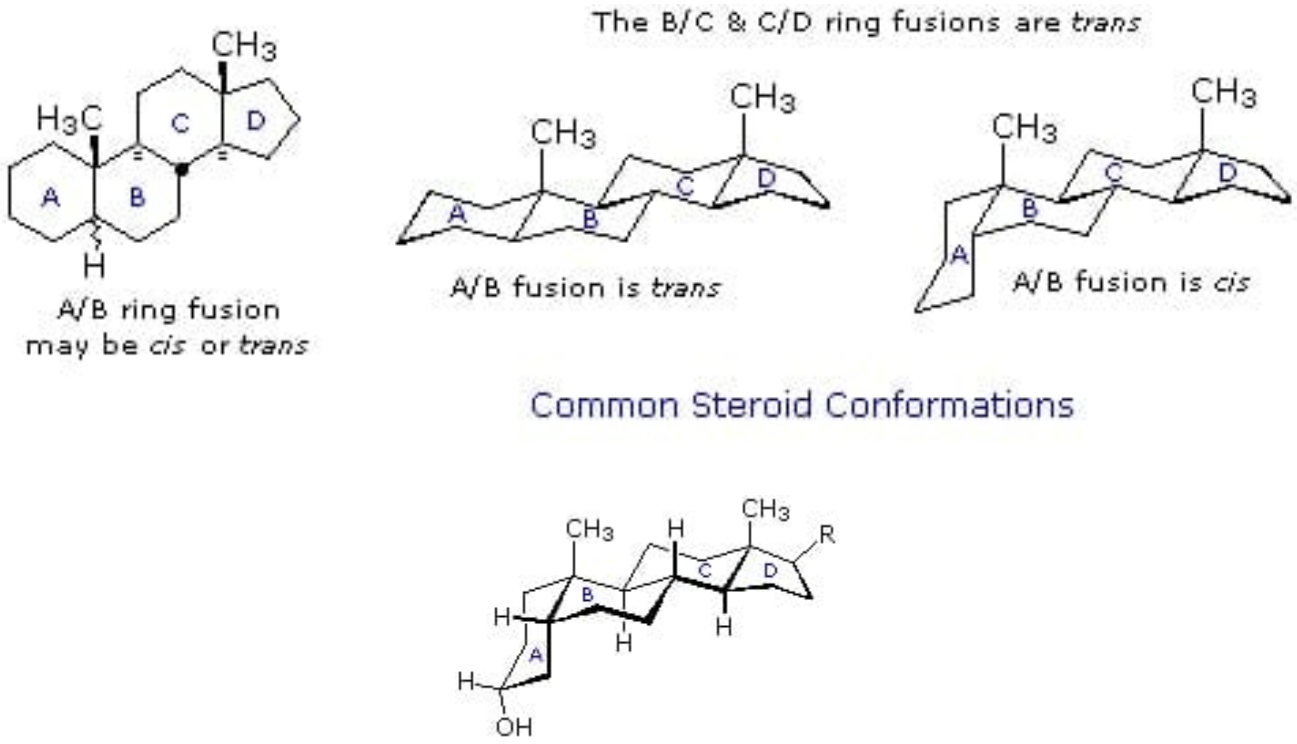
The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above 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.

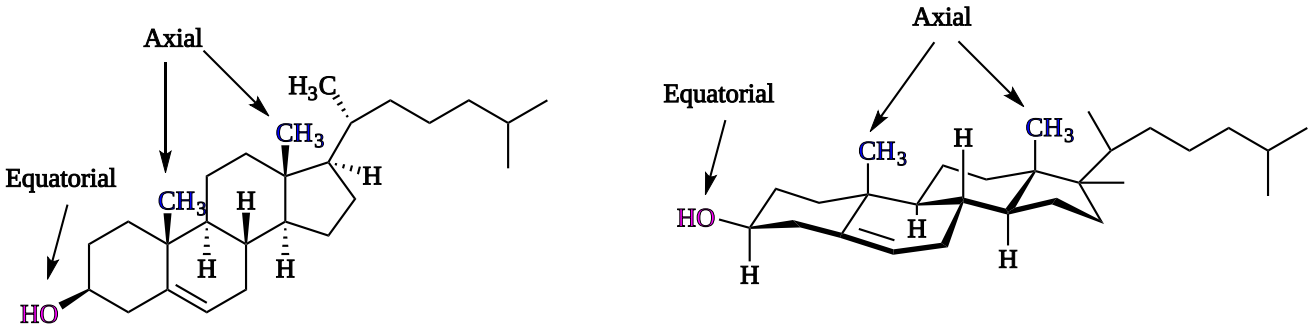
Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following 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.

Steroid Conformations

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the same conformational 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.



Much like cyclohexanes substituents (**Section 4-7**) on a steroid ring system can be either an axial or equatorial position. Fused rings makes steroids ridge and unable to undergo cyclohexane ring-flips Because of sterics, substituents in the equatorial posltion tend to be more energetically favorable. The -OH group present in cholesterol is in the more stable equatorial position while the two -CH_3 groups on the steroid ring are both in an axial position.

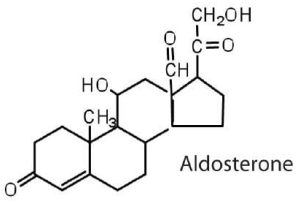
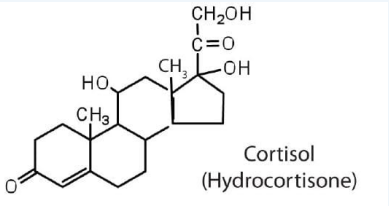
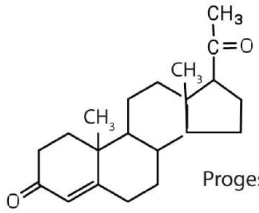
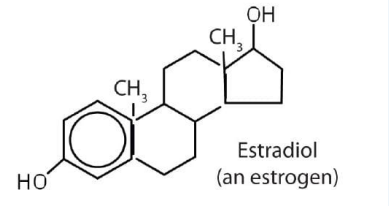
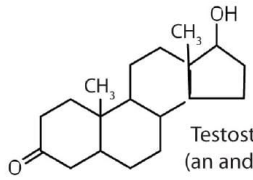


Steroid Hormones

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 27.6.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 27.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

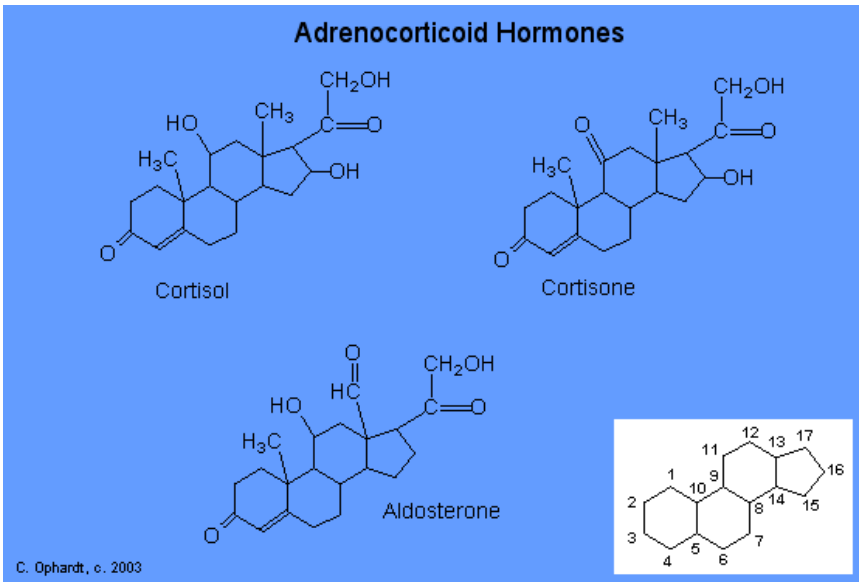
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Adrenocorticoid Hormones

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important adrenocorticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

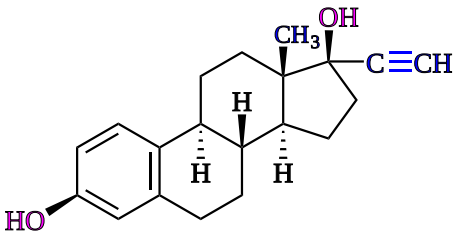
Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to inflammatory effects. Cortisone or similar synthetic derivatives such as prednisolone are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects with the use of cortisone drugs, so there use must be monitored carefully.

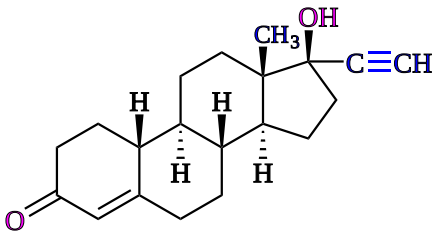


Synthetic Steroids

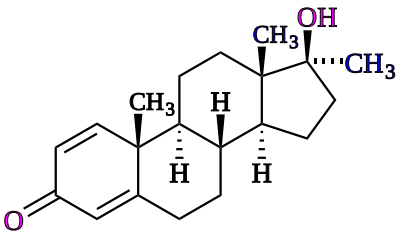
In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and test by pharmaceutical companies. The two classes of synthetic steroids most commonly know by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the hormones estrogen (ethynylestradiol) and progestin (norethindrone). They prevent pregnancy by interfering with ovulation, fertilization, and/or implantation of the fertilized egg. Anabolic steroids (methandrostenolone) mimic the effects of natural testosterone.



Ethynylestradiol
(A synthetic estrogen)



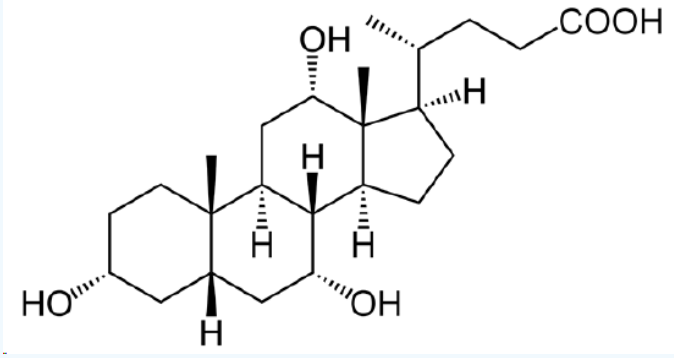
Norethindrone
(A synthetic progestin)



Methandrostenolone
(A synthetic androgen)

Exercise 7.8.1

The following molecule is cholic acid. Draw it showing the chair conformations. Determine if the three fused bonds have a *cis* or *trans* configuration. Determine if the OH groups are axial or equatorial.

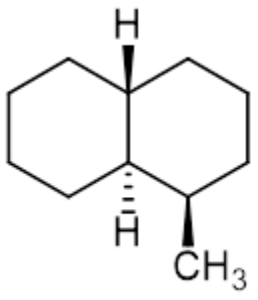


Answer available at the end of this section.

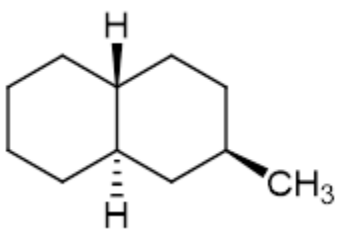
Exercise 7.8.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)



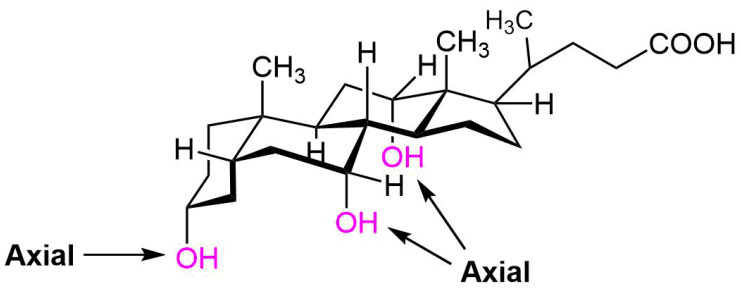
b)

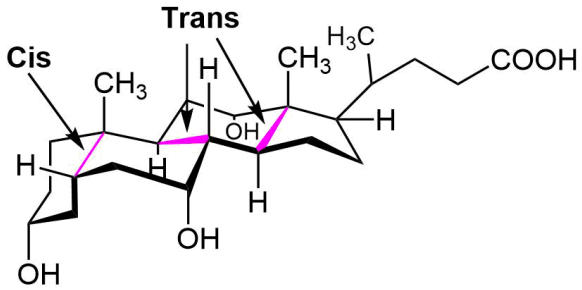


Answer available at the end of this section.

Answers

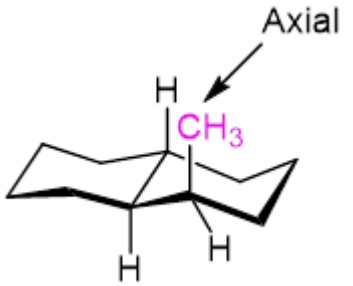
Exercise 7.8.1



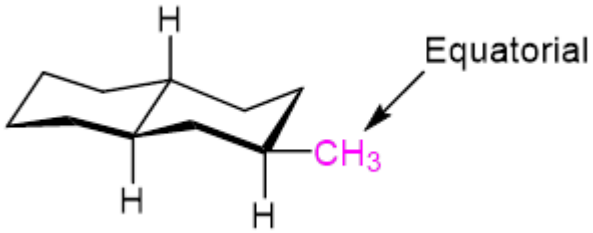


Exercise 7.8.2

a)



b)



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8: INTRODUCTION TO ALKYL HALIDES, ALCOHOLS, ETHERS, THIOLS, AND SULFIDES

8.1: Alkyl Halides

8.2: Haloalkanes

8.2.1: Alkyl Halide Occurrence

8.3: Nomenclature of Alcohols

8.3.1: Nomenclature of Alcohols

8.4: Thiols (Mercaptans)

8.5: Nomenclature of Ethers

8.6: Solvents

8.6.1: Boiling Points

8.6.2: Solvent-Solutes

8.7: Acidity of Alcohols and Phenols

8.8: Grignard and Organolithium Reagents

8.9: Grignard Reagents

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8.1: Alkyl Halides

A class of simple alkyl halides called chlorofluorocarbons (CFCs) was once very widely used in aerosol sprays and as refrigerants. One such example is $\mathrm{CCl_3F}$, or trichlorofluoromethane. Unfortunately, CFCs are harmful to the ozone layer of our upper atmosphere. Ozone is critical in limiting the amount of damaging ultraviolet radiation that reaches the Earth. CFCs react with the ozone and damage it, leaving the earth less protected.

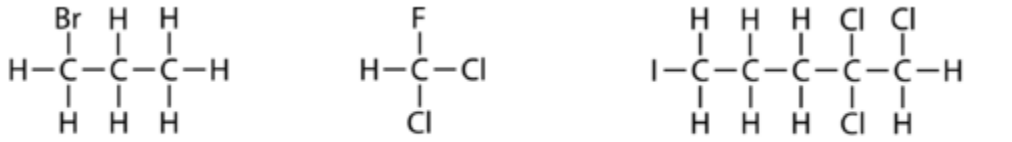
Beginning in the late 1970s, ozone depletion was recognized as a significant environmental issue. The most dramatic decrease in ozone occurs seasonally over the continent of Antarctica. The size and duration of the ozone hole steadily increased, with the largest hole recorded in 2006. Fortunately, most countries have recognized the danger of CFCs and dramatically curtailed their use in recent years. It is hoped that ozone depletion will slow, and that the ozone layer may eventually be restored to its earlier levels.

Alkyl Halides

An **alkyl halide** is an organic compound in which one or more halogen atoms are substituted for one or more hydrogen atoms in a hydrocarbon. The general formulas for organic molecules with functional groups use the letter R to stand for the rest of the molecule outside of the functional group. Because there are four possible halogen atoms (fluorine, chlorine, bromine, or iodine) that can act as the functional group, we use the general formula $\mathrm{R{-}X}$ to represent an alkyl halide. The rules for naming simple alkyl halides are listed below.

1. Name the parent compound by finding the longest continuous carbon atom chain that also contains the halogen. Add a prefix for the particular halogen atom. The prefixes for each of the four halogens are *fluoro-*, *chloro-*, *bromo-*, and *iodo-*. If more than one kind of halogen atom is present, put them in alphabetical order. If there is more than one of the same halogen on a given carbon atom, use the prefixes *di-*, *tri-*, or *tetra-* before the prefix for the halogen.
2. As with hydrocarbons, number the carbon chain in a way that makes the sum of halogen numbers as low as possible. If different halogens are in equivalent positions, give the lower number to the one that comes first in alphabetical order.
3. Add the numerical prefix into the name before the halogen prefix.
4. Separate numbers with commas, and separate numbers from names or prefixes with a hyphen. There are no spaces in the name.

Listed below are some examples of names and structural formulas of a few alkyl halides.



Note that for the structure based on methane, no number needs to be used, since there is only one carbon atom. In the third example, the *chloro-* is listed first alphabetically and the chain is numbered so that the sum of the numbers is as low as possible.

Uses of Alkyl Halides

Alkyl halides are often used as synthetic intermediates in the laboratory. Although these compounds were once widely used as dry cleaning solvents, coolants in refrigerators and air conditioners, and propellants in hairsprays and deodorants, increasing awareness of their toxicity has led to a widespread decrease in applications for these materials. Some specific compounds are still used. Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) is still used in some situations as an inhalation anesthetic. The compound DDT is a very effective pesticide, but is only used when nothing else works, because of its harmful effects on the environment.

Summary

- An alkyl halide is an organic compound in which one or more halogen atoms are substituted for one or more hydrogen atoms in a hydrocarbon.
- Alkyl halides are often used as synthetic intermediates in the laboratory.

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8.2: HALOALKANES

- Topic hierarchy

8.2.1: Alkyl Halide Occurrence

The haloalkanes, also known as alkyl halides, are a group of chemical compounds comprised of an alkane with one or more hydrogens replaced by a halogen atom (fluorine, chlorine, bromine, or iodine).

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

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

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 incease 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.

Haloalkanes 0.4.bmp

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.

Haloalkanes 0.5.bmp

Contributors

- Rachael Curtis (UC Davis)

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8.2.1: Alkyl Halide Occurrence

Halogen containing organic compounds are relatively rare in terrestrial plants and animals. The thyroid hormones T_3 and T_4 are exceptions; as is fluoroacetate, the toxic agent in the South African shrub *Dichapetalum cymosum*, known as "gifblaar". However, the halogen rich environment of the ocean has produced many interesting natural products incorporating large amounts of halogen. Some examples are shown below. The ocean is the largest known source for atmospheric methyl bromide and methyl iodide. Furthermore, the ocean is also estimated to supply 10-20% of atmospheric methyl chloride, with other significant contributions coming from biomass burning, salt marshes and wood-rotting fungi. Many subsequent chemical and biological processes produce poly-halogenated methanes.

Synthetic organic halogen compounds are readily available by direct halogenation of hydrocarbons and by addition reactions to alkenes and alkynes. Many of these have proven useful as intermediates in traditional synthetic processes. Some halogen compounds, shown in the box. have been used as pesticides, but their persistence in the environment, once applied, has led to restrictions, including banning, of their use in developed countries. Because DDT is a cheap and effective mosquito control agent, underdeveloped countries in Africa and Latin America have experienced a dramatic increase in malaria deaths following its removal, and arguments are made for returning it to limited use. 2,4,5-T and 2,4-D are common herbicides that are sold by most garden stores. Other organic halogen compounds that have been implicated in environmental damage include the polychloro- and polybromo-biphenyls (PCBs and PBBs), used as heat transfer fluids and fire retardants; and freons (e.g. CCl_2F_2 and other chlorofluorocarbons) used as refrigeration gases and fire extinguishing agents.

Contributors

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

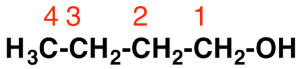
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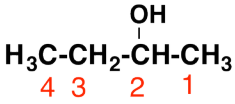
8.3: NOMENCLATURE OF ALCOHOLS

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.

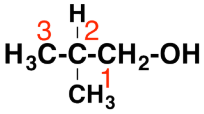
Alcohols are usually named by the first procedure and are designated by an -**ol** suffix, as in ethanol, CH_3CH_2OH (note that a locator number is unnecessary on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(CH_3)_2C{=}CHCH(OH)CH_3$ 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).



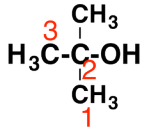
1-butanol
(butyl alcohol)
a 1° alcohol



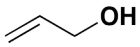
2-butanol
(sec-butyl alcohol)
a 2° alcohol



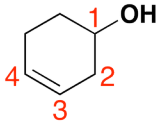
2-methyl-1-propanol
(isobutyl alcohol)
a 1° alcohol



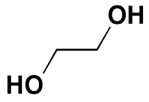
2-methyl-2-propanol
(tert-butyl alcohol)
a 3° alcohol



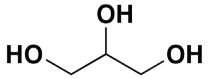
2-propen-1-ol
(allyl alcohol)



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.

Contributors

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

8.3.1: Nomenclature of Alcohols

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8.3.1: Nomenclature of Alcohols

Alcohols are one of the most important functional groups in organic chemistry. Alcohols are a good source of reagents for synthesis reactions. The ability to identify alcohols is important especially when looking at IR and NMR spectra. The alcohol signal is very easy to spot on IR graphs, because they have a strong signal near the 3200 cm^{-1} region.

Introduction

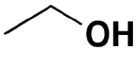
The following is list of some common primary alcohols based on the IUPAC naming system.

Name	Molecular Formula
Methanol (methyl alcohol)	CH_3OH
Ethanol (ethyl alcohol)	C_2H_5OH
Propanol	C_3H_7OH
Butanol	C_4H_9OH
Pentanol	$C_5H_{11}OH$
Hexanol	$C_6H_{13}OH$
Heptanol	$C_7H_{15}OH$
Octanol	$C_8H_{17}OH$

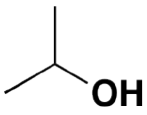
Rules for naming the alcohols

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.**

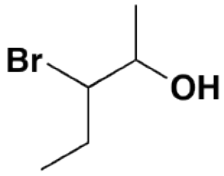
Examples

Ethan**e**: CH_3CH_3 ----->Ethan**ol**: 

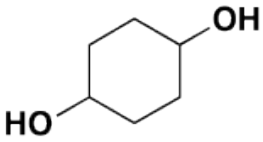
(the alcohol found in beer, wine and other consumed sprits)

Secondary alcohol: 

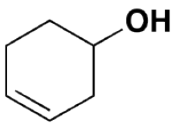
2-propanol

Other functional groups on an alcohol: 

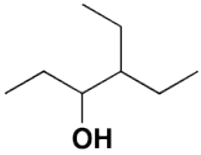
3-bromo-2-pentanol

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)

Outside Links

- http://en.wikipedia.org/wiki/Alcohol#Simple_alcohols

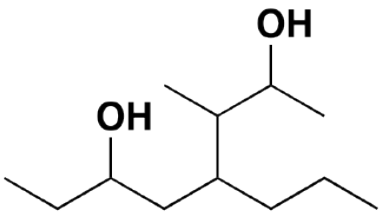
References

- Thurlow, K.J.. Chemical Nomenclature. Netherlands: Kluwer Academic Publishers, 1998.

Problems

Name the following alchols:

1.



3-methyl-4-propyl-octane-2,6-diol

Contributors

- Abhiram Kondajji (UCD)

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8.4: Thiols (Mercaptans)

Objectives

After completing this section, you should be able to

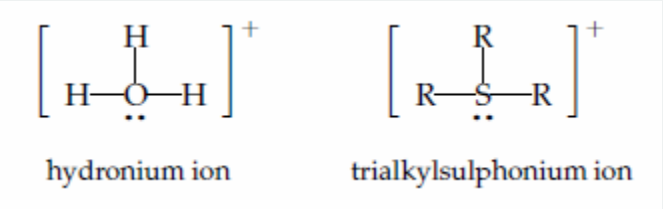
1. Nomenclature and Reactivity
   a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   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

- 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 (see Section 11.5, pages 389-394 of the textbook). 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 trialkylsulphonium 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.

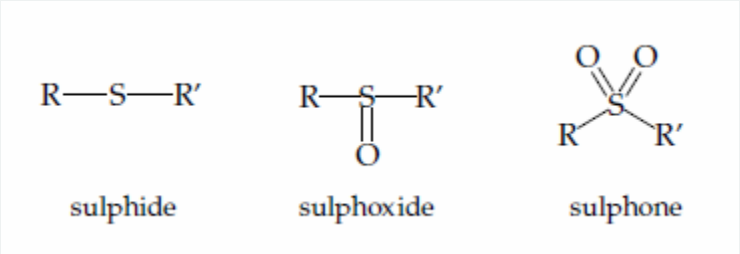


Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Oxygen-containing Compound	Sulphur Analogue
ether, R—O—R′	sulphide, R—S—R′
R—O—, alkoxy group	R—S—, alkylthio group
$R—O^-$, alkoxy anion	$R—S^-$, thiolate anion
alcohol, R—OH	thiol, R—SH
—OH, hydroxy group	—SH, mercapto group
R—O—O—R′, peroxide	R—S—S—R′, disulphide

Table 18.1 Comparison of compounds containing oxygen and sulphur

Note that when we name thiols, we include the "e" of the alkane name. Thus, CH_3CH_2SH is called "ethanethiol," not "ethanthiol."

Oxidation States of Sulfur CompoundsEdit section

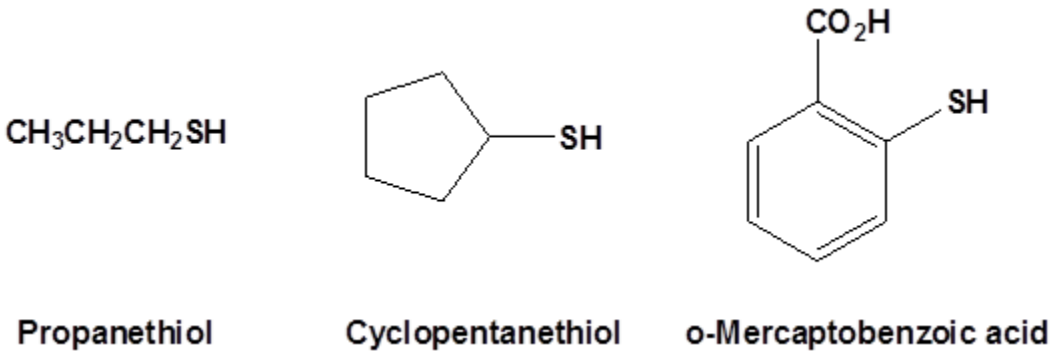
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

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

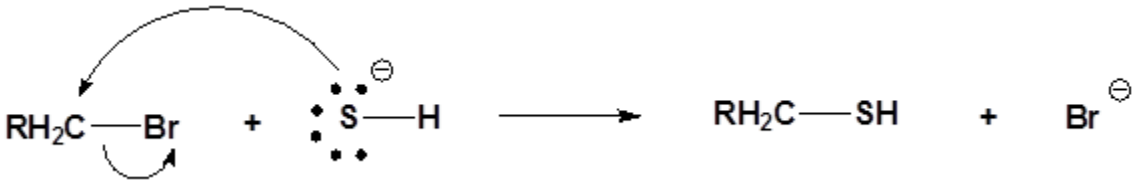
Thiols

Thiols, which are also called mercaptans, are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix *-thiol* is used in place of *-ol*. By itself the -SH group is called a mercapto group.

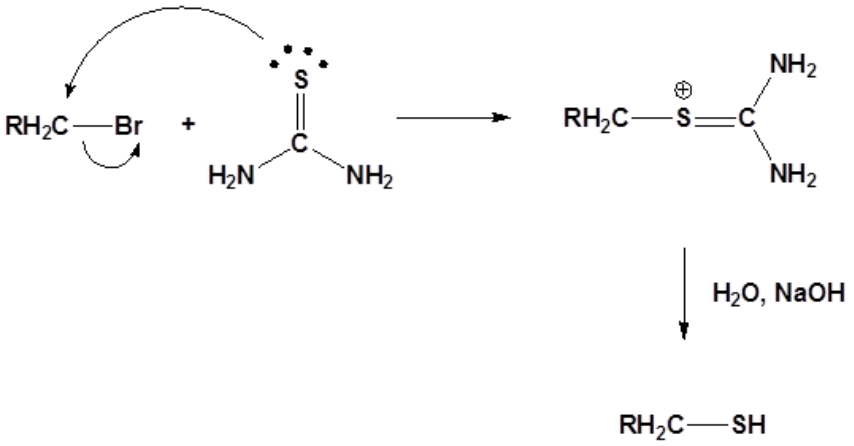


Propanethiol Cyclopentanethiol o-Mercaptobenzoic acid

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a neucleophile in an S_N2 reaction with alkyl halides.

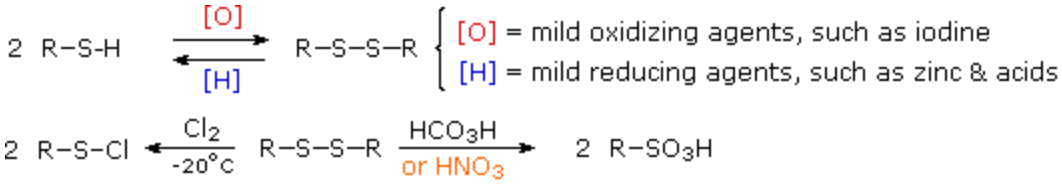


On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



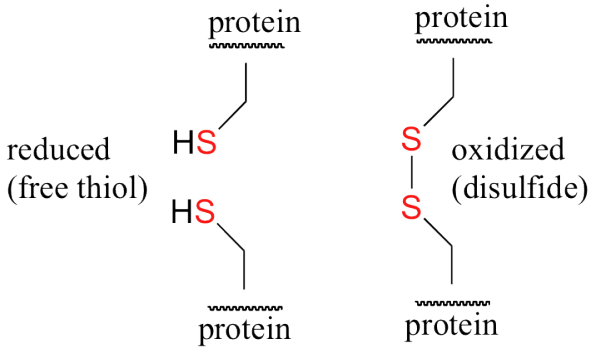
Disulfides

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.



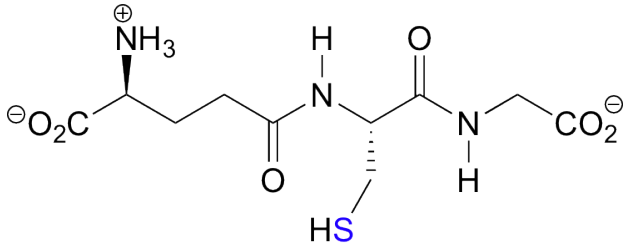
Disulfide bridges in proteinsEdit section

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.

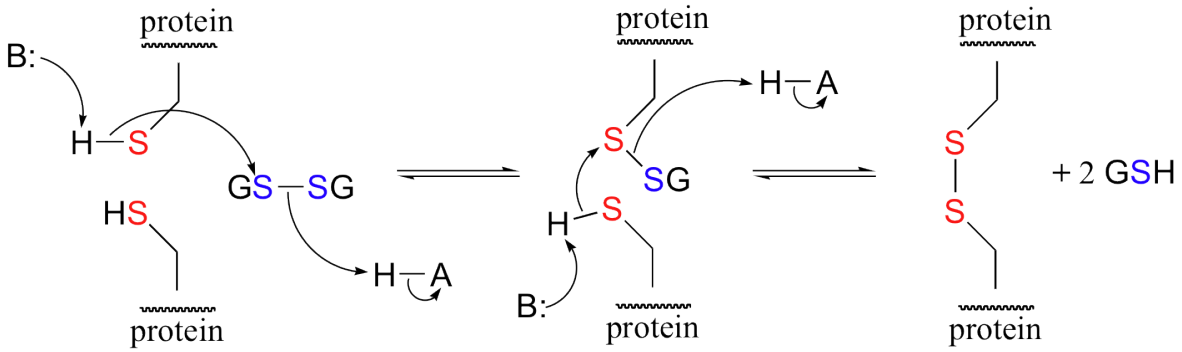
The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure 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 GSSH, 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.

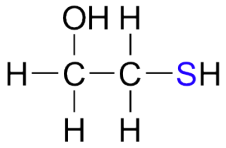


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

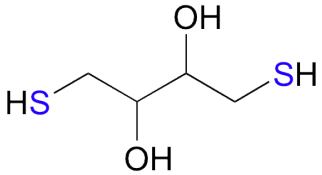
Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to $FADH_2$ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.



β-mercaptoethanol
(BME)



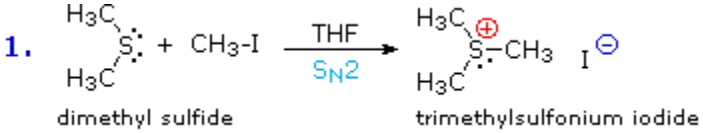
dithiothreitol
(DTT)

Sulfides

Sulfur analogs of ethers are called **sulfides**. The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

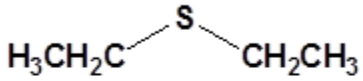
$$R\text{–}S^{(-)}\ Na^{(+)} + (CH_3)_2CH\text{–}Br \longrightarrow (CH_3)_2CH\text{–}S\text{–}R + Na^{(+)}\ Br^{(-)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is 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. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3°-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

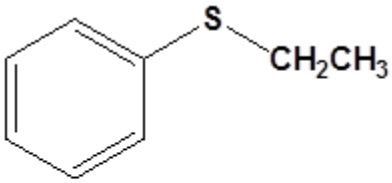


sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance

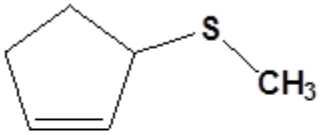
alkylthio is used instead of alkoxy.



Diethyl sulfide



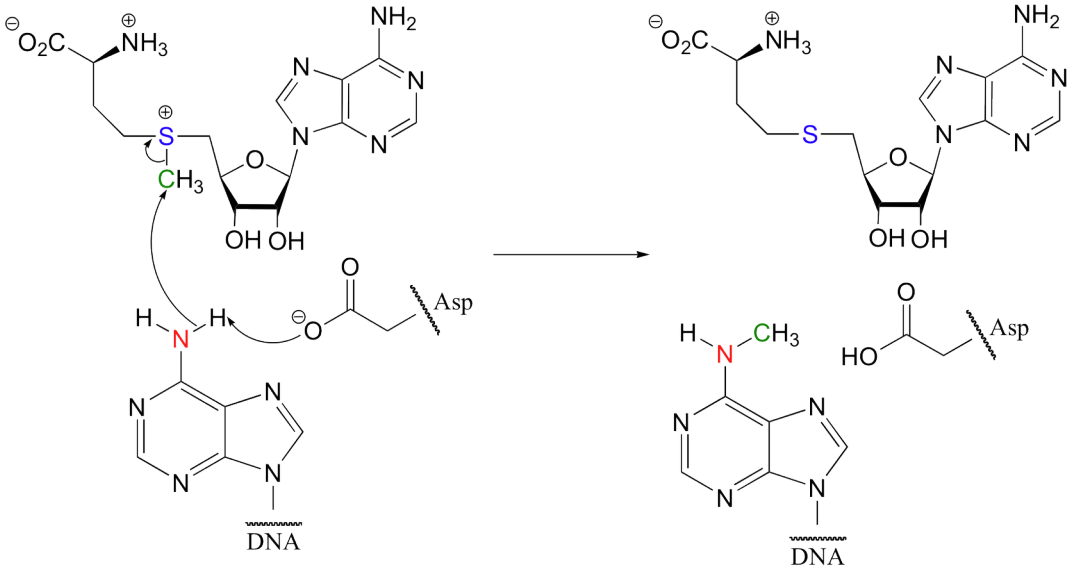
Ethyl phenyl sulfide



3-(Methylthio)cyclopentene

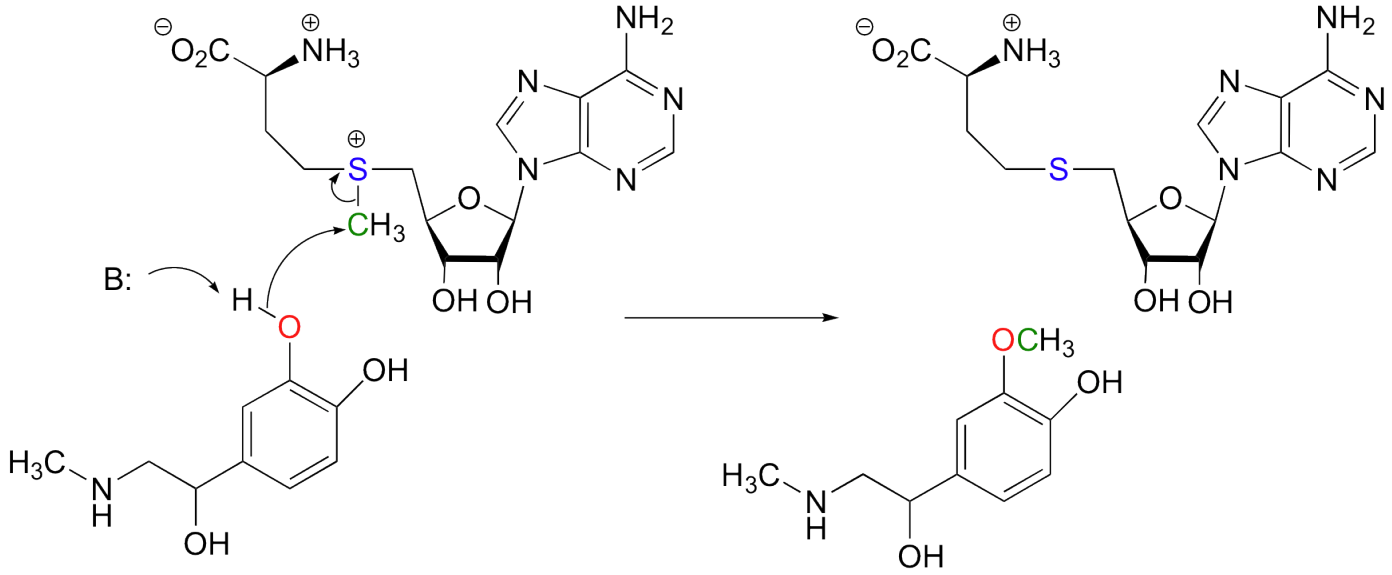
SAM methyltransferasesEdit section

The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



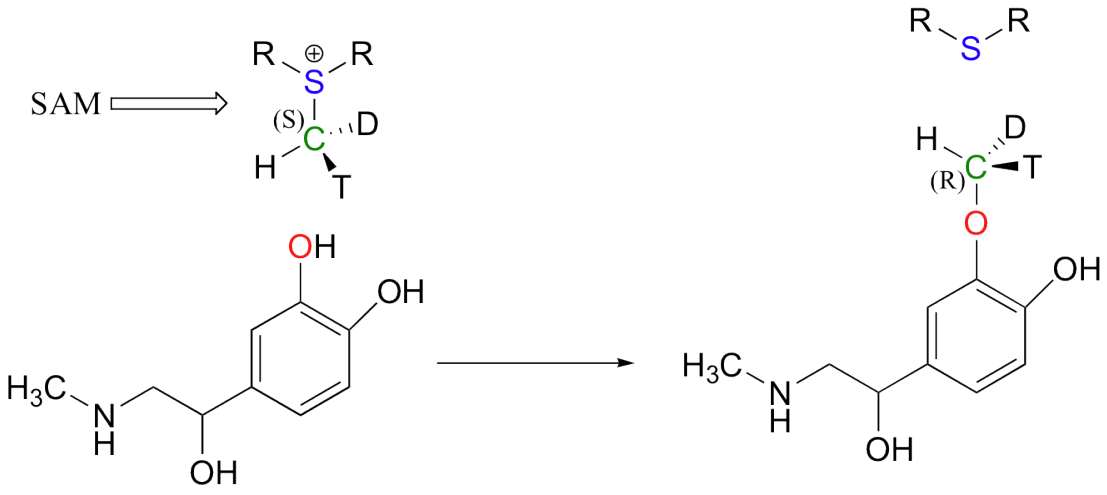
(*Nucleic Acids Res.* **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



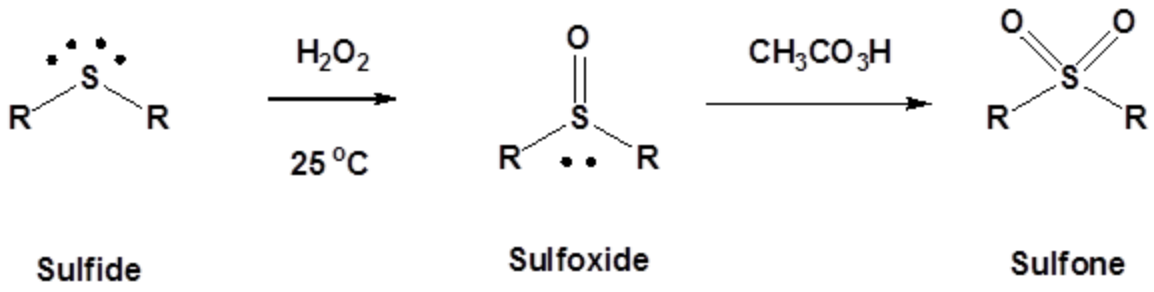
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^3H, T) and deuterium (^2H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255*, 9124).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room termpeature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is polar aprotic solvent.

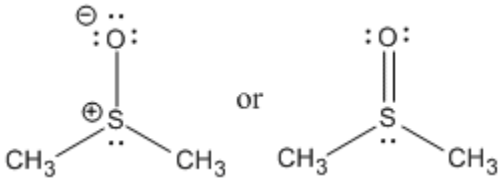


Figure AB16.3. DMSO is a very polar, aprotic solvent.

Contributors

- 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)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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8.5: Nomenclature 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

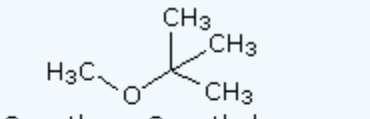
Example 8.5.1

CH_3-CH_2-O-CH_3 is called ethyl methyl ether or methoxyethane.

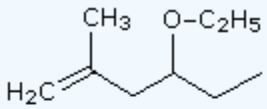
The smaller, shorter alkyl group becomes the alkoxy substituent. The larger, longer alkyl group side becomes the alkane base name. Each alkyl group on each side of the oxygen is numbered separately. The numbering priority is given to the carbon closest to the oxgen. The alkoxy side (shorter side) has 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 8.5.2

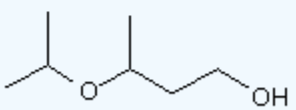
- $CH_3CH_2OCH_2CH_3$, diethyl ether (sometimes referred to as just ether)
- $CH_3OCH_2CH_2OCH_3$, ethylene glycol dimethyl ether (glyme).



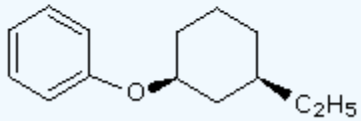
2-methoxy-2-methylpropane
tert-butyl methyl ether



4-ethoxy-2-methyl-1-hexene



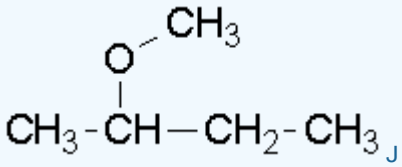
3-isopropoxy-1-butanol



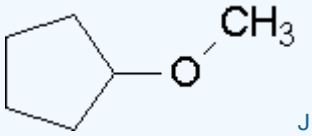
cis-1-ethyl-3-phenoxycyclohexane

Exercises 8.5.2

Try to name the following compounds using these conventions:



J



J

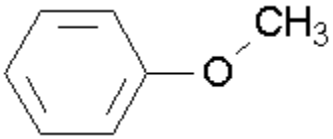
Try to draw structures for the following compounds:

- 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**

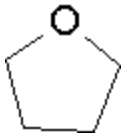


1,2-epoxyethane, ethylene oxide, dimethylene oxide, oxacyclopropane,

- **furan (this compound is aromatic)**

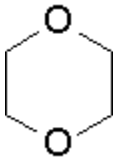


tetrahydrofuran



oxacyclopentane, 1,4-epoxybutane, tetramethylene oxide,

- **dioxane**



1,4-dioxacyclohexane

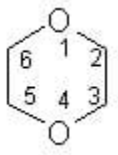
Exercise 8.5.2

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

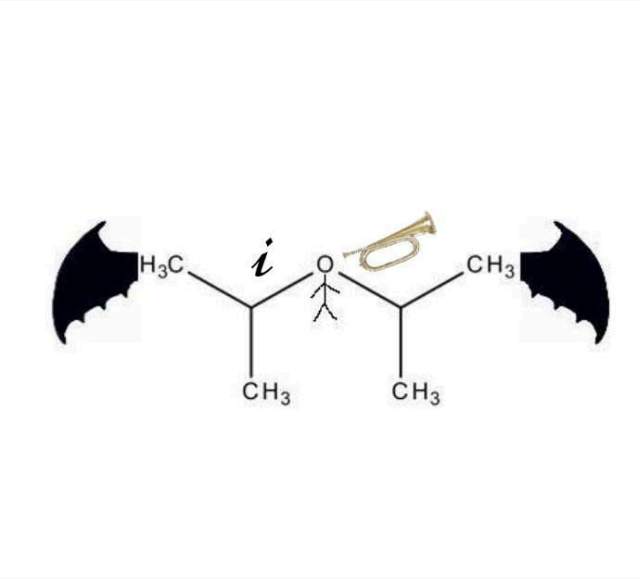
Name the following ethers:

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 8.5.3

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)

Answers

Exercise 8.5.3

A one-eyed one-horned flying propyl people ether

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8.6: SOLVENTS

Solvents

Introduction

The vast majority of chemical reactions are performed in solution. The solvent fulfills several functions during a chemical reaction. It solvates the reactants and reagents so that they dissolve. This facilitates collisions between the reactant(s) and reagents that must occur in order to transform the reactant(s) to product(s). The solvent also provides a means of temperature control, either to increase the energy of the colliding particles so that they will react more quickly, or to absorb heat that is generated during an exothermic reaction. The selection of an appropriate solvent is guided by theory and experience. Generally a good solvent should meet the following criteria.

- It should be inert to the reaction conditions.
- It should dissolve the reactants and reagents.
- It should have an appropriate boiling point.
- It should be easily removed at the end of the reaction.

The second criterion invokes the adage "Like dissolves like". Non-polar reactants will dissolve in non-polar solvents. Polar reactants will dissolve in polar solvents. For our purposes there are three measures of the polarity of a solvent:

1. Dipole moment
2. Dielectric constant
3. Miscibility with water

Molecules with large dipole moments and high dielectric constants are considered polar. Those with low dipole moments and small dielectric constants are classified as non-polar. On an operational basis, solvents that are miscible with water are polar, while those that are not are non-polar; remember the saying "Oil and water don't mix".

Chemists have classified solvents into three categories according to their polarity.

1. polar protic
2. dipolar aprotic
3. non-polar.

Polar Protic Solvents

Let's start with the meaning of the adjective protic. In the context used here, protic refers to a hydrogen atom attached to an electronegative atom. For our purposes that electronegative atom is almost exclusively oxygen. In other words, polar protic solvents are compounds that can be represented by the general formula ROH. The polarity of the polar protic solvents stems from the bond dipole of the $\mathrm{O-H}$ bond. The large difference in electronegativities of the oxygen and the hydrogen atom, combined with the small size of the hydrogen atom, warrant separating molecules that contain an OH group from those polar compounds that do not. Examples of polar protic solvents are water (HOH), methanol ($\mathrm{CH_3OH}$), and acetic acid ($\mathrm{CH_3CO_2H}$).

Dipolar Aprotic Solvents

Here the key word is aprotic. In the context used here, aprotic describes a molecule that does not contain an $\mathrm{O-H}$ bond. Solvents in this class all contain a bond that has a large bond dipole. Typically this bond is a multiple bond between carbon and either oxygen or nitrogen. Most dipolar aprotic solvents contain a $\mathrm{C-O}$ double bond. Examples are acetone, $\mathrm{(CH_3)_2C{=}O}$, and ethyl acetate, $\mathrm{CH_3CO_2CH_2CH_3}$.

Non-Polar Solvents

Non-polar solvents are compounds that have low dielectric constants and are not miscible with water. Examples include benzene ($ceC6H6$), carbon tetrachloride (CCl_4), and diethyl ether ($CH_3CH_2OCH_2CH_3$).

Table 1 presents a list of solvents that are commonly used in chemical reactions. The boiling point, dipole moment, and dielectric constant of each solvent is included. All of these solvents are clear, colorless liquids. The hydrogen atoms of the protic solvents are highlighted in red.

Click on the name of a solvent in Table 1 to load a model of it from the MO menu of the JSMol VMK. Then, use the Model Tools to get a sense of the compound's polarity by loading partial charge information and/or the electrostatic potential map for the solvent in question.

Name	Structure	bp, °C	dipole moment	dielectric constant
water	$HO-H$	100	1.85	80
methanol	CH_3O-H	68	1.70	33
ethanol	CH_3CH_2O-H	78	1.69	24.3
1-propanol	$CH_3CH_2CH_2O-H$	97	1.68	20.1
1-butanol	$CH_3CH_2CH_2CH_2O-H$	118	1.66	17.8
formic acid	formic acid	100	1.41	58
acetic acid	acetic acid	118	1.74	6.15
formamide	formamide	210	3.73	109
....	....	....	....	....
acetone	acetone	56	2.88	20.7
tetrahydrofuran	THF	66	1.63	7.52
2-butanone (MEK)	MEK	80	2.78	18.5
ethyl acetate	ethyl acetate	78	1.78	6.02
acetonitrile	$H_3C-C\equiv N$	81	3.92	36.6
dimethyl formamide (DMF)	DMF	153	3.82	38.3
dimethyl sulfoxide (DMSO)	DMSO	189	3.96	47.2
....	....	....	....	....
hexane	$CH_3(CH_2)_4CH_3$	69	----	2.02
benzene	benzene	80	0	2.28
diethyl ether	$CH_3CH_2OCH_2CH_3$	35	1.15	4.34
methylene chloride	CH_2Cl_2	40	1.60	9.08
carbon tetrachloride	CCl_4	76	0	2.24

Table 1: *Common Solvents for Organic Reactions*

It should be apparent from the table that there are no sharp boundaries between polar and non-polar solvents, at least if you use dielectric constants or dipole moments as a measure. There is, however, a correlation between chemical structure and dielectric constant that provides a useful way to think about polarity. Look at the series of polar protic compounds water, methanol, ethanol, 1-propanol, and 1-butanol. As Figure 1 demonstrates, each compound in the series differs from the ones before and after it by one CH_2 group.

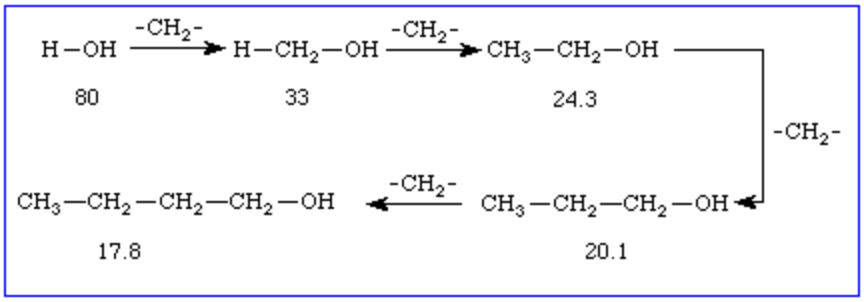


Figure 1: *Structure-Property Correlations*

As the number of CH_2 groups in ROH increases, the dielectric constant decreases. If you think of these molecules as containing a polar component (OH) and a non-polar component (R), then the polarity of a compound reflects the balance between these two components. As the relative amount of hydrocarbon character increases, the polarity decreases. Note that hexane, which is 100% hydrocarbon, is the least polar solvent in the table.

Exercise 1 Classify each of the following solvents as polar protic (P) , dipolar aprotic (D) , or non-polar (N) by entering the appropriate letter in the text field next to each structure.

$CHCl_3$	C_6H_5Cl	$HCO_2CH_2CH_3$
HFA	HFIPA	HMPA
dioxa...	NH_2NH_2	TFAA
CF_3CO_2H	$C_6H_5CH_3$	CH_3CH_2CN

Now that we've looked at the various types of solvents that you can expect to see, let's examine how those solvents interact with solutes.

Contributors

- Otis Rothenberger (Illinois State University) and Thomas Newton University of Southern Maine)

8.6.1: Boiling Points

8.6.2: Solvent-Solutes

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8.6.1: Boiling Points

Correlating Polarity and Physical Properties: Boiling Points

Introduction

Understanding the nature of intermolecular interactions enables us to understand many chemical and physical phenomena. In fact, it was the investigation of such phenomena that led to our understanding of intermolecular interactions in the first place. In the discussion that follows, we will refer to Coulomb's law several times, so it may be worthwhile to review the mathematical statement of that law:

Coulomb's Law

$$F_c \propto \frac{q_1 q_2}{r^2}$$

In terms of intermolecular interactions, the law says that the force of attraction between two molecules increases as the distance between them decreases. It also states that the force of attraction increases as the magnitude of the opposite charges increase.

Boiling Points

In the gas phase, the distance between molecules is large in comparison to the size of the molecules. Since the distance is very large, Coulomb's law tells us that the force of attraction between the molecules is very small. In gases it is essentially zero.

In the liquid state, the separation between molecules is much smaller, and the interactions between them much larger than in the gas phase. The boiling point of a liquid is a measure of the amount of energy required to overcome these intermolecular Coulombic attractions. Let's compare the boiling points of three small molecules, dihydrogen, methane and water. Dihydrogen boils at -259°C, methane boils at -164°C, water at +100°C. Obviously the intermolecular forces holding water molecules together are much stronger than those holding dihydrogen or methane molecules together. If we assume that in the liquid phase the intermolecular distances are about the same for all three molecules, then it must be differences in the values of q_1 and q_2 that are responsible for the differences in boiling points. It is important to remember that in this situation q_1 and q_2 are the charges associated with the bond dipoles. Figure 1 serves as a reminder of the interactions that we are considering. Here X represents any atom or group and the dashed red lines indicate the Coulombic attractions between opposite charges.

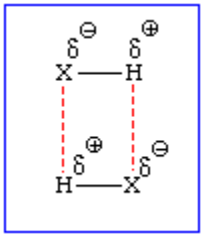


Figure 1: *Even Partial Charges Attract*

Let's compare water and methane first. Because oxygen is more electronegative than carbon, an $\mathrm{O-H}$ bond has a larger bond dipole than a $\mathrm{C-H}$ bond. Hence the force of attraction between two water molecules is greater than it is between two methane molecules. Water has the higher boiling point.

Now let's compare methane and dihydrogen. We could invoke the same argument here that we did in comparing methane and water. The $\mathrm{C-H}$ bond has a larger bond dipole than the $\mathrm{H-H}$ bond. Therefore, methane has the higher boiling point. The real question is why does dihydrogen become a liquid at any temperature? It has no permanent bond dipole, so the values of q_1 and q_2 should be zero, and the force of attraction between dihydrogen molecules should also be zero. The key word here is permanent. As we have seen, the motion of the electrons in the H-H bond induces transient dipoles. The distortion of the electron

distribution in one molecule of dihydrogen induces complementary distortions in other , nearby dihydrogen molecules. It is this fleeting development of charge that we call upon to rationalize the fact that dihydrogen does finally liquefy at -259°C.

Finally, let's consider the boiling points of a series of alkanes and a comparable series of alcohols. Figure 2 presents plots of the boiling points of a homologous series of linear alkanes and linear alcohols.

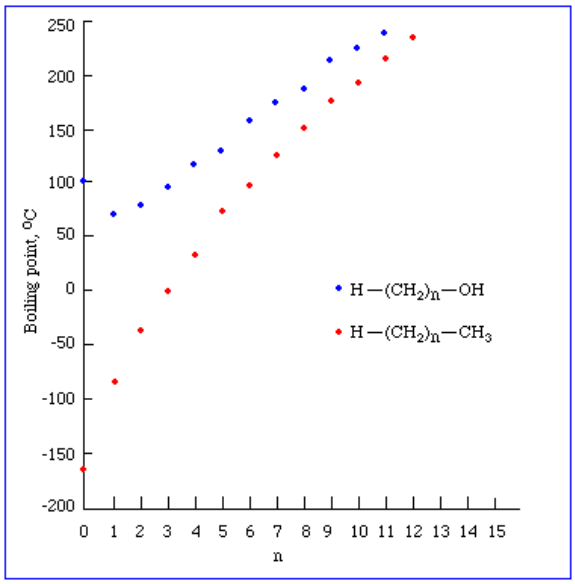


Figure 2: *Comin' to a Boil*

There are several trends in this figure that are noteworthy.

- First, it's obvious that alcohols have higher boiling points than alkanes of comparable size.
- Second, the differences in boiling points become smaller as n increases. (When n = 1, the difference in boiling points is 156°C. When n = 10, the difference is 26 ^{o}C.)
- Third, in both series, the boiling points increase as n increases.

Exercise 1 What factor is responsible for the first trend?

Figure 3 offers a pictorial rationalization of the correlation between boiling points and n.

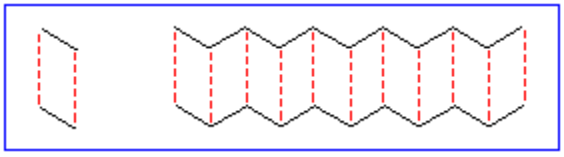


Figure 3: *Touch Me, Touch Me*

Here the dashed red lines represent the induced dipole-induced dipole interactions between molecules. The more interactions, the higher the boiling point.

Finally, it's important to understand that the different types of interactions we have been discussing are not mutually exclusive. It is possible to have several types of intermolecular interactions occuring simultaneously. In discussing the solubility of 1-bromobutane in ethanol, we alluded to the idea that there were intermolecular forces in addition to dipole-dipole interactions. Figure 4 illustrates the idea.

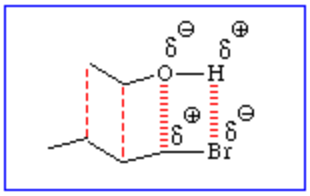


Figure 4: *Different Strokes*

Here the narrow dashed red lines represent induced dipole-induced dipole interactions, while the broad dashed lines highlight the stronger dipole-dipole interactions.

Contributors

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8.6.2: Solvent-Solutes

Solvent-Solute Interactions

Introduction

Now that you understand how chemists classify solvents, it's time to consider a similar classification system for the compounds that dissolve in them, i.e. for solutes. At the risk of oversimplifying, we will divide solutes into 3 groups:

1. ionic
2. polar covalent
3. non-polar covalent

We will use the adage "like dissolves like" as our guide to understanding the forces that enable a solute to dissolve in a solvent. Remember that this adage is really a variation on the statement of Coulomb's law that says "opposite charges attract". The force of attraction depends upon the nature of the solvent and the nature of the solute. We will look at four types of interactions:

- charge-dipole
- dipole-dipole
- dipole-induced dipole
- induced dipole-induced dipole

It is important here to distinguish between intermolecular interactions and the intramolecular interactions that we call covalent bonding. The strengths of covalent sigma bonds range from a low of about 50 kcal/mol to a high of around 125 kcal/mol. The interactive forces described below range from 2-10 kcal/mol. Because they are so much less than typical covalent bonding forces, these interactions are sometimes called secondary bonding interactions.

Charge-Dipole Interactions

This is the classic case of an ionic salt such as sodium chloride dissolving in water. Figure 1 presents a picture of the Coulombic interactions between a positively charged sodium ion and 6 water molecules as well as the corresponding interactions between a negatively charged chloride ion and 6 other water molecules. In the case of the sodium ion, the positive charge attracts the negative end of each water molecule's dipole. The negative charge of the chloride ion attracts the positive end of the $\mathrm{O{-}H}$ bond dipole. The straight dashed lines indicate these charge-dipole interactions. Each ion is encased in a shell of water molecules. The shells insulate the ions from each other, allowing the oppositely charged particles to separate. Molecules that have high dielectric constants are good electrical insulators because of their ability to shield the oppositely charged ions in this way.

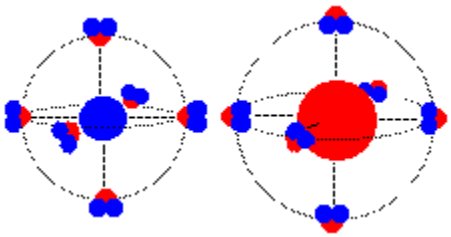


Figure 1: *You're All Wet*

The image of solutes surrounded by solvents is a useful one to keep in mind. However, it does not lend itself to a compact representation of intermolecular interactions. We'll use an alternative notation to depict dipole-dipole interactions.

Dipole-Dipole Interactions

Equation 1 describes the dehydrobromination of 1-bromobutane, a classic example of a 1,2-elimination reaction.

$$CH_3CH_2CH_2CH_2Br + KOH \longrightarrow CH_3CH_2CH{=}CH_2 + KBr + H_2O(1)$$

As an experimentalist you would have to select an appropriate solvent for this reaction. Considering only solubility for the moment, you would want a solvent in which both the 1-bromobutane and the KOH would dissolve. While KOH is very soluble in water, 1-bromobutane is not. Conversely, while 1-bromobutane will dissolve in hexane, KOH is completely insoluble. What's needed is a solvent that has just the right balance of polar and non-polar character. In fact, both methanol and ethanol are suitable choices.

Figure 2 uses the δ^+-δ^- notation to focus on the Coulombic attraction between the $C{-}Br$ bond dipole of 1-bromobutane and the $H{-}O$ bond dipole of an ethanol molecule. Because the opposite charges that are attracting each other are only partial charges, dipole-dipole interactions are inherently weaker than charge-dipole interactions.

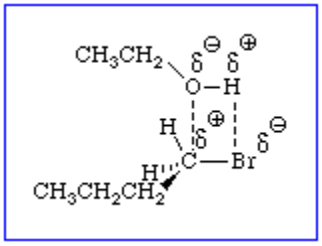


Figure 2: *Dipole-Dipole Interactions*

When one of the bonds involved in a dipole-dipole interaction is an $O{-}H$ bond, the interaction is given the special, but common, designation hydrogen bonding.

As we'll see shortly, there are additional intermolecular interactions between these two molecules. Before we look at them, however, we're going to consider intermolecular forces that are even weaker than dipole-dipole interactions.

Dipole-Induced Dipole Interactions

Polar protic and dipolar aprotic molecules both have permanent bond dipoles. Non-polar molecules do not, or if they do, their dipole moments are very small. However, when a molecule with a permanent bond dipole comes close to one with no bond dipole, the electric field associated with the permanent dipole can temporarily distort the electron distribution in the non-polar molecule, thereby inducing a temporary bond dipole. This concept is animated in Figure 3.

DipoleInuced

Figure 3: *Try To See Things My Way*

Dipole-induced dipole interactions are invoked when a non-polar molecule dissolves in a polar or a dipolar solvent. The assumption is that the solute dissolves because the forces of attraction between the solvent and the solute are stronger than the intermolecular forces holding the non-polar solute molecule together. The interactions between non-polar molecules are the weakest secondary bonding forces we will consider. They are called induced dipole-induced dipole interactions or London forces.

Induced Dipole-Induced Dipole Interactions

Imagine that you have a camera with macro lens that allows you to see electrons and a shutter speed so fast it can freeze their motion. If you were to take a series of slides of the electrons in dihydrogen, each slide would be different because each picture would catch the electrons at different positions between the hydrogen nuclei. If you superimposed the slides, the composite image would show that electron distribution between the two nuclei was symmetrical, i.e. that dihydrogen is non-polar. However, each individual slide would reveal the electron distribution between the nuclei was not symmetrical. In other words, there is an instantaneous dipole moment induced by the movement of the electrons. Furthermore, the induced dipole in one molecule influences the electron distribution in other, nearby molecules. This is called an induced dipole-induced dipole interaction. Figure 4 simulates this process.

LondonForces

Figure 4: *Dance with Me Henry*

Since these induced dipoles are transient, the intermolecular interactions between them, the London forces, are very weak. Chemists invoke these very weak forces to rationalize the interactions between non-polar molecules. We'll see an example of that when we discuss the relationship between intermolecular interactions and boiling points.

Contributors

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8.7: Acidity of Alcohols and Phenols

Overview - Aqueous vs Organic Solvents

In aqueous solutions, phenols are weakly acidic and lower the pH of a solution. Sodium hydroxide can be used to fully deprotonate a phenol. Water soluble alcohols do not change the pH of the solution and are considered neutral. Aqueous solutions of sodium hydroxide can NOT deprotonate alcohols to a high enough concentration to be synthetically useful.

In solutions of organic solvents, more extreme reaction conditions can be created. Sodium metal can be added to an alcohol in an organic solvent system to fully deprotonate the alcohol to form alkoxide ions.

Acidity 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:

$$C_2H_5OH + Na^{\oplus}NH_2^{\ominus} \rightleftharpoons C_2H_5O^{\ominus}Na^{\oplus} + NH_3$$

sodium amide (sodamide) — sodium ethoxide

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

$$C_2H_5OH + Na^{\oplus}H^{\ominus} \longrightarrow C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

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 lies more on the side of ROH as R is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered less acidic than ethanol:

$$ROH + OH^- \rightleftharpoons RO^- + HOH \tag{8.7.1}$$

However, in the gas phase the order of acidity is reversed, and the equilibrium position for lies increasingly on the side of the alkoxide as R is changed from primary to secondary to tertiary, tert-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. In solution, the larger 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:

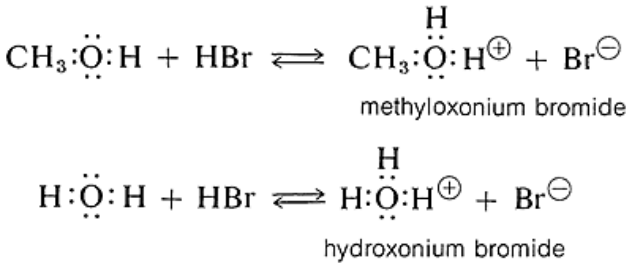


Acidity of alcohols therefore decreases as the size of the conjugate base increases. However, “naked” gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is.

Basicity of Alcohols

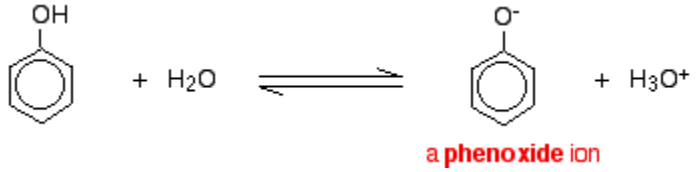
Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen

bromide and water:

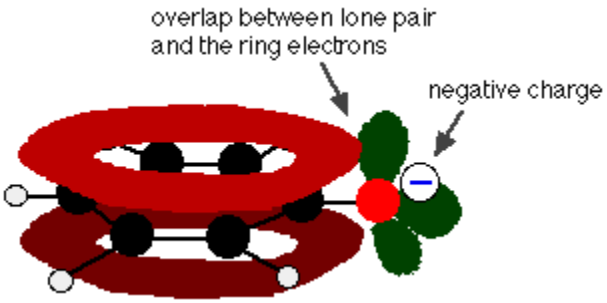


Acidity of Phenol

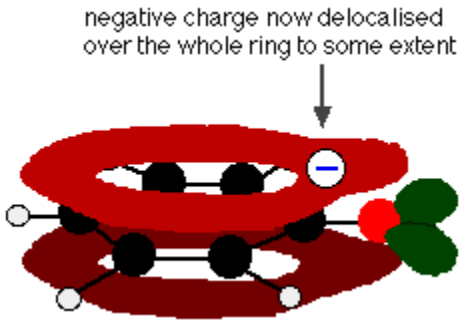
Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even 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:



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.

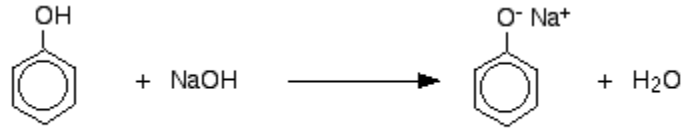


Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that

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.

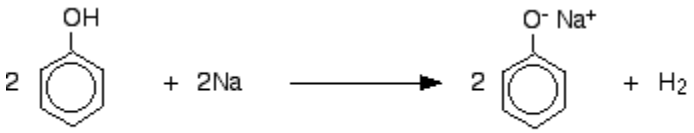
The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer 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.



sodium phenoxide

In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

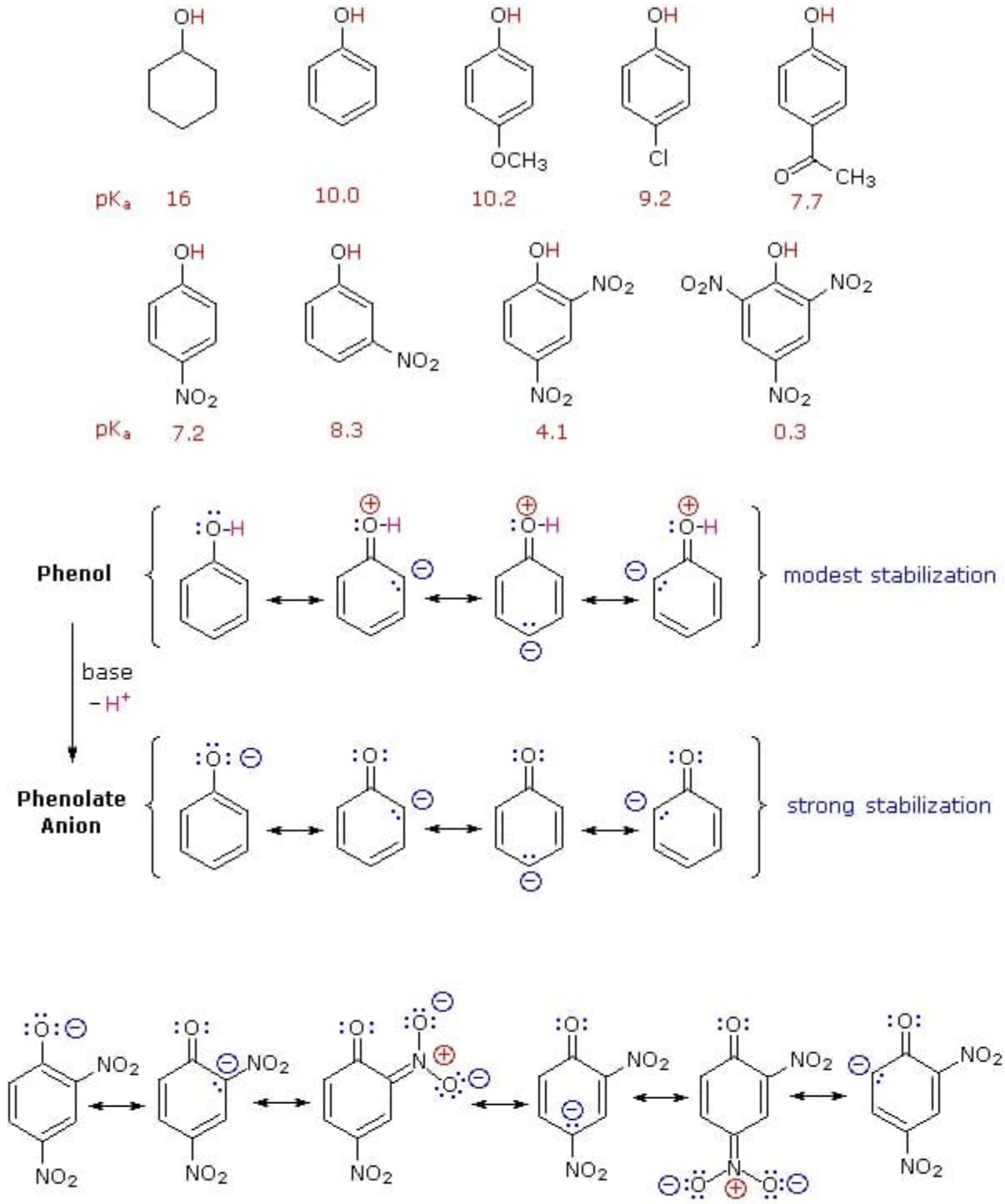
Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off. The mixture left in the tube will contain sodium phenoxide.



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.

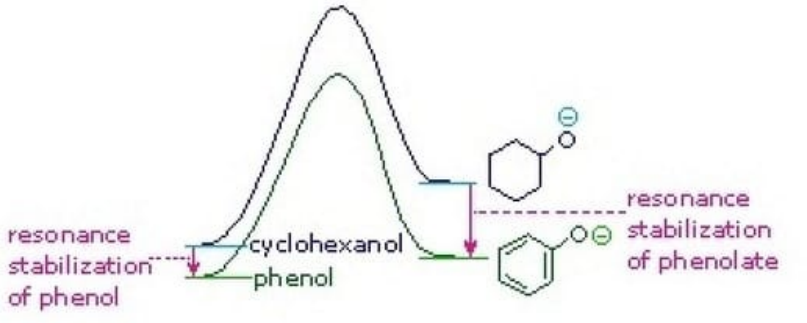


Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents

Comparing the Acidity of Alcohols with Phenols

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

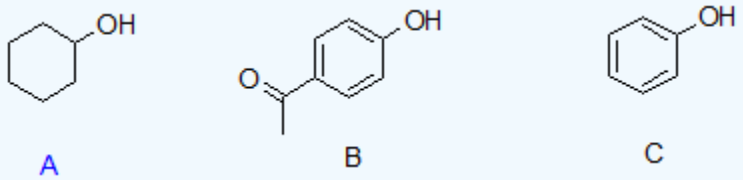
for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.



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.

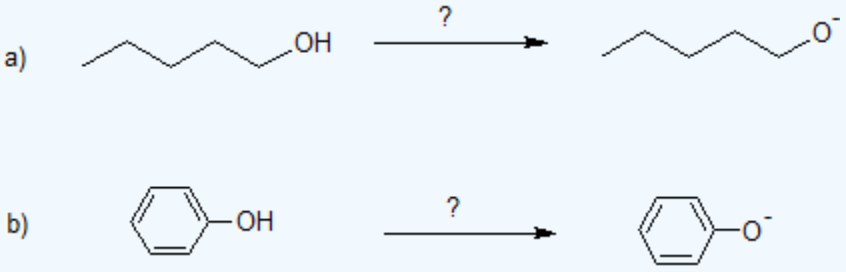
Exercise

9. Arrange the following compounds in order of decreasing acidity when they are in solution.



A B C

10. Specify the base needed to deprotonate each reactant.



Answer available at the end of this section.

Contributors

- Prof. Steven Farmer (Sonoma State University)

- 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

Exercise

9. B > C > A

10. a) Na or NaH or NNH_2

b) NaOH or KOH or LiOH

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8.8: Grignard and Organolithium Reagents

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**

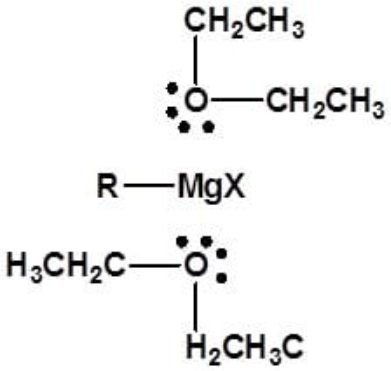
$$\mathrm{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{8.8.1}$$

- **A Grignard Regent**

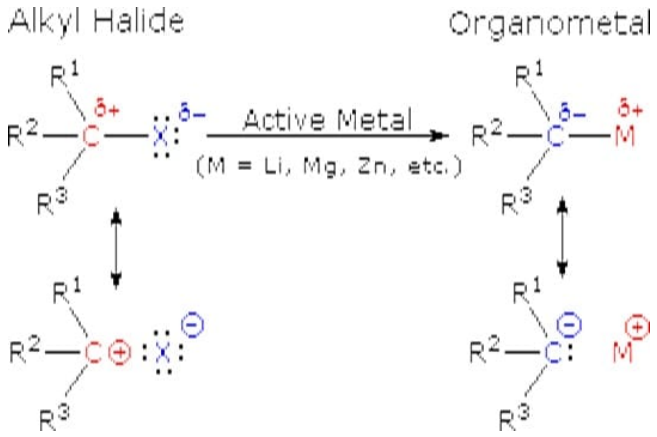
$$\mathrm{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{8.8.2}$$

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.

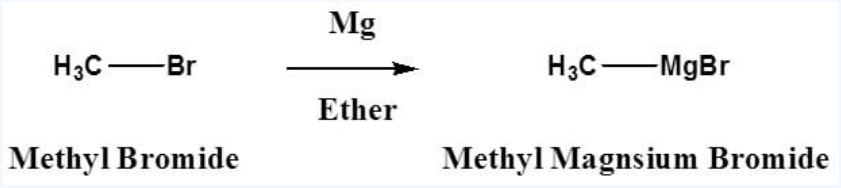
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent 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.

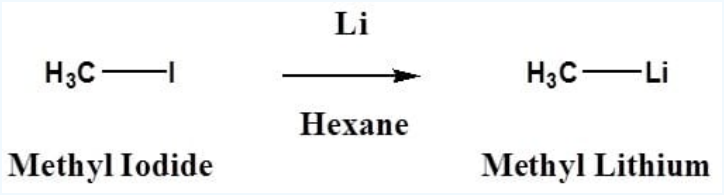


These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

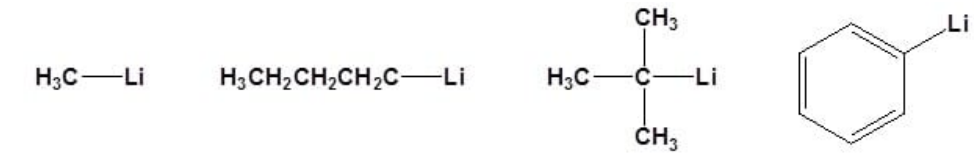


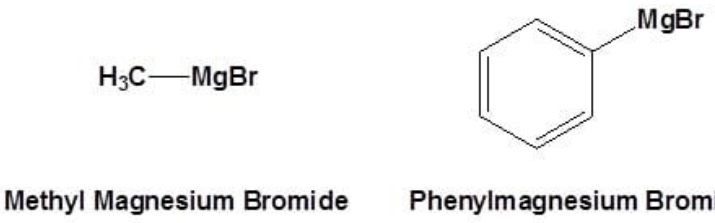
Example 8.8.1:





Common Organometallic Reagents

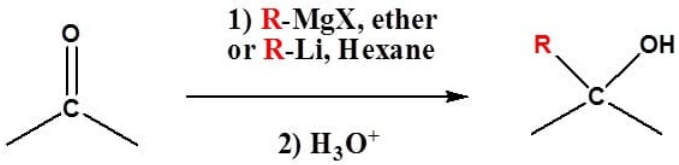




Reaction of Organometallic Reagents with Various Carbonyls

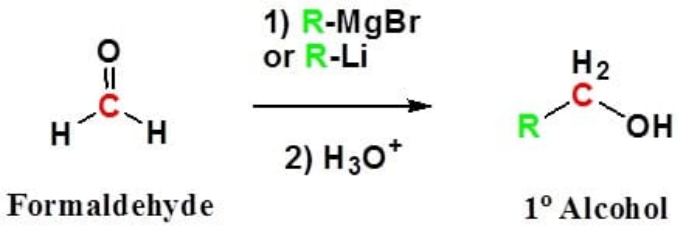
Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the

carbonyl to form alcohols.

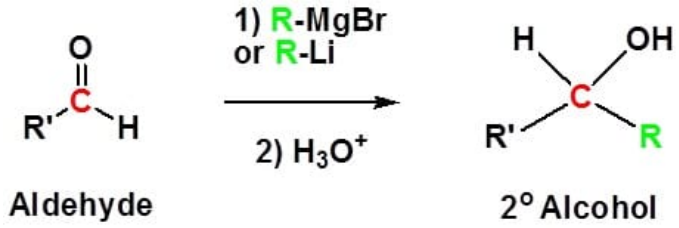


Both Grignard and Organolithium Reagents will perform these reactions.

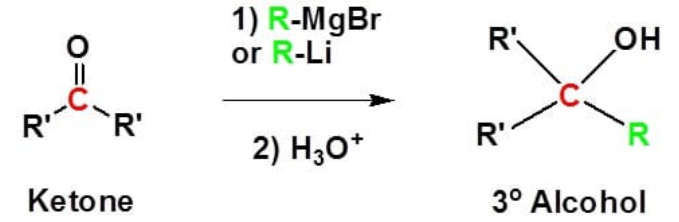
Addition to formaldehyde gives 1° alcohols



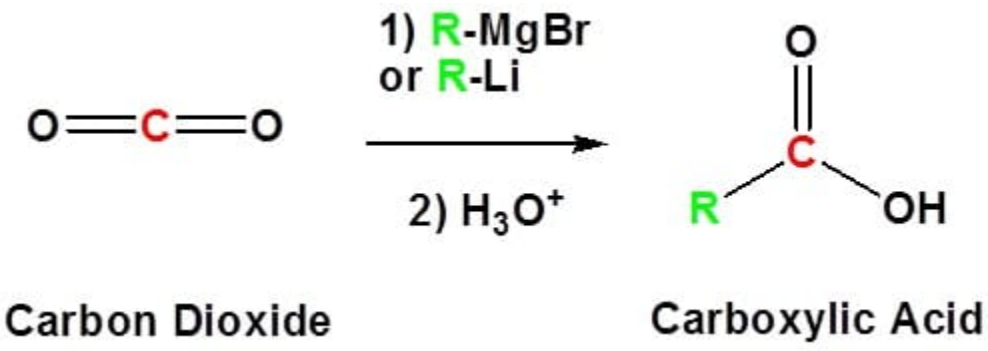
Addition to aldehydes gives 2° alcohols



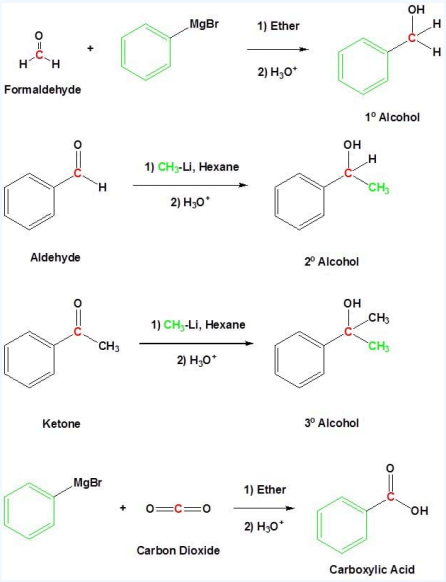
Addition to ketones gives 3° alcohols



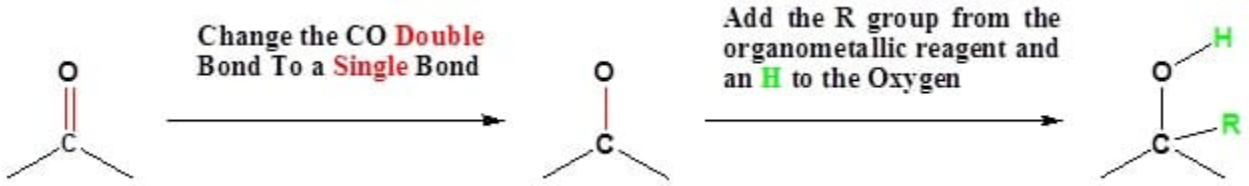
Addition to carbon dioxide (CO_2) forms a carboxylic acid



Example 8.8.1:



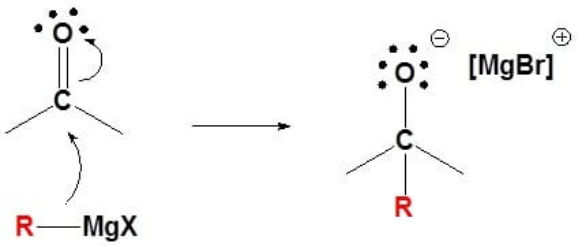
Going from Reactants to Products Simplified



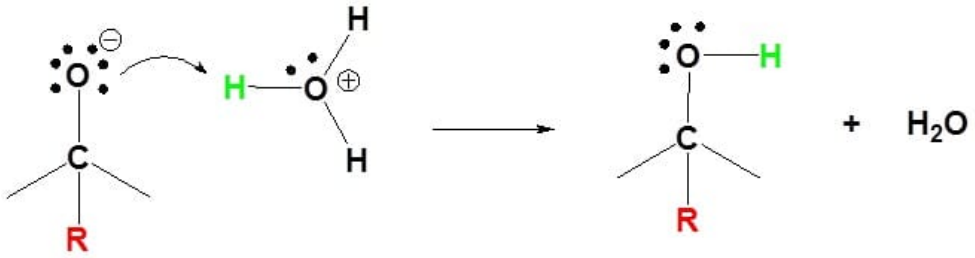
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown; the mechanism for an organometallic reagent is the same.

1) Nucleophilic attack

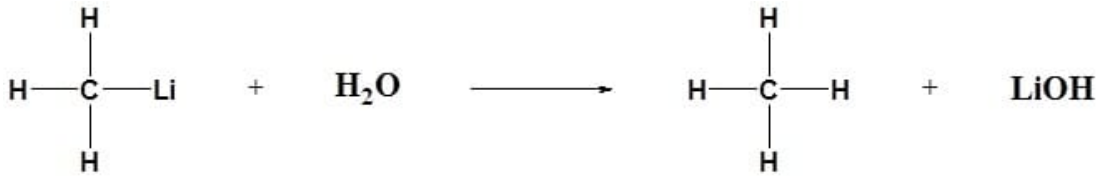


2) Protonation

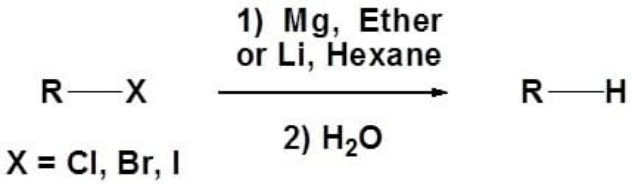


Organometallic Reagents as Bases

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.

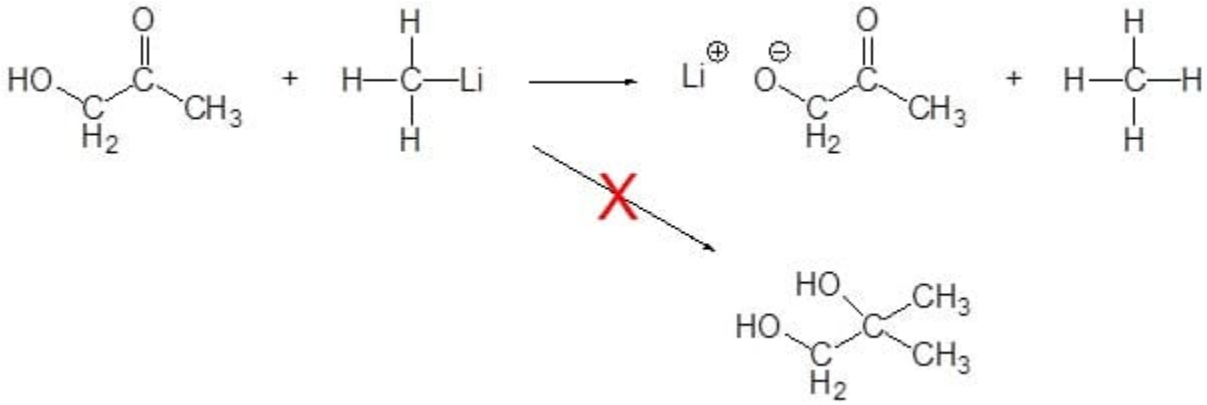


In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



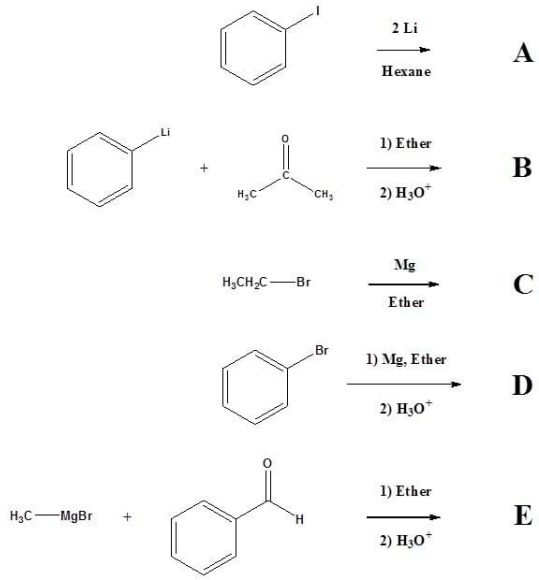
Limitation of Organometallic Reagents

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.

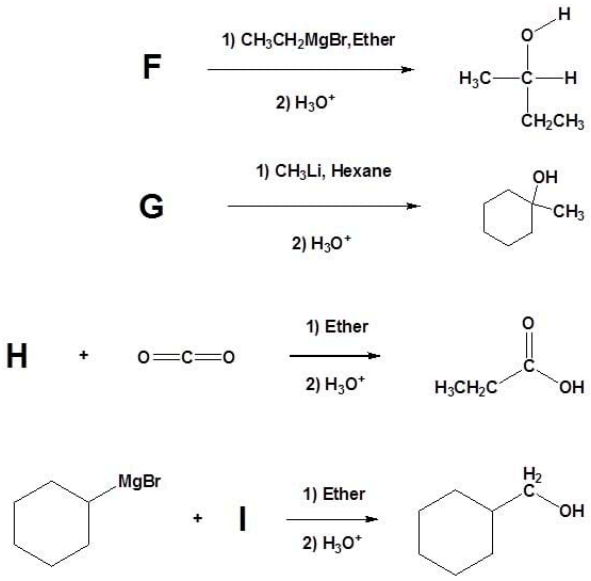


Problems

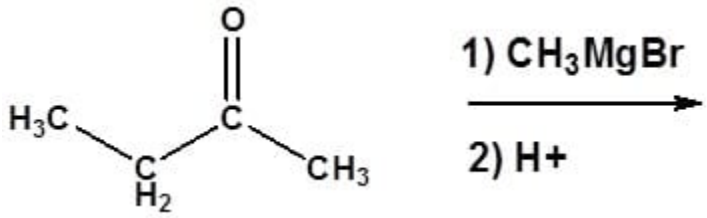
1) Please write the product of the following reactions.



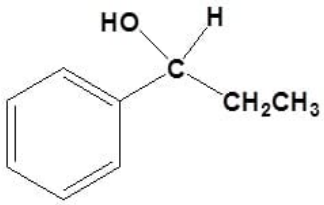
2) Please indicate the starting material required to produce the product.



3) Please give a detailed mechanism and the final product of this reaction

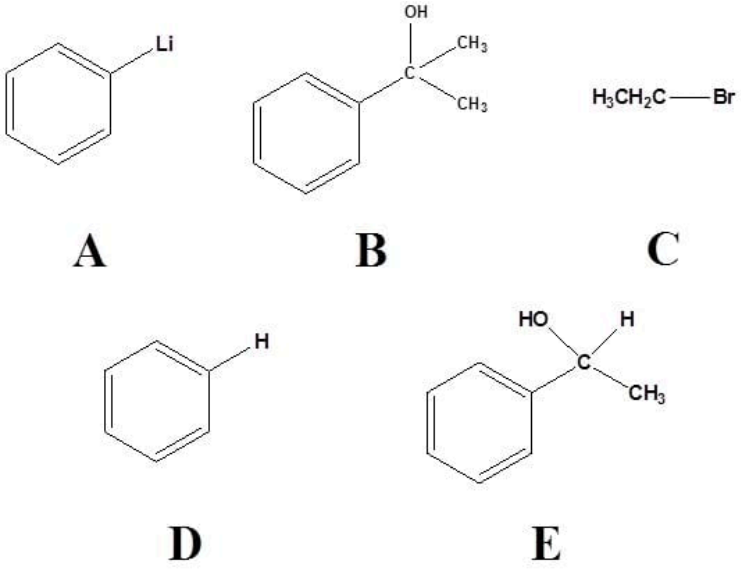


4) Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.

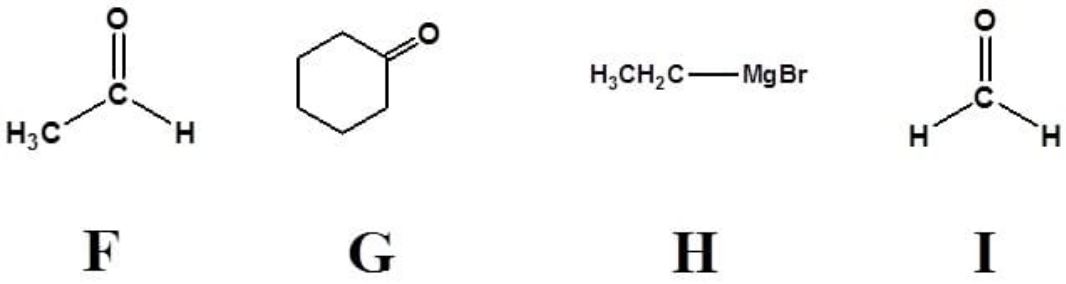


Answers

1)

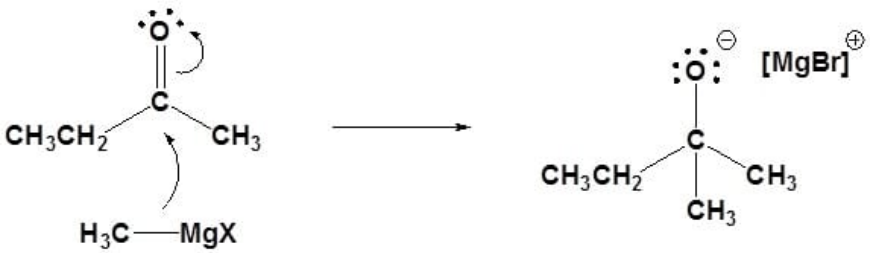


2)

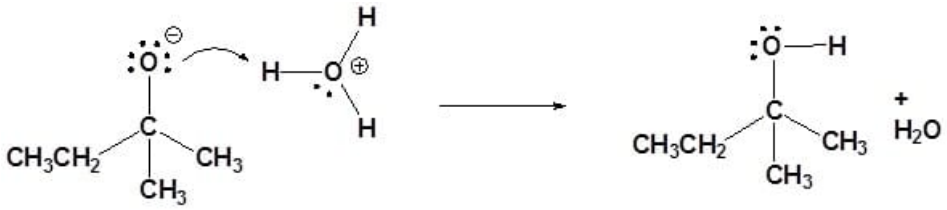


3)

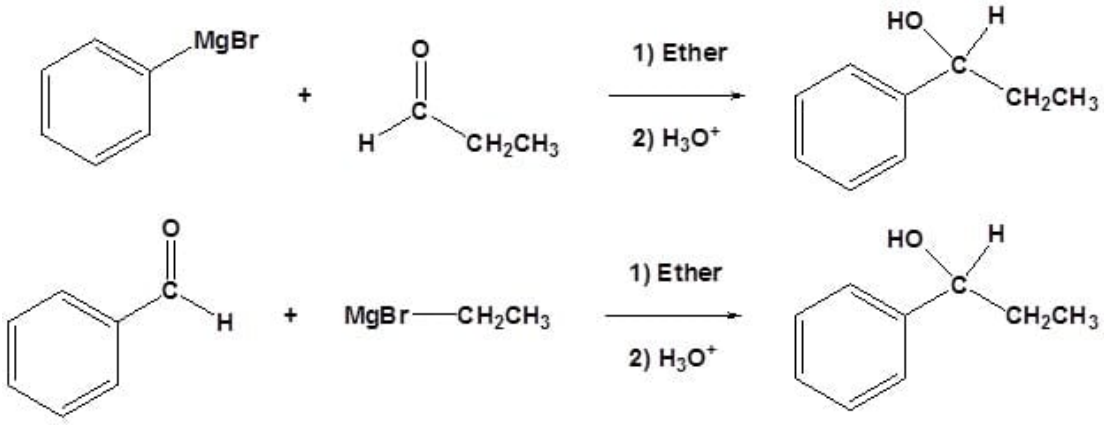
Nucleophilic attack



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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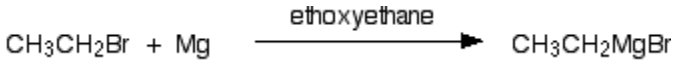
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8.9: Grignard Reagents

This page takes an introductory look at how Grignard reagents are made from halogenoalkanes (haloalkanes or alkyl halides), and introduces some of their reactions.

Introduction

A Grignard reagent has a formula RMgX where X is a halogen, and R is an alkyl or aryl (based on a benzene ring) group. For the purposes of this page, we shall take R to be an alkyl group. A typical Grignard reagent might be $\mathrm{CH_3CH_2MgBr}$. Grignard reagents are made by adding the halogenoalkane to small bits of magnesium in a flask containing ethoxyethane (commonly called diethyl ether or just "ether"). The flask is fitted with a *reflux condenser*, and the mixture is warmed over a water bath for 20 - 30 minutes.



Everything **must** be perfectly dry because Grignard reagents react with water (see below). Any reactions using the Grignard reagent are carried out with the mixture produced from this reaction. You can't separate it out in any way.

Grignard reagents and water

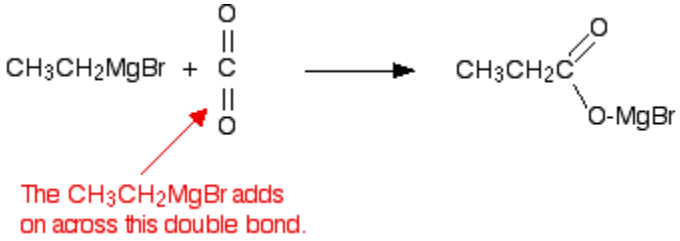
Grignard reagents react with water to produce alkanes. This is the reason that everything has to be **very dry** during the preparation above. For example:

$$CH_3CH_2MgBr + H_2O \rightarrow CH_3CH_3 + Mg(OH)Br \tag{8.9.1}$$

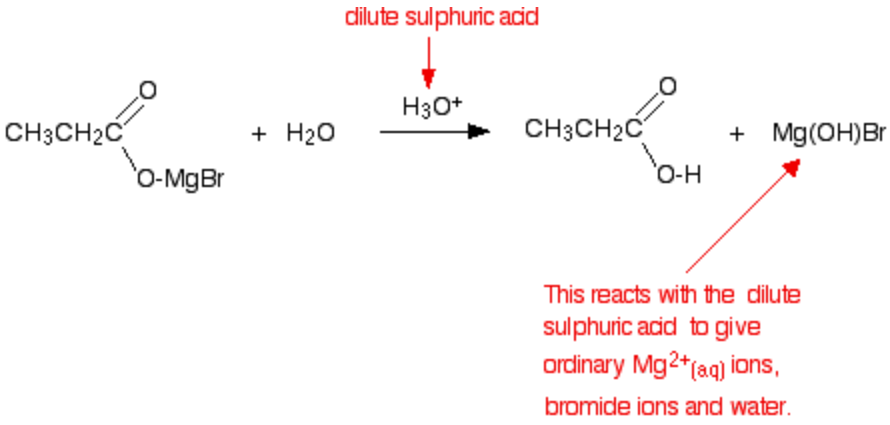
The inorganic product, $Mg(OH)Br$, is referred to as a "basic bromide" and is a sort of half-way stage between magnesium bromide and magnesium hydroxide.

Grignard reagents and carbon dioxide

Grignard reagents react with carbon dioxide in two stages. In the first, you get an addition of the Grignard reagent to the carbon dioxide. Dry carbon dioxide is bubbled through a solution of the Grignard reagent in ethoxyethane, made as described above. For example:



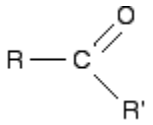
The product is then hydrolyzed (reacted with water) in the presence of a dilute acid. Typically, you would add dilute sulfuric acid or dilute hydrochloric acid to the solution formed by the reaction with the CO_2. A carboxylic acid is produced with one more carbon than the original Grignard reagent. The usually quoted equation is (without the red bits):



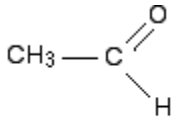
Almost all sources quote the formation of a basic halide such as Mg(OH)Br as the other product of the reaction. That is actually misleading because these compounds react with dilute acids. What you end up with would be a mixture of ordinary hydrated magnesium ions, halide ions and sulfate or chloride ions - depending on which dilute acid you added.

Grignard reagents and carbonyl compounds

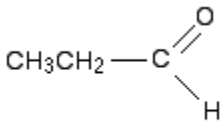
Carbonyl compounds contain the C=O double bond. The simplest ones have the form:



R and R' can be the same or different, and can be an alkyl group or hydrogen. If one (or both) of the R groups are hydrogens, the compounds are called aldehydes. For example:

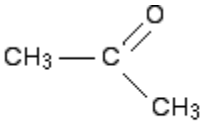


ethanal

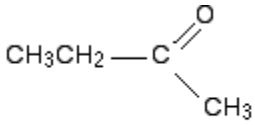


propanal

If both of the R groups are alkyl groups, the compounds are called ketones. Examples include:



propanone

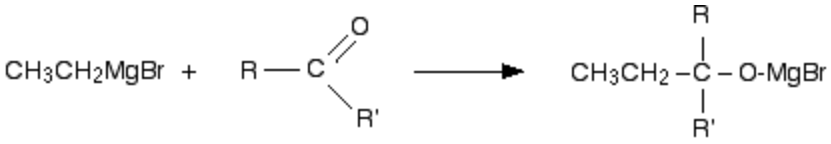


butanone

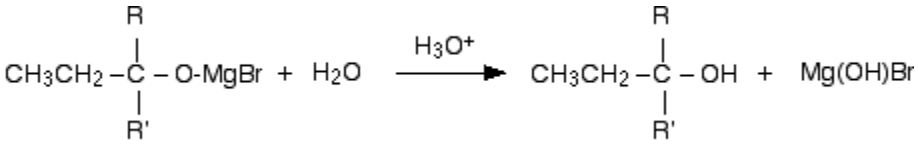
General Reaction between Grignards and carbonyls

The reactions between the various sorts of carbonyl compounds and Grignard reagents can look quite complicated, but in fact they all react in the same way - all that changes are the groups attached to the carbon-oxygen double bond. It is much easier to understand what is going on by looking closely at the general case (using "R" groups rather than specific groups) - and then slotting in the various real groups as and when you need to.

The reactions are essentially identical to the reaction with carbon dioxide - all that differs is the nature of the organic product. In the first stage, the Grignard reagent adds across the carbon-oxygen double bond:



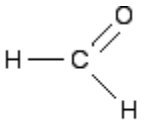
Dilute acid is then added to this to hydrolyse it. (I am using the normally accepted equation ignoring the fact that the Mg(OH)Br will react further with the acid.)



An alcohol is formed. One of the key uses of Grignard reagents is the ability to make complicated alcohols easily. What sort of alcohol you get depends on the carbonyl compound you started with - in other words, what R and R' are.

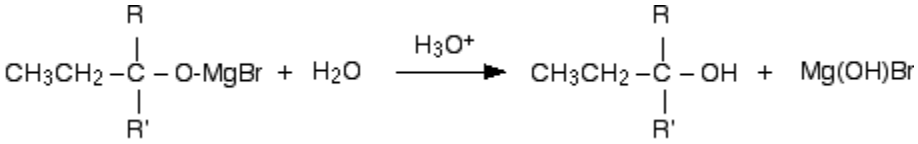
Reaction between Grignard reagents and methanal

In methanal, both R groups are hydrogen. Methanal is the simplest possible aldehyde.



methanal

Assuming that you are starting with CH_3CH_2MgBr and using the general equation above you get always has the form:



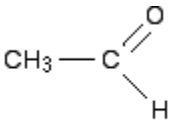
Since both R groups are hydrogen atoms, the final product will be:



A primary alcohol is formed. A primary alcohol has only one alkyl group attached to the carbon atom with the -OH group on it. You could obviously get a different primary alcohol if you started from a different Grignard reagent.

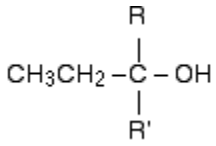
Reaction between Grignards and other aldehydes

The next biggest aldehyde is ethanal. One of the R groups is hydrogen and the other CH_3.



ethanal

Again, think about how that relates to the general case. The alcohol formed is:



So this time the final product has one CH_3 group and one hydrogen attached:

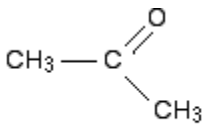


A secondary alcohol has two alkyl groups (the same or different) attached to the carbon with the -OH group on it. You could change the nature of the final secondary alcohol by either:

- changing the nature of the Grignard reagent - which would change the CH_3CH_2 group into some other alkyl group;
- changing the nature of the aldehyde - which would change the CH_3 group into some other alkyl group.

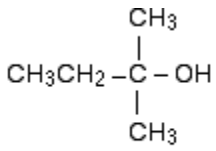
The reaction between Grignard reagents and ketones

Ketones have two alkyl groups attached to the carbon-oxygen double bond. The simplest one is propanone.



propanone

This time when you replace the R groups in the general formula for the alcohol produced you get a tertiary alcohol.



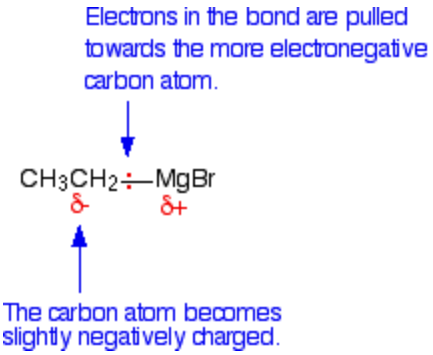
a tertiary alcohol

A tertiary alcohol has three alkyl groups attached to the carbon with the -OH attached. The alkyl groups can be any combination of same or different. You could ring the changes on the product by

- changing the nature of the Grignard reagent - which would change the CH_3CH_2 group into some other alkyl group;
- changing the nature of the ketone - which would change the CH_3 groups into whatever other alkyl groups you choose to have in the original ketone.

Why do Grignard reagents react with carbonyls?

The bond between the carbon atom and the magnesium is polar. Carbon is more electronegative than magnesium, and so the bonding pair of electrons is pulled towards the carbon. That leaves the carbon atom with a slight negative charge.



The carbon-oxygen double bond is also highly polar with a significant amount of positive charge on the carbon atom. The nature of this bond is described in detail elsewhere on this site. The Grignard reagent can therefore serve as a nucleophile because of the attraction between the slight negativeness of the carbon atom in the Grignard reagent and the positiveness of the carbon in the carbonyl compound. A nucleophile is a species that attacks positive (or slightly positive) centers in other molecules or ions.

Contributors

- Jim Clark (Chemguide.co.uk)

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9: THE CHEMISTRY OF ALKYL HALIDES

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9.2: Elimination Reactions

9.3: Rate Laws in Nucleophilic Substitution

9.4: Reaction Rates and Rate Laws

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9.6: E2 Elimination

9.7: SN1 Reaction

9.7.1: 6.06.1 Kinetics, Stereochemistry and Energy Diagram

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9.1: An Overview of Nucleophilic Substitution

NS1. Introduction to Aliphatic Nucleophilic Substitution

Aliphatic nucleophilic substitution is a mouthful, but each piece tells you something important about this kind of reaction.

In *substitution* reactions, one piece of a molecule is replaced by another. For example, ligands can be replaced in transition metal complexes. Oxygen atoms in organic carbonyl compounds can be replaced by nitrogen atoms or sulfur atoms, in a particular variation of carbonyl addition reactions.

These reactions all involve the addition of a *nucleophile* to an electrophilic atom or ion. They are all nucleophilic substitution reactions.

Aliphatic systems involve chains of saturated hydrocarbons, in which carbons are attached to each other only through single bonds. Aliphatic nucleophilic substitution is the substitution of a nucleophile at a tetrahedral or sp^3 carbon.

Aliphatic nucleophilic substitutions do not play a glamourous, central role in the world of chemistry. They don't happen in every important process, the way carbonyl additions and carboxyloid substitutions appear to in biochemistry. Instead, they are ubiquitous little reactions that play important, small roles in all kinds of places.

For example, polyethylene gloycol (PEG) is a commonly used polymer in lots of biomedical applications. PEG frequently has hydroxyl groups at each end of the polymer. Capping the ends of the polymer through reaction with another group can lead to very different physical properties.

For another example, many biochemical processes require prenylation of proteins. That would involve a nucleophilic substitution in which a sulfur in a cysteine residue adds to a tetrahedral carbon in a prenyl group, replacing a phosphate group.

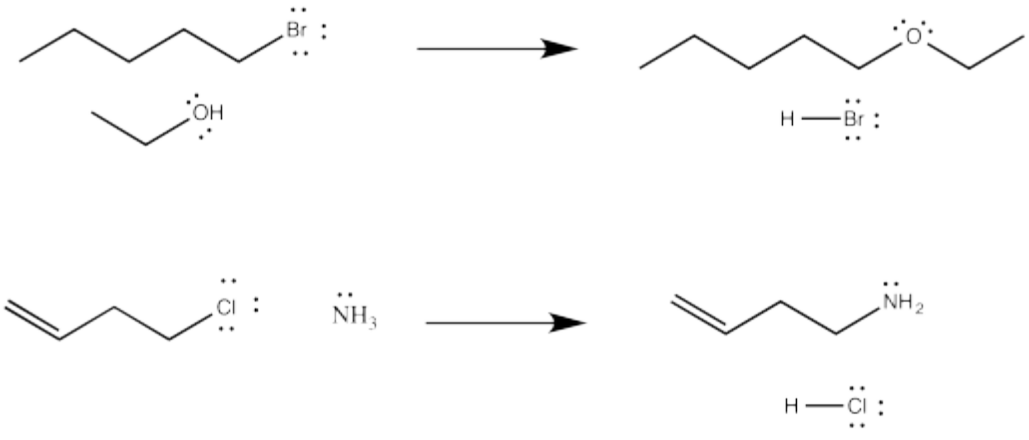
In order to be an electrophile, that tetrahedral carbon should have at least some partial positive charge on it. In the simplest cases, this electrophilic carbon is attached to a halogen: chlorine, bromine or iodine. These compounds are called alkyl halides (or alkyl chlorides, alkyl bromides and alkyl iodides).

Problem NS1.1.

Draw structures of the following alkyl halides.

a) 2-bromopentane b) 2-methyl-2-chlorobutane c) benzyl iodide d) allyl chloride

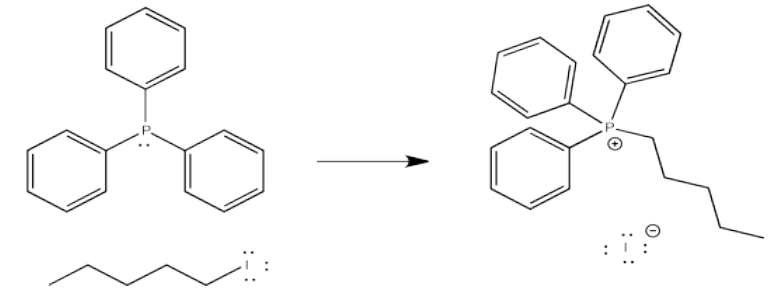
Lots of things can be nucleophiles in these reactions. Sometimes, the nucleophile is a neutral compound with a lone pair, such as ammonia or water (or, by extension, an amine or an alcohol).

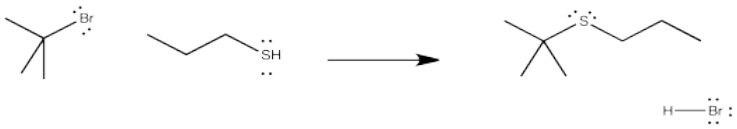


Problem NS1.2.

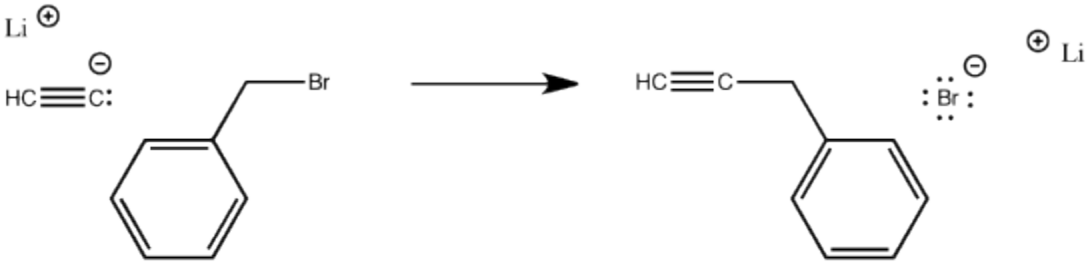
Sometimes, addition of a mild base is helpful in reactions of neutral nucleophiles. Show, with mechanistic arrows, how sodium carbonate (K_2CO_3) would play a role in the reaction.

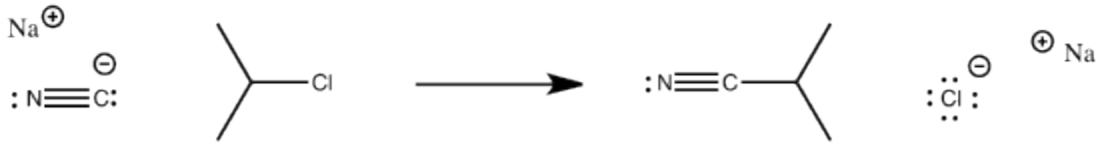
The third row analogs of these nucleophiles, in which the nucleophlic atom is a phosphorus or a sulfur, are also good nucleophiles in these reactions.





Sometimes, the nucleophile is an anion. Cyanide anion is a good nucleophile, as are the structurally similar acetylides.





Enols, enolates and enamines are also very good nucleophiles in this type of reaction.

Semi-anionic nucleophiles such as Grignard (or organomagnesium) reagents and alkyl lithium reagents can sometimes act as nucleophiles in this reactions, but they are not very reliable. Complications often lead to other reactions instead. Gilman (or organocopper) reagents, in which a carbon atom is attached to a copper atom, can usually react with alkyl halides. However, they probably act via a different mechanism from the ones described in this chapter.

Contributors

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

Further Reading

MasterOrganicChemistry

Nucleophilic Substitution

Khan Academy

Nucleophile/Electrophile and the Schwartz Rule

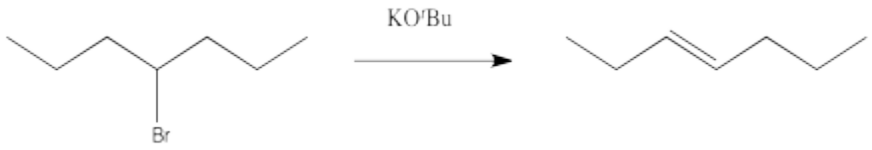
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9.2: Elimination Reactions

NS12. Elimination

Sometimes, elimination reactions occur instead of aliphatic nucleophilic substitutions. In an elimination reaction, instead of connecting to the electrophilic carbon, the nucleophile takes a proton from the next carbon away from it. The halide or other leaving group is still displaced. A double bond forms between the two carbons.



Thus, there are actually more than two competing mechanisms occurring at once here. In addition to unimolecular and bimolecular substitution, a reaction involving deprotonation is also possible.

Problem NS12.1.

Draw a mechanism for the elimination reaction above. Assume the reaction is bimolecular.

The mechanism of an elimination reaction is almost exactly the same as an aliphatic nucleophilic substitution, except that the nucelophile misses its mark. It hits a proton instead of a carbon and acts as a base instead of a nucleophile. This process can happen at the same time as the leaving group's departure or it can happen afterwards. These mechanisms are called E1 and E2.

Problem NS12.2.

Draw another mechanism for the elimination reaction above, but this time, suppose the reaction is unimolecular.

Problem NS12.3.

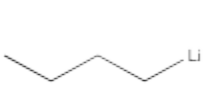
Given the mechanism in NS12.2., other products would also be expected.

1. What are they?
2. What does their absence suggest about the mechanism of the reaction?

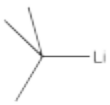
Why might a reaction undergo elimination rather than substitution? The most important reason concerns the nature of the nucleophile. The more basic the nucleophile, the more likely it will induce elimination.

- Basic nucleophiles lead to elimination.

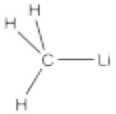
Very strong bases include carbon and nitrogen anions and semi-anions. Examples include butyllithium and sodium amide. Very strong bases are highly likely to engage in elimination, rather than substitution.



butyllithium or BuLi

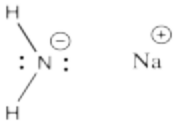


tert-butyllithiun or ^{t}BuLi

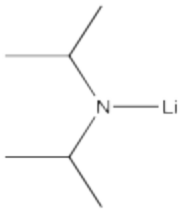


methyllithium

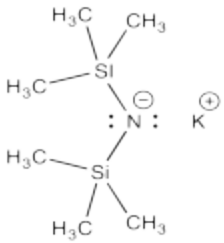
Strong bases include non-stabilized oxygen anions. Examples include sodium hydroxide as well as alkoxides such as potassium tert-butoxide or sodium ethoxide. Strong bases favour elimination, too. Nevertheless, they can sometimes undergo either elimination or substitution, depending on other factors (see below).



sodium amide

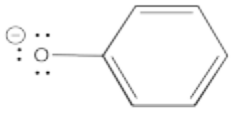


lithium diisopropylamide or LDA

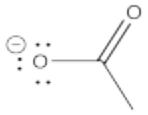


potassium hexamethyldisilazide (KHMDS)
or potassium bis(TMS)amide

Weak bases include cyanide, stabilized oxygen anions such as carboxylates and aryloxides, fluoride ion and neutral amines. Weak bases are much more likely to undergo substitution than elimination.



phenoxide or phenolate anion
(an aryloxide)



acetate or ethanoate anion
(a carboxylate)

Very weak bases include heavy halides such as chloride, bromide or iodide, as well as phosphorus and sulfur nucleophiles. Very weak bases undergo elimination only rarely.

Problem NS12.4.

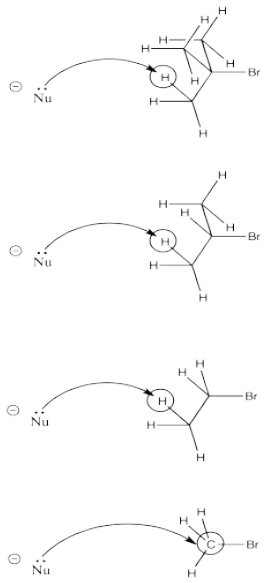
Typically, strong bases and very strong bases are more likely to react via the E2 mechanism; they react so quickly that the deprotonation step triggers C-LGp ionization, rather than the other way around. However, E1 mechanisms also occur with these bases, especially at low concentrations. Explain why.

Problem NS12.5.

Why is it that an anion such as cyanide is a weak base, whereas CH_3Li is a strong base? Give two reasons.

Another factor is sterics. The more crowded the electyrophile, the more likely the nucleophile will encounter a proton on its way to the electrophilic carbon.

As a nucleophile approaches *tert*-butyl bromide, coming from the side opposite the bromine in order to undergo nucleophilic substitution, it is pretty likely to collide with a proton on its way to the electrophilic carbon. The same thing has a good chance of happening with *iso*-propyl bromide. However, it is much less likely to happen with bromoethane. Finally, bromomethane doesn't even have a beta-hydrogen, so the chance of elimination in that case is zero.

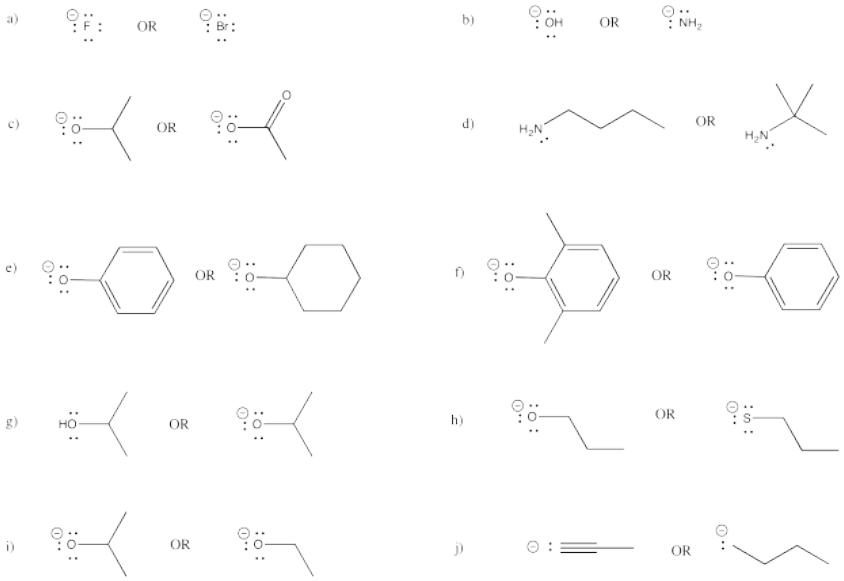


- Crowding leads to elimination.

Note that the crowding could involve either the structure of the base or the structure of the electrophile. A large, bulky base may be more likely to deprotonate than find its way in to the electrophilic carbon atom.

Problem NS12.6.

Given the following pairs of nucleophiles, which one is more likely to undergo elimination?



Problem NS12.7.

Although acetylides (such as sodium acetylide, Na CCH) are actually more basic than alkoxides (such as sodium isopropoxide, Na $OCH(CH_3)_2$), acetylides frequently undergo substitution rather than elimination. Propose a reason for this difference.

A third factor is temperature. An elimination reaction involves the cleavage of two bonds, whereas a substitution reaction requires only one bond to break. Thus, an elimination reaction is more energy-intensive, and it is more likely to occur at higher temperatures, when more energy is available.

- Higher temperatures lead to elimination.

Problem NS12.8.

An additional factor in the energy dependence of eliminations and substitutions is entropy.

1. Use simple rules about to determine which products are favoured by entropy: Elimination or substitution?
2. Given the relationship $\Delta G = \Delta H - T \Delta S$, which thermodynamic factor dominates free energy change at high temperature?
3. Therefore, which product is favoured at high temperature?

Contributors

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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9.3: Rate Laws in Nucleophilic Substitution

Aliphatic Nucleophilic Substitution: Rate Laws

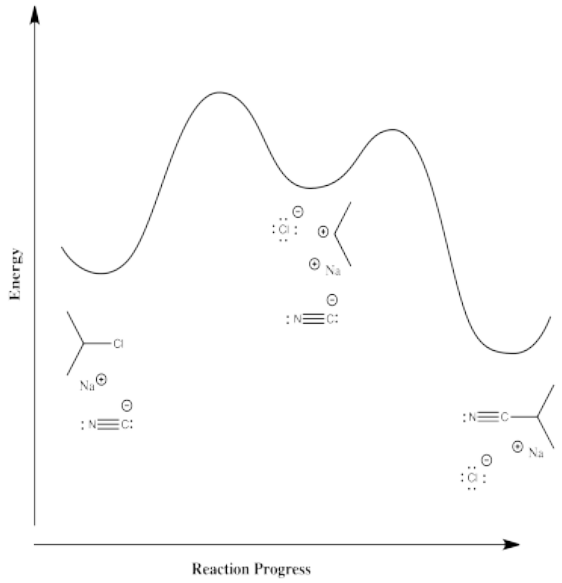
In aliphatic nucleophilic substitution, a nucleophile (abbreviated Nu) replaces a halogen "leaving group" (abbreviated LGp) from a tetrahedral carbon. Aliphatic nucleophilic substitution may take place through two different mechanisms:

- C-LGp bond breaking, followed by C-Nu bond formation.

or

- C-Nu bond formation at the same time as C-LGp bond breaking.

A look at the reaction progress diagrams for these two reactions illustrates some big differences. We will look at cyanide anion, a nucleophile, substituting for chloride in 2-chloropropane.



In the first case, some energy must be added in order to break the carbon-chlorine bond. The chlorine forms an anion, leaving a cation on the carbon. This ion pair is an intermediate along the reaction pathway. The cyanide ion then connects with this cation to form the nitrile product. Thus, there are **two** **elementary steps** in this mechanism.

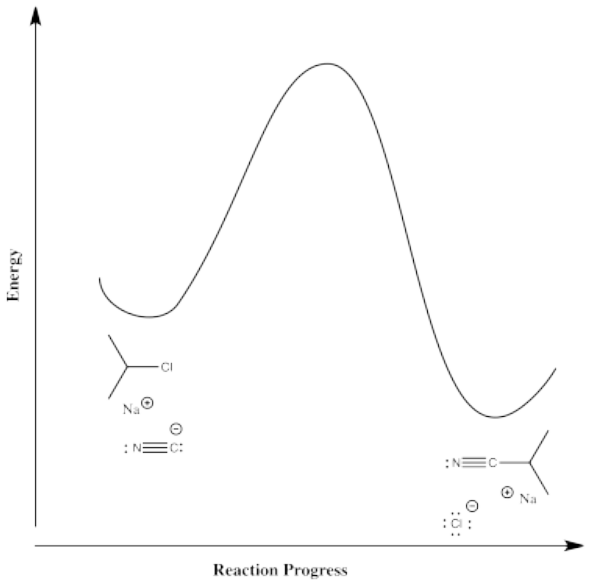
Most likely, the first step is the rate-determining step. Breaking bonds costs energy, whereas making bonds releases energy. It is hard to imagine that there could be a significant barrier to the second step; the anion and cation should come together almost automatically.

The rate law for this stepwise mechanism is:

$$Rate = k[^{i}PrCl] \tag{9.3.1}$$

that is, the rate depends on the first elementary step, but not on the second one. The second step happens pretty much automatically as soon as the first one has finally gotten around to happening.

In the second case, the nucleophile displaces the chloride directly in one step. There is only one elementary step in this reaction, and it requires both compounds to come together at once.



The rate law for this concerted mechanism is:

$$Rate = k[^{i}PrCl][^{-}CN] \tag{9.3.2}$$

These two rate laws are very different, and offer an additional way for us to tell how this reaction is taking place. In principle, if we try the reaction with different concentrations of cyanide (but keep the 2-chloropropane concentration constant), we can see whether that has an effect on how quickly the product appears. If it has the predictable effect, maybe the reaction happens in one step. If not, maybe it is a two-step reaction.

Because the rate laws for these two mechanisms are so different, there has arisen a catchy shorthand for describing these reactions based on their rate laws, coined by C.K. Ingold. The rate of the stepwise reaction depends only on one concentration and is referred to as a "unimolecular reaction"; Ingold's shorthand for this kind of nucleophilic substitution was "S_N1".

The rate of the concerted reaction depends on two different concentrations and is referred to as a bimolecular reaction; Ingold's shorthand for this reaction was "S_N2".

Problem NS3.1.

Suppose you run this reaction with three different concentrations of cyanide: 0.1 mol/L, 0.2 mol/L and 0.3 mol/L. You keep the 2-chloropropane concentration constant at 0.05 mol/L.

a. The reaction turns out to be proceeding via a S_N1 mechanism. Plot a graph of rate vs.[$^{-}$CN].
b. The reaction turns out to be proceeding via a S_N2 mechanism. Plot a graph of rate vs.[$^{-}$CN].

Now you switch things up and run this reaction with three different concentrations of 2-chloropropane: 0.1 mol/L, 0.2 mol/L and 0.3 mol/L. You keep the 2-chloropropane concentration constant at 0.05 mol/L.

c. The reaction turns out to be proceeding via a S_N1 mechanism. Plot a graph of rate vs.[^{i}PrCl].
d. The reaction turns out to be proceeding via a S_N2 mechanism. Plot a graph of rate vs.[^{i}PrCl].

Why would the mechanism proceed in one way and not the other? Molecular choices between pathways like this are often described on the basis of "steric and electronic effects"; in other words, it's either something to do with charge or something to do with crowdedness. We will see soon how these effects can influence the course of the reaction, and how the mechanism can itself have consequences in the formation of different products.

Problem NS3.2.

How might crowdedness or steric effects influence the pathway taken by the reaction between cyanide and 2-chloropropane?

Problem NS3.3.

How might charge stability influence the pathway taken by the reaction between cyanide and 2-chloropropane?

Contributors

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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9.4: Reaction Rates and Rate Laws



Prince George's Community College General Chemistry for Engineering CHM 2000



Learning Objective

- To determine the reaction rate.
- To understand the meaning of a rate law.

The factors discussed in Section 13.1 affect the reaction rate of a chemical reaction, which may determine whether a desired product is formed. In this section, we will show you how to quantitatively determine the reaction rate.

Reaction Rates

Reaction rates are usually expressed as the concentration of reactant consumed or the concentration of product formed per unit time. The units are thus moles per liter per unit time, written as M/s, M/min, or M/h. To measure reaction rates, chemists initiate the reaction, measure the concentration of the reactant or product at different times as the reaction progresses, perhaps plot the concentration as a function of time on a graph, and then calculate the *change* in the concentration per unit time.

The progress of a simple reaction (A → B) is shown in Figure 13.2.1 where the beakers are snapshots of the composition of the solution at 10 s intervals. The number of molecules of reactant (A) and product (B) are plotted as a function of time in the graph. Each point in the graph corresponds to one beaker in Figure 13.2.1. The reaction rate is the change in the concentration of either the reactant or the product over a period of time. The concentration of A decreases with time, while the concentration of B increases with time.

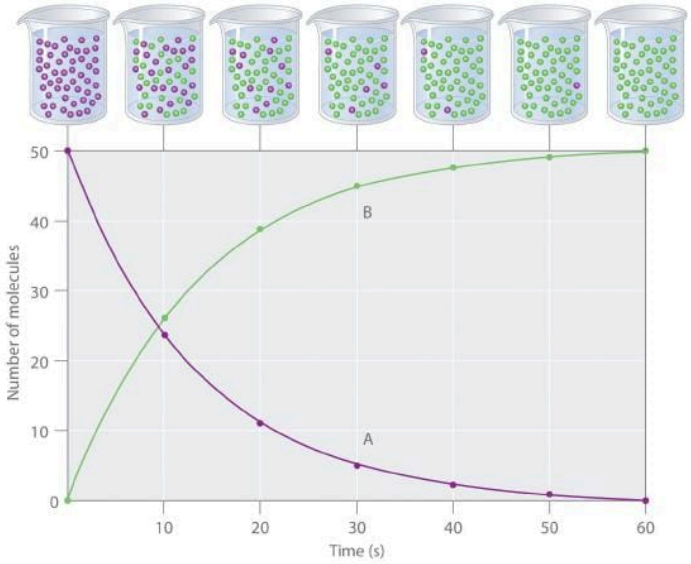


Figure 13.2.1 The Progress of a Simple Reaction (A → B) The mixture initially contains only A molecules (purple). With increasing time, the number of A molecules decreases and more B molecules (green) are formed (top). The graph shows the change in the number of A and B molecules in the reaction as a function of time over a 1 min period (bottom).

$$rate = \frac{d[B]}{dt} = -\frac{d[A]}{dt}$$

Square brackets indicate molar concentrations. We use derivatives to indicate infinitesmal changes with respect to time. On occassion we will use the capital Greek delta (Δ) for a large change over considerable time. Because chemists follow the convention of expressing all reaction rates as positive numbers, however, a negative sign is inserted in front of d[A]/d*t* to convert that expression to a positive number. The reaction rate we would calculate for the reaction A → B using Equation 13.2.1 would be different for each interval. (This is not true for every reaction, as you will see later.) A much greater change occurs in [A] and [B] during the first 10 s interval, for example, than during the last, which means that the reaction rate is fastest at first. This is consistent with the concentration effects described in Section 13.1 because the concentration of A is greatest at the beginning of the reaction.

Note the Pattern

Reaction rates generally decrease with time as reactant concentrations decrease.

Determining the Reaction Rate of Hydrolysis of Aspirin

We can use Equation 13.2.1 to determine the reaction rate of hydrolysis of aspirin, probably the most commonly used drug in the world. (More than 25,000,000 kg are produced annually worldwide.) Aspirin (acetylsalicylic acid) reacts with water (such as water in body fluids) to give salicylic acid and acetic acid.

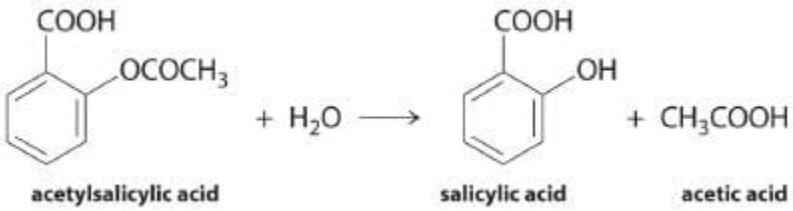


Figure 13.2.2 Because salicylic acid is the actual substance that relieves pain and reduces fever and inflammation, a great deal of research has focused on understanding this reaction and the factors that affect its rate. Data for the hydrolysis of a sample of aspirin are in Table 13.2.1 and are shown in the graph in Figure 13.2.3. These data were obtained by removing samples of

the reaction mixture at the indicated times and analyzing them for the concentrations of the reactant (aspirin) and one of the products (salicylic acid).

Table 13.2.1 Data for Aspirin Hydrolysis in Aqueous Solution at pH 7.0 and 37°C*

Time (h)	[Aspirin] (M)	[Salicylic Acid] (M)
0	5.55×10^{-3}	0
2.0	5.51×10^{-3}	0.040×10^{-3}
5.0	5.45×10^{-3}	0.10×10^{-3}
10	5.35×10^{-3}	0.20×10^{-3}
20	5.15×10^{-3}	0.40×10^{-3}
30	4.96×10^{-3}	0.59×10^{-3}
40	4.78×10^{-3}	0.77×10^{-3}
50	4.61×10^{-3}	0.94×10^{-3}
100	3.83×10^{-3}	1.72×10^{-3}
200	2.64×10^{-3}	2.91×10^{-3}
300	1.82×10^{-3}	3.73×10^{-3}
***The reaction at pH 7.0 is very slow. It is *much* faster under acidic conditions, such as those found in the stomach.**		

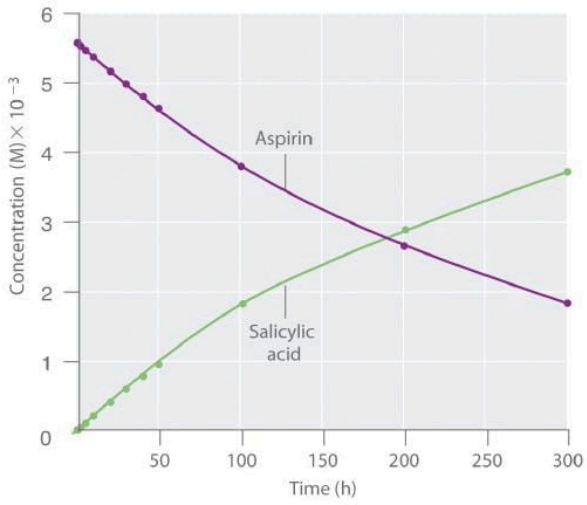


Figure 13.2.3 The Hydrolysis of Aspirin *This graph shows the concentrations of aspirin and salicylic acid as a function of time, based on the hydrolysis data in Table 13.2.1. The time dependence of the concentration of the other product, acetate, is not shown, but based on the stoichiometry of the reaction, it is identical to the data for salicylic acid. Since the difference between points is hours we use Δ[A]/Δt.*

We can calculate the average reaction rateThe reaction rate calculated for a given time interval from the concentrations of either the reactant or one of the products at the beginning of the interval time

$$rate_{(t=0-2.0\ h)} = \frac{[salicylic\ acid]_2 - [salicylic\ acid]_0}{2.0\ h - 0.0\ h}$$

$$= \frac{0.040 \times 10^{-3}\ M - 0.000\ M}{2.0\ h - 0.0\ h} = 2 \times 10^{-5}\ \ M/h$$

We can also calculate the reaction rate from the concentrations of aspirin at the beginning and the end of the same interval, remembering to insert a negative sign, because its concentration decreases:

$$rate_{(t=0-2.0\ h)} = \frac{[aspirin]_2 - [aspirin]_0}{2.0\ h - 0.0\ h}$$

$$rate_{(t=0-2.0\ h)} = \frac{5.51 \times 10^{-3}\ M - 5.55 \times 10^{-3}\ M}{2.0\ h - 0.0\ h} = 2.0 \times 10^{-5}\ \ M/h\text{\;h} \)$$

If we now calculate the reaction rate during the last interval given in Table 13.2.1 (the interval between 200 h and 300 h after the start of the reaction), we find that the reaction rate is significantly slower than it was during the first interval (*t* = 0–2.0 h):

$$rate_{(t=200-300\ h)} = \frac{[salicylic\ acid]_{300} - [salicylic\ acid]_{200}}{300\ h - 200\ h}$$

$$= \frac{3.73 \times 10^{-3}\ M - 2.91 \times 10^{-3}\ M}{100; h} = 8.2 \times 10^{-6}\ \ M/h$$

(You should verify from the data in Table 13.2.1 that you get the same rate using the concentrations of aspirin measured at 200 h and 300 h.)

Calculating the Reaction Rate of Fermentation of Sucrose

In the preceding example, the stoichiometric coefficients in the balanced chemical equation are the same for all reactants and products; that is, the reactants and products all have the coefficient 1. Let us look at a reaction in which the coefficients are *not* all the same: the fermentation of sucrose to ethanol and carbon dioxide.

$$\underset{sucrose}{C_{12}H_{22}O_{11}\,(aq)} + H_2O\,(l) \rightarrow 4C_2H_5OH\,(aq) + \$CO_2\,(g)$$

The coefficients show us that the reaction produces four molecules of ethanol and four molecules of carbon dioxide for every one molecule of sucrose consumed. As before, we can find the reaction rate by looking at the change in the concentration of any reactant or product. In this particular case, however, a chemist would probably use the concentration of either sucrose or ethanol because gases are usually measured as volumes and, as you learned in Chapter 6, the volume of CO_2 gas formed will depend on the total volume of the solution being studied and the solubility of the gas in the solution, not just the concentration of sucrose. The coefficients in the balanced chemical equation tell us that the reaction rate at which ethanol is formed is always four times faster than the reaction rate at which sucrose is consumed:

$$rate = \frac{d\,[C_2H_5OH]}{dt} = -\frac{4d\,[sucrose])}{dt}$$

The concentration of the reactant—in this case sucrose—*decreases* with increasing time, so the value of Δ[sucrose] is negative. Consequently, a minus sign is inserted in front of Δ[sucrose] in Equation 13.2.3 so that the rate of change of the sucrose concentration is expressed as a positive value. Conversely, the ethanol concentration *increases* with increasing time, so its rate of change is automatically expressed as a positive value.

Often the reaction rate is expressed in terms of the reactant or product that has the smallest coefficient in the balanced chemical equation. The smallest coefficient in the sucrose fermentation reaction (Equation 13.2.2) corresponds to sucrose, so the reaction rate is generally defined as follows:

$$rate = -\frac{d\,[sucrose]}{dt} = \frac{1}{4}\left(\frac{d\,[C_2H_5OH]}{dt}\right)$$

Example 13.2.1

Consider the thermal decomposition of gaseous N_2O_5 to NO_2 and O_2 via the following equation:

$$2N_2O_5\,(g) \overset{\Delta}{\rightarrow} 4NO_2\,(g) + O_2\,(g)$$

Write expressions for the reaction rate in terms of the rates of change in the concentrations of the reactant and each product with time.

Given: balanced chemical equation

Asked for: reaction rate expressions

Strategy:

A Choose the species in the equation that has the smallest coefficient. Then write an expression for the rate of change of that species with time.

B For the remaining species in the equation, use molar ratios to obtain equivalent expressions for the reaction rate.

Solution:

A Because O_2 has the smallest coefficient in the balanced chemical equation for the reaction, we define the reaction rate as the rate of change in the concentration of O_2 and write that expression.

B We know from the balanced chemical equation that 2 mol of N_2O_5 must decompose for each 1 mol of O_2 produced and that 4 mol of NO_2 are produced for every 1 mol of O_2 produced. The molar ratios of O_2 to N_2O_5 and to NO_2 are thus 1:2 and 1:4, respectively. This means that we divide the rate of change of $[N_2O_5]$ and $[NO_2]$ by its stoichiometric coefficient to obtain equivalent expressions for the reaction rate. For example, because NO_2 is produced at four times the rate of O_2, we must divide the rate of production of NO_2 by 4. The reaction rate expressions are as follows:

$$rate = \frac{d\,[O_2]}{dt} = \frac{d\,[NO_2]}{4dt} = -\frac{d\,[N_2O_5]}{2dt}$$

Exercise

The key step in the industrial production of sulfuric acid is the reaction of SO_2 with O_2 to produce SO_3.

$$2SO_2\,(g) + O_2\,(g) \rightarrow 2SO_3\,(g)$$

Write expressions for the reaction rate in terms of the rate of change of the concentration of each species.

Answer:

$$rate = -\frac{d\,[O_2]}{dt} = -\frac{d\,[SO_2]}{dt} = \frac{d\,[SO_3]}{2dt}$$

Example 13.2.2

Using the reaction shown in Example 1, calculate the reaction rate from the following data taken at 56°C:

$2N_2O_5(g) \rightarrow 4NO_2(g) + O_2(g)$			
Time (s)	**$[N_2O_5]$ (M)**	**$[NO_2]$ (M)**	**$[O_2]$ (M)**
240	0.0388	0.0314	0.00792
600	0.0197	0.0699	0.0175

Given: balanced chemical equation and concentrations at specific times

Asked for: reaction rate

Strategy:

A Using the equations in Example 1, subtract the initial concentration of a species from its final concentration and substitute that value into the equation for that species.

B Substitute the value for the time interval into the equation. Make sure your units are consistent.

Solution:

A We are asked to calculate the reaction rate in the interval between t_1 = 240 s and t_2 = 600 s. From Example 1, we see that we can evaluate the reaction rate using any of three expressions:

$$rate = \frac{\Delta\left[O_2\right]}{\Delta t} = \frac{\Delta\left[NO_2\right]}{4\Delta t} = -\frac{\Delta\left[N_2O_5\right]}{2\Delta t}$$

Subtracting the initial concentration from the final concentration of N_2O_5 and inserting the corresponding time interval into the rate expression for N_2O_5,

$$rate = -\frac{\Delta\left[N_2O_5\right]}{2\Delta t} = -\frac{\left[N_2O_5\right]_{600} - \left[N_2O_5\right]_{240}}{2\left(600\ s - 240\ s\right)}$$

B Substituting actual values into the expression,

$$rate = -\frac{0.197\ M - 0.0388\ M}{2\left(360\ s\right)}$$

Similarly, we can use NO_2 to calculate the reaction rate:

$$rate = -\frac{\Delta\left[NO_2\right]}{4\Delta t} = -\frac{\left[NO_2\right]_{600} - \left[NO_2\right]_{240}}{4\left(600\ s - 240\ s\right)} = \frac{0.0699\ M - 0.0314\ M}{4\left(360\right)} = 2.67 \times 10^{-5}\ \ M/s$$

If we allow for experimental error, this is the same rate we obtained using the data for N_2O_5, as it should be because the reaction rate should be the same no matter which concentration is used. We can also use the data for O_2:

$$rate = -\frac{\Delta\left[O_2\right]}{\Delta t} = -\frac{\left[O_2\right]_{600} - \left[O_2\right]_{240}}{\left(600\ s - 240\ s\right)} = \frac{0.0175\ M - 0.00792\ M}{360\ s} = 2.66 \times 10^{-5}\ \ M/s$$

Again, this is the same value we obtained from the N_2O_5 and NO_2 data. Thus the reaction rate does not depend on which reactant or product is used to measure it.

Exercise

Using the data in the following table, calculate the reaction rate of SO_2(g) with O_2(g) to give SO_3(g).

$2SO_2(g) + O_2(g) \rightarrow 2SO_3(g)$			
Time (s)	**[SO_2] (M)**	**[O_2] (M)**	**[SO_3] (M)**
300	0.0270	0.0500	0.0072
720	0.0194	0.0462	0.0148

Answer: 9.0 × 10^{-6} M/s

Instantaneous Rates of Reaction

So far, we have determined average reaction rates over particular intervals of time. We can also determine the instantaneous rateThe reaction rate of a chemical reaction at any given point in time. of a reaction, which is the reaction rate at any given point in time. As the period of time used to calculate an average rate of a reaction becomes shorter and shorter, the average rate approaches the instantaneous rate. If you have studied calculus, you may recognize that the instantaneous rate of a reaction at a given time corresponds to the slope of a line tangent to the concentration-versus-time curve at that point—that is, the derivative of concentration with respect to time.

Think of the distinction between the instantaneous and average rates of a reaction as being similar to the distinction between the actual speed of a car at any given time on a trip and the average speed of the car for the entire trip. Although you may travel for a long time at 65 mph on an interstate highway during a long trip, there may be times when you travel only 25 mph in construction zones or 0 mph if you stop for meals or gas. Thus your average speed on the trip may be only 50 mph, whereas your instantaneous speed on the interstate at a given moment may be 65 mph. Whether you are able to stop the car in time to avoid an accident depends on your instantaneous speed, not your average speed. There are important differences between the speed of a car during a trip and the speed of a chemical reaction, however. The speed of a car may vary unpredictably over the length of a trip, and the initial part of a trip is often one of the slowest. In a chemical reaction, the initial interval normally has the fastest rate (though this is not always the case), and the reaction rate generally changes smoothly over time.

In chemical kinetics, we generally focus on one particular instantaneous rate, which is the initial reaction rate, $t = 0$. Initial rates are determined by measuring the reaction rate at various times and then extrapolating a plot of rate versus time to $t = 0$.

Rate Laws

In Section 13.1, you learned that reaction rates generally decrease with time because reactant concentrations decrease as reactants are converted to products. You also learned that reaction rates generally increase when reactant concentrations are increased. We now examine the mathematical expressions called rate lawsMathematical expressions that describe the relationships between reactant rates and reactant concentrations in a chemical reaction., which describe the relationships between reactant rates and reactant concentrations. Rate laws are laws as defined in Chapter 1; they are mathematical descriptions of experimentally verifiable data.

Rate laws may be written from either of two different but related perspectives. A differential rate lawA rate law that expresses the reaction rate in terms of changes in the concentration of one or more reactants (Δ[R]) over a specific time interval (Δt) expresses the reaction rate in terms of *changes* in the concentration of one or more reactants (Δ[R]) over a specific time interval (Δt). In contrast, an integrated rate lawA rate law that expresses the reaction rate in terms of the initial concentration $[R]_0$ and the measured concentration of one or more reactants ([R]) after a given amount of time (t) describes the reaction rate in terms of the *initial* concentration ($[R]_0$) and the *measured* concentration of one or more reactants ([R]) after a given amount of time (t); we will discuss integrated rate laws in Section 13.3. The integrated rate law can be found by using calculus to integrate the differential rate law. *Whether you use a differential rate law or integrated rate law, always make sure that the rate law gives the proper units for the reaction rate, usually moles per liter per second (M/s).*

Reaction Orders

For a reaction with the general equation

$$aA + bB \rightarrow cC + dD$$

the experimentally determined rate law usually has the following form:

$$rate = k\,[A]^m\,[B]^n$$

The *proportionality constant* (k) is called the rate constantA proportionality constant whose value is characteristic of the reaction and the reaction conditions and whose numerical value does not change as the reaction progresses under a given set of conditions., and its value is characteristic of the reaction and the reaction conditions. A given reaction has a particular value of the rate constant under a given set of conditions, such as temperature, pressure, and solvent; varying the temperature or the solvent usually changes the value of the rate constant. The numerical value of k, however, does *not* change as the reaction progresses under a given set of conditions.

Thus the reaction rate depends on the rate constant for the given set of reaction conditions and the concentration of A and B raised to the powers m and n, respectively. The values of m and n are derived from experimental measurements of the changes in reactant concentrations over time and indicate the reaction orderNumbers that indicate the degree to which the reaction rate depends on the concentration of each reactant., the degree to which the reaction rate depends on the concentration of each reactant; m and n need not be integers. For example, Equation 13.2.6 tells us that Equation 13.2.5 is mth order in reactant A and nth order in reactant B. It is important to remember that n and m are not related to the stoichiometric coefficients a and b in the balanced chemical equation and must be determined experimentally. The *overall reaction order* is the sum of all the exponents in the rate law: $m + n$.

Note the Pattern

Under a given set of conditions, the value of the rate constant does not change as the reaction progresses.

Although differential rate laws are generally used to describe what is occurring on a molecular level during a reaction, integrated rate laws are used to determine the reaction order and the value of the rate constant from experimental measurements. (We present general forms for integrated rate laws in Section 13.3.) To illustrate how chemists interpret a differential rate law, we turn to the experimentally derived rate law for the hydrolysis of *t*-butyl bromide in 70% aqueous acetone. This reaction produces *t*-butanol according to the following equation:

$$(CH_3)_3\,CBr\,(soln) + H_2O\,(soln) \rightarrow (CH_3)_3\,COH\,(soln) + HBr\,(soln)$$

Combining the rate expression in Equation 13.2.1 and Equation 13.2.6 gives us a general expression for the differential rate law:

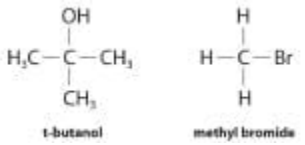
$$rate = -\frac{d\,[A]}{dt} = k\,[A]^m\,[B]^n$$

Inserting the identities of the reactants into Equation 13.2.8 gives the following expression for the differential rate law for the reaction:

$$rate = -\frac{d\,[(CH_3)_3\,CBr]}{dt} = k\,[(CH_3)_3\,CBr]^m\,[H_2O]^n$$

Experiments done to determine the rate law for the hydrolysis of *t*-butyl bromide show that the reaction rate is directly proportional to the concentration of $(CH_3)_3CBr$ but is independent of the concentration of water. Thus *m* and *n* in Equation 13.2.9 are 1 and 0, respectively, and

$$rate = k\,[(CH_3)_3\,CBr]^1\,[H_2O]^0 = k\,[(CH_3)_3\,CBr]$$



Because the exponent for the reactant is 1, the reaction is *first order* in $(CH_3)_3CBr$. It is *zeroth order* in water because the exponent for $[H_2O]$ is 0. (Recall that anything raised to the zeroth power equals 1.) Thus the overall reaction order is 1 + 0 = 1. What the reaction orders tell us in practical terms is that doubling the concentration of $(CH_3)_3CBr$ doubles the reaction rate of the hydrolysis reaction, halving the concentration of $(CH_3)_3CBr$ halves the reaction rate, and so on. Conversely, increasing or decreasing the concentration of water has *no effect* on the reaction rate. (Again, when you work with rate laws, there is no simple correlation between the stoichiometry of the reaction and the rate law. The values of *k*, *m*, and *n* in the rate law *must* be determined experimentally.) Experimental data show that *k* has the value $5.15 \times 10^{-4}\ s^{-1}$ at 25°C. The rate constant has units of reciprocal seconds (s^{-1}) because the reaction rate is defined in units of concentration per unit time (M/s). The units of a rate constant depend on the rate law for a particular reaction.

Under conditions identical to those for the *t*-butyl bromide reaction, the experimentally derived differential rate law for the hydrolysis of methyl bromide (CH_3Br) is as follows:

$$rate = -\frac{d\,[CH_3Br]}{dt} = k'\,[CH_3Br]$$

This reaction also has an overall reaction order of 1, but the rate constant in Equation 13..2.11 is approximately 10^6 times smaller than that for *t*-butyl bromide. Thus methyl bromide hydrolyzes about 1 million times more slowly than *t*-butyl bromide, and this information tells chemists how the reactions differ on a molecular level.

Frequently, changes in reaction conditions also produce changes in a rate law. In fact, chemists often change reaction conditions to obtain clues about what is occurring during a reaction. For example, when *t*-butyl bromide is hydrolyzed in an aqueous acetone solution containing OH^- ions rather than in aqueous acetone alone, the differential rate law for the hydrolysis reaction does not

change. For methyl bromide, in contrast, the differential rate law becomes rate = $k''[CH_3Br][OH^-]$, with an overall reaction order of 2. Although the two reactions proceed similarly in neutral solution, they proceed very differently in the presence of a base, which again provides clues as to how the reactions differ on a molecular level.

Note the Pattern

Differential rate laws are generally used to describe what is occurring on a molecular level during a reaction, whereas integrated rate laws are used for determining the reaction order and the value of the rate constant from experimental measurements.

Example 13.2.3

We present three reactions and their experimentally determined differential rate laws. For each reaction, give the *units* of the rate constant, give the reaction *order* with respect to each reactant, give the *overall reaction order*, and predict what happens to the reaction rate when the concentration of the first species in each chemical equation is doubled.

1. $2HI\,(g) \overset{Pt}{\rightarrow} H_2\,(g) + I_2\,(g) rate = -\frac{1}{2}\frac{d\,[HI]}{dt} = k\,[HI]^2$
2. $2N_2O\,(g) \overset{\Delta}{\rightarrow} 2N_2\,(g) + O_2\,(g)$
   $rate = \frac{1}{2}\frac{d\,[N_2O]}{dt} = k$
3. $cyclopropane\,(g) \overset{\Delta}{\rightarrow} propane\,(g)$
   $rate = \frac{1}{2}\frac{d\,[cyclopropance]}{dt} = k\,[cyclopropane]$

Given: balanced chemical equations and differential rate laws

Asked for: units of rate constant, reaction orders, and effect of doubling reactant concentration

Strategy:

A Express the reaction rate as moles per liter per second [mol/(L·s), or M/s]. Then determine the units of each chemical species in the rate law. Divide the units for the reaction rate by the units for all species in the rate law to obtain the units for the rate constant.

B Identify the exponent of each species in the rate law to determine the reaction order with respect to that species. Sum all exponents to obtain the overall reaction order.

C Use the mathematical relationships as expressed in the rate law to determine the effect of doubling the concentration of a single species on the reaction rate.

Solution:

1. **A** $[HI]^2$ will give units of (moles per liter)^2. For the reaction rate to have units of moles per liter per second, the rate constant must have reciprocal units [1/(M·s)]:

   $$\frac{M}{s} = kM^2 \Rightarrow k = \frac{M/s}{M^2} = \frac{1}{M \cdot s} = M^{-1}s^{-1}$$

   B The exponent in the rate law is 2, so the reaction is second order in HI. Because HI is the only reactant and the only species that appears in the rate law, the reaction is also second order overall.

   C If the concentration of HI is doubled, the reaction rate will increase from $k[HI]_0^2$ to $k(2[HI])_0^2 = 4k[HI]_0^2$. The reaction rate will therefore quadruple.

2. **A** Because no concentration term appears in the rate law, the rate constant must have M/s units for the reaction rate to have M/s units.

   B The rate law tells us that the reaction rate is constant and independent of the N_2O concentration. That is, the reaction is

zeroth order in N_2O and zeroth order overall.

C Because the reaction rate is independent of the N_2O concentration, doubling the concentration will have no effect on the reaction rate.

3. **A** The rate law contains only one concentration term raised to the first power. Hence the rate constant must have units of reciprocal seconds (s^{-1}) to have units of moles per liter per second for the reaction rate: $M{\cdot}s^{-1}$ = M/s.

   B The only concentration in the rate law is that of cyclopropane, and its exponent is 1. This means that the reaction is first order in cyclopropane. Cyclopropane is the only species that appears in the rate law, so the reaction is also first order overall.

   C Doubling the initial cyclopropane concentration will increase the reaction rate from k[cyclopropane]$_0$ to $2k$[cyclopropane]$_0$. This doubles the reaction rate.

Exercise

Given the following two reactions and their experimentally determined differential rate laws: determine the *units* of the rate constant if time is in seconds, determine the reaction *order* with respect to each reactant, give the *overall reaction order*, and predict what will happen to the reaction rate when the concentration of the first species in each equation is doubled.

1. $CH_3N{=}CH_3N\,(g) \rightarrow C_2H_6\,(g) + N_2\,(g)$
   $rate = -\dfrac{d\,[CH_3N{=}CH_3N]}{dt} = k\,[CH_3N{=}CH_3N]$
2. $2NO_2\,(g) + F_2\,(g) \rightarrow 2NO_2F\,(g)$
   $rate = -\dfrac{d\,[F_2]}{dt} = -\dfrac{1}{2}\dfrac{d\,[NO_2]}{dt} = k\,[NO_2]\,[F_2]$

Answer:

1. s^{-1}; first order in $CH_3N{=}NCH_3$; first order overall; doubling [$CH_3N{=}NCH_3$] will double the reaction rate.
2. $M^{-1}{\cdot}s^{-1}$; first order in NO_2, first order in F_2; second order overall; doubling [NO_2] will double the reaction rate.

Summary

Reaction rates are reported either as the **average rate** over a period of time or as the **instantaneous rate** at a single time.

The **rate law** for a reaction is a mathematical relationship between the reaction rate and the concentrations of species in solution. Rate laws can be expressed either as a **differential rate law**, describing the change in reactant or product concentrations as a function of time, or as an **integrated rate law**, describing the actual concentrations of reactants or products as a function of time.

The **rate constant** (k) of a rate law is a constant of proportionality between the reaction rate and the reactant concentration. The power to which a concentration is raised in a rate law indicates the **reaction order**, the degree to which the reaction rate depends on the concentration of a particular reactant.

Key Takeaways

- Reaction rates can be determined over particular time intervals or at a given point in time.
- A rate law describes the relationship between reactant rates and reactant concentrations.

Key Equations

general definition of rate for A → B

Equation 13.2.1: $rate = \dfrac{d\,[B]}{dt} = -\dfrac{d\,[A]}{dt}$

general form of rate law when A and B are reactants

Equation 13.2.6: $rate = k\,[A]^m\,[B]^n$

Conceptual Problems

1. Explain why the reaction rate is generally fastest at early time intervals. For the second-order A + B → C, what would the plot of the concentration of C versus time look like during the course of the reaction?
2. Explain the differences between a differential rate law and an integrated rate law. What two components do they have in common? Which form is preferred for obtaining a reaction order and a rate constant? Why?
3. Diffusion-controlled reactions have rates that are determined only by the reaction rate at which two reactant molecules can diffuse together. These reactions are rapid, with second-order rate constants typically on the order of 10^{10} L/(mol·s). Would you expect the reactions to be faster or slower in solvents that have a low viscosity? Why? Consider the reactions $H_3O^+ + OH^- \rightarrow 2H_2O$ and $H_3O^+ + N(CH_3)_3 \rightarrow H_2O + HN(CH_3)_3^+$ in aqueous solution. Which would have the higher rate constant? Why?
4. What information can you get from the reaction order? What correlation does the reaction order have with the stoichiometry of the overall equation?
5. During the hydrolysis reaction $A + H_2O \rightarrow B + C$, the concentration of A decreases much more rapidly in a polar solvent than in a nonpolar solvent. How do you expect this effect to be reflected in the overall reaction order?

Answers

1. Reactant concentrations are highest at the beginning of a reaction. The plot of [C] versus *t* is a curve with a slope that becomes steadily less positive.
2.
3. Faster in a less viscous solvent because the rate of diffusion is higher; the H_3O^+/OH^- reaction is faster due to the decreased relative size of reactants and the higher electrostatic attraction between the reactants.
4.
5.

Numerical Problems

1. The reaction rate of a particular reaction in which A and B react to make C is as follows:

   $$rate = -\frac{\Delta\,[A]}{\Delta t} = \frac{1}{2}\frac{d\,[C]}{dt}$$

   Write a reaction equation that is consistent with this rate law. What is the rate expression with respect to time if 2A are converted to 3C?
2. While commuting to work, a person drove for 12 min at 35 mph, then stopped at an intersection for 2 min, continued the commute at 50 mph for 28 min, drove slowly through traffic at 38 mph for 18 min, and then spent 1 min pulling into a parking space at 3 mph. What was the average rate of the commute? What was the instantaneous rate at 13 min? at 28 min?
3. Why do most studies of chemical reactions use the initial rates of reaction to generate a rate law? How is this initial rate determined? Given the following data, what is the reaction order? Estimate.

Time (s)	[A] (M)
120	0.158
240	0.089
360	0.062

4. Predict how the reaction rate will be affected by doubling the concentration of the first species in each equation.

    1. $C_2H_5I \rightarrow C_2H_4 + HI$: rate = $k[C_2H_5I]$
    2. $SO + O_2 \rightarrow SO_2 + O$: rate = $k[SO][O_2]$
    3. $2CH_3 \rightarrow C_2H_6$: rate = $k[CH_3]^2$
    4. $ClOO \rightarrow Cl + O_2$: rate = k

5. Cleavage of C_2H_6 to produce two CH_3· radicals is a gas-phase reaction that occurs at 700°C. This reaction is first order, with $k = 5.46 \times 10^{-4}\ s^{-1}$. How long will it take for the reaction to go to 15% completion? to 50% completion?

6. Three chemical processes occur at an altitude of approximately 100 km in Earth's atmosphere.

$$N_2^+ + O_2 \xrightarrow{k_1} N_2 + O_2^+$$

$$O_2^+ + O \xrightarrow{k_2} O_2 + O^+$$

$$O^+ + N_2 \xrightarrow{k_3} N + NO^+$$

    Write a rate law for each elementary reaction. If the rate law for the overall reaction were found to be rate = $k[N_2^+][O_2]$, which one of the steps is rate limiting?

7. The oxidation of aqueous iodide by arsenic acid to give I_3^- and arsenous acid proceeds via the following reaction:

$$H_3AsO_4\,(aq) + 3I^-\,(aq) + 2H^+\,(aq) \overset{k_f}{\rightleftharpoons} H_3AsO_3\,(aq) + I_3^-\,(aq) + H_2O\,(l)$$

    Write an expression for the initial rate of decrease of $[I_3^-]$, $\Delta[I_3^-]/\Delta t$. When the reaction rate of the forward reaction is equal to that of the reverse reaction: $k_f/k_r = [H_3AsO_3][I_3^-]/[H_3AsO_4][I^-]^3[H^+]^2$. Based on this information, what can you say about the nature of the rate-determining steps for the reverse and the forward reactions?

Answer

1.
2.
3.
4.

5. 298 s; 1270 s
6.
7.

Contributors

- Anonymous

Modified by Joshua Halpern (Howard University), Scott Sinex, and Scott Johnson (PGCC)

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9.5: The SN2 Reaction

- Topic hierarchy

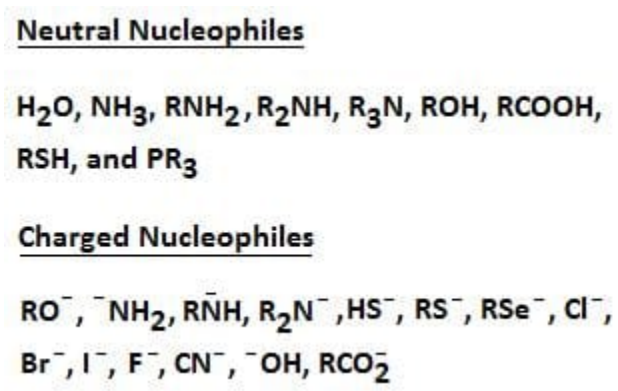
Nucleophilic Substitution

Previously (Physical Properties of Haloalkanes), we learned that haloalkanes contain a polarized C-X bond, leaving a carbon that is partially positive and a halogen that is partially negative.

- An **electrophile** is an electron poor species that can accept a pair of electrons. A carbon that is connected to a halogen in a haloalkane, for example, is an electrophilic carbon.
- A **nucleophile** is an electron rich species that can donate a pair of electrons. You will be exposed to many different kinds of nucleophiles throughout your course of study. Some nucleophiles will be negatively charged species; others will be neutral.
- **Nucleophiles can react with electrophiles.** One way in which this occurs is through a process called **nucleophilic substitution**. In nucleophilic substitution reactions, an electron rich nucleophile bonds with or attacks an electron poor electrophile, resulting in the displacement of a group or atom called the **leaving group**.
- **Nucleophilic substitution of haloalkanes can be described by two reactions**. These two types of reactions are shown in the diagram below. In the first reaction, a negatively charged nucleophile attacks the electrophilic carbon of a haloalkane. Upon attack, the leaving group, which is the halogen of the haloalkane, leaves. The end result is a neutral R-Nu species and an anion. In the second reaction, a neutral nucleophile attacks the electrophilic carbon of a haloalkane. The end result of this attack however, is positively charged product and an anion.

Haloalkanes 02.bmp

Examples of Negatively Charged and Neutral Nucleophiles



In the S_N2 reaction, the addition of the nucleophile and the departure of the leaving group occur in a **concerted**(taking place in a single step) manner, hence the name S_N2: substitution, nucleophilic, bimolecular. In the S_N2 reaction, the nucleophile approaches the carbon atom to which the leaving group is attached. As the nucleophile forms a bond with this carbon atom, the bond between the carbon atom and the leaving group breaks. The bond making and bond breaking actions occur simultaneously. Eventually, the nucleophile has formed a complete bond to the carbon atom and the bond between the carbon atom and the leaving group is completely broken.

In the image below, we introduce the concepts of **arrow pushing** and of a **reaction mechanism**. Recall that electrons compose the bonds in molecules. Hence for any reaction to occur, electrons must move. In arrow pushing, the movement of electrons is indicated by arrows. Arrows may show electrons forming or breaking bonds or traveling as lone pairs or negative charges on atoms. A complete schematic showing all steps in a reaction, including arrow pushing to indicate the movement of electrons, constitutes a reaction mechanism. In the reaction mechanism below, observe that the electrons from a negative charge on the nucleophile "attack" or form a bond with the carbon atom to which the leaving group is attached. In the center image, the partially

formed bond is visible, as well as the partially broken bond to the leaving group. In the final image, the bond to the leaving group is broken when its electrons become a negative charge on the leaving group.

Figure 1: *SN2 reaction showing concerted, bimolecular participation of nucleophile and leaving group*

A consequence of the concerted, bimolecular nature of the S_N2 reaction is that the nucleophile must attack from the side of the molecule opposite to the leaving group. This geometry of reaction is called **back side attack**. In a back side attack, as the nucleophile approaches the molecule from the side opposite to the leaving group, the other three bonds move away from the nucleophile and its attacking electrons. Eventually, these three bonds are all in the same plane as the carbon atom (center image). As the bond to the leaving group breaks, these bonds retreat farther away from the nucleophile and its newly formed bond to carbon atom. As a result of these geometric changes, the stereochemical configuration of the molecule is inverted during an S_N2 reaction to the opposite enantiomer. This stereochemical change is called **inversion of configuration**.

The concerted mechanism and nature of the nucleophilic attack in an S_N2 reaction give rise to several important results:

1. The rate of the reaction depends on the concentration of both the nucleophile and the molecule undergoing attack. The reaction requires a collision between the nucleophile and the molecule, so increasing the concentration of either will increase the rate of the reaction.
2. Since the unique geometry of back side attack is required, the most important factor in determining whether an S_N2 reaction will occur is **steric effects**. Steric effects refer to the unfavorable interaction created when atoms are brought too close together. In effect, if the nucleophile or the molecule undergoing attack have too many substituents or substituents which are too bulky, the reaction cannot occur since the nucleophile will be unable to get close enough to the molecule to do a backside attack.

Now let's look at two actual examples of these two general equations. In the first reaction shown below, the negative nucleophile, hydroxide, reacts with methyl iodide. Hydroxide takes the place of the leaving group, iodide, forming neutral methanol and an iodide ion. This reaction is the same as the first type of nucleophilic substitution shown above. In the second reaction shown below, the nuetral nucleophile, ammonia, reacts with iodoethane. Ammonia takes the place of the leaving group, iodide, forming the positively charged product, ethylammonium iodide, and an iodide ion. This reaction is the same as the second type of nucleophilic substitution shown above.

Haloalkanes 03.bmp

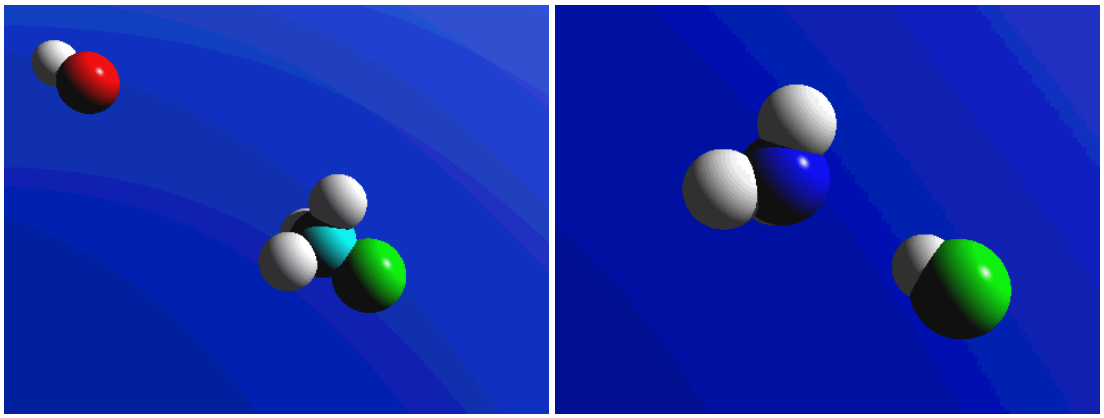


Figure 2. S_N2 reaction of methyl chloride and hydroxide ion (left) and ammonia reaction with HCl (right).

Four Factors to Consider in Determining the Relative Ease at Which SN_2 Displacement Occurs

- The nature of the leaving group (SN_2 Reactions-The Leaving Group)
- The reactivity of the nucleophile (SN_2 Reactions-The Nucleophile)

- The solvent (SN_2 Reactions-The Nucleophile)
- The structure of the alkyl portion of the substrate (SN_2 Reactions-The Substrate)

Next section: Using Electron-Pushing Arrows

Contributors

- Rachael Curtis (UCD)
- Jonathan Mooney (McGill University)

Richard Banks (Boise State University)

Additional Resources

Michigan State Virtual Textbook of Organic Chemistry

Second-Order Nucleophilic Substitution: The S_N2 Reaction

MasterOrganicChemistry

The SN2 Mechanism

Why The SN2 Is Powerful

Carey 4th Edition On-Line Activity

Second-Order Nucleophilic Substitution: The S_N2 Reaction

Khan Academy

The S_N2 Reaction

Leah4Sci

SN2 Reaction Rate and Mechanism (vid 1 of 3) Bimolecular Substitution

SN2 Reaction (vid 2 of 3) Chirality and Mechanism of Bimolecular Substitution

SN2 Reaction vid (3 of 3) Bimolecular Nucleophilic Substitution

Cliffs Notes

Mechanism

Web Pages

SN2 reaction description

All about the SN2 reactions

SN2 reaction information

Videos

Reaction examples

S_N2 reaction description

Video on S_N2 Reactions

Tutorial

S_N2 Handout

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9.6: E2 Elimination

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.

General Reaction

In this reaction Ba represents the base and X represents 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.

General Reaction1.bmp

An E2 reaction has certain requirements to proceed:

- Secondary and **tertiary alkyl halides** will **proceed** with E2 in the **presence** 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 sterically hindered base will result in the least substituted product.

Reaction Coordinate.bmp

Reaction Coordinate

Problems

1.

E2-1.bmp

2. What is the major product and why?

3. What is the major prodcut when 2-bromo-2-methylbutane reacts with with sodium ethoxide?

4.

E2-4.bmp

5.

E2-5.bmp

Further Reading

Michigan State Virtual Textbook of Organic Chemistry

E2 Elimination

MasterOrganicChemistry

The E2 Mechanism

Elimination Reactions And Cyclohexane Rings

Carey 4th Edition On-Line Activity

E2 mechanism

Khan Academy

Mechanism

Regioselectivity

Stereoselectivity

Stereospecificity

Substituted Cyclohexanes

Leah4Sci

E2 Reaction Rate & Mechanism (vid 1 of 4) Bimolecular Beta-Elimination by Leah Fisch

E2 Reaction (vid 2 of 4) Using Newman Projections To Predict Products by Leah4sci

E2 reaction (vid 3 of 4) using chair conformations for anti coplanar reactions

E2 Reaction (vid 4 of 4) Big Bulky Base for Anti-Zaitsev Product

Cliffs Notes

Slide Presentations

Web Pages

Sparknotes on S_N2 and E2

basics of e2 elmination

Videos

E2 elimination video

E2 elimination and examples

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9.7: SN1 REACTION

S_N1 Mechanism

Reaction **7**, is clearly different from the other cases we have examined. It not only shows first order kinetics, but the chiral 3°-alkyl bromide reactant undergoes substitution by the modest nucleophile water with extensive racemization. In all of these features this reaction fails to meet the characteristics of the S_N2 mechanism. A similar example is found in the hydrolysis of tert-butyl chloride, shown below. Note that the initial substitution product in this reaction is actually a hydronium ion, which rapidly transfers a proton to the chloride anion. This second acid-base proton transfer is often omitted in writing the overall equation, as in the case of reaction **7**.

$$(CH_3)_3C\text{-}Cl + H_2O \rightarrow (CH_3)_3C\text{-}OH_2^{(+)} + Cl^{(-)} \rightarrow (CH_3)_3C\text{-}OH + HCl$$

Although the hydrolysis of tert-butyl chloride, as shown above, might be interpreted as an S_N2 reaction in which the high and constant concentration of solvent water does not show up in the rate equation, there is good evidence this is not the case. First, the equivalent hydrolysis of ethyl bromide is over a thousand times slower, whereas authentic S_N2 reactions clearly show a large rate increase for 1°-alkyl halides. Second, a modest increase of hydroxide anion concentration has no effect on the rate of hydrolysis of tert-butyl chloride, despite the much greater nucleophilicity of hydroxide anion compared with water.

The first order kinetics of these reactions suggests a two-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide, as shown in the diagram below. In this mechanism, a carbocation is formed as a high-energy intermediate, and this species bonds immediately to nearby nucleophiles. If the nucleophile is a neutral molecule, the initial product is an "onium" cation, as drawn above for t-butyl chloride, and presumed in the energy diagram. In evaluating this mechanism, we may infer several outcomes from its function.

1. The only reactant that is undergoing change in the first (rate-determining) step is the alkyl halide, so we expect such reactions would be unimolecular and follow a first-order rate equation. Hence the name **S_N1** is applied to this mechanism.
2. 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. Recombination of the halide anion with the carbocation intermediate simply reforms the starting compound. Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The hydrolysis of t-butyl chloride is an example.
3. 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	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	$CH_2{=}CH\text{-}CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

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.

Fourth, in order to facilitate the charge separation of an ionization reaction, as required by the first step, a good ionizing solvent will be needed. Two solvent characteristics will be particularly important in this respect. The first is the ability of solvent molecules to orient themselves between ions so as to attenuate the electrostatic force one ion exerts on the other. This characteristic is related to the **dielectric constant, ε,** of the solvent. Solvents having high dielectric constants, such as water (ε=81), formic acid (ε=58), dimethyl sulfoxide (ε=45) & acetonitrile (ε=39) are generally considered better ionizing solvents than are some common organic solvents such as ethanol (ε=25), acetone (ε=21), methylene chloride (ε=9) & ether (ε=4). The second factor is **solvation**, which refers to the solvent's ability to stabilize ions by encasing them in a sheath of weakly bonded solvent molecules. Anions

are solvated by hydrogen-bonding solvents, as noted earlier. Cations are often best solvated by nucleophilic sites on a solvent molecule (e.g. oxygen & nitrogen atoms), but in the case of carbocations these nucleophiles may form strong covalent bonds to carbon, thus converting the intermediate to a substitution product. This is what happens in the hydrolysis reactions described above.

Fifth, the stereospecificity of these reactions may vary. The positively-charged carbon atom of a carbocation has a trigonal (flat) configuration (it prefers to be sp^2 hybridized), and can bond to a nucleophile equally well from either face. If the intermediate from a chiral alkyl halide survives long enough to encounter a random environment, the products are expected to be racemic (a 50:50 mixture of enantiomers). On the other hand, if the departing halide anion temporarily blocks the front side, or if a nucleophile is oriented selectively at one or the other face, then the substitution might occur with predominant inversion or even retention of configuration.

Contributors

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

Additional Resources

Michigan State Virtual Textbook of Organic Chemistry

S_N1 Reaction

MasterOrganicChemistry

The SN1 Mechanism

Carey 4th Edition On-Line Activity

S_N1 Reaction

Khan Academy

S_N1 Reaction

Mechanism

Leah4Sci

SN1 Reaction Rate and Mechanism - Unimolecular Nucleophilic Substitution Part 1

SN1 Reaction Mechanism (vid 2 of 3) Examples of Unimolecular Substitution

SN1 Reaction Mechanism (vid 3 of 3) with Hydride Shift and Carbocation Rearrangement

Cliffs Notes

Mechanism

Slide Presentations

Web Pages

S_N1 Mechanism

S_N1 Basics

Videos

S_N1 video

SN1 video

9.7.1: 6.06.1 Kinetics, Stereochemistry and Energy Diagram

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9.7.1: 6.06.1 Kinetics, Stereochemistry and Energy Diagram

Additional Resources

Khan Academy

Stereochemistry

Web Pages

Details of S_N1 reaction

Rate law and the S_N1 mechanism

Videos

S_N1 energy diagram

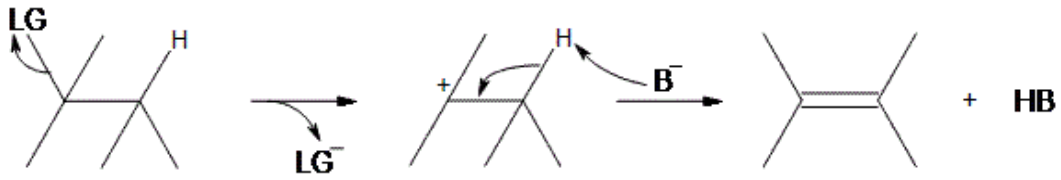
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9.8: E1 Eliminations

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.

Outside Sources

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry Structure and Function. New York: W. H. Freeman, 2007.
2. McMurry, J., Simanek, E. Fundamentals of Organic Chemistry, 6th edition. Cengage Learning, 2007.

Problems

1) Which of these steps is the rate determining step (A or B)?

What is the major product formed (C or D)?

problem 1.bmp

2) In order to produce the most stable alkene product, from which carbon should the base deprotonate (A, B, or C)?

If the carbocation were to rearrange, on which carbon would the positive charge go onto without sacrificing stability (A, B, or C)?

problem 2.bmp

3) Predict the major product of the following reaction.

problem 3.bmp

4) (True or False) – There is no way of controlling the product ratio of E1 / S_n1 reactions.

5) Explain why the presence of a weak base / nucleophile favors E1 reactions over E2.

Answers

1. A , C

2. B, B

3.

answer 3.bmp

4. False - They can be thermodynamically controlled to favor a certain product over another.

5. By definition, an E1 reaction is a Unimolecular Elimination reaction. This means the only rate determining step is that of the dissociation of the leaving group to form a carbocation. Since E2 is bimolecular and the nucleophilic attack is part of the rate determining step, a weak base/nucleophile disfavors it and ultimately allows E1 to dominate. (Don't forget about Sn1 which still pertains to this reaction simultaneously).

Contributors

- Satish Balasubramanian

Additional Resources

Michigan State Virtual Textbook of Organic Chemistry

E1 Elimination

MasterOrganicChemistry

Walkthrough of Elimination Reactions (1) – Introduction

Two Types of Elimination Reactions

The E1 Mechanism

Comparing The SN1 and E1 Reactions

E1 Reactions With Rearrangements

Carey 4th Edition On-Line Activity

Elimination overview

E1 mechanism

Khan Academy

E1 Elimination

Leah4Sci

E1 Reaction Rate and Mechanism - Unimolecular beta-elimination (vid 1 of 3) by Leah4sci

Cliffs Notes

Elimination Reactions

Mechanism of Elimination Reactions

Web Pages

Sparknotes on S_N1 and E1

Videos

E1 Video

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9.9: Comparison of SN2 and SN1

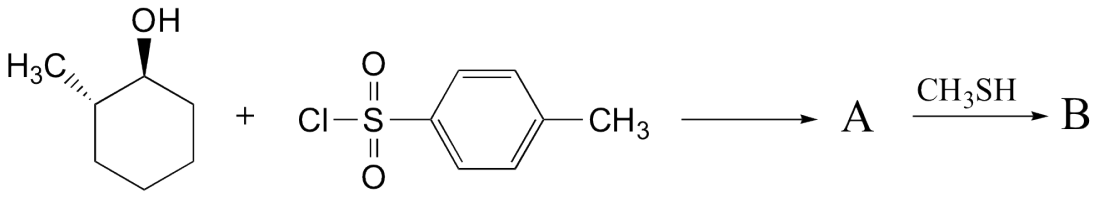
8.5A: What makes a good leaving group?

In 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.

When the C-X bond breaks in a nucleophilic substitution, the pair of electrons in the bond goes with the leaving group. In this way, the leaving group is analogous to the conjugate base in a Brønsted-Lowry acid-base reaction. When we were evaluating the strength of acids in chapter 7, what we were really doing was evaluating the stability of the conjugate base that resulted from the proton transfer. All of the concepts that we used to evaluate the stability of conjugate bases we can use again to evaluate leaving groups – essentially they are one and the same. In other words, the trends in basicity are parallel to the trends in leaving group potential - the weaker the base, the better the leaving group. Just as with conjugate bases, the most important question regarding leaving groups is this: when a leaving group leaves and takes a pair of electrons with it, how well is the extra electron density stabilized?

In laboratory synthesis reactions, halides often act as leaving groups. Iodide, which is the *least* basic of the four main halides, is also the *best* leaving group – it is the most stable as a negative ion. Fluoride is the least effective leaving group among the halides, because fluoride anion is the most basic.

Exercise 8.14: Predict the structures of A and B in the following reaction:



Solution

Template:ExampleEnd

8.5D: 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:

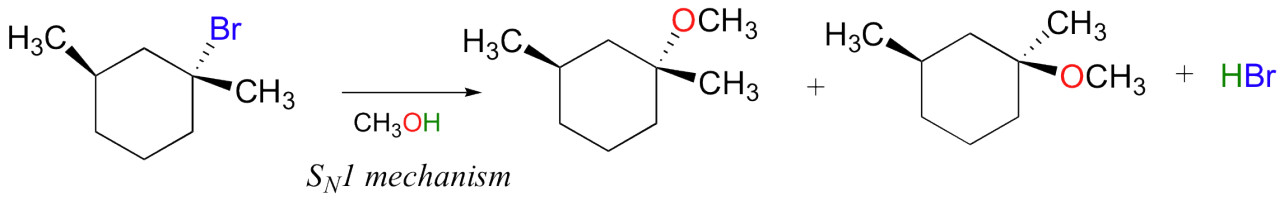
1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a 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.

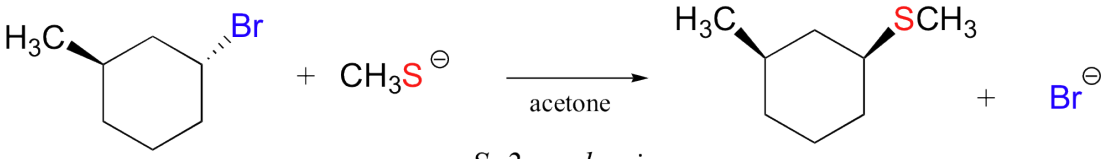
For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent

(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

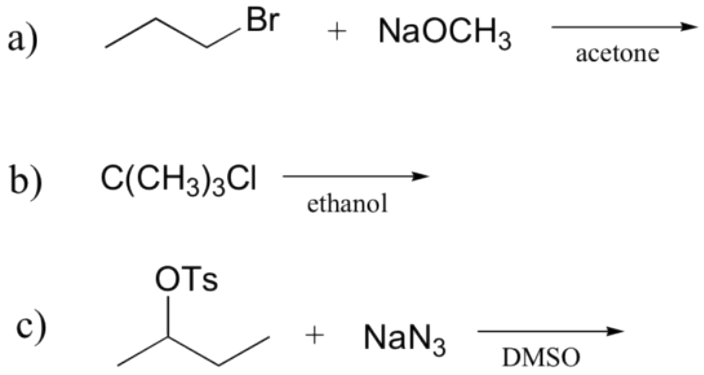
In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar protic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



S_N2 mechanism

Template:ExampleStart

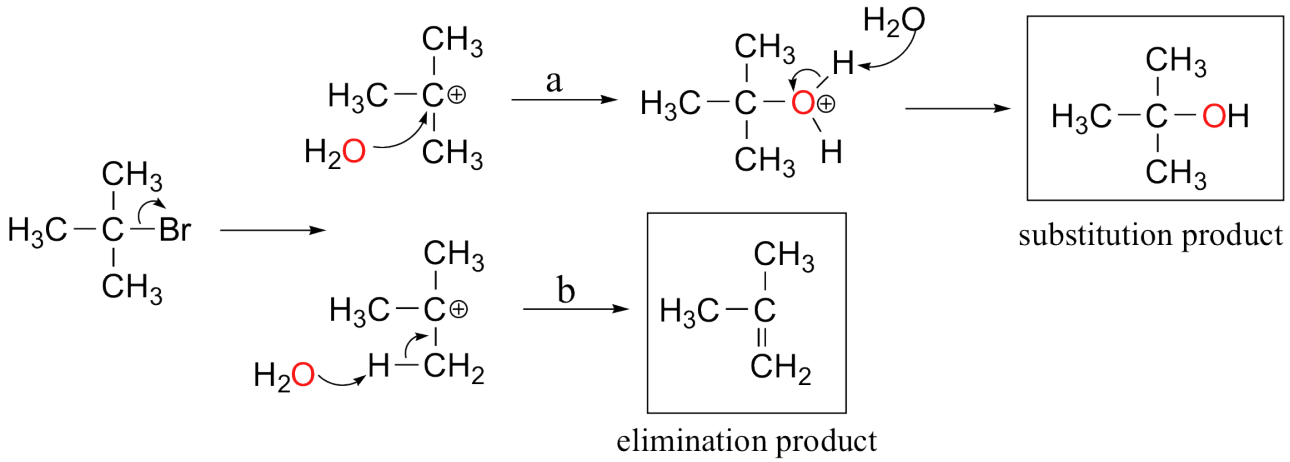
Exercise 8.15: Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism.



Solution

Template:ExampleEnd

In all of our discussion so far about nucleophilic substitutions, we have ignored another important possibility. In many cases, including the two examples above, substitution reactions compete with a type of reaction known as **elimination**. Consider, for example, the two courses that a reaction could take when *tert*-butyl bromide reacts with water:



We begin with formation of the carbocation intermediate. In pathway 'a', water acts as a nucleophile – this is, of course, the familiar S_N1 reaction. However, a water molecule encountering the carbocation intermediate could alternatively act as a *base* rather than as a nucleophile, plucking a proton from one of the methyl carbons and causing the formation of a new carbon-carbon p bond. This alternative pathway is called an elimination reaction, and in fact with the conditions above, both the substitution and the elimination pathways will occur in competition with each other.

We will have lots more to say about elimination reactions in chapter 14, focusing on biochemical eliminations but also thinking about the competition between substitution and elimination that occurs with many nonenzymatic reactions.

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

Further Reading

MasterOrganicChemistry

Steric Hindrance is Like A Fat Goalie

Khan Academy

Steric Hinderance

Solvent Effects

Another Solvent Effect Video

Summary

Leah4Sci

Choosing Between SN1 and SN2 Reactions (vid 1 of 2) By Leah4sci

SN1 vs SN2 Practice Examples (vid 2 of 2) by Leah4sci

Cliffs Notes

Comparison of S_N2 and S_N1

Slide Presentations

S_N1 and S_N2 workshop

Substitution lectures powerpoint files

Web Pages

Handout comparing S_N1 and S_N2

Transtutors S_N1 and S_N2

Summary of S_N1 and S_N2

Summary of nucleophilic substitution

Comparison of S_N1 and S_N2

Comparing stereochemistry of substitution reactions

Substitution overview

Nucleophilic Substitution mechanisms

Substitution overview

Busy page on nucleophilic substitution mechanisms

Two mechanisms

*Sloppy handout

All about substuttion reactions

Great discussion of SN2 and SN1 reactions

Handout about substitution reactions

Videos

Comparing S_N2 and S_N1

S_N1 vs S_N2 made easy

Intro to S_N1 and S_N2

S_N2 and S_N1 mechanisms

Intro to Nucleophilic reactions

Nucleophilic substitution explained

Yale lecture on substitution reactions

SN2 and SN1 made easy

Comparing SN1 and SN2 video

summary of SN1 and SN2

Nucleophilic substitution video

Comparison of SN1 and SN2 video

SN1 vs SN2 video

Factors that affect SN2 and SN1

Tutorial

Nuggets of Knowledge on S_N1 and S_N2

Guide to comparing S_N1 and S_N2

Practice Problems

Good quiz

Good problem set

Nucleophilic Substitution reactions

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9.10: Comparing E1 and E2

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.* $ClCH_2CH_2Cl + KOH \longrightarrow CH_2{=}CHCl$	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.

Contributors

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

Further Reading

MasterOrganicChemistry

Comparing the E1 and E2 Reactions

Elimination Reactions Are Favored By Heat

Comparing the E1 and E2 Reactions

Bulky Bases In Elimination Reactions

Web Pages

Elimination mechanisms

Videos

E1 and E2 made easy

E1 and E2

E1 and E2 elimination video

E1 and E2 Elimination Reaction video

Comparing E1 and E2 reactions

Practice Problems

Carey problems

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9.11: Determining SN2, SN¬1, E2 or E1

- Topic hierarchy

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 below.

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.

The characteristics noted above lead us to anticipate certain types of reactions that are likely to occur with alkyl halides. 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**	**Ionic 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
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Contributors

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

Additional Resources

MasterOrganicChemistry

Trapped In SN1/SN2/E1/E2 Hell? Some Resources

Deciding SN1/SN2/E1/E2 (1) – The Substrate

Deciding SN1/SN2/E1/E2 (2) – The Nucleophile/Base

Deciding SN1/SN2/E1/E2 (3) – The Solvent

Deciding SN1/SN2/E1/E2 (4) – The Temperature

Wrapup – The Quick N' Dirty Guide To SN1/SN2/E1/E2

Khan Academy

Nucleophilicity and Basicity

Primary and tertiary alkyl halides

Secondary Alkyl Halides

Leah4Sci

Alkyl Halide Carbon Chain Analysis for SN1 SN2 E1 E2 Reactions

Slide Presentations

SN1 SN2 E1 E2 comparison slides

Web Pages

Elimination vs Substitution

S_N1, S_N2, E1, E2 Summary

Summary of S_N1, S_N2, E1 and E2

*Comparison of S_N1, S_N2, E1, E2

Substituation vs elimination considerations

Relationship between Sn1 and E1

Substitution vs Elimination summary

Good summation of SN2/SN1/E1/E2 reaction properties

Good handouts of substitution and elimination

Good summary of SN1, Sn2, E1, E2

SN1 SN2 E1 E2 comparison

Videos

S_N1, S_N2, E1, E2

Role of solvent in S_N1, S_N2, E1, E2

LONG video on SN1 SN2 E1 E2

Practice Problems

Answers to elimination questions

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9.12: Carbenes

A carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. The general formula is R-(C:)-R' or R=C:. The term "carbene" may also refer to the specific compound H2C:, also called methylene, the parent hydride from which all other carbene compounds are formally derived. Carbenes are classified as either singlets or triplets depending upon their electronic structure. Most carbenes are very short lived, although persistent carbenes are known. One well studied carbene is Cl2C:, or dichlorocarbene, which can be generated in situ from chloroform and a strong base.

Singlet and triplet carbenes

The two classes of carbenes are singlet and triplet carbenes. Singlet carbenes are spin-paired. In the language of valence bond theory, the molecule adopts an sp2 hybrid structure. Triplet carbenes have two unpaired electrons. They may be either linear or bent, i.e. sp or sp2 hybridized, respectively. Most carbenes have a nonlinear triplet ground state, except for those with nitrogen, oxygen, or sulfur atoms, and halides directly bonded to the divalent carbon.

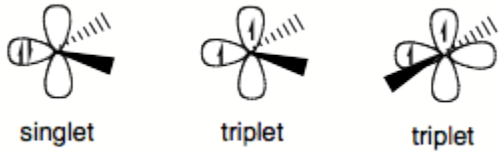
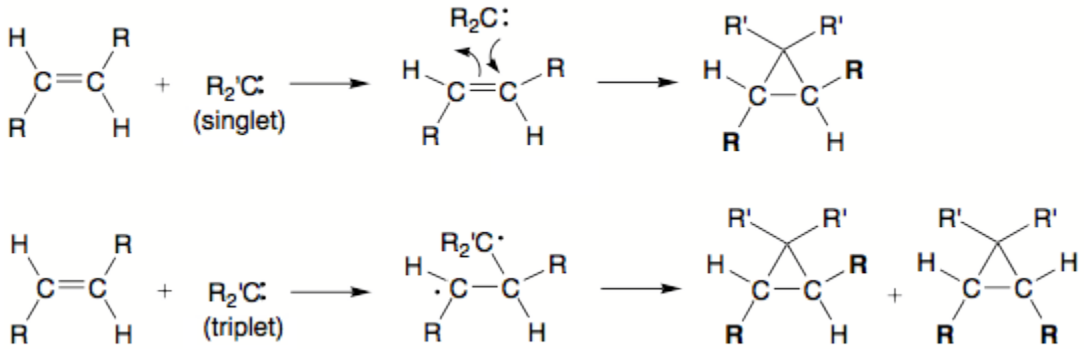


Figure 1: Image used with permission from Wikipedia

Carbenes are called singlet or triplet depending on the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they persist long enough. The total spin of singlet carbenes is zero while that of triplet carbenes is one (in units of [\hbar]). Bond angles are 125-140° for triplet methylene and 102° for singlet methylene (as determined by EPR). Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

For simple hydrocarbons, triplet carbenes usually have energies 8 kcal/mol (33 kJ/mol) lower than singlet carbenes (see also Hund's rule of maximum multiplicity), thus, in general, triplet is the more stable state (the ground state) and singlet is the excited state species.Substituents that can donate electron pairs may stabilize the singlet state by delocalizing the pair into an empty p-orbital. If the energy of the singlet state is sufficiently reduced it will actually become the ground state. No viable strategies exist for triplet stabilization. The carbene called 9-fluorenylidene has been shown to be a rapidly equilibrating mixture of singlet and triplet states with an approximately 1.1 kcal/mol (4.6 kJ/mol) energy difference.[3] It is, however, debatable whether diaryl carbenes such as the fluorene carbene are true carbenes because the electrons can delocalize to such an extent that they become in fact biradicals. In silico experiments suggest that triplet carbenes can be thermodynamically stabilized with electropositive heteroatoms such as in silyl and silyloxy carbenes, especially trifluorosilyl carbenes.[4]

Reactivity



Carbene addition to alkenes

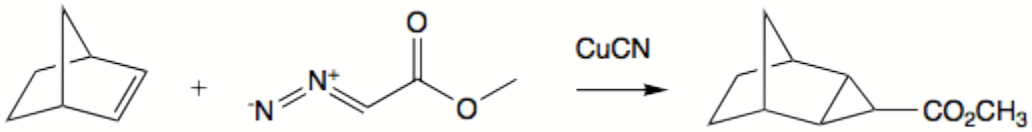
Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene or with *trans*-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product: *cis* from *cis* and *trans* from *trans*, which proves that the methylene is a singlet.[5] If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.

Reactivity of a particular carbene depends on the substituent groups. Their reactivity can be affected by metals. Some of the reactions carbenes can do are insertions into C-H bonds, skeletal rearrangements, and additions to double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.

Cyclopropanation

Carbenes add to double bonds to form cyclopropanes. A concerted mechanism is available for singlet carbenes. Triplet carbenes do not retain stereochemistry in the product molecule. Addition reactions are commonly very fast and exothermic. The slow step in most instances is generation of carbene. A well-known reagent employed for alkene-to-cyclopropane reactions is Simmons-Smith reagent. This reagent is a system of copper, zinc, and iodine, where the active reagent is believed to be iodomethylzinc iodide. Reagent is complexed by hydroxy groups such that addition commonly happens syn to such group.



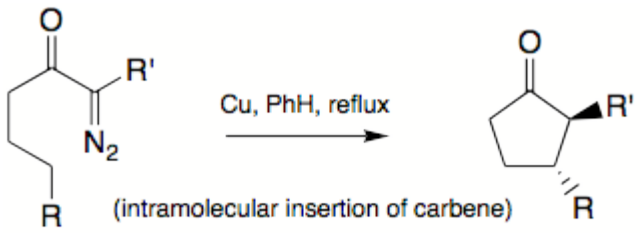
Carbene cyclopropanation

C—H insertion

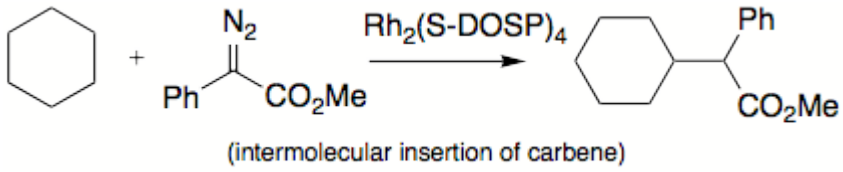
Carbene insertion

Insertions are another common type of carbene reactions. The carbene basically interposes itself into an existing bond. The order of preference is commonly: 1. X–H bonds where X is not carbon 2. C–H bond 3. C–C bond. Insertions may or may not occur in single step.

Intramolecular insertion reactions present new synthetic solutions. Generally, rigid structures favor such insertions to happen. When an intramolecular insertion is possible, no intermolecular insertions are seen. In flexible structures, five-membered ring formation is preferred to six-membered ring formation. Both inter- and intramolecular insertions are amendable to asymmetric induction by choosing chiral ligands on metal centers.

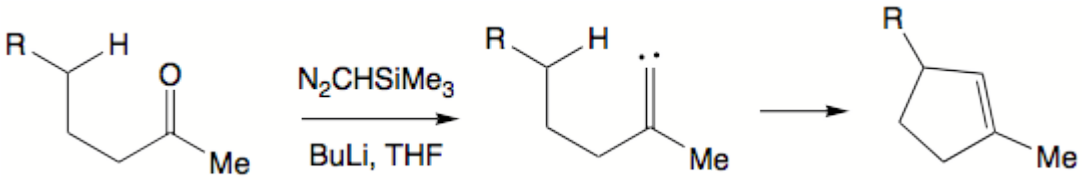


Carbene intramolecular reaction



Carbene intermolecular reaction

Alkylidene carbenes are alluring in that they offer formation of cyclopentene moieties. To generate an alkylidene carbene a ketone can be exposed to trimethylsilyl diazomethane.



Alkylidene carbene

Carbene dimerization

Carbenes and carbenoid precursors can undergo dimerization reactions to form alkenes. While this is often an unwanted side reaction, it can be employed as a synthetic tool and a direct metal carbene dimerization has been used in the synthesis of polyalkynylethenes. Persistent carbenes exist in equilibrium with their respective dimers. This is known as the Wanzlick equilibrium.

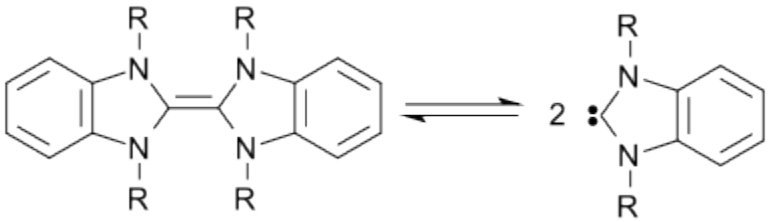


Figure : Wanzlick equilibrium

Carbene ligands in organometallic chemistry

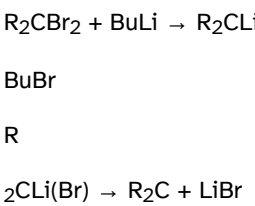
In organometallic species, metal complexes with the formulae L_nMCRR' are often described as carbene complexes. Such species do not however react like free carbenes and are rarely generated from carbene precursors, except for the persistent carbenes. The transition metal carbene complexes can be classified according to their reactivity, with the first two classes being the most clearly defined:

- Fischer carbenes, in which the carbene is bonded to a metal that bears an electron-withdrawing group (usually a carbonyl).

In such cases the carbenoid carbon is mildly electrophilic.
- Schrock carbenes, in which the carbene is bonded to a metal that bears an electron-donating group. In such cases the carbenoid carbon is nucleophilic and resembles Wittig reagent (which are not considered carbene derivatives).
- Persistent carbenes, also known as Arduengo or Wanzlick carbenes. These include the class of *N*-heterocyclic carbenes (NHCs) and are often are used as ancillary ligands in organometallic chemistry. Such carbenes are spectator ligands of low reactivity.

Generation of carbenes

- A method that is broadly applicable to organic synthesis is induced elimination of halides from gem-dihalides employing organolithium reagents. It remains uncertain if under these conditions free carbenes are formed or metal-carbene complex. Nevertheless, these metallocarbenes (or carbenoids) give the expected organic products.



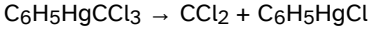
$$R_2CBr_2 + BuLi \rightarrow R_2CLi(Br) +$$

$$BuBr$$

$$R$$

$$_2CLi(Br) \rightarrow R_2C + LiBr$$

- For cyclopropanations, zinc is employed in the Simmons–Smith reaction. In a specialized but instructive case, alpha-halomercury compounds can be isolated and separately thermolyzed. For example, the "Seyferth reagent" releases CCl_2 upon heating.



$$C_6H_5HgCCl_3 \rightarrow CCl_2 + C_6H_5HgCl$$

- Most commonly, carbenes are generated from diazoalkanes, via photolytic, thermal, or transition metal-catalyzed routes. Catalysts typically feature rhodium and copper. The Bamford-Stevens reaction gives carbenes in aprotic solvents and carbenium ions in protic solvents.
- Base-induced elimination HX from haloforms (CHX_3) with under phase-transfer conditions.
- Photolysis of diazirines and epoxides can also be employed. Diazirines are cyclic forms of diazoalkanes. The strain of the small ring makes photoexcitation easy. Photolysis of epoxides gives carbonyl compounds as side products. With asymmetric epoxides, two different carbonyl compounds can potentially form. The nature of substituents usually favors formation of one over the other. One of the C-O bonds will have a greater double bond character and thus will be stronger and less likely to break. Resonance structures can be drawn to determine which part will contribute more to the formation of carbonyl. When one substituent is alkyl and another aryl, the aryl-substituted carbon is usually released as a carbene fragment.
- Carbenes are intermediates in the Wolff rearrangement

See also

- Transition metal carbene complexes, also known as carbenoids
- Atomic carbon a single carbon atom with the chemical formula :C:, in effect a twofold carbene. Also has been used to make "true carbenes" in situ.
- Foiled carbenes derive their stability from proximity of a double bond (i.e. their ability to form conjugated systems).
- Carbene analogs
- Carbenium ions, protonated carbenes
- Ring opening metathesis polymerization

References

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9.13: Cyclopropane Synthesis

Objectives

After completing this section, you should be able to

1. describe, and write the detailed mechanism for, the formation of a carbene, such as dichlorocarbene.
2. describe the structure of a carbene in terms of the hybridization of the central carbon atom.
3. write an equation for the formation of a substituted cyclopropane from an alkene and a carbene.
4. identify the reagents, the alkene, or both, needed to prepare a given substituted cyclopropane by addition of a carbene to a double bond.
5. 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.

dichlorocyclopropane structure from alkene and an in situ dichlorocarbene

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.

mechanism of carbene generation from chloroform

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

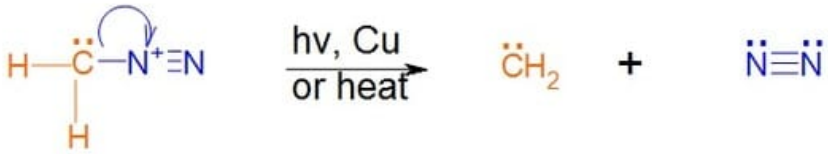
Carbenes were once only thought of as short lived intermediates. The reactions of this section only deal with these short lived carbenes which are mostly prepared in situ, in conjunction with the main reaction. However, there do exist so called persistent carbenes. These persistent carbenes are stabilized 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 (although, 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.

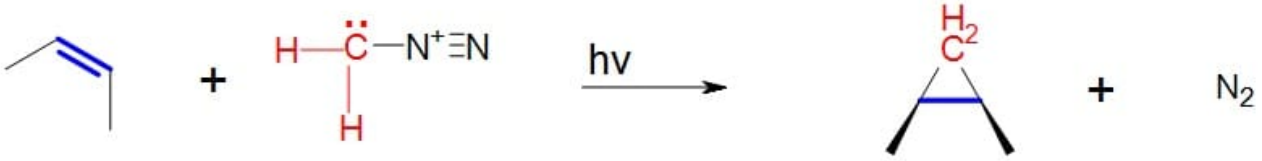
Preparation of methylene

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.

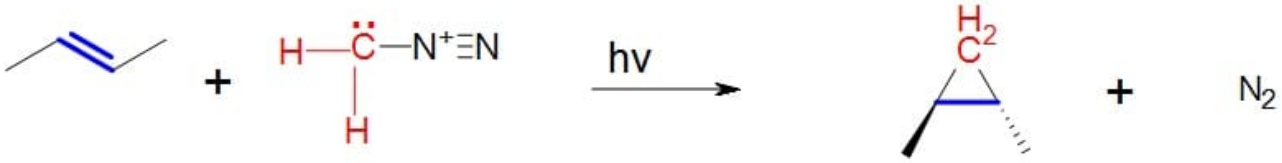


Carbene reaction with alkenes

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.



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. 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 Simmons-Smith reaction which utilizes the carbenoid ICH_2ZnI. The carbenoid is formed in situ via the mixing of a Zn-Cu couple with CH_2I_2.Since this reacts the same as a carbene, the same methods can be applied to determine the product. An example of this is given as problem 5.

Outside links

- http://en.Wikipedia.org/wiki/Simmons-Smith_reaction
- http://en.Wikipedia.org/wiki/Carbene

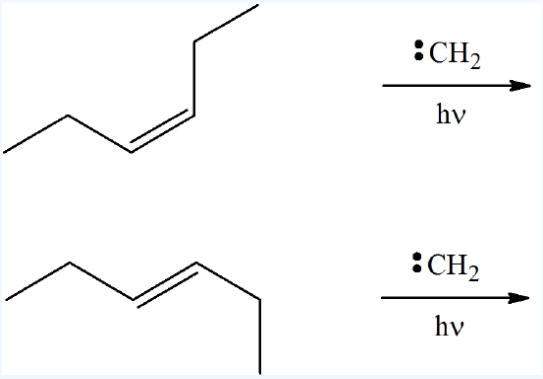
References

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Exercises

Exercise 9.13.1

Predict the resulting products. Will they be the same product?



Answer available at the end of this section.

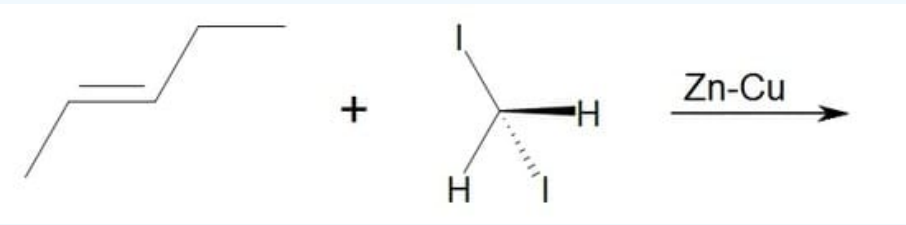
Exercise 9.13.2

What would be the result of a Simmons-Smith reaction that used *trans*-3-pentene as a reagent?

Answer available at the end of this section.

Exercise 9.13.3

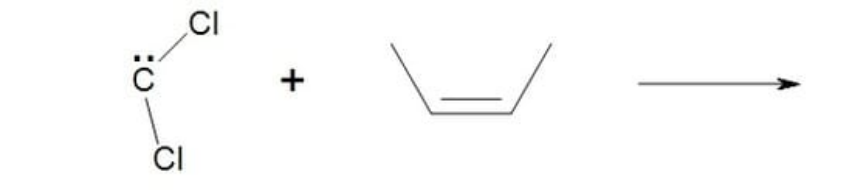
Draw the product of this reaction. What type of reaction is this?



Answer available at the end of this section.

Exercise 9.13.4

What would the following reaction yield?

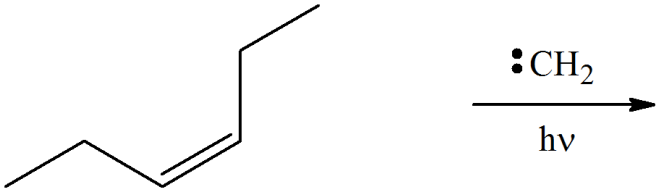


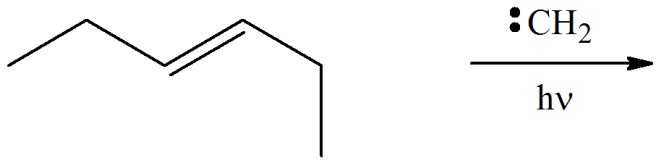
Answer available at the end of this section.

Questions

Q8.9.1

Predict the following products. Will they be the same product?

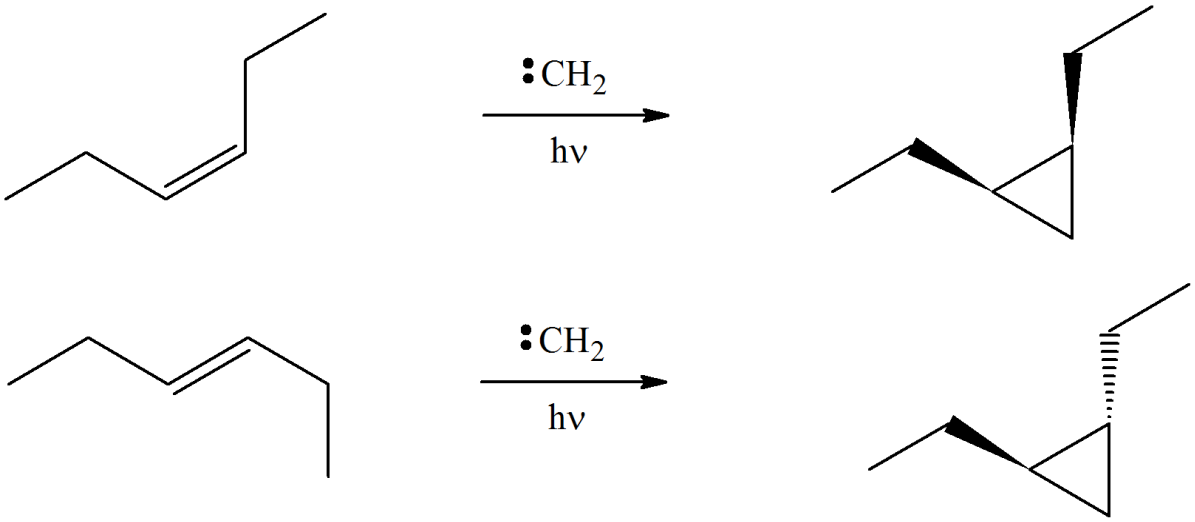




Solutions

S8.9.1

No they will not be the same product, they will be isomers of each other.



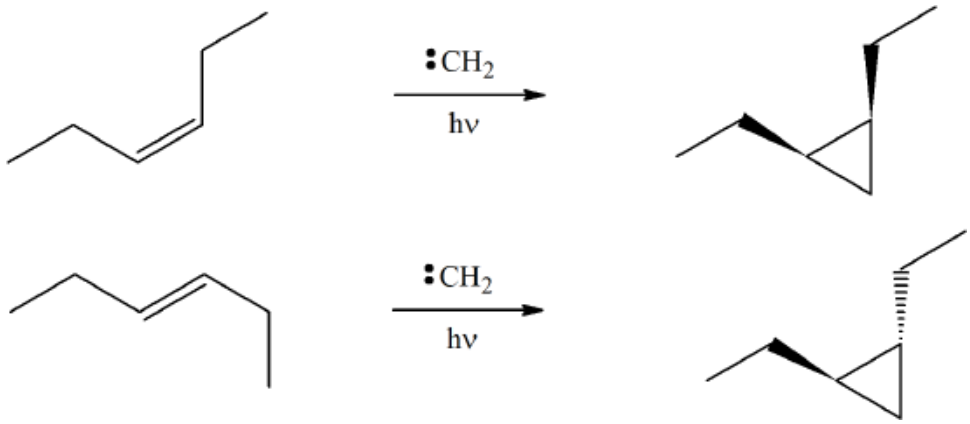
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Paul Tisher

Answers

Exercise 9.13.1

No they will not be the same product, they will be isomers of each other.

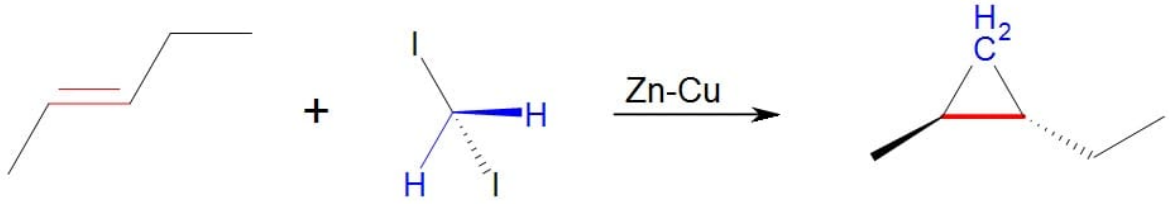


Exercise 9.13.2

The stereochemistry will be retained making a cyclopropane with trans methyl and ethyl groups. *Trans*-1-ethyl-2-methylcyclopropane

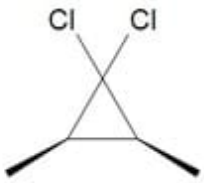
Exercise 9.13.3

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.



Exercise 9.13.4

The halogenated carbene will react the same as methylene yielding, *cis*-1,1-dichloro-2,3dimethylcyclopropane.



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10: THE CHEMISTRY OF ALCOHOLS AND THIOLS

10.1: Dehydration Reactions of Alcohols

10.2: Reactions of Alcohols with Hydrohalic Acids

10.3: Converting an Alcohol to a Sulfonate Ester

10.4: Oxidation and Reduction in Organic Chemistry

10.5: Oxidation of Alcohols

10.6: The Formation of Carboxylic Acids

10.7: Nicotinamide Adenine Dinucleotide (NAD)

10.8: Dehydrogenases

10.9: Prochirality

10.10: Thiols and Sulfides

10.11: Nucleophilicity of Sulfur Compounds

10.12: Redox Reactions of Thiols and Disulfides

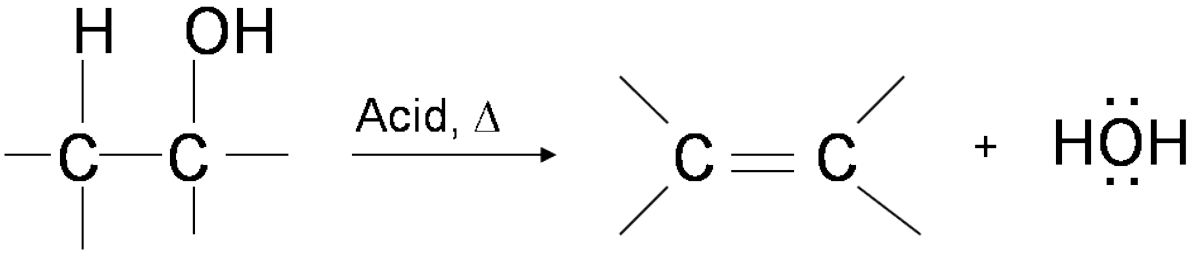
10.13: An Introduction to Organic Synthesis

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10.1: Dehydration Reactions of Alcohols

Dehydration of Alcohols to Yield Alkenes

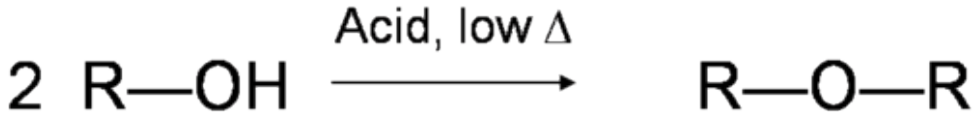
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



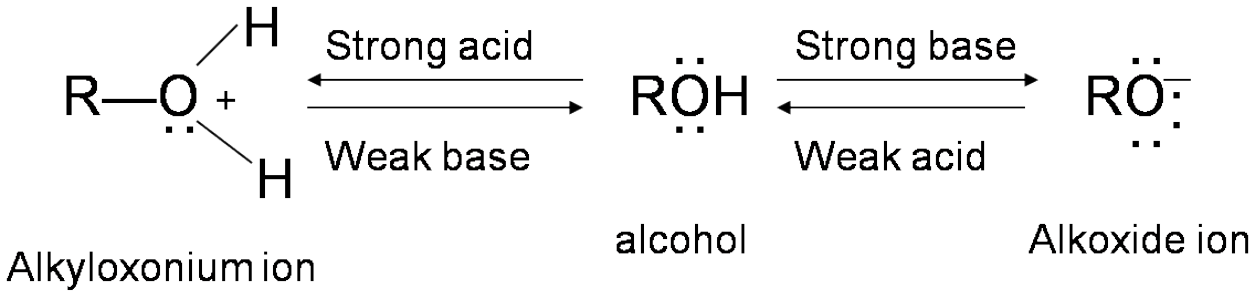
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 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 as both 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 +OH2 (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

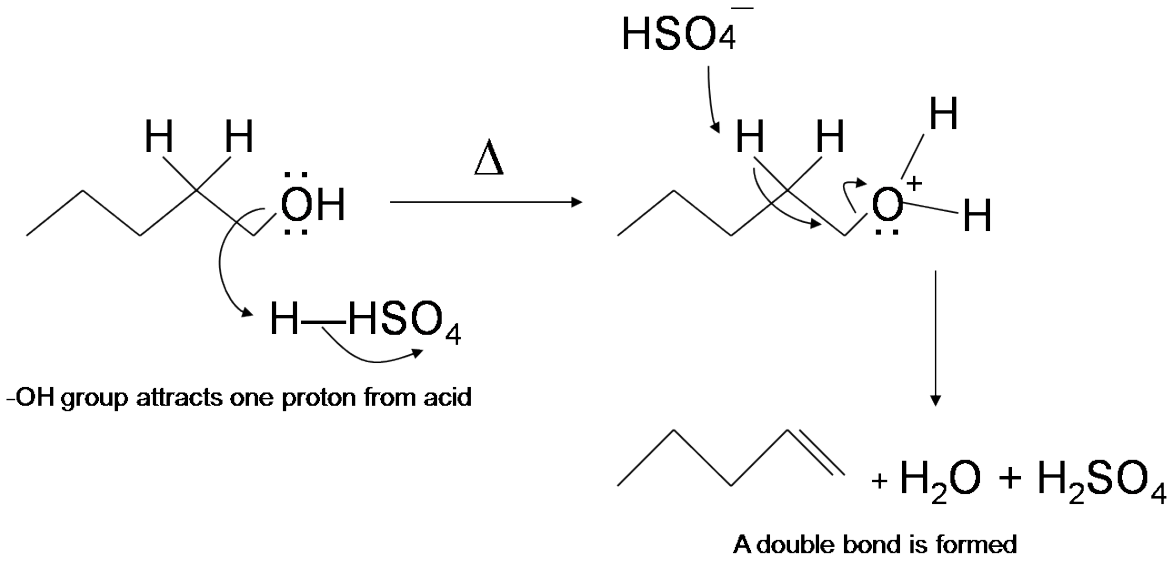
Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind

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 base) then reacts with 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 reactions is ranked as follows:

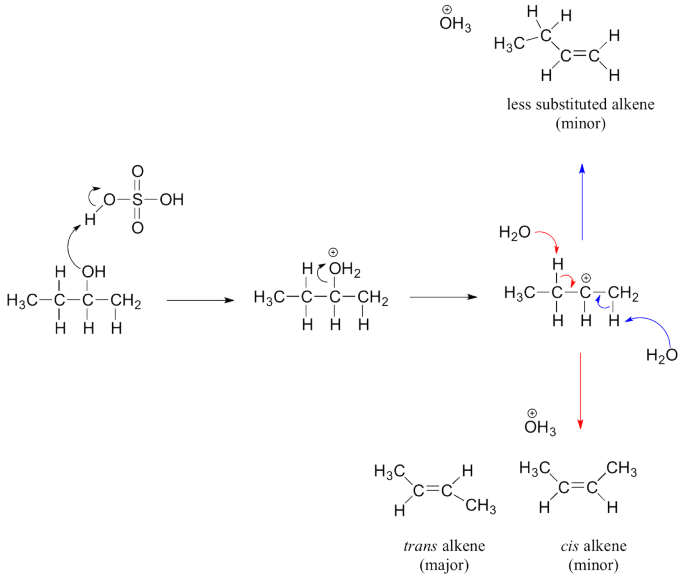
Methanol < primary < secondary < tertiary

Primary alcohols dehydrate through the E2 mechanism. The hydroxyl oxygen donates two electrons to a proton from sulfuric acid (H_2SO_4), forming an alkyloxonium ion. Then the conjugate base, HSO_4^-, reacts with one of the adjacent (beta) hydrogen atoms while the alkyloxonium ion leaves in a concerted process, forming a double bond.



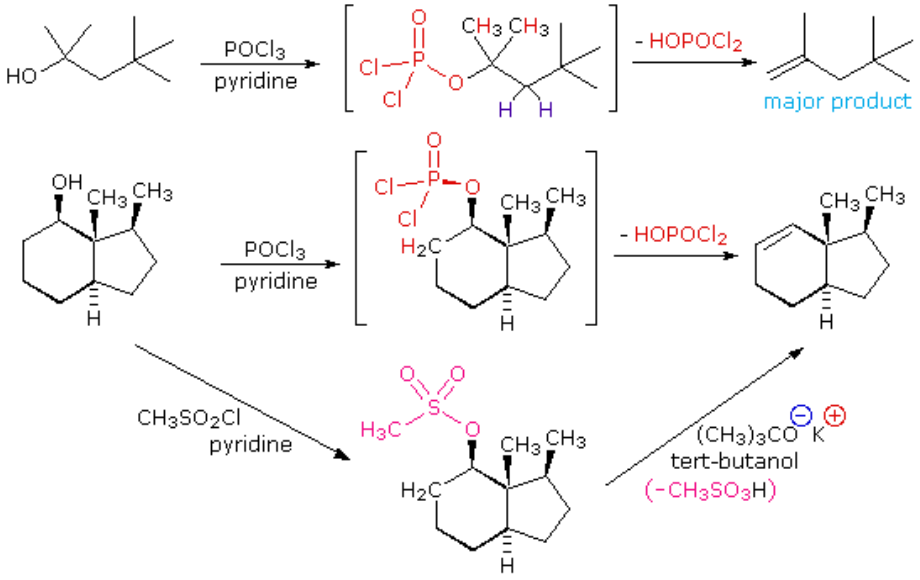
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon to form a double bond. Notice in the mechanism below that the alkene 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 that according to Zaitsev's Rule, the more substituted alkenes are formed preferentially because they are more stable than less substituted alkenes. Additinally, trans alkenes are more stable than cis alkenes and are also the major product formed. For the example below, the trans diastereomer of the 2-butene product is most abundant.

Dehydration reaction of secondary alcohol



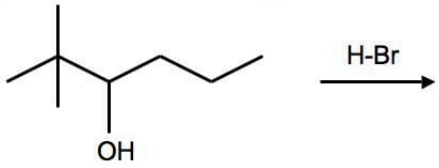
The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

The E2 elimination of 3°-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. This procedure is also effective with hindered 2°-alcohols, but for unhindered and 1°-alcohols an S_N2 chloride ion substitution of the chlorophosphate intermediate competes with elimination. Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3°-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2°-alcohol. The first uses the single step POCl3 method, which works well in this case because SN2 substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.

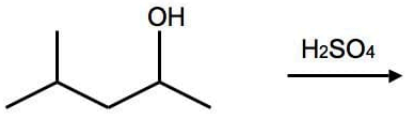


Practice Problems (aka Exercises)

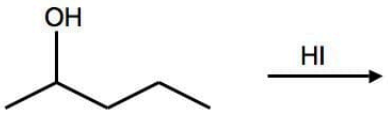
1) Please show the arrow pushing mechanism and the major final product:



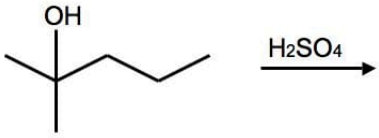
2) Please show the mechanism with **hydride shift** and show the final product:



3) Show both major and minor products of the given reaction:

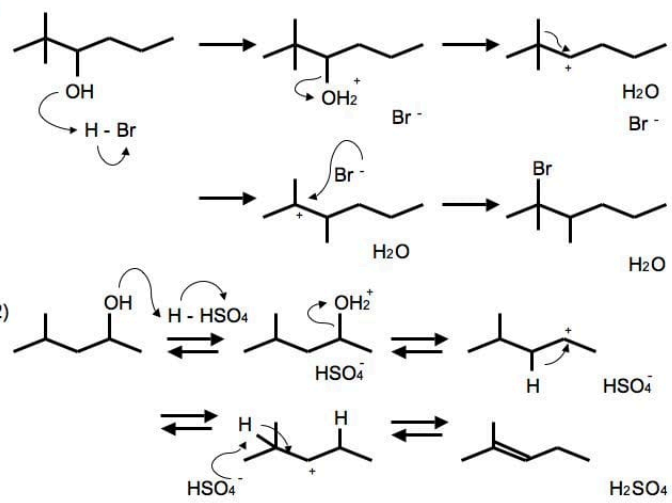


4) Show both major and minor products of the given reaction:



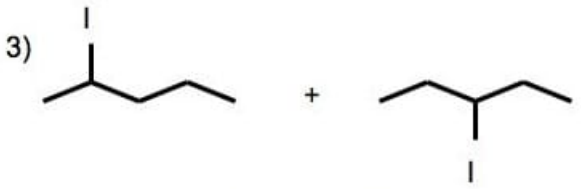
Answers to Practice Problems:

1)



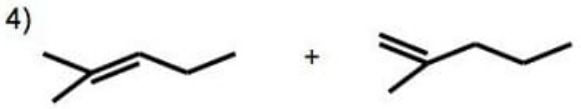
2)

3)

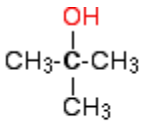


Equal amounts

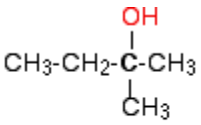
4)



Major product Minor product



2-methylpropan-2-ol

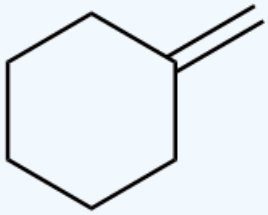


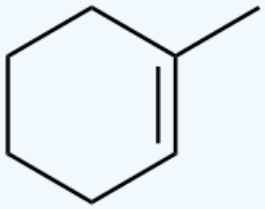
2-methylbutan-2-ol

Exercises

6. Starting with cyclohexanol, describe how you would prepare cyclohexene.

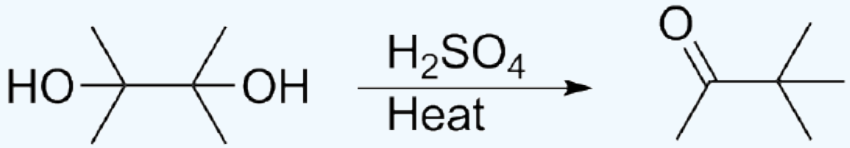
7. In the dehydration of 1-methylcyclohexanol, which product is favored?





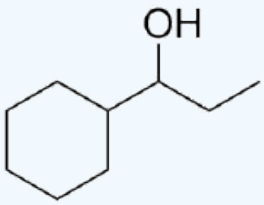
8.

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint a rearrangement occurs)



9.

Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.



Answer

Answer available at the end of this section.

Contributors and Attributions

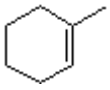
- Jeffrey Ma

Answers

Exercises

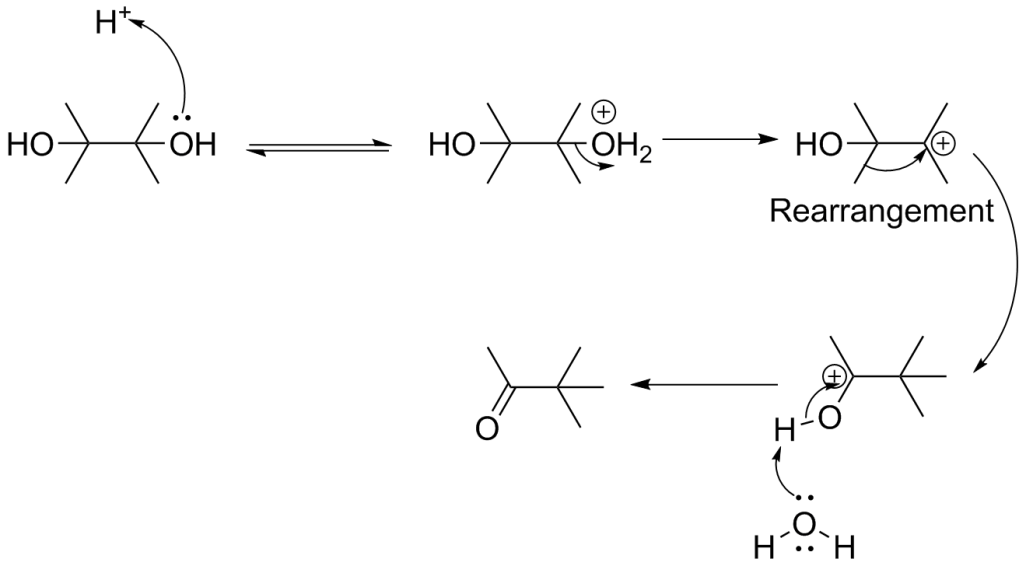
6. H_2SO_4 with heat since there are no concerns about C+ rearrangement

7. The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.



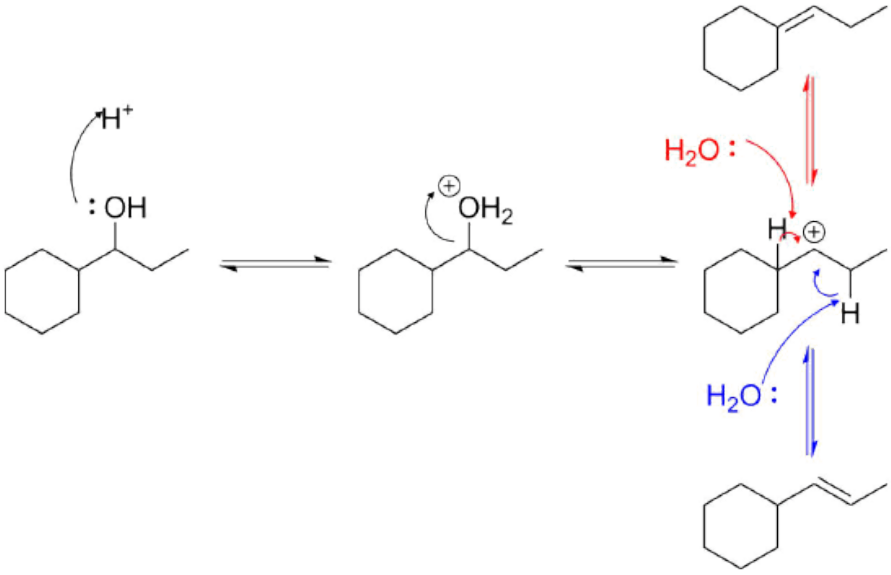
8.

This reaction is known as the Pinacol rearrangement.



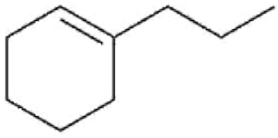
Note how the carbocation after the rearrangement is resonance stabilized by the oxygen

9. Note: While the mechanism is instructive for the first part of the this answer. The carbocation rearrangement would occur and determine the major and minor products as explained in the second part of this answer.



The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

Note: With the secondary carbocation adjacent a tertiary carbon center, a 1,2 hydride shift (rearrangement) would occur to form a tertiary carbocation and vcompound below would be the major product. The minor product being the same product as the one formed from the red arrows.

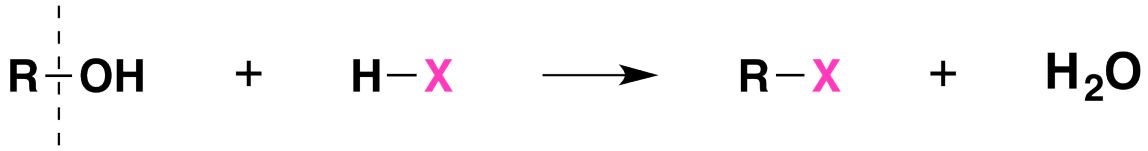


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10.2: Reactions of Alcohols with Hydrohalic Acids

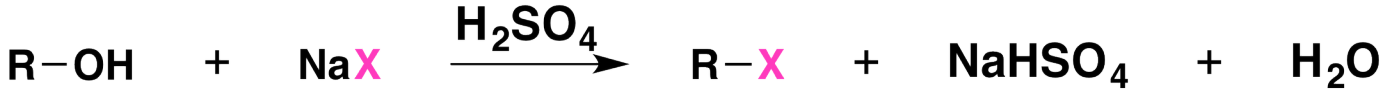
Conversion of Alcohols into Alkyl Halides

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

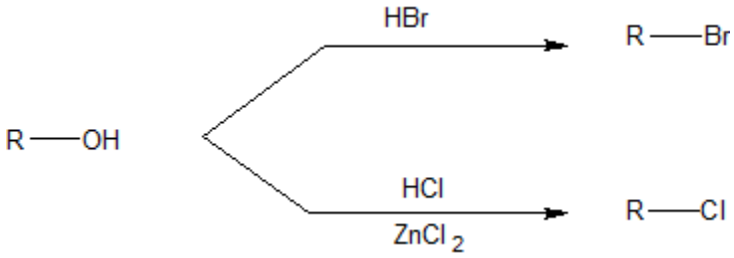


- The order of reactivity of alcohols is 3° > 2° > 1° methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:



Because Cl- is a weaker nucleophile than Br-, the reaction with HCl requires a catalyst such as ZnCl2 as shown below.

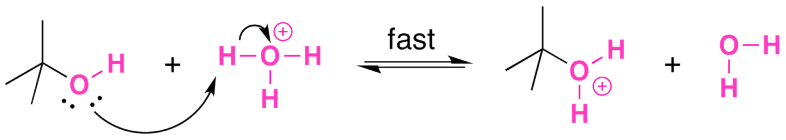


Mechanisms of the Reactions of Alcohols with HX

Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as the substrate.

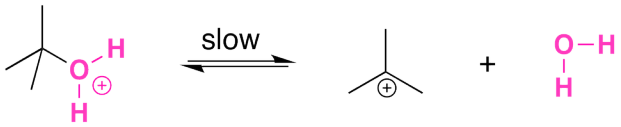
The S_N1 mechanism is illustrated by the reaction tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_n1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation (R^+) and H_2O. Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group water, H_2O, which makes the dissociation step of the S_N1 mechanism more favorable.

Step 1



the alcohol accepts a proton

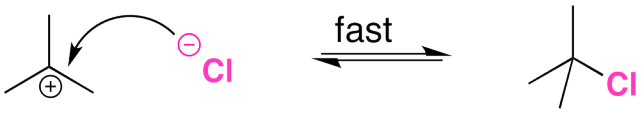
Step 2



the protonated hydroxyl group departs as a leaving group to form a carbocation and water

In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

Step 3

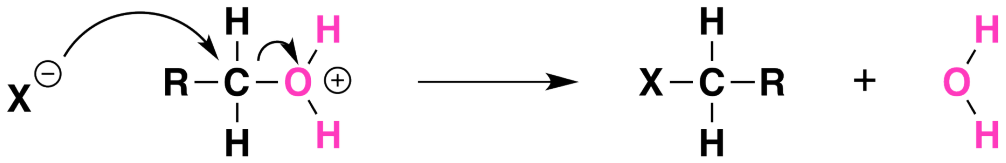


a halide anion reacts with the carbocation

When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

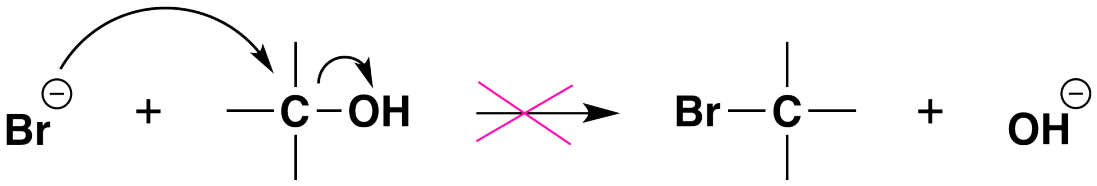
In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



(protonated 1° alcohol or methanol)

(A good leaving group)

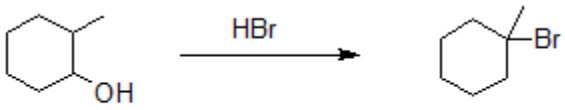
Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

Carbocation rearrangements are extremely common in organic chemistry reactions are are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial

molecule. However, this phenomenon is not as simple as it sounds.

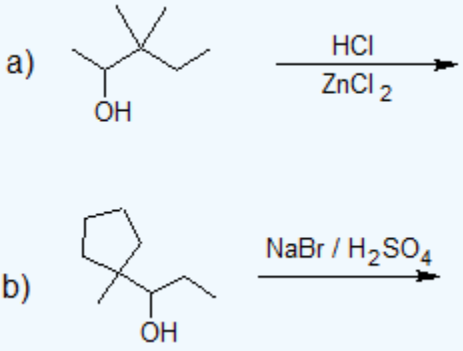


The carbocation intermediate undergoes a 1,2-hydride shift.

The most common methods for converting 1°- and 2°-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use. The alcohol reactions with thionyl chloride or phosphorus tribromide are discussed in the next section.

Exercises

1. Predict the product of each reaction below.



Answer available at the end of this section.

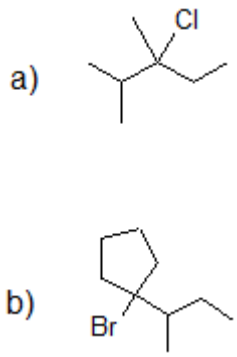
Contributors and Attributions

- 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

Exercises

1.



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10.3: Converting an Alcohol to a Sulfonate Ester

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.

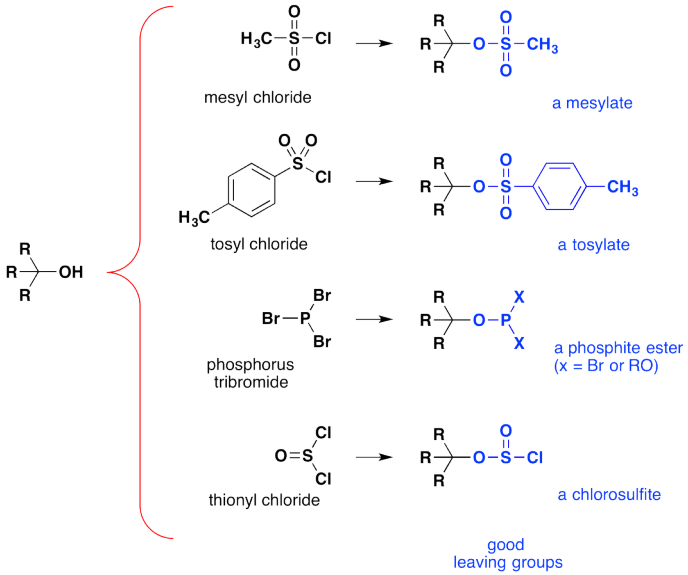
$CH_3CH_2CH_2CH_2–Br + Na^{(+)}\ CN^{(-)} \longrightarrow CH_3CH_2CH_2CH_2–CN + Na^{(+)}\ Br^{(-)}$
$CH_3CH_2CH_2CH_2–OH + Na^{(+)}\ CN^{(-)} \longrightarrow$ No Reaction

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.

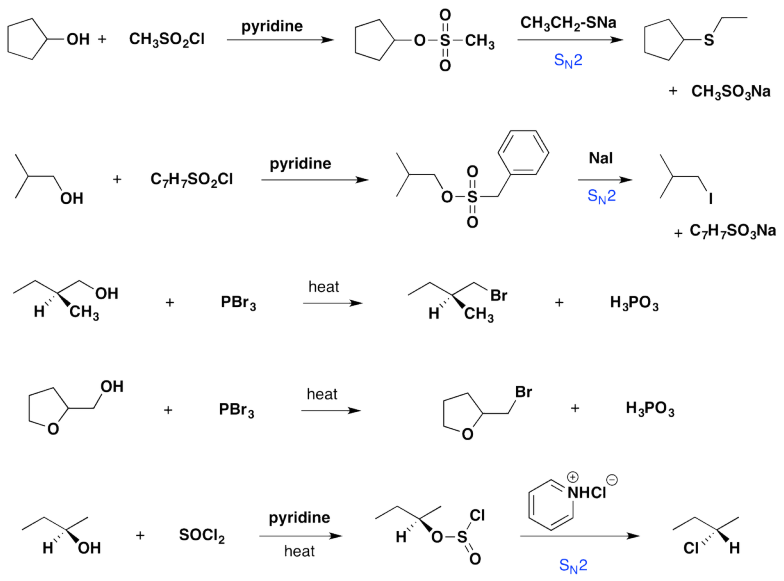


The importance of sulfonate ester intermediates in general nucleophilic substitution reactions of alcohols may be illustrated by the following conversion of 1-butanol to pentanenitrile (butyl cyanide), a reaction that does not occur with the alcohol alone. The phosphorus and thionyl halides, on the other 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**

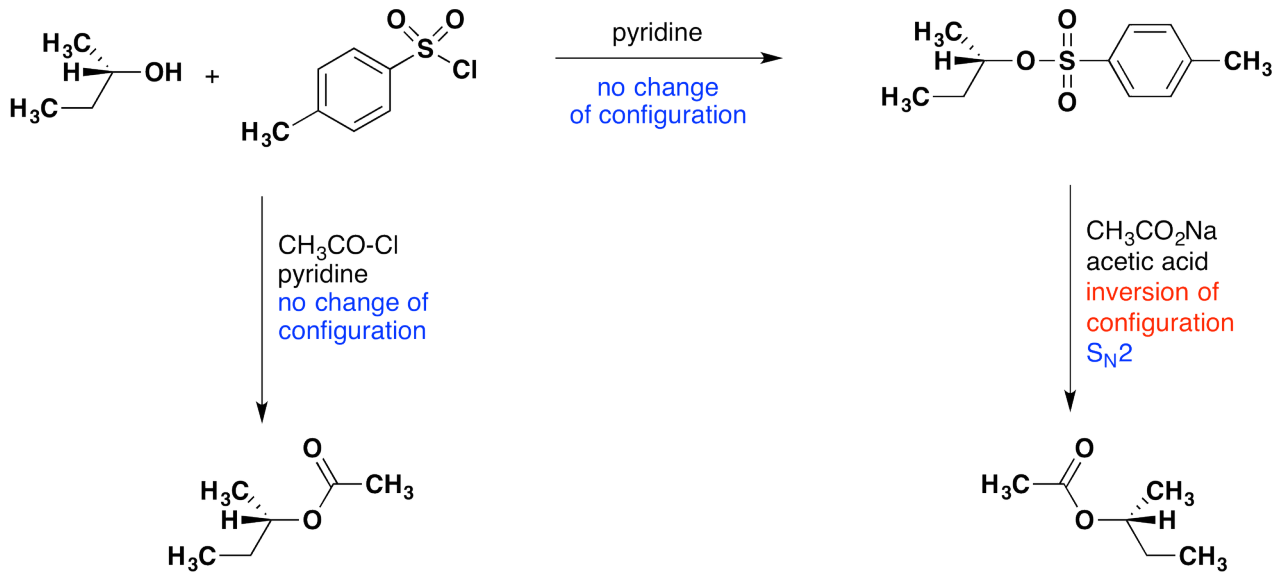
Tertiary alcohols are not commonly used for substitution reactions of the type discussed here because S_N1 and E1 reaction paths are dominant and are difficult to control.



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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10.4: Oxidation and Reduction in Organic Chemistry

Objectives

After completing this section, you should be able to

- identify organic reactions as being oxidations, reductions, or neither.
- rank given compounds in order of their oxidation level.

Key Terms

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

- oxidation
- reduction
- heteroatom

General Redox Reactions

General chemistry courses describe oxidation and reduction - when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. Also, oxidation and reduction half reactions occur in pairs: if one species is oxidized, another must be reduced at the same time. Thus, the combination of an oxidation and a reduction half reaction is termed a 'redox reaction.' Most of the redox reactions you have seen previously in general chemistry typically involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$\mathrm{Cu^{+2}\,(aq) + Zn\,(s) \longrightarrow Cu\,(s) + Zn^{+2}\,(aq)}$$

$$\mathrm{Cu^{+2}\,(aq) + 2\,e^{-} \longrightarrow Cu\,(s)}$$

Reduction

$$\mathrm{Zn\,(s) \longrightarrow Zn^{+2}\,(aq) + 2\,e^{-}}$$

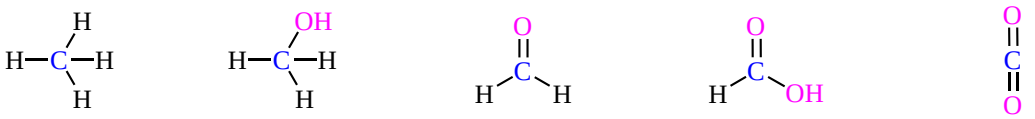
Oxidation

In order, to keep track of electrons in organic molecules an oxidation state formalism is used. Oxidation states do not represent the actual charge on an atom, but it will allow the number of electrons being gained or lost by a particular atom to be determined during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative atom, such as nitrogen, oxygen, sulfur, or a halogen.

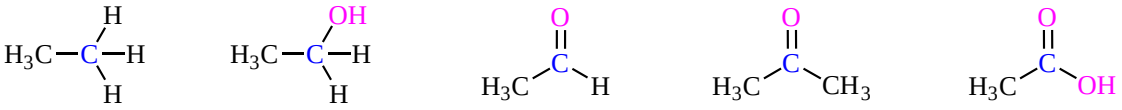
When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized. We'll take a series of single carbon compounds as an example. Methane (CH_4) is at the lowest oxidation level of carbon because is has the maximum possible number of bonds to hydrogen. Carbon dioxide (CO_2) is at the highest oxidation level because it has the maximum number of bonds to an electronegative atom.



	methane	methanol	formaldehyde	methanoic Acid	carbon dioxide
Oxidation State:	4(−1) + 0 = −4	3(−1) + 1 = −2	2(−1) + 2(+1) = 0	1(−1) + 3(+1) = +2	0(−1) + 4(+1) = +4

most reduced ⟹ **most oxidized**

This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



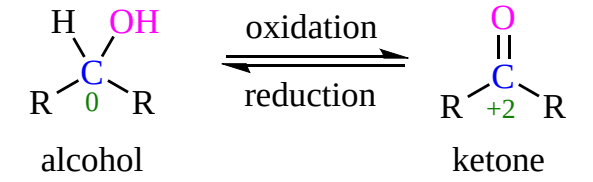
	ethane	ethanol	ethanal	propanone	ethanoic acid
Oxidation State:	3(−1) + 0 = −3	2(−1) + 1 + 0 = −1	2(+1) − 1 + 0 = +1	2(+1) + 2(0) = +2	3(+1) + 0 = +3

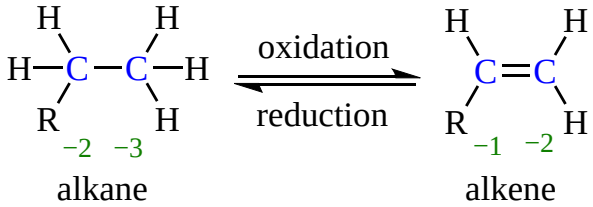
most reduced ⟹ **most oxidized**

Organic Redox Reactions

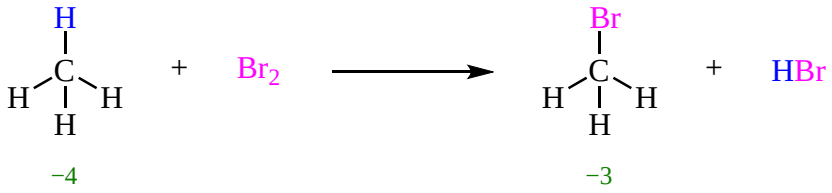
It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized. If a reaction converts a compound to a higher oxidation level that is an oxidation. If it converts a compound to a lower oxidation level it is a reduction. If the oxidation level of the reactant does not change it is not a redox reaction.

Two examples of organic redox reactions are shown below. The conversion of an alcohol to a ketone is considered an oxidation because the oxidation level of the carbon increases from 0 to +2. This implies that the reaction would require an oxidizing agent. Likewise, the conversion of a ketone to an alcohol is a reduction and would require a reducing agent. The conversion of an alkane to alkene is an oxidation because the oxidation state on both carbons is increasing while the reverse reaction would be a reduction.



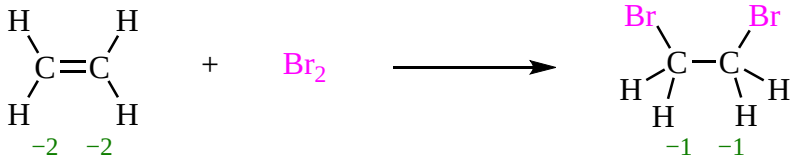


Now reaction previously discussed in this textbook can be considered to determine if they are in fact redox reaction. The free radical bromination of methane to bromomethane would be an oxidation because the oxidation level of carbon is raised from -4 to -3.

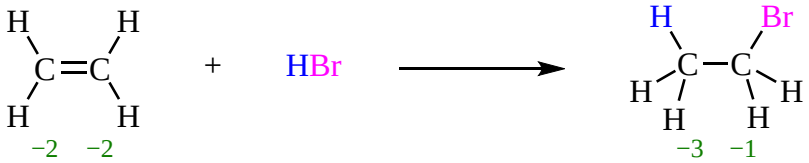


free radical halogenation: **oxidation**

The electrophilic addition of Br_2 to an alkene to provide a 1,2-dibromide is an oxidation because both carbons increase their oxidation level from -2 to -1. However, the electrophilic addion of HBr to an alkene to provide an alkyl halide is not a redox reaction because the overall oxidation state of carbons involved are not changed. One carbon has its oxidation level decreased from -2 to -3 while the other carbon's oxidation level is increased from -2 to -1. Overall, the change in oxidation level cancels out to leave an overall change of oxidcation level in the compound of 0.

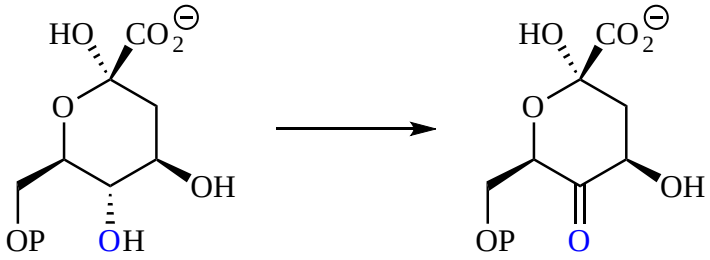


electrophilic addition of Br_2: **oxidation**

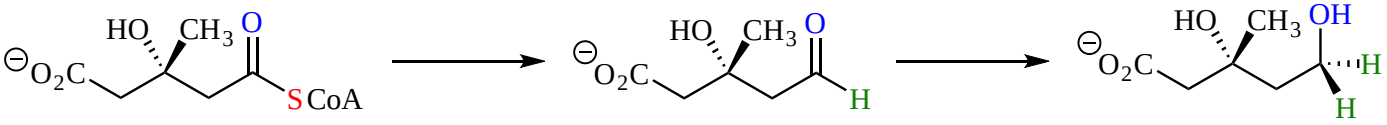


electrophilic addition of HBr: **not redox**

You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant . Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.

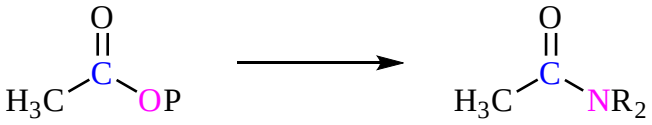


Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



thioester aldehyde alcohol

An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



carbon is in same oxidation state: **not redox**

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

Worked Example 10.4.1

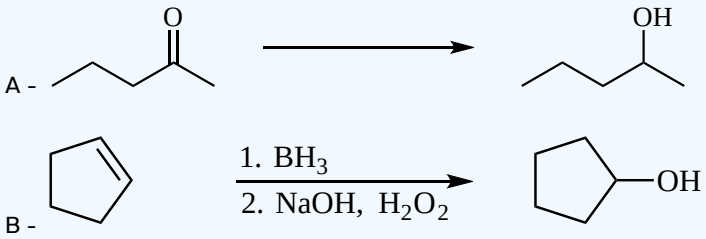
Rank the following compounds in order of increasing oxidation level:



Answer available at the end of this section.

Exercise 10.4.2

In each case state whether the reaction is an oxidation or reduction of the organic compound.

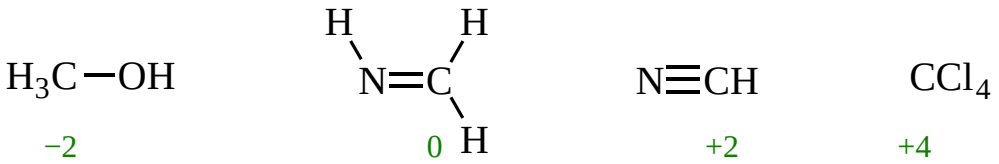


Answer available at the end of this section.

Answers

Worked Example 10.4.1

The easiest way to solve this problem is to calculate the oxidation level of the carbon in each compound. Remembering that hydrogens decrease the oxidation level by one, electronegative elements increase the oxidation level by one, and carbons do not change the oxidation level, the oxidation level of each carbon can be calculate. The carbon in CH_3OH has three bonds to hydrogens and one bond to oxygen so it oxidation level is 3(-1) + 1(+1) = -2. The carbon in HCN has one bond to hydrogens and three bonds to nitrogen so it oxidation level is 1(-1) + 3(+1) = +2. The carbon in CH_2NH has two bonds to hydrogens and two bond to nitrogen so it oxidation level is 2(-1) + 2(+1) = 0. The carbon in CCl_4 has zero bonds to hydrogens and four bonds to chlorine so it oxidation level is o(-1) + 4(+1) = +4. The compounds now can be listing in the following order of increasing oxidation level.



Exercise 10.4.2

A – Reduction

B – Oxidation

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10.5: Oxidation of Alcohols

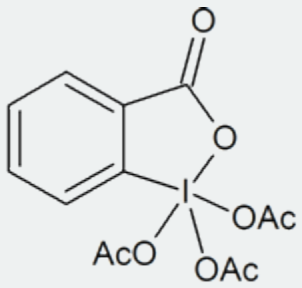
Objectives

After completing this section, you should be able to

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

Study Notes

The reading mentions that pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by **Dess-Martin periodinane (DMP)**, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983.



Dess–Martin periodinane (DMP)

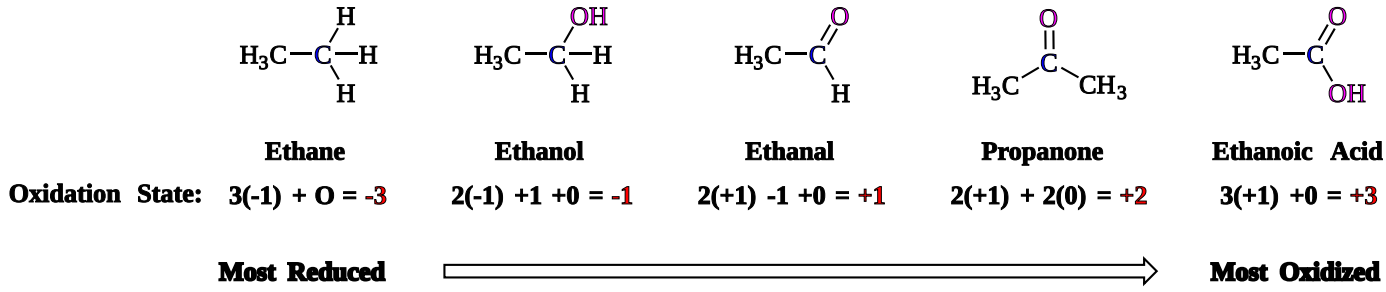
Oxidation States of Carbon

The general idea of oxidation and reduction reactions learned in general chemistry is that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. In order, to keep track of electrons in organic molecules a oxidation state formalism is used. Oxidation states to not represent the actual charge but it will allow the number of electrons being gained or lost by a particular atom during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

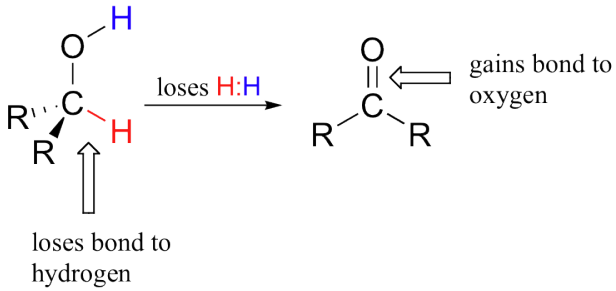
1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, such as nitrogen, oxygen, sulfur, or a halogen.

When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized.



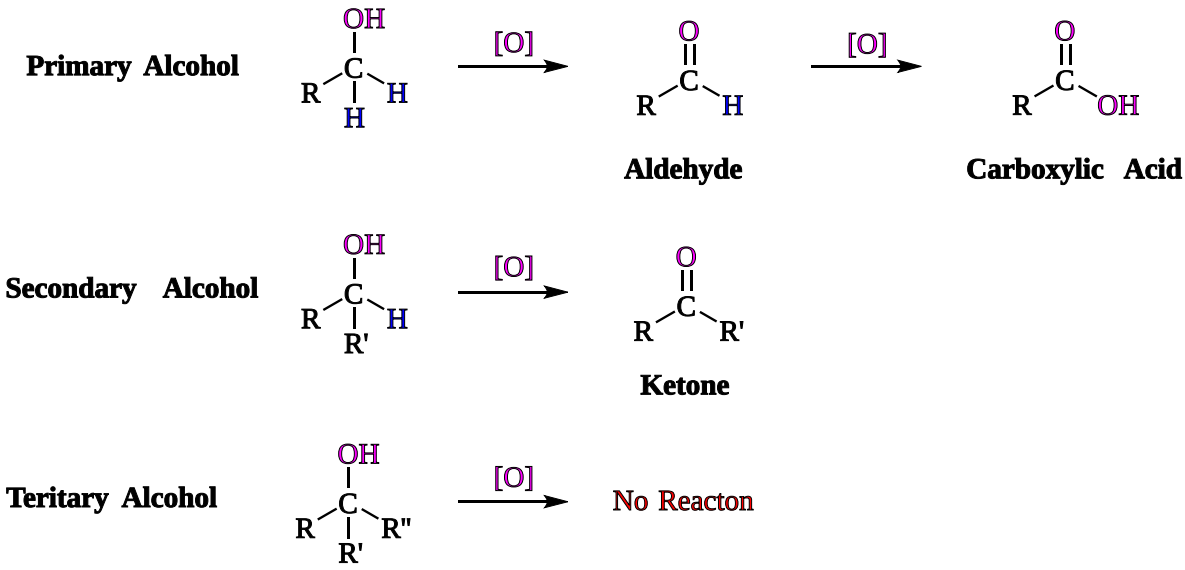
For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.

Dehydrogenation (oxidation) of an alcohol



Oxidation of Alcohols

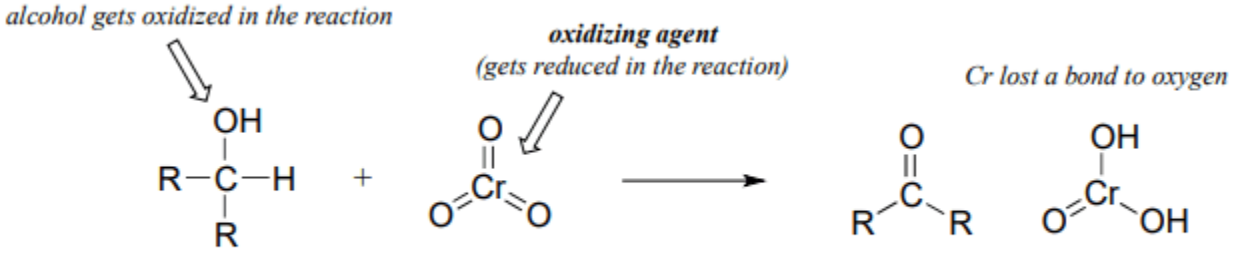
On of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehyde, ketones, and carboxylic acid. Typically primary alcohols, depending on the reagent used, produce aldehydes or carboxylic acids during oxidations. Secondary alcohols are oxidized to produce ketones, and tertiary alcohols are usually not affected by oxidations.



Alcohol Oxidizing Agents

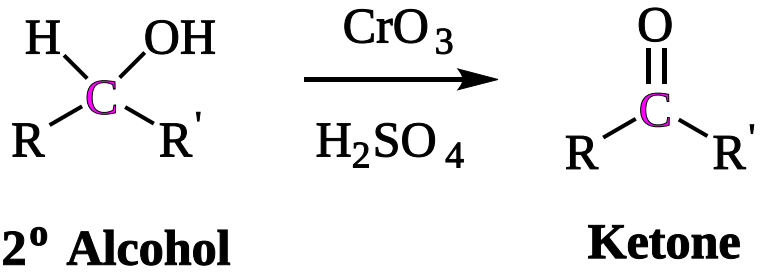
Oxidation and reduction reactions always occurs in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is

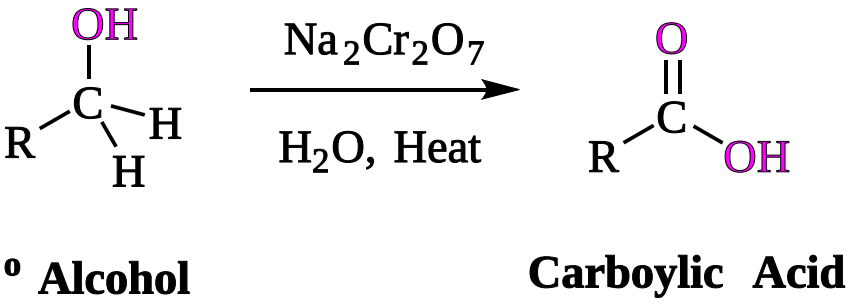
also called the oxidizing agent. For example, chromium trioxide (CrO_3) is a common oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone. During this reaction CrO_3 is being reduced to form H_2CrO_3. A common method for oxidizing secondary alcohols to ketones uses **chromic acid** (**H_2CrO_4**) as the oxidizing agent. Chromic acid, also known as **Jones reagent**, is prepared by adding chromium trioxide (CrO_3) to aqueous sulfuric acid.

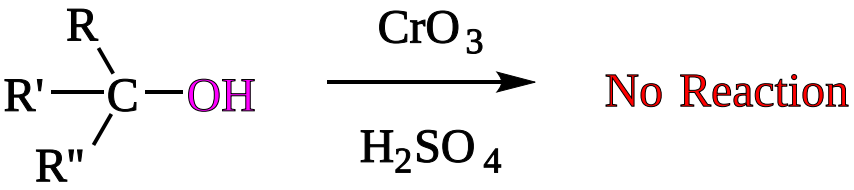


There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3, other commonly used oxidizing agents include potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$). Any of these reagents can be used to oxidize secondary alcohols to form ketones and primary alcohols to form carboxylic acids. Tertiary alcohols remain unreactive to oxidation.

General Reactions

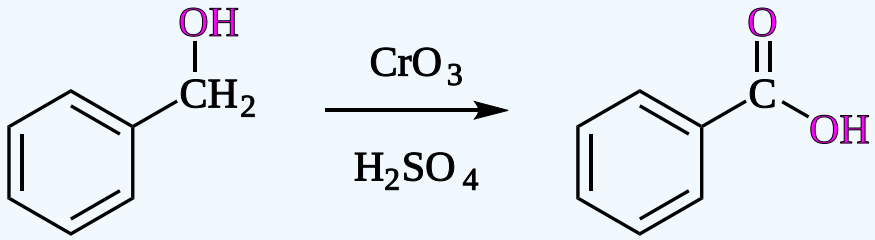




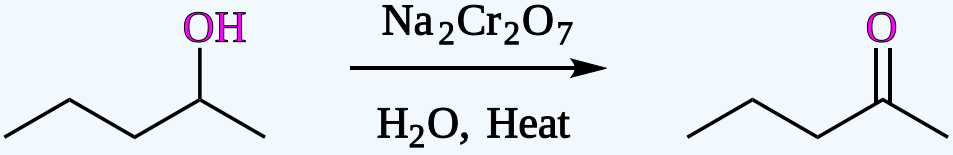


3° Alcohol

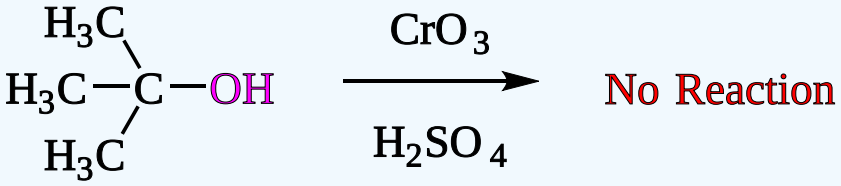
Example 10.5.1



Oxidation of Benzyl Alcohol to Benzoic Acid

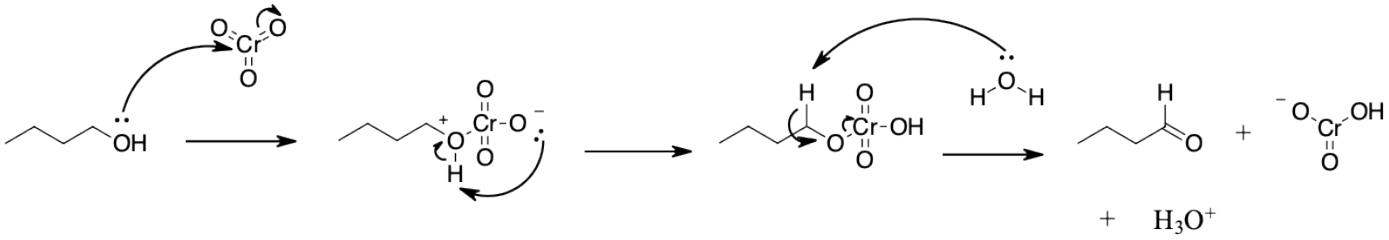


Oxidation of 2-Pentanol to 2-Pentanone



Mechanism

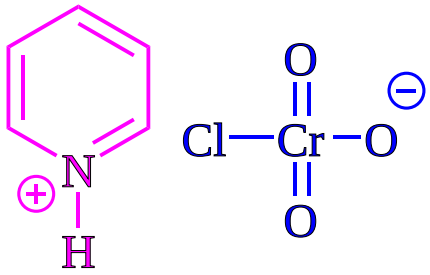
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



Examples

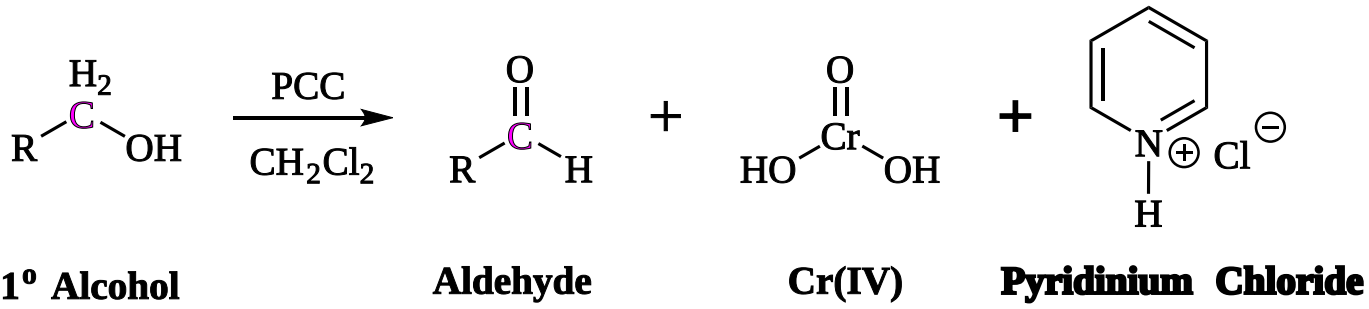
Oxidation of 1° Alcohols with PCC to form Aldehydes

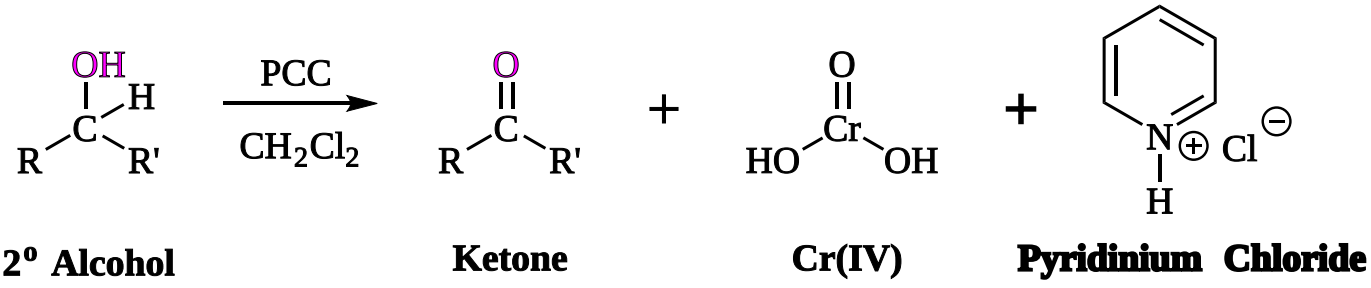
P**yridinium chlorochromate (PCC)** is a milder version of chromic acid. PCC oxidizes 1° alcohols one rung up the oxidation ladder, turning primary alcohols into aldehydes and secondary alcohols into ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Cr(IV) as well as pyridinium chloride are produced as byproducts of this reaction.



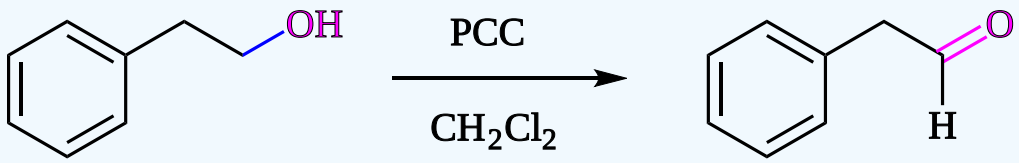
Pyridinium chlorochromate (PCC)

General Reactions

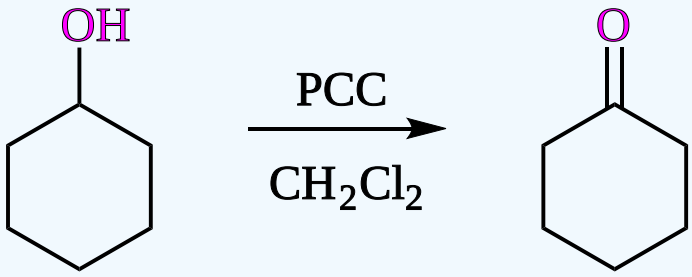




Example 10.5.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde

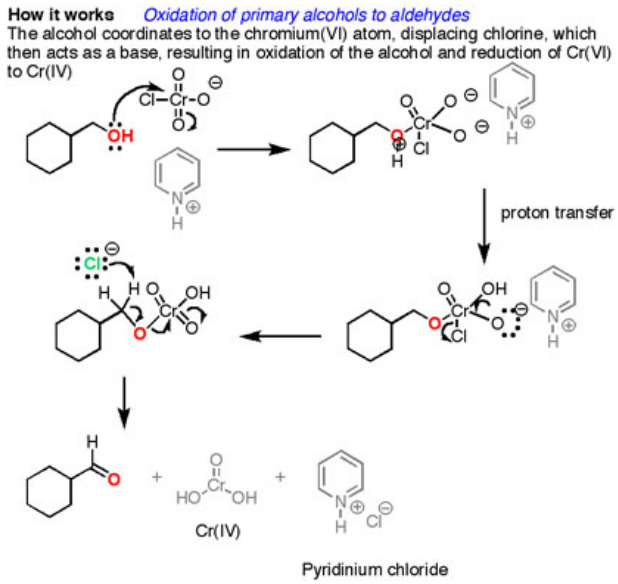


Oxidation of Cyclohexanol to Cyclohexanone

Mechanism

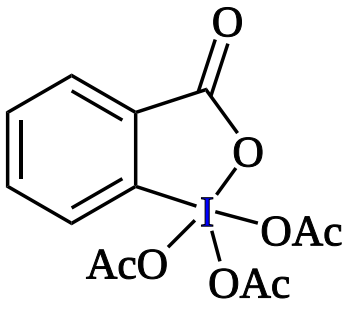
The first step of the mechanism is attack of alcohol oxygen on the chromium atom to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these acidic conditions. In an E2 reaction, the electrons from the C-H bond move to form the C=O bond, and in the process break the O-Cr bond. During this step Cr(VI) gains two electrons to become Cr(IV) (drawn here as $O{=}Cr(OH)_2$).



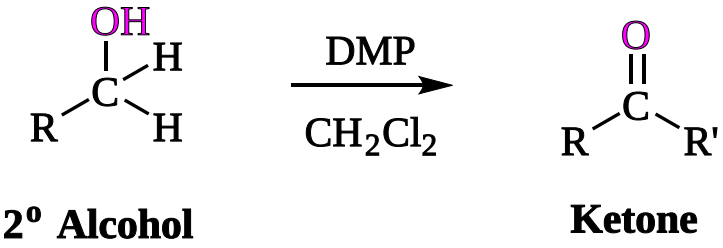
Oxidation of 1° Alcohols with Dess-Martin Periodinane (DMP) to form Aldehydes

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

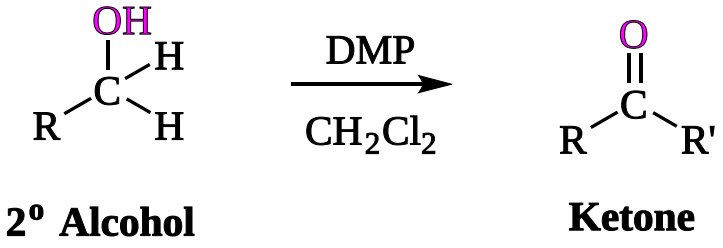


Dess-Martin periodinane (DMP)

General Reactions

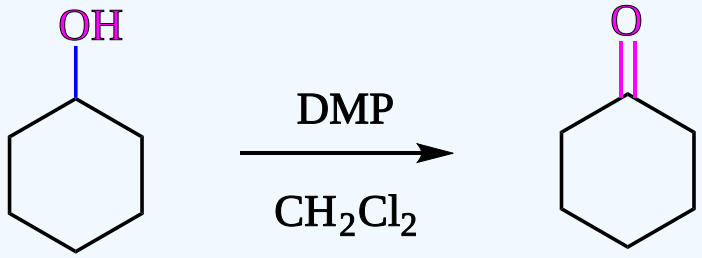


2° Alcohol **Ketone**

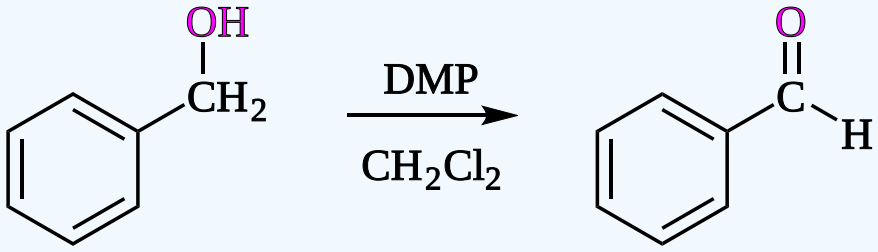


2° Alcohol **Ketone**

Example 10.5.3



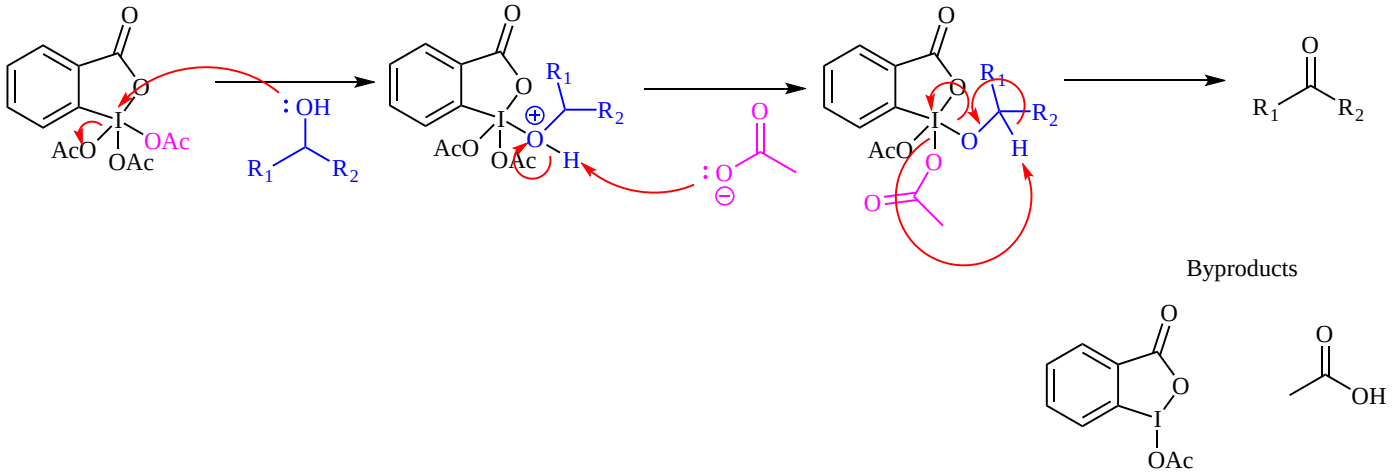
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

Mechanism

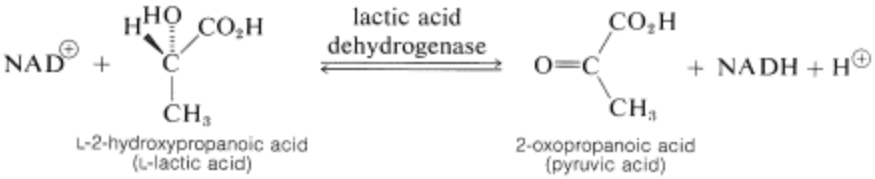
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

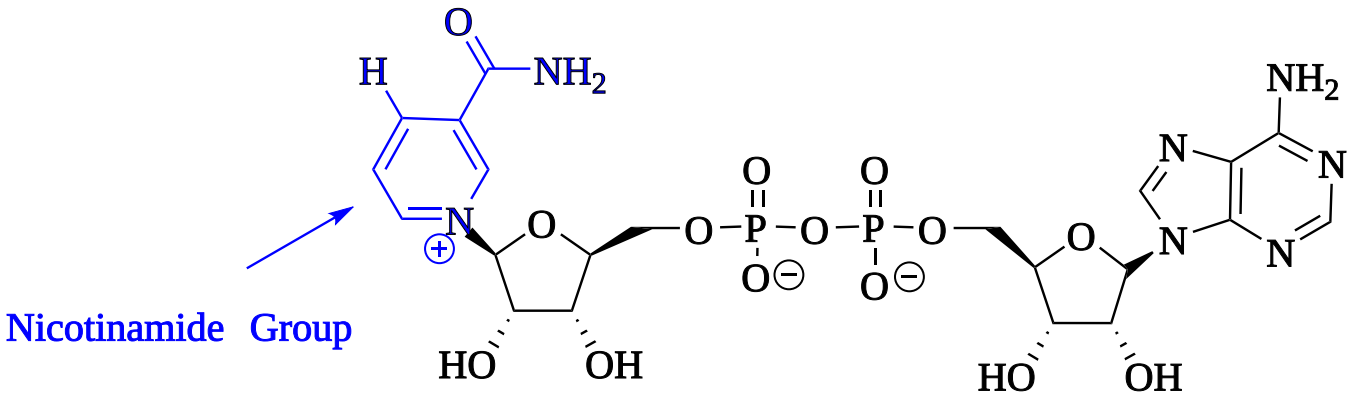


Biological Alcohol Oxidations

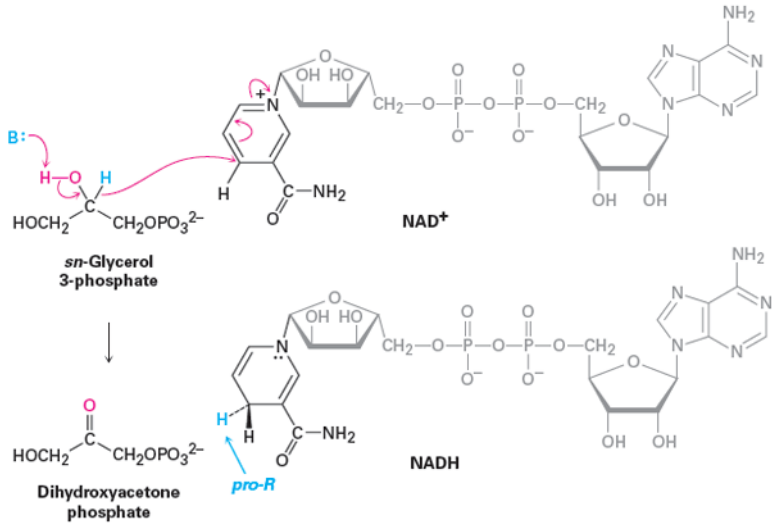
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*. An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide (NAD^+) is an example. This very complex molecule functions to accept hydride ($H:^-$) or the equivalent ($H^+ + 2e^-$) from the α carbon of an alcohol. The reduced form of NAD^+ is abbreviated as NADH and the $H:^-$ is added at the 4-position of the pyridine ring. It is important to note that the hydride adds exclusively to the *Re* face of the pyridine ring giving NADH a *pro*-R stereochemistry.

An example of the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose is the reduction of 2-oxopropanoic (pyruvic) acid to L-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of L-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the L-enantiomer of lactic acid. During this reaction a base removes the alcohol hydrogen. The resulting alkoxide ion then forms the C=O bond causing a hydride ion to transfer to NAD^+.



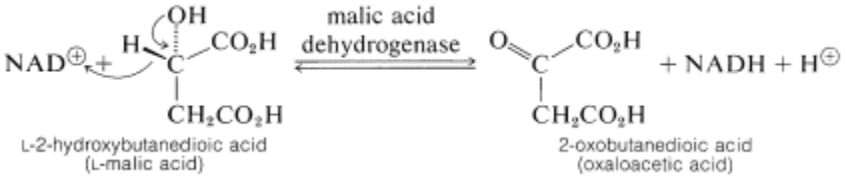


The Structure of NAD+



From an outside source. Convert mechanism to use lactic acid.

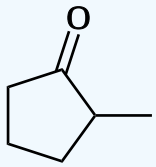
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:

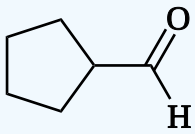


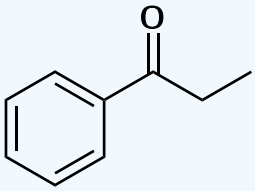
Exercises

Exercise 10.5.1

Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

a) 

b) 

c) 

Answer available at the end of this section.

Exercise 10.5.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

Answer available at the end of this section.

Exercise 10.5.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

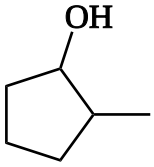
Answer available at the end of this section.

Answers

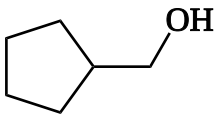
Exercise 10.5.1

1)

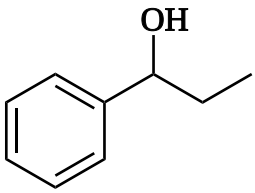
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.

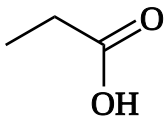


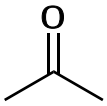
b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work



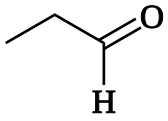
c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.

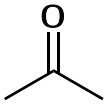






Exercise 10.5.3





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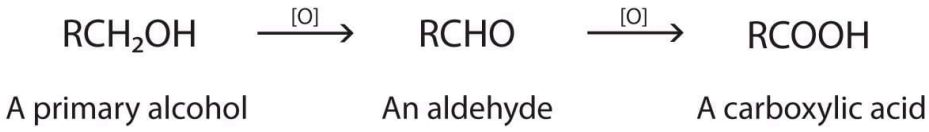
- 17.7: Oxidation of Alcohols by Dietmar Kennepohl, James Ashenhurst, James Kabrhel, Jim Clark, Steven Farmer is licensed CC BY-SA 4.0.

10.6: The Formation of Carboxylic Acids

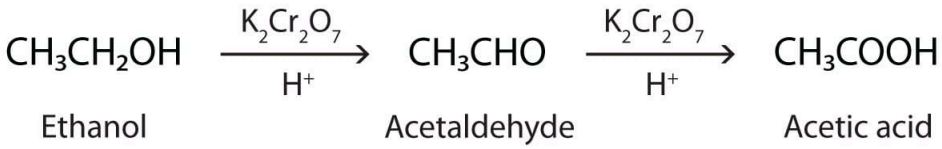
Learning Objectives

- To describe the preparation of carboxylic acids.

As we noted previously, the oxidation of aldehydes or primary alcohols forms carboxylic acids:



In the presence of an oxidizing agent, ethanol is oxidized to acetaldehyde, which is then oxidized to acetic acid.



This process also occurs in the liver, where enzymes catalyze the oxidation of ethanol to acetic acid.

$$\mathrm{CH_3CH_2OH} \xrightarrow[\text{oxidizing agent}]{\text{alcohol dehydrogenase}} \mathrm{CH_3CHO} \xrightarrow[\text{oxidizing agent}]{\text{alcohol dehydrogenase}} \mathrm{CH_3COOH}$$

Acetic acid can be further oxidized to carbon dioxide and water.

Summary

Whether in the laboratory or in the body, the oxidation of aldehydes or primary alcohols forms carboxylic acids.

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- 15.2: The Formation of Carboxylic Acids by Anonymous is licensed CC BY-NC-SA 3.0. Original source: https://2012books.lardbucket.org/books/introduction-to-chemistry-general-organic-and-biological.

10.7: Nicotinamide Adenine Dinucleotide (NAD)

Nicotinamide is from the niacin vitamin. The NAD^+ coenzyme is involved with many types of oxidation reactions where alcohols are converted to ketones or aldehydes. It is also involved in the first enzyme complex 1 of the electron transport chain.The structure for the coenzyme, NAD^+, Nicotinamide Adenine Dinucleotide is shown in Figure 10.7.1.

Role of NAD^+

One role of NAD^+ is to initiate the electron transport chain by the reaction with an organic **metabolite** (intermediate in metabolic reactions). This is an oxidation reaction where 2 hydrogen atoms (or 2 hydrogen ions and 2 electrons) are removed from the organic metabolite. (The organic metabolites are usually from the citric acid cycle and the oxidation of fatty acids--details in following pages.) The reaction can be represented simply where M = any metabolite.

$$MH_2 + NAD^+ \rightarrow NADH + H^+ + M : + \text{energy} \tag{10.7.1}$$

One hydrogen is removed with 2 electrons as a hydride ion (H^-) while the other is removed as the positive ion ($H+$). Usually the metabolite is some type of alcohol which is oxidized to a ketone.

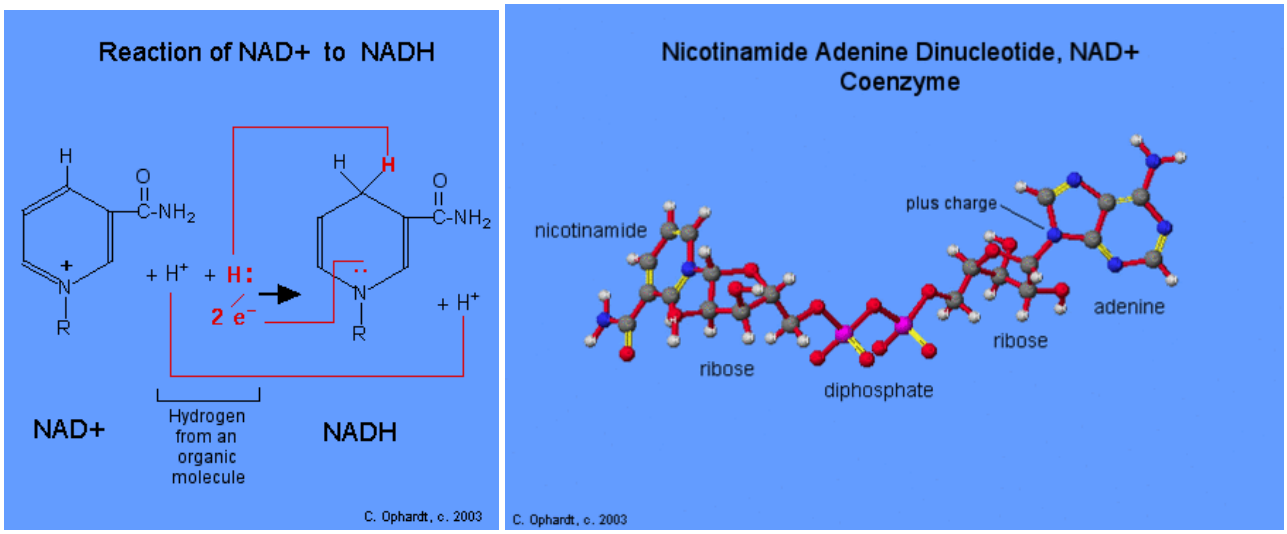


Figure 10.7.1

Alcohol Dehydrogenase

The NAD^+ is represented as cyan in Figure 10.7.2. The alcohol is represented by the space filling red, gray, and white atoms. The reaction is to convert the alcohol, ethanol, into ethanal, an aldehyde.

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CH = O + NADH + H^+ \tag{10.7.2}$$

This is an oxidation reaction and results in the removal of two hydrogen ions and two electrons which are added to the NAD^+, converting it to NADH and H^+. This is the first reaction in the metabolism of alcohol. The active site of ADH has two binding regions. The coenzyme binding site, where NAD^+ binds, and the substrate binding site, where the alcohol binds. Most of the binding site for the NAD^+ is hydrophobic as represented in green. Three key amino acids involved in the catalytic oxidation of alcohols to aldehydes and ketones. They are ser-48, phe 140, and phe 93.

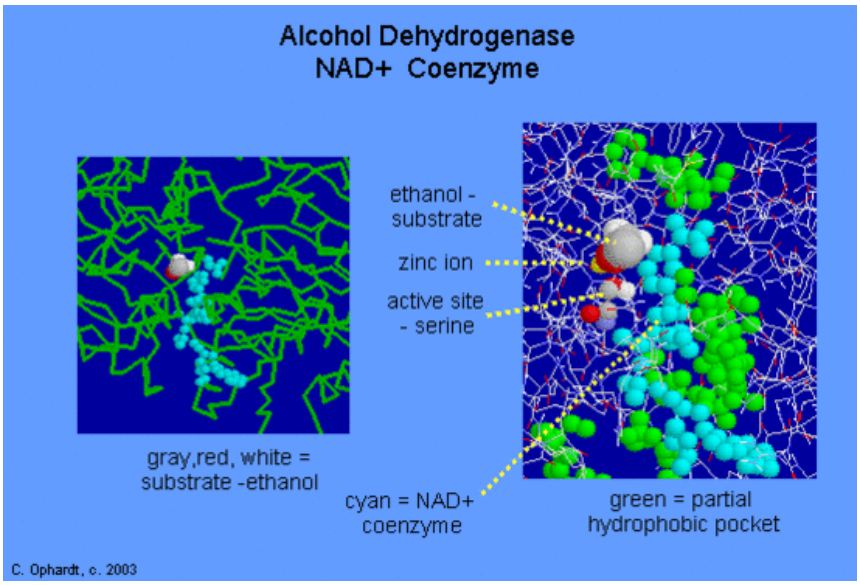


Figure 10.7.2***:*** *Active site of Alcohol Dehydrogenase*

Contributors and Attributions

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

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10.8: Dehydrogenases

Dehydrogenases enzymes usually involve NAD+/NADH and are named for the substrate that is oxidized by NAD+. For instance in the reaction:

$$\text{pyruvate} + \text{NADH} \rightleftharpoons \text{lactate} + \text{NAD}^+ \tag{10.8.1}$$

which is used to regenerate NAD+ under anerobic conditions, the enzyme is named lactate dehydrogenase. As in acid/base reactions, when the preferred direction for the reaction (from a ΔGo perspective) is from stronger acid to weaker (conjugate) acid, the preferred direction for a redox reaction is in the direction from strong to weak oxidizing/reducing agents. This can easily be determined from charts of standard reduction potentials, and using the equation:

$$\Delta G^o = -nF\Delta E^o \tag{10.8.2}$$

- where F is the Faraday constant (96,494 Coulombs/mol e- = 96, 494 J/(V.mol) = 23.06 kcal/(V.mol). One Faraday is the charge per one mol of electrons).
- and \(ΔE^o\), the standard EMF or standard cell potential (total voltage at standard state conditions), which can be determined by adding the standard reduction potentials (**Eo**) for the two appropriate half-reactions, after reversing the equation for the half-reaction that represents the oxidation.

When n=2 (number of electrons) which is common for oxidations of organic molecules,

\[ΔG^o (kcal/mol) = - 46.12\,ΔE^o \]

or for government work

\[ΔGo (kcal/mol) \approx - 50ΔE^o\]

Notice when ΔEo > 0, ΔGo < 0, the reaction as written is favored under standard conditions. Note in the table below that many of the half reactions involve protons. For biological reactions involving free protons, the standard state concentration for the protons are not 1 M as for other solutes in solution, but defined to be the hydronium ion concentration at pH 7.0. The ΔEo and ΔGo values for the reactions involving hydrogen ions at a standard state of pH 7.0 are usually written as ΔEo' and ΔGo'

Table: Standard Reduction Potential Table (E0'), 25oC

oxidant	reductant	n (electrons)	Eoï¿½ (volts)
Acetate + carbon dioxide	pyruvate	2	-0.70
succinate + CO_2 + $2H^+$	α–ketoglutarate + H_2O	2	-0.67
acetate	acetaldehyde	2	-0.60
glycerate-3-P	glyceraldehyde-3-P + H_2O	2	-0.55
O_2	O2-	1	-0.45
ferredoxin (ox)	ferredoxin (red)	1	-0.43
Carbon dioxide	formate	2	-0.42

oxidant	reductant	n (electrons)	Eoï¿½ (volts)
2H+	H_2	2	-0.42
α-ketoglutarate + CO_2 + $2H^+$	isocitrate	2	-0.38
acetoacetate	β-hydroxybutyrate	2	-0.35
Cystine	cysteine	2	-0.34
Pyruvate + CO_2	malate	2	-0.33
NAD^+ + $2H^+$	NADH + H^+	2	-0.32
$NADP^+$ + $2H^+$	NADPH + H^+	2	-0.32
FMN (enzyme bound)	$FMNH_2$	2	-0.30
Lipoic acid, ox	Lipoic acid, red	2	-0.29
1,3 bisphosphoglycerate + $2H^+$	glyceraldehyde-3-P + Pi	2	-0.29
Glutathione, ox	red	2	-0.23
FAD (free) + $2H^+$	$FADH_2$	2	-0.22
Acetaldehyde + $2H^+$	ethanol	2	-0.20
Pyruvate + $2H^+$	lactate	2	-0.19
Oxalacetate + $2H^+$	malate	2	-0.17
α-ketoglutarate + NH_4^+	glutamate	2	-0.14
FAD + $2H^+$ (bound)	$FADH_2$ (bound)	2	0.003-0.09

oxidant	reductant	n (electrons)	Eoï¿½ (volts)
Methylene blue, ox	Methylene blue, red	2	0.01
Fumarate + $2H^+$	succinate	2	0.03
CoQ (Ubiquinone - UQ + H^+	$UQH^·$	1	0.031
UQ + $2H^+$	UQH_2	2	0.06
Dehydroascorbic acid	ascorbic acid	2	0.06
Ubiquinone; ox	red	2	0.10
Cytochrome b_2; Fe^{3+}	Cytochrome b_2; Fe^{2+}	1	0.12
Cytochrome c_1; Fe^{3+}	Cytochrome c_1; Fe^{2+}	1	0.22
Cytochrome c; Fe^{3+}	Cytochrome c; Fe^{2+}	1	0.25
Cytochrome a; Fe^{3+}	Cytochrome a; Fe^{2+}	1	0.29
1/2 O_2 + H_2O	H_2O_2	2	0.30
Cytochrome a_3; Fe^{3+}	Cytochrome a_3; Fe^{2+}	1	0.35
Ferricyanide	ferrocyanide	2	0.36
Cytochrome f; Fe^{3+}	Cytochrome f; Fe^{2+}	1	0.37
Nitrate	nitrite	1	0.42
Photosystem P700	.	.	0.43
Fe^{3+}	Fe^{2+}	1	0.77

oxidant	reductant	n (electrons)	Eoï¿½ (volts)
1/2 O_2 + $2H^+$	H_2O	2	0.816

- EXTERNAL Recommendations for nomenclature and tables in biochemical thermodynamics (from the International Union of Biochemistry and Molecular Biology and the IUPAC)

The mechanism for the oxidation of a substrate by NAD + involves concerted hydride transfer to one face of NAD+.

Consider for example the oxidation of ethanol to acetaldehyde by alcohol dehydrogenase.

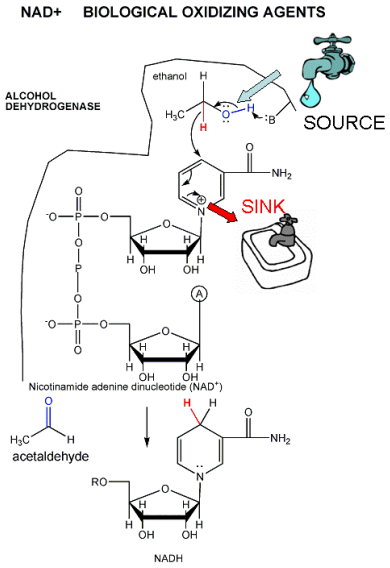


Figure: oxidation of ethanol to acetaldehyde by alcohol dehydrogenase

For substrates like ethanol that loses a hydride from a methylene carbon atom that has two H's, only one of the H's is lost (either the proR or proS) from the prochiral center. (Remember the reaction of prochiral glycerol to give phospholipids.)

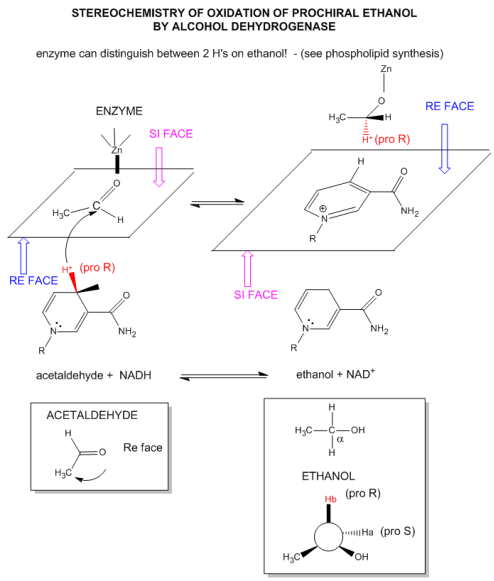
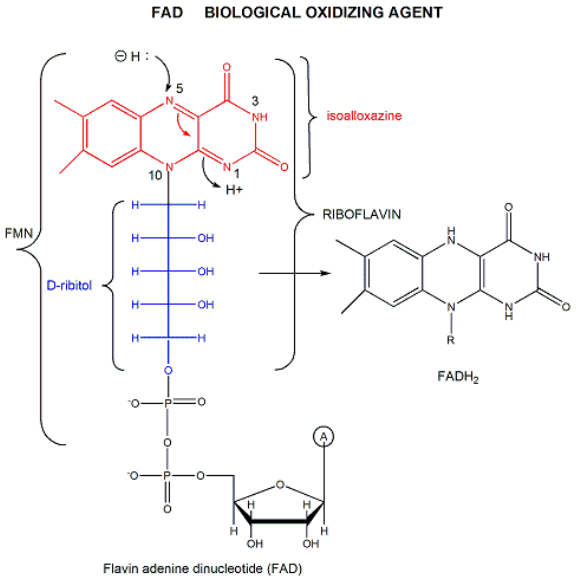


Figure: STEREOCHEMISTRY OF NAD+/NADH REDOX REACTIONS WITH ALCOHOL DEHYDROGENASE

FAD has a more positive reduction potential than NAD+ so it is used for more "demanding" oxidation reactions, such as dehydrogenation of a C-C bond to form an alkene. You

will notice on standard reduction potential tables that the potential of FAD is often listed several times and depends on the enzyme. This is because the FAD is tightly bound to the enzyme so its tendency to acquire electrons depends on its environment, in much the same fashion as the pKa of an amino acid side chain (which reflects is tendency to release protons) is affected by the environment of the amino acid side chain in the protein. The standard reduction potential for flavin enzymes varies from -465 mV to + 149 mV. Compare this to the reduction potential of free FAD/FADH2, which in aqueous solution is -208 mV. The standard reduction potential of the flavin in D-amino acid oxidase, a flavoprotein, is about 0.0 V. Remember, the more positive the standard reduction potential, the more likely the reactant will be reduced and hence act as an oxidizing agent. Hence the FAD in D-amino acid oxidase is a better oxidizing agent than free FAD. The Kd for binding of FAD to the enzyme is 10-7M compared to the Kd for binding of FADH2, which is 10-14M. By gaining electrons, the flavin binds more tightly, which preferentially stabilizes the bound FADH2 compared to the bound FAD. This shifts the equilibrium of FAD <=> FADH2 to the right, making the bound FAD a stronger oxidizing agent.

Figure: FAD AND OXIDATIONS: MECHANISM




Jmol: Updated Flavin dehydrogenase Jmol14 (Java) | JSMol (HTML5)

Can the standard reduction potential of a redox active center in a protein be tuned by changing the environment of that center, much as the pKa of an acid side chain can by changing the polarity of the environment? The answer is yes. The active site of azurin, a cupredoxin, has a redox active copper ion coordinated by a Cys and two His residues in a trigonal planar fashion. Met 121 serves as a weak axial ligand. Marshall et al. have reported a feasible method to manipulate the redox potential (Eo) of this active site. The wild type azurin was mutated to alter the hydrophobicity and hydrogen bonding capabilities, while maintaining the overall architecture of the metal binding site. Ser 46 was selected for mutation since it occupied a position similar to Asn in another curedoxin that was involved in an important H bond binding two ligand binding loops. An N47S-mutation, which strengthened the hydrogen bond between the two ligand-containing loops increased Eo by ~130 mV while preserving metal binding site architecture as determined by UV-Vis spectroscopy. They also compared a M121Q mutant with wild-type M121 and with a M121L mutant. A plot of Eo vs log partition coefficient for transfer of the side chain from water to octanol was essentially linear with a positive slope, showing that the standard reduction potential depended on the hydrophobicity of the weakly coordinating ligand in the metal binding region. This behavior extended to double mutants (where one set of mutants involved M121). The investigators were able to tune the Eo over a 700 mv range! New Role for NAD.

Contributors and Attributions

- Prof. Henry Jakubowski (College of St. Benedict/St. John's University)

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10.9: Prochirality

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.

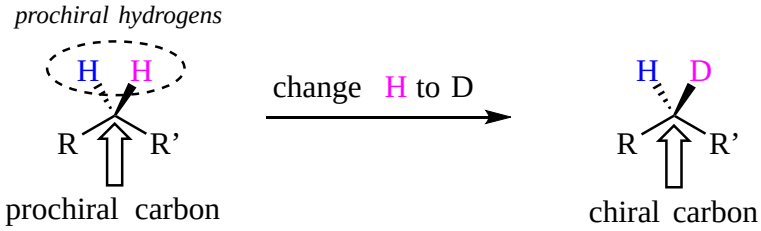
Key Terms

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

- prochiral
- *pro-R*
- *pro-S*
- *Re*
- *Si*

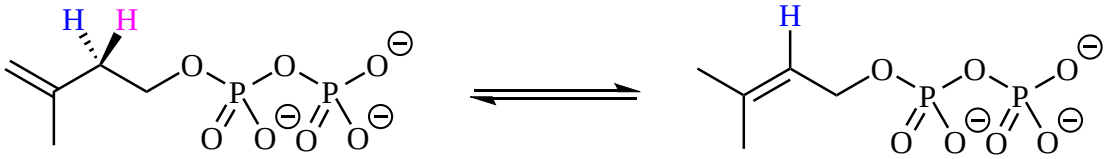
Prochiral Carbons

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'.



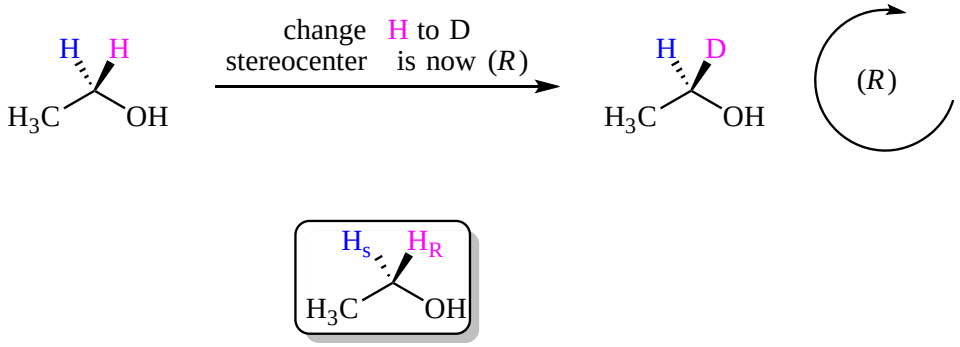
Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the ^{2}H isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

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.



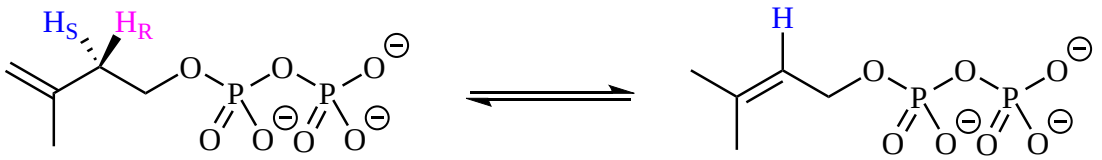
isopentenyl diphosphate dimethylallyl diphosphate

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).



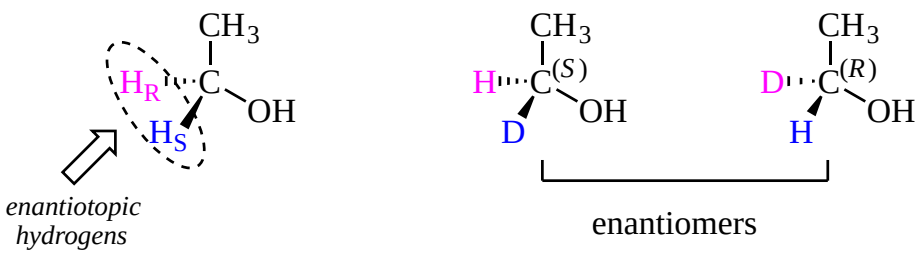
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it H_R. Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be S, so we can refer to blue H as the *pro*-S hydrogen of ethanol, and label it H_S.

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.



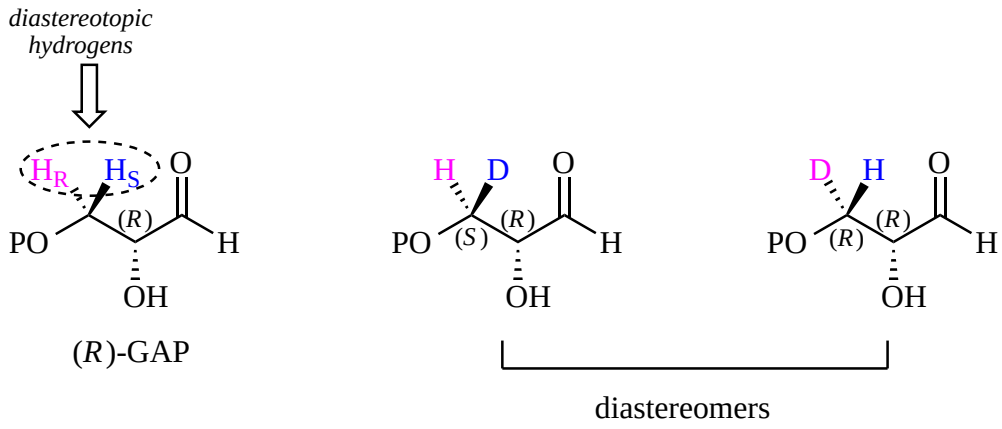
isopentenyl diphosphate dimethylallyl diphosphate

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).



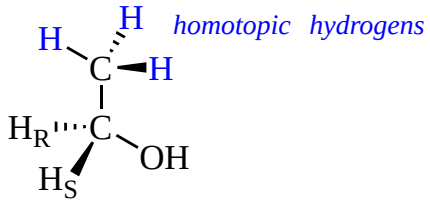
Thus, these two hydrogens are referred to as **enantiotopic**.

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.

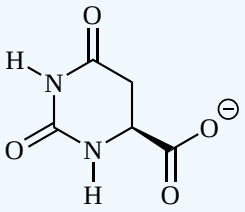
Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl (CH_3) group of ethanol (and on *any* methyl group) are homotopic. An enzyme cannot distinguish among homotopic hydrogens.



Example 10.9.1

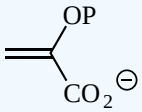
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as H_R or H_S.

a)



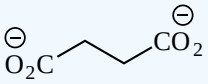
dihydroorotate
(a nucleotide biosynthesis intermediate)

b)



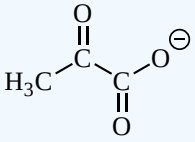
phosphoenolpyruvate
(a glycolysis intermediate)

c)



succinate
(a citric acid cycle intermediate)

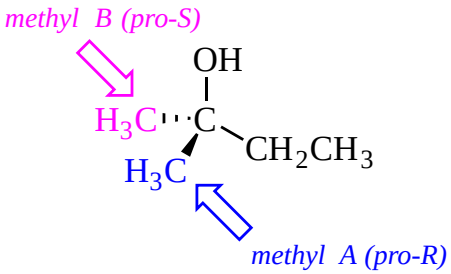
d)



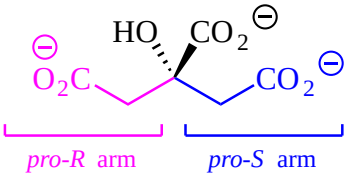
pyruvate
(endpoint of glycolysis)

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*.

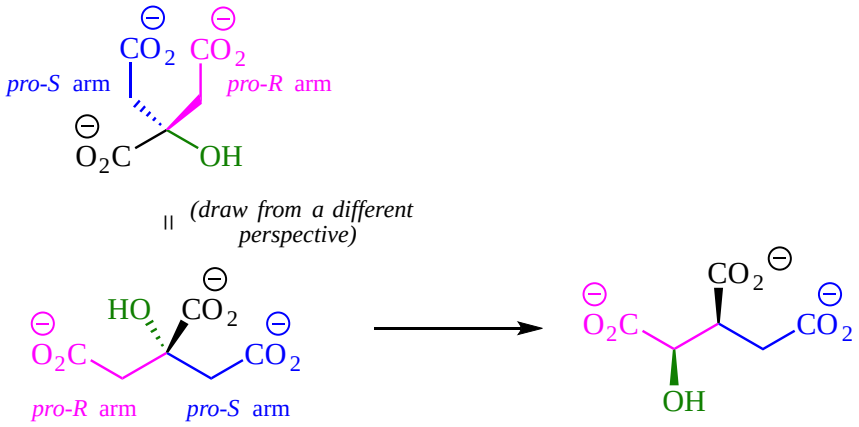


Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro*-S.



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).



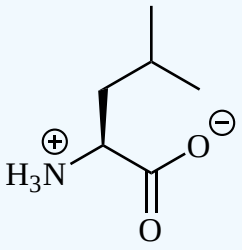
citrate

isocitrate

(hydroxide moved specifically to the pro-R arm)

Exercise 10.9.1

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?

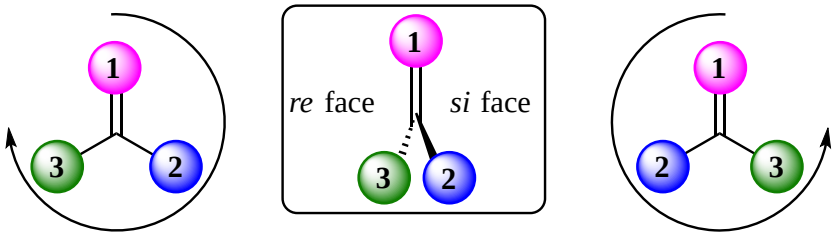


leucine

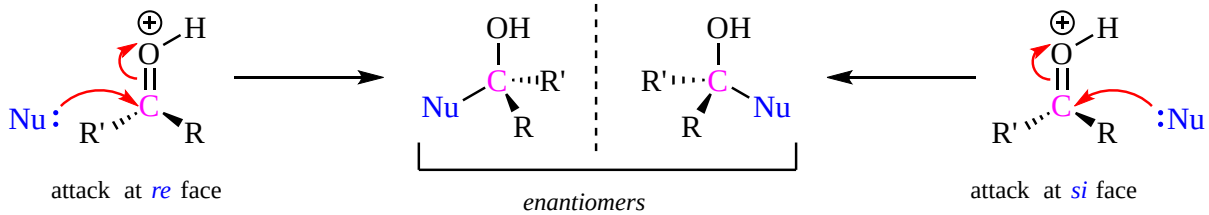
Answer available at the end of this section.

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.

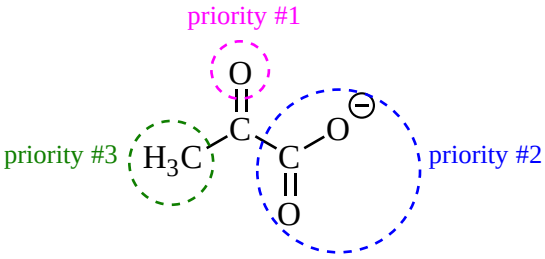


When the two groups adjacent to a carbonyl (C=O) are not the same, we can distinguish between the re and si 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. 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.

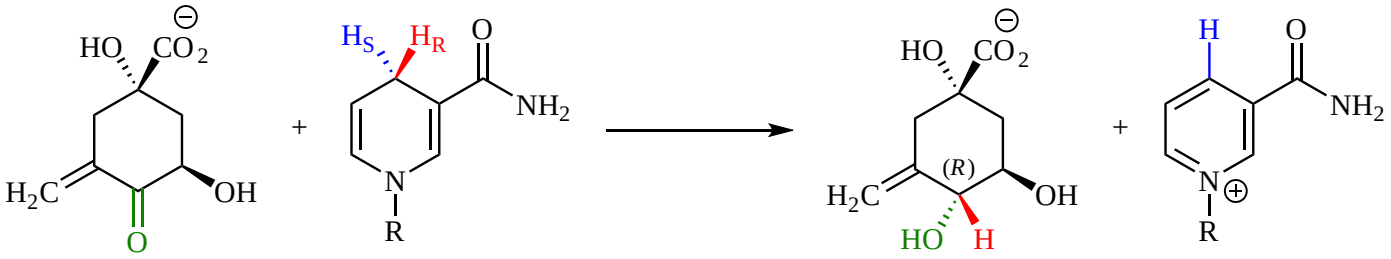


Note: R is higher priority than R'

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.

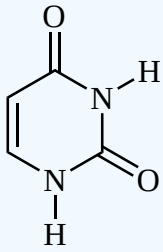


*looking at the **si** face of the ketone*

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 10.9.2

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.

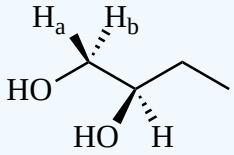


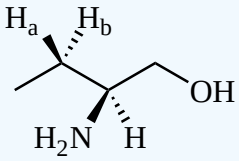
uracil

Answer available at the end of this section.

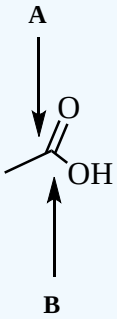
Exercise 10.9.3

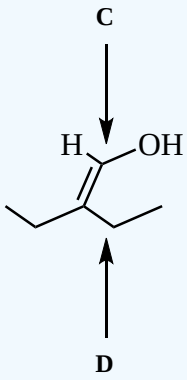
a) State which of the following hydrogen atoms are *pro-R* or *pro-S*.





b) Identify which side is Re or Si.



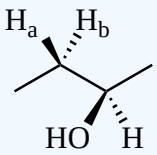


Answer available at the end of this section.

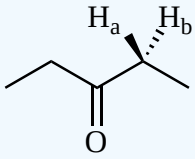
Exercise 10.9.4

State whether the H's indicated below are pro-*R* or pro-S for the following structures.

a)



b)

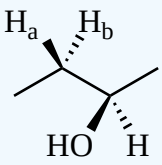


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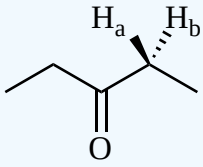
Exercise 10.9.5

In the structures below, determine if the H's are homotopic, enantiotopic, or diastereotopic.

a)



b)

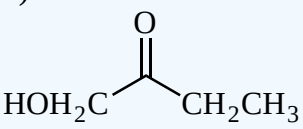


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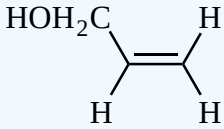
Exercise 10.9.6

State whether you are looking down at the molecule from the re face or si face.

a)



b)

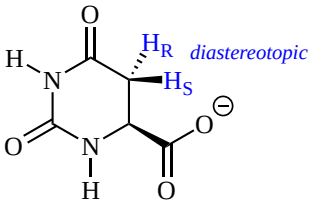


Answer available at the end of this section.

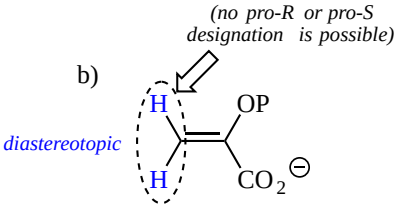
Answers

Example 10.9.1

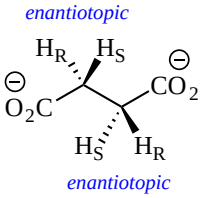
a)



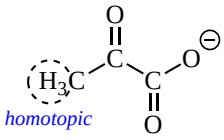
b)



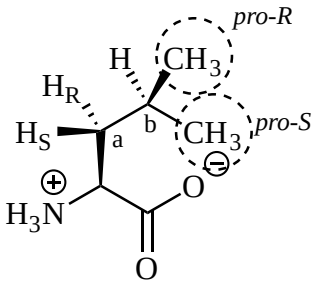
c)



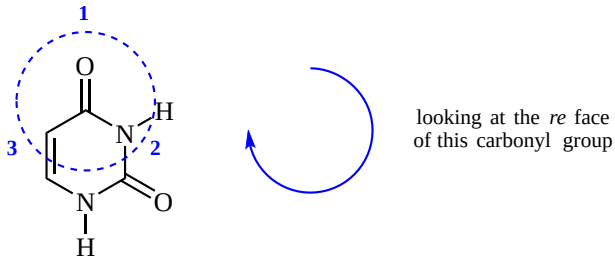
d)

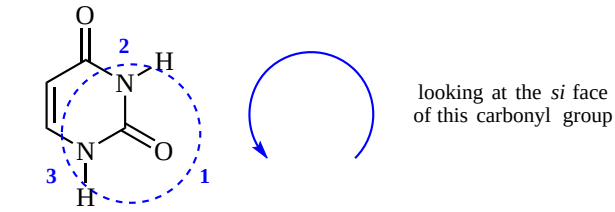


Exercise 10.9.1



Exercise 10.9.2





Exercise 10.9.3

a) Left compound: H_a = *pro*-S and H_b = *pro-R*; Right compound: H_a = *pro-R* and H_b = *pro*-S

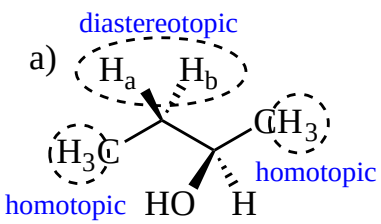
b) A – Re; B – Si; C – Re; D – Si\)

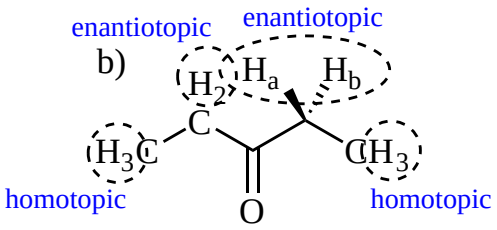
Exercise 10.9.4

Exercise 10.9.5

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.





Exercise 10.9.6

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.

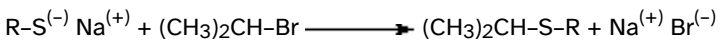
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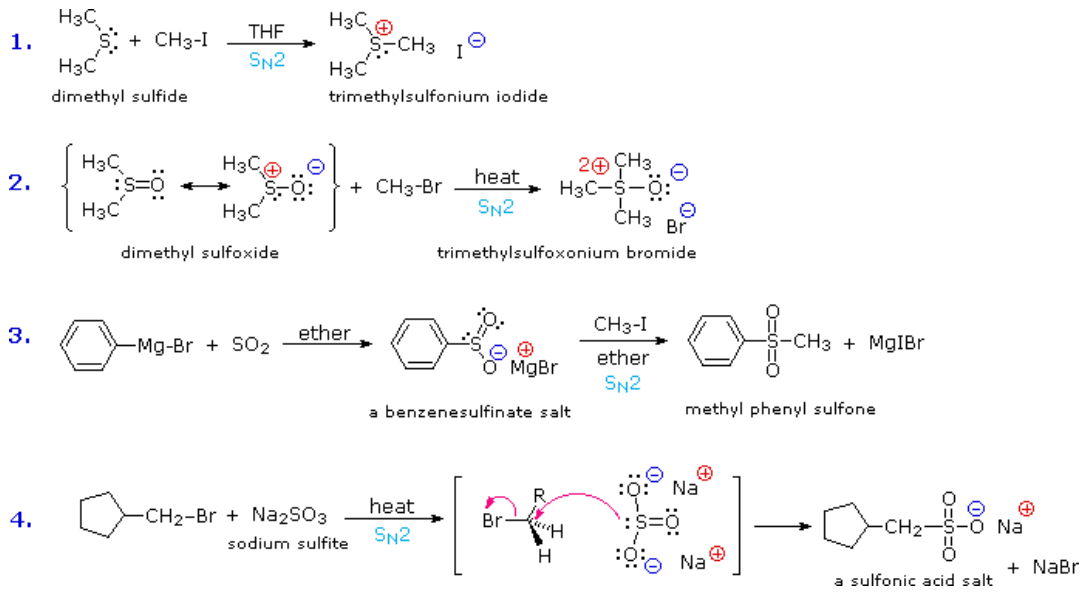
10.10: Thiols and Sulfides

1. Nucleophilicity of Sulfur Compounds

Sulfur analogs of alcohols are called **thiols** or **mercaptans**, and ether analogs are called **sulfides**. The chemical behavior of thiols and sulfides contrasts with that of alcohols and ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.



Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is 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. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3°-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive. Remarkably, sulfoxides (equation # 2), sulfinate salts (# 3) and sulfite anion (# 4) also alkylate on sulfur, despite the partial negative formal charge on oxygen and partial positive charge on sulfur.



2. Oxidation States of Sulfur Compounds

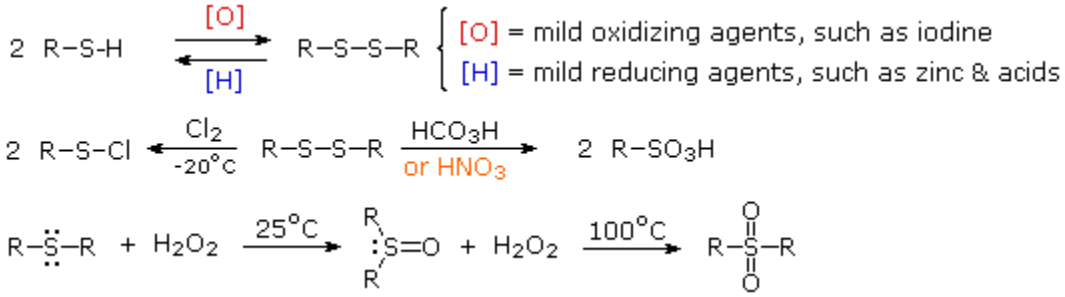
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

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

Try drawing Lewis-structures for the sulfur atoms in these compounds. If you restrict your formulas to valence shell electron octets, most of the higher oxidation states will have formal charge separation, as in equation 2 above. The formulas written here neutralize this charge separation by double bonding that expands the valence octet of sulfur. Indeed, the S=O double bonds do not consist of the customary σ & π-orbitals found in carbon double bonds. As a third row element, sulfur has **five empty 3d-orbitals** that may be used for p-d bonding in a fashion similar to p-p (π) bonding. In this way sulfur may expand an argon-like valence shell octet by two (e.g. sulfoxides) or four (e.g. sulfones) electrons. Sulfoxides have a fixed pyramidal shape (the sulfur non-bonding electron pair occupies one corner of a tetrahedron with sulfur at the center). Consequently, sulfoxides having two different alkyl or aryl substituents are chiral. Enantiomeric sulfoxides are stable and may be isolated.

Thiols also differ dramatically from alcohols in their oxidation chemistry. Oxidation of 1° and 2°-alcohols to aldehydes and ketones changes the oxidation state of carbon but not oxygen. Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.
Mild oxidation of disufides with chlorine gives alkylsulfenyl chlorides, but more vigorous oxidation forms sulfonic acids (2nd example). Finally, oxidation of sulfides with hydrogen peroxide (or peracids) leads first to sulfoxides and then to sulfones.



The nomenclature of sulfur compounds is generally straightforward. The prefix **thio** denotes replacement of a functional oxygen by sulfur. Thus, -SH is a thiol and C=S a thione. The prefix **thia** denotes replacement of a carbon atom in a chain or ring by sulfur, although a single ether-like sulfur is usually named as a sulfide. For example, $C_2H_5SC_3H_7$ is ethyl propyl sulfide and $C_2H_5SCH_2SC_3H_7$ may be named 3,5-dithiaoctane. Sulfonates are sulfonate acid esters and sultones are the equivalent of lactones. Other names are noted in the table above.

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10.11: Nucleophilicity of Sulfur Compounds

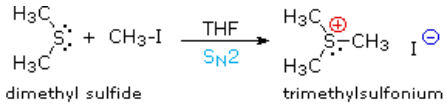
Compounds incorporating a C–S–H functional group are named **thiols** or **mercaptans**. Despite their similarity, they are stronger acids and more powerful nucleophiles than alcohols. The IUPAC name of $(CH_3)_3C–SH$ is 2-methyl-2-propanethiol, commonly called tert-butyl mercaptan.

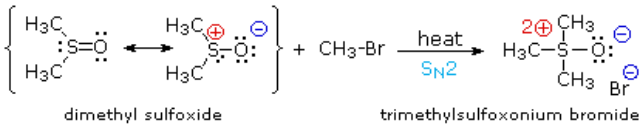
Nucleophilicity of Sulfur Compounds

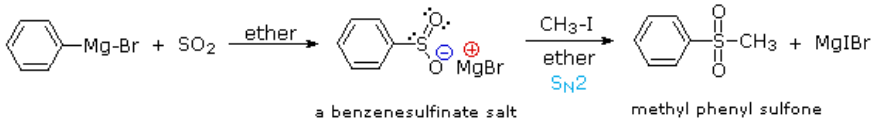
Sulfur analogs of alcohols are called **thiols** or **mercaptans**, and ether analogs are called **sulfides**. The chemical behavior of thiols and sulfides contrasts with that of alcohols and ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

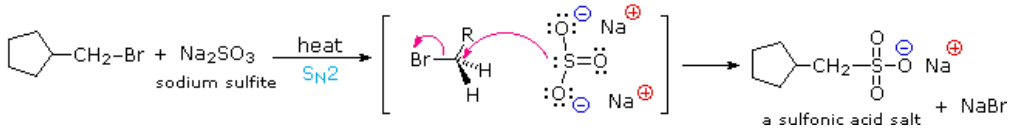
$$R–S^{(-)}\ Na^{(+)} + (CH_3)_2CH–Br \longrightarrow (CH_3)_2CH–S–R + Na^{(+)}\ Br^{(-)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is 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. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3°-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive. Remarkably, sulfoxides (equation # 2), sulfinate salts (# 3) and sulfite anion (# 4) also alkylate on sulfur, despite the partial negative formal charge on oxygen and partial positive charge on sulfur.

1. 

2. 

3. 

4. 

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).

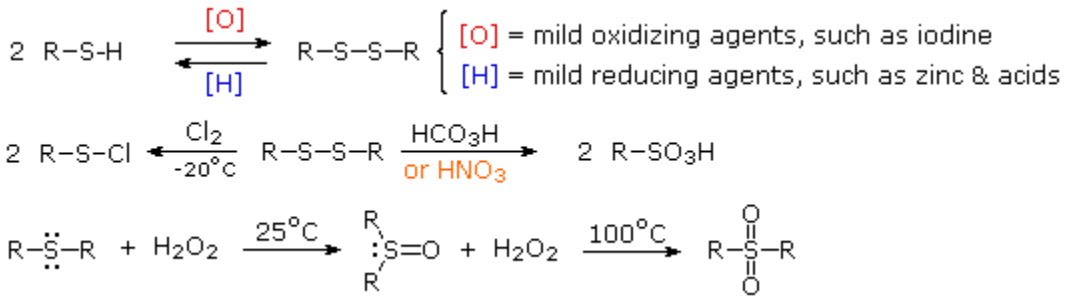
Sulfur Oxidation States in Organic Compounds

-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

Try drawing Lewis-structures for the sulfur atoms in these compounds. If you restrict your formulas to valence shell electron octets, most of the higher oxidation states will have formal charge separation, as in equation 2 above. The formulas written here neutralize this charge separation by double bonding that expands the valence octet of sulfur. Indeed, the S=O double bonds do not consist of the customary σ & π-orbitals found in carbon double bonds. As a third row element, sulfur has **five empty 3d-orbitals** that may be used for p-d bonding in a fashion similar to p-p (π) bonding. In this way sulfur may expand an argon-like valence shell octet by two (e.g. sulfoxides) or four (e.g. sulfones) electrons. Sulfoxides have a fixed pyramidal shape (the sulfur non-bonding electron pair occupies one corner of a tetrahedron with sulfur at the center). Consequently, sulfoxides having two different alkyl or aryl substituents are chiral. Enantiomeric sulfoxides are stable and may be isolated.

Thiols also differ dramatically from alcohols in their oxidation chemistry. Oxidation of 1° and 2°-alcohols to aldehydes and ketones changes the oxidation state of carbon but not oxygen. Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.

Mild oxidation of disufides with chlorine gives alkylsulfenyl chlorides, but more vigorous oxidation forms sulfonic acids (2nd example). Finally, oxidation of sulfides with hydrogen peroxide (or peracids) leads first to sulfoxides and then to sulfones.

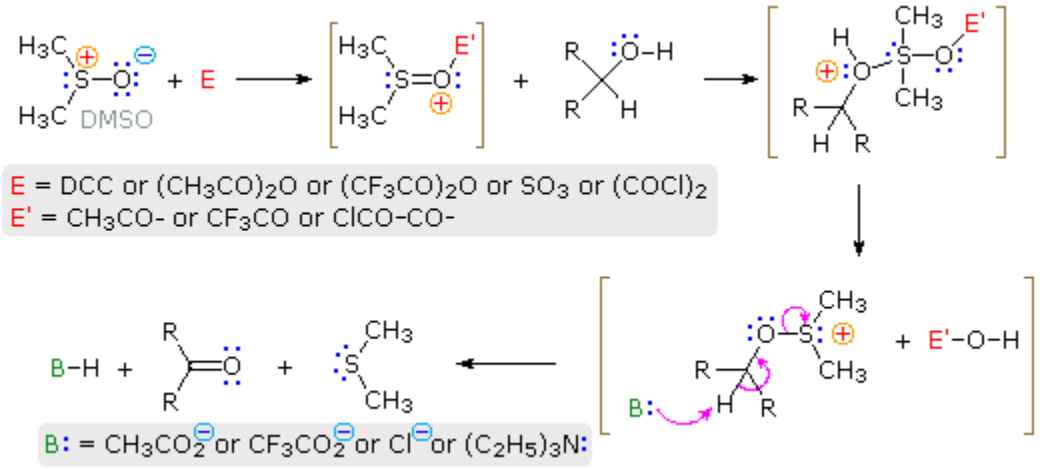


The nomenclature of sulfur compounds is generally straightforward. The prefix **thio** denotes replacement of a functional oxygen by sulfur. Thus, -SH is a thiol and C=S a thione. The prefix **thia** denotes replacement of a carbon atom in a chain or ring by sulfur, although a single ether-like sulfur is usually named as a sulfide. For example, $C_2H_5SC_3H_7$ is ethyl propyl sulfide and $C_2H_5SCH_2SC_3H_7$ may be named 3,5-dithiaoctane. Sulfonates are sulfonate acid esters and sultones are the equivalent of lactones. Other names are noted in the table above.

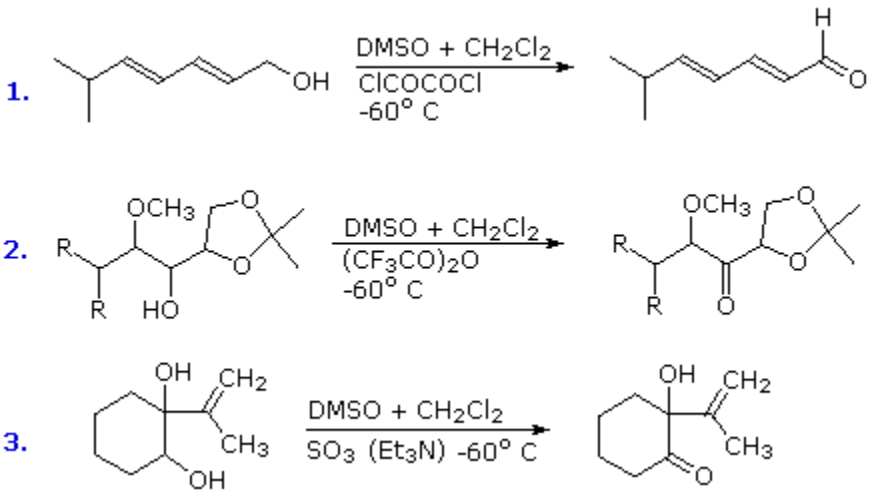
Oxidation of Alcohols by DMSO

The conversion of 1° and 2°-alcohols to aldehydes and ketones is an important reaction which, in its simplest form, can be

considered a dehydrogenation (loss of H_2). By providing an oxygen source to fix the product hydrogen as water, the endothermic dehydrogenation process may be converted to a more favorable exothermic one. One source of oxygen that has proven effective for the oxidation of alcohols is the simple sulfoxide solvent, DMSO. The reaction is operationally easy: a DMSO solution of the alcohol is treated with one of several electrophilic dehydrating reagents (E). The alcohol is oxidized; DMSO is reduced to dimethyl sulfide; and water is taken up by the electrophile. Due to the exothermic nature of the reaction, it is usually run at -50 °C or lower. Co-solvents such as methylene chloride or THF are needed, since pure DMSO freezes at 18°. The reaction of oxalyl chloride with DMSO may generate chlorodimethylsulfonium chloride which then oxidizes the alcohol (**Swern Oxidation**). Alternatively, a plausible general mechanism for this interesting and useful reaction is drawn below.



Because so many different electrophiles have been used to effect this oxidation, it is difficult to present a single general mechanism. Most of the electrophiles are good acylating reagents, so it is reasonable to expect an initial acylation of the sulfoxide oxygen. (The use of DCC as an acylation reagent was described elsewhere.) The electrophilic character of the sulfur atom is enhanced by acylation. Bonding of sulfur to the alcohol oxygen atom then follows. The remaining steps are eliminations, similar in nature to those proposed for other alcohol oxidations. In some cases triethyl amine is added to provide an additional base. Three examples of these DMSO oxidations are given in the following diagram. Note that this oxidation procedure is very mild and tolerates a variety of other functional groups, including those having oxidizable nitrogen and sulfur atoms.



Contributors

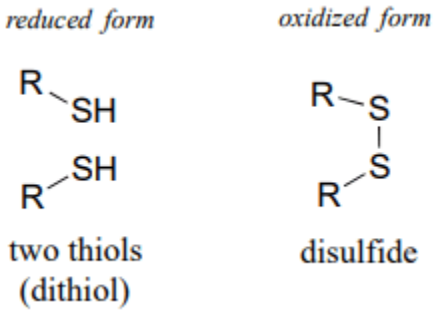
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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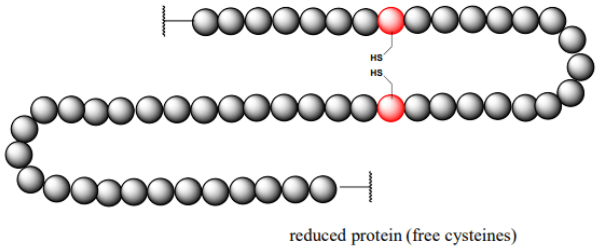
10.12: Redox Reactions of Thiols and Disulfides

A **disulfide bond** is a sulfur-sulfur bond, usually formed from two free thiol groups.

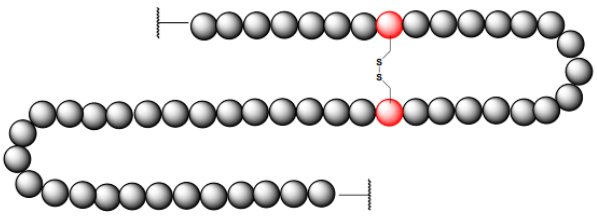


The interconversion between dithiol and disulfide groups is a redox reaction: the free dithiol form is in the reduced state, and the disulfide form is in the oxidized state. Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to sulfur.

As you should recall from your Biology courses, disulfide bonds between cysteine residues are an integral component of the three-dimensional structure of many extracellular proteins and signaling peptides.

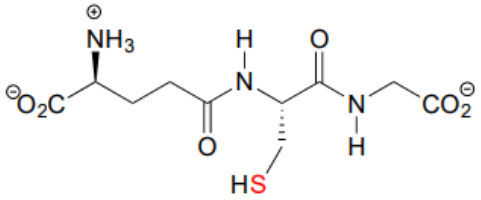


reduced protein (free cysteines)

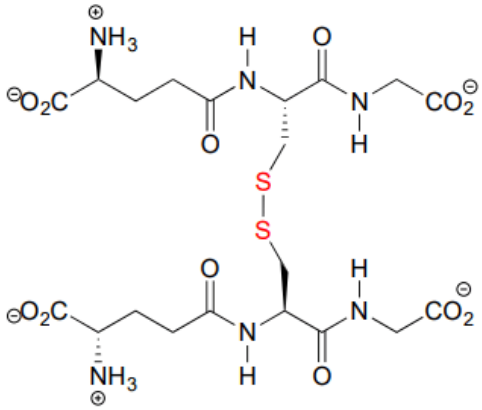


oxidized protein (disulfide)

A thiol-containing coenzyme called glutathione is integrally involved in many thiol-disulfide redox processes (recall that glutathione was a main player in this chapter's introductory story about concussion research). In its reduced (thiol) form, glutathione is abbreviated 'GSH'. In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.



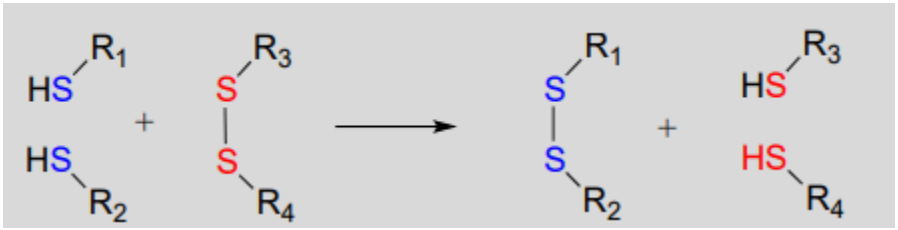
glutathione (GSH)
reduced state



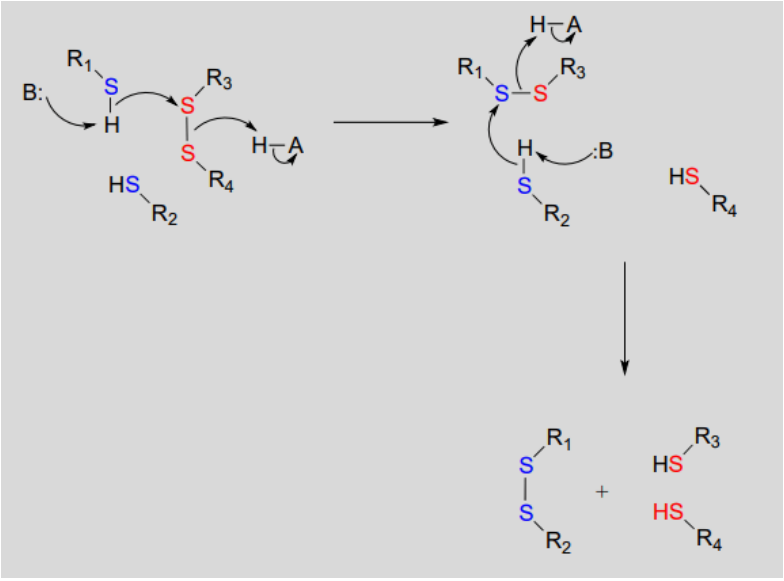
glutathione dimer (GSSG)
oxidized state

Disulfide bonds and free thiol groups in both proteins and smaller organic molecules like glutathione can 'trade places' through a disulfide exchange reaction. This process is essentially a combination of two direct displacement (S_N2-like) events, with sulfur atoms acting as nucleophile, electrophile and leaving group.

Disulfide exchange reaction

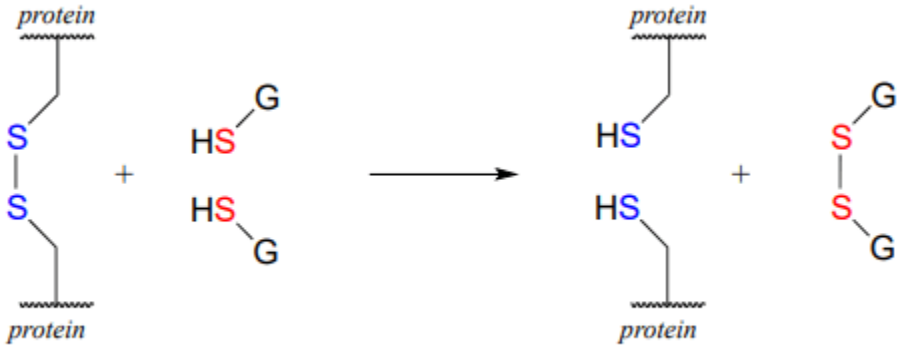


Mechanism:



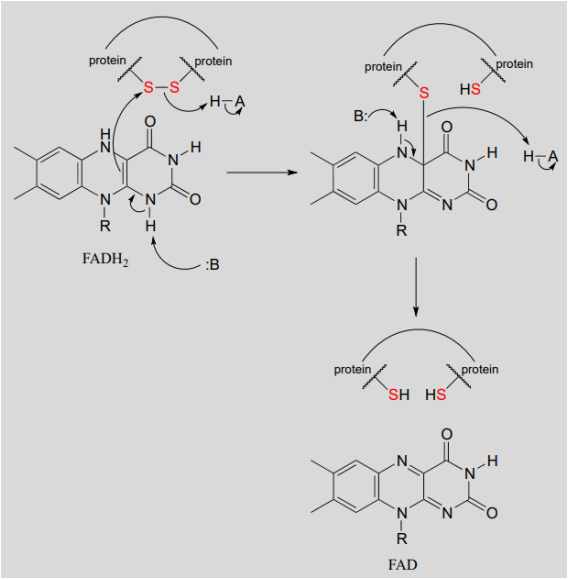
In eukaryotes, the cysteine side chains of intracellular (inside the cell) proteins are almost always in the free thiol (reduced) state due to the high concentration of reduced glutathione (GSH) in the intracellular environment. A disulfide bond in an intracellular

protein will be rapidly reduced in a disulfide exchange reaction with excess glutathione.

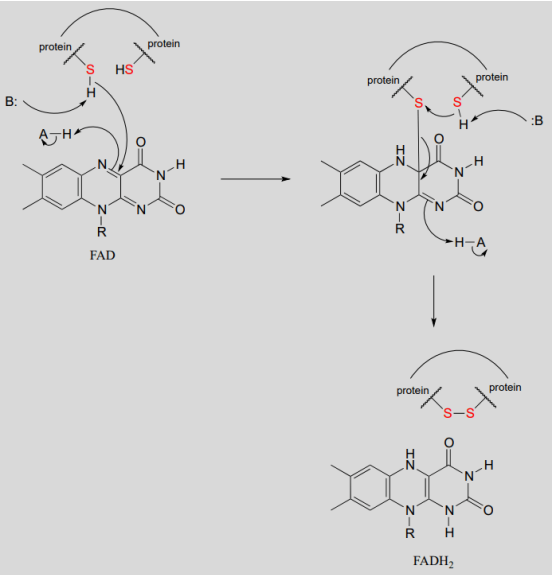


The interconversion of free thiols and disulfides is also mediated by flavin in some enzymes.

Flavin-mediated reduction of a protein disulfide bond

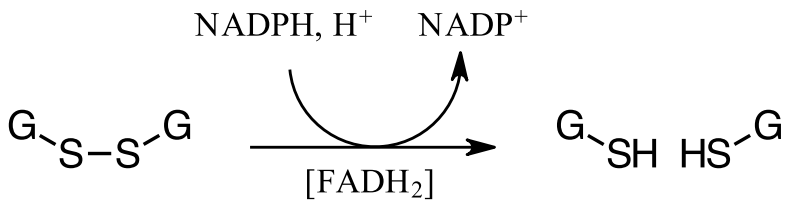


Flavin-mediated oxidation of a protein disulfide bond



As was stated earlier, a high intracellular concentration of reduced glutathione (GSH) serves to maintain proteins in the free thiol (reduced) state. An enzyme called glutathione reductase catalyzes the reduction of GSSG in a flavin-mediated process, with $NADH$ acting as the ultimate hydride donor.

Gluthione reductase reaction:



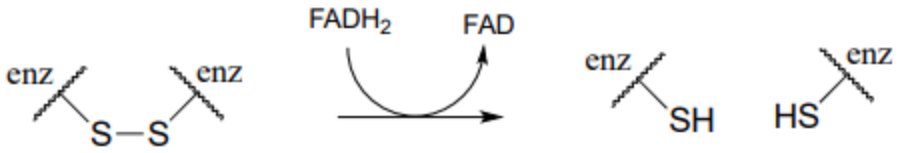
This figure shows oxidized glutathione converted to reduced glutathione by NADPH.

The mechanism for this and other similar reactions is not yet completely understood, but evidence points to an initial thiol-disulfide exchange reaction with a pair of cysteines from the enzyme, (phase 1 below) followed by flavin-dependent reduction of the cysteine-cysteine disulfide (phase 2). Finally, (phase 3) FAD is reduced back to $FADH_2$ by $NADH$. Frey and Hegeman, Enzymatic Reaction Mechanisms, p. 699

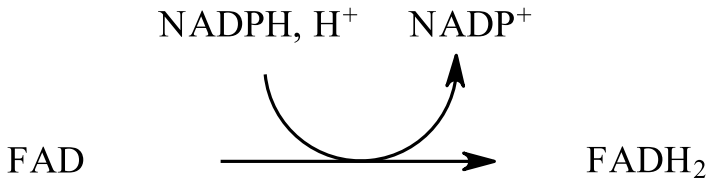
Phase 1: thiol-disulfide exchange (see earlier figure for mechanism):



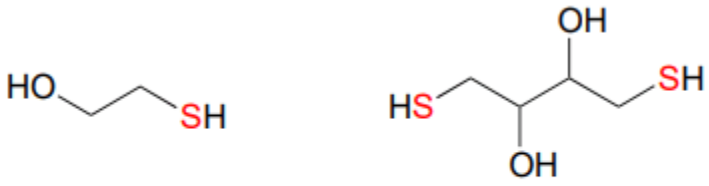
Phase 2: Reduction of protein disulfide by $FADH_2$ (see earlier figure for mechanism)



Phase 3: regeneration of $FADH_2$ by $NADH$ (see section 15.4B for mechanism)



In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of β-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, can form an intramolecular disulfide in its oxidized form.



b-mercaptoethanol (BME)

dithiothreitol (DTT)

Exercise 15.7.1

Draw structures of the oxidized (disulfide) forms of BME and DTT.

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10.13: An Introduction to Organic Synthesis

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

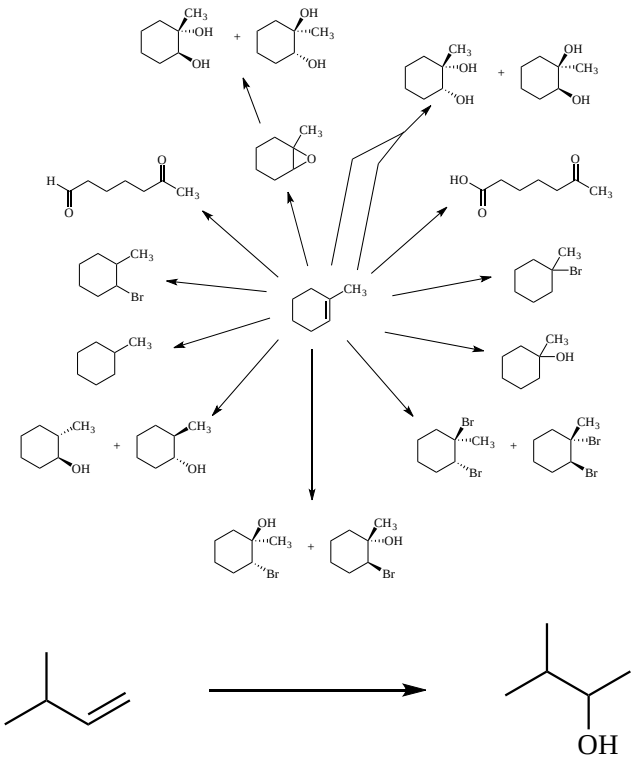
You should have noticed that some of the assigned problems have required that you string together a number of organic reactions to convert one organic compound to another when there is no single reaction to achieve this goal. Such a string of reactions is called an “organic synthesis.” One of the major 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.

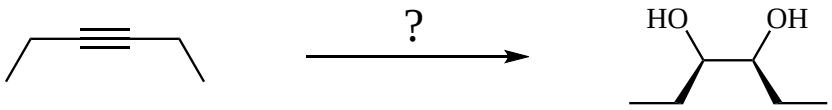
Alkene Reaction Map

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.

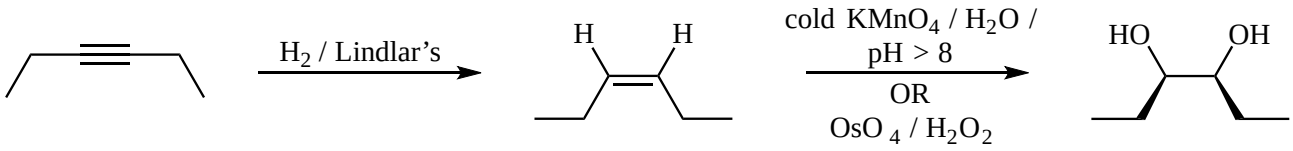


Simple Multi-Step Syntheses

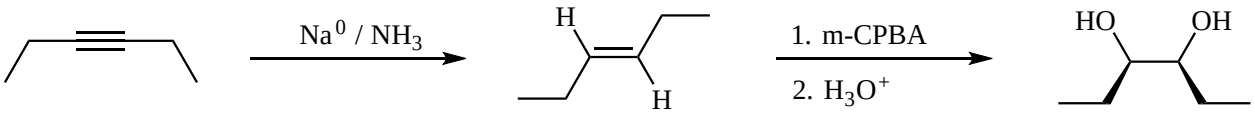
A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.



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.

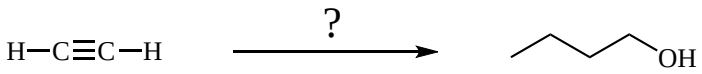


Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope 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

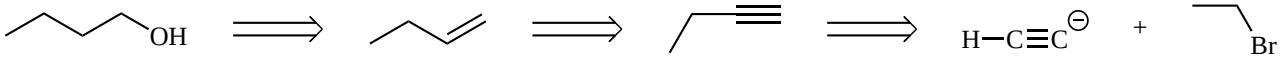
The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. 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.

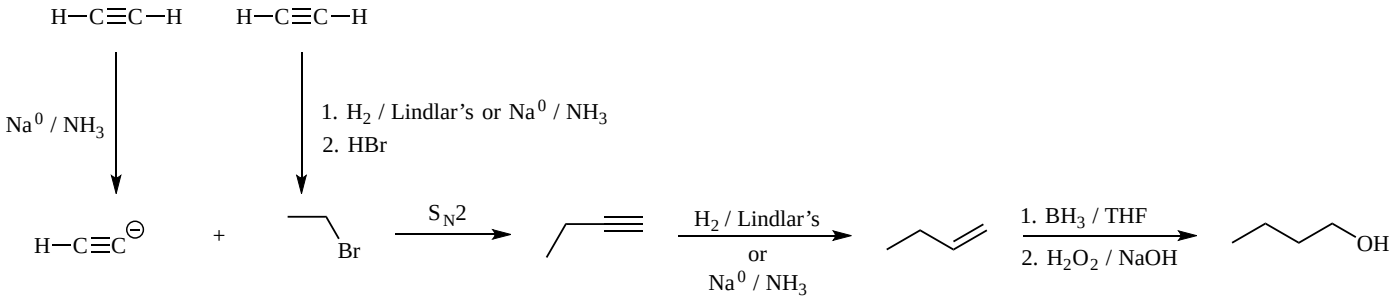


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.

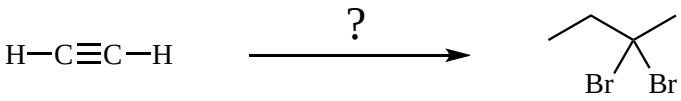
Retro-Synthesis



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.

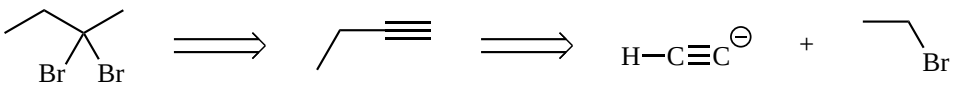


In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.

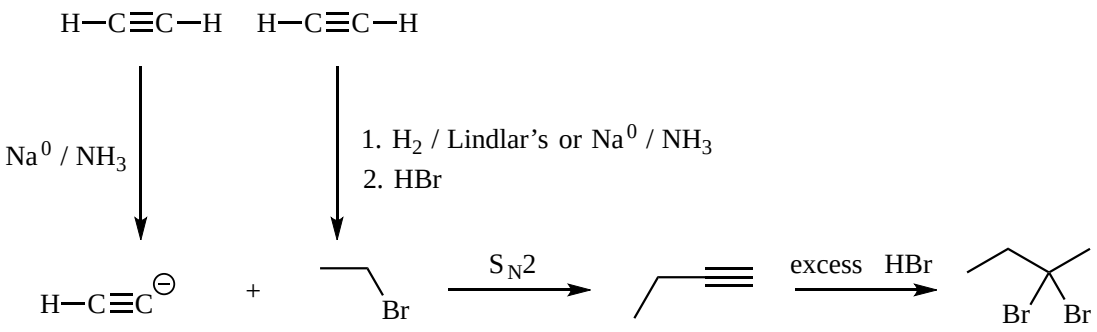


Once again there is an increase in the carbon chain length indicating an acetylide S_N2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne 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.

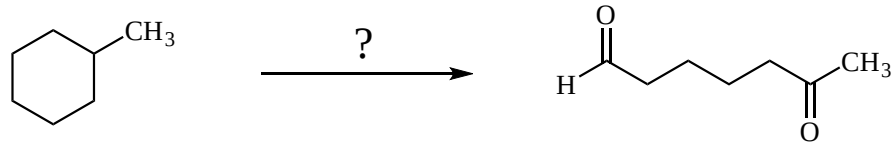
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.

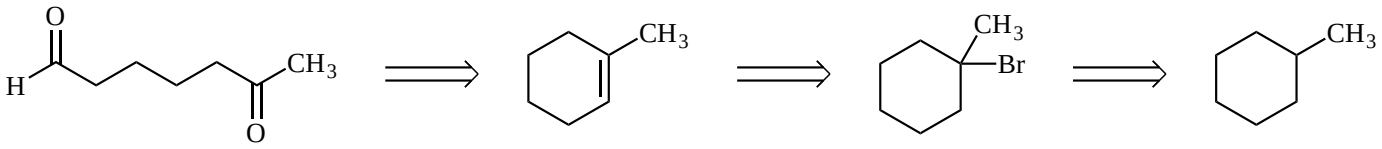


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.

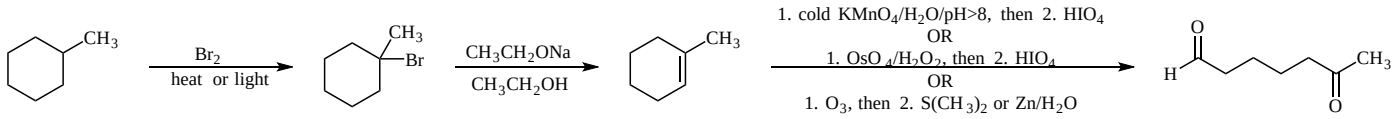


Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or 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.

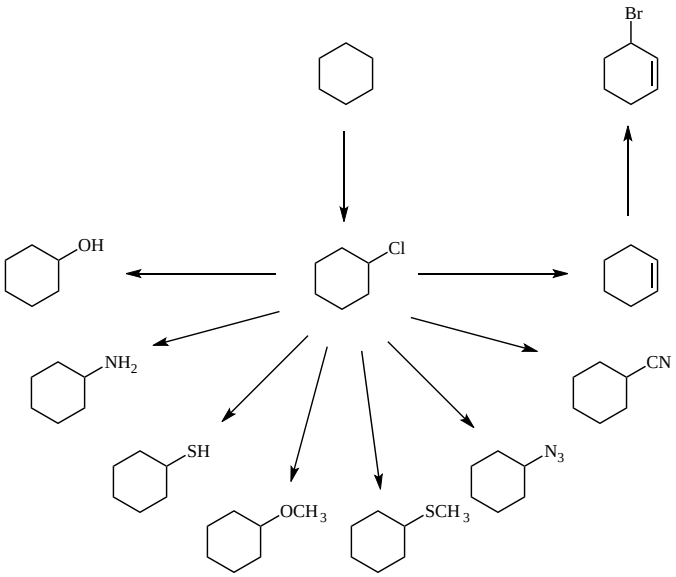


Reaction Maps to Build Functional Group Conversion Mastery

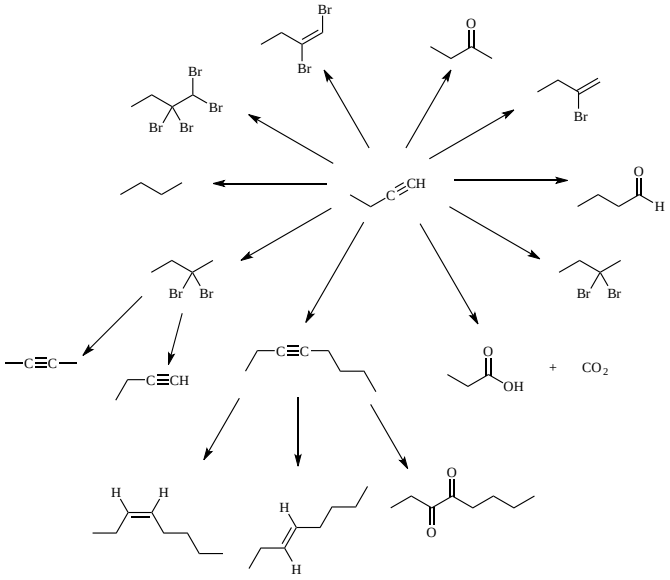
After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

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

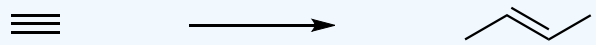
c) 3-hexanol.

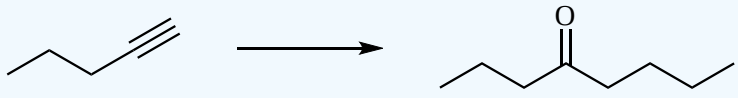
2) Starting with acetylene and any alkyl halides propose a synthesis to make

a) pentanal

b) hexane.

3) Show how you would accomplish the following synthetic transformations.

a) 

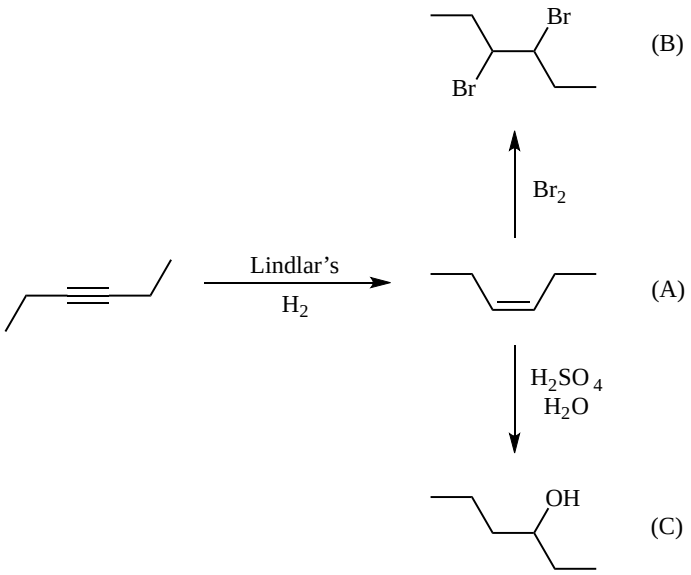
b) 

Answer available at the end of this section.

Answers

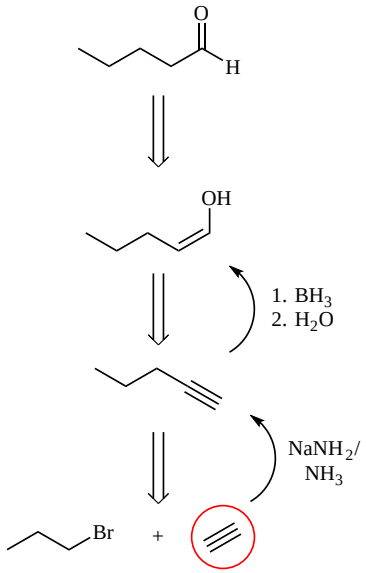
Exercise

1)

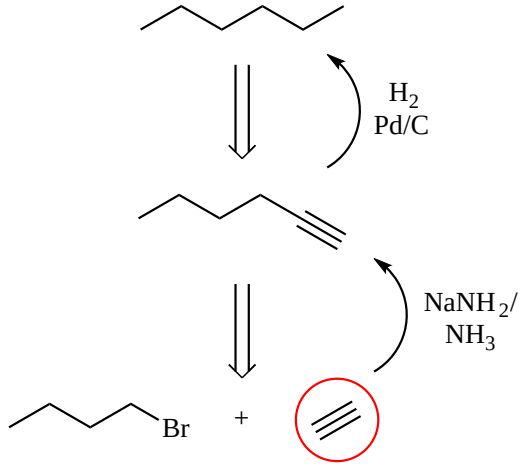


2)

a)

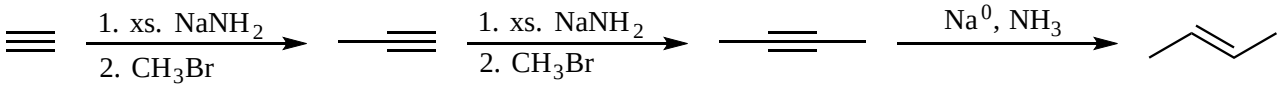


b)

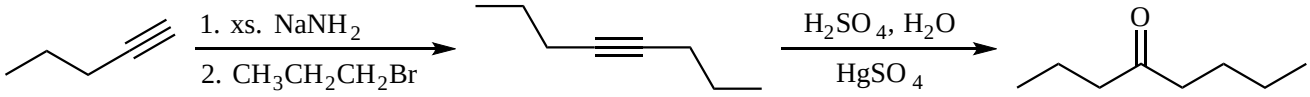


3)

a)



b)



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11: THE CHEMISTRY OF ETHERS, EPOXIDES, GLYCOLS, AND SULFIDES

11.1: Williamson Ether Synthesis

11.2: Synthesis of Epoxides

11.3: Acidic Cleavage of Ethers

11.4: Opening of Epoxides

11.5: Dihydroxylation of Alkenes

11.6: Periodate cleavage of 1,2-diols (glycols)

11.7: Epoxidation

11.8: Sharpless Epoxidation

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11.1: 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

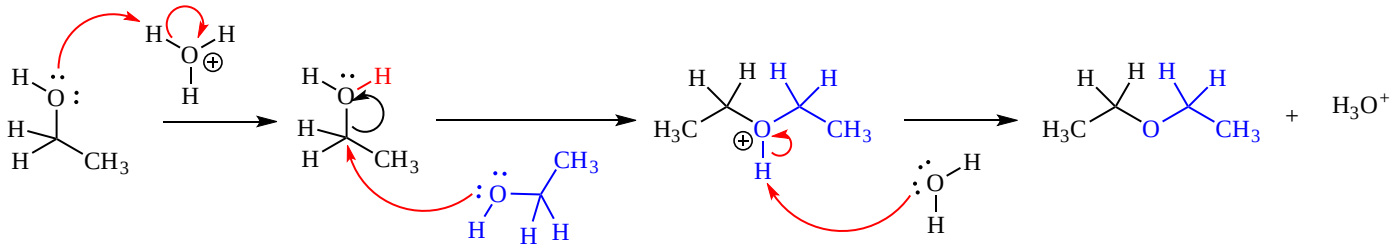
Acid-catalyzed dehydration of small 1°-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2°

and 3° alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \qquad (18.2.1)$$

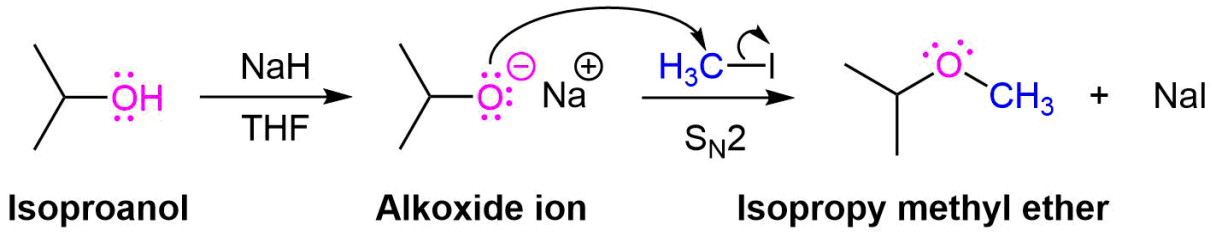
Mechanism

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

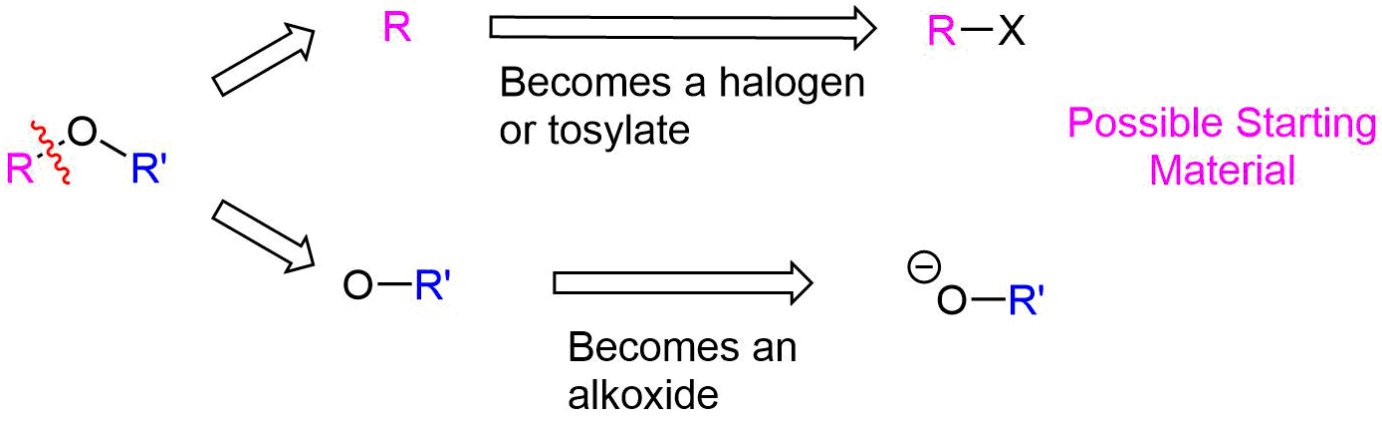
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in **Section 17-2**, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium 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

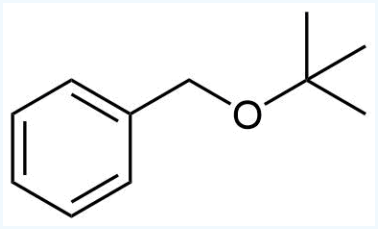
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, 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 11.1.1

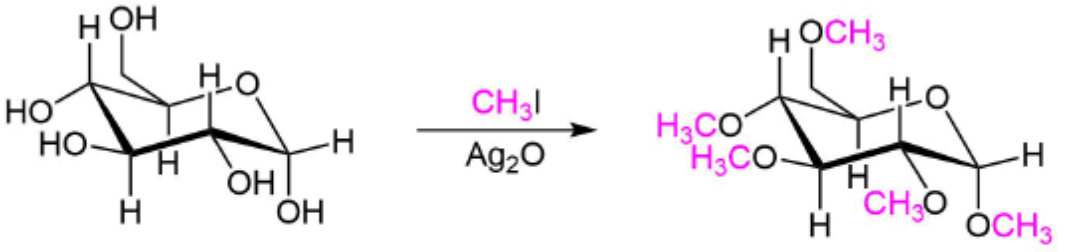
How would you prepare the following molecule using a Williamson Ether Synthesis?



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.

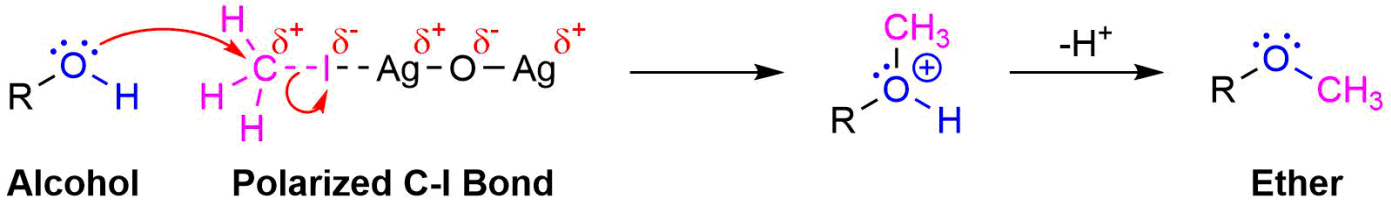


α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

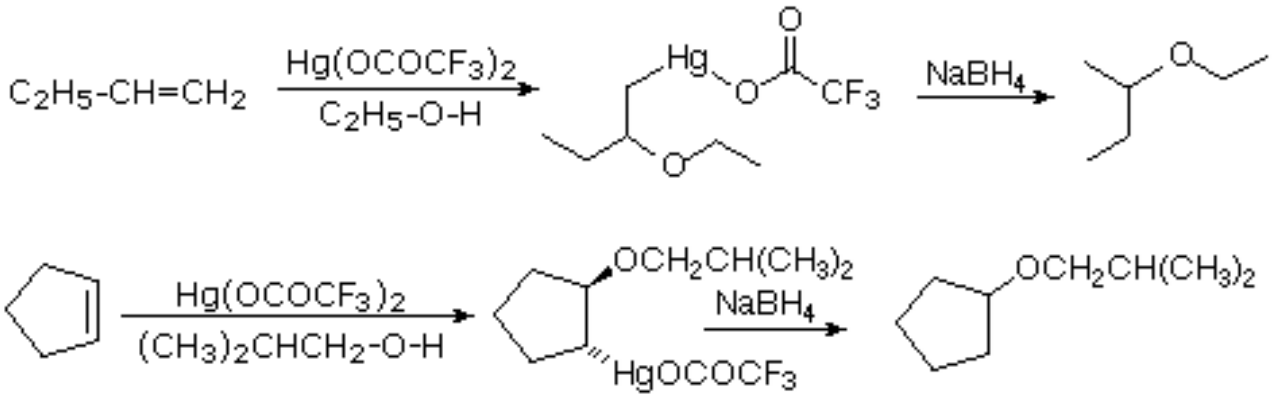
Mechanism

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.



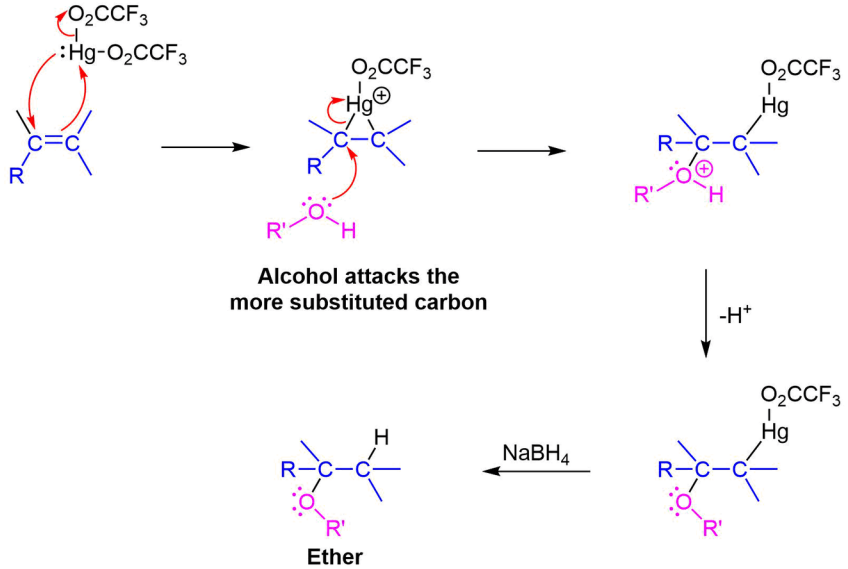
Ether Synthesis Using Alkoxymercuration

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°, 2°, 3° alcohols can be successfully used for this reaction.



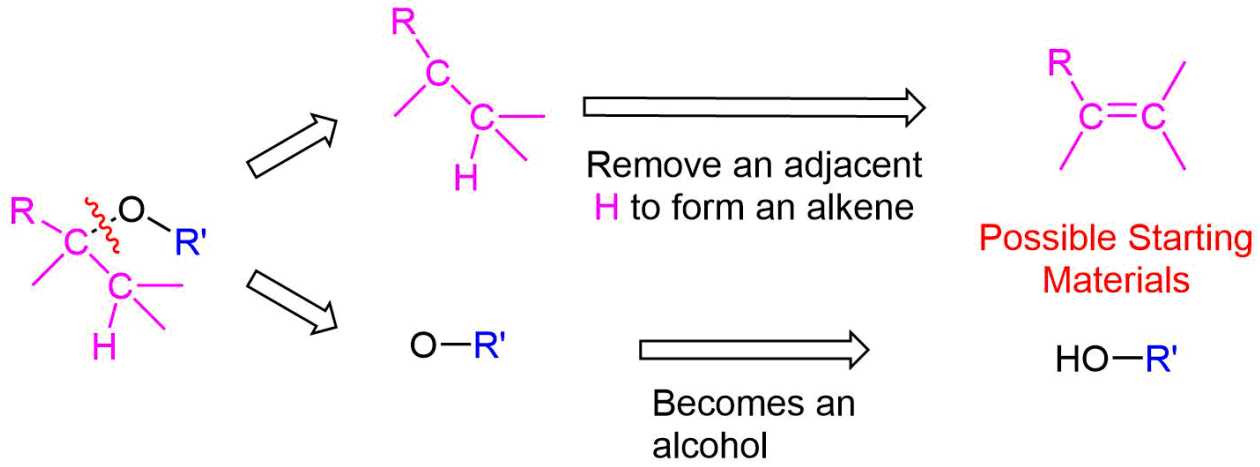
Mechanism

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.



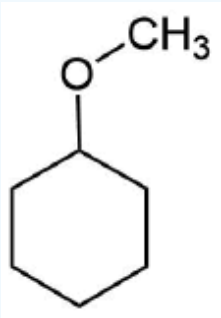
Planning the Synthesis of an Ether using Alkoxymercuration

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 11.1.2

How would you prepare the following molecule using a alkoxymercuration?



Answer available at the end of this section.

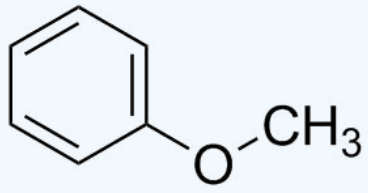
Exercise 11.1.1

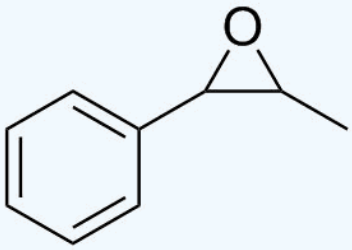
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

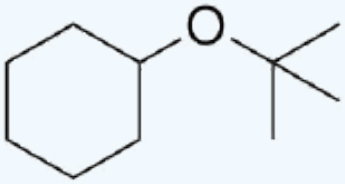
Answer available at the end of this section.

Exercise 11.1.2

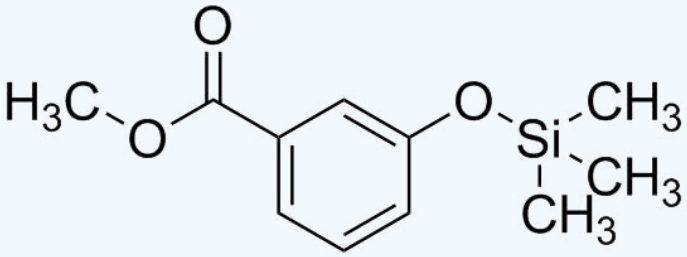
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

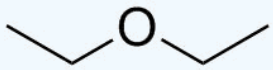
(a) 

(b) 

(c) 

(d)



(e) 

Answer available at the end of this section.

Exercise 11.1.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer available at the end of this section.

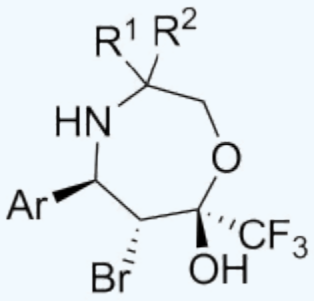
Exercise 11.1.4

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 11.1.5

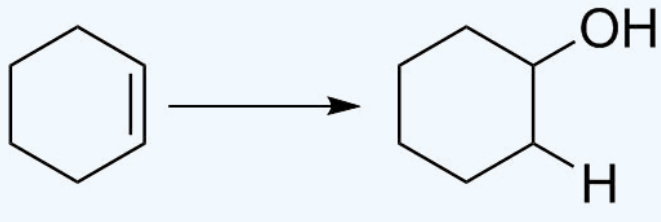
Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



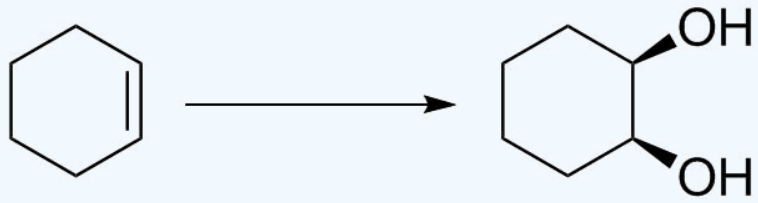
Answer available at the end of this section.

Exercise 11.1.6

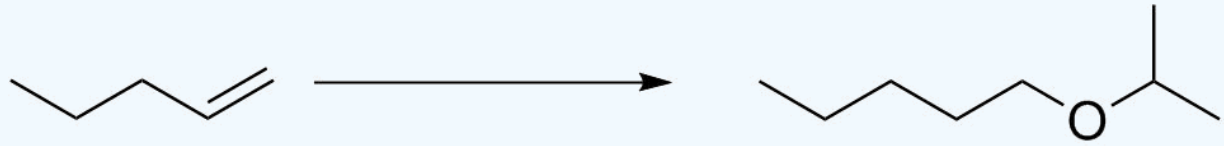
What reagents would you use to perform the following transformations?



(a)



(b)

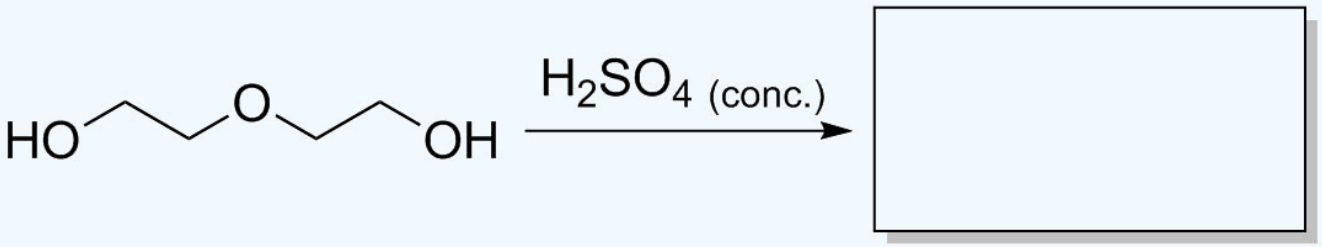


(c)

Answer available at the end of this section.

Exercise 11.1.7

Predict the product of the following.



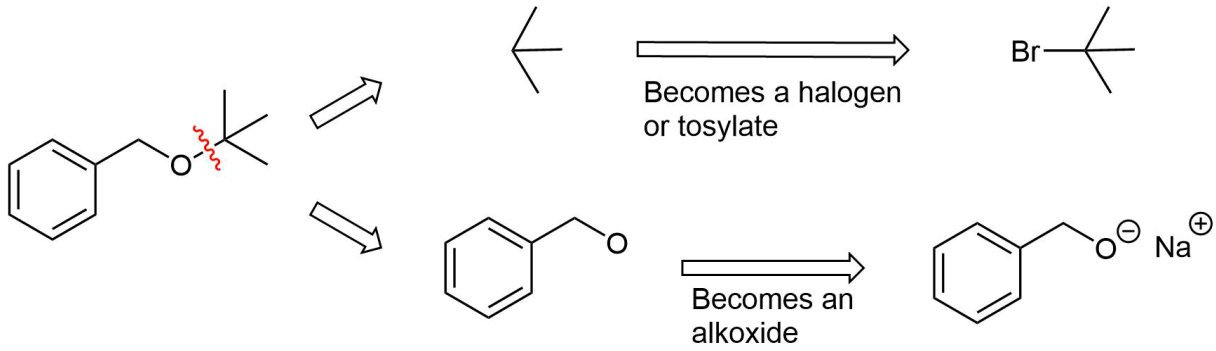
Answer available at the end of this section.

Answers

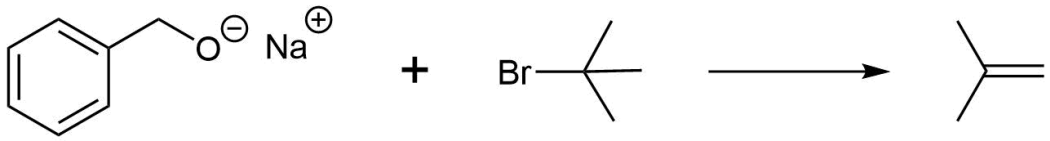
Worked Example 11.1.1

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



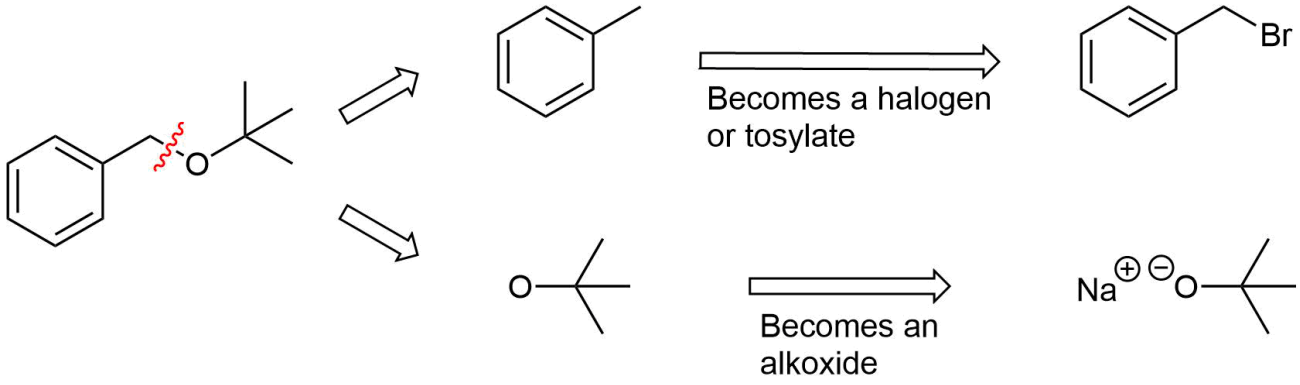
Solution 1



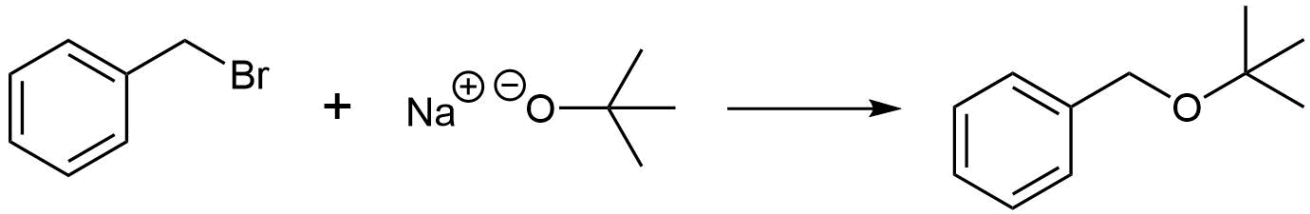
3° Halogen

E2 Elimination product most likely due to using a 3° halogen

Pathway 2



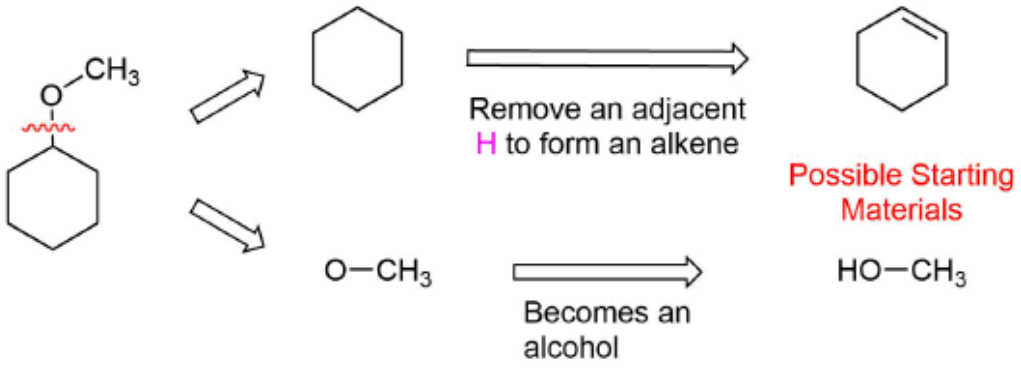
Solution 2



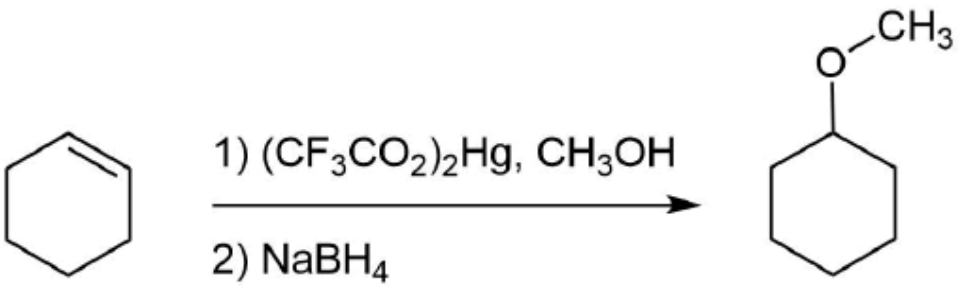
Worked Example 11.1.2

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.

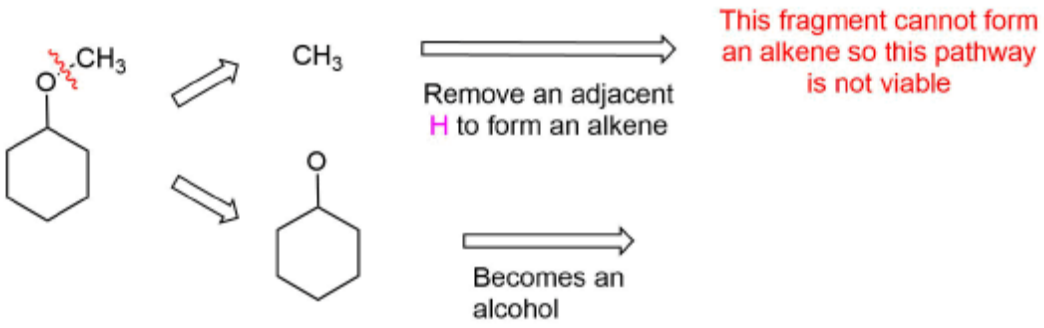
Pathway 1



Solution 1



Pathway 2



Exercise 11.1.1

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.

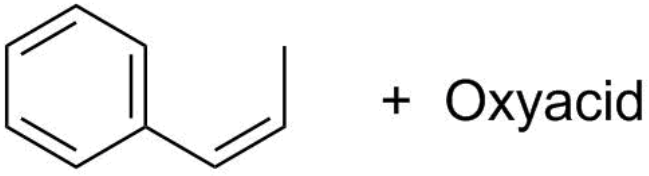
Exercise 11.1.2

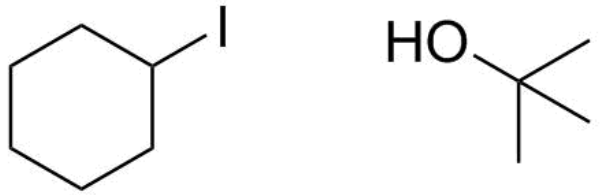
The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

(a)

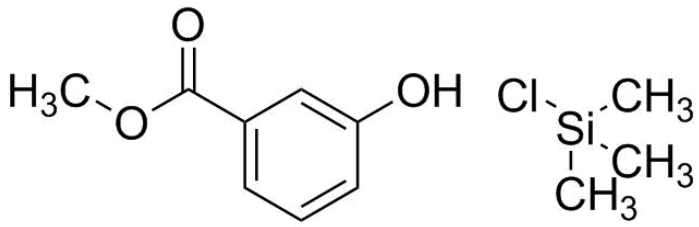


(b)





(c)



(d)

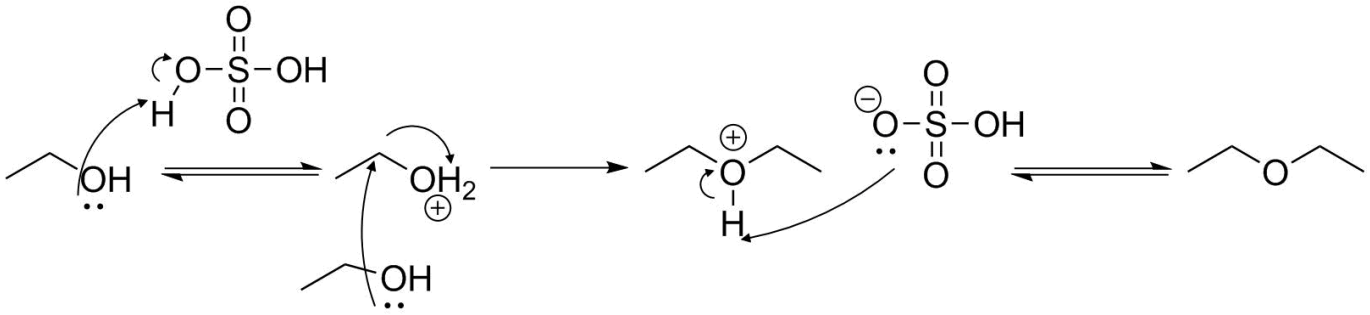
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.



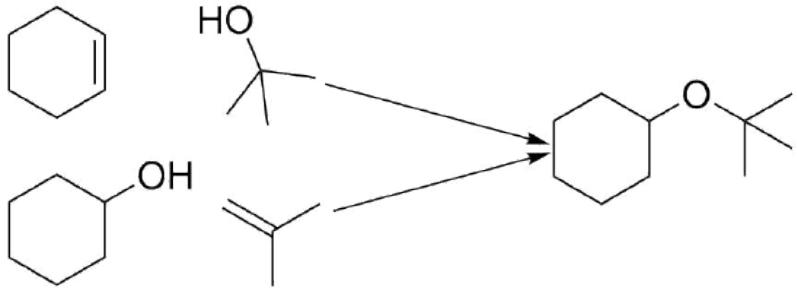
(e)

Exercise 11.1.3

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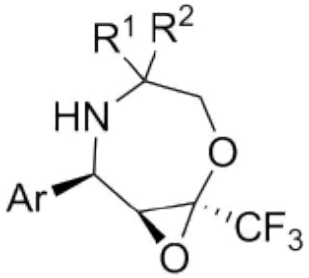


Exercise 11.1.4

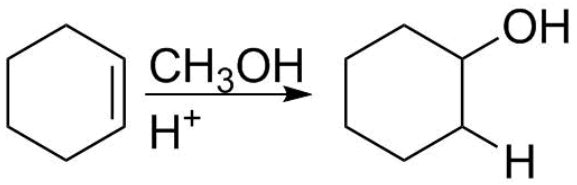


While both are possible, the top route is likely easier because both starting materials are a liquid.

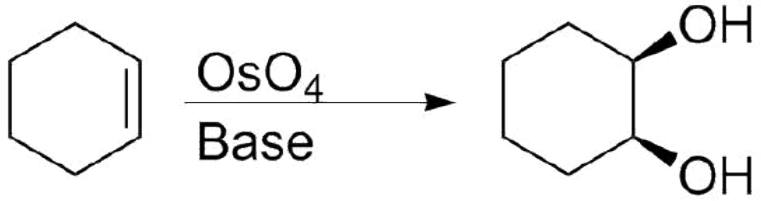
Exercise 11.1.5



Exercise 11.1.6

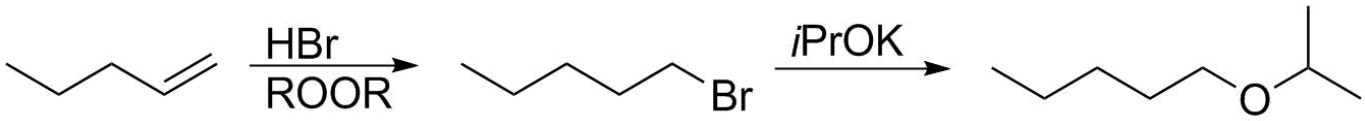


(a)



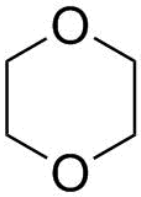
(b) Note the cis addition

(c)



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 11.1.7



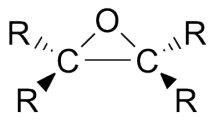
The result is the production of dioxane, a common solvent.

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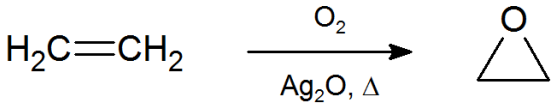
- 18.2: Preparing Ethers by Dietmar Kennepohl, Steven Farmer is licensed CC BY-SA 4.0.

11.2: Synthesis of Epoxides

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons. Edit section



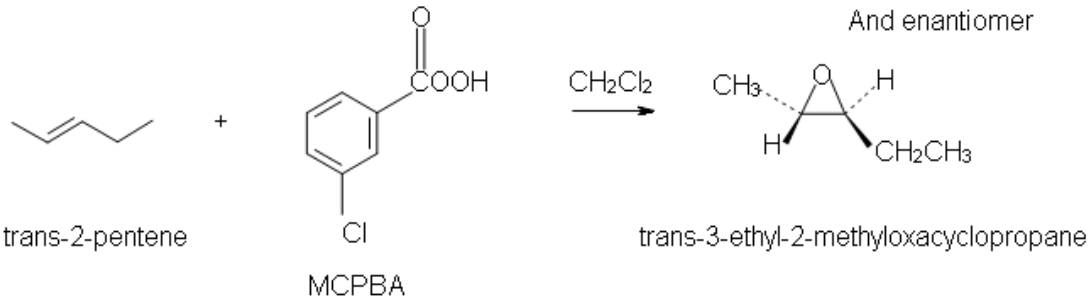
The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air.



Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.

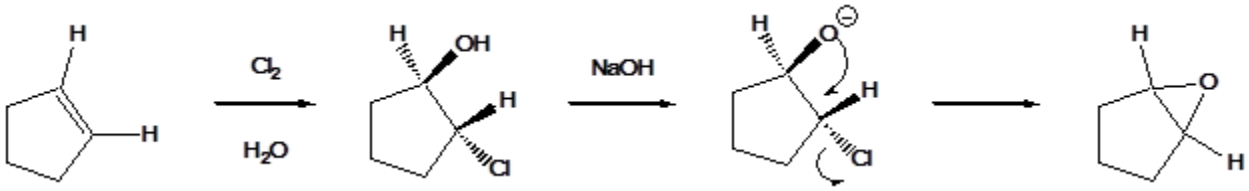
Peroxyacid reactions with Alkenes

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.



Intramolecular Williamson Ether Synthesis via Halohydrins

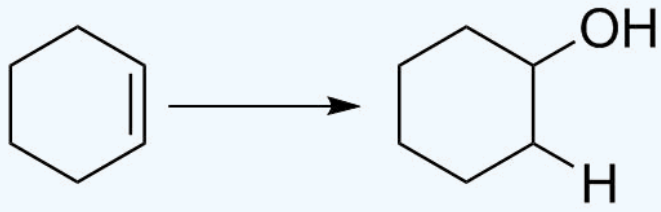
Epoxides can also be synthesized by the treatment of a halohydrin with a base. This causes an intramolecular Williamson ether synthesis.



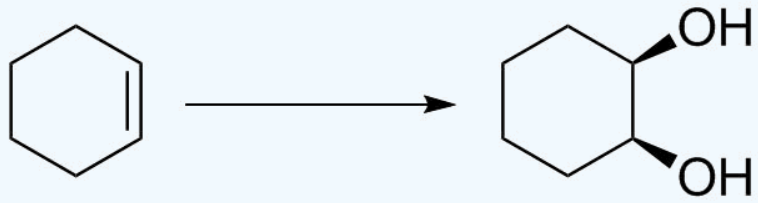
Exercise

8. What reagents would you use to perform the following transformations?

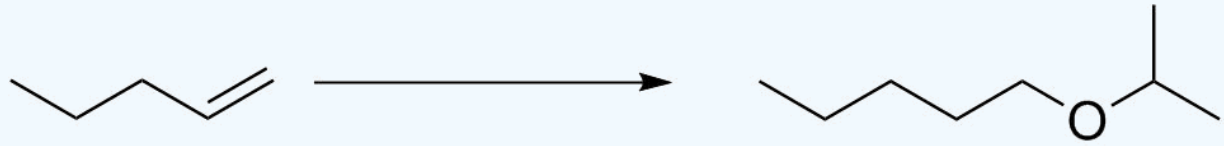
(a)



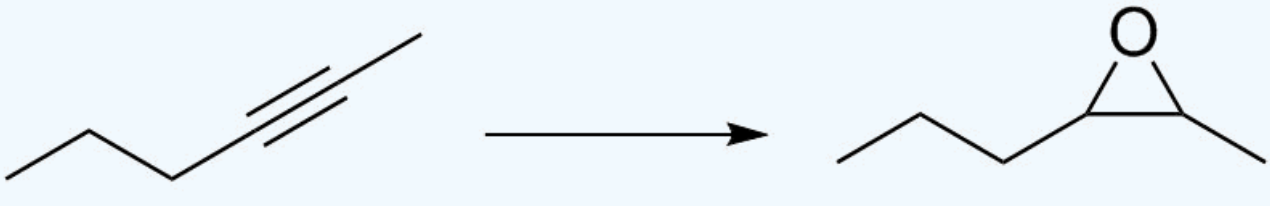
(b)



(c)



(d)



Answer available at the end of this section.

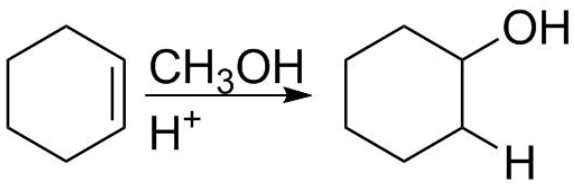
Contributors and Attributions

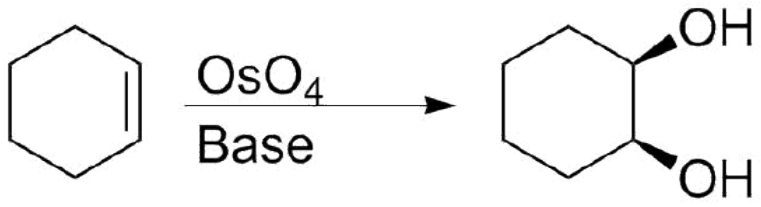
Answers

Exercise

8.

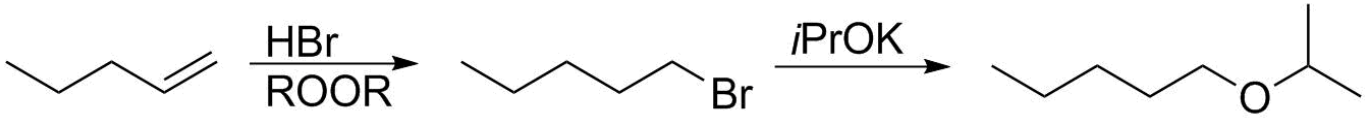
(a)





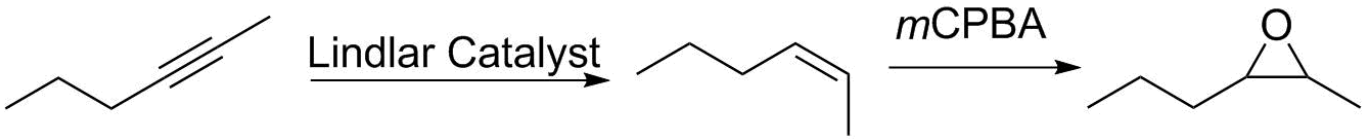
(b) Note the cis addition

(c)



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.

(d)

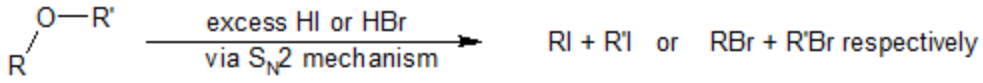


Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

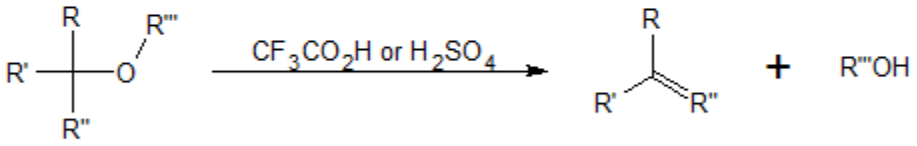
This page titled 11.2: Synthesis of Epoxides is shared under a license and was authored, remixed, and/or curated by LibreTexts.

11.3: Acidic Cleavage of Ethers

The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S_N1 or E1 mechanisms for 3°-alkyl groups or by an S_N2 mechanism for 1°-alkyl groups.

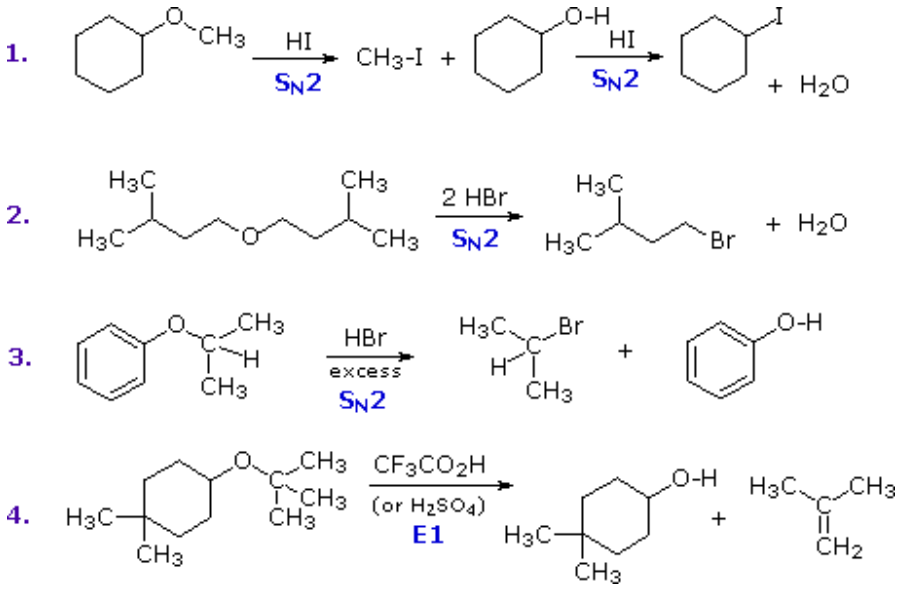


R groups need to be primary
or unhindered secondary.



A bulky R group
will favor an
elimination reaction.

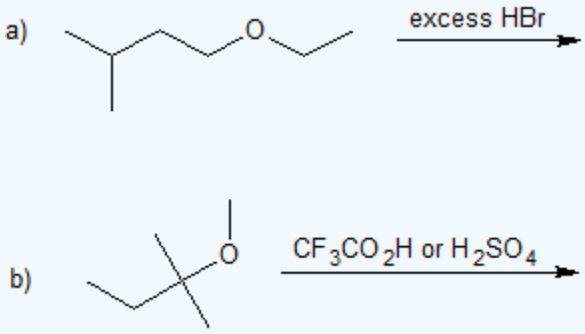
Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, just as conjugate acids were intermediates in certain alcohol reactions.



The first two reactions proceed by a sequence of S_N2 steps in which the iodide or bromide anion displaces an alcohol in the first step, and then converts the conjugate acid of that alcohol to an alkyl halide in the second. Since S_N2 reactions are favored at least hindered sites, the methyl group in example #1 is cleaved first. The 2°-alkyl group in example #3 is probably cleaved by an S_N2 mechanism, but the S_N1 alternative cannot be ruled out. The phenol formed in this reaction does not react further, since S_N2, S_N1 and E1 reactions do not take place on aromatic rings. The last example shows the cleavage of a 3°-alkyl group by a strong acid. Acids having poorly nucleophilic conjugate bases are often chosen for this purpose so that E1 products are favored.

Exercise

7. Draw the bond-line structures of the product(s) for each reaction below.



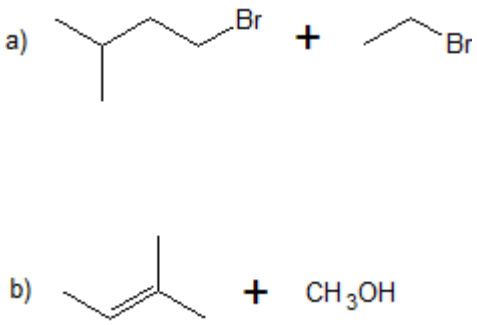
Answer available at the end of this section.

Contributors and Attributions

Answers

Exercise

7.



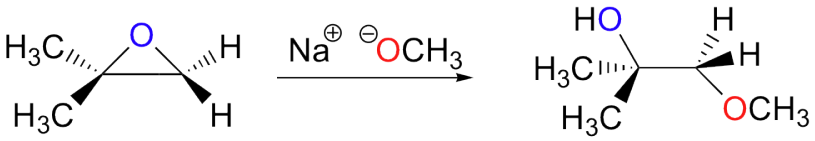
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11.4: Opening of Epoxides

Epoxide ring-opening reactions - S_N1 vs. S_N2, regioselectivity, and stereoselectivity

The ring-opening reactions of epoxides provide an excellent review of the differences between S_N1 and S_N2 reactions. Both mechanisms are 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). 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. For the S_N1 mechanism, the stability of the charged intermediate determines the regioselectivity. For the concerted S_N2 mechanism, sterics are the dominating consideration. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic reaction, leading to what we will refer to as product B:

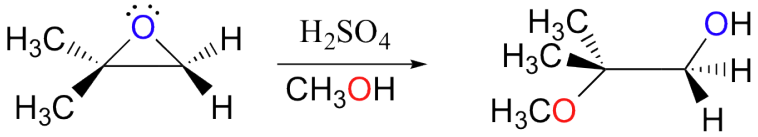
basic ring-opening:



product **B**

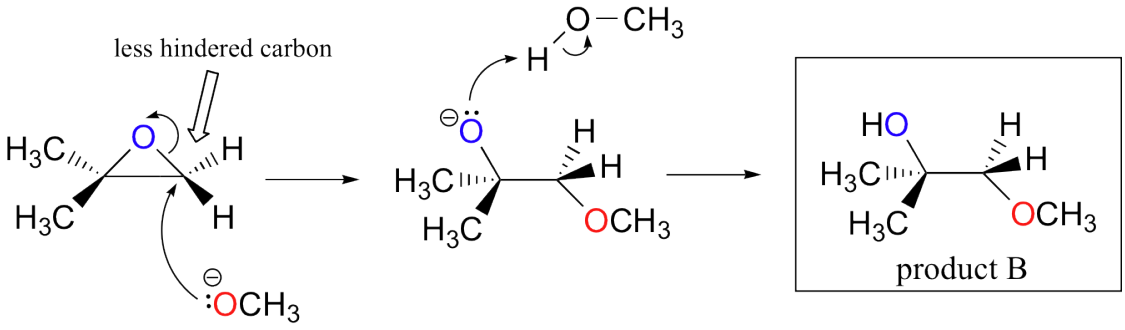
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of reaction. As a result, product A predominates.

acidic ring-opening:



product **A**

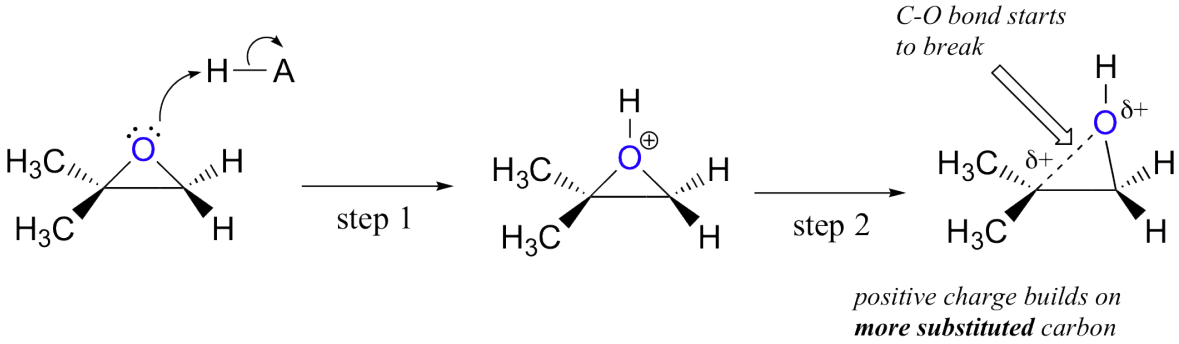
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



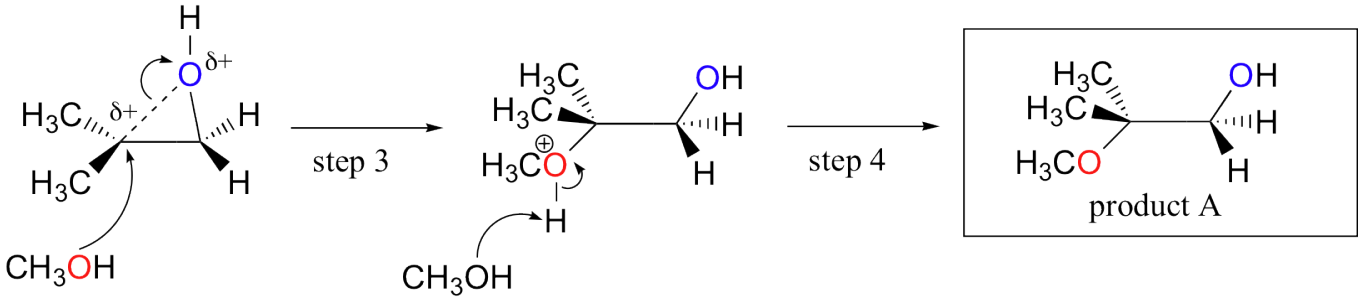
The nucleophile itself is a potent, deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? 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, bimolecular, nucleophilic substitution reactions take place from the backside, resulting in inversion at the electrophilic carbon.

The acid-catalyzed epoxide ring-opening reaction mechanism is analogous to the formation of the bromonium ion in halogenation of alkenes and mercurium ion formation in oxymercuration/demercuratioin or alkoxymercuration/demercuration. 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 carbocation stability).



Unlike in an S_N2 reaction, the nucleophile reacts with the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

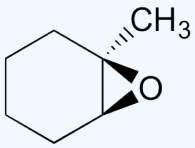


The reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile reacts with the more substituted carbon because this carbon that holds a greater degree of positive charge.

Example

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

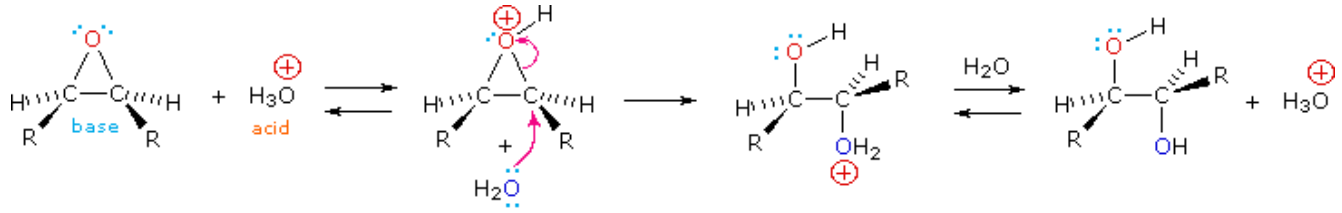


*Hint: be sure to consider both regiochemistry **and** stereochemistry!*

Answer available at the end of this section.

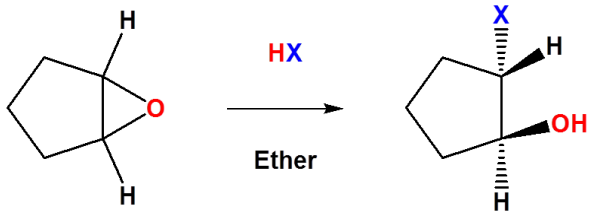
Anti DihydroxylationEdit section

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction. 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 the following equation this procedure is illustrated for a cis-disubstituted epoxide, which can be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



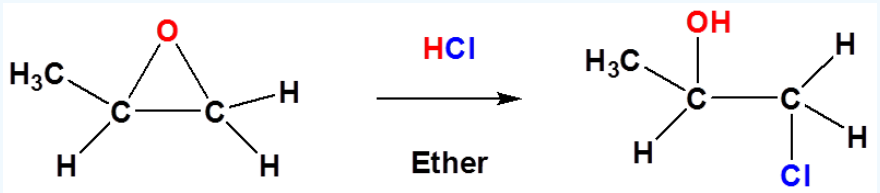
Addition of HX

Epoxides can also be opened by other anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will react with the less substituted carbon and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily react with the tertiary carbon in a S_N1 like reaction.

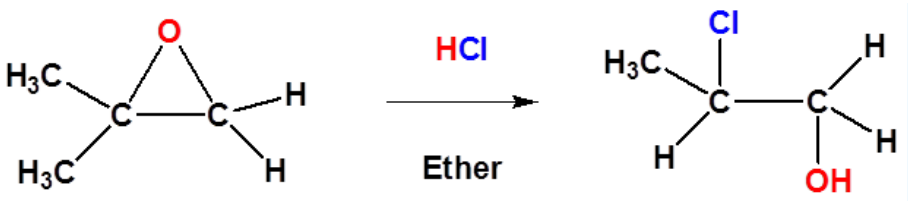


Example

In the first example, the epoxide is formed by a secondary and primary carbon. The reaction with the Cl^- nucleophile proceeds via the S_N2 mechanism and reacts with the least substituted carbon.

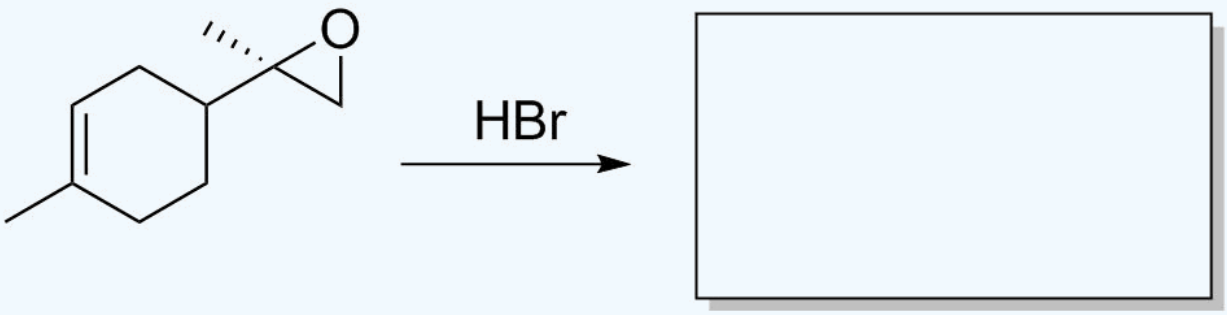


In the second example, the epoxide is formed by a tertiary and primary carbon. The reaction with Cl^- nucleophile proceeds via the S_N1 like mechanism and reacts with the most substituted carbon because it carries the greater partial positive charge.

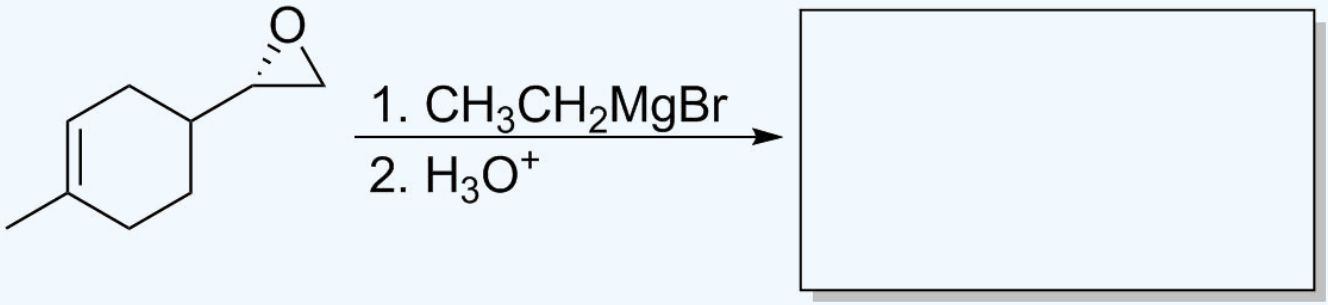


Exercise

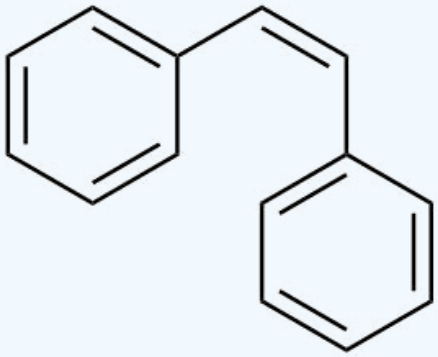
9. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



10. Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)



11. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



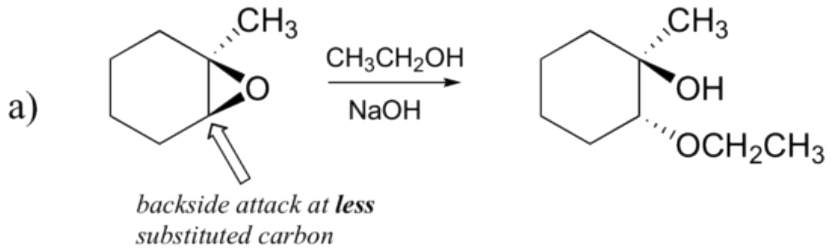
Answer available at the end of this section.

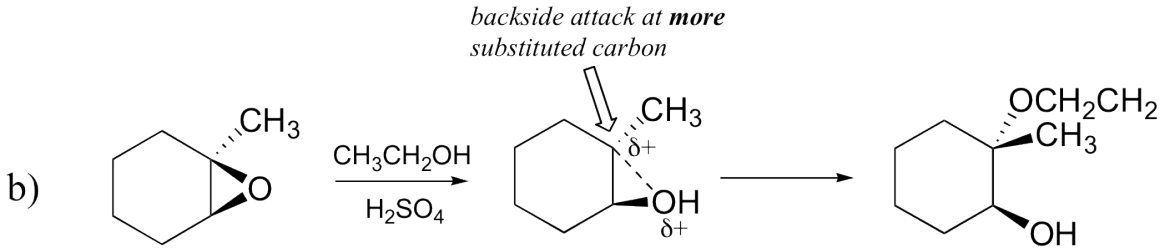
Contributors and Attributions

- 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

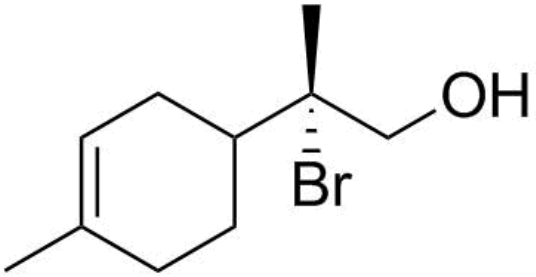
Example





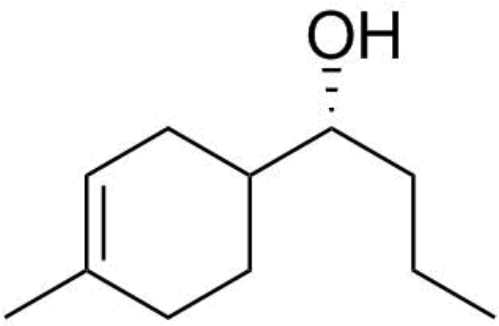
Exercise

9.



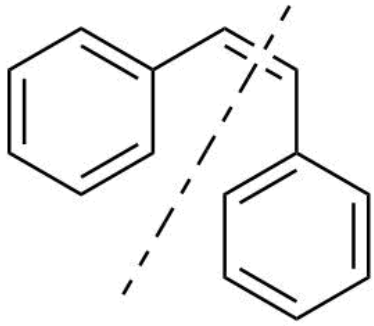
Note that the stereochemistry has been inverted

10.

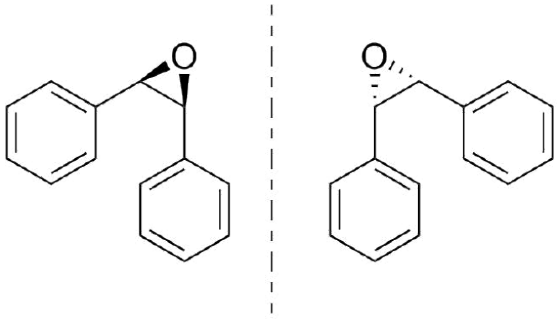


11.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

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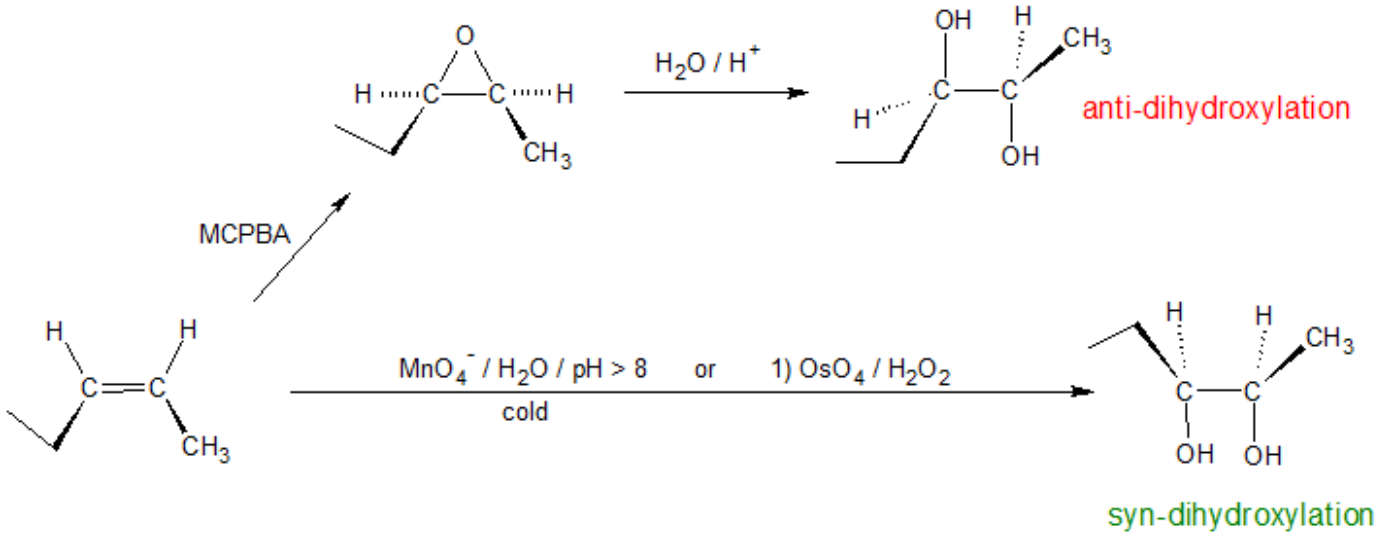
11.5: Dihydroxylation of Alkenes

Learning Objective

- predict the products/specify the reagents for dihydroxylation of alkenes

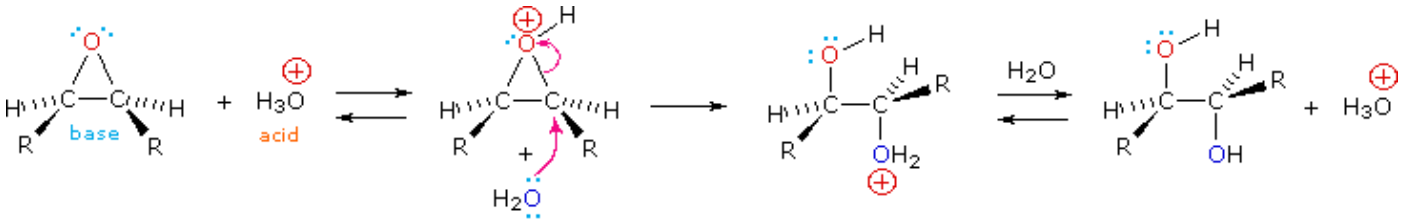
Dihydroxylation of alkenes

Alkenes can be dihydroxylated by two different stereochemical pathways: anti-dihydroxylation or syn-dihydroxylation. The opening of epoxides follows the anti-dihydroxylation mechanism, while potassium permanganate or osmium tetroxide produce the syn-dihydroxylated products. The osmium tertroxide reaction can also take place by a two-step process: 1) OsO_4 in pyridine followed by 2) H_2S or $NaHSO_3$. It is important to note that different professors will emphasize different reagent systems to accomplish the same chemical reaction. In these situations, it can be helpful to recognize the role of each reagent to discern patterns.



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. The mechanism for the ring opening of epoxides depends on the reaction conditions and is discussed in more detail in the next section of this chapter.



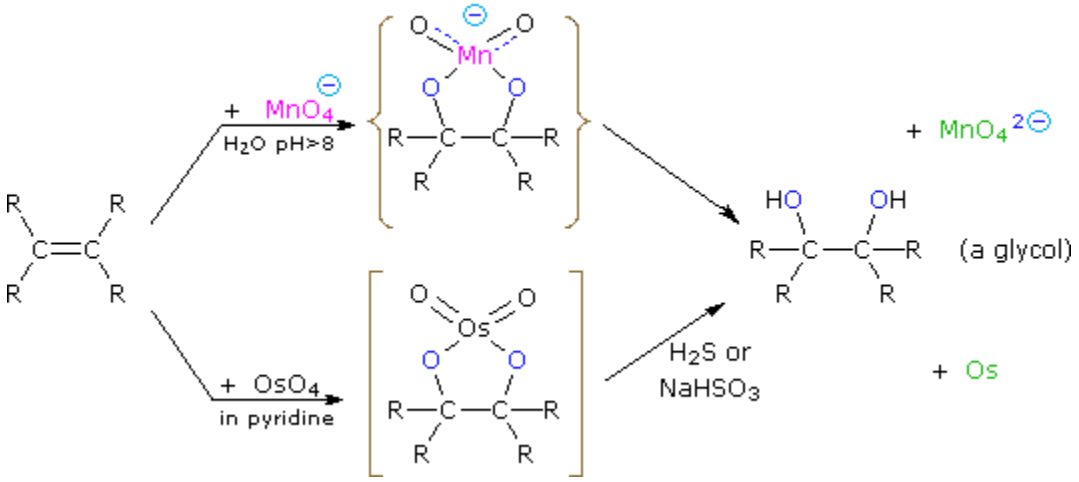
Syn Dihydroxylation

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.

glycol.bmp

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.



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.

Cis alkenes.bmp

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:

$$Os_{(s)} + 2O_{2\ (g)} \rightarrow OS_4 \tag{11.5.1}$$

Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of 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 OsO_4 was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $KMnO_4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of *overoxidation*.

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.

Exercise

1. Give the major product.

Problem 1 (1).bmp

2. What is the product in the dihydroxylation of (Z)-3-hexene?

Problem 2.bmp

3. What is the product in the dihydroxylation of (E)-3-hexene?

Problem 3.bmp

4. Draw the intermediate of this reaction.

Problem 4.bmp

5. Fill in the missing reactants, reagents, and product.

Problem 5.bmp

Answer 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.

Contributors and Attributions

- Shivam Nand

Answers

Exercise

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

Answer 1.bmp

2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.

Answer 2.bmp

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

Answer 3.bmp

4. A cyclic osmic ester is formed.

Answer 4.bmp

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.

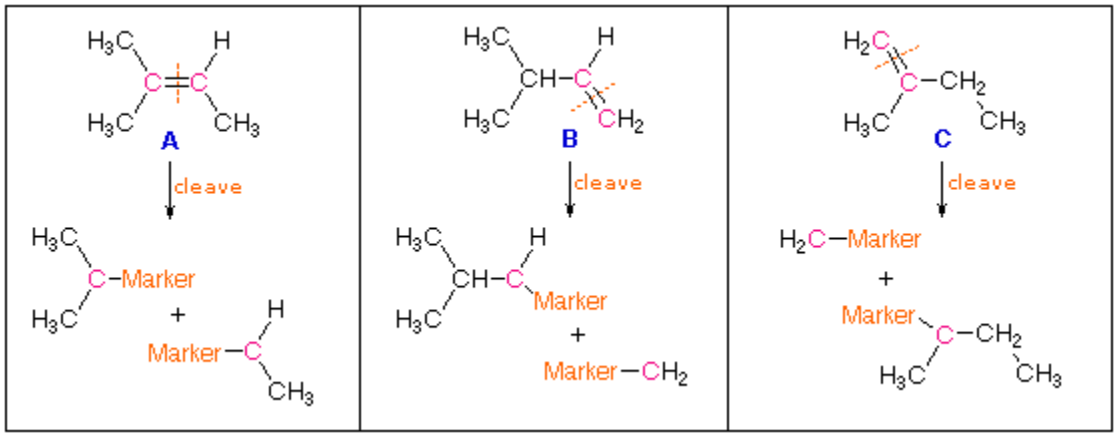
Answer 5.bmp

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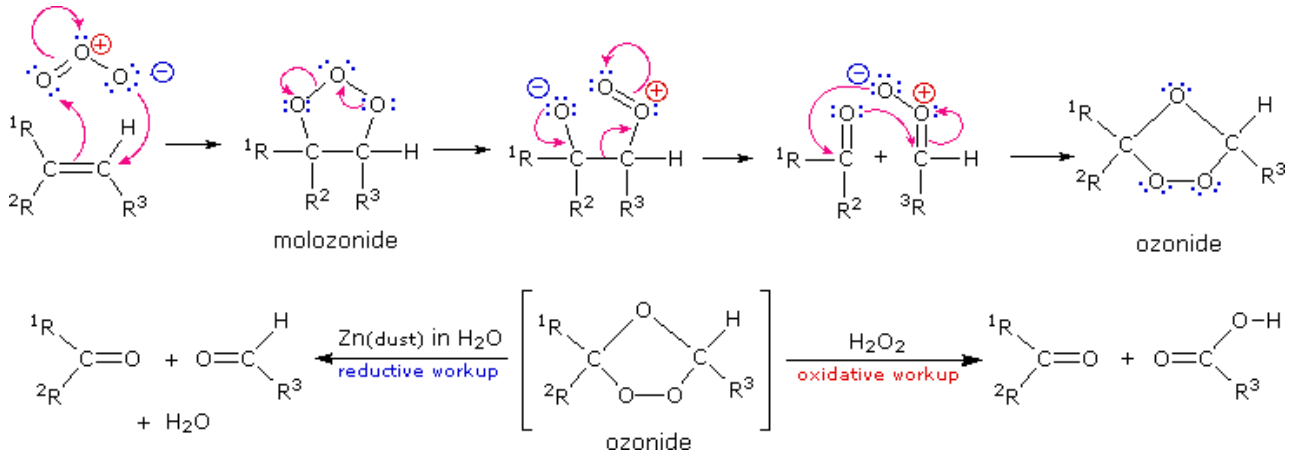
11.6: Periodate cleavage of 1,2-diols (glycols)

Ozonolysis

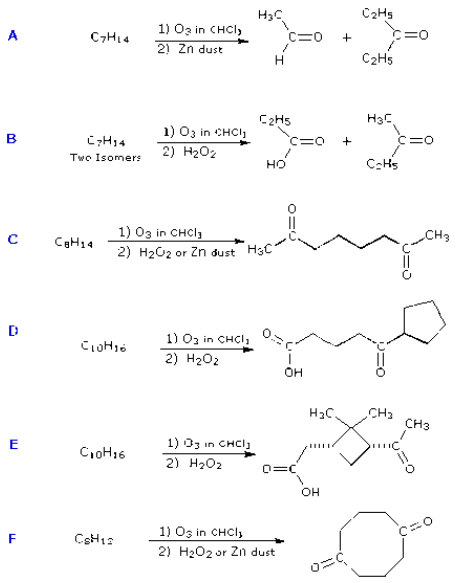
In determining the structural formula of an alkene, it is often necessary to find the location of the double bond within a given carbon framework. One way of accomplishing this would be to selectively break the double bond and mark the carbon atoms that originally formed that bond. For example, there are three isomeric alkenes that all give 2-methylbutane on catalytic hydrogenation. These are 2-methyl-2-butene (compound A), 3-methyl-1-butene (compound B) and 2-methyl-1-butene (compound C), shown in the following diagram. If the double bond is cleaved and the fragments marked at the cleavage sites, the location of the double bond is clearly determined for each case. A reaction that accomplishes this useful transformation is known. It is called **ozonolysis.**



Ozone, O_3, is an allotrope of oxygen that adds rapidly to carbon-carbon double bonds. Since the overall change in ozonolysis is more complex than a simple addition reaction, its mechanism has been extensively studied. Reactive intermediates called ozonides have been isolated from the interaction of ozone with alkenes, and these unstable compounds may be converted to stable products by either a reductive workup (Zn dust in water or alcohol) or an oxidative workup (hydrogen peroxide). The results of an oxidative workup may be seen by clicking the "Show Reaction" button a second time. Continued clicking of this button repeats the cycle. The chief difference in these conditions is that reductive workup gives an aldehyde product when hydrogen is present on a double bond carbon atom, whereas oxidative workup gives a carboxylic acid or carbon dioxide in such cases. The following equations illustrate ozonide formation, a process that is believed to involve initial syn-addition of ozone, followed by rearrangement of the extremely unstable molozonide addition product. They also show the decomposition of the final ozonide to carbonyl products by either a reductive or oxidative workup.

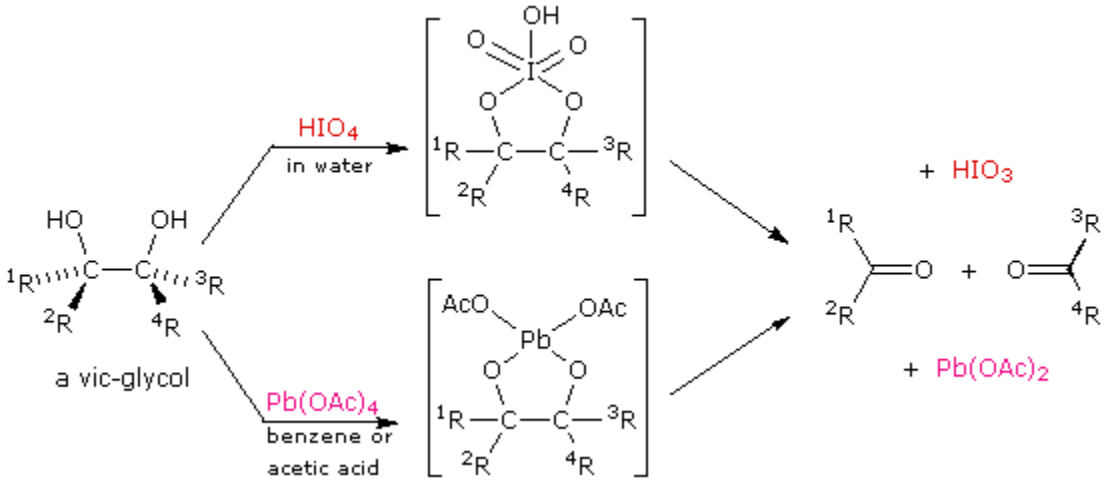


From this analysis and the examples given here, you should be able to deduce structural formulas for the alkenes that give the following ozonolysis products:



Glycol Cleavage

The vicinal glycols prepared by alkene hydroxylation (reaction with osmium tetroxide or permanganate) are cleaved to aldehydes and ketones in high yield by the action of **lead tetraacetate** ($Pb(OAc)_4$) or **periodic acid** (HIO_4). This oxidative cleavage of a carbon-carbon single bond provides a two-step, high-yield alternative to ozonolysis, that is often preferred for small scale work involving precious compounds. A general equation for these oxidations is shown below. As a rule, cis-glycols react more rapidly than trans-glycols, and there is evidence for the intermediacy of heterocyclic intermediates (as shown), although their formation is not necessary for reaction to occur.



Contributors

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

Further Reading

Wikipedia

Sodium Periodate

Glycol Cleavage

Carey 5th Ed Online

Oxidative Cleavage of 1,2-Diols

Chemtube3D

Periodate Cleavage of 1,2-Diol

MasterOrganicChemistry

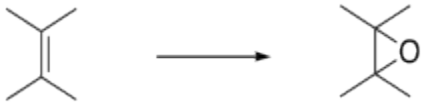
Sodium Periodate

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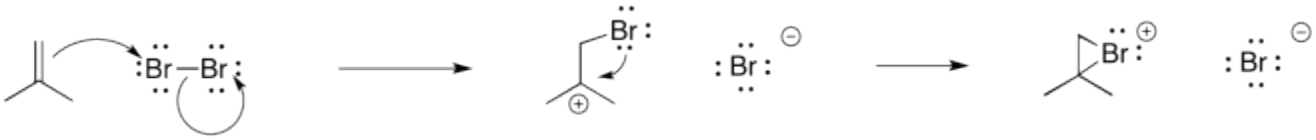
- Oxidative Cleavage of Double Bonds is licensed CC BY-NC-SA 4.0.

11.7: Epoxidation

Epoxidation is the addition of a single oxygen atom across a C=C double bond.



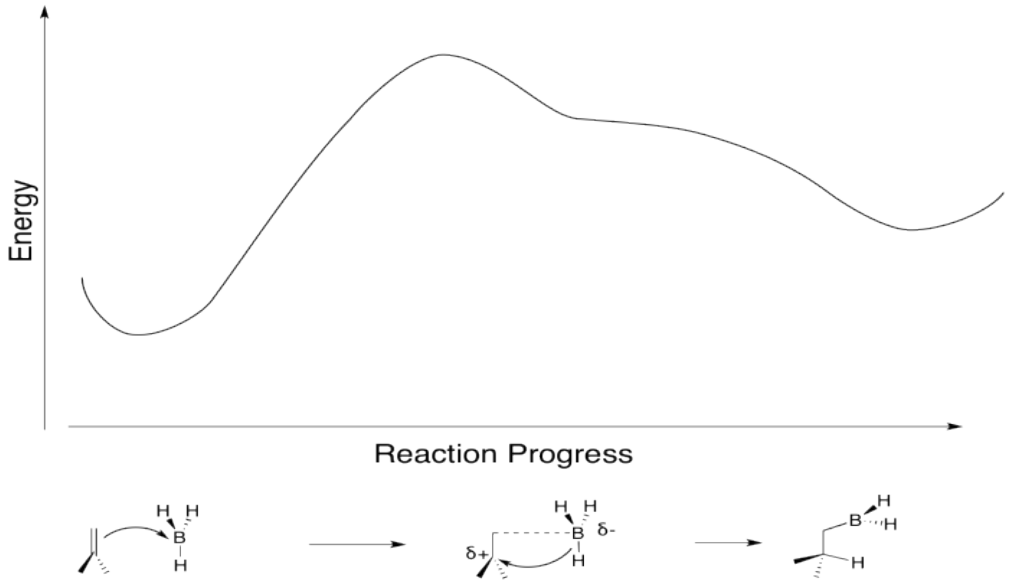
Earlier, we saw that alkenes can donate their pi electrons to electrophiles such as "Br^+". In the bromonium ion that results, a lone pair on the bromine can donate back to the incipient carbocation, leading to a more stable intermediate.



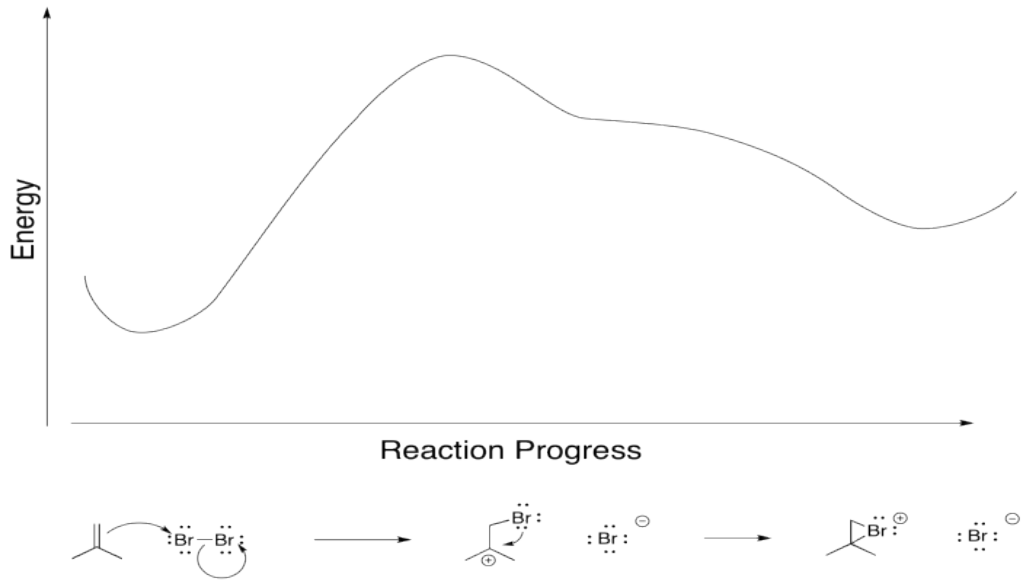
We have also seen that addition to alkenes can sometimes be concerted, happening all at once, rather than one step at a time. For example, in hydroboration, the boron and the hydrogen add to the double bond at the same time.



The boron is adding just slightly ahead of the hydrogen. The initial interaction is donation from the pi bond to the Lewis acidic boron. However, as soon as positive charge starts to build up on carbon, and negative charge starts to build up on boron, the hydride is immediately donated. Time is not allowed for the charged intermediate to fully form before proceeding.



Really, that's what is happening to the bromine, too. As the alkene starts to donate its pi electrons to the bromine and begins to build up positive charge, the bromine's lone pair is drawn back to the alkene. As a result, the intermediate that we imagine with a full positive charge on carbon and no charge on bromine exists too fleetingly to be considered an intermediate at all. As soon as it begins to form, it is already turning into something else.

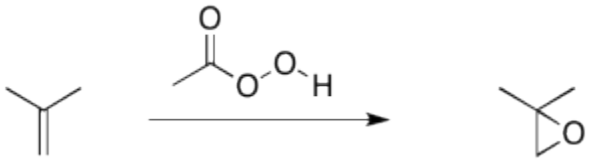


That sort of concerted addition happens with some other electrophiles, too. If an atom is electrophilic, but also has a lone pair to donate, that cyclic transition state can lead to the product in one step.

Alkene epoxidation is another example of this kind of reaction. An epoxidation is the transfer of an oxygen atom from a peroxy compound to an alkene. Peroxides contain O-O bonds, which are relatively weak and reactive.



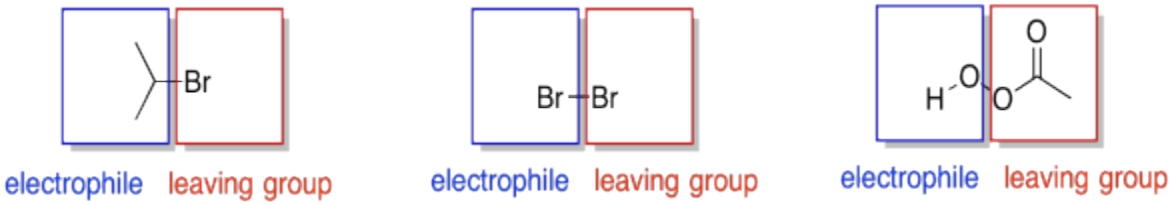
To simplify a little bit, just look at the reaction from the point of view of the alkene. It's just picking up an oxygen atom, because the peroxide had an extra one.



When the oxygen atom is transferred, it forms an epoxide (sometimes called an oxirane). It is a three-membered ring containing two carbons and an oxygen.

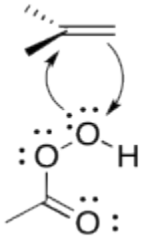
- Epoxidation results in transfer of an oxygen atom from a peroxide to an alkene.
- Peroxides are compounds containing weak O-O bonds.

Like in a bromination, the electrophile is deceptive. It is an oxygen atom, which we more naturally think of as a nucleophile. However, just as Br_2 contains an atom attached to a good leaving group (Br^-), so do the kinds of oxygen compounds used in epoxidation. Most often, these are "peroxy acids", carboxylic acids containing an extra oxygen.

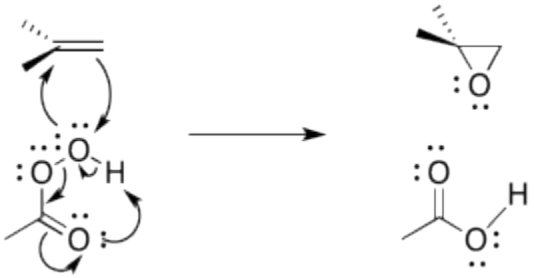


As in the bromination, as soon as the alkene begins donating to the electrophile, a lone pair can donate back, so that an unstable

cation does not have to form.



The entire mechanism is believed to be concerted, based on a number of lines of experimental evidence. A number of things need to be accomplished; in addition to the oxygen donation, the leaving group must leave, and a proton must be transferred.



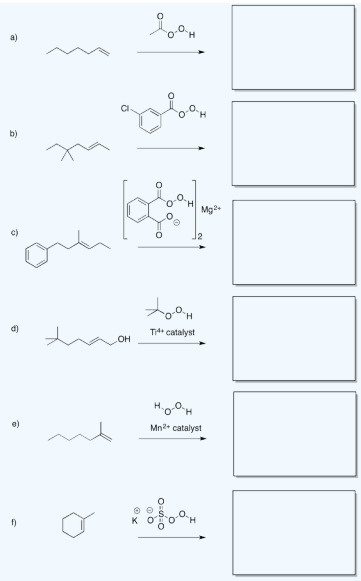
The reaction mechanism can be cleaned up slightly because it is thought to be an example of a pericyclic reaction. Pericylcic reactions frequently involving three pairs of electrons moving in a circle. Like the three pairs of electrons in a benzene ring, this structure is thought to be unusually stable.



Apart from peroxy acids, many other peroxides can be involved in epoxidations, as well as some metal oxides. In some cases, the reaction is extremely slow, but works better in the presence of a catalyst.

Exercise 11.7.1

Predict the products of the following reactions.



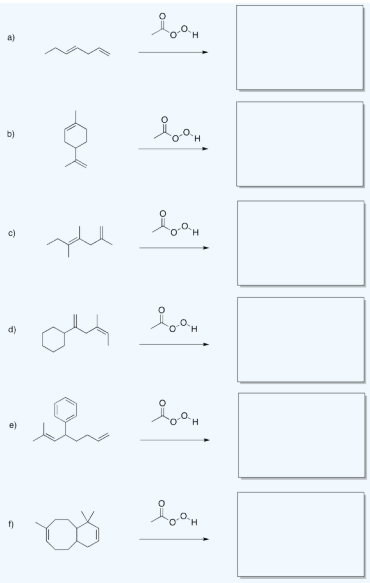
Answer available at the end of this section.

Epoxidation reactions display an almost counter-intuitive selectivity. Unlike hydrogenation reactions, which are generally easier with less-substituted alkenes, epoxidations are much faster with more-substituted alkenes. In the case of hydrogenations, the selectivity can be understood as a combination of steric factors (the alkene must bind to a catalyst) as well as thermodynamicic factors (more substituted alkenes are more stable, so they are less likely to react). However, in epoxidations, the more electron-rich the alkene, the more easily it can be induced to react with the peroxide. More substituted alkenes are generally more electron-rich than those that are substituted only with electron-poor hydrogens.



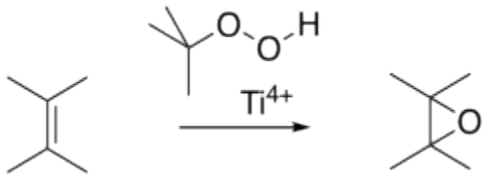
Exercise 11.7.2

Predict the products of the following reactions.

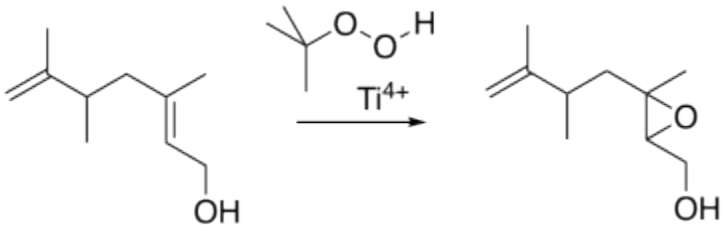


Answer available at the end of this section.

The Sharpless epoxidation is one of the most common methods of catalytically adding an oxygen across a double bond. The method generally employs a titanium catalyst; similar approaches use vanadium catalysts or other metallic species. As mentioned before, metal ions can sometimes accelerate epoxidations.

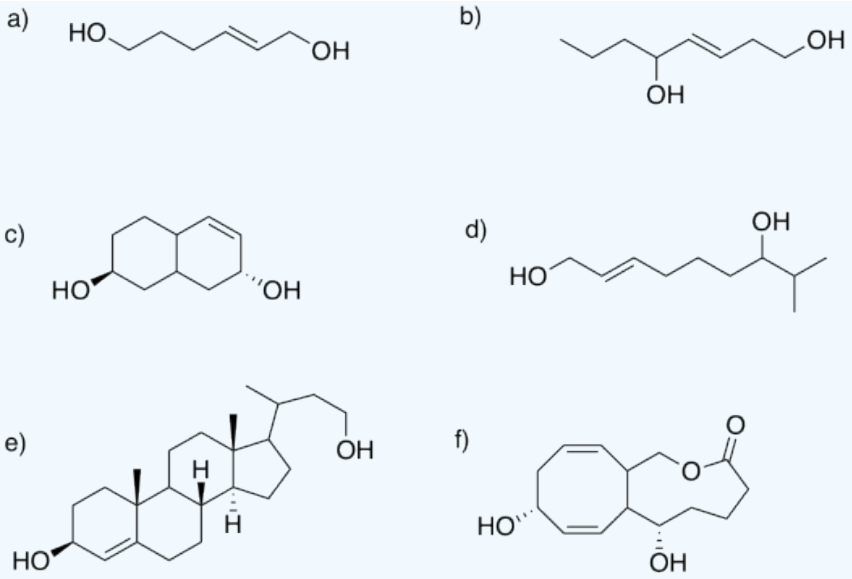


The Sharpless epoxidation is important partly because it selectively epoxidizes allylic alcohols: compounds containing a C=C-C-OH unit. That means that, in addition to being able to selectively epoxidize more-substituted double bonds in the presence of less-substituted double bonds, we can also select double bonds that are close to alcohols.



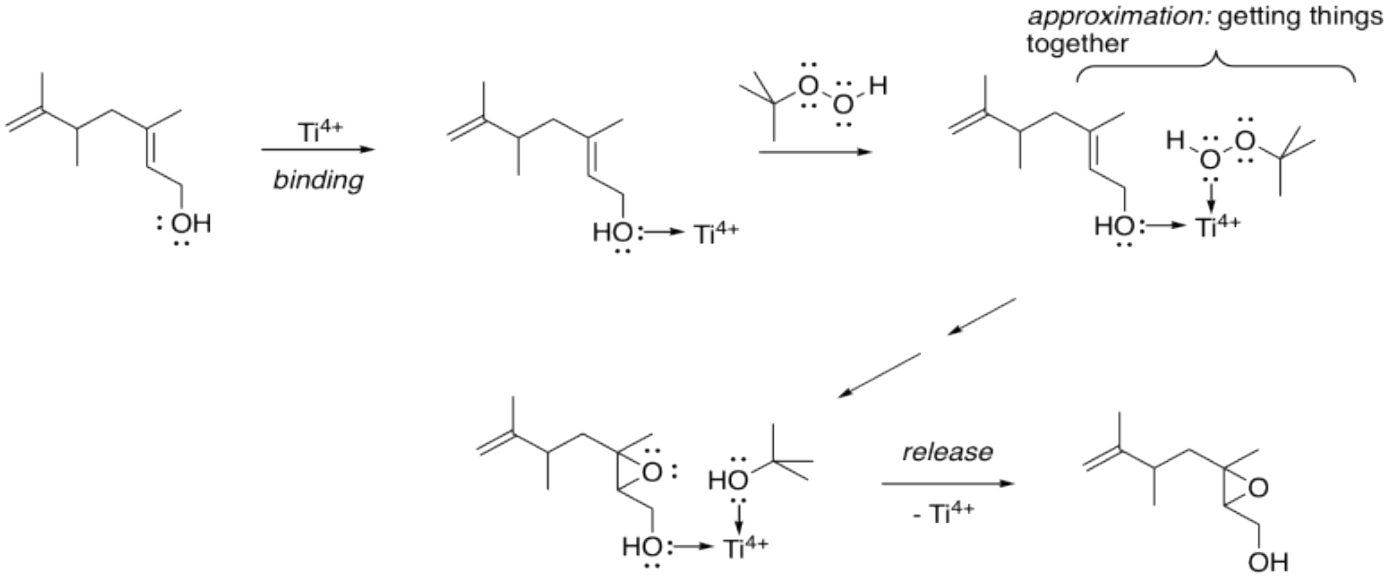
Exercise 11.7.3

Circle the allylic alcohol in each of the following compounds.



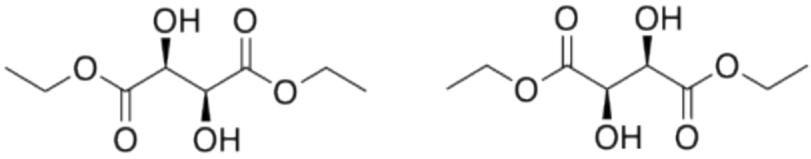
Answer available at the end of this section.

How does the metal catalysis selectively identify that position? Remember, one of the important strategies in enzyme catalysis is approximation: the act of bringing two things together. An alcohol is a potential lone pair donor, so it could become a ligand for a metal ion. Ti^{4+} and V^{4+} happen to be very oxophilic -- they bind well to oxygen -- and so they are particularly suited for this task.



In this scheme, we're not worrying about exactly how the titanium ion gets to peroxide to give up its extra oxygen to the alkene; that's complicated. However, the fact that both the allylic alcohol and the peroxide can bind to the titanium gets them closer together, and makes them more likely to react with each other.

That's only part of the story of the Sharpless epoxidation. The other reason this method is important is its stereoselectivity. To get stereoselectivity, a chiral ligand is added for the titanium. It's usually diethyl tartrate (DET) or diisopropyl tartrate (DIT). Tartrate is chiral; there is a D-(-)-enantiomer and a L-(+)-enantiomer. The D and L are common symbols used to designate enantiomers in sugars; they relate the structure back to the biochemical grandparents of all sugars, D-glyceraldehyde and L-glyceraldehyde. The (-) and (+) symbols refer to the characteristics of this particular compound in polarimetry; the (+) enantiomer rotates plane polarized light in a clockwise direction, whereas the (-) enantiomer rotates plane polarized light in a counter-clockwise direction.



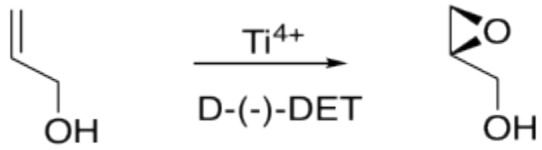
D-(-)-DET L-(+)-DET

Exercise 11.7.4

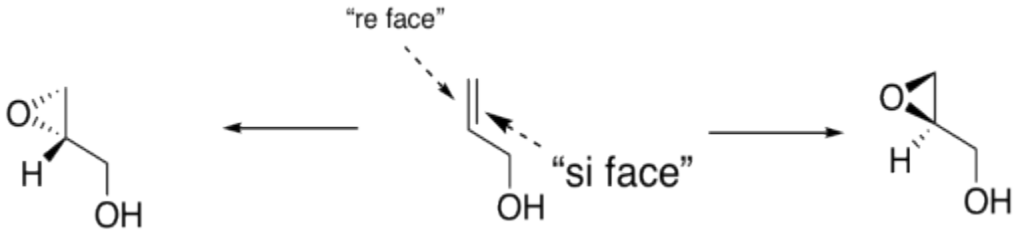
Assign stereochemical configurations (R and S) to the tartrates to confirm that they are enantiomers of each other.

Answer available at the end of this section.

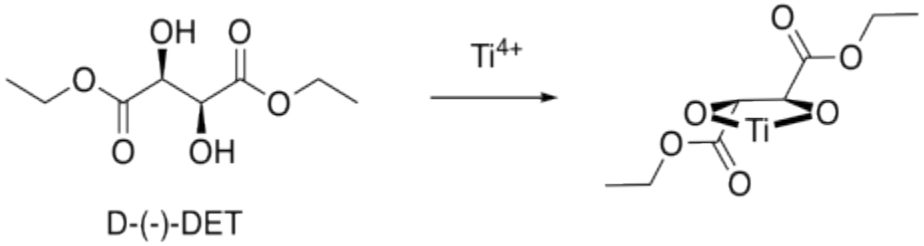
If the D-(-)-isomer is added, one possible enantiomer of the product is obtained. If the L-(+)-isomer is added, the other possible enantiomer is obtained.



In general, we would get one enantiomer if the oxygen were added to one face of the alkene and the other enantiomer if the oxygen were added to the other face. In the drawing below, the face of the alkene towards us is sometimes called the "re face" (pronounced, ray face). The face of the alkene away from us is called the "si face" (see face). These words sound related to *R* and *S* configuration, and they sort of are like that, but they are used to describe two different faces of a flat molecule. Adding oxygen to the re face gives on enantiomer; addign oxygen to the si face gives another.



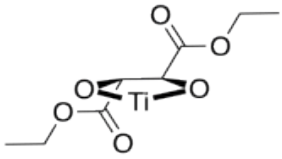
How does this preferred reactivity work? How does the metal manage to add the oxygen to one face but not to the other? Tartrates are oxygen-rich and so they bind very well to titanium. Remember, if we have a reaction site and we make it chiral, one enantiomer of the product is generally preferred. Enzymes are very compicated, chiral molecules, and they are good at producing one enantiomer of a product. By comparison, the titanium DET complex is a relatively simple chiral molecule, but it uses the same idea.

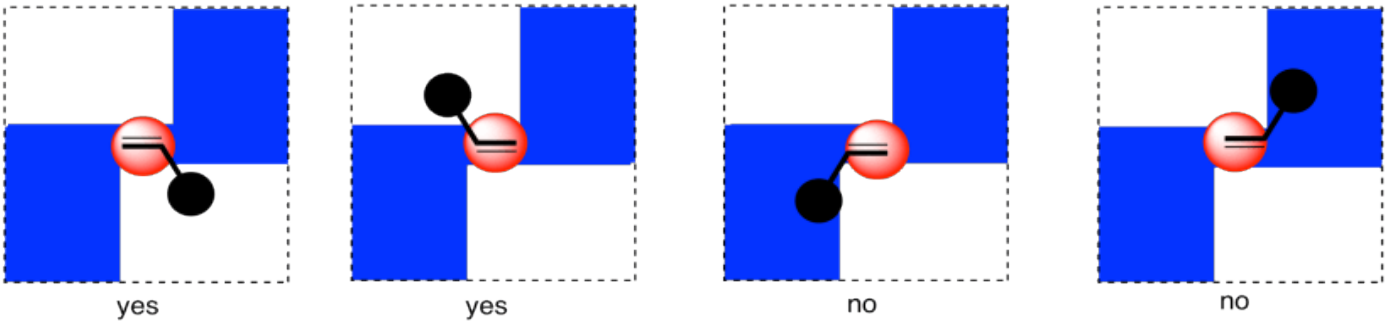


D-(-)-DET

Now, it is really very difficult to look at these conditions and predict exactly which enantiomer would be formed in a reaction. However, we can look at a factor that might illustrate an underlying reason for the preference. In quadrant analysis, we look at the general shape formed by that bidentate tartrate ligand on the metal. In the pictures below, the red ball is the metal atom. The tartrate ligand extends up and to the right as it sits on the metal, and also down and to the left; it is cartooned in blue. As a result,

if we think of the metal as sitting in the middle of a square, alternating corners of that square are filled, and the other corners are empty.





Imagine the alkene approaching that metal. The alkene will probably have a preferred orientation in which it will bind. Just for example, maybe it needs to bind with the double bond in the same plane as the ring formed by the titanium and the oxygens (horizontally in the picture). If it does that, it can reduce steric interactions with the ligand by binding one face of the alkene preferentially to the metal, keeping the biggest substituent on the alkane (the black ball) in a relatively open space. The alkene could also bind if rotated upside down compared to the first picture, but the same face would still be towards the titanium.

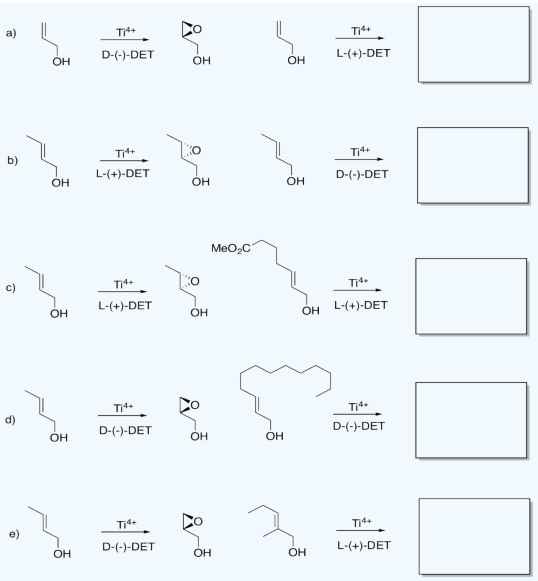
On the other hand, if the alkene tries to bind through the other face of the pi bond, the largest substituent would be in a more crowded space. That might be less favorable.

Overall, if the alkene has a preferred face that it will bind to the metal, then anything delivered from that metal will land on that face, and not the opposite one.

There are lots of variations on this model. Maybe it isn't steric interactions that influence how the alkene approaches the metal. Maybe it is some other factor, like hydrogen bonding, that pulls in the alkene oriented in one direction and not another. Nevertheless, although the details of a particular case make the outcome very difficult to predict, the general idea is a familiar one: a chiral molecule will fit preferentially one way with another molecule, because of its asymmetric shape.

Exercise 11.7.5

Although you may not be able to predict off the top of your head which enantiomer is formed in a Sharpless epoxidation, given one result, you may be able to guess another. Given the reaction on the left, see what you can tell about the reaction on the right.

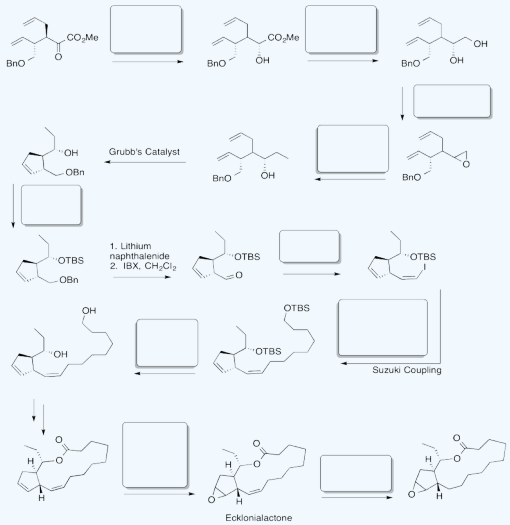


Answer available at the end of this section.

Exercise 11.7.6

Fill in the boxes in the following synthesis.

Becker, Butt, Kiedrowski, Mieschler, Quentin and Hiersemann, Total Synthesis of (-)-Ecklonialactone B, *Org. Lett.*, **2013**, *15* (23), 5982-5985.

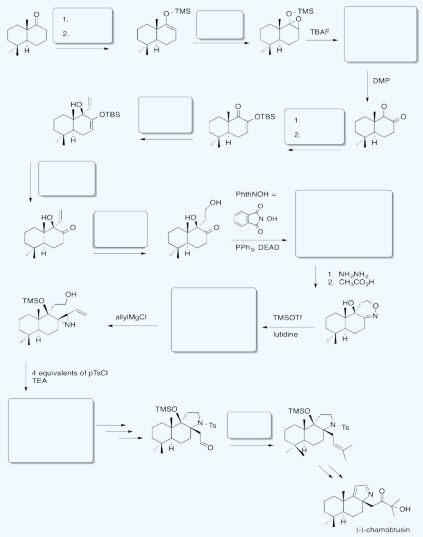


Answer available at the end of this section.

Exercise 11.7.7

Fill in the boxes in the following synthesis.

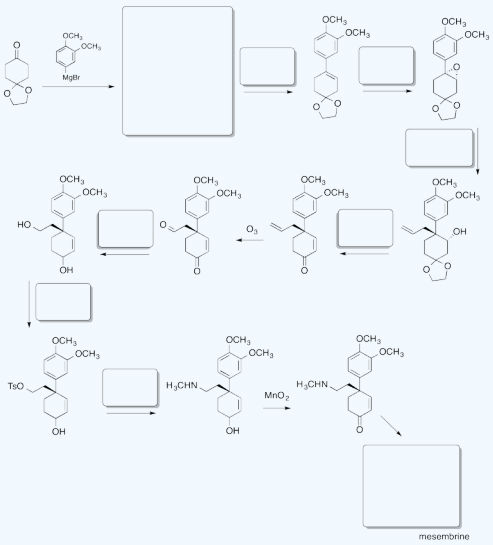
Suzuki and Aoyagi, Total Synthesis of (-)-Chamobtusin A, *Org. Lett.*, **2012**, *14* (24), 6374-6376.



Answer available at the end of this section.

Exercise 11.7.8

Fill in the boxes in the following synthesis.

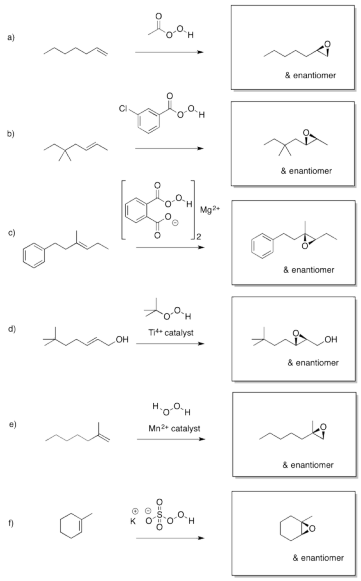


Taber and He, Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (-)-Mesembrine, *J. Org. Chem.*, **2005**, *70*, 7711-7714.

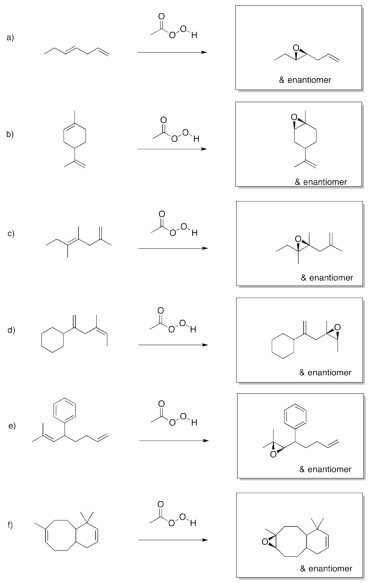
Answer available at the end of this section.

Answers

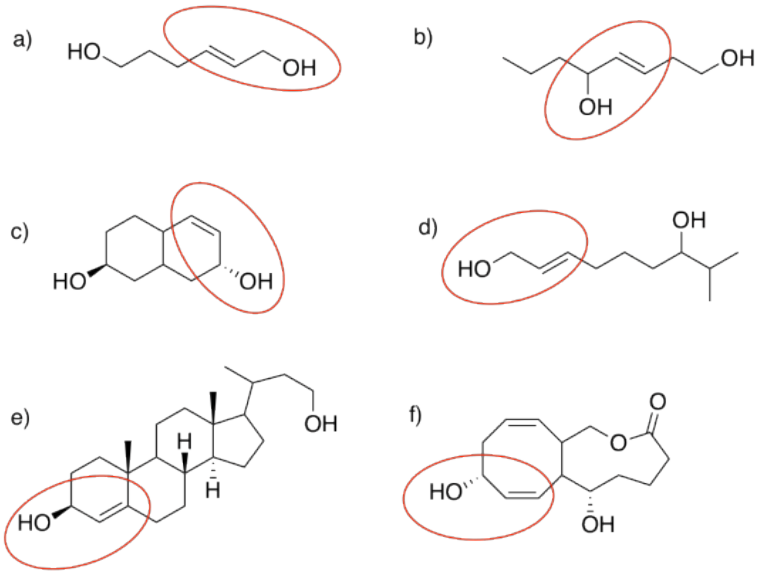
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Exercise 11.7.2



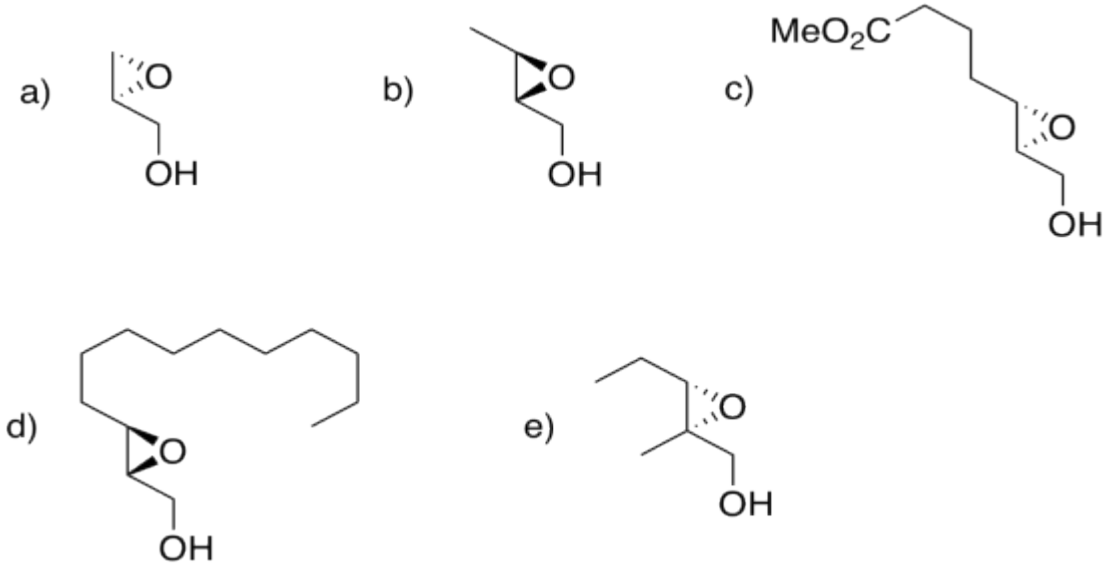
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Exercise 11.7.4

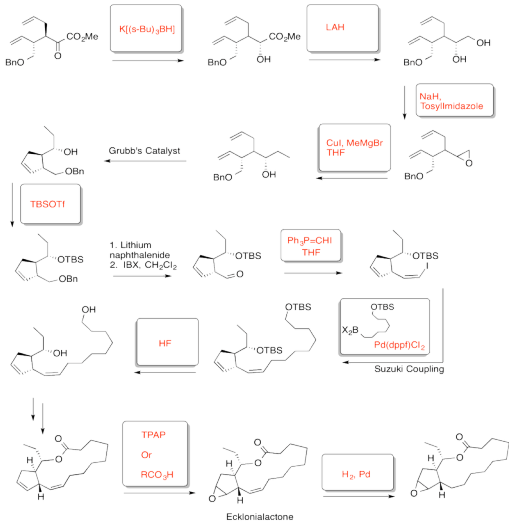
D-(-)-tartrate is the (*2S,3S*)-isomer. L-(+)-tartrate is the (*2R,3R*)-isomer.Each chiral center is configured opposite to the corresponding one in the other molecule, so the molecules are enantiomers.

Exercise 11.7.5



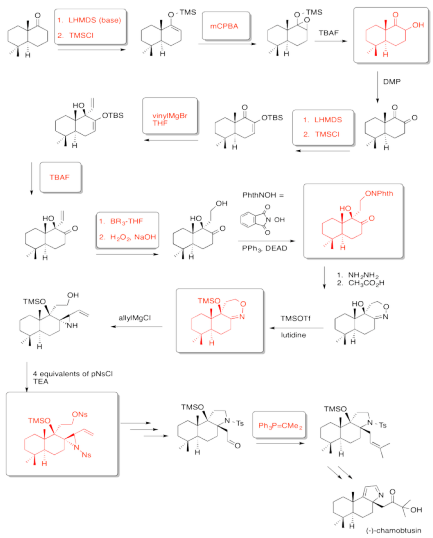
Exercise 11.7.6

Becker, Butt, Kiedrowski, Mieschler, Quentin and Hiersemann, Total Synthesis of (-)-Ecklonialactone B, *Org. Lett.*, **2013**, *15* (23), 5982-5985.

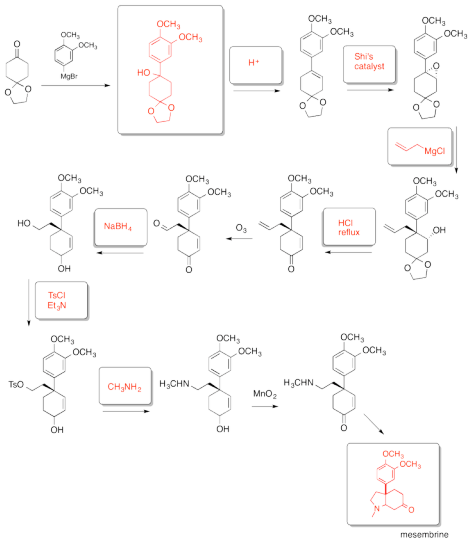


Exercise 11.7.7

Suzuki and Aoyagi, Total Synthesis of (-)-Chamobtusin A, *Org. Lett.*, **2012**, *14* (24), 6374-6376.



Exercise 11.7.8



Taber and He, Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (+)-Mesembrine, *J. Org. Chem.*, **2005**, *70*, 7711-7714.

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11.8: Sharpless Epoxidation

Epoxides are very useful intermediates in organic synthesis. Because most naturally occurring molecules (including those with medicinal properties) are chiral, control of stereochemistry is one of the most important challenges facing a synthetic chemist attempting to synthesize a naturally occurring molecule in the laboratory. In what was arguably one of the most important discoveries in synthetic organic chemistry in recent decades, Barry Sharpless of Stanford University reported in 1980 that he and his colleagues had developed a method to stereoselectively epoxidize asymmetric alkenes which contained an alcohol in the allylic position. The '**Sharpless asymmetric oxidation**' is achieved with the use of a chiral catalyst composed of (+) or (-) diethyltartrate and an organotitanium compound (*J. Am. Chem. Soc.* **1980**, *102*, 5974). Depending on which stereoisomer of diethyltartrate is used, the peroxyacid oxygen tends to add to either the top or bottom plane of the alkene.

This technique allows for the specific introduction of two new stereocenters at an alkene position, which as you can imagine makes it an extremely useful synthetic tool.

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

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