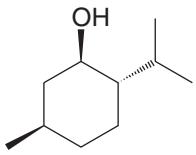
11

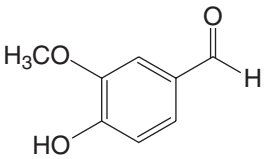
Alcohols and Ethers

Synthesis and Reactions

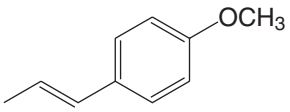
The flavors and scents of nature include many examples of alcohols and ethers. Menthol, found in peppermint oil, is an alcohol used both for flavoring and for medicinal purposes. Vanillin, isolated from vanilla beans, contains an ether functional group, as does anethole, the licorice flavor associated with fennel. Ethanol, the alcohol produced by fermentation, is, of course, another flavor of nature. Borneol, which can be isolated from artemesia, is an alcohol with a fascinating molecular architecture. And eucalyptol, which shares the ending of its name with other alcohols but is actually an ether, comes from eucalyptus leaves (shown in the left photo above) and is used as a flavoring, scent, and medicinal agent. Nature is an abundant source of alcohols and ethers, and we study the chemistry of these important functional groups in this chapter.



(–)-Menthol
(from peppermint)



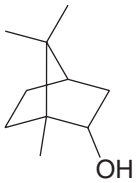
Vanillin
(from vanilla beans)



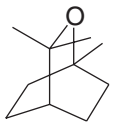
Anethole
(from fennel)

CH_3CH_2OH

Ethanol
(from fermentation)



Borneol
(from artemesia)



Eucalyptol
(from eucalyptus)

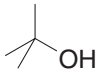
11.1 Structure and Nomenclature

Alcohols have a hydroxyl (—OH) group bonded to a *saturated* carbon atom. The alcohol carbon atom may be part of a simple alkyl group, as in some of the following examples, or it may be part of a more complex molecule, such as cholesterol.

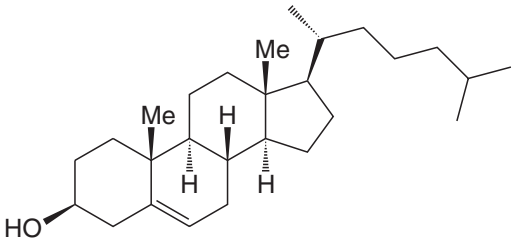
Methanol (methyl alcohol)

Ethanol (ethyl alcohol), *a 1° alcohol*

2-Propanol (isopropyl alcohol), *a 2° alcohol*

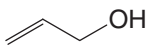


2-Methyl-2-propanol (*tert*-butyl alcohol), *a 3° alcohol*

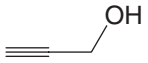


Cholesterol

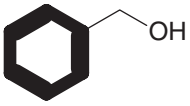
The alcohol carbon atom may also be a saturated carbon atom of an alkenyl or alkynyl group, or the carbon atom may be a saturated carbon atom that is attached to a benzene ring:



2-Propenol (or prop-2-en-1-ol, or allyl alcohol), *an allylic alcohol*

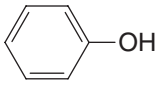


2-Propynol (or prop-2-yn-1-ol, or propargyl alcohol)

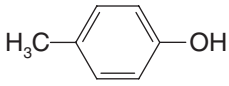


Benzyl alcohol (*a benzylic alcohol*)

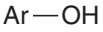
Compounds that have a hydroxyl group attached *directly* to a benzene ring are called **phenols**. (Phenols are discussed in detail in Chapter 21.)



Phenol



p*-Methylphenol, *a substituted phenol

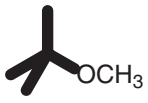


General formula for a phenol

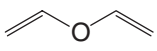
Ethers differ from alcohols in that the oxygen atom of an ether is bonded to two carbon atoms. The hydrocarbon groups may be alkyl, alkenyl, vinyl, alkynyl, or aryl. Several examples are shown here:

Diethyl ether

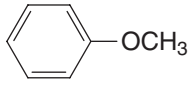
Allyl methyl ether



***tert*-Butyl methyl ether**



Divinyl ether



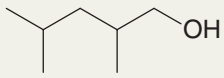
Methyl phenyl ether

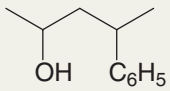
11.1A Nomenclature of Alcohols

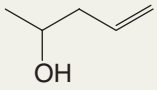
We studied the IUPAC system of nomenclature for alcohols in Sections 2.6 and 4.3F. As a review consider the following problem.

Solved Problem 11.1

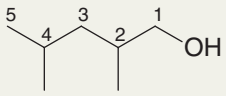
Give IUPAC substitutive names for the following alcohols:

(a) 

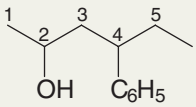
(b) 

(c) 

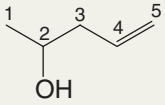
ANSWER The longest chain ***to which the hydroxyl group is attached*** gives us the ***base name***. The ending is **-ol**. We then number ***the longest chain from the end that gives the carbon bearing the hydroxyl group the lower number***. Thus, the names, in both of the accepted IUPAC formats, are

(a) 

2,4-Dimethyl-1-pentanol
(or 2,4-dimethylpentan-1-ol)

(b) 

4-Phenyl-2-pentanol
(or 4-phenylpentan-2-ol)

(c) 

4-Penten-2-ol
(or pent-4-en-2-ol)

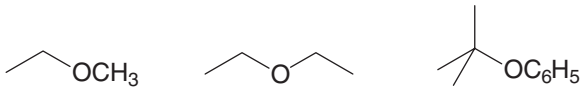
The hydroxyl group has precedence over double bonds and triple bonds in deciding which functional group to name as the suffix [see example (c) above].

In common functional class nomenclature (Section 2.6) alcohols are called **alkyl alcohols** such as methyl alcohol, ethyl alcohol, and so on.

Review Problem 11.1 What is wrong with the use of such names as "isopropanol" and "*tert*-butanol"?

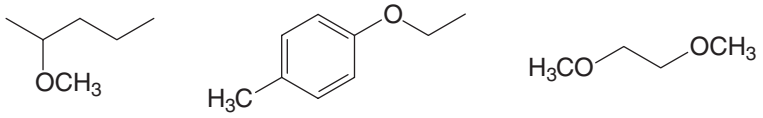
11.1B Nomenclature of Ethers

Simple ethers are frequently given common functional class names. One simply lists (in alphabetical order) both groups that are attached to the oxygen atom and adds the word *ether*:



Ethyl methyl ether **Diethyl ether** ***tert*-Butyl phenyl ether**

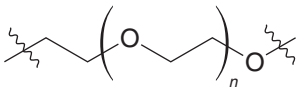
IUPAC substitutive names should be used for complicated ethers, however, and for compounds with more than one ether linkage. In this IUPAC style, ethers are named as alkoxyalkanes, alkoxyalkenes, and alkoxyarenes. The RO— group is an **alkoxy** group.



2-Methoxypentane **1-Ethoxy-4-methylbenzene** **1,2-Dimethoxyethane (DME)**

Cyclic ethers can be named in several ways. One simple way is to use **replacement nomenclature**, in which we relate the cyclic ether to the corresponding hydrocarbon ring system and use the prefix **oxa**- to indicate that an oxygen atom replaces a CH_2 group. In another system, a cyclic three-membered ether is named **oxirane** and a four-membered ether is called **oxetane.** Several simple cyclic ethers also have common names; in the examples below, these common names are given in parentheses. Tetrahydrofuran (THF) and 1,4-dioxane are useful solvents:

Oxacyclopropane or oxirane (ethylene oxide) | **Oxacyclobutane or oxetane** | **Oxacyclopentane (tetrahydrofuran or THF)** | **1,4-Dioxacyclohexane (1,4-dioxane)**



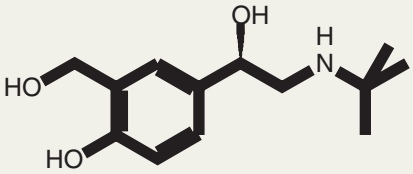
Polyethylene oxide (PEO) (a water-soluble polymer made from ethylene oxide)

Polyethylene oxide is used in some skin creams.

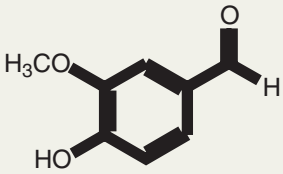
Ethylene oxide is the starting material for polyethylene oxide (PEO, also called polyethylene glycol, PEG). Polyethylene oxide has many practical uses, including covalent attachment to therapeutic proteins such as interferon, a use that has been found to increase the circulatory lifetime of the drug. PEO is also used in some skin creams, and as a laxative prior to digestive tract procedures.

Solved Problem 11.2

Albuterol (used in some commonly prescribed respiratory medications) and vanillin (from vanilla beans) each contain several functional groups. Name the functional groups in albuterol and vanillin and, if appropriate for a given group, classify them as primary (1°), secondary (2°), or tertiary (3°).



Albuterol (an asthma medication)



Vanillin (from vanilla beans)

Albuterol is used in some respiratory medications.

STRATEGY AND ANSWER Albuterol has the following functional groups: 1° alcohol, 2° alcohol, phenol, and 2° amine. Vanillin has aldehyde, ether, and phenol functional groups. See Chapter 2 for a review of how to classify alcohol and amine functional groups as 1°, 2°, or 3°.

Review Problem 11.2

Give bond-line formulas and appropriate names for all of the alcohols and ethers with the formulas (**a**) C_3H_8O and (**b**) $C_4H_{10}O$.

11.2 Physical Properties of Alcohols and Ethers

The physical properties of a number of alcohols and ethers are given in Tables 11.1 and 11.2.

- Ethers have boiling points that are roughly comparable with those of hydrocarbons of the same molecular weight (MW).

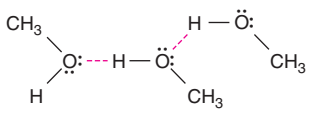
For example, the boiling point of diethyl ether (MW = 74) is 34.6°C; that of pentane (MW = 72) is 36°C.

Propylene glycol (1,2-propanediol) is used as an environmentally friendly engine coolant because it is biodegradable, has a high boiling point, and is miscible with water.

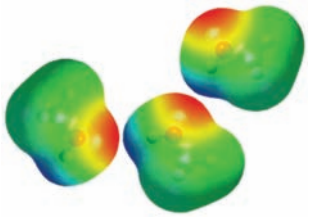
- Alcohols have much higher boiling points than comparable ethers or hydrocarbons.

The boiling point of butyl alcohol (MW = 74) is 117.7°C. We learned the reason for this behavior in Section 2.13C.

- Alcohol molecules can associate with each other through **hydrogen bonding,** whereas those of ethers and hydrocarbons cannot.



Hydrogen bonding between molecules of methanol



Ethers, however, *are* able to form hydrogen bonds with compounds such as water. Ethers, therefore, have solubilities in water that are similar to those of alcohols of the same molecular weight and that are very different from those of hydrocarbons.

Diethyl ether and 1-butanol, for example, have the same solubility in water, approximately 8 g per 100 mL at room temperature. Pentane, by contrast, is virtually insoluble in water.

Methanol, ethanol, both propyl alcohols, and *tert*-butyl alcohol are completely miscible with water (Table 11.1). The remaining butyl alcohols have solubilities in water between 8.3 and 26.0 g per 100 mL. The solubility of alcohols in water gradually decreases as the hydrocarbon portion of the molecule lengthens; long-chain alcohols are more "alkane-like" and are, therefore, less like water.

TABLE 11.1 Physical Properties of Alcohols

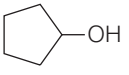
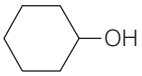
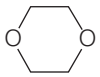
Name	Formula	mp (°C)	bp (°C) (1 atm)	Water Solubility (g/100 mL H_2O)
	Monohydroxy Alcohols			
Methanol	CH_3OH	−97	64.7	∞
Ethanol	CH_3CH_2OH	−117	78.3	∞
Propyl alcohol	$CH_3CH_2CH_2OH$	−126	97.2	∞
Isopropyl alcohol	$CH_3CH(OH)CH_3$	−88	82.3	∞
Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	−90	117.7	8.3
Isobutyl alcohol	$CH_3CH(CH_3)CH_2OH$	−108	108.0	10.0
sec-Butyl alcohol	$CH_3CH_2CH(OH)CH_3$	−114	99.5	26.0
tert-Butyl alcohol	$(CH_3)_3COH$	25	82.5	∞
Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	−78.5	138.0	2.4
Hexyl alcohol	$CH_3(CH_2)_4CH_2OH$	−52	156.5	0.6
Heptyl alcohol	$CH_3(CH_2)_5CH_2OH$	−34	176	0.2
Octyl alcohol	$CH_3(CH_2)_6CH_2OH$	−15	195	0.05
Cyclopentanol		−19	140	
Cyclohexanol		24	161.5	3.6
Benzyl alcohol	$C_6H_5CH_2OH$	−15	205	4
	Diols and Triols			
Ethylene glycol	CH_2OHCH_2OH	−12.6	197	∞
Propylene glycol	$CH_3CHOHCH_2OH$	−59	187	∞
Trimethylene glycol	$CH_2OHCH_2CH_2OH$	−30	215	∞
Glycerol	$CH_2OHCHOHCH_2OH$	18	290	∞

TABLE 11.2 Physical Properties of Ethers

Name	Formula	mp (°C)	bp (°C) (1 atm)
Dimethyl ether	CH_3OCH_3	−138	−24.9
Ethyl methyl ether	$CH_3OCH_2CH_3$		10.8
Diethyl ether	$CH_3CH_2OCH_2CH_3$	−116	34.6
Dipropyl ether	$(CH_3CH_2CH_2)_2O$	−122	90.5
Diisopropyl ether	$(CH_3)_2CHOCH(CH_3)_2$	−86	68
Dibutyl ether	$(CH_3CH_2CH_2CH_2)_2O$	−97.9	141
1,2-Dimethoxyethane (DME)	$CH_3OCH_2CH_2OCH_3$	−68	83
Oxirane		−112	12
Tetrahydrofuran (THF)		−108	65.4
1,4-Dioxane		11	101

Solved Problem 11.3

1,2-Propanediol (propylene glycol) and 1,3-propanediol (trimethylene glycol) have higher boiling points than any of the butyl alcohols (see Table 11.1), even though they all have roughly the same molecular weight. Propose an explanation.

STRATEGY AND ANSWER The presence of two hydroxyl groups in each of the diols allows their molecules to form more hydrogen bonds than the butyl alcohols. Greater hydrogen-bond formation means that the molecules of 1,2-propanediol and 1,3-propanediol are more highly associated and, consequently, their boiling points are higher.

11.3 Important Alcohols and Ethers

11.3A Methanol

At one time, most methanol was produced by the destructive distillation of wood (i.e., heating wood to a high temperature in the absence of air). It was because of this method of preparation that methanol came to be called "wood alcohol." Today, most methanol is prepared by the catalytic hydrogenation of carbon monoxide. This reaction takes place under high pressure and at a temperature of 300–400°C:

$$CO + 2\,H_2 \xrightarrow[200\text{–}300\ \text{atm}\ \ ZnO\text{–}Cr_2O_3]{300\text{–}400^\circ C} CH_3OH$$

Methanol is highly toxic. Ingestion of even small quantities of methanol can cause blindness; large quantities cause death. Methanol poisoning can also occur by inhalation of the vapors or by prolonged exposure to the skin.

11.3B Ethanol

Ethanol can be made by the fermentation of sugars, and it is the alcohol of all alcoholic beverages. The synthesis of ethanol in the form of wine by the fermentation of the sugars of fruit juices was probably our first accomplishment in the field of organic synthesis.

Vineyard grapes for use in fermentation.

Sugars from a wide variety of sources can be used in the preparation of alcoholic beverages. Often, these sugars are from grains, and it is this derivation that accounts for ethanol having the synonym "grain alcohol."

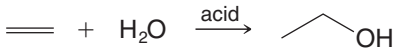
Fermentation is usually carried out by adding yeast to a mixture of sugars and water. Yeast contains enzymes that promote a long series of reactions that ultimately convert a simple sugar ($C_6H_{12}O_6$) to ethanol and carbon dioxide:

$$C_6H_{12}O_6 \xrightarrow{\text{yeast}} 2\ CH_3CH_2OH + 2\ CO_2$$

(~95% yield)

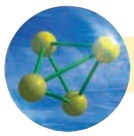
Fermentation alone does not produce beverages with an ethanol content greater than 12–15% because the enzymes of the yeast are deactivated at higher concentrations. To produce beverages of higher alcohol content, the aqueous solution must be distilled.

Ethanol is an important industrial chemical. Most ethanol for industrial purposes is produced by the acid-catalyzed hydration of ethene:



About 5% of the world's ethanol supply is produced this way.

Ethanol is a *hypnotic* (sleep producer). It depresses activity in the upper brain even though it gives the illusion of being a stimulant. Ethanol is also toxic, but it is much less toxic than methanol. In rats the lethal dose of ethanol is 13.7 g kg^{-1} of body weight.



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Ethanol as a Biofuel

Ethanol is said to be a renewable energy source because it can be made by fermentation of grains and other agricultural sources such as switchgrass and sugarcane. The crops themselves grow, of course, by converting light energy from the sun to chemical energy through photosynthesis. Once obtained, the ethanol can be combined with gasoline in varying proportions and used in internal combustion engines. During the year 2007, the United States led the world in ethanol production with 6.5 billion U.S. gallons, followed closely by Brazil with 5 billion gallons.

When used as a replacement for gasoline, ethanol has a lower energy content, by about 34% per unit volume. This, and other factors, such as costs in energy required to produce the agricultural feedstock, especially corn, have created doubts about the wisdom of an ethanol-based program as a renewable energy source. Production of ethanol from corn is 5 to 6 times less efficient than producing it from sugarcane, and it also diverts production of a food crop into an energy source. World food shortages may be a result.

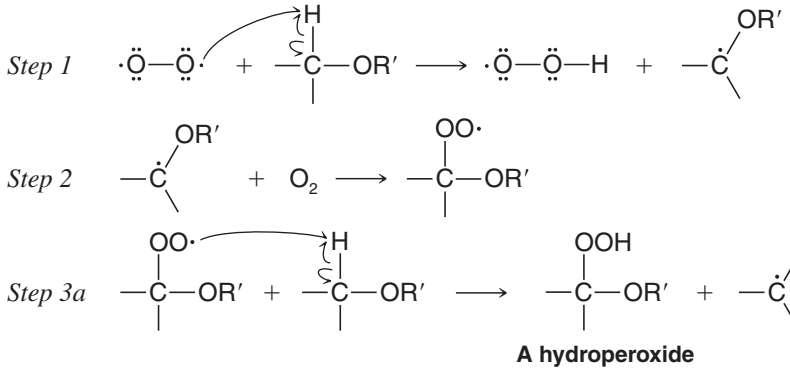
11.3C Ethylene and Propylene Glycols

Ethylene glycol ($HOCH_2CH_2OH$) has a low molecular weight, a high boiling point, and is miscible with water. These properties made ethylene glycol a good automobile antifreeze. Unfortunately, however, ethylene glycol is toxic. Propylene glycol (1,2-propanediol) is now widely used as a low-toxicity, environmentally friendly alternative to ethylene glycol.

11.3D Diethyl Ether

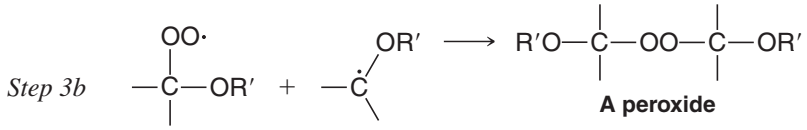
Diethyl ether is a very low boiling, highly flammable liquid. Care should always be taken when diethyl ether is used in the laboratory, because open flames or sparks from light switches can cause explosive combustion of mixtures of diethyl ether and air.

Most ethers react slowly with oxygen by a radical process called **autoxidation** (see Section 10.11D) to form hydroperoxides and peroxides:



Hydrogen abstraction adjacent to the ether oxygen occurs readily.

or



Hydroperoxides and peroxides can be explosive.

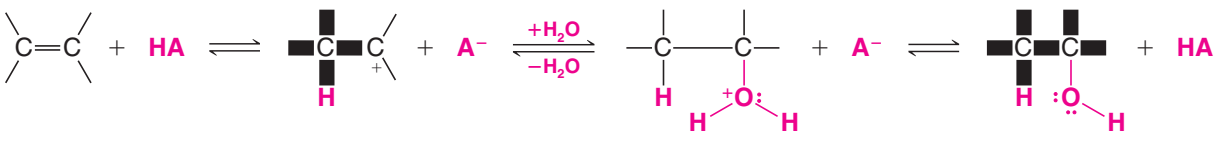
These hydroperoxides and peroxides, which often accumulate in ethers that have been stored for months or longer in contact with air (the air in the top of the bottle is enough), are dangerously explosive. They often detonate without warning when ether solutions are distilled to near dryness. Since ethers are used frequently in extractions, one should take care to test for and decompose any peroxides present in the ether before a distillation is carried out. (Consult a laboratory manual for instructions.)

Diethyl ether was at one time used as a surgical anesthetic.The most popular modern anesthetic is halothane ($CF_3CHBrCl$). Unlike diethyl ether, halothane is not flammable.

11.4 Synthesis of Alcohols from Alkenes

We have already studied the acid-catalyzed **hydration of alkenes**, **oxymercuration–demercuration**, and **hydroboration–oxidation** as methods for the synthesis of alcohols from alkenes (see Sections 8.5, 8.6, and 8.7, respectively). Below, we briefly summarize these methods.

1. **Acid-Catalyzed Hydration of Alkenes** Alkenes add water in the presence of an acid catalyst to yield alcohols (Section 8.5). The addition takes place with **Markovnikov regioselectivity.** The reaction is reversible, and the mechanism for the acid-catalyzed hydration of an alkene is simply the reverse of that for the dehydration of an alcohol (Section 7.7).



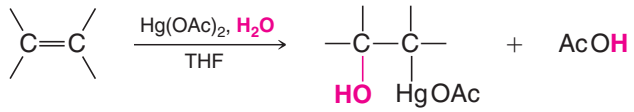
Alkene Alcohol

Acid-catalyzed hydration of alkenes has limited synthetic utility, however, because the carbocation intermediate may rearrange if a more stable or isoenergetic carbocation is possible by hydride or alkanide migration. Thus, a mixture of isomeric alcohol products may result.

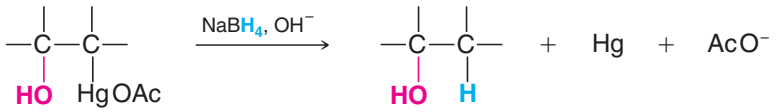
2. **Oxymercuration–Demercuration** Alkenes react with mercuric acetate in a mixture of water and tetrahydrofuran (THF) to produce (hydroxyalkyl)mercury compounds. These can be reduced to alcohols with sodium borohydride and water (Section 8.6).

Mercury compounds are hazardous. Before you carry out a reaction involving mercury or its compounds, you should familiarize yourself with current procedures for its use and disposal.

Oxymercuration



Demercuration



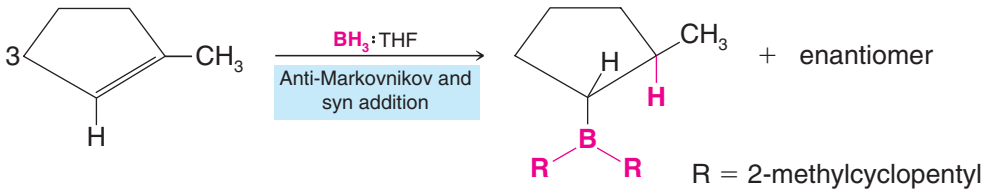
In the oxymercuration step, water and mercuric acetate add to the double bond; in the demercuration step, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. The net addition of H— and —OH takes place with **Markovnikov regioselectivity** and **generally takes place without the complication of rearrangements**, as sometimes occurs with acid-catalyzed hydration of alkenes. The overall alkene hydration is not stereoselective because even though the oxymercuration step occurs with anti addition, the demercuration step is not stereoselective (radicals are thought to be involved), and hence a mixture of syn and anti products results.

Helpful Hint

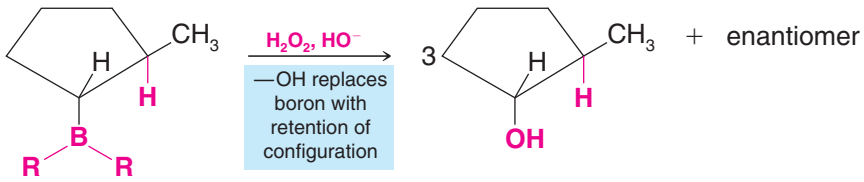
Oxymercuration–demercuration and hydroboration–oxidation have complementary regioselectivity.

3. **Hydroboration–Oxidation** An alkene reacts with BH_3:THF or diborane to produce an alkylborane. Oxidation and hydrolysis of the alkylborane with hydrogen peroxide and base yield an alcohol (Section 8.7).

Hydroboration



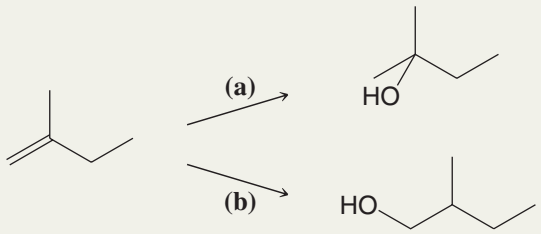
Oxidation



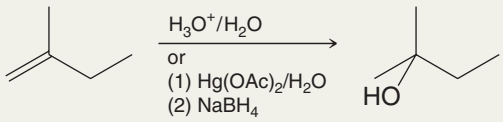
In the first step, boron and hydrogen undergo syn addition to the alkene; in the second step, treatment with hydrogen peroxide and base replaces the boron with —OH with retention of configuration. The net addition of —H and —OH occurs with **anti-Markovnikov regioselectivity** and **syn stereoselectivity.** Hydroboration–oxidation, therefore, serves as a useful regiochemical complement to oxymercuration–demercuration.

Solved Problem 11.4

What conditions would you use for each reaction?

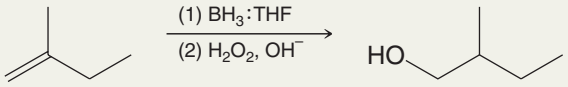


STRATEGY AND ANSWER We recognize that synthesis by path (a) would require a Markovnikov addition of water to the alkene. So, we could use either acid-catalyzed hydration or oxymercuration–demercuration.



Markovnikov addition of H— and —OH

Synthesis by path (b) requires an anti-Markovnikov addition, so we would choose hydroboration–oxidation.

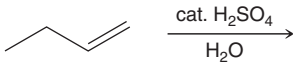


anti-Markovnikov addition of H— and —OH

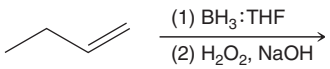
Review Problem 11.3

Predict the major products of the following reactions

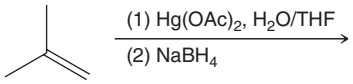
(a)



(b)

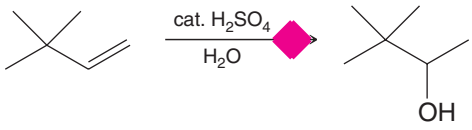


(c)



Review Problem 11.4

The following reaction does not produce the product shown.



(a) Predict the major product from the conditions shown above, and write a detailed mechanism for its formation.

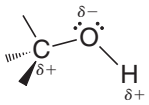
(b) What reaction conditions would you use to successfully synthesize the product shown above (3,3-dimethyl-2-butanol).

11.5 Reactions of Alcohols

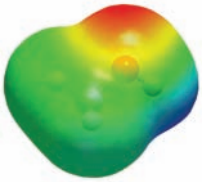
The reactions of alcohols have mainly to do with the following:

- The oxygen atom of the hydroxyl group is nucleophilic and weakly basic.
- The hydrogen atom of the hydroxyl group is weakly acidic.
- The hydroxyl group can be converted to a leaving group so as to allow substitution or elimination reactions.

Our understanding of the reactions of alcohols will be aided by an initial examination of the electron distribution in the alcohol functional group and of how this distribution affects its reactivity. The oxygen atom of an alcohol polarizes both the C—O bond and the O—H bond of an alcohol:



The C—O and O—H bonds of an alcohol are polarized

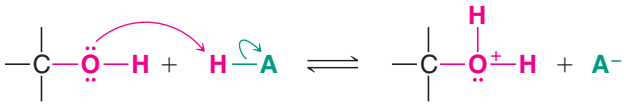


An electrostatic potential map for methanol shows partial negative charge at the oxygen and partial positive charge at the hydroxyl proton.

Polarization of the O—H bond makes the hydrogen partially positive and explains why alcohols are weak acids (Section 11.6). Polarization of the C—O bond makes the carbon atom partially positive, and if it were not for the fact that OH^- is a strong base and, therefore, a very poor leaving group, this carbon would be susceptible to nucleophilic attack.

The electron pairs on the oxygen atom make it both ***basic*** and ***nucleophilic***. In the presence of strong acids, alcohols act as bases and accept protons in the following way:

Protonation of an alcohol.

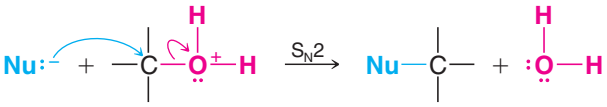


- Protonation of the alcohol converts a poor leaving group (OH^-) into a good one (H_2O).

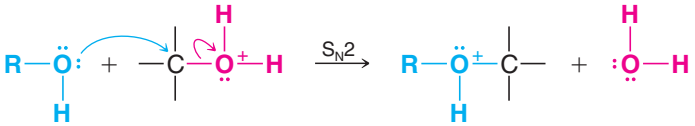
Protonation also makes the carbon atom even more positive (because $—OH_2^+$ is more electron withdrawing than —OH) and, therefore, even more susceptible to nucleophilic attack.

- Once the alcohol is protonated substitution reactions become possible (S_N2 or S_N1, depending on the class of alcohol, Section 11.8).

The protonated hydroxyl group is a good leaving group (H_2O).



Because alcohols are nucleophiles, they, too, can react with protonated alcohols. This, as we shall see in Section 11.11A, is an important step in one synthesis of ethers:



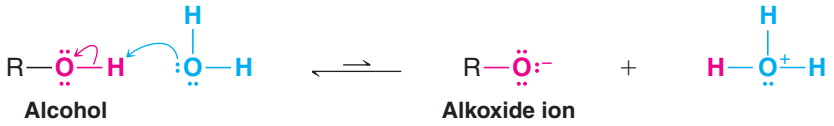
At a high enough temperature and in the absence of a good nucleophile, protonated alcohols are capable of undergoing E1 or E2 reactions. This is what happens in alcohol dehydrations (Section 7.7).

Alcohols also react with PBr_3 and $SOCl_2$ to yield alkyl bromides and alkyl chlorides. These reactions, as we shall see in Section 11.9, are initiated by the alcohol using its unshared electron pairs to act as a nucleophile.

11.6 Alcohols as Acids

- Alcohols have acidities similar to that of water.

Methanol is a slightly stronger acid than water ($pK_a = 15.7$) but most alcohols are somewhat weaker acids. Values of pK_a for several alcohols are listed in Table 11.3.



Alcohol **Alkoxide ion**

(If R is bulky, there is less stabilization of the alkoxide by solvation, and consequently the equilibrium lies even further toward the alcohol.)

TABLE 11.3 pK_a Values for Some Weak Acids

Acid	pK_a
CH_3OH	15.5
H_2O	15.74
CH_3CH_2OH	15.9
$(CH_3)_3COH$	18.0

- Sterically hindered alcohols such as *tert*-butyl alcohol are less acidic, and hence their conjugate bases more basic, than unhindered alcohols such as ethanol or methanol.

One reason for this difference in acidity has to do with the effect of solvation. With an unhindered alcohol, water molecules can easily surround, solvate, and hence stabilize the alkoxide anion that would form by loss of the alcohol proton to a base. As a consequence of this stabilization, formation of the alcohol's conjugate base is easier, and therefore its acidity is increased. If the R group of the alcohol is bulky, solvation of the alkoxide anion is hindered. Stabilization of the conjugate base is not as effective, and consequently the hindered alcohol is a weaker acid. Another reason that hindered alcohols are less acidic has to do with the inductive electron-donating effect of alkyl groups. The alkyl groups of a hindered alcohol donate electron density, making formation of an alkoxide anion more difficult than with a less hindered alcohol.

Helpful Hint

Remember: Any factor that stabilizes the conjugate base of an acid increases its acidity.

- All alcohols are much stronger acids than terminal alkynes, and they are very much stronger acids than hydrogen, ammonia, and alkanes (see Table 3.1).

Relative Acidity

Water and alcohols are the strongest acids in this series.

$$H_2O > ROH > RC{\equiv}CH > H_2 > NH_3 > RH$$

Sodium and potassium alkoxides can be prepared by treating alcohols with sodium or potassium metal or with the metal hydride (Section 6.15B). Because most alcohols are weaker acids than water, most alkoxide ions are stronger bases than the hydroxide ion.

- Conjugate bases of compounds with higher pK_a values than an alcohol will deprotonate an alcohol.

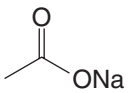
Relative Basicity

$$R^- > NH_2^- > H^- > RC{\equiv}C^- > RO^- > HO^-$$

Hydroxide is the weakest base in this series.

Review Problem 11.5

Write equations for the acid–base reactions that would occur (if any) if ethanol were added to solutions of each of the following compounds. In each reaction, label the stronger acid, the stronger base, and so forth (consult Table 3.1).

(a) $NaNH_2$ **(b)** $H{-}{\equiv}{:}^-Na^+$ **(c)**  **(d)** NaOH

Sodium and potassium alkoxides are often used as bases in organic syntheses (Section 6.15B). We use alkoxides, such as ethoxide and *tert*-butoxide, when we carry out reactions that require stronger bases than hydroxide ion but do not require exceptionally powerful bases, such as the amide ion or the anion of an alkane. We also use alkoxide ions when (for reasons of solubility) we need to carry out a reaction in an alcohol solvent rather than in water.

11.7 Conversion of Alcohols into Alkyl Halides

In this and several following sections we will be concerned with reactions that involve substitution of the alcohol hydroxyl group.

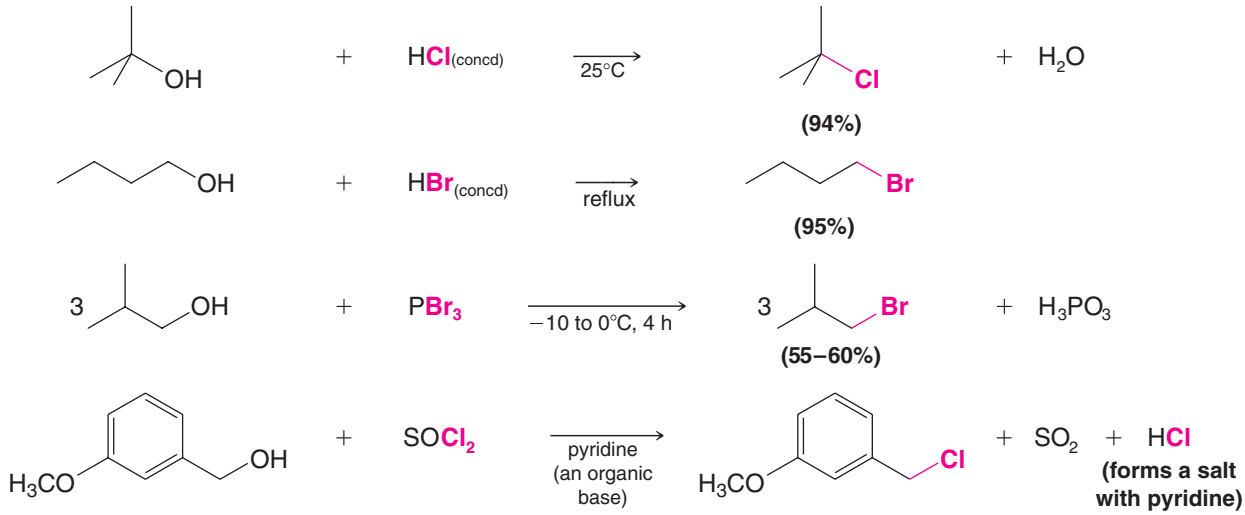
- A hydroxyl group is such a poor leaving group (it would depart as hydroxide) that a common theme of these reactions will be conversion of the hydroxyl to a group that can depart as a weak base.

These processes begin by reaction of the alcohol oxygen as a base or nucleophile, after which the modified oxygen group undergoes substitution. First, we shall consider reactions that convert alcohols to alkyl halides.

The most commonly used reagents for conversion of alcohols to alkyl halides are the following:

- Hydrogen halides (HCl, HBr, HI)
- Phosphorus tribromide (PBr_3)
- Thionyl chloride ($SOCl_2$)

Examples of the use of these reagents are the following. All of these reactions result in cleavage of the C—O bond of the alcohol. In each case, the hydroxyl group is first converted to a suitable leaving group. We will see how this is accomplished when we study each type of reaction.



11.8 Alkyl Halides from the Reaction of Alcohols with Hydrogen Halides

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

$$R{-}OH + HX \longrightarrow R{-}X + H_2O$$

- 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:

$$ROH + NaX \xrightarrow{H_2SO_4} RX + NaHSO_4 + H_2O$$

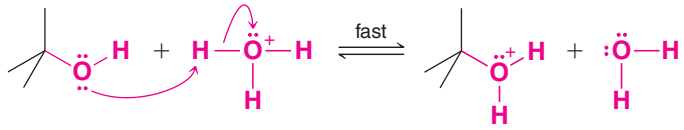
11.8A Mechanisms of the Reactions of Alcohols with HX

- Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation—a mechanism that we first saw in Section 3.14 and that you should now recognize *as an S_N1 reaction with the protonated alcohol acting as the substrate*.

We again illustrate this mechanism with the reaction of *tert*-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-).

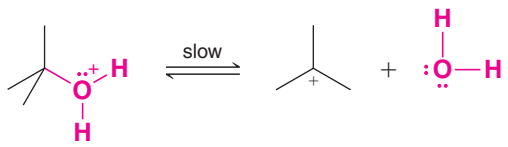
The first two steps in this S_N1 substitution mechanism are the same as in the mechanism for the dehydration of an alcohol (Section 7.7).

Step 1



The alcohol accepts a proton.

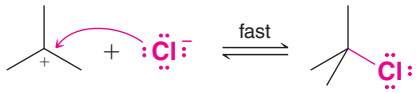
Step 2



The protonated hydroxyl group departs as a leaving group to form a carbocation and water.

In step 3 the mechanisms for the dehydration of an alcohol and the formation of an alkyl halide differ. In dehydration reactions the carbocation loses a proton in an E1 reaction to form an alkene. In the formation of an alkyl halide, the carbocation reacts with a nucleophile (a halide ion) in an S_N1 reaction.

Step 3



A halide anion reacts with the carbocation.

- How can we account for S_N1 substitution in this case versus elimination in others?

When we dehydrate alcohols, we usually carry out the reaction in concentrated sulfuric acid and at high temperature. The hydrogen sulfate (HSO_4^-) present after protonation of the alcohol is a weak nucleophile, and at high temperature the highly reactive carbocation forms a more stable species by losing a proton and becoming an alkene. Furthermore, the alkene is usually volatile and distills from the reaction mixture as it is formed, thus drawing the equilibrium toward alkene formation. The net result is *an E1 reaction*.

In the reverse reaction, that is, the hydration of an alkene (Section 8.5), the carbocation *does* react with a nucleophile. It reacts with water. Alkene hydrations are carried out in dilute sulfuric acid, where the water concentration is high. In some instances, too, carbocations may react with HSO_4^- ions or with sulfuric acid, itself. When they do, they form alkyl hydrogen sulfates ($R—OSO_2OH$).

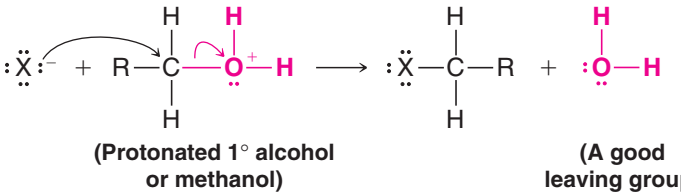
When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and *in the presence of halide ions*, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, 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.

These two reactions, dehydration and the formation of an alkyl halide, also furnish us another example of the competition between nucleophilic substitution and elimination (see Section 6.18). Very often, in conversions of alcohols to alkyl halides, we find that the reaction is accompanied by the formation of some alkene (i.e., by elimination). The free energies of activation for these two reactions of carbocations are not very different from one another. Thus, not all of the carbocations become stable products by reacting with nucleophiles; some lose a β proton to form an alkene.

Primary Alcohols Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations.

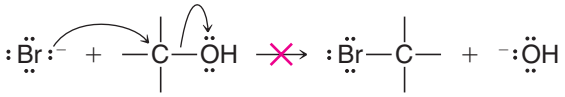
- Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

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:



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.

- Reactions like the following do not occur because the leaving group would have to be a strongly basic hydroxide ion:



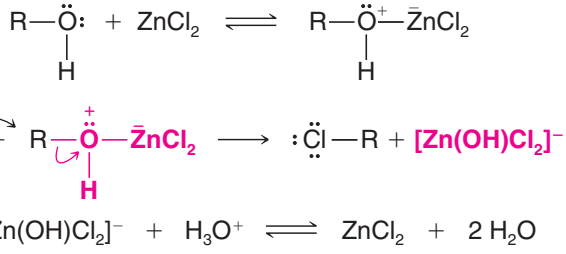
Helpful Hint

The reverse reaction, that is, the reaction of an alkyl halide with hydroxide ion, does occur and is a method for the synthesis of alcohols. We saw this reaction in Chapter 6.

We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

- Acid protonates the alcohol hydroxyl group, making it a good leaving group.

Because the chloride ion is a weaker nucleophile than bromide or iodide ions, hydrogen chloride does not react with primary or secondary alcohols unless zinc chloride or some similar Lewis acid is added to the reaction mixture as well. Zinc chloride, a good Lewis acid, forms a complex with the alcohol through association with an unshared pair of electrons on the oxygen atom. This enhances the hydroxyl's leaving group potential sufficiently that chloride can displace it.

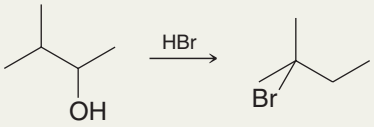


- As we might expect, many reactions of alcohols with hydrogen halides, particularly those in which carbocations are formed, *are accompanied by rearrangements*.

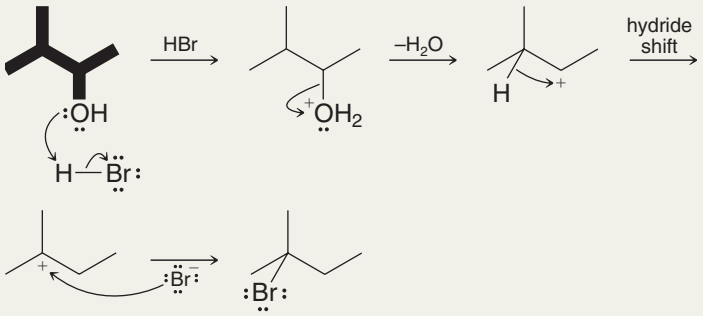
How do we know that rearrangements can occur when secondary alcohols are treated with a hydrogen halide? Results like that in Solved Problem 11.5 indicate this to be the case.

Solved Problem 11.5

Treating 3-methyl-2-butanol (see the following reaction) yields 2-bromo-2-methylbutane as the sole product. Propose a mechanism that explains the course of the reaction.

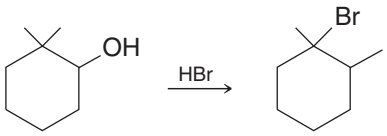


STRATEGY AND ANSWER The reaction must involve a rearrangement by a hydride shift from the initially formed carbocation.



Review Problem 11.6

Write a detailed mechanism for the following reaction.



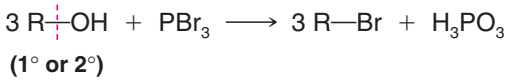
Review Problem 11.7

(**a**) What factor explains the observation that tertiary alcohols react with HX faster than secondary alcohols? (**b**) What factor explains the observation that methanol reacts with HX faster than a primary alcohol?

Since rearrangements can occur when some alcohols are treated with hydrogen halides, how can we successfully convert a secondary alcohol to an alkyl halide without rearrangement? The answer to this question comes in the next section, where we discuss the use of reagents such as thionyl chloride ($SOCl_2$) and phosphorus tribromide (PBr_3).

11.9 Alkyl Halides from the Reaction of Alcohols with PBr_3 or $SOCl_2$

Primary and secondary alcohols react with phosphorus tribromide to yield alkyl bromides.

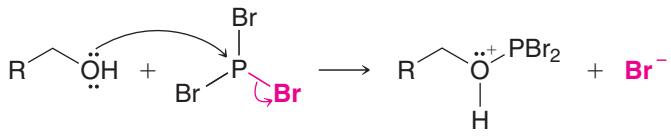


Helpful Hint

PBr_3: A reagent for synthesizing 1° and 2° alkyl bromides.

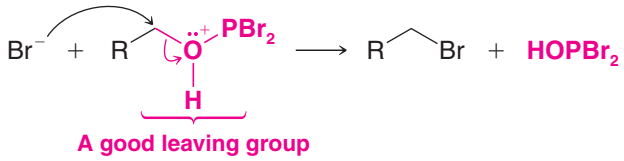
- The reaction of an alcohol with PBr_3 does not involve the formation of a carbocation and *usually occurs without rearrangement* of the carbon skeleton (especially if the temperature is kept below 0°C).
- Phosphorus tribromide is often preferred as a reagent for the transformation of an alcohol to the corresponding alkyl bromide.

The mechanism for the reaction involves attack of the alcohol group on the phosphorus atom, displacing a bromide ion and forming a protonated alkyl dibromophosphite:



Protonated alkyl dibromophosphite

In a second step a bromide ion acts as a nucleophile to displace $HOPBr_2$, a good leaving group due to the electronegative atoms bonded to the phosphorus:

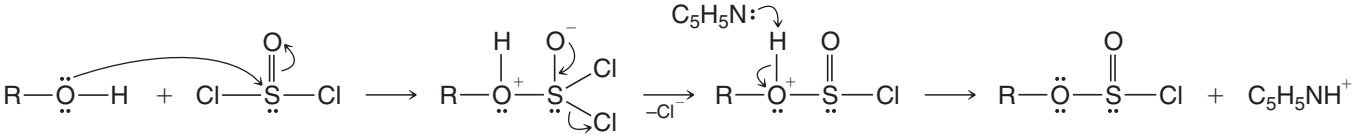


$HOPBr_2$ can react with 2 more moles of alcohol, so the net result is conversion of 3 mol of alcohol to alkyl bromide by 1 mol of phosphorus tribromide.

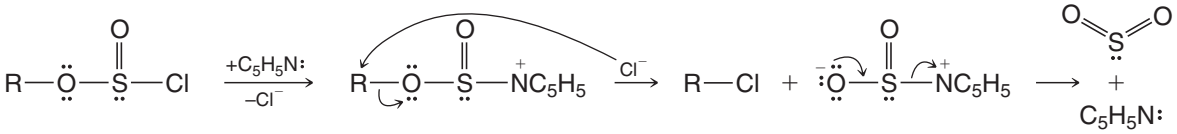
Helpful Hint

$SOCl_2$: A reagent for synthesizing 1° and 2° alkyl chlorides.

Thionyl chloride ($SOCl_2$) converts primary and secondary alcohols to alkyl chlorides. Pyridine (C_5H_5N) is often included to promote the reaction. The alcohol substrate attacks thionyl chloride as shown below, releasing a chloride anion and losing its proton to a molecule of pyridine. The result is an alkylchlorosulfite.



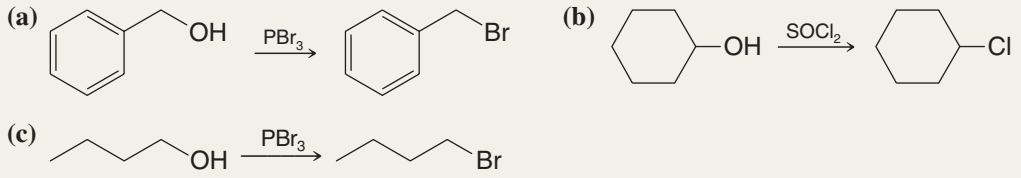
The alkylchlorosulfite intermediate then reacts rapidly with another molecule of pyridine, in the same fashion as the original alcohol, to give a pyridinium alkylsulfite intermediate, with release of the second chloride anion. A chloride anion then attacks the substrate carbon, displacing the sulfite leaving group, which in turn decomposes to release gaseous SO_2 and pyridine. (In the absence of pyridine the reaction occurs with retention of configuration. See Problem 11.55.)



Solved Problem 11.6

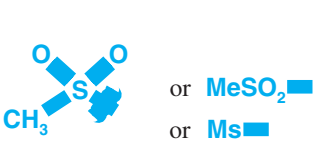
Starting with alcohols, outline a synthesis of each of the following: (**a**) benzyl bromide, (**b**) cyclohexyl chloride, and (**c**) butyl bromide.

POSSIBLE ANSWERS

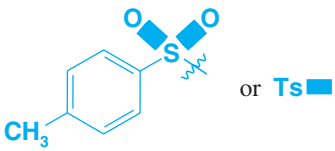


11.10 *Tosylates, Mesylates, and Triflates: Leaving Group Derivatives of Alcohols*

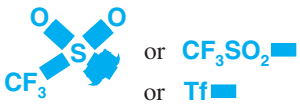
The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a **sulfonate ester** derivative. The most common sulfonate esters used for this purpose are methanesulfonate esters ("**mesylates**"), *p*-toluenesulfonate esters ("**tosylates**"), and trifluoromethanesulfonates ("**triflates**").



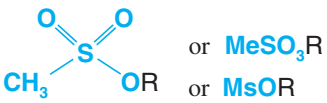
The mesyl group



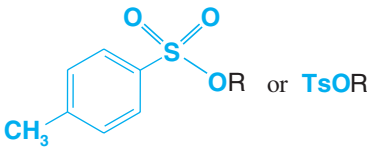
The tosyl group



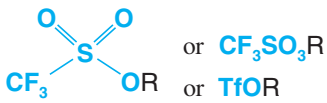
The trifyl group



An alkyl mesylate



An alkyl tosylate

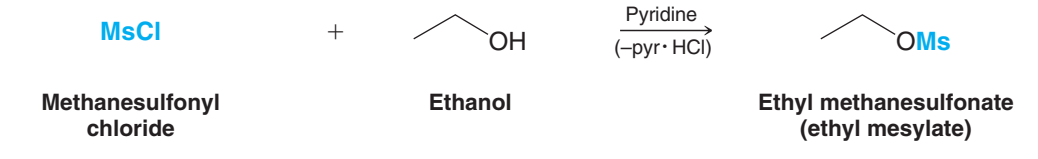


An alkyl triflate

The desired sulfonate ester is usually prepared by reaction of the alcohol in pyridine with the appropriate sulfonyl chloride, that is, methanesulfonyl chloride (mesyl chloride) for a mesylate, *p*-toluenesulfonyl chloride (tosyl chloride) for a tosylate, or trifluoromethanesulfonyl chloride [or trifluoromethanesulfonic anhydride (triflic anhydride)] for a triflate. Pyridine (C_5H_5N, pyr) serves as the solvent and to neutralize the HCl formed. Ethanol, for example, reacts with methanesulfonyl chloride to form ethyl methanesulfonate and with *p*-toluenesulfonyl chloride to form ethyl *p*-toluenesulfonate:

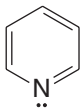
Helpful Hint

A method for making an alcohol hydroxyl group into a leaving group.

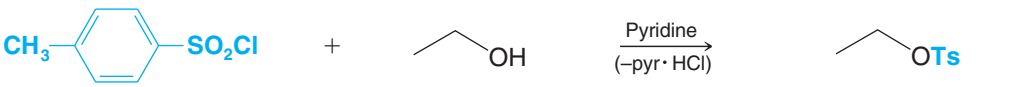


Methanesulfonyl chloride — Ethanol — Ethyl methanesulfonate (ethyl mesylate)

Pyridine =



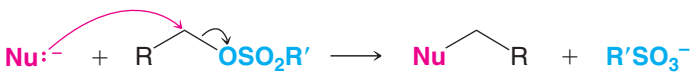
C_5H_5N



p-Toluenesulfonyl chloride (TSCl) — Ethanol — Ethyl *p*-toluenesulfonate (ethyl tosylate)

It is important to note that formation of the sulfonate ester does not affect the stereochemistry of the alcohol carbon, because the C—O bond is not involved in this step. Thus, if the alcohol carbon is a chirality center, no change in configuration occurs on making the sulfonate ester—the reaction proceeds with **retention of configuration.** On reaction of the sulfonate ester with a nucleophile, the usual parameters of nucleophilic substitution reactions become involved.

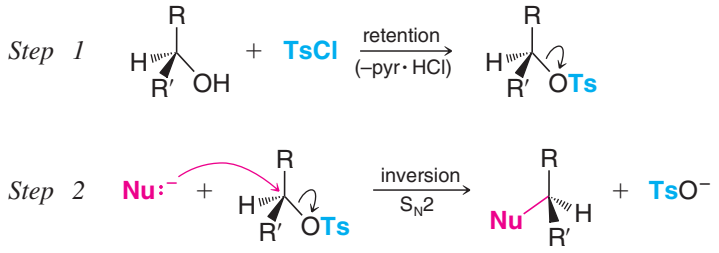
Substrates for Nucleophilic Substitution Mesylates, tosylates, and triflates, because they are good leaving groups, are frequently used as substrates for nucleophilic substitution reactions. They are good leaving groups because the sulfonate anions they become when they depart are very weak bases. The triflate anion is the weakest base in this series, and is thus the best leaving group among them.



An alkyl sulfonate (tosylate, mesylate, etc.) — A sulfonate ion (a very weak base– a good leaving group)

- To carry out a nucleophilic substitution on an alcohol, we first convert the alcohol to an alkyl sulfonate and then, in a second reaction, allow it to react with a nucleophile.

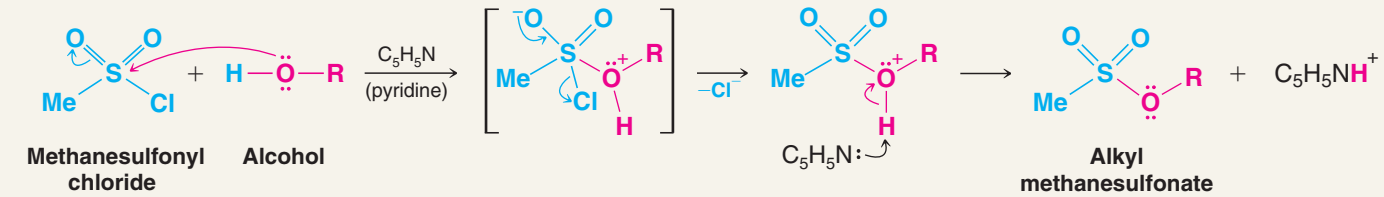
- If the mechanism is S_N2, as shown in the second reaction of the following example, **inversion of configuration** takes place at the carbon that originally bore the alcohol hydroxyl group:



The fact that the C—O bond of the alcohol does not break during formation of the sulfonate ester is accounted for by the following mechanism. Methanesulfonyl chloride is used in the example.

A MECHANISM FOR THE REACTION

Conversion of an Alcohol into a Mesylate (an Alkyl Methanesulfonate)



Methanesulfonyl chloride **Alcohol** **Alkyl methanesulfonate**

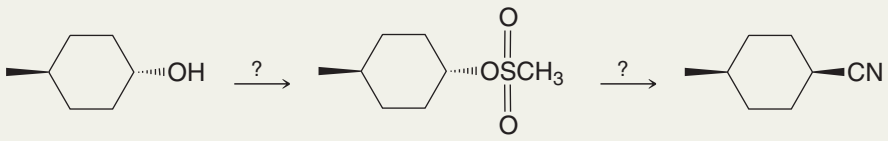
The alcohol oxygen attacks the sulfur atom of the sulfonyl chloride.

The intermediate loses a chloride ion.

Loss of a proton leads to the product.

Solved Problem 11.7

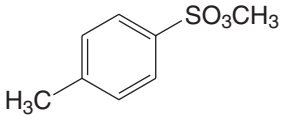
Supply the missing reagents.

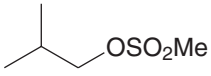


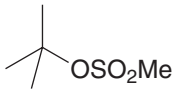
STRATEGY AND ANSWER The overall transformation over two steps involves replacing an alcohol hydroxyl group by a cyano group with inversion of configuration. To accomplish this, we need to convert the alcohol hydroxyl to a good leaving group in the first step, which we do by making it a methanesulfonate ester (a mesylate) using methanesulfonyl chloride in pyridine. The second step is an S_N2 substitution of the methanesulfonate (mesyl) group, which we do using potassium or sodium cyanide in a polar aprotic solvent such as dimethylformamide (DMF).

Review Problem 11.8

Show how you would prepare the following compounds from the appropriate sulfonyl chlorides.

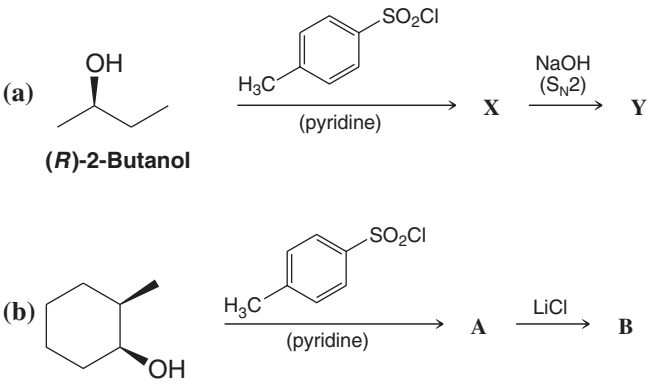
(a) 

(b) 

(c) 

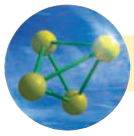
Review Problem 11.9

Write structures for products **X, Y, A**, and **B**, showing stereochemistry.



Review Problem 11.10

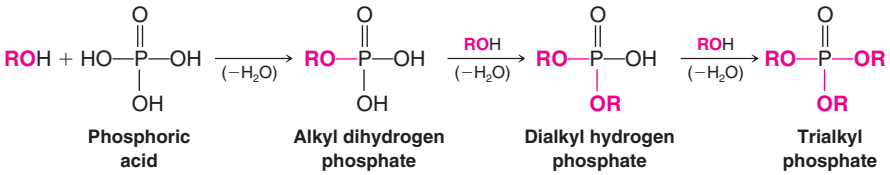
Suggest an experiment using an isotopically labeled alcohol that would prove that the formation of an alkyl sulfonate does not cause cleavage at the C—O bond of the alcohol.



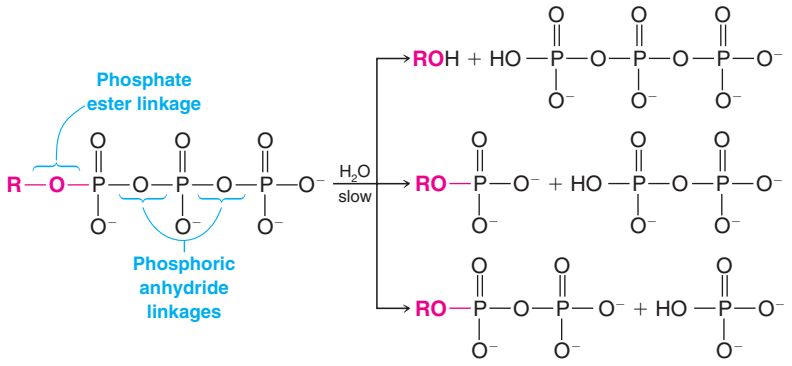
THE CHEMISTRY OF. . .

Alkyl Phosphates

Alcohols react with phosphoric acid to yield alkyl phosphates:



Esters of phosphoric acids are important in biochemical reactions. Especially important are triphosphate esters. Although hydrolysis of the ester group or of one of the anhydride linkages of an alkyl triphosphate is exothermic, these reactions occur very slowly in aqueous solutions. Near pH 7, these triphosphates exist as negatively charged ions and hence are much less susceptible to nucleophilic attack. Alkyl triphosphates are, consequently, relatively stable compounds in the aqueous medium of a living cell.



Enzymes, on the other hand, are able to catalyze reactions of these triphosphates in which the energy made available when their anhydride linkages break helps the cell make other chemical bonds. We shall have more to say about this in Chapter 22 when we discuss the important triphosphate called adenosine triphosphate (or ATP).

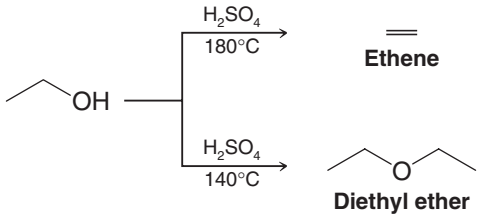
11.11 *Synthesis of Ethers*

11.11A Ethers by Intermolecular Dehydration of Alcohols

Alcohols can dehydrate to form alkenes. We studied this in Sections 7.7 and 7.8. Primary alcohols can also dehydrate to form ethers:

$$\text{R—OH} + \text{HO—R} \xrightarrow[-\text{H}_2\text{O}]{\text{HA}} \text{R—O—R}$$

Dehydration to an ether usually takes place at a lower temperature than dehydration to the alkene, and dehydration to the ether can be aided by distilling the ether as it is formed. Diethyl ether is made commercially by dehydration of ethanol. Diethyl ether is the predominant product at 140°C; ethene is the major product at 180°C:

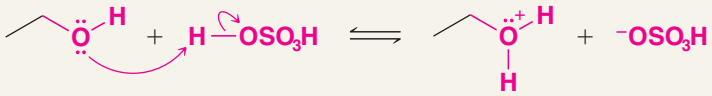


The formation of the ether occurs by an S_N2 mechanism with one molecule of the alcohol acting as the nucleophile and another protonated molecule of the alcohol acting as the substrate (see Section 11.5).

A MECHANISM FOR THE REACTION

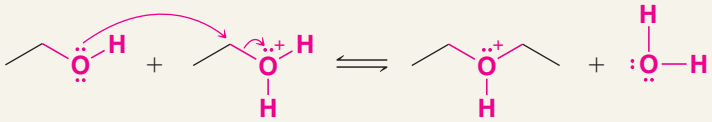
Intermolecular Dehydration of Alcohols to Form an Ether

Step 1



This is an acid–base reaction in which the alcohol accepts a proton from the sulfuric acid.

Step 2



Another molecule of the alcohol acts as a nucleophile and attacks the protonated alcohol in an S_N2 reaction.

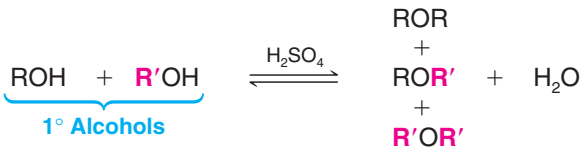
Step 3

Another acid–base reaction converts the protonated ether to an ether by transferring a proton to a molecule of water (or to another molecule of the alcohol).

Complications of Intermolecular Dehydration The method of synthesizing ethers by intermolecular dehydration has some important limitations.

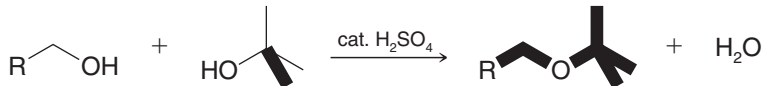
- Attempts to synthesize ethers by intermolecular dehydration of secondary alcohols are usually unsuccessful because alkenes form too easily.

- Attempts to make ethers with tertiary alkyl groups lead exclusively to the alkenes.
- Intermolecular dehydration is not useful for the preparation of unsymmetrical ethers from primary alcohols because the reaction leads to a mixture of products:



An exception to what we have just said has to do with syntheses of unsymmetrical ethers in which one alkyl group is a *tert*-butyl group and the other group is primary. For example, this synthesis can be accomplished by adding *tert*-butyl alcohol to a mixture of the primary alcohol and H_2SO_4 at room temperature.

Review Problem 11.11



Give a likely mechanism for this reaction and explain why it is successful.

11.11B The Williamson Synthesis of Ethers

An important route to unsymmetrical ethers is a nucleophilic substitution reaction known as the **Williamson synthesis**.

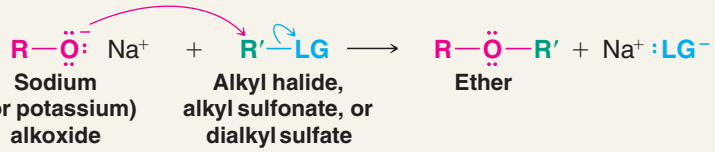
Helpful Hint

Alexander William Williamson was an English chemist who lived between 1824 and 1904. His method is especially useful for synthesis of unsymmetrical ethers.

- The Williamson ether synthesis consists of an S_N2 reaction of a sodium alkoxide with an alkyl halide, alkyl sulfonate, or alkyl sulfate.

A MECHANISM FOR THE REACTION

The Williamson Ether Synthesis

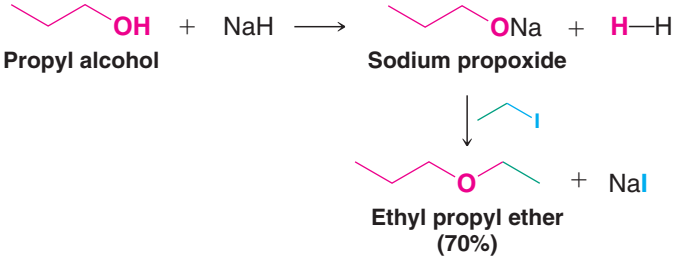


The alkoxide ion reacts with the substrate in an S_N2 reaction, with the resulting formation of an ether. The substrate must be unhindered and bear a good leaving group. Typical substrates are 1° or 2° alkyl halides, alkyl sulfonates, and dialkyl sulfates, that is,

The following reaction is a specific example of the Williamson synthesis. The sodium alkoxide can be prepared by allowing an alcohol to react with NaH:

Helpful Hint

Conditions that favor a Williamson ether synthesis.



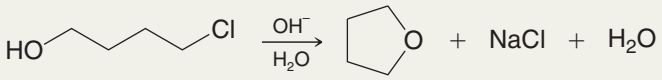
The usual limitations of S_N2 reactions apply here. Best results are obtained when the alkyl halide, sulfonate, or sulfate is primary (or methyl). **If the substrate is tertiary, elimination is the exclusive result**. Substitution is also favored over elimination at lower temperatures.

Review Problem 11.12

(a) Outline two methods for preparing isopropyl methyl ether by a Williamson synthesis.
(b) One method gives a much better yield of the ether than the other. Explain which is the better method and why.

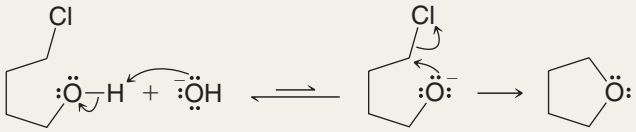
Solved Problem 11.8

The cyclic ether tetrahydrofuran (THF) can be synthesized by treating 4-chloro-1-butanol with aqueous sodium hydroxide (see below). Propose a mechanism for this reaction.



Tetrahydrofuran

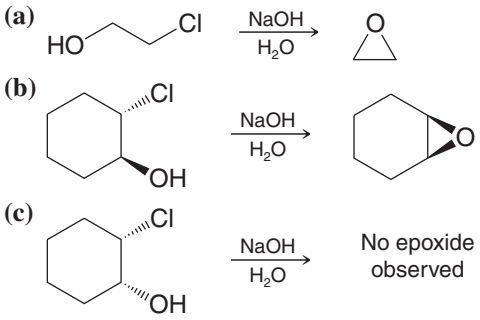
STRATEGY AND ANSWER Removal of a proton from the hydroxyl group of 4-chloro-1-butanol gives an alkoxide ion that can then react with itself in an intramolecular S_N2 reaction to form a ring.



Even though treatment of the alcohol with hydroxide does not favor a large equilibrium concentration of the alkoxide, the alkoxide anions that are present react rapidly by the intramolecular S_N2 reaction. As alkoxide anions are consumed by the substitution reaction, their equilibrium concentration is replenished by deprotonation of additional alcohol molecules, and the reaction is drawn to completion.

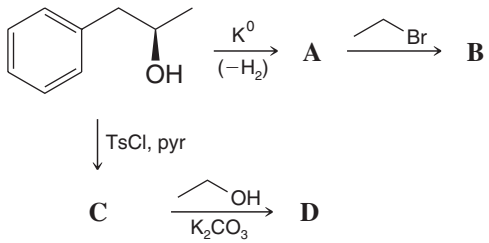
Review Problem 11.13

Epoxides can be synthesized by treating halohydrins with aqueous base. Propose a mechanism for reactions (a) and (b), and explain why no epoxide formation is observed in (c).



Review Problem 11.14

Write structures for products **A, B, C**, and **D**, showing stereochemistry. (*Hint:* **B** and **D** are stereoisomers.)

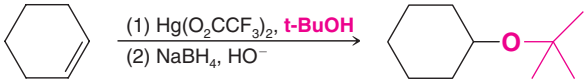


11.11C Synthesis of Ethers by Alkoxymercuration–Demercuration

Alkoxymercuration–demercuration is another method for synthesizing ethers.

- The reaction of an alkene with an alcohol in the presence of a mercury salt such as mercuric acetate or trifluoroacetate leads to an alkoxymercury intermediate, which on reaction with sodium borohydride yields an ether.

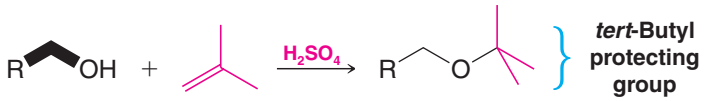
When the alcohol reactant is also the solvent, the method is called solvomercuration–demercuration. This method directly parallels hydration by oxymercuration–demercuration (Section 8.6):



(98% Yield)

11.11D *tert*-Butyl Ethers by Alkylation of Alcohols: Protecting Groups

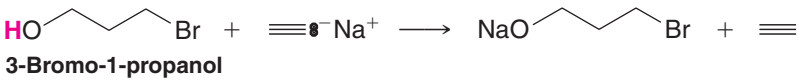
Primary alcohols can be converted to *tert*-butyl ethers by dissolving them in a strong acid such as sulfuric acid and then adding isobutylene to the mixture. (This procedure minimizes dimerization and polymerization of the isobutylene.)



***tert*-Butyl protecting group**

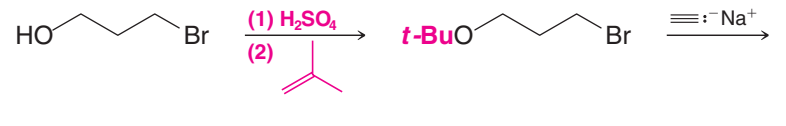
- A *tert*-butyl ether can be used to "protect" the hydroxyl group of a primary alcohol while another reaction is carried out on some other part of the molecule.
- A *tert*-butyl **protecting group** can be removed easily by treating the ether with dilute aqueous acid.

Suppose, for example, we wanted to prepare 4-pentyn-1-ol from 3-bromo-1-propanol and sodium acetylide. If we allow them to react directly, the strongly basic sodium acetylide will react first with the hydroxyl group:



3-Bromo-1-propanol

However, if we protect the —OH group first, the synthesis becomes feasible:

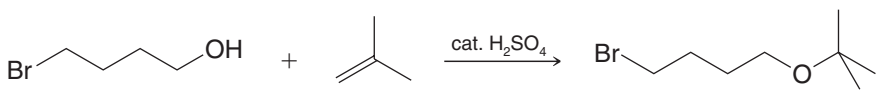


4-Pentyn-1-ol

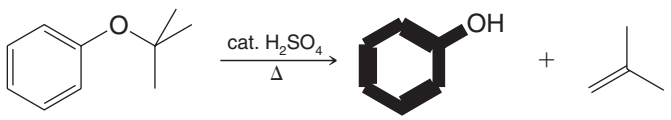
Review Problem 11.15

Propose mechanisms for the following reactions.

(a)



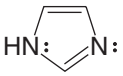
(b)



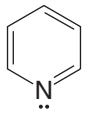
11.11E Silyl Ether Protecting Groups

- A hydroxyl group can also be protected by converting it to a silyl ether group.

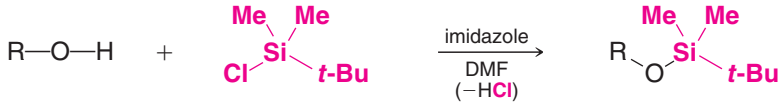
One of the most common silyl ether protecting groups is the *tert*-butyldimethylsilyl ether group [*tert*-butyl(Me)$_2$Si—O—R, or TBS—O—R], although triethylsilyl, triisopropylsilyl, *tert*-butyldiphenylsilyl, and others can be used. The *tert*-butyldimethylsilyl ether is stable over a pH range of roughly 4–12. A TBS group can be added by allowing the alcohol to react with *tert*-butyldimethylsilyl chloride in the presence of an aromatic amine (a base) such as imidazole or pyridine:



Imidazole

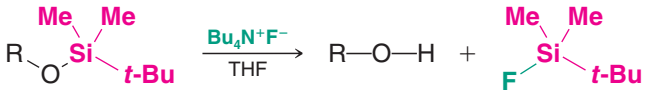


Pyridine



***tert*-Butylchlorodimethylsilane (TBSCl)** **(R—O—TBS)**

- The TBS group can be removed by treatment with fluoride ion (tetrabutylammonium fluoride or aqueous HF is frequently used).

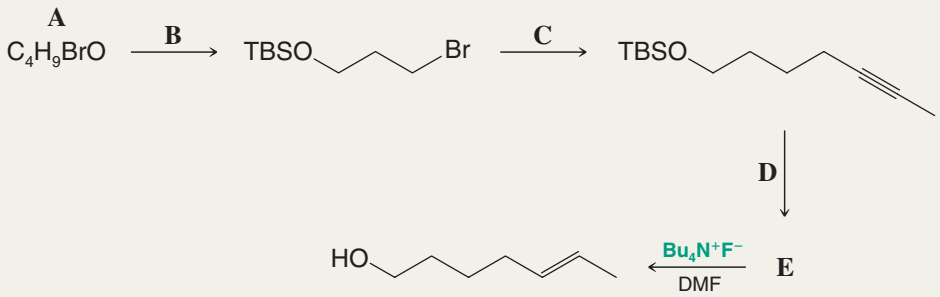


(R—O—TBS)

Converting an alcohol to a silyl ether also makes it much more volatile. This increased volatility makes the alcohol (as a silyl ether) much more amenable to analysis by gas chromatography. Trimethylsilyl ethers are often used for this purpose. (The trimethylsilyl ether group is too labile to use as a protecting group in most reactions, however.)

Solved Problem 11.9

Supply the missing reagents and intermediates **A–E**.



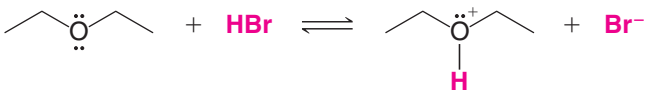
STRATEGY AND ANSWER We start by noticing several things: a TBS (*tert*-butyldimethylsilyl) protecting group is involved, the carbon chain increases from four carbons in **A** to seven in the final product, and an alkyne is reduced to a trans alkene. **A** does not contain any silicon atoms, whereas the product after the reaction under conditions **B** does. Therefore, **A** must be an alcohol that is protected as a TBS ether by conditions specified as **B. A** is therefore 4-bromo-1-butanol, and conditions **B** are TBSCl (*tert*-butyldimethylsilyl chloride) with imidazole in DMF. Conditions **C** involve loss of the bromine and chain extension by three carbons with incorporation of an alkyne. Thus, the reaction conditions for **C** must involve sodium propynide, which would come from deprotonation of propyne using an appropriate base, such as $NaNH_2$ or CH_3MgBr. The conditions leading from **E** to the final product are those for removal of a TBS group, and not those for converting an alkyne to a trans alkene; thus, **E** must still contain the TBS ether but already contain the trans alkene. Conditions **D**, therefore, must be (1) Li, Et_2NH, (2) NH_4Cl, which are those required for converting the alkyne to a trans alkene. **E**, therefore, must be the TBS ether of 5-heptyn-1-ol (which can also be named 1-*tert*-butyldimethylsiloxy-5-heptynol).

11.12 Reactions of Ethers

Dialkyl ethers react with very few reagents other than acids. The only reactive sites that molecules of a dialkyl ether present to another reactive substance are the C—H bonds of the alkyl groups and the —Ö— group of the ether linkage. Ethers resist attack by nucleophiles (why?) and by bases. This lack of reactivity coupled with the ability of ethers to solvate cations (by donating an electron pair from their oxygen atom) makes ethers especially useful as solvents for many reactions.

Ethers are like alkanes in that they undergo halogenation reactions (Chapter 10), but these reactions are of little synthetic importance. They also undergo slow autoxidation to form explosive peroxides (see Section 11.3D).

The oxygen of the ether linkage makes ethers basic. Ethers can react with proton donors to form **oxonium salts**:



An oxonium salt

11.12A Cleavage of Ethers

Heating dialkyl ethers with very strong acids (HI, HBr, and H_2SO_4) causes them to undergo reactions in which the carbon–oxygen bond breaks. Diethyl ether, for example, reacts with hot concentrated hydrobromic acid to give two molecular equivalents of ethyl bromide:

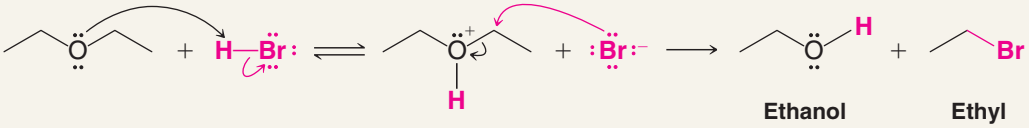
Cleavage of an ether

The mechanism for this reaction begins with formation of an oxonium cation. Then, an S_N2 reaction with a bromide ion acting as the nucleophile produces ethanol and ethyl bromide. Excess HBr reacts with the ethanol produced to form the second molar equivalent of ethyl bromide.

A MECHANISM FOR THE REACTION

Ether Cleavage by Strong Acids

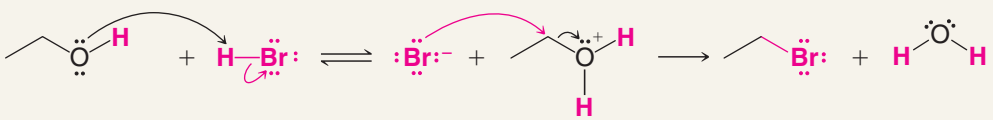
Step 1



Ethanol **Ethyl bromide**

In Step 2, the ethanol (just formed) reacts with HBr (present in excess) to form a second molar equivalent of ethyl bromide.

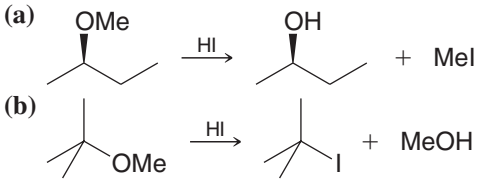
Step 2



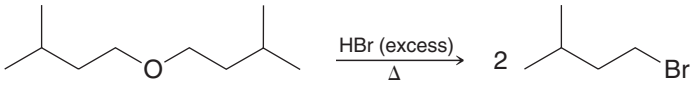
Review Problem 11.16 When an ether is treated with *cold* concentrated HI, cleavage occurs as follows:

$$R{-}O{-}R + HI \longrightarrow ROH + RI$$

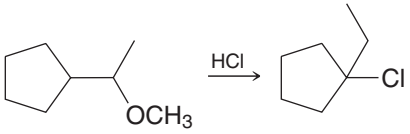
When mixed ethers are used, the alcohol and alkyl iodide that form depend on the nature of the alkyl groups. Use mechanisms to explain the following observations:



Review Problem 11.17 Write a detailed mechanism for the following reaction.

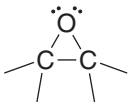


Review Problem 11.18 Provide a mechanism for the following reaction.



11.13 Epoxides

Epoxides are cyclic ethers with three-membered rings. In IUPAC nomenclature epoxides are called **oxiranes**. The simplest epoxide has the common name ethylene oxide:

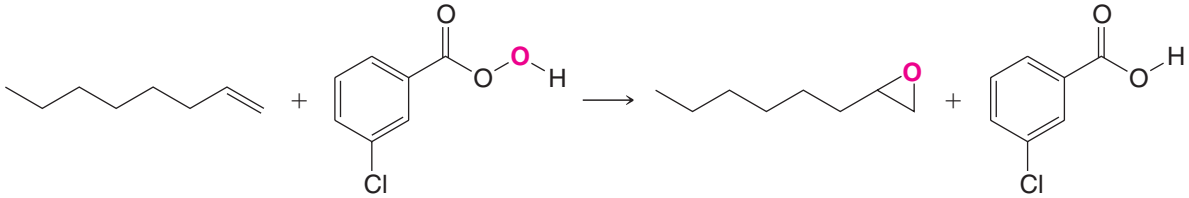


An epoxide

IUPAC name: oxirane
Common name: ethylene oxide

11.13A Synthesis of Epoxides: Epoxidation

Epoxides can be synthesized by the reaction of an alkene with an organic **peroxy acid** (RCO_3H—sometimes called simply a **peracid**), a process that is called **epoxidation**. *Meta*-Chloroperoxybenzoic acid (MCPBA) is one peroxy acid reagent commonly used for epoxidation. The following reaction is an example.



1-Octene **MCPBA** **(81%)** ***meta*-Chlorobenzoic acid**

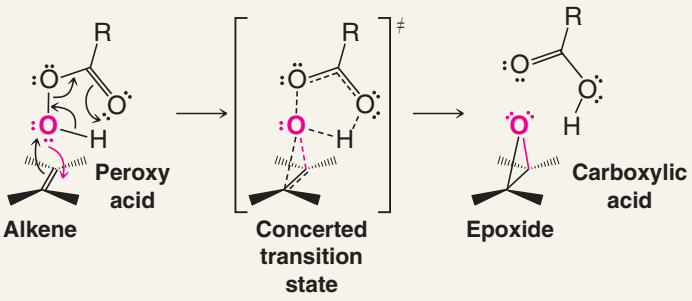
meta-Chlorobenzoic acid is a by-product of the reaction. Often it is not written in the chemical equation, as the following example illustrates.

(77%)

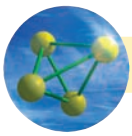
As the first example illustrates, the peroxy acid transfers an oxygen atom to the alkene. The following mechanism has been proposed.

A MECHANISM FOR THE REACTION

Alkene Epoxidation



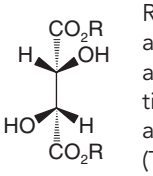
The peroxy acid transfers an oxygen atom to the alkene in a cyclic, single-step mechanism. The result is the syn addition of the oxygen to the alkene, with the formation of an epoxide and a carboxylic acid.



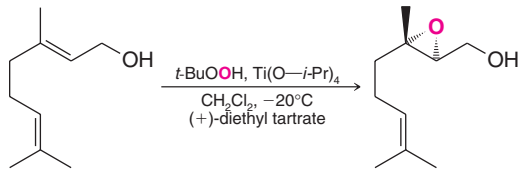
THE CHEMISTRY OF. . .

The Sharpless Asymmetric Epoxidation

In 1980, K. B. Sharpless (then at the Massachusetts Institute of Technology, presently at The Scripps Research Institute) and co-workers reported a method that has since become one of the most valuable tools for chiral synthesis. The Sharpless asymmetric epoxidation is a method for converting allylic alcohols (Section 11.1) to chiral epoxy alcohols with very high enantioselectivity (i.e., with preference for one enantiomer rather than formation of a racemic mixture). In recognition of this and other work in asymmetric oxidation methods (see Section 8.16A), Sharpless received half of the 2001 Nobel Prize in Chemistry (the other half was awarded to W. S. Knowles and R. Noyori; see Section 7.14). The Sharpless asymmetric epoxidation involves treating the allylic alcohol with *tert*-butyl hydroperoxide, titanium(IV) tetraisopropoxide [$Ti(O—i\text{-}Pr)_4$], and a specific stereoisomer of a tartrate ester. (The tartrate stereoisomer that is chosen depends on the specific enantiomer of the epoxide desired). The following is an example:

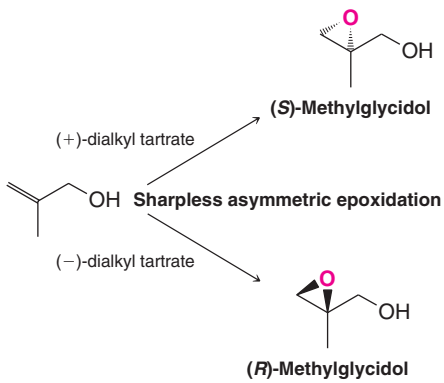


A (+)-dialkyl tartrate ester



Geraniol **77% yield (95% enantiomeric excess)**

The oxygen that is transferred to the allylic alcohol to form the epoxide is derived from *tert*-butyl hydroperoxide. The enantioselectivity of the reaction results from a titanium complex among the reagents that includes the enantiomerically pure tartrate ester as one of the ligands. The choice of whether to use the (+)- or (−)-tartrate ester for stereochemical control depends on which enantiomer of the epoxide is desired. [The (+)- and (−)-tartrates are either diethyl or diisopropyl esters.] The stereochemical preferences of the reaction have been well studied, such that it is possible to prepare either enantiomer of a chiral epoxide in high enantiomeric excess, simply by choosing the appropriate (+)- or (−)-tartrate stereoisomer as the chiral ligand:



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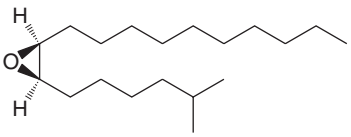
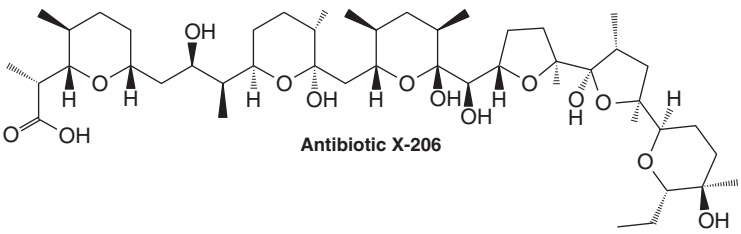
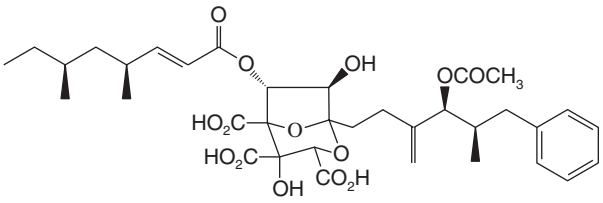


(7*R*,8*S*)-Disparlure

Compounds of this general structure are extremely useful and versatile synthons because combined in one molecule are an epoxide functional group (a highly reactive electrophilic site), an alcohol functional group (a potentially nucleophilic site), and at least one chirality center that is present in high enantiomeric purity. The synthetic utility of chiral epoxy alcohol synthons produced by the Sharpless asymmetric epoxidation has been demonstrated over and over in enantioselective syntheses of many important compounds. Some examples include the synthesis of the polyether antibiotic X-206 by E. J. Corey (Harvard), the J. T. Baker commercial synthesis of the gypsy moth pheromone (7*R*,8*S*)-disparlure, and synthesis by K. C. Nicolaou (University of California San Diego and Scripps Research Institute) of zaragozic acid A (which is also called squalestatin S1 and has been shown to lower serum cholesterol levels in test animals by inhibition of squalene biosynthesis; see "The Chemistry of. . .Cholesterol Biosynthesis," Chapter 8).



Antibiotic X-206

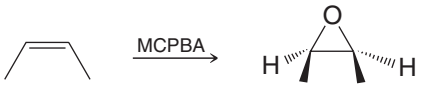


Zaragozic acid A (squalestatin S1)

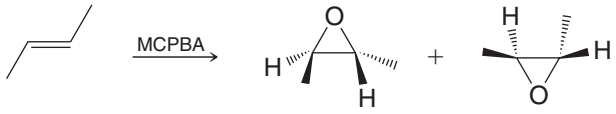
11.13B Stereochemistry of Epoxidation

- The reaction of alkenes with peroxy acids is, of necessity, a **syn** addition, and it is **stereospecific**. Furthermore, the oxygen atom can add to either face of the alkene.

For example, *trans*-2-butene yields racemic *trans*-2,3-dimethyloxirane, because addition of oxygen to each face of the alkene generates an enantiomer. *cis*-2-Butene, on the other hand, yields only *cis*-2,3-dimethyloxirane, no matter which face of the alkene accepts the oxygen atom, due to the plane of symmetry in both the reactant and the product. If additional chirality centers are present in a substrate, then diastereomers would result.



***cis*-2-Butene** ***cis*-2,3-Dimethyloxirane (a meso compound)**



***trans*-2-Butene** **Enantiomeric *trans*-2,3-dimethyloxiranes**

In Special Topic C (Section C.3) we present a method for synthesizing epoxides from aldehydes and ketones.

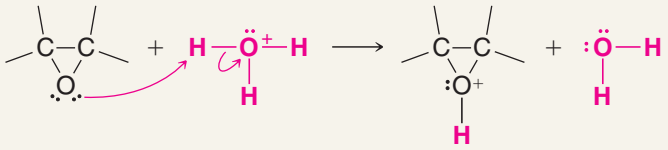
11.14 Reactions of Epoxides

- The highly strained three-membered ring of epoxides makes them much more reactive toward nucleophilic substitution than other ethers.

Acid catalysis assists epoxide ring opening by providing a better leaving group (an alcohol) at the carbon atom undergoing nucleophilic attack. This catalysis is especially important if the nucleophile is a weak nucleophile such as water or an alcohol. An example is the acid-catalyzed hydrolysis of an epoxide.

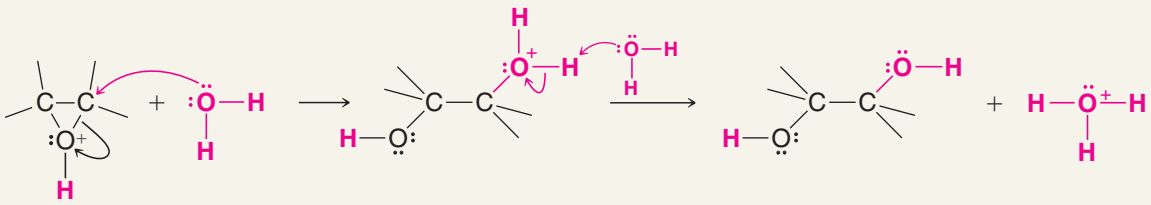
A MECHANISM FOR THE REACTION

Acid-Catalyzed Ring Opening of an Epoxide



Epoxide **Protonated epoxide**

The acid reacts with the epoxide to produce a protonated epoxide.



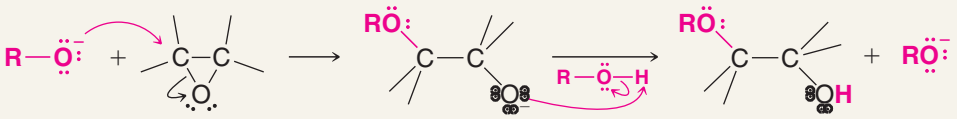
Protonated epoxide **Weak nucleophile** **Protonated 1,2-diol** **1,2-Diol**

The protonated epoxide reacts with the weak nucleophile (water) to form a protonated 1,2-diol, which then transfers a proton to a molecule of water to form the 1,2-diol and a hydronium ion.

Epoxides can also undergo base-catalyzed ring opening. Such reactions do not occur with other ethers, but they are possible with epoxides (because of ring strain), provided that the attacking nucleophile is also a strong base such as an alkoxide ion or hydroxide ion.

A MECHANISM FOR THE REACTION

Base-Catalyzed Ring Opening of an Epoxide



Strong nucleophile **Epoxide** **An alkoxide ion**

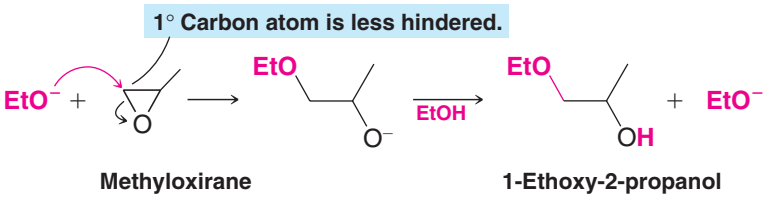
A strong nucleophile such as an alkoxide ion or a hydroxide ion is able to open the strained epoxide ring in a direct S_N2 reaction.

Helpful Hint

Regioselectivity in the opening of epoxides.

- If the epoxide is unsymmetrical, in **base-catalyzed ring opening**, attack by the alkoxide ion occurs primarily ***at the less substituted carbon atom***.

For example, methyloxirane reacts with an alkoxide ion mainly at its primary carbon atom:

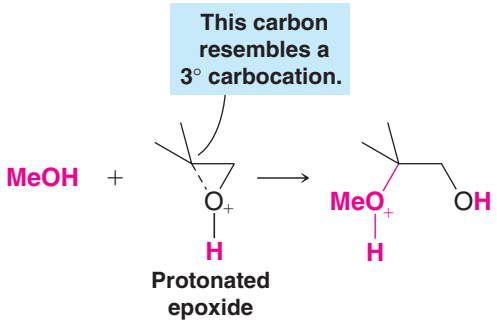


This is just what we should expect: The reaction is, after all, an S_N2 reaction, and, as we learned earlier (Section 6.13A), primary substrates react more rapidly in S_N2 reactions because they are less sterically hindered.

- In the **acid-catalyzed ring opening** of an unsymmetrical epoxide the nucleophile attacks primarily ***at the more substituted carbon atom***.

For example,

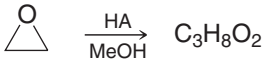
The reason: Bonding in the protonated epoxide (see the following reaction) is unsymmetrical, with the more highly substituted carbon atom bearing a considerable positive charge; the reaction is S_N1 like. The nucleophile, therefore, attacks this carbon atom even though it is more highly substituted:

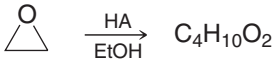


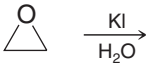
The more highly substituted carbon atom bears a greater positive charge because it resembles a more stable tertiary carbocation. [Notice how this reaction (and its explanation) resembles that given for halohydrin formation from unsymmetrical alkenes in Section 8.14 and attack on mercurinium ions.]

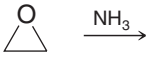
Review Problem 11.19

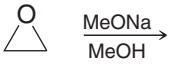
Propose structures for each of the following products derived from oxirane (ethylene oxide):

(a)  $C_3H_8O_2$ **Methyl Cellosolve**

(b)  $C_4H_{10}O_2$ **Ethyl Cellosolve**

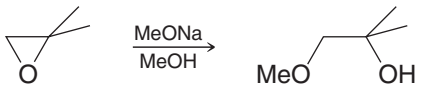
(c)  C_2H_5IO

(d)  C_2H_7NO

(e)  $C_3H_8O_2$

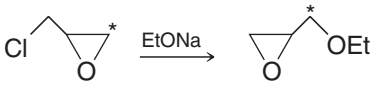
Provide a mechanistic explanation for the following observation.

Review Problem 11.20



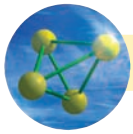
When sodium ethoxide reacts with 1-(chloromethyl)oxirane (also called epichlorohydrin), labeled with ^{14}C as shown by the asterisk in **I**, the major product is **II**. Provide a mechanistic explanation for this result.

Review Problem 11.21



I **II**

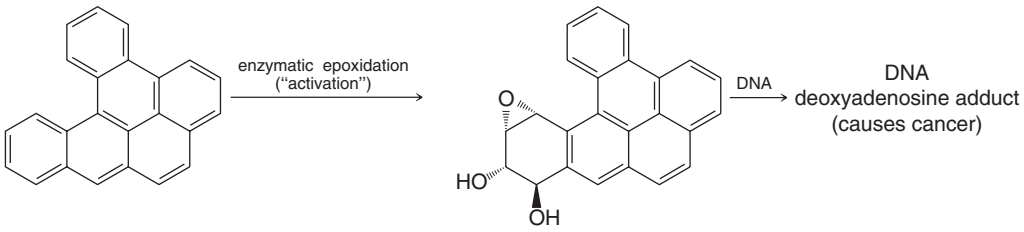
1-(Chloromethyl)oxirane (epichlorohydrin)



THE CHEMISTRY OF. . .

Epoxides, Carcinogens, and Biological Oxidation

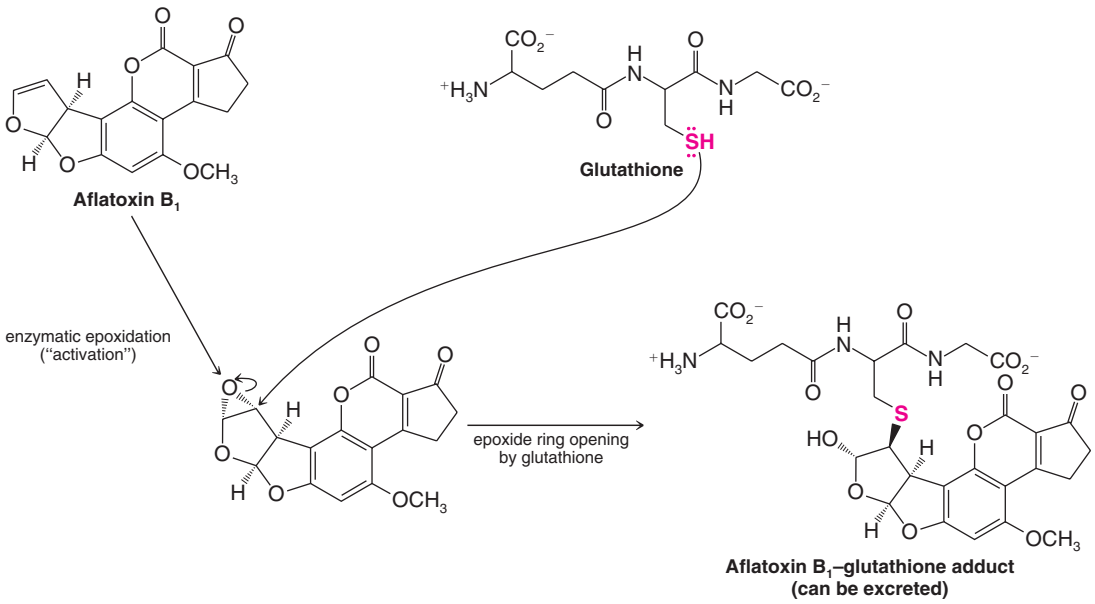
Certain molecules from the environment become carcinogenic by "activation" through metabolic processes that are normally involved in preparing them for excretion. This is the case with two of the most carcinogenic compounds known: dibenzo[*a,l*]pyrene, a polycyclic aromatic hydrocarbon, and aflatoxin B_1, a fungal metabolite. During the course of oxidative processing in the liver and intestines, these molecules undergo epoxidation by enzymes called P450 cytochromes. Their epoxide products, as you might expect, are exceptionally reactive electrophiles, and it is precisely because of this that they are carcinogenic. The dibenzo[*a,l*]pyrene and aflatoxin B_1 epoxides undergo very facile nucleophilic substitution reactions with DNA. Nucleophilic sites on DNA react to open the epoxide ring, causing alkylation of the DNA by formation of a covalent bond with the carcinogen. Modification of the DNA in this way causes onset of the disease state.



Dibenzo[*a,l*]pyrene **Dibenzo[*a,l*]pyrene-11,12-diol-13,14-epoxide**

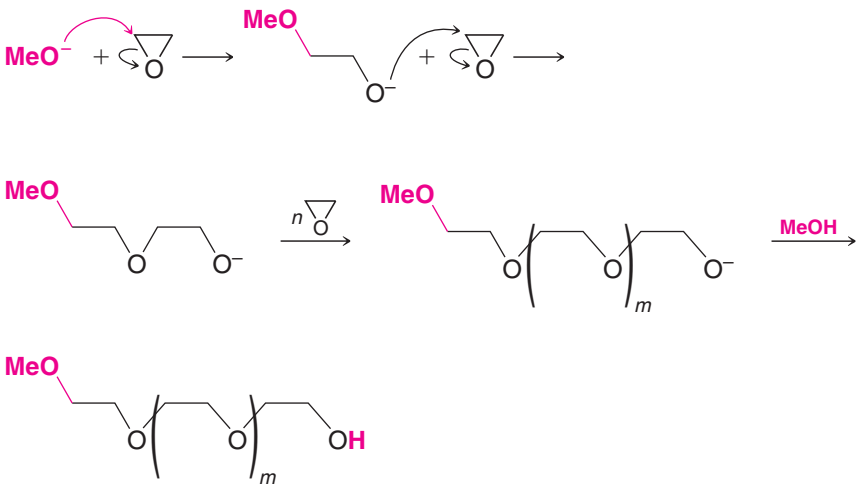
The normal pathway toward excretion of foreign molecules like dibenzo[*a,l*]pyrene and aflatoxin B_1, however, also involves nucleophilic substitution reactions of their epoxides. One pathway involves opening of the epoxide ring by nucleophilic substitution with glutathione. Glutathione is a relatively polar molecule that has a strongly nucleophilic sulfhydryl group. After reaction of the sulfhydryl group with the epoxide, the newly formed covalent derivative, because it is substantially more polar than the original epoxide, is readily excreted through aqueous pathways.

(continues on the next page)



11.14A Polyethers from Epoxides

Treating ethylene oxide with sodium methoxide (in the presence of a small amount of methanol) can result in the formation of a **polyether**:

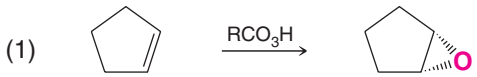


This is an example of **anionic polymerization** (Section 10.10). The polymer chains continue to grow until methanol protonates the alkoxide group at the end of the chain. The average length of the growing chains and, therefore, the average molecular weight of the polymer can be controlled by the amount of methanol present. The physical properties of the polymer depend on its average molecular weight.

Polyethers have high water solubilities because of their ability to form multiple hydrogen bonds to water molecules. Marketed commercially as **carbowaxes**, these polymers have a variety of uses, ranging from use in gas chromatography columns to applications in cosmetics.

11.15 Anti 1,2-Dihydroxylation of Alkenes via Epoxides

Epoxidation (1) of cyclopentene produces 1,2-epoxycyclopentane:

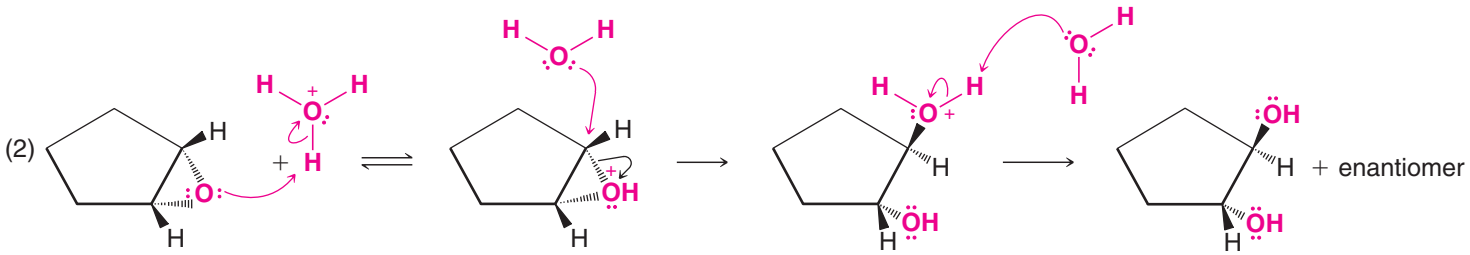


Cyclopentene **1,2-Epoxycyclopentane**

Acid-catalyzed hydrolysis (2) of 1,2-epoxycyclopentane yields a trans diol, *trans*-1,2-cyclopentanediol. Water acting as a nucleophile attacks the protonated epoxide from the side opposite the epoxide group. The carbon atom being attacked undergoes an inversion of configuration. We show here only one carbon atom being attacked. Attack at the other carbon atom of this symmetrical system is equally likely and produces the enantiomeric form of *trans*-1,2-cyclopentanediol:

Helpful Hint

A synthetic method for anti 1,2-dihydroxylation.



***trans*-1,2-Cyclopentanediol**

Epoxidation followed by acid-catalyzed hydrolysis gives us, therefore, a method for **anti 1,2-dihydroxylation** of a double bond (as opposed to syn 1,2-dihydroxylation, Section 8.16). The stereochemistry of this technique parallels closely the stereochemistry of the bromination of cyclopentene given earlier (Section 8.13).

Review Problem 11.22

Outline a mechanism similar to the one just given that shows how the enantiomeric form of *trans*-1,2-cyclopentanediol is produced.

Solved Problem 11.10

In Section 11.13B we showed the epoxidation of *cis*-2-butene to yield *cis*-2,3-dimethyloxirane and epoxidation of *trans*-2-butene to yield *trans*-2,3-dimethyloxirane. Now consider acid-catalyzed hydrolysis of these two epoxides and show what product or products would result from each. Are these reactions stereospecific?

ANSWER (a) The meso compound, *cis*-2,3-dimethyloxirane (Fig. 11.1), yields on hydrolysis (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol. These products are enantiomers. Since the attack by water at either carbon [path (a) or path (b) in Fig. 11.1] occurs at the same rate, the product is obtained in a racemic form.

When either of the *trans*-2,3-dimethyloxirane enantiomers undergoes acid-catalyzed hydrolysis, the only product that is obtained is the meso compound, (2*R*,3*S*)-2,3-butanediol. The hydrolysis of one enantiomer is shown in

Fig. 11.2. (You might construct a similar diagram showing the hydrolysis of the other enantiomer to convince yourself that it, too, yields the same product.)

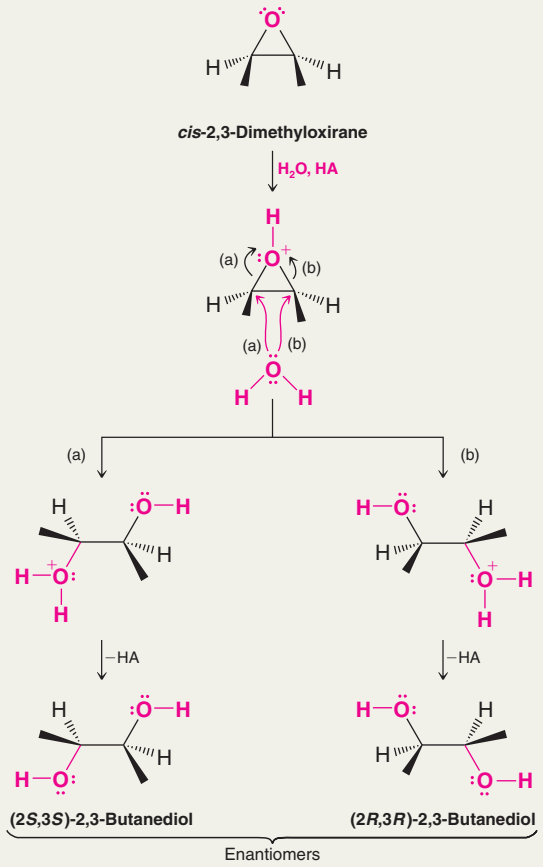


Figure 11.1 Acid-catalyzed hydrolysis of *cis*-2,3-dimethyloxirane yields (2*S*,3*S*)-2,3-butanediol by path (a) and (2*R*,3*R*)-2,3-butanediol by path (b). (Use models to convince yourself.)

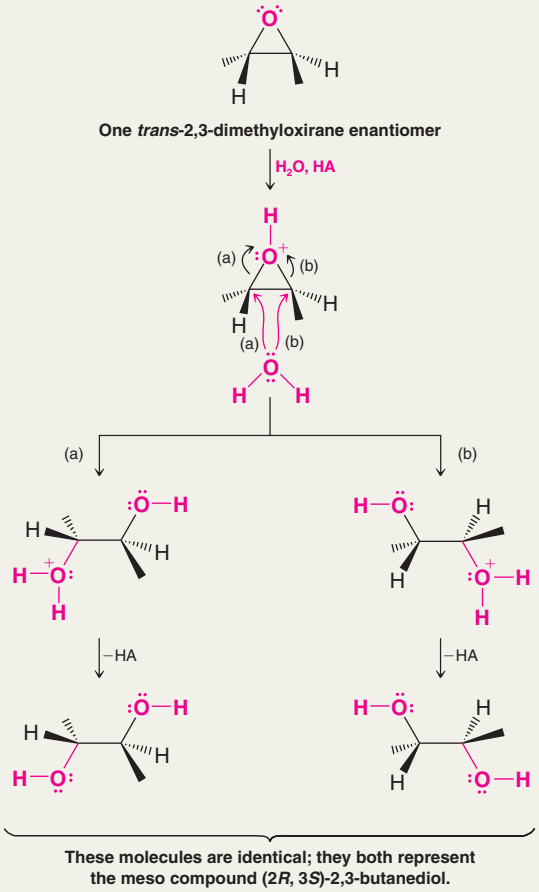


Figure 11.2 The acid-catalyzed hydrolysis of one *trans*-2,3-dimethyloxirane enantiomer produces the meso compound, (2*R*,3*S*)-2,3-butanediol, by path (a) or by path (b). Hydrolysis of the other enantiomer (or the racemic modification) would yield the same product. (You should use models to convince yourself that the two structures given for the products do represent the same compound.)

(b) Since both steps in this method for the conversion of an alkene to a 1,2-diol (glycol) are stereospecific (i.e., both the epoxidation step and the acid-catalyzed hydrolysis), the net result is a stereospecific anti 1,2-dihydroxylation of the double bond (Fig. 11.3).

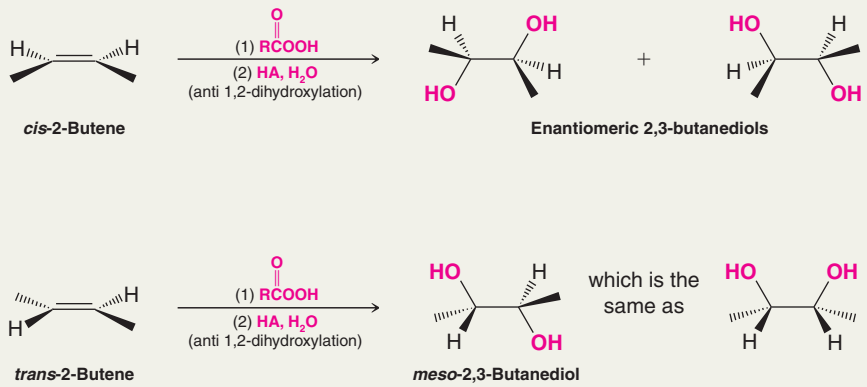
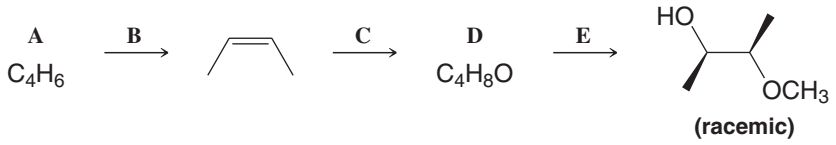
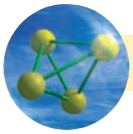


Figure 11.3 The overall result of epoxidation followed by acid-catalyzed hydrolysis is a stereospecific anti 1,2-dihydroxylation of the double bond. *cis*-2-Butene yields the enantiomeric 2,3-butanediols; *trans*-2-butene yields the meso compound.

Supply the missing reagents and intermediates **A–E**.

Review Problem 11.23



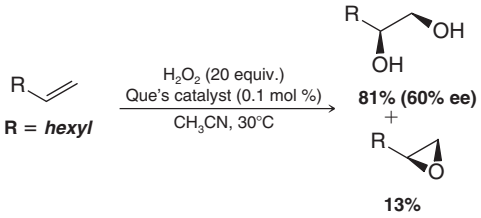


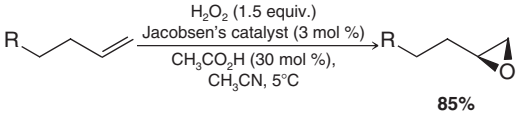
THE CHEMISTRY OF. . .

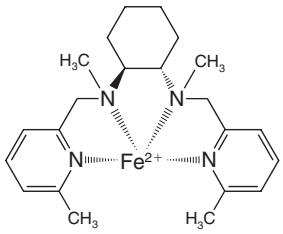
Environmentally Friendly Alkene Oxidation Methods

The effort to develop synthetic methods that are environmentally friendly is a very active area of chemistry research. The push to devise "green chemistry" procedures includes not only replacing the use of potentially hazardous or toxic reagents with ones that are more friendly to the environment but also developing catalytic procedures that use smaller quantities of potentially harmful reagents when other alternatives are not available. The catalytic syn 1,2-dihydroxylation methods that we described in Section 8.16 (including the Sharpless asymmetric dihydroxylation procedure) are environmentally friendly modifications of the original procedures because they require only a small amount of OsO_4 or other heavy metal oxidant.

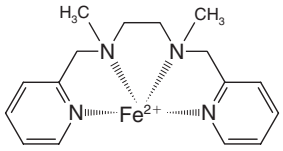
Nature has provided hints for ways to carry out environmentally sound oxidations as well. The enzyme methane monooxygenase (MMO) uses iron to catalyze hydrogen peroxide oxidation of small hydrocarbons, yielding alcohols or epoxides, and this example has inspired development of new laboratory methods for alkene oxidation. A 1,2-dihydroxylation procedure developed by L. Que (University of Minnesota) yields a mixture of 1,2-diols and epoxides by action of an iron catalyst and hydrogen peroxide on an alkene. (The ratio of diol to epoxide formed depends on the reaction conditions, and in the case of dihydroxylation, the procedure shows some enantioselectivity.) Another green reaction is the epoxidation method developed by E. Jacobsen (Harvard University). Jacobsen's procedure uses hydrogen peroxide and a similar iron catalyst to epoxidize alkenes (without the complication of diol formation). Que's and Jacobsen's methods are environmentally friendly because their procedures employ catalysts containing a nontoxic metal, and an inexpensive, relatively safe oxidizing reagent is used that is converted to water in the course of the reaction.







Que's catalyst

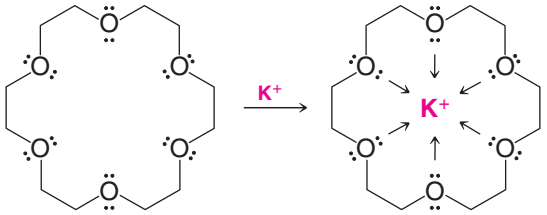


Jacobsen's catalyst

The quest for more methods in green chemistry, with benign reagents and by-products, catalytic cycles, and high yields, will no doubt drive further research by present and future chemists. In coming chapters we shall see more examples of green chemistry in use or under development.

11.16 Crown Ethers

Crown ethers are compounds having structures like that of 18-crown-6, below. 18-Crown-6 is a cyclic oligomer of ethylene glycol. Crown ethers are named as *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. A key property of crown ethers is that they are able to bind cations, as shown below for 18-crown-6 and a potassium ion.

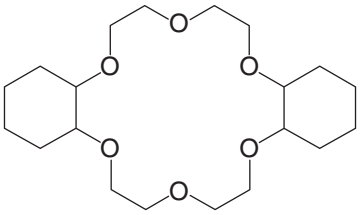


18-Crown-6

Crown ethers render many salts soluble in nonpolar solvents. For this reason they are called **phase transfer catalysts**. When a crown ether coordinates with a metal cation it masks the ion with a hydrocarbon-like exterior. 18-Crown-6 coordinates very effectively with potassium ions because the cavity size is correct and because the six oxygen atoms are ideally situated to donate their electron pairs to the central ion in a Lewis acid–base complex.

The relationship between a crown ether and the ion it binds is called a **host–guest relationship**.

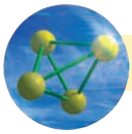
Salts such as KF, KCN, and potassium acetate can be transferred into aprotic solvents using catalytic amounts of 18-crown-6. Use of a crown ether with a nonpolar solvent can be very favorable for an S_N2 reaction because the nucleophile (such as F^-, CN^-, or acetate from the compounds just listed) is unencumbered by solvent in an aprotic solvent, while at the same time the cation is prevented by the crown ether from associating with the nucleophile. Dicyclohexano-18-crown-6 is another example of a phase transfer catalyst. It is even more soluble in nonpolar solvents than 18-crown-6 due to its additional hydrocarbon groups. Phase transfer catalysts can also be used for reactions such as oxidations. (There are phase transfer catalysts that are not crown ethers, as well.)



Dicyclohexano-18-crown-6

The development of crown ethers and other molecules "with structure specific interactions of high selectivity" led to awarding of the 1987 Nobel Prize in Chemistry to Charles J. Pedersen (retired from the DuPont Company), Donald J. Cram (University of California, Los Angeles, deceased 2001), and Jean-Marie Lehn (Louis Pasteur University, Strasbourg, France). Their contributions to our understanding of what is now called "molecular recognition" have implications for how enzymes recognize their substrates, how hormones cause their effects, how antibodies recognize antigens, how neurotransmitters propagate their signals, and many other aspects of biochemistry.

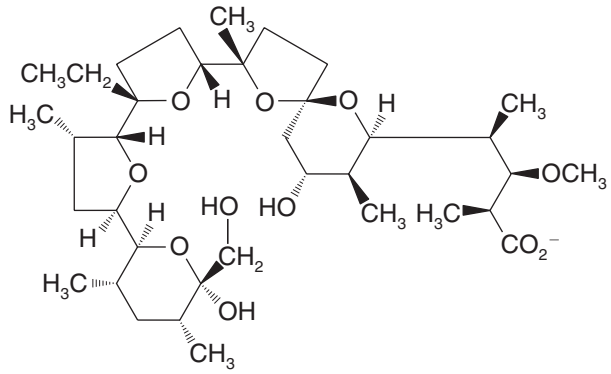
Review Problem 11.24 Write structures for (**a**) 15-crown-5 and (**b**) 12-crown-4.



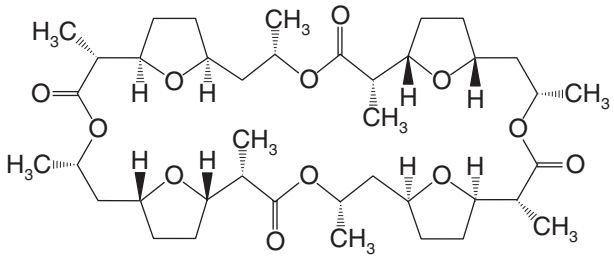
THE CHEMISTRY OF. . .

Transport Antibiotics and Crown Ethers

There are several antibiotics called ionophores. Some notable examples are monensin, nonactin, gramicidin, and valinomycin. The structures of monensin and nonactin are shown below. Ionophore antibiotics like monensin and nonactin coordinate with metal cations in a manner similar to crown ethers. Their mode of action has to do with disrupting the natural gradient of ions on each side of the cell membrane.



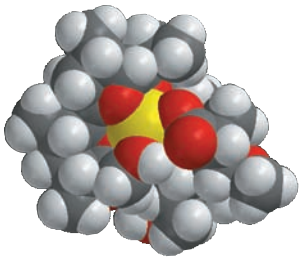
Monensin



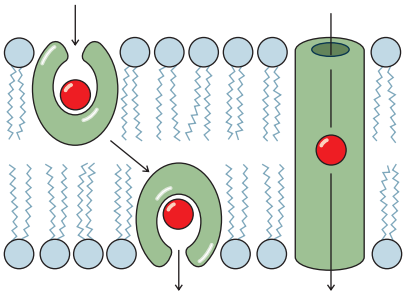
Nonactin

The cell membrane, in its interior, is like a hydrocarbon because it consists in this region primarily of the hydrocarbon portions of lipids (Chapter 23). Normally, cells must maintain a gradient between the concentrations of sodium and potassium ions inside and outside the cell membrane. Potassium ions are "pumped" in, and sodium ions are pumped out. This gradient is essential to the functions of nerves, transport of nutrients into the cell, and maintenance of proper cell volume. The biochemical transport of sodium and potassium ions through the cell membrane is slow, and requires an expenditure of energy by the cell. (The 1997 Nobel Prize in Chemistry was awarded in part for work regarding sodium and potassium cell membrane transport.*)

Monensin is called a carrier ionophore because it binds with sodium ions and carries them across the cell membrane. Gramicidin and valinomycin are channel-forming antibiotics because they open pores that extend through the membrane. The ion-trapping ability of monensin results principally from its many ether functional groups, and as such, it is an example of a polyether antibiotic. Its oxygen atoms bind with sodium ions by Lewis acid–base interactions, forming the octahedral complex shown here in the molecular model. The complex is a hydrophobic "host" for the cation that allows it to be carried as a "guest" of monensin from one side of the cell membrane to the other. The transport process destroys the critical sodium concentration gradient needed for cell function. Nonactin is another ionophore that upsets the concentration gradient by binding strongly to potassium ions, allowing the membrane to be permeable to potassium ions, also destroying the essential concentration gradient.



The ionophore antibiotic monensin complexed with a sodium cation.



Carrier (left) and channel-forming modes of transport ionophores. (Reprinted with permission of John Wiley & Sons, Inc. from Voet, D. and Voet, J. G. *Biochemistry*, Second Edition. © 1995 Voet, D. and Voet, J. G.)

*Discovery and characterization of the actual molecular pump that establishes the sodium and potassium concentration gradient (Na^+,K^+-ATPase) earned Jens Skou (Aarhus University, Denmark) half of the 1997 Nobel Prize in Chemistry. The other half went to Paul D. Boyer (UCLA) and John E. Walker (Cambridge) for elucidating the enzymatic mechanism of ATP synthesis.

11.17 Summary of Reactions of Alkenes, Alcohols, and Ethers

Helpful Hint

Some tools for synthesis.

We have studied reactions in this chapter and in Chapter 8 that can be extremely useful in designing syntheses. Most of these reactions involving alcohols and ethers are summarized in Fig. 11.4 on the last page of the chapter, after the Problems.

- We can use alcohols to make alkyl halides, sulfonate esters, ethers, and alkenes.
- We can oxidize alkenes to make epoxides, diols, aldehydes, ketones, and carboxylic acids (depending on the specific alkene and conditions).
- We can use alkenes to make alkanes, alcohols, and alkyl halides.
- If we have a terminal alkyne, such as could be made from an appropriate vicinal dihalide, we can use the alkynide anion derived from it to form carbon–carbon bonds by nucleophilic substitution.

All together, we have a repertoire of reactions that can be used to directly or indirectly interconvert almost all of the functional groups we have studied so far. In Section 11.17A we summarize some reactions of alkenes.

11.17A How Alkenes Can Be Used in Synthesis

- Alkenes are an entry point to virtually all of the other functional groups that we have studied.

For this reason, and because many of the reactions afford us some degree of control over the regiochemical and/or stereochemical form of the products, alkenes are versatile intermediates for synthesis.

- We have two methods to **hydrate a double bond in a Markovnikov orientation**: (1) *oxymercuration–demercuration* (Section 8.6), and (2) *acid-catalyzed hydration* (Section 8.5).

Of these methods oxymercuration–demercuration is the most useful in the laboratory because it is easy to carry out and *is not accompanied by rearrangements*.

- We can **hydrate a double bond in an anti-Markovnikov orientation** by *hydroboration–oxidation* (Section 8.7). With hydroboration–oxidation we can also achieve a *syn addition of the* H— *and* —OH *groups*.

Remember, too, **the boron group of an organoborane can be replaced by hydrogen, deuterium, or tritium** (Section 8.11), and that hydroboration, itself, involves a *syn addition of* H— *and* —B—.

- We can **add HX to a double bond in a Markovnikov sense** (Section 8.2) using HF, HCl, HBr, or HI.
- We can **add HBr in an anti-Markovnikov orientation** (Section 10.9), by treating an alkene with HBr *and a peroxide*. (The other hydrogen halides do not undergo anti-Markovnikov addition when peroxides are present.)
- We can **add bromine or chlorine to a double bond** (Section 8.12) and the addition is an *anti addition* (Section 8.13).
- We can also **add X— and —OH** to a double bond (i.e., synthesize a halohydrin) by carrying out a bromination or chlorination in water (Section 8.14). This addition, too, is an *anti addition*.
- We can carry out a **syn 1,2-dihydroxylation of a double bond** using either $KMnO_4$ in cold, dilute, and basic solution or OsO_4 followed by $NaHSO_3$ (Section 8.16). Of these two methods, the latter is preferable because of the tendency of $KMnO_4$ to overoxidize the alkene and cause cleavage at the double bond.

- We can carry out **anti 1,2-dihydroxylation of a double bond** by converting the alkene to an *epoxide* and then carrying out an acid-catalyzed hydrolysis (Section 11.15).

Equations for most of these reactions are given in the Synthetic Connections reviews for Chapters 7 and 8 and this chapter.

Key Terms and Concepts

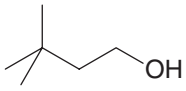
The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

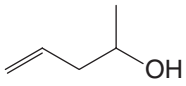
Problems

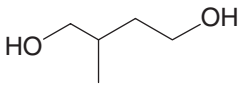
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

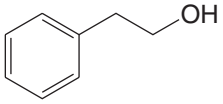
NOMENCLATURE

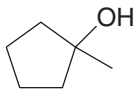
11.25 Give an IUPAC substitutive name for each of the following alcohols:

(a) 

(b) 

(c) 

(d) 

(e) 

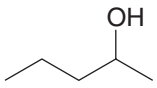
(f) 

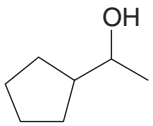
11.26 Write structural formulas for each of the following:

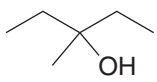
(a) (*Z*)-But-2-en-1-ol
(b) (*R*)-Butane-1,2,4-triol
(c) (1*R*,2*R*)-Cyclopentane-1,2-diol
(d) 1-Ethylcyclobutanol
(e) 2-Chlorohex-3-yn-1-ol
(f) Tetrahydrofuran
(g) 2-Ethoxypentane
(h) Ethyl phenyl ether
(i) Diisopropyl ether
(j) 2-Ethoxyethanol

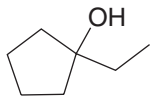
REACTIONS AND SYNTHESIS

11.27 Provide the alkene needed to synthesize each of the following by oxymercuration–demercuration.

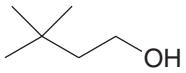
(a) 

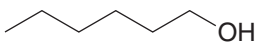
(b) 

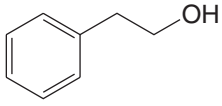
(c) 

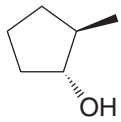
(d) 

11.28 Provide the alkene needed to synthesize each of the following by hydroboration–oxidation.

(a) 

(b) 

(c) 

(d) 

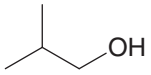
11.29 Starting with each of the following, outline a practical synthesis of 1-butanol:

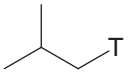
(a) 1-Butene **(b)** 1-Chlorobutane **(c)** 2-Chlorobutane **(d)** 1-Butyne

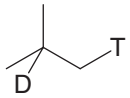
11.30 Show how you might prepare 2-bromobutane from

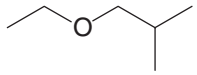
(a) 2-Butanol **(b)** 1-Butanol **(c)** 1-Butene **(d)** 1-Butyne

11.31 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following (T = tritium, D = deuterium):

(a) 

(b) 

(c) 

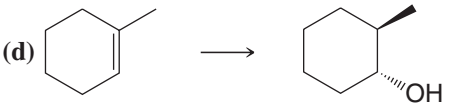
(d) 

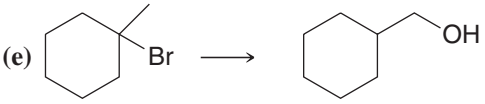
11.32 Show how you might carry out the following transformations:

(a) 

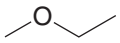
(b) 

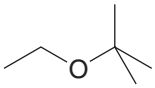
(c) 

(d) 

(e) 

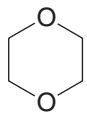
11.33 What compounds would you expect to be formed when each of the following ethers is refluxed with excess concentrated hydrobromic acid?

(a) 

(b) 

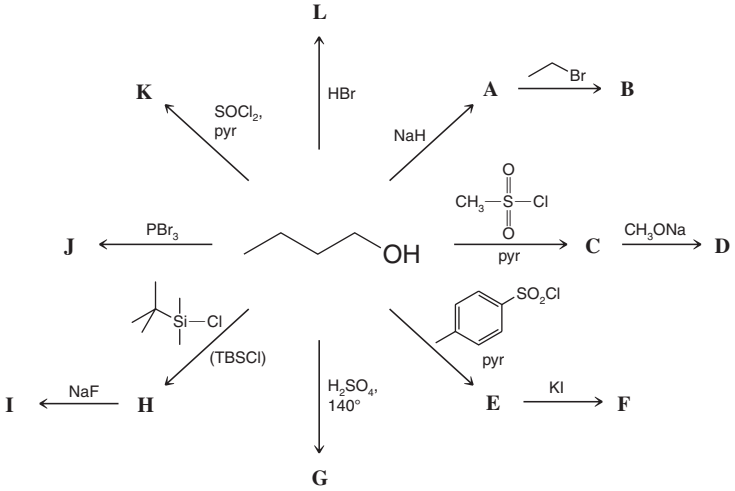
(c) 

(THF)

(d) 

(1,4-dioxane)

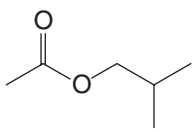
11.34 Considering **A–L** to represent the major products formed in each of the following reactions, provide a structure for each of **A** through **L**. If more than one product can reasonably be conceived from a given reaction, include those as well.

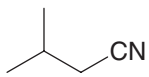


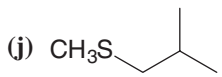
11.35 Write structures for the products that would be formed under the conditions in Problem 11.34 if cyclopentanol had been used as the starting material. If more than one product can reasonably be conceived from a given reaction, include those as well.

11.36 Starting with isobutane, show how each of the following could be synthesized. (You need not repeat the synthesis of a compound prepared in an earlier part of this problem.)

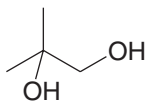
(a) *tert*-Butyl bromide
(b) 2-Methylpropene
(c) Isobutyl bromide
(d) Isobutyl iodide
(e) Isobutyl alcohol (two ways)
(f) *tert*-Butyl bromide
(g) Isobutyl methyl ether

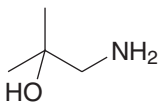
(h) 

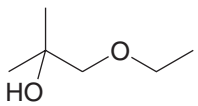
(i) 

(j) 

(k) 

(l) 

(m) 

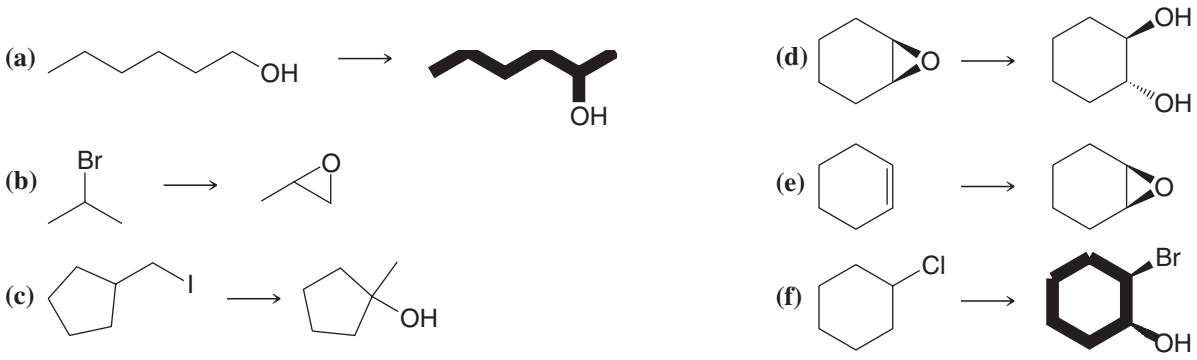
(n) 

11.37 Outlined below is a synthesis of the gypsy moth sex attractant disparlure (a pheromone). Give the structure of disparlure and intermediates **A–D**.

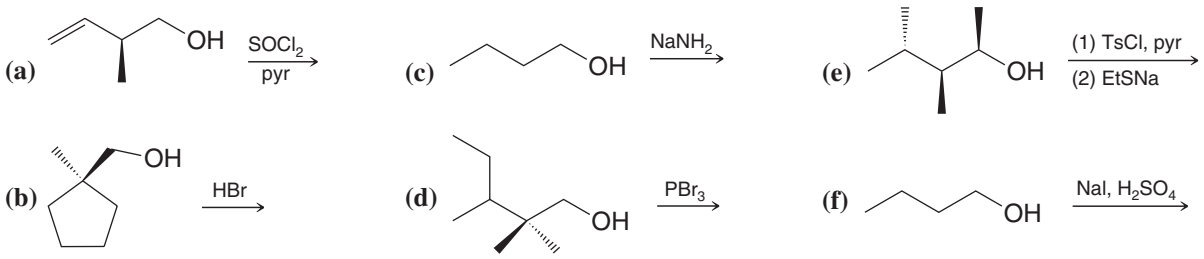
$$HC{\equiv}CNa \xrightarrow[\text{liq. } NH_3]{\text{1-bromo-5-methylhexane}} \mathbf{A}\ (C_9H_{16}) \xrightarrow[\text{liq. } NH_3]{NaNH_2} \mathbf{B}\ (C_9H_{15}Na)$$

$$\xrightarrow{\text{1-bromodecane}} \mathbf{C}\ (C_{19}H_{36}) \xrightarrow[Ni_2B\ (P\text{-}2)]{H_2} \mathbf{D}\ (C_{19}H_{38}) \xrightarrow{\text{MCPBA}} \textbf{Disparlure}\ (C_{19}H_{38}O)$$

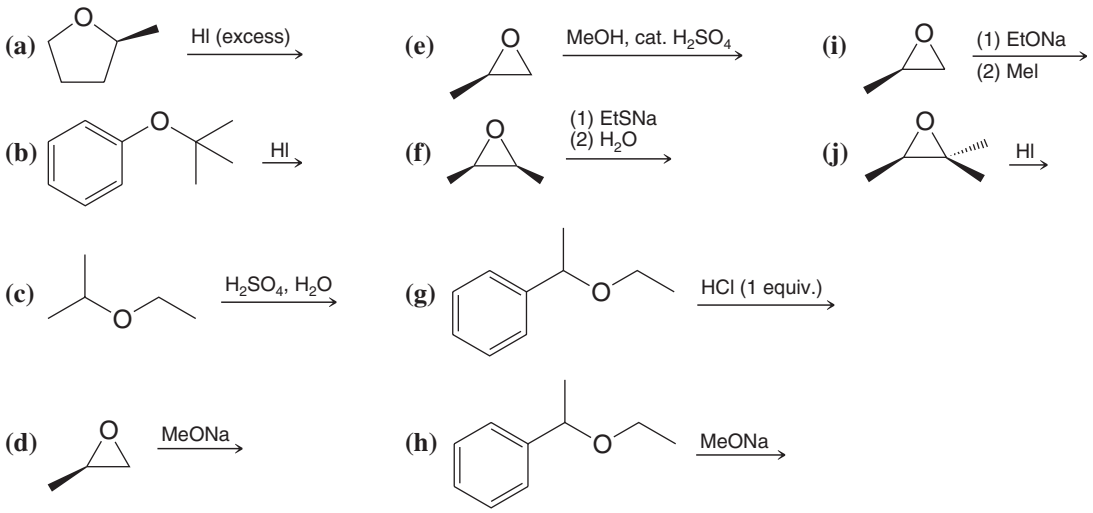
11.38 Provide the reagents necessary for the following syntheses. More than one step may be required.



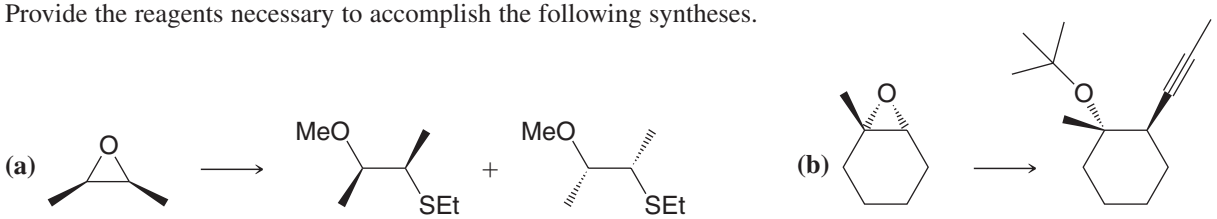
11.39 Predict the major product from each of the following reactions.

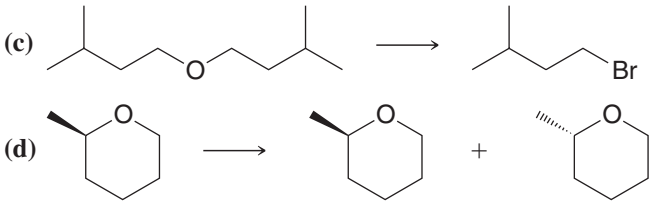


11.40 Predict the products from each of the following reactions.

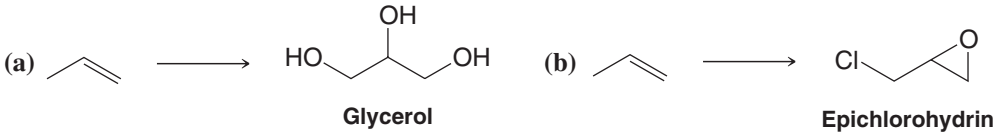


11.41 Provide the reagents necessary to accomplish the following syntheses.

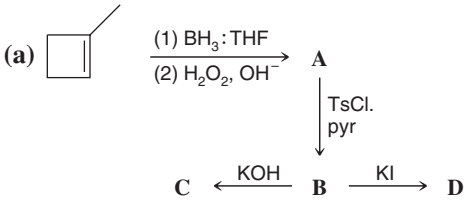




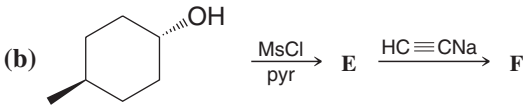
11.42 Provide reagents that would accomplish the follwing syntheses.

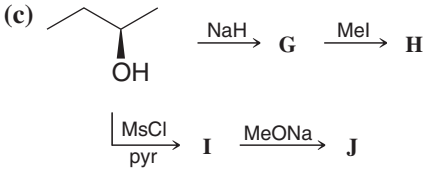


11.43 Write structures for compounds **A–J** showing stereochemistry where appropriate.



What is the stereochemical relationship between **A** and **C**?

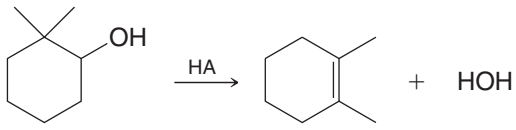




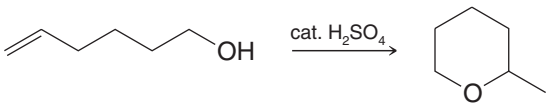
What is the stereochemical relationship between **H** and **J**?

MECHANISMS

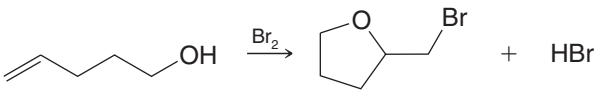
11.44 Write a mechanism that accounts for the following reaction:



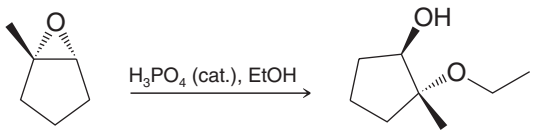
11.45 Propose a reasonable mechanism for the following reaction.



11.46 Propose a reasonable mechanism for the following reaction.

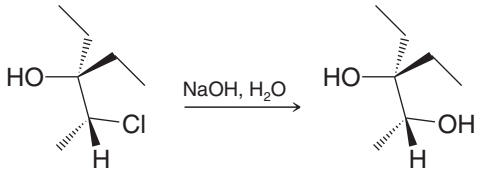


11.47 Propose a reasonable mechanism for the following reaction.

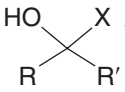


11.48 Vicinal halo alcohols (halohydrins) can be synthesized by treating epoxides with HX. (**a**) Show how you would use this method to synthesize 2-chlorocyclopentanol from cyclopentene. (**b**) Would you expect the product to be *cis*-2-chlorocyclopentanol or *trans*-2-chlorocyclopentanol; that is, would you expect a net syn addition or a net anti addition of —Cl and —OH? Explain.

11.49 Base-catalyzed hydrolysis of the 1,2-chlorohydrin **1** is found to give a chiral glycol **2** with retention of configuration. Propose a reasonable mechanism that would account for this transformation. Include all formal charges and arrows showing the movement of electrons.

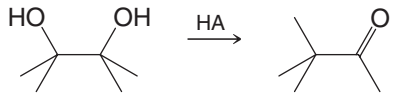


1 **2**

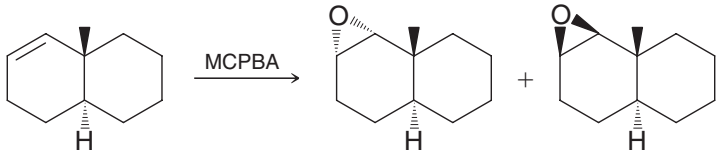
11.50 Compounds of the type 

, called α-haloalcohols, are unstable and cannot be isolated. Propose a mechanistic explanation for why this is so.

11.51 While simple alcohols yield alkenes on reaction with dehydrating acids, diols form carbonyl compounds. Rationalize mechanistically the outcome of the following reaction:



11.52 When the bicyclic alkene **I**, a *trans*-decalin derivative, reacts with a peroxy acid, **II** is the major product. What factor favors the formation of **II** in preference to **III**? (You may find it helpful to build a handheld molecular model.)



I **II (major)** **III (minor)**

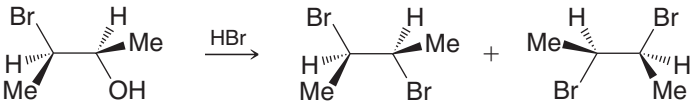
11.53 Use Newman projection formulas for ethylene glycol (1,2-ethanediol) and butane to explain why the gauche conformer of ethylene glycol is expected to contribute more to its ensemble of conformers than would the gauche conformer of butane to its respective set of conformers.

Challenge Problems

11.54 When the 3-bromo-2-butanol with the stereochemical structure **A** is treated with concentrated HBr, it yields *meso*-2,3-dibromobutane; a similar reaction of the 3-bromo-2-butanol **B** yields (±)-2,3-dibromobutane. This classic experiment performed in 1939 by S. Winstein and H. J. Lucas was the starting point for a series of investigations of what are called *neighboring group effects*. Propose mechanisms that will account for the stereochemistry of these reactions.

A **2,3-Dibromobutane (meso)**

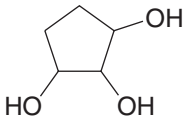
versus



B **2,3-Dibromobutane (racemic)**

11.55 Reaction of an alcohol with thionyl chloride in the presence of a tertiary amine (e.g., pyridine) affords replacement of the OH group by Cl *with inversion of configuration* (Section 11.9). However, if the amine is omitted, the result is usually replacement with retention of configuration. The same chlorosulfite intermediate is involved in both cases. Suggest a mechanism by which this intermediate can give the chloro product without inversion.

11.56 Draw all of the stereoisomers that are possible for 1,2,3-cyclopentanetriol. Label their chirality centers and say which are enantiomers and which are diastereomers.



[*Hint*: Some of the isomers contain a "pseudoasymmetric center," one that has two possible configurations, each affording a different stereoisomer, each of which is identical to its mirror image. Such stereoisomers can only be distinguished by the order of attachment of ***R*** versus ***S*** groups at the pseudoasymmetric center. Of these the ***R*** group is given higher priority than the ***S***, and this permits assignment of configuration as ***r*** or ***s***, lowercase letters being used to designate the pseudoasymmetry.]

11.57 Dimethyldioxirane (DMDO), whose structure is shown below, is another reagent commonly used for alkene epoxidation. Write a mechanism for the epoxidation of (*Z*)-2-butene by DMDO, including a possible transition state structure. What is the by-product of a DMDO epoxidation?

Dimethyldioxirane (DMDO)

11.58 Two configurations can actually be envisioned for the transition state in the DMDO epoxidation of (*Z*)-2-butene, based on analogy with geometric possibilities fitting within the general outline for the transition state in a peroxycarboxylic acid epoxidation of (*Z*)-2-butene. Draw these geometries for the DMDO epoxidation of (*Z*)-2-butene. Then, open the molecular models on the book's website for these two possible transition state geometries in the DMDO epoxidation of (*Z*)-2-butene and speculate as to which transition state would be lower in energy.

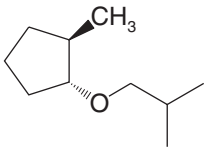
Learning Group Problems

1. Devise two syntheses for *meso*-2,3-butanediol starting with acetylene (ethyne) and methane. Your two pathways should take different approaches during the course of the reactions for controlling the origin of the stereochemistry required in the product.

2. **(a)** Write as many chemically reasonable syntheses as you can think of for ethyl 2-methylpropyl ether (ethyl isobutyl ether). Be sure that at some point in one or more of your syntheses you utilize the following reagents (not all in the same synthesis, however): PBr_3, $SOCl_2$, *p*-toluenesulfonyl chloride (tosyl chloride), NaH, ethanol, 2-methyl-1-propanol (isobutyl alcohol), concentrated H_2SO_4, $Hg(OAc)_2$, ethene (ethylene).

(b) Evaluate the relative merits of your syntheses on the basis of selectivity and efficiency. [Decide which ones could be argued to be the "best" syntheses and which might be "poorer" syntheses.]

3. Synthesize the compound shown below from methylcyclopentane and 2-methylpropane using those compounds as the source of the carbon atoms and any other reagents necessary. Synthetic tools you might need include Markovnikov or anti-Markovnikov hydration, Markovnikov or anti-Markovnikov hydrobromination, radical halogenation, elimination, and nucleophilic substitution reactions.



Summary and Review Tools

Some Synthetic Connections of Alkenes, Alkynes, Alcohols, Alkyl Halides, and Ethers

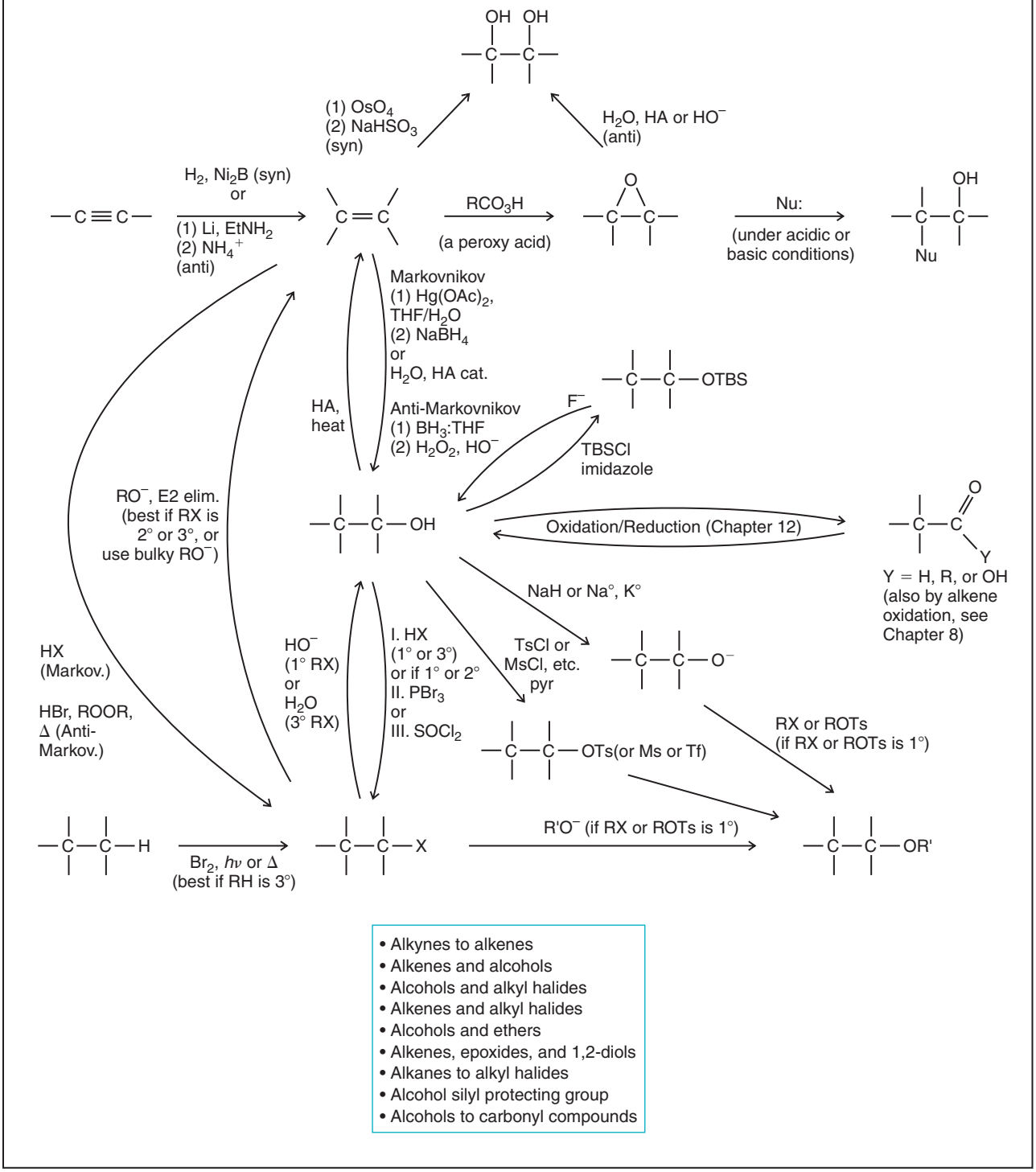
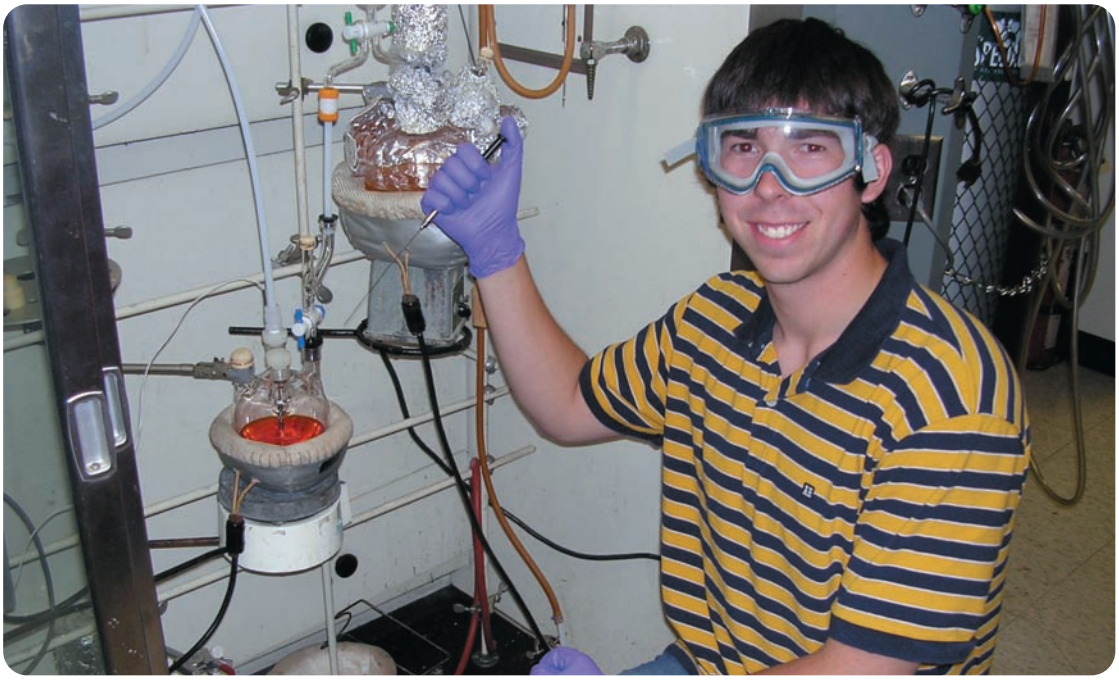


Figure 11.4 Some synthetic connections of alkynes, alkenes, alcohols, alkyl halides, and ethers.

12

Alcohols from Carbonyl Compounds

Oxidation–Reduction and Organometallic Compounds



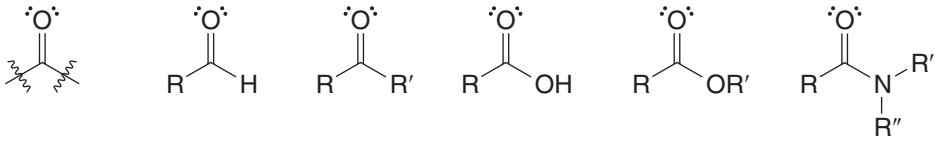
Some reactions with carbonyl compounds involve reagents that we transfer by syringe to keep them away from moisture and air.

Ask an organic chemist about their favorite functional group, and many will probably name a group that contains a carbonyl group. Why? Because carbonyl groups are at the heart of many key functional groups such as aldehydes, ketones, carboxylic acids, amides, and others. The carbonyl group is also very versatile. It serves as a nexus for interconversions between a number of functional groups. Add to these factors that reactions of carbonyl groups include two fascinating and related mechanistic pathways—nucleophilic addition and nucleophilic addition–elimination—and you have one blockbuster group in terms of its chemistry.

Another important aspect of carbonyl groups is that many natural and synthetic compounds contain them. We have previously mentioned a few, such as vanillin, androsterone, and others. Carbonyl groups are intrinsic to synthetic materials such as nylon and certain other polymers, as well. And, carbonyl groups are central to the organic chemistry of life, as well, which we shall see later when we discuss carbohydrates and other aspects of biological chemistry. Now, therefore, is a good time to introduce you to some methods for interconverting carbonyl compounds with alcohols, and how we can use carbonyl compounds for carbon–carbon bond-forming reactions with organometallic reagents. This will prepare us for delving into other aspects of carbonyl chemistry later in the book. We begin with an introduction and some review.

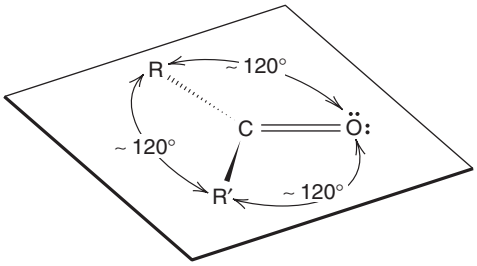
12.1 Structure of the Carbonyl Group

Carbonyl compounds are a broad group of compounds that includes aldehydes, ketones, carboxylic acids, esters, and amides.

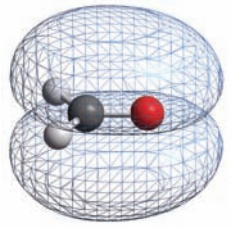


The carbonyl group | **An aldehyde** | **A ketone** | **A carboxylic acid** | **An ester** | **An amide**

The carbonyl carbon atom is sp^2 hybridized; thus it and the three atoms attached to it lie in the same plane. The bond angles between the three attached atoms are what we would expect of a trigonal planar structure; they are approximately 120°:



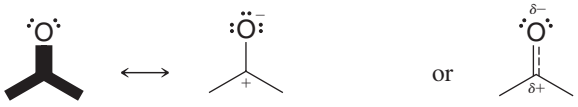
The carbon–oxygen double bond consists of two electrons in a σ bond and two electrons in a π bond. The π bond is formed by overlap of the carbon p orbital with a p orbital from the oxygen atom. The electron pair in the π bond occupies both lobes (above and below the plane of the σ bonds).



The π bonding molecular orbital of formaldehyde (HCHO). The electron pair of the π bond occupies both lobes.

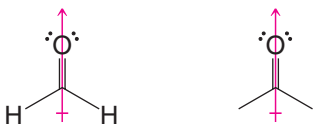
- The more electronegative oxygen atom strongly attracts the electrons of both the σ bond and the π bond, causing the carbonyl group to be highly polarized; the carbon atom bears a substantial positive charge and the oxygen atom bears a substantial negative charge.

Polarization of the π bond can be represented by the following resonance structures for the carbonyl group:

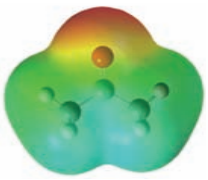


Resonance structures for the carbonyl group | **Hybrid**

Evidence for the polarity of the carbon–oxygen bond can be found in the rather large dipole moments associated with carbonyl compounds.



Formaldehyde $\mu = 2.27$ D | **Acetone** $\mu = 2.88$ D

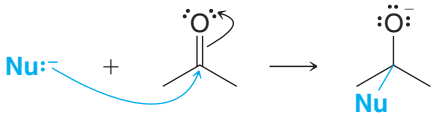


An electrostatic potential map for acetone indicates the polarity of the carbonyl group.

12.1A Reactions of Carbonyl Compounds with Nucleophiles

One of the most important reactions of carbonyl compounds is **nucleophilic addition** to the carbonyl group. The carbonyl group is susceptible to nucleophilic attack because, as we have just seen, the carbonyl carbon bears a partial positive charge.

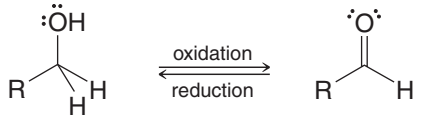
- When a nucleophile adds to the carbonyl group, it uses an electron pair to form a bond to the carbonyl carbon atom and an electron pair from the carbon–oxygen double bond shifts out to the oxygen:



As the reaction takes place, the carbon atom undergoes a change from trigonal planar geometry and sp^2 hybridization to tetrahedral geometry and sp^3 hybridization.

- Two important nucleophiles that add to carbonyl compounds are **hydride ions** from compounds such as $NaBH_4$ or $LiAlH_4$ (Section 12.3) and **carbanions** from compounds such as RLi or RMgX (Section 12.7C).

Another related set of reactions are reactions in which alcohols and carbonyl compounds are **oxidized** and **reduced** (Sections 12.2–12.4). For example, primary alcohols can be oxidized to aldehydes, and aldehydes can be reduced to alcohols:



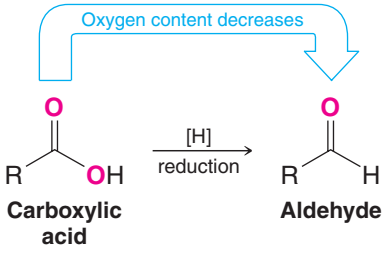
A primary alcohol **An aldehyde**

Let us begin by examining some general principles that apply to the oxidation and reduction of organic compounds.

12.2 Oxidation–Reduction Reactions in Organic Chemistry

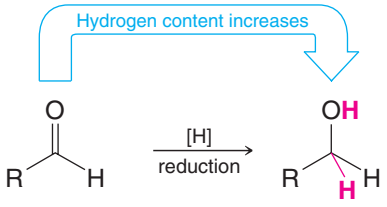
- **Reduction** of an organic molecule usually corresponds to increasing its hydrogen content or to decreasing its oxygen content.

For example, converting a carboxylic acid to an aldehyde is a reduction because the oxygen content is decreased:

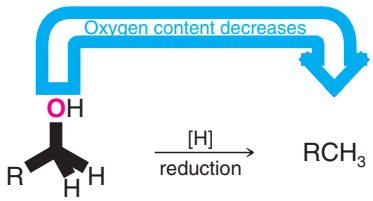


Carboxylic acid **Aldehyde**

Converting an aldehyde to an alcohol is a reduction:



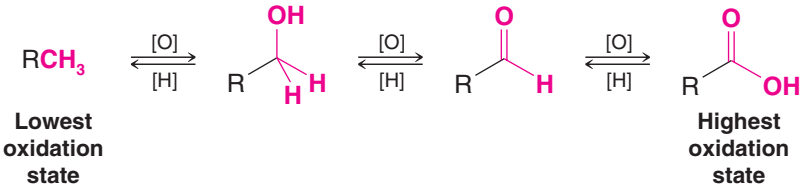
Converting an alcohol to an alkane is also a reduction:



In these examples we have used the symbol [H] to indicate that a reduction of the organic compound has taken place. We do this when we want to write a general equation without specifying what the reducing agent is.

- The opposite of reduction is **oxidation**. Increasing the oxygen content of an organic molecule or decreasing its hydrogen content is an **oxidation**.

The reverse of each reaction that we have just given is an oxidation of the organic molecule, and we can summarize these oxidation–reduction reactions as shown below. We use the symbol [O] to indicate in a general way that the organic molecule has been oxidized.

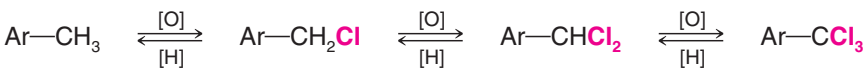


Helpful Hint

Note the general interpretation of oxidation–reduction regarding organic compounds.

- Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon.

For example, replacing hydrogen atoms by chlorine atoms is an oxidation:



Of course, when an organic compound is reduced, something else—the **reducing agent**—must be oxidized. And when an organic compound is oxidized, something else—the **oxidizing agent**—is reduced. These oxidizing and reducing agents are often inorganic compounds, and in the next two sections we shall see what some of them are.

12.2A Oxidation States in Organic Chemistry

One method for assigning oxidation states in organic compounds is similar to the method we used for assigning formal charges (Section 1.7). We base the assignment on **the groups attached to the carbon (or carbons) whose oxidation state undergoes change in the reaction we are considering**. Recall that with formal charges we assumed that electrons in covalent bonds are shared equally. *When assigning oxidation states to carbon atoms we assign electrons to the more electronegative element* (see Section 1.4A and Table 1.2). For example, a bond to hydrogen (or to any atom less electronegative than carbon) makes that carbon negative by one unit (−1), and a bond to oxygen, nitrogen, or a halogen (F, Cl, and Br) makes the carbon positive by one unit (+1). A bond to another carbon does not change its oxidation state.

Using this method the carbon atom of methane, for example, is assigned an oxidation state of −4, and that of carbon dioxide, +4.

Helpful Hint

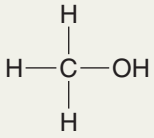
A method for balancing organic oxidation–reduction reactions is described in the Study Guide that accompanies this text.

Solved Problem 12.1

Using the method just described, assign oxidation states to the carbon atoms of methanol (CH_3OH), formaldehyde ($HCHO$), and formic acid (HCO_2H) and arrange these compounds along with carbon dioxide and methane (see above) in order of increasing oxidation state.

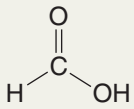
(continues on the next page)

STRATEGY AND ANSWER We calculate the oxidation state of each carbon based on the number of bonds it is forming to atoms more (or less) electronegative than carbon.



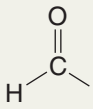
Bonds to C
3 to H = −3
1 to O = +1
Total = −2
= Oxid. state of C

Methanol



Bonds to C
1 to H = −1
3 to O = +3
Total = +2
= Oxid. state of C

Formic acid



Bonds to C
2 to H = −2
2 to O = +2
Total = 0
= Oxid. state of C

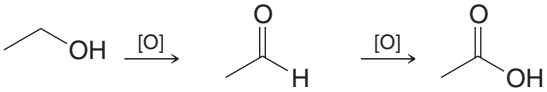
Formaldehyde

The order overall, based on the oxidation state of carbon in each compound, is

$$CH_4 = -4 < CH_3OH = -2 < HCHO = 0 < HCOOH = +2 < CO_2 = +4$$

Lowest Oxid. state of carbon — **Highest Oxid. state of carbon**

Review Problem 12.1



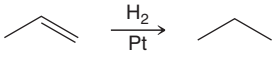
Ethanol **Acetaldehyde** **Acetic acid**

(a) Assign oxidation states to each carbon of ethanol, acetaldehyde, and acetic acid.

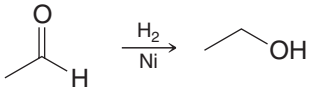
(b) What do these numbers indicate about the oxidation reactions?

Review Problem 12.2

(a) Although we have described the hydrogenation of an alkene as an addition reaction, organic chemists often refer to it as a "reduction." Use the method described in Section 12.2A for assigning oxidation states to explain this usage of the word "reduction".



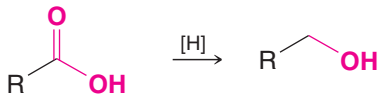
(b) Provide a similar analysis for this reaction:



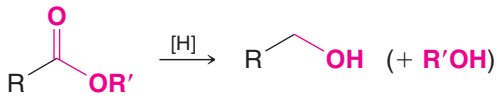
12.3 *Alcohols by Reduction of Carbonyl Compounds*

Unless special precautions are taken, lithium aluminum hydride reductions can be very dangerous. You should consult an appropriate laboratory manual before attempting such a reduction, and the reaction should be carried out on a small scale.

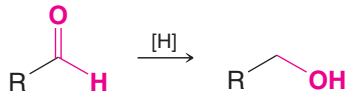
Primary and secondary alcohols can be synthesized by the reduction of a variety of compounds that contain the carbonyl group. Several general examples are shown here:



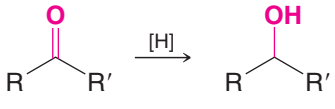
Carboxylic acid **1° Alcohol**



Ester **1° Alcohol**



Aldehyde **1° Alcohol**

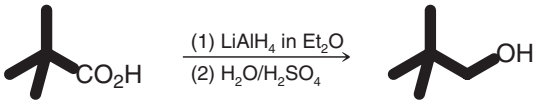


Ketone **2° Alcohol**

12.3A Lithium Aluminum Hydride

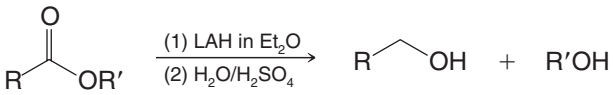
- Lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) reduces carboxylic acids and esters to primary alcohols.

An example of lithium aluminum hydride reduction is conversion of 2,2-dimethylpropanoic acid to 2,2-dimethylpropanol (neopentyl alcohol).



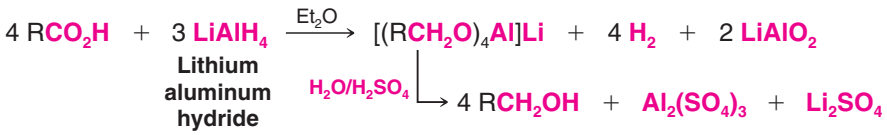
2,2-Dimethylpropanoic acid **Neopentyl alcohol (92%)**

LAH reduction of an ester yields two alcohols, one derived from the carbonyl part of the ester group, and the other from the alkoxyl part of the ester.



Carboxylic acids and esters are more difficult to reduce than aldehydes and ketones. LAH, however, is a strong enough reducing agent to accomplish this transformation. Sodium borohydride ($NaBH_4$), which we shall discuss shortly, is commonly used to reduce aldehydes and ketones, but it is not strong enough to reduce carboxylic acids and esters.

Great care must be taken when using LAH to avoid the presence of water or any other weakly acidic solvent (e.g., alcohols). **LAH reacts violently with proton donors to release hydrogen gas**. Anhydrous diethyl ether (Et_2O) is a commonly used solvent for LAH reductions. After all of the LAH has been consumed by the reduction step of the reaction, however, water and acid are added to neutralize the resulting salts and facilitate isolation of the alcohol products. The stoichiometry of the LAH reduction of a carboxylic acid is shown below.

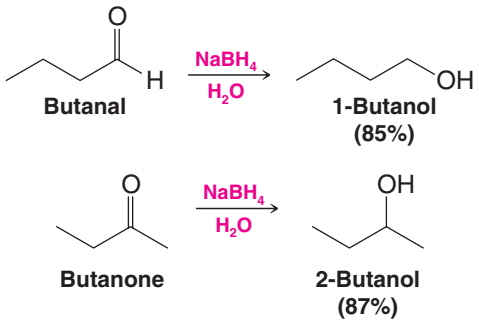


Lithium aluminum hydride

12.3B Sodium Borohydride

- Aldehydes and ketones are easily reduced by sodium borohydride ($NaBH_4$).

Sodium borohydride is usually preferred over LAH for the reduction of aldehydes and ketones. Sodium borohydride can be used safely and effectively in water as well as alcohol solvents, whereas special precautions are required when using LAH.

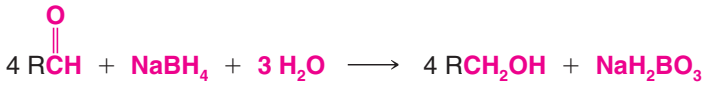


Butanal **1-Butanol (85%)**

Butanone **2-Butanol (87%)**

Aldehydes and ketones can be reduced using hydrogen and a metal catalyst, as well, and by sodium metal in an alcohol solvent.

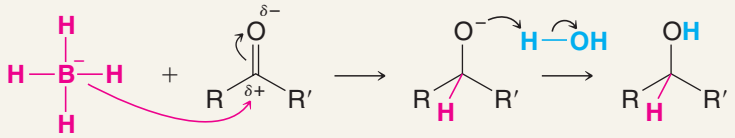
The stoichiometry of $NaBH_4$ reduction of an aldehyde (or ketone) is as follows.



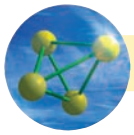
The key step in the reduction of a carbonyl compound by either lithium aluminum hydride or sodium borohydride is the transfer of a **hydride ion** from the metal to the carbonyl carbon. In this transfer the hydride ion acts as a *nucleophile*. The mechanism for the reduction of a ketone by sodium borohydride is illustrated here.

A MECHANISM FOR THE REACTION

Reduction of Aldehydes and Ketones by Hydride Transfer



These steps are repeated until all hydrogen atoms attached to boron have been transferred.

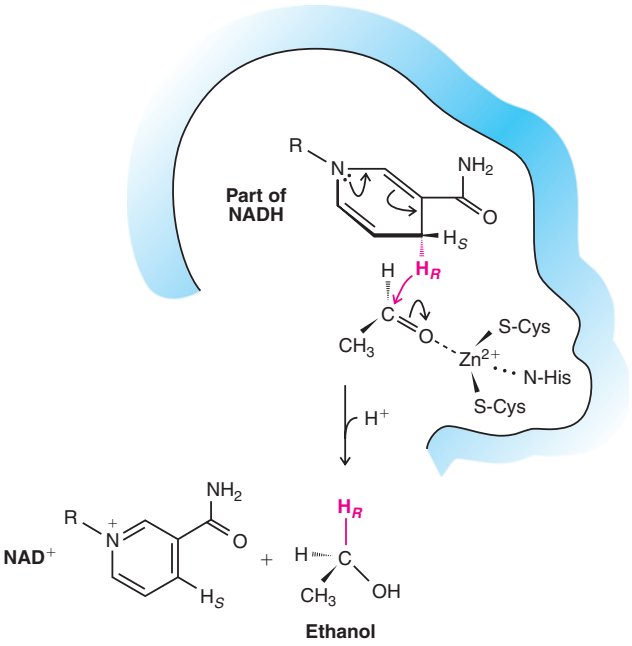


THE CHEMISTRY OF . . .

Alcohol Dehydrogenase—A Biochemical Hydride Reagent

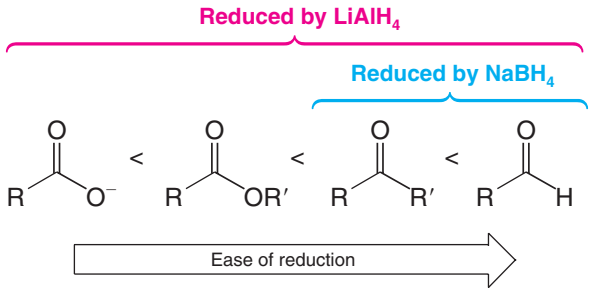
When the enzyme alcohol dehydrogenase converts acetaldehyde to ethanol, NADH acts as a reducing agent by transferring a hydride from C4 of the nicotinamide ring to the carbonyl group of acetaldehyde. The nitrogen of the nicotinamide ring facilitates this process by contributing its nonbonding electron pair to the ring, which together with loss of the hydride converts the ring to the energetically more stable ring found in NAD^+ (we shall see why it is more stable in Chapter 14). The ethoxide anion resulting from hydride transfer to acetaldehyde is then protonated by the enzyme to form ethanol.

Although the carbonyl carbon of acetaldehyde that accepts the hydride is inherently electrophilic because of its electronegative oxygen, the enzyme enhances this property by providing a zinc ion as a Lewis acid to coordinate with the carbonyl oxygen. The Lewis acid stabilizes the negative charge that develops on the oxygen in the transition state. The role of the enzyme's protein scaffold, then, is to hold the zinc ion, coenzyme, and substrate in the three-dimensional array required to lower the energy of the transition state. The reaction is entirely reversible, of course, and when the relative concentration of ethanol is high, alcohol dehydrogenase carries out the oxidation of ethanol by removal of a hydride. This role of alcohol dehydrogenase is important in detoxification. In "The Chemistry of . . . Stereoselective Reductions of Carbonyl Groups" we discuss the stereochemical aspect of alcohol dehydrogenase reactions.



12.3C Overall Summary of $LiAlH_4$ and $NaBH_4$ Reactivity

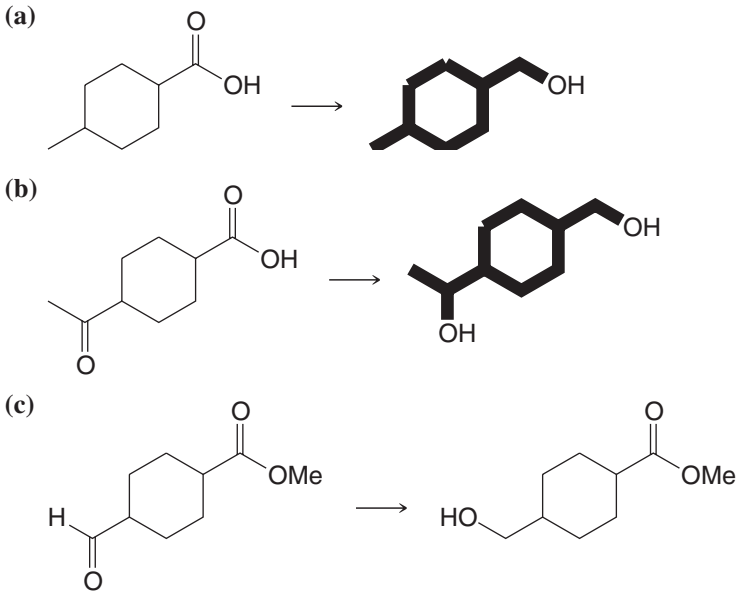
Sodium borohydride is a less powerful reducing agent than lithium aluminum hydride. Lithium aluminum hydride reduces acids, esters, aldehydes, and ketones, but sodium borohydride reduces only aldehydes and ketones:

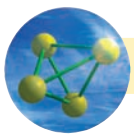


Lithium aluminum hydride reacts violently with water, and therefore reductions with lithium aluminum hydride must be carried out in anhydrous solutions, usually in anhydrous ether. (Ethyl acetate is added cautiously after the reaction is over to decompose excess $LiAlH_4$; then water is added to decompose the aluminum complex.) Sodium borohydride reductions, by contrast, can be carried out in water or alcohol solutions.

Review Problem 12.3

Which reducing agent, $LiAlH_4$ or $NaBH_4$, would you use to carry out the following transformations?





THE CHEMISTRY OF . . .

Stereoselective Reductions of Carbonyl Groups

Enantioselectivity

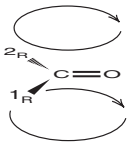
The possibility of **stereoselective** reduction of a carbonyl group is an important consideration in many syntheses. Depending on the structure about the carbonyl group that is being reduced, the tetrahedral carbon that is formed by transfer of a hydride could be a new chirality center. Achiral reagents, like $NaBH_4$ and $LiAlH_4$, react with equal rates at either face of an achiral trigonal planar substrate, leading to a racemic form of the product. But enzymes, for example, are chiral, and reactions involving a chiral reactant typically lead to a predominance of one enantiomeric form of a chiral product. Such a reaction is said to be **enantioselective**. Thus, when enzymes like alcohol dehydrogenase reduce carbonyl groups using the coenzyme NADH (see "The Chemistry of . . . Alcohol Dehydrogenase"), they discriminate between the two faces of the trigonal planar carbonyl substrate, such that a predominance of one of the two possible stereoisomeric forms of the tetrahedral product results.

(continues on the next page)

(If the original reactant was chiral, then formation of the new chirality center may result in preferential formation of one *diastereomer* of the product, in which case the reaction is said to be **diastereoselective**.)

Thermophilic bacteria, growing in hot springs like these at Yellowstone National Park, produce heat-stable enzymes called extremozymes that have proven useful for a variety of chemical processes.

The two faces of a trigonal planar center are designated *re* and *si*, according to the direction of Cahn–Ingold–Prelog priorities (Section 5.7) for the groups bonded at the trigonal center when viewed from one face or the other (*re* is clockwise, *si* is counterclockwise):

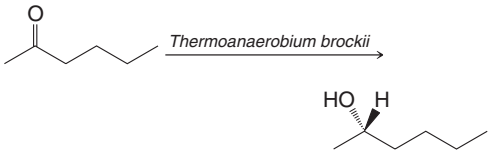


***re* face (when looking at this face, there is a clockwise sequence of priorities)**

***si* face (when looking at this face, there is a counterclockwise sequence of priorities)**

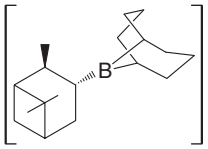
The *re* and *si* faces of a carbonyl group (where O > ^{1}R > ^{2}R in terms of Cahn-Ingold-Prelog priorities)

The preference of many NADH-dependent enzymes for either the *re* or *si* face of their respective substrates is known. This knowledge has allowed some of these enzymes to become exceptionally useful stereoselective reagents for synthesis. One of the most widely used is yeast alcohol dehydrogenase. Others that have become important are enzymes from thermophilic bacteria (bacteria that grow at elevated temperatures). Use of heat-stable enzymes (called **extremozymes**) allows reactions to be completed faster due to the rate-enhancing factor of elevated temperature (over 100 °C in some cases), although greater enantioselectivity is achieved at lower temperatures.



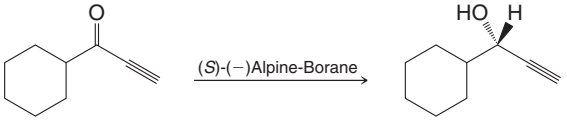
96% enantiomeric excess (85% yield)

A number of chemical reagents that are chiral have also been developed for the purpose of stereoselective reduction of carbonyl groups. Most of them are derivatives of standard aluminum or boron hydride reducing agents that involve one or more chiral organic ligands. (*S*)-Alpine-Borane and (*R*)-Alpine-Borane, for example, are reagents derived from diborane (B_2H_6) and either (−)-α-pinene or (+)-α-pinene (enantiomeric natural hydrocarbons), respectively. Reagents derived from $LiAlH_4$ and chiral amines have also been developed. The extent of stereoselectivity achieved either by enzymatic reduction or reduction by a chiral reducing agent depends on the specific structure of the substrate.



(*R*)-Alpine-Borane

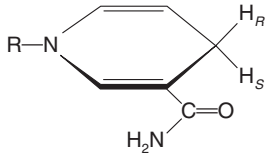
Often it is necessary to test several reaction conditions in order to achieve optimal stereoselectivity.



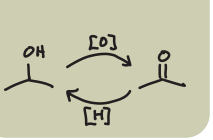
97% enantiomeric excess (60–65% yield)

Prochirality

A second aspect of the stereochemistry of NADH reactions results from NADH having two hydrogens at C4, either of which could, in principle, be transferred as a hydride in a reduction process. For a given enzymatic reaction, however, only one specific hydride from C4 in NADH is transferred. Just which hydride is transferred depends on the specific enzyme involved, and we designate it by a useful extension of stereochemical nomenclature. The hydrogens at C4 of NADH are said to be **prochiral**. We designate one **pro-*R***, and the other **pro-*S***, depending on whether the configuration would be *R* or *S* when, in our imagination, each is replaced by a group of higher priority than hydrogen. If this exercise produces the *R* configuration, the hydrogen "replaced" is pro-*R*, and if it produces the *S* configuration it is pro-*S*. In general, a **prochiral center** is one for which addition of a group to a trigonal planar atom (as in reduction of a ketone) or replacement of one of two identical groups at a tetrahedral atom leads to a new chirality center.



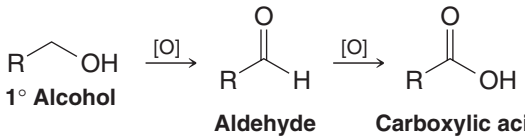
Nicotinamide ring of NADH, showing the pro-*R* and pro-*S* hydrogens



12.4 Oxidation of Alcohols

12.4A Oxidation of Primary Alcohols to Aldehydes: $RCH_2OH \longrightarrow RCHO$

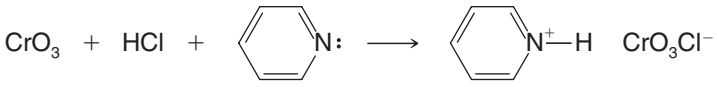
Primary alcohols can be oxidized to aldehydes and carboxylic acids:



1° Alcohol — Aldehyde — Carboxylic acid

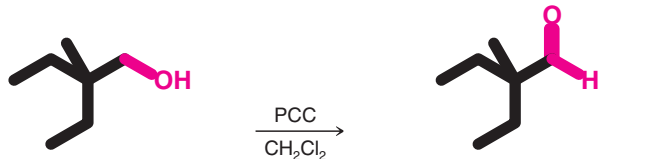
- The oxidation of aldehydes to carboxylic acids in aqueous solutions is easier than oxidation of primary alcohols to aldehydes.
- It is, therefore, difficult to stop the oxidation of a primary alcohol at the aldehyde stage unless specialized reagents are used.

An excellent reagent to use for converting a primary alcohol to an aldehyde is **pyridinium chlorochromate** (abbreviated PCC), the compound formed when CrO_3 is dissolved in hydrochloric acid and then treated with pyridine:



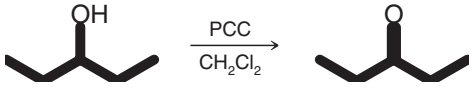
Pyridine (C_5H_5N) — Pyridinium chlorochromate (PCC)

- PCC, when dissolved in methylene chloride (CH_2Cl_2), will oxidize a primary alcohol to an aldehyde and stop at that stage:



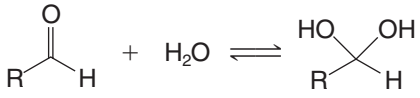
2-Ethyl-2-methyl-1-butanol — 2-Ethyl-2-methylbutanal

- PCC will also oxidize a secondary alcohol to a ketone.



Pyridinium chlorochromate does not attack double bonds.

One reason for the success of oxidation with pyridinium chlorochromate is that the oxidation can be carried out in a solvent such as CH_2Cl_2, in which PCC is soluble. Aldehydes themselves are not nearly so easily oxidized as are the *aldehyde hydrates*, $RCH(OH)_2$, that form (Section 16.7A) when aldehydes are dissolved in water, the usual medium for oxidation by chromium compounds:

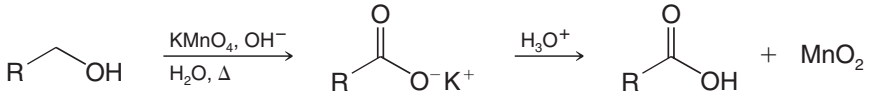


We explain this further in Section 12.4D.

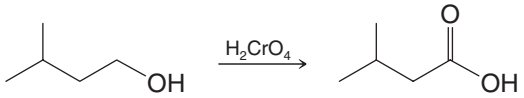
12.4B Oxidation of Primary Alcohols to Carboxylic Acids: $RCH_2OH \longrightarrow RCO_2H$

- Primary alcohols can be oxidized to **carboxylic acids** by potassium permanganate ($KMnO_4$), or chromic acid (H_2CrO_4).

(Both $KMnO_4$ and H_2CrO_4 can also be used to oxidize a secondary alcohol to a ketone, as we shall see in Section 12.4C.) The reaction with $KMnO_4$ is usually carried out in basic aqueous solution, from which MnO_2 precipitates as the oxidation takes place. After the oxidation is complete, filtration allows removal of the MnO_2 and acidification of the filtrate gives the carboxylic acid:

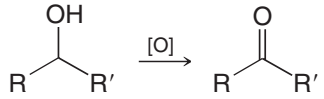


The following is an example with H_2CrO_4.

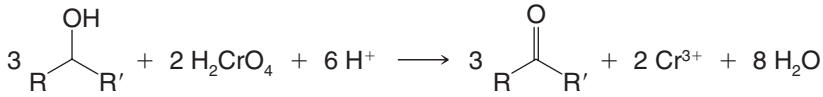


12.4C Oxidation of Secondary Alcohols to Ketones:

Secondary alcohols can be oxidized to ketones. The reaction usually stops at the ketone stage because further oxidation requires the breaking of a carbon–carbon bond:



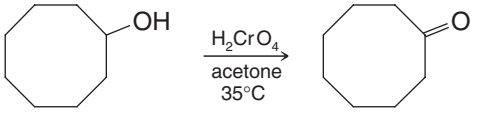
Various oxidizing agents based on Cr(VI) have been used to oxidize secondary alcohols to ketones. The most commonly used reagent is chromic acid (H_2CrO_4). Chromic acid is usually prepared by adding Cr(VI) oxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) to aqueous sulfuric acid, a mixture known as **Jones reagent**. Oxidations of secondary alcohols are generally carried out by adding Jones reagent to a solution of the alcohol in acetone or acetic acid. This procedure rarely affects double bonds present in the molecule. The balanced equation is shown here:



Helpful Hint

The color change from orange to green that accompanies this change in oxidation state allows chromic acid to be used as a test for primary and secondary alcohols (Section 12.4E).

As chromic acid oxidizes the alcohol to the ketone, chromium is reduced from the +6 oxidation state (H_2CrO_4) to the +3 oxidation state (Cr^{3+}). Chromic acid oxidations of secondary alcohols generally give ketones in excellent yields if the temperature is controlled. A specific example is the oxidation of cyclooctanol to cyclooctanone:



PCC will also oxidize a secondary alcohol to a ketone.

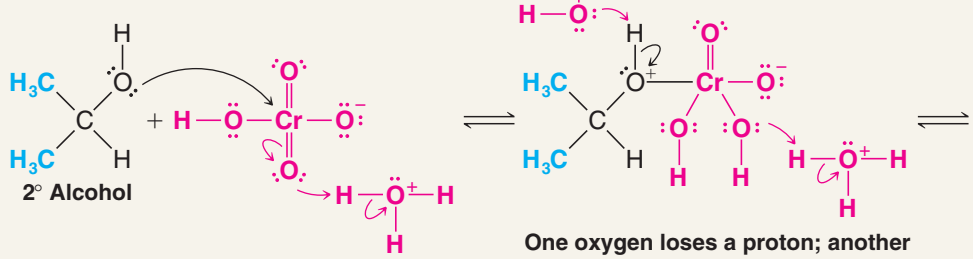
12.4D Mechanism of Chromate Oxidations

The mechanism of chromic acid oxidations of alcohols has been investigated thoroughly. It is interesting because it shows how changes in oxidation states occur in a reaction between an organic and an inorganic compound. The first step is the formation of a chromate ester of the alcohol. Here we show this step using a 2° alcohol.

A MECHANISM FOR THE REACTION

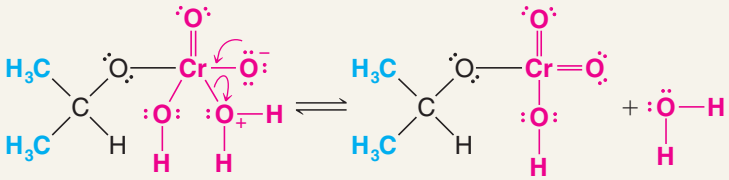
Chromate Oxidations: Formation of the Chromate Ester

Step 1



The alcohol donates an electron pair to the chromium atom, as an oxygen accepts a proton.

One oxygen loses a proton; another oxygen accepts a proton.

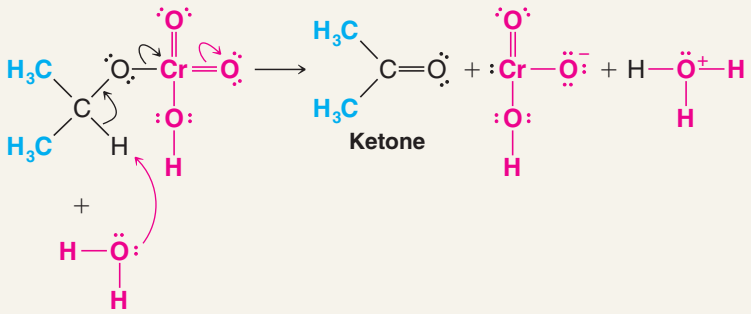


A molecule of water departs as a leaving group as a chromium–oxygen double bond forms.

The chromate ester is unstable and is not isolated. It transfers a proton to a base (usually water) and simultaneously eliminates an $HCrO_3^-$ ion.

Chromate Oxidations: The Oxidation Step

Step 2



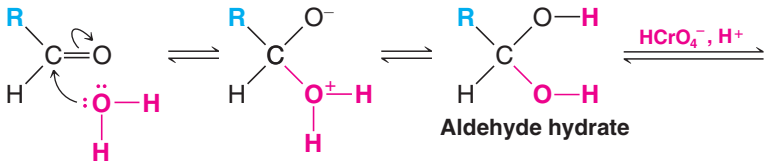
The chromium atom departs with a pair of electrons that formerly belonged to the alcohol; the alcohol is thereby oxidized and the chromium reduced.

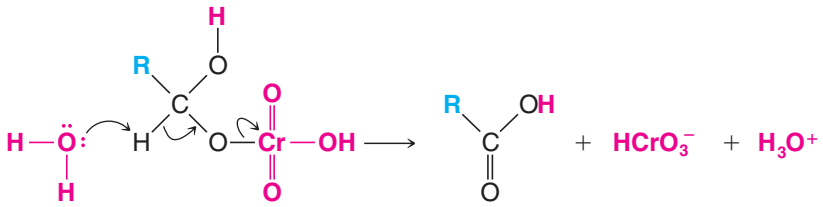
The overall result of the second step is the reduction of $HCrO_4^-$ to $HCrO_3^-$, a two-electron ($2\ e^-$) change in the oxidation state of chromium, from Cr(VI) to Cr(IV). At the same time the alcohol undergoes a $2\ e^-$ oxidation to the ketone.

The remaining steps of the mechanism are complicated and we need not give them in detail. Suffice it to say that further oxidations (and disproportionations) take place, ultimately converting Cr(IV) compounds to Cr^{3+} ions.

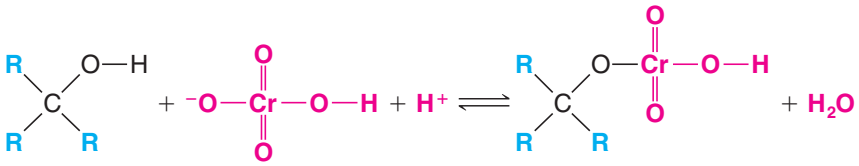
The requirement for the formation of a chromate ester in step 1 of the mechanism helps us understand why 1° alcohols are easily oxidized beyond the aldehyde stage in aqueous solutions (and, therefore, why oxidation with PCC in CH_2Cl_2 stops at the aldehyde stage).

The aldehyde initially formed from the 1° alcohol (produced by a mechanism similar to the one we have just given) reacts with water to form an aldehyde hydrate. The aldehyde hydrate can then react with $HCrO_4^-$ (and H^+) to form a chromate ester, and this can then be oxidized to the carboxylic acid. In the absence of water (i.e., using PCC in CH_2Cl_2), the aldehyde hydrate does not form; therefore, further oxidation does not take place.





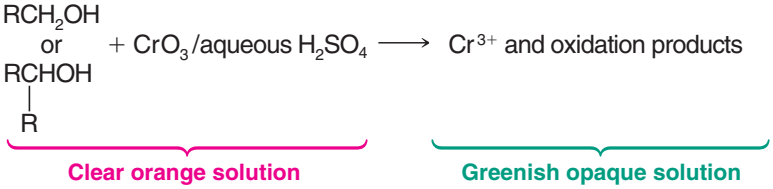
The elimination that takes place in step 2 of the preceding mechanism helps us to understand why 3° alcohols do not generally react in chromate oxidations. Although 3° alcohols have no difficulty in forming chromate esters, the ester that is formed does not bear a hydrogen that can be eliminated, and therefore no oxidation takes place.



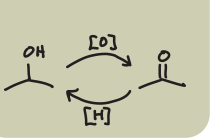
This chromate ester cannot undergo elimination of H_2CrO_3 because there is no hydrogen bonded to the alcohol carbon.

12.4E A Chemical Test for Primary and Secondary Alcohols

The relative ease of oxidation of primary and secondary alcohols compared with the difficulty of oxidizing tertiary alcohols forms the basis for a convenient chemical test. Primary and secondary alcohols are rapidly oxidized by a solution of CrO_3 in aqueous sulfuric acid. Chromic oxide (CrO_3) dissolves in aqueous sulfuric acid to give a clear orange solution containing $Cr_2O_7^{2-}$ ions. A positive test is indicated when this clear orange solution becomes opaque and takes on a greenish cast within 2 seconds:

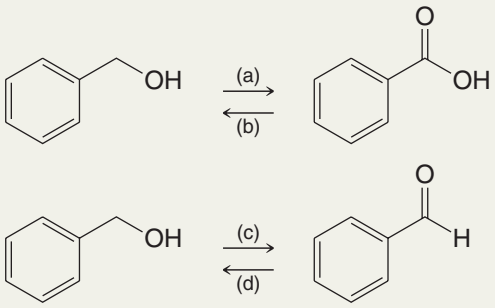


Not only will this test distinguish primary and secondary alcohols from tertiary alcohols, it will distinguish primary and secondary alcohols from most other compounds except aldehydes. This color change, associated with the reduction of $Cr_2O_7^{2-}$ to Cr^{3+}, is also the basis for "Breathalyzer tubes," used to detect intoxicated motorists. In the Breathalyzer the dichromate salt is coated on granules of silica gel.



Solved Problem 12.2

Which reagents would you use to accomplish the following transformations?



STRATEGY AND ANSWER

(a) To oxidize a primary alcohol to a carboxylic acid, use (1) potassium permanganate in aqueous base, followed by (2) H_3O^+, or use chromic acid (H_2CrO_4).

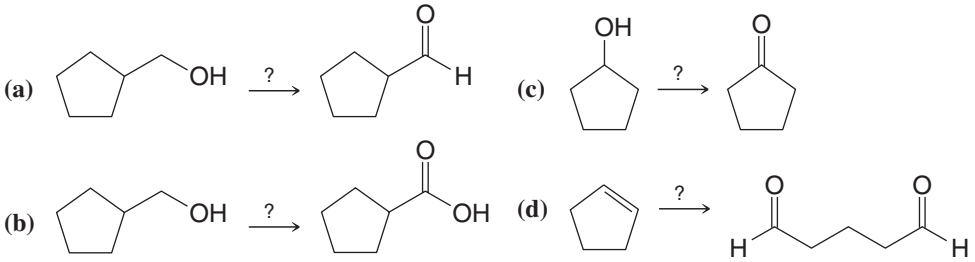
(b) To reduce a carboxylic acid to a primary alcohol, use $LiAlH_4$.

(c) To oxidize a primary alcohol to an aldehyde, use pyridinium chlorochromate (PCC).

(d) To reduce an aldehyde to a primary alcohol, use $NaBH_4$ (preferably) or $LiAlH_4$.

Review Problem 12.4

Show how each of the following transformations could be accomplished:



12.4F Spectroscopic Evidence for Alcohols

- Alcohols give rise to broad O—H stretching absorptions from 3200 to 3600 cm^{-1} in infrared spectra.
- The alcohol hydroxyl hydrogen typically produces a broad ^1H NMR signal of variable chemical shift which can be eliminated by exchange with deuterium from D_2O (see Table 9.1).
- Hydrogen atoms on the carbon of a primary or secondary alcohol produce a signal in the ^1H NMR spectrum between δ 3.3 and δ 4.0 (see Table 9.1) that integrates for 2 and 1 hydrogens, respectively.
- The ^{13}C NMR spectrum of an alcohol shows a signal between δ 50 and δ 90 for the alcohol carbon (see Table 9.2).

12.5 Organometallic Compounds

- Compounds that contain carbon–metal bonds are called **organometallic compounds**.

The nature of the carbon–metal bond varies widely, ranging from bonds that are essentially ionic to those that are primarily covalent. Whereas the structure of the organic portion of

the organometallic compound has some effect on the nature of the carbon–metal bond, the identity of the metal itself is of far greater importance. Carbon–sodium and carbon–potassium bonds are largely ionic in character; carbon–lead, carbon–tin, carbon–thallium, and carbon–mercury bonds are essentially covalent. Carbon–lithium and carbon–magnesium bonds lie between these extremes.

Primarily ionic (M = Na^+ or K^+) | **(M = Mg or Li)** | **Primarily covalent (M = Pb, Sn, Hg, or Tl)**

Helpful Hint

A number of organometallic reagents are very useful for carbon–carbon bond forming reactions (see Section 12.8, and Special Topic G).

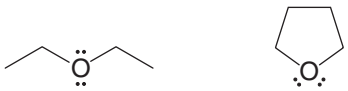
The reactivity of organometallic compounds increases with the percent ionic character of the carbon–metal bond. Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful of bases. They react explosively with water and burst into flame when exposed to air. Organomercury and organolead compounds are much less reactive; they are often volatile and are stable in air. They are all poisonous. They are generally soluble in nonpolar solvents. Tetraethyllead, for example, was once used as an "antiknock" compound in gasoline, but because of the lead pollution it contributed to the environment it has been replaced by other antiknock agents. *tert*-Butyl methyl ether is another antiknock additive, though there are concerns about its presence in the environment, as well.

Organometallic compounds of lithium and magnesium are of great importance in organic synthesis. They are relatively stable in ether solutions, but their carbon–metal bonds have considerable ionic character. Because of this ionic nature, the carbon atom that is bonded to the metal atom of an organolithium or organomagnesium compound is a strong base and powerful nucleophile. We shall soon see reactions that illustrate both of these properties.

12.6 Preparation of Organolithium and Organomagnesium Compounds

12.6A Organolithium Compounds

Organolithium compounds are often prepared by the reduction of organic halides with lithium metal. These reductions are usually carried out in ether solvents, and since organolithium compounds are strong bases, care must be taken to exclude moisture. (Why?) The ethers most commonly used as solvents are diethyl ether and tetrahydrofuran. (Tetrahydrofuran is a cyclic ether.)



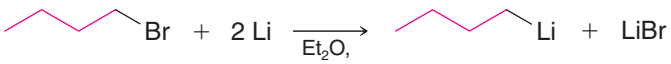
Diethyl ether (Et_2O) | **Tetrahydrofuran (THF)**

- Organolithium compounds are prepared in this general way:

(or Ar—X) | **(or ArLi)**

The order of reactivity of halides is RI > RBr > RCl. (Alkyl and aryl fluorides are seldom used in the preparation of organolithium compounds.)

For example, butyl bromide reacts with lithium metal in diethyl ether to give a solution of butyllithium:



Butyl bromide | **Butyllithium (80–90%)**

Several alkyl- and aryllithium reagents are commercially available in hexane and other hydrocarbon solvents.

12.6B Grignard Reagents

Organomagnesium halides were discovered by the French chemist Victor Grignard in 1900. Grignard received the Nobel Prize for his discovery in 1912, and organomagnesium halides are now called **Grignard reagents** in his honor. Grignard reagents have great use in organic synthesis.

- Grignard reagents are prepared by the reaction of an organic halide with magnesium metal in an anhydrous ether solvent:

$$\left.\begin{aligned} \mathrm{RX} + \mathrm{Mg} &\xrightarrow{\mathrm{Et_2O}} \mathrm{RMgX} \\ \mathrm{ArX} + \mathrm{Mg} &\xrightarrow{\mathrm{Et_2O}} \mathrm{ArMgX} \end{aligned}\right\} \text{Grignard reagents}$$

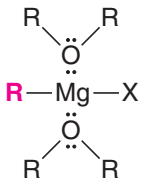
The order of reactivity of halides with magnesium is also RI > RBr > RCl. Very few organomagnesium fluorides have been prepared. Aryl Grignard reagents are more easily prepared from aryl bromides and aryl iodides than from aryl chlorides, which react very sluggishly. Once prepared, a Grignard reagent is usually used directly in a subsequent reaction.

The actual structures of Grignard reagents are more complex than the general formula RMgX indicates. Experiments have established that for most Grignard reagents there is an equilibrium between an alkylmagnesium halide and a dialkylmagnesium.

$$\underset{\text{Alkylmagnesium halide}}{2\ \mathrm{RMgX}} \rightleftharpoons \underset{\text{Dialkylmagnesium}}{\mathrm{R_2Mg}} + \mathrm{MgX_2}$$

For convenience in this text, however, we shall write the formula for the Grignard reagent as though it were simply RMgX.

A Grignard reagent forms a complex with its ether solvent; the structure of the complex can be represented as follows:



Complex formation with molecules of ether is an important factor in the formation and stability of Grignard reagents.

The mechanism by which Grignard reagents form is complicated and has been a matter of debate. There seems to be general agreement that radicals are involved and that a mechanism similar to the following is likely:

$$\mathrm{R{-}X} + \mathrm{:Mg} \longrightarrow \mathrm{R\cdot} + \mathrm{\cdot MgX}$$
$$\mathrm{R\cdot} + \mathrm{\cdot MgX} \longrightarrow \mathrm{RMgX}$$

12.7 Reactions of Organolithium and Organomagnesium Compounds

12.7A Reactions with Compounds Containing Acidic Hydrogen Atoms

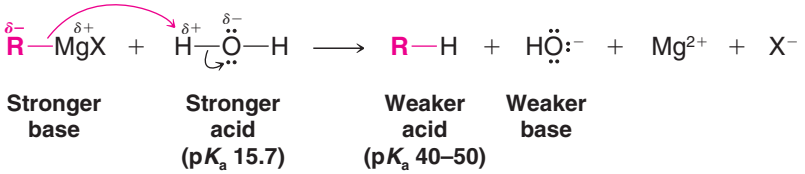
- Grignard reagents and organolithium compounds are very strong bases. They react with any compound that has a hydrogen atom attached to an electronegative atom such as oxygen, nitrogen, or sulfur.

We can understand how these reactions occur if we represent the Grignard reagent and organolithium compounds in the following ways:

$$\mathrm{R{:}^{\delta-}MgX^{\delta+}} \quad \text{and} \quad \mathrm{R{:}^{\delta-}Li^{\delta+}}$$

When we do this, we can see that the reactions of Grignard reagents with water and alcohols are nothing more than acid–base reactions; they lead to the formation of the weaker conjugate acid and weaker conjugate base.

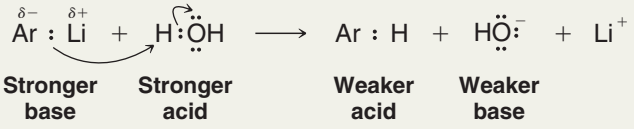
- A Grignard reagent behaves as if it contained the anion of an alkane, *as if it contained a carbanion*:



Solved Problem 12.3

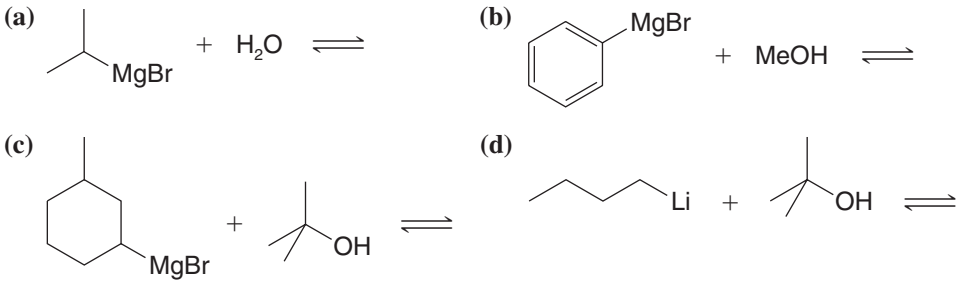
Write an equation for the reaction that would take place when phenyllithium is treated with water. Designate the stronger acid and stronger base.

STRATEGY AND ANSWER Recognizing that phenyllithium, like a Grignard reagent, acts as though it contains a carbanion, a very powerful base (pK_a = 40–50), we conclude that the following acid–base reaction would occur.



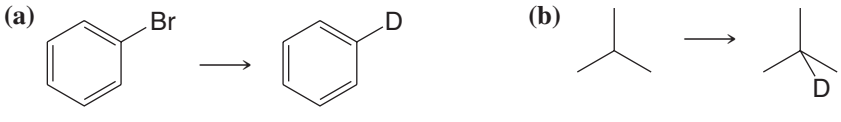
Review Problem 12.5

Predict the products of the following acid–base reactions. Using pK_a values, indicate which side of each equilibrium reaction is favored, and label the species representing the stronger acid and stronger base in each case.



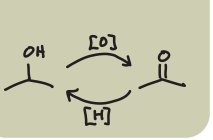
Review Problem 12.6

Provide the reagents necessary to achieve the following transformations.

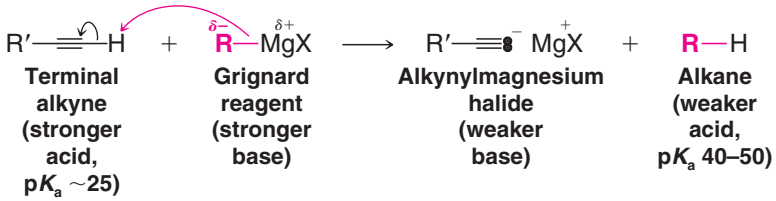


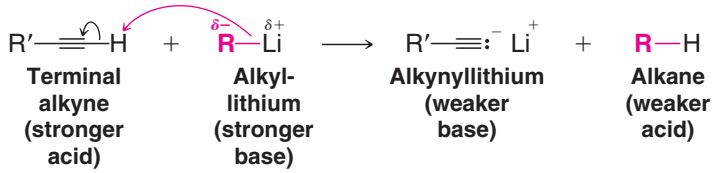
(D = deuterium)

Grignard reagents and organolithium compounds remove protons that are much less acidic than those of water and alcohols.



- Grignard reagents react with the terminal hydrogen atoms of 1-alkynes by an acid–base reaction, and this is a useful method for the preparation of alkynylmagnesium halides and alkynyllithiums.





The fact that these reactions go to completion is not surprising when we recall that alkanes have pK_a values of 40–50, whereas those of terminal alkynes are ~25 (Table 3.1).

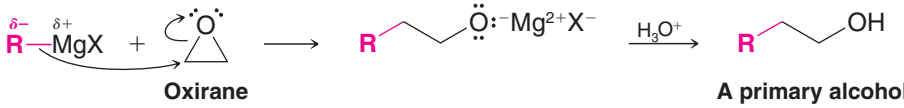
Not only are Grignard reagents strong bases, they are also *powerful nucleophiles*.

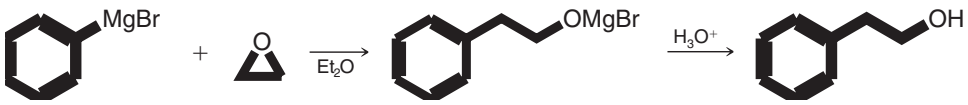
- Reactions in which Grignard reagents act as nucleophiles are by far the most important and we shall consider these next.

12.7B Reactions of Grignard Reagents with Epoxides (Oxiranes)

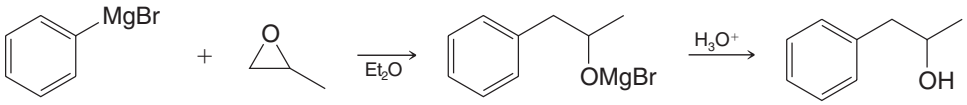
- Grignard reagents react as nucleophiles with epoxides (oxiranes), providing convenient synthesis of alcohols.

The nucleophilic alkyl group of the Grignard reagent attacks the partially positive carbon of the epoxide ring. Because it is highly strained, the ring opens, and the reaction leads to the alkoxide salt of an alcohol. Subsequent acidification produces the alcohol. (Compare this reaction with the base-catalyzed ring opening we studied in Section 11.14.) The following are examples with oxirane.





- Grignard reagents react primarily at the less-substituted ring carbon atom of a substituted epoxide.



12.7C Reactions of Grignard Reagents with Carbonyl Compounds

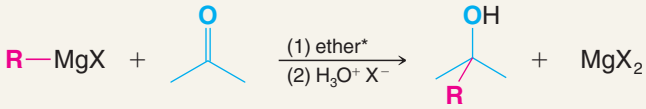
- The most important synthetic reactions of Grignard reagents and organolithium compounds are those in which they react as nucleophiles and attack an unsaturated carbon—*especially the carbon of a carbonyl group*.

We saw in Section 12.1A that carbonyl compounds are highly susceptible to nucleophilic attack. Grignard reagents react with carbonyl compounds (aldehydes and ketones) in the following way.

A MECHANISM FOR THE REACTION

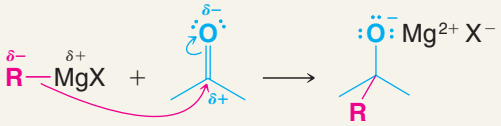
The Grignard Reaction

REACTION



MECHANISM

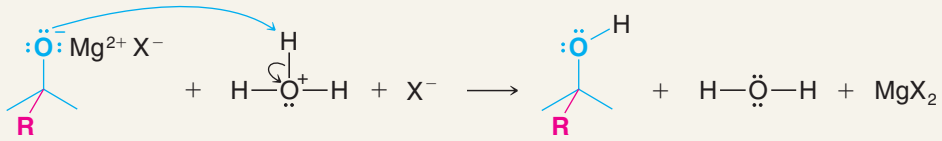
Step 1



Grignard reagent | **Carbonyl compound** | **Halomagnesium alkoxide**

The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with Mg^{2+} and X^-.

Step 2



Halomagnesium alkoxide | **Alcohol**

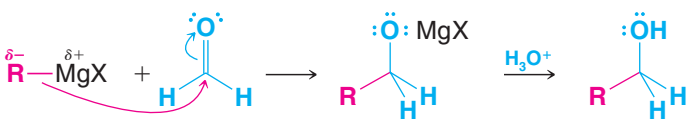
In the second step, the addition of aqueous HX causes protonation of the alkoxide ion; this leads to the formation of the alcohol and MgX_2.

*By writing "(1) ether" over the arrow and "(2) H_3O^+ X^-" under the arrow, we mean that in the first laboratory step the Grignard reagent and the carbonyl compound are allowed to react in an ether solvent. Then in a second step, after the reaction of the Grignard reagent and the carbonyl compound is over, we add aqueous acid (e.g., dilute HX) to convert the salt of the alcohol (ROMgX) to the alcohol itself. If the alcohol is tertiary, it will be susceptible to acid-catalyzed dehydration. In this case, a solution of NH_4Cl in water is often used because it is acidic enough to convert ROMgX to ROH while not allowing acid-catalyzed reactions of the resulting tertiary alcohol.

12.8 *Alcohols from Grignard Reagents*

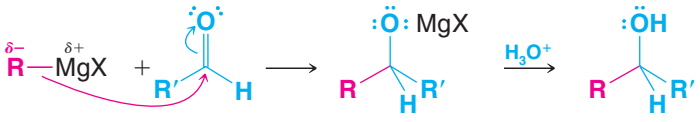
Grignard additions to carbonyl compounds are especially useful because they can be used to prepare primary, secondary, or tertiary alcohols:

1. Grignard Reagents React with Formaldehyde to Give a Primary Alcohol



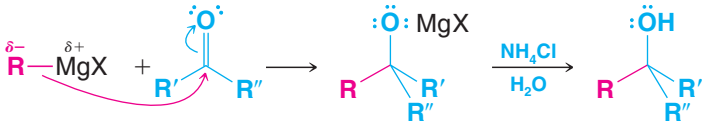
Formaldehyde | **1° Alcohol**

2. Grignard Reagents React with All Other Aldehydes to Give Secondary Alcohols



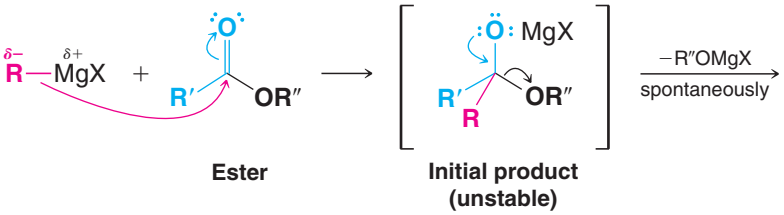
Higher aldehyde — 2° Alcohol

3. Grignard Reagents React with Ketones to Give Tertiary Alcohols

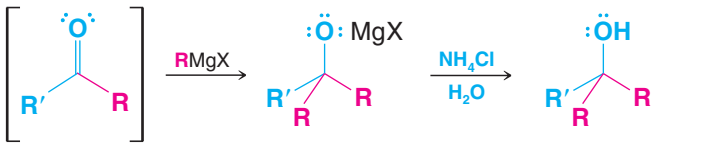


Ketone — 3° Alcohol

4. Esters React with Two Molar Equivalents of a Grignard Reagent to Form Tertiary Alcohols When a Grignard reagent adds to the carbonyl group of an ester, the initial product is unstable and loses a magnesium alkoxide to form a ketone. Ketones, however, are more reactive toward Grignard reagents than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of the Grignard reagent. After hydrolysis, **the product is a tertiary alcohol with two identical alkyl groups**, groups that correspond to the alkyl portion of the Grignard reagent:

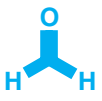
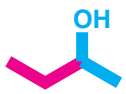


Ester — Initial product (unstable)



Ketone — Salt of an alcohol (not isolated) — 3° Alcohol (with two or three identical R groups)

Specific examples of these reactions are shown here.

Grignard Reagent	Carbonyl Reactant				Final Product
Reaction with Formaldehyde					
		Et_2O		H_3O^+	
Phenylmagnesium bromide	Formaldehyde				Benzyl alcohol (90%)
Reaction with a Higher Aldehyde					
		Et_2O		H_3O^+	
Ethylmagnesium bromide	Acetaldehyde				2-Butanol (80%)

Reaction with a Ketone

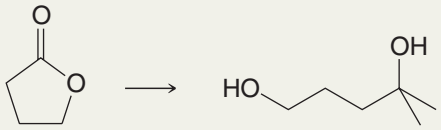
Butylmagnesium bromide **Acetone** **2-Methyl-2-hexanol (92%)**

Reaction with an Ester

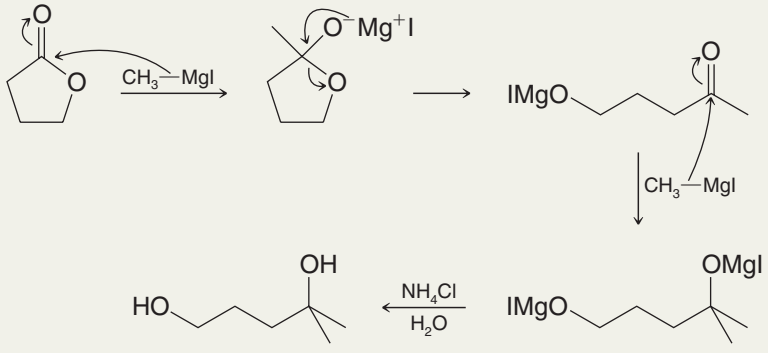
Ethylmagnesium bromide **Ethyl acetate**

Solved Problem 12.4

How would you carry out the following synthesis?

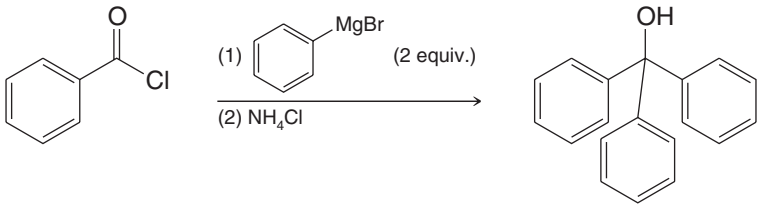


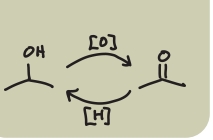
STRATEGY AND ANSWER Here we are converting an ester (a cyclic ester) to **a tertiary alcohol with two identical alkyl groups** (methyl groups). So, we should use two molar equivalents of the Grignard reagent that contains the required alkyl groups, in this case, methyl magnesium iodide.



Review Problem 12.7

Provide a mechanism for the following reaction, based on your knowledge of the reaction of esters with Grignard reagents.

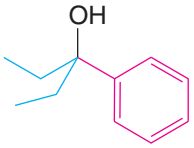




12.8A How to Plan a Grignard Synthesis

We can synthesize almost any alcohol we wish by skillfully using a Grignard synthesis. In planning a Grignard synthesis we must simply choose the correct Grignard reagent and the correct aldehyde, ketone, ester, or epoxide. We do this by examining the alcohol we wish to prepare and by paying special attention to the groups attached to the carbon atom bearing the —OH group. Many times there may be more than one way of carrying out the synthesis. In these cases our final choice will probably be dictated by the availability of starting compounds. Let us consider an example.

Suppose we want to prepare 3-phenyl-3-pentanol. We examine its structure and we see that the groups attached to the carbon atom bearing the —OH are a *phenyl group* and *two ethyl groups*:

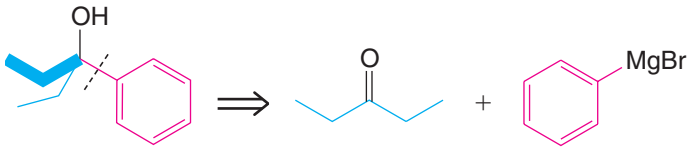


3-Phenyl-3-pentanol

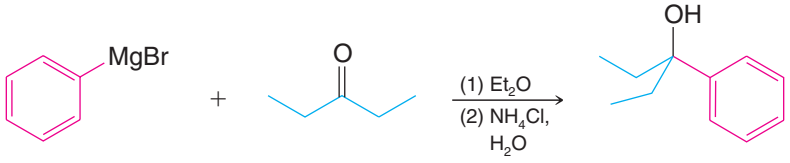
This means that we can synthesize this compound in several different ways:

1. We can use a ketone with two ethyl groups (3-pentanone) and allow it to react with phenylmagnesium bromide:

Retrosynthetic Analysis



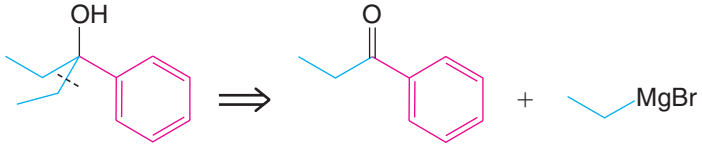
Synthesis



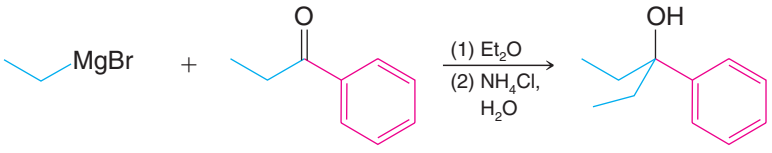
Phenylmagnesium bromide **3-Pentanone** **3-Phenyl-3-pentanol**

2. We can use a ketone containing an ethyl group and a phenyl group (ethyl phenyl ketone) and allow it to react with ethylmagnesium bromide:

Retrosynthetic Analysis



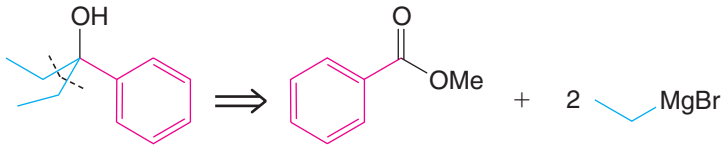
Synthesis



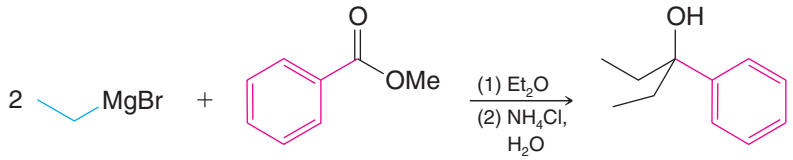
Ethylmagnesium bromide **Ethyl phenyl ketone** **3-Phenyl-3-pentanol**

3. We can use an ester of benzoic acid and allow it to react with two molar equivalents of ethylmagnesium bromide:

Retrosynthetic Analysis



Synthesis

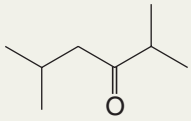


Ethylmagnesium bromide | **Methyl benzoate** | **3-Phenyl-3-pentanol**

All of these methods will likely give us our desired compound in high yields.

Solved Problem 12.5

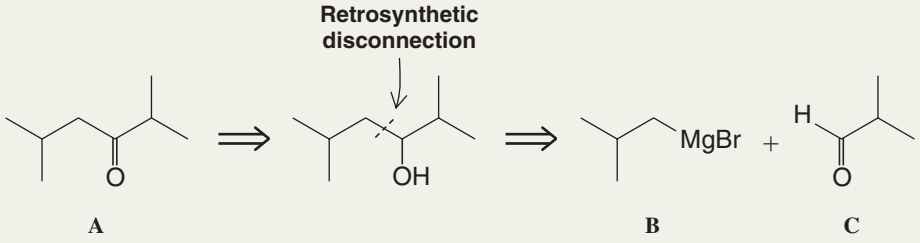
ILLUSTRATING A MULTISTEP SYNTHESIS Using an alcohol of no more than four carbon atoms as your only organic starting material, outline a synthesis of **A**:



A

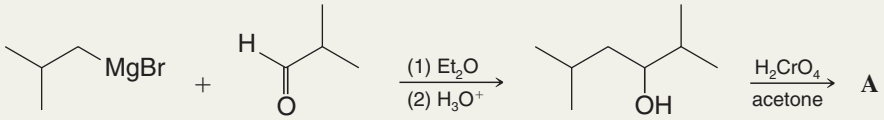
ANSWER We can construct the carbon skeleton from two four-carbon compounds using a Grignard reaction. Then oxidation of the alcohol produced will yield the desired ketone.

Retrosynthetic Analysis



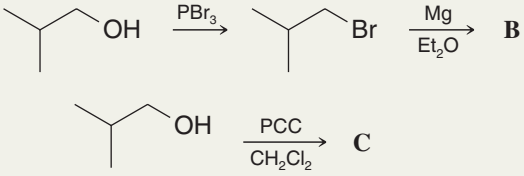
A **B** **C**

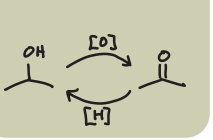
Synthesis



B **C**

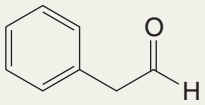
We can synthesize the Grignard reagent (**B**) and the aldehyde (**C**) from isobutyl alcohol:





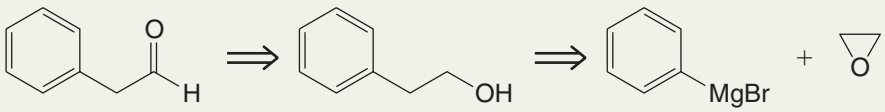
Solved Problem 12.6

ILLUSTRATING A MULTISTEP SYNTHESIS Starting with bromobenzene and any other needed reagents, outline a synthesis of the following aldehyde:

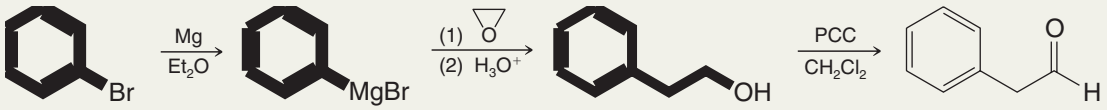


ANSWER Working backward, we remember that we can synthesize the aldehyde from the corresponding alcohol by oxidation with PCC (Section 12.4A). The alcohol can be made by treating phenylmagnesium bromide with oxirane. [Adding oxirane to a Grignard reagent is a very useful method for adding a $-CH_2CH_2OH$ unit to an organic group (Section 12.7B).] Phenylmagnesium bromide can be made in the usual way, by treating bromobenzene with magnesium in an ether solvent.

Retrosynthetic Analysis

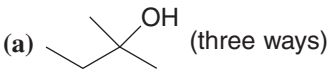


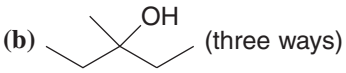
Synthesis

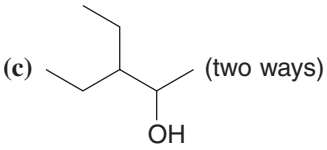


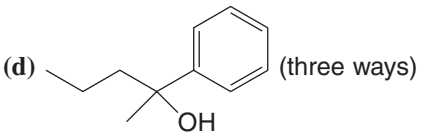
Review Problem 12.8

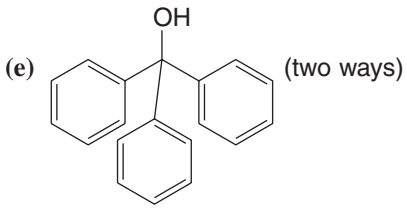
Provide retrosynthetic analyses and syntheses for each of the following alcohols, starting with appropriate alkyl or aryl halides.

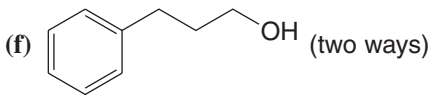






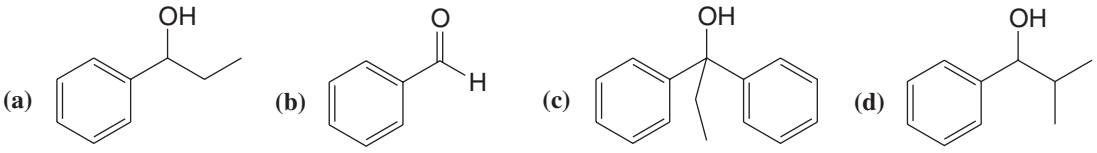






Review Problem 12.9

Provide a retrosynthetic analysis and synthesis for each of the following compounds. Permitted starting materials are phenylmagnesium bromide, oxirane, formaldehyde, and alcohols or esters of four carbon atoms or fewer. You may use any inorganic reagents and oxidizing agents such as pyridinium chlorochromate (PCC).



12.8B Restrictions on the Use of Grignard Reagents

Although the Grignard synthesis is one of the most versatile of all general synthetic procedures, it is not without its limitations. Most of these limitations arise from the very feature of the Grignard reagent that makes it so useful, its *extraordinary reactivity as a nucleophile and a base*.

The Grignard reagent is a very powerful base; in effect it contains a carbanion.

- It is not possible to prepare a Grignard reagent from a compound that contains any hydrogen more acidic than the hydrogen atoms of an alkane or alkene.

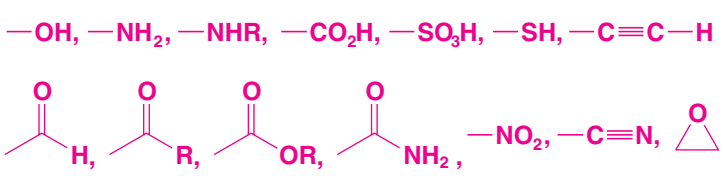
We cannot, for example, prepare a Grignard reagent from a compound containing an —OH group, an —NH— group, an —SH group, a $—CO_2H$ group, or an $—SO_3H$ group. If we were to attempt to prepare a Grignard reagent from an organic halide containing any of these groups, the formation of the Grignard reagent would simply fail to take place. (Even if a Grignard reagent were to form, it would immediately be neutralized by the acidic group.)

- Since Grignard reagents are powerful nucleophiles, we cannot prepare a Grignard reagent from any organic halide that contains a carbonyl, epoxy, nitro, or cyano (—CN) group.

If we were to attempt to carry out this kind of reaction, any Grignard reagent that formed would only react with the unreacted starting material:

Helpful Hint

A protecting group can sometimes be used to mask the reactivity of an incompatible group (see Sections 11.11D, 11.11E, and 12.9).



Grignard reagents cannot be prepared in the presence of these groups because they will react with them.

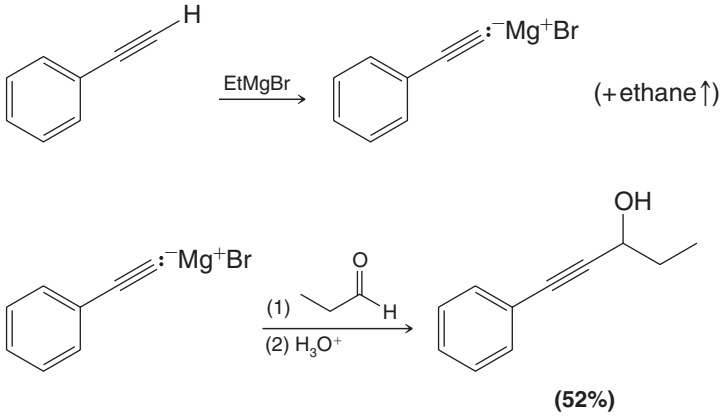
This means that when we prepare Grignard reagents, we are effectively limited to alkyl halides or to analogous organic halides containing carbon–carbon double bonds, internal triple bonds, ether linkages, and $—NR_2$ groups.

Grignard reactions are so sensitive to acidic compounds that when we prepare a Grignard reagent we must take special care to exclude moisture from our apparatus, and we must use an anhydrous ether as our solvent.

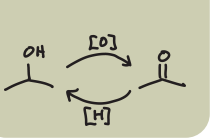
As we saw earlier, acetylenic hydrogens are acidic enough to react with Grignard reagents. This is a limitation that we can use, however.

- We can make acetylenic Grignard reagents by allowing terminal alkynes to react with alkyl Grignard reagents (cf. Section 12.7A).

We can then use these acetylenic Grignard reagents to carry out other syntheses. For example,

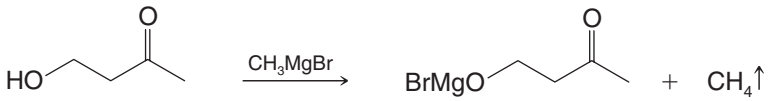


(52%)



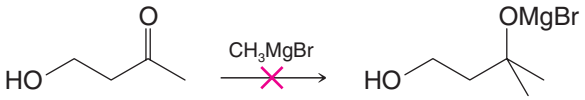
- When we plan a Grignard synthesis, we must also take care that any aldehyde, ketone, epoxide, or ester that we use as a substrate does not also contain an acidic group (other than when we deliberately let it react with a terminal alkyne).

If we were to do this, the Grignard reagent would simply react as a base with the acidic hydrogen rather than reacting at the carbonyl or epoxide carbon as a nucleophile. If we were to treat 4-hydroxy-2-butanone with methylmagnesium bromide, for example, the reaction that would take place is

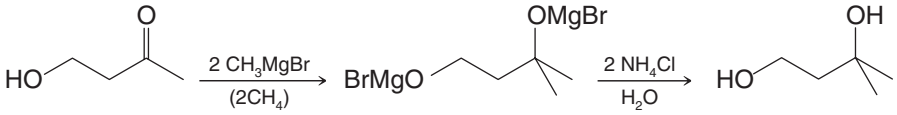


4-Hydroxy-2-butanone

rather than



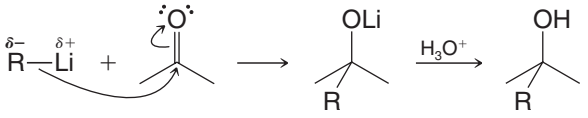
If we were prepared to waste one molar equivalent of the Grignard reagent, we can treat 4-hydroxy-2-butanone with two molar equivalents of the Grignard reagent and thereby get addition to the carbonyl group:



This technique is sometimes employed in small-scale reactions when the Grignard reagent is inexpensive and the other reagent is expensive.

12.8C The Use of Lithium Reagents

Organolithium reagents (RLi) react with carbonyl compounds in the same way as Grignard reagents and thus provide an alternative method for preparing alcohols.

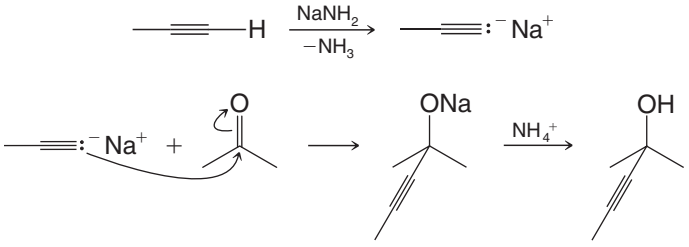


Organo-lithium reagent **Aldehyde or ketone** **Lithium alkoxide** **Alcohol**

Organolithium reagents have the advantage of being somewhat more reactive than Grignard reagents although they are more difficult to prepare and handle.

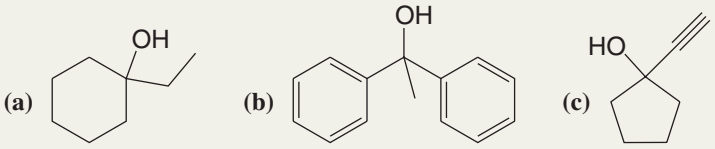
12.8D The Use of Sodium Alkynides

Sodium alkynides also react with aldehydes and ketones to yield alcohols. An example is the following:



Solved Problem 12.7

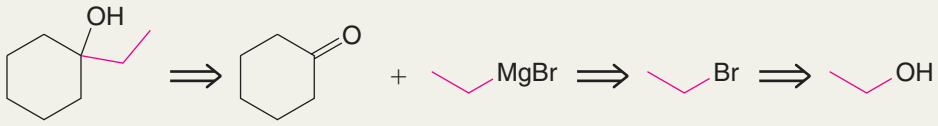
ILLUSTRATING MULTISTEP SYNTHESES For the following compounds, write a retrosynthetic scheme and then synthetic reactions that could be used to prepare each one. Use hydrocarbons, organic halides, alcohols, aldehydes, ketones, or esters containing six carbon atoms or fewer and any other needed reagents.



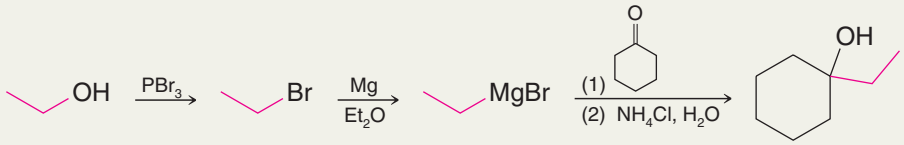
ANSWERS

(a)

Retrosynthetic Analysis

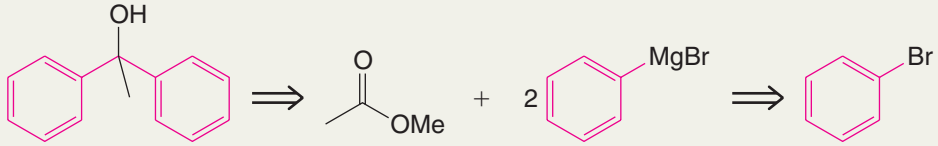


Synthesis

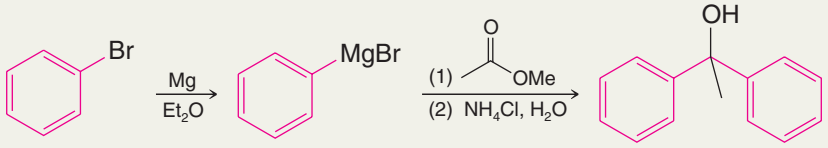


(b)

Retrosynthetic Analysis

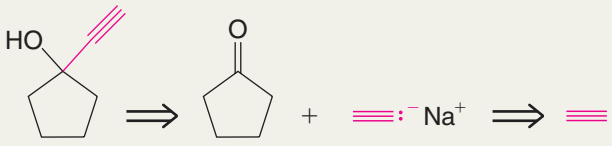


Synthesis

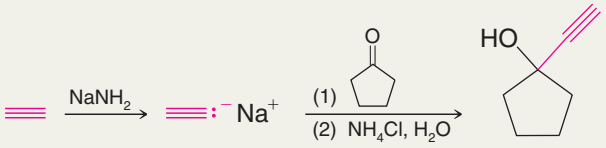


(c)

Retrosynthetic Analysis



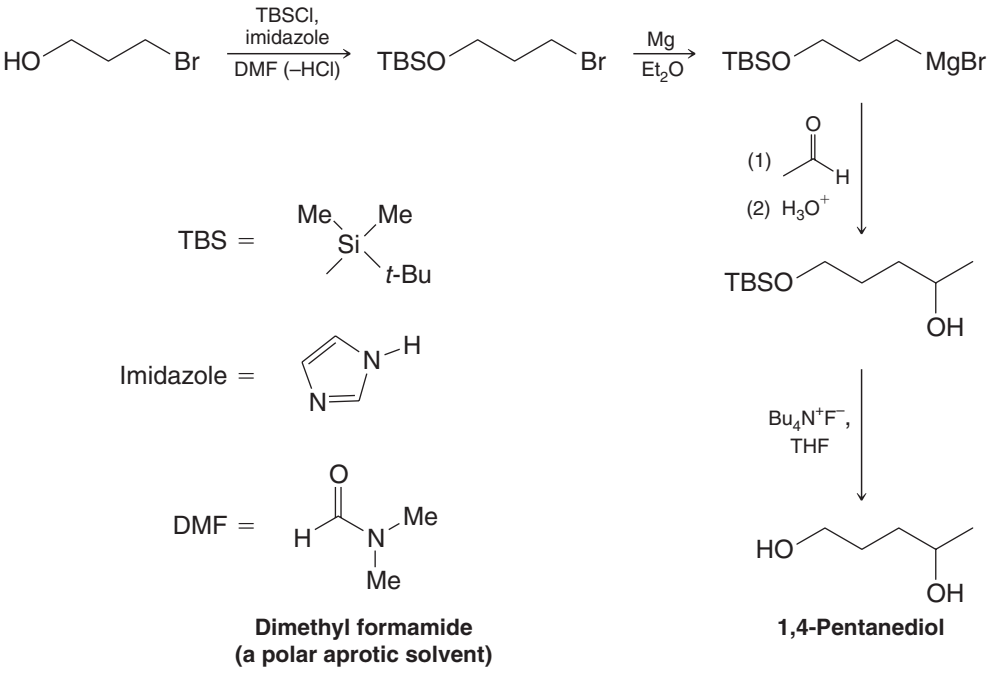
Synthesis



12.9 Protecting Groups

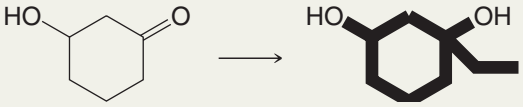
- A **protecting group** can be used in some cases where a reactant contains a group that is incompatible with the reaction conditions necessary for a given transformation.

For example, if it is necessary to prepare a Grignard reagent from an alkyl halide that already contains an alcohol hydroxyl group, the Grignard reagent can still be prepared if the alcohol is first protected by conversion to a functional group that is stable in the presence of a Grignard reagent, for example, a *tert*-butyldimethylsilyl (TBS) ether (Section 11.11E). The Grignard reaction can be conducted, and then the original alcohol group can be liberated by cleavage of the silyl ether with fluoride ion (see Problem 12.36). An example is the following synthesis of 1,4-pentanediol. This same strategy can be used when an organolithium reagent or alkynide anion must be prepared in the presence of an incompatible group. In later chapters we will encounter strategies that can be used to protect other functional groups during various reactions (Section 16.7C).

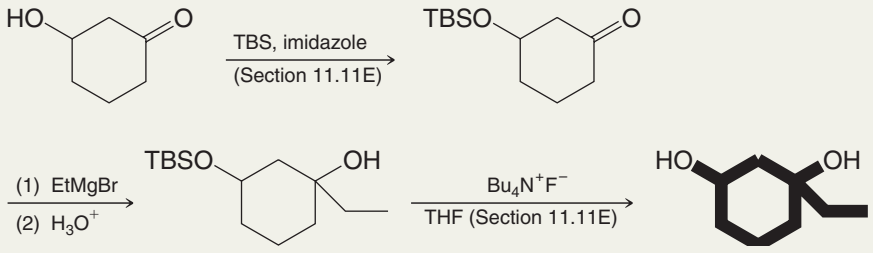


Solved Problem 12.8

Show how the following synthesis could be accomplished using a protecting group.



STRATEGY AND ANSWER First protect the —OH group by converting it to a *tert*-butyldimethylsilyl (TBS) ether (Section 11.11E), then treat the product with ethyl magnesium bromide followed by dilute acid. Then remove the protecting group.



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

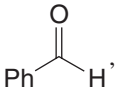
Note to Instructors: Many of the homework problems are available for assignment via ***WileyPLUS***, an online teaching and learning solution.

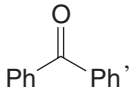
REAGENTS AND REACTIONS

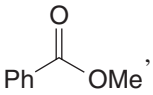
12.10 What products would you expect from the reaction of ethylmagnesium bromide (CH_3CH_2MgBr) with each of the following reagents?

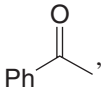
(a) H_2O

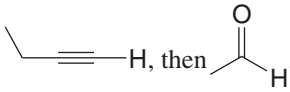
(b) D_2O

(c)  , then H_3O^+

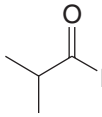
(d)  , then NH_4Cl, H_2O

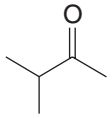
(e)  , then NH_4Cl, H_2O

(f)  , then NH_4Cl, H_2O

(g)  , then H_3O^+

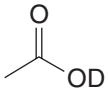
12.11 What products would you expect from the reaction of propyllithium ($CH_3CH_2CH_2Li$) with each of the following reagents?

(a)  , then H_3O^+

(b)  , then NH_4Cl, H_2O

(c) 1-Pentyne, then  , then NH_4Cl, H_2O

(d) Ethanol

(e) 

12.12 What product (or products) would be formed from the reaction of 1-bromo-2-methylpropane (isobutyl bromide) under each of the following conditions?

(a) OH^-, H_2O

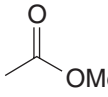
(b) CN^-, ethanol

(c) *t*-BuOK, *t*-BuOH

(d) MeONa, MeOH

(e) (1) Li, Et_2O; (2)  ; (3) NH_4Cl, H_2O

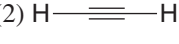
(f) Mg, Et_2O, then  , then H_3O^+

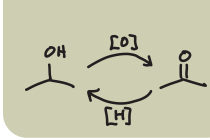
(g) (1) Mg, Et_2O; (2)  ; (3) NH_4Cl, H_2O

(h) (1) Mg, Et_2O; (2)  ; (3) H_3O^+

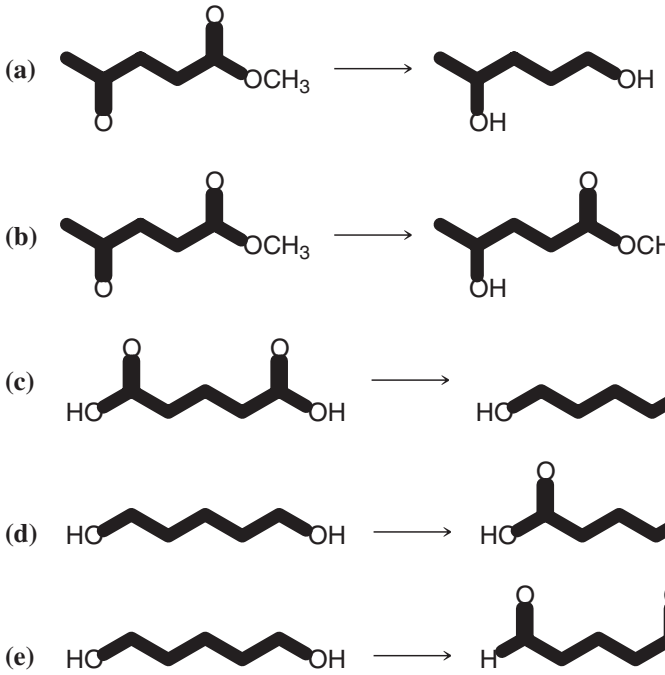
(i) (1) Mg, Et_2O; (2)  ; (3) NH_4Cl, H_2O

(j) Li, Et_2O; (2) MeOH

(k) Li, Et_2O; (2) 

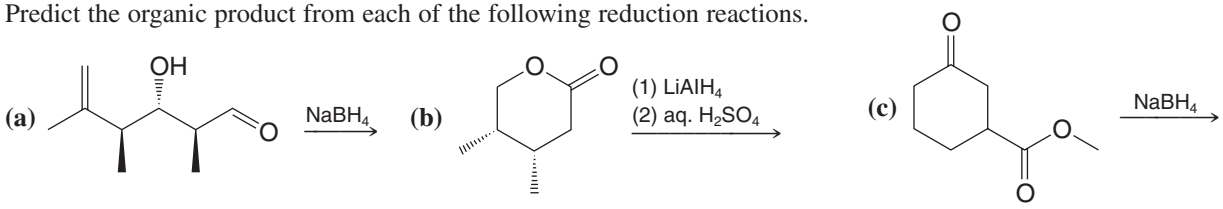


12.13 Which oxidizing or reducing agent would you use to carry out the following transformations?

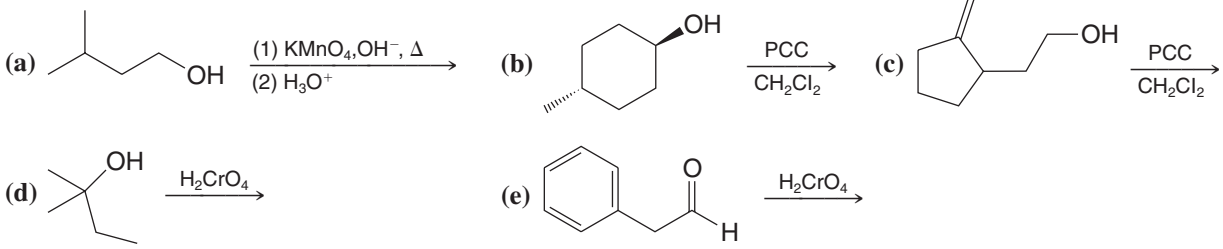


12.14 Predict the products of the following reactions.

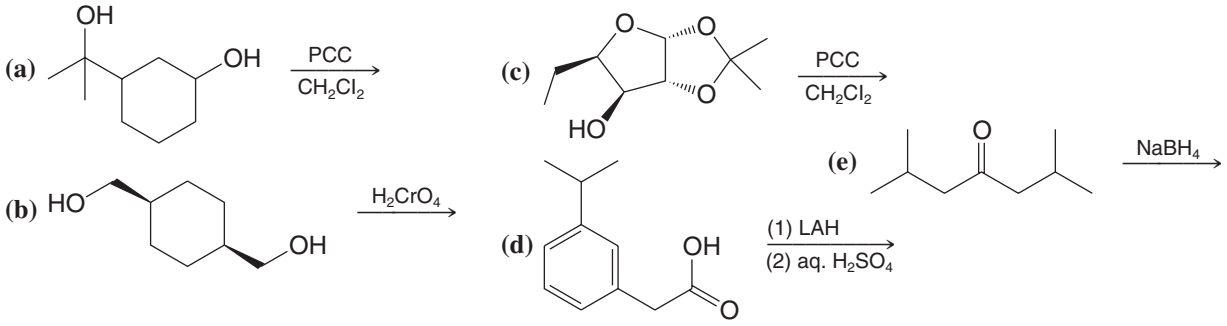
12.15 Predict the organic product from each of the following reduction reactions.



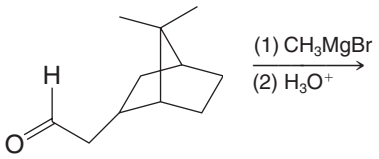
12.16 Predict the organic product from each of the following oxidation reactions.

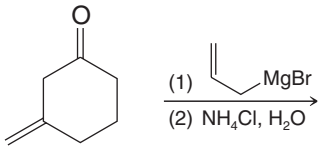


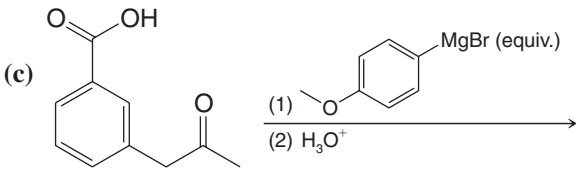
12.17 Predict the organic product from each of the following oxidation and reduction reactions.

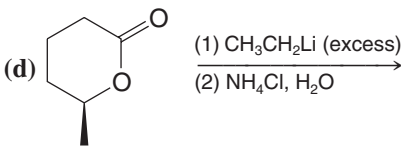


12.18 Predict the major organic product from each of the following reactions.

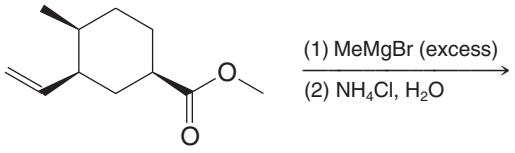
(a) 

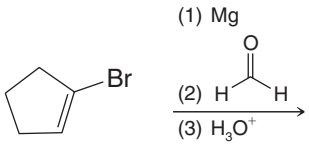
(b) 

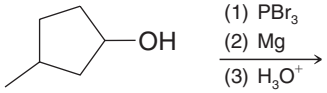
(c) 

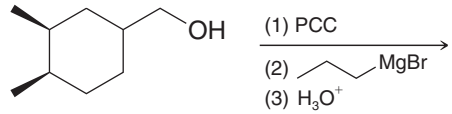
(d) 

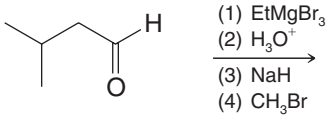
12.19 Predict the major organic product from each of the following reaction sequences.

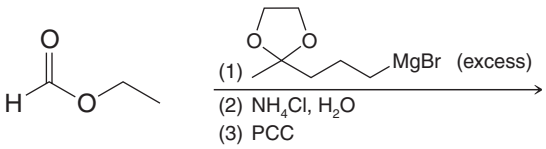
(a) 

(b) 

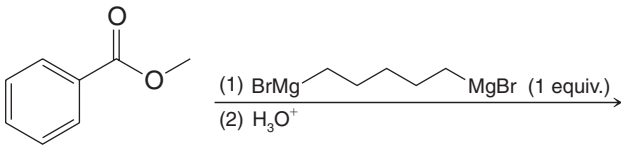
(c) 

(d) 

(e) 

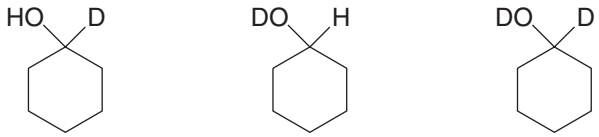
(f) 

12.20 Predict the product of the following reaction.

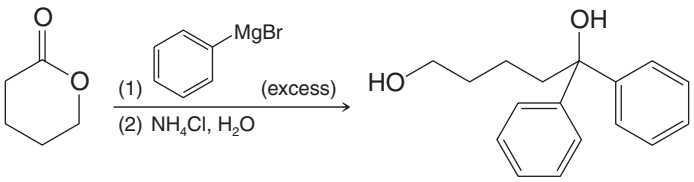


MECHANISMS

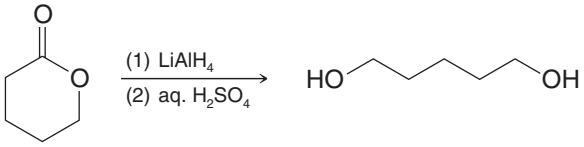
12.21 Synthesize each of the following compounds from cyclohexanone. Use D to specify deuterium in any appropriate reagent or solvent where it would take the place of hydrogen.

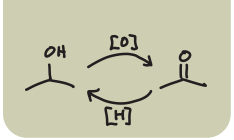


12.22 Write a mechanism for the following reaction. Include formal charges and curved arrows to show the movement of electrons in all steps.



12.23 Write a mechanism for the following reaction. You may use H^- to represent hydride ions from $LiAlH_4$ in your mechanism. Include formal charges and curved arrows to show the movement of electrons in all steps.



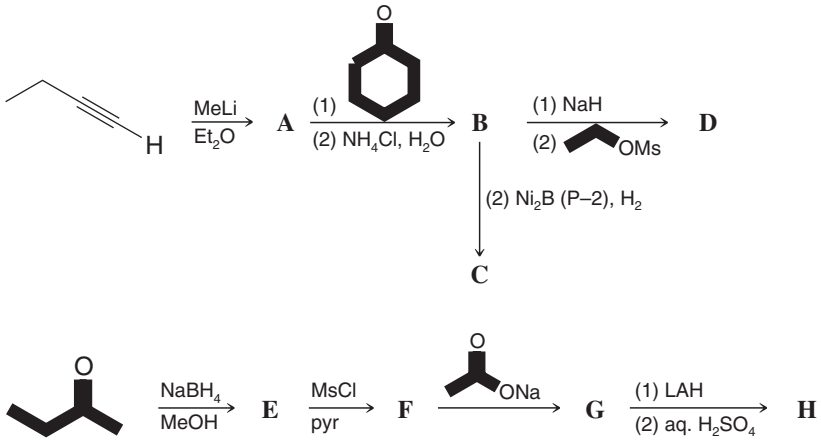


12.24 Although oxirane (oxacyclopropane) and oxetane (oxacyclobutane) react with Grignard and organolithium reagents to form alcohols, tetrahydrofuran (oxacyclopentane) is so unreactive that it can be used as the solvent in which these organometallic compounds are prepared. Explain the difference in reactivity of these oxygen heterocycles.

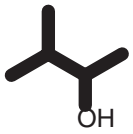
12.25 Studies suggest that attack by a Grignard reagent at a carbonyl group is facilitated by involvement of a second molecule of the Grignard reagent that participates in an overall cyclic ternary complex. The second molecule of Grignard reagent assists as a Lewis acid. Propose a structure for the ternary complex and write all of the products that result from it.

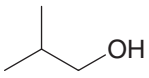
SYNTHESIS

12.26 What organic products **A–H** would you expect from each of the following reactions?

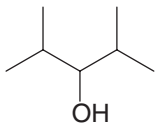


12.27 Outline all steps in a synthesis that would transform 2-propanol (isopropyl alcohol) into each of the following:

(a) 

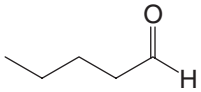
(b) 

(c) 

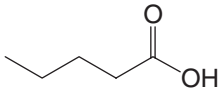
(d) 

(e) 

12.28 Show how 1-pentanol could be transformed into each of the following compounds. (You may use any needed inorganic reagents and you need not show the synthesis of a particular compound more than once.)

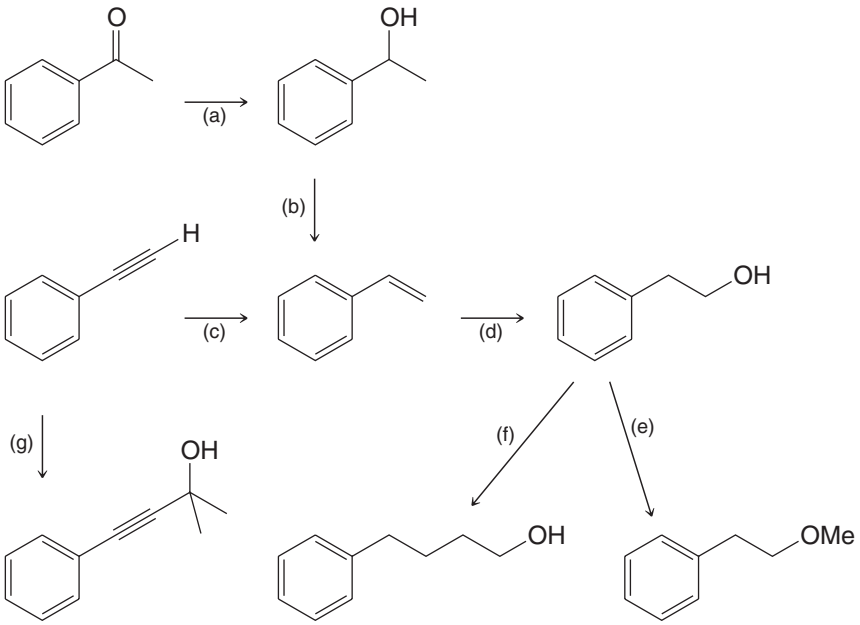
(a) 1-Bromopentane
(b) 1-Pentene
(c) 2-Pentanol
(d) Pentane
(e) 2-Bromopentane
(f) 1-Hexanol
(g) 1-Heptanol
(h) Pentanal, 

(i) 2-Pentanone, 

(j) Pentanoic acid, 

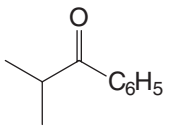
(k) Dipentyl ether (two ways)
(l) 1-Pentyne
(m) 2-Bromo-1-pentene
(n) Pentyllithium
(o) 4-Methyl-4-nonanol

12.29 Provide the reagents needed to accomplish transformations (a)–(g). More than one step may be necessary.

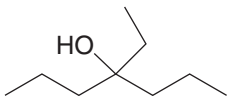


12.30 Assuming that you have available only alcohols or esters containing no more than four carbon atoms, show how you might synthesize each of the following compounds. Begin by writing a retrosynthetic analysis for each. You must use a Grignard reagent at one step in the synthesis. If needed, you may use oxirane and you may use bromobenzene, but you must show the synthesis of any other required organic compounds. Assume you have available any solvents and any inorganic compounds, including oxidizing and reducing agents, that you require.

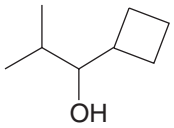
(a)



(b)



(c)



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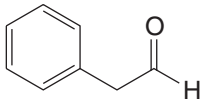

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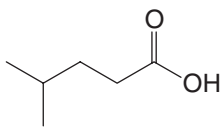

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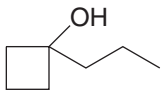
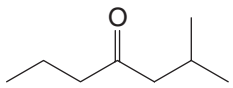
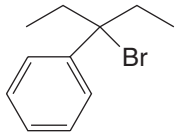


(g)

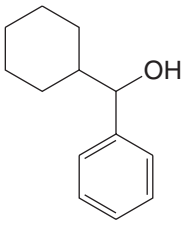


(h)

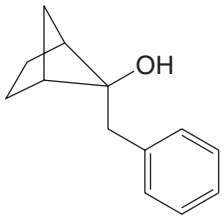


12.31 For each of the following alcohols, write a retrosynthetic analysis and synthesis that involves an appropriate organometallic reagent (either a Grignard or alkyllithium reagent).

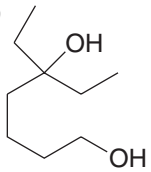
(a)



(b)

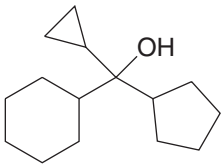


(c)

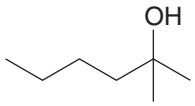


12.32 Synthesize each of the following compounds starting from primary or secondary alcohols containing seven carbons or less and, if appropriate, bromobenzene.

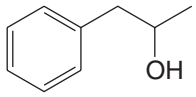
(a)



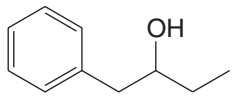
(b)



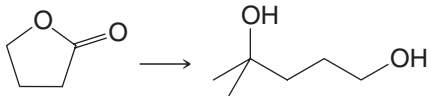
(c)



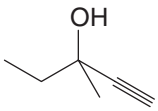
12.33 The alcohol shown below is used in making perfumes. Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare this alcohol from bromobenzene and 1-butene.



12.34 Show how a Grignard reagent might be used in the following synthesis:

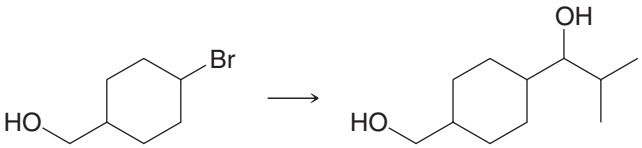


12.35 Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare racemic Meparfynol, a mild hypnotic (sleep-inducing compound), starting with compounds of four carbon atoms or fewer.

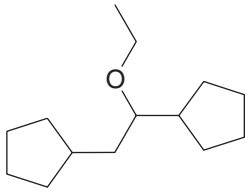


Meparfynol

12.36 Write a retrosynthetic analysis and synthesis for the following transformation.

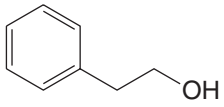


12.37 Synthesize the following compound using cyclopentane and ethyne (acetylene) as the sole source of carbon atoms.

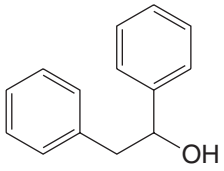


Challenge Problems

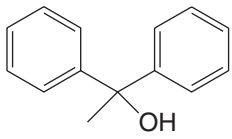
12.38 Explain how ^{1}H NMR, ^{13}C NMR, and IR spectroscopy could be used to differentiate among the following compounds.



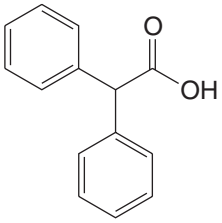
2-Phenylethanol



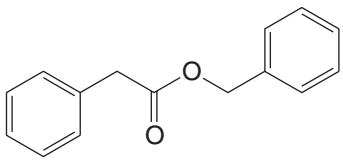
1,2-Diphenylethanol



1,1-Diphenylethanol

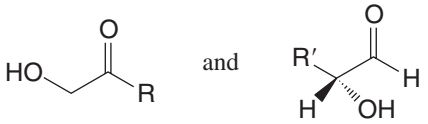


2,2-Diphenylethanoic acid



Benzyl 2-phenylethanoate

12.39 When sucrose (common table sugar) is treated with aqueous acid, it is cleaved and yields simpler sugars of these types:

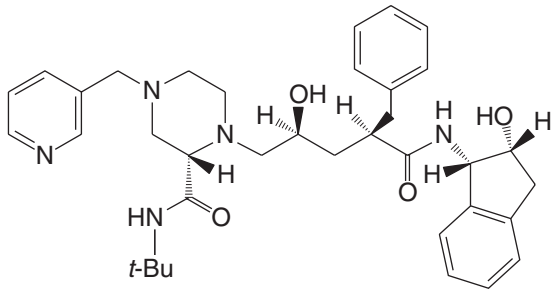


For reasons to be studied later, in the use of this procedure for the identification of the sugars incorporated in a saccharide like sucrose, the product mixtures are often treated with sodium borohydride before analysis. What limitation(s) does this put on identification of the sugar building blocks of the starting saccharide?

12.40 An unknown **X** shows a broad absorption band in the infrared at 3200–3550 cm^{-1} but none in the 1620–1780 cm^{-1} region. It contains only C, H, and O. A 116-mg sample was treated with an excess of methylmagnesium bromide, producing 48.7 mL of methane gas collected over mercury at 20°C and 750 mm Hg. The mass spectrum of **X** has its molecular ion (barely detectable) at 116 *m/z* and a fragment peak at 98. What does this information tell you about the structure of **X**?

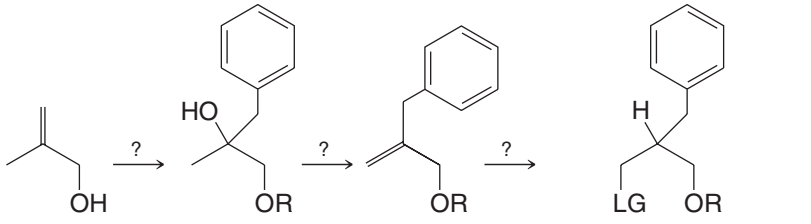
Learning Group Problems

The problem below is directed toward devising a hypothetical pathway for the synthesis of the acyclic central portion of Crixivan (Merck and Company's HIV protease inhibitor). Note that your synthesis might not adequately control the stereochemistry during each step, but for this particular exercise that is not expected.

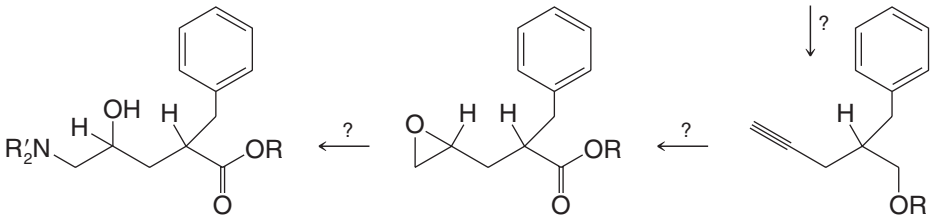


Crixivan

Fill in missing compounds and reagents in the following outline of a hypothetical synthesis of the acyclic central portion of Crixivan. Note that more than one intermediate compound may be involved between some of the structures shown below.



LG = some leaving group



(R would be H initially. Then, by reactions which you do not need to specify, it would be converted to an alkyl group.)

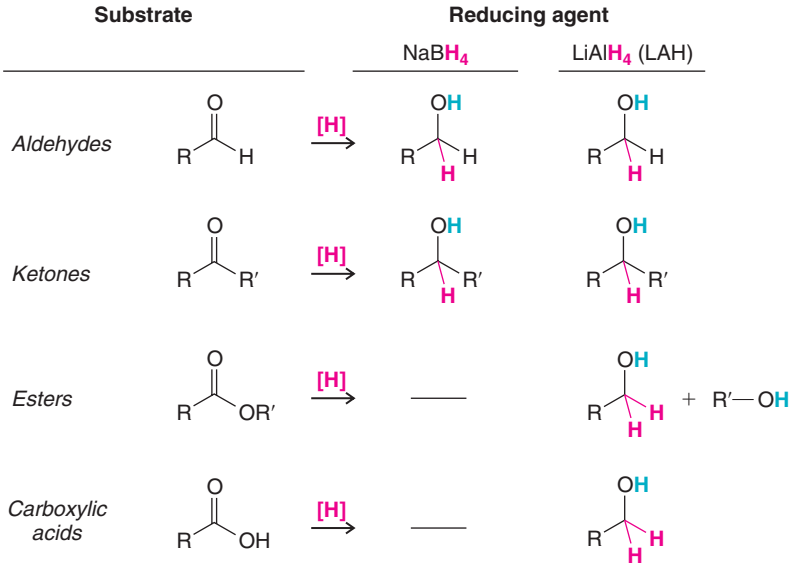
Summary of Reactions

Summaries of reactions discussed in this chapter are shown below. Detailed conditions for the reactions that are summarized can be found in the chapter section where each is discussed.

Synthetic Connections of Alcohols and Carbonyl Compounds

1. Carbonyl Reduction Reactions

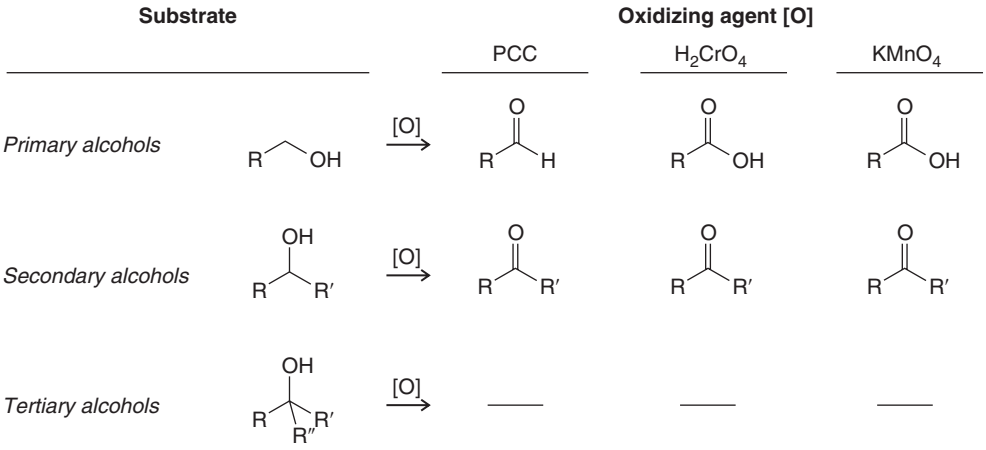
- Aldehydes to primary alcohols
- Ketones to secondary alcohols
- Esters to alcohols
- Carboxylic acids to primary alcohols



(Hydrogen atoms in blue are added during the reaction workup by water or aqueous acid.)

2. Alcohol Oxidation Reactions

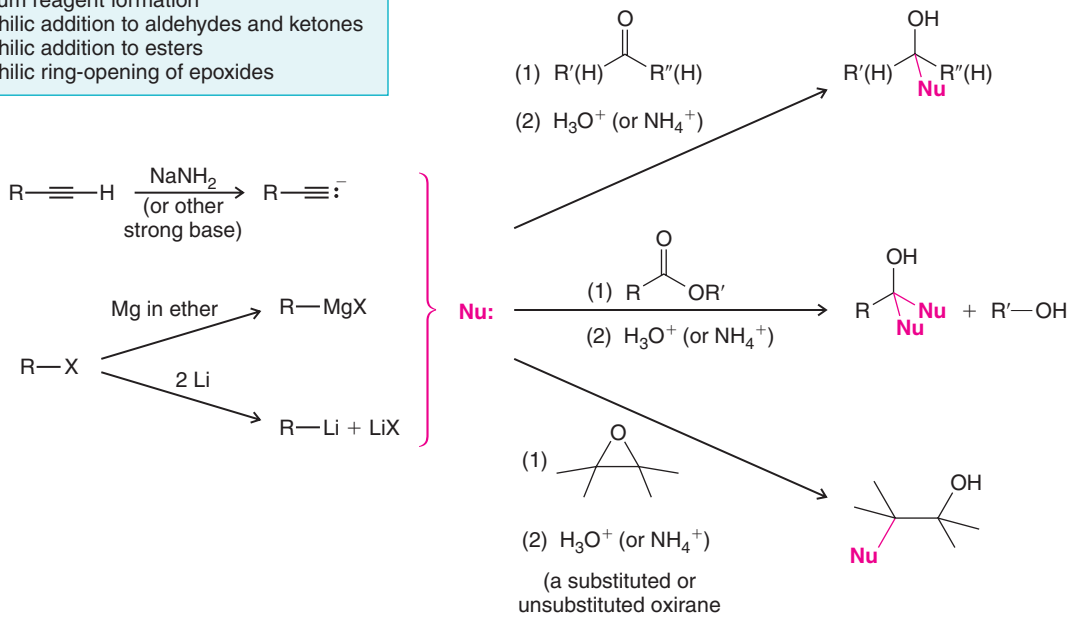
- Primary alcohols to aldehydes
- Primary alcohols to carboxylic acids
- Secondary alcohols to ketones



Synthetic Connections of Alcohols and Carbonyl Compounds

3. Carbon-Carbon Bond Forming Reactions

- Alkynide anion formation
- Grignard reagent formation
- Alkyllithium reagent formation
- Nucleophilic addition to aldehydes and ketones
- Nucleophilic addition to esters
- Nucleophilic ring-opening of epoxides



Nu = alkynyl group, or alkyl group from Grignard or alkyllithium reagent

WILEY PLUS See *First Review Problem Set* in *WileyPLUS*

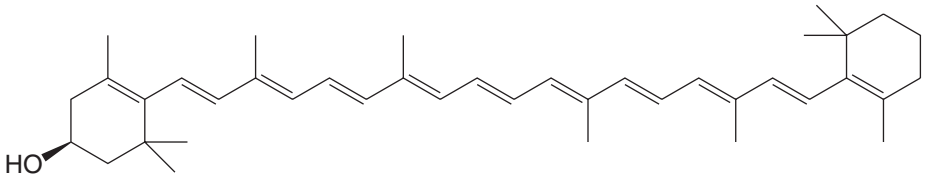
13

Conjugated Unsaturated Systems

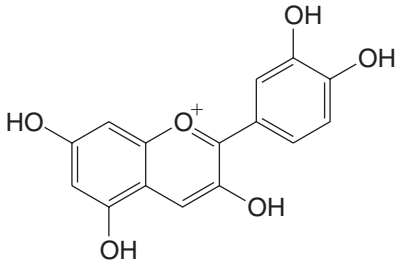
All of the brilliant colors of fall foliage have one thing in common. The colors of fall are caused by molecules that contain conjugated unsaturated systems.

- A conjugated unsaturated system is a molecular unit containing π electrons that can be delocalized over three or more contiguous atoms.

The carotenes, xanthophylls, and anthocyanins are some families of natural pigments that contain conjugated unsaturated systems. A few examples are shown here.



Cryptoxanthin (a xanthophyll)

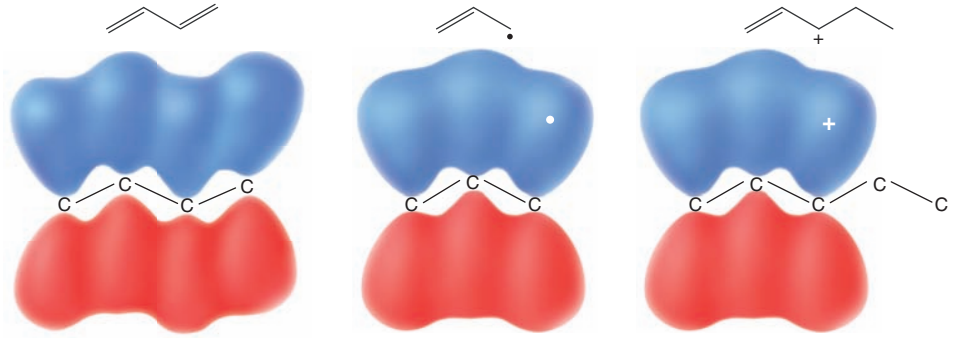


Cyanidin (an anthocyanin)

In this chapter we shall study conjugated systems and find that they have special aspects of reactivity. Radicals, cations, and anions that are formed as part of a conjugated system have greater stability than their nonconjugated counterparts, making them especially important reaction intermediates. Conjugated unsaturated systems also absorb energy in the ultraviolet and visible regions of the spectrum, the latter of which accounts for the colors we observe in organic pigments. And lastly, conjugated dienes undergo a very important ring-forming reaction called the Diels–Alder reaction, for which the Nobel Prize was awarded to Otto Diels and Kurt Alder.

13.1 Introduction

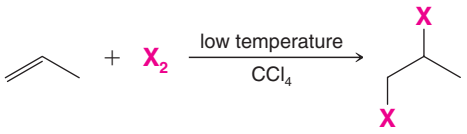
At its essence, a conjugated system involves at least one atom with a *p* orbital adjacent to at least one π bond. The adjacent atom with the *p* orbital can be part of another π bond, as in 1,3-butadiene, or a radical, cationic, or anionic reaction intermediate. If an example specifically derives from a propenyl group, a common name for this group is **allyl**. More generally when we are considering a radical, cation, or anion that is adjacent to one or more π bonds in a molecule larger than propene or propene itself, the adjacent position is called **allylic**.



As we shall see next, radical substitution at an allylic position is especially favorable because the intermediate radical is part of a conjugated system.

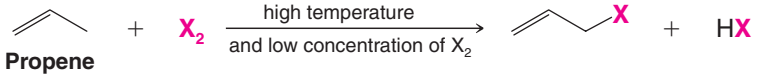
13.2 Allylic Substitution and the Allyl Radical

When propene reacts with bromine or chlorine at low temperatures, the reaction that takes place is the usual addition of halogen to the double bond:



At low temperature an addition reaction occurs.

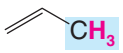
However, when propene reacts with chlorine or bromine at very high temperatures or under conditions in which the concentration of the halogen is very small, the reaction that occurs is a **substitution.** These two examples illustrate how we can often change the course of an organic reaction simply by changing the conditions. (They also illustrate the need for specifying the conditions of a reaction carefully when we report experimental results.)



At high temperature (or in the presence of a radical initiator) and low concentration of X_2 a substitution reaction occurs.

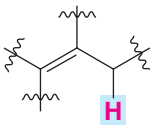
In this substitution a halogen atom replaces one of the hydrogen atoms of the methyl group of propene.

- The hydrogens on the sp^3 carbon adjacent to the double bond are called the **allylic hydrogen atoms**.
- The reaction is an **allylic substitution**:



Allylic hydrogen atoms

Allylic hydrogen atom and *allylic substitution* are general terms as well. The hydrogen atoms of any saturated carbon atom adjacent to a double bond are called allylic hydrogen atoms. Any reaction in which an allylic hydrogen atom is replaced is called an allylic substitution.

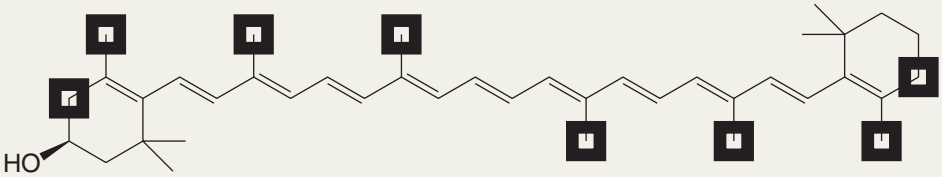


An allylic hydrogen atom that can undergo allylic substitution.

Solved Problem 13.1

Identify all of the positions bearing allylic hydrogen atoms in cryptoxanthin (shown earlier in this chapter).

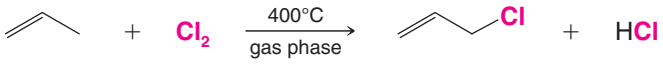
STRATEGY AND ANSWER Allylic hydrogen atoms in cryptoxanthin are found on the sp^3-hybridized carbons adjacent to π bonds. These positions are labeled by boxes in the formula below.



Cryptoxanthin (with positions bearing allylic hydrogen atoms shown in boxes)

13.2A Allylic Chlorination (High Temperature)

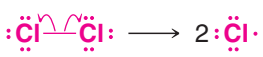
Propene undergoes allylic chlorination when propene and chlorine react in the gas phase at 400°C. This method for synthesizing allyl chloride is called the Shell process.



Propene **3-Chloropropene (allyl chloride)**

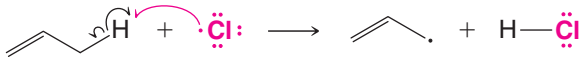
The mechanism for allylic substitution is the same as the chain mechanism for alkane halogenations that we saw in Chapter 10. In the chain-initiating step, the chlorine molecule dissociates into chlorine atoms.

Chain-Initiating Step



In the first chain-propagating step the chlorine atom abstracts one of the allylic hydrogen atoms.

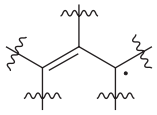
First Chain-Propagating Step



Allyl radical

The radical that is produced in this step is called an **allyl radical**.

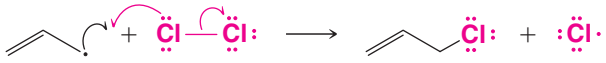
- A radical of the general type shown here is called an *allylic* radical.



An allylic radical

In the second chain-propagating step the allyl radical reacts with a molecule of chlorine.

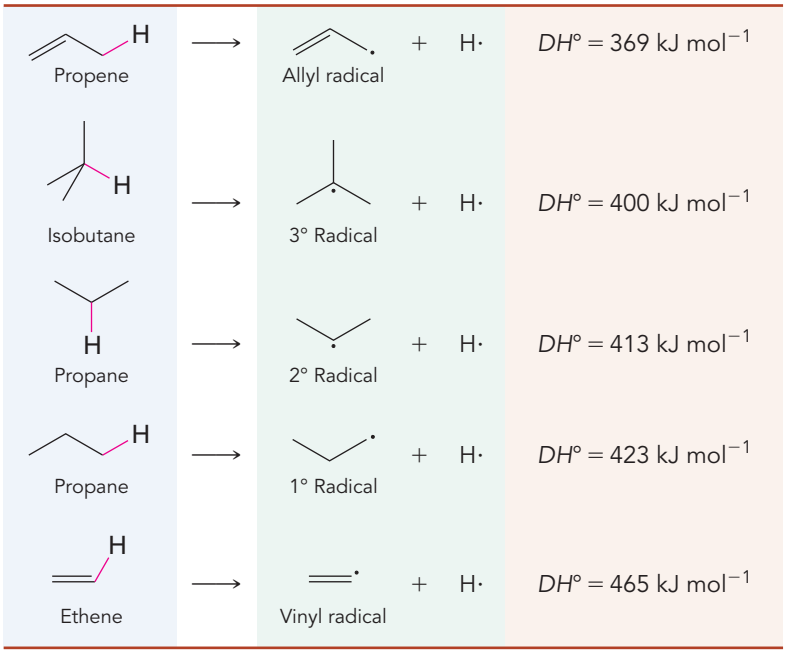
Second Chain-Propagating Step



Allyl chloride

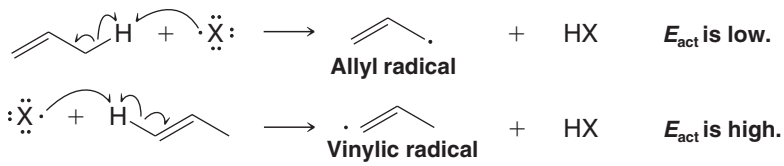
This step results in the formation of a molecule of allyl chloride and a chlorine atom. The chlorine atom then brings about a repetition of the first chain-propagating step. The chain reaction continues until the usual chain-terminating steps (see Section 10.4) consume the radicals.

The reason for substitution at the allylic hydrogen atoms of propene will be more understandable if we examine the bond dissociation energy of an allylic carbon–hydrogen bond and compare it with the bond dissociation energies of other carbon–hydrogen bonds.



See Table 10.1 for a list of additional bond dissociation energies.

We see that an allylic carbon–hydrogen bond of propene is broken with greater ease than even the tertiary carbon–hydrogen bond of isobutane and with far greater ease than a vinylic carbon–hydrogen bond:



- The ease with which an allylic carbon–hydrogen bond is broken means that relative to primary, secondary, tertiary, and vinylic free radicals an allylic radical is the *most stable* (Fig. 13.1):

Relative stability: allylic or allyl > 3° > 2° > 1° > vinyl or vinylic

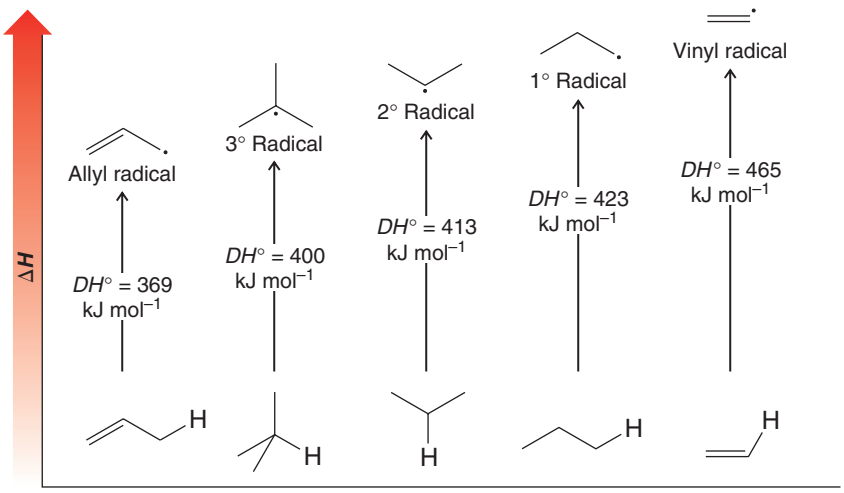
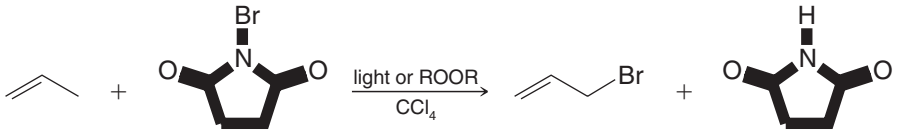


Figure 13.1 The relative stability of the allyl radical compared to 1°, 2°, 3°, and vinyl radicals. (The stabilities of the radicals are relative to the hydrocarbon from which each was formed, and the overall order of stability is allyl > 3° > 2° > 1° > vinyl.)

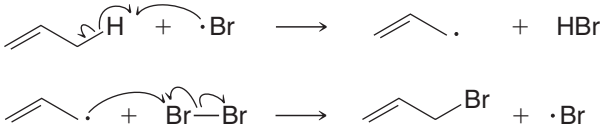
13.2B Allylic Bromination with *N*-Bromosuccinimide (Low Concentration of Br_2)

Propene undergoes allylic bromination when it is treated with *N*-bromosuccinimide (NBS) in CCl_4 in the presence of peroxides or light:

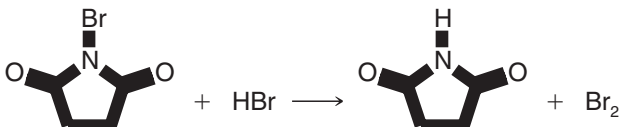


***N*-Bromosuccinimide (NBS)** — **3-Bromopropene (allyl bromide)** — **Succinimide**

The reaction is initiated by the formation of a small amount of $Br\cdot$ (possibly formed by dissociation of the N—Br bond of the NBS). The main propagation steps for this reaction are the same as for allylic chlorination (Section 13.2A):

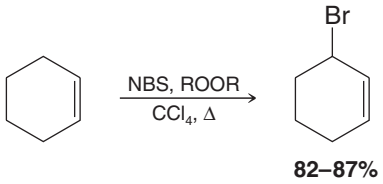


N-Bromosuccinimide is a solid that is nearly insoluble in CCl_4 which provides a constant but very low concentration of bromine in the reaction mixture. It does this by reacting very rapidly with the HBr formed in the substitution reaction. Each molecule of HBr is replaced by one molecule of Br_2.



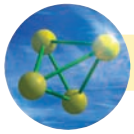
Under these conditions, that is, *in a nonpolar solvent and with a very low concentration of bromine*, very little bromine adds to the double bond; it reacts by substitution and replaces an allylic hydrogen atom instead.

The following reaction with cyclohexene is another example of allylic bromination with NBS.



82–87%

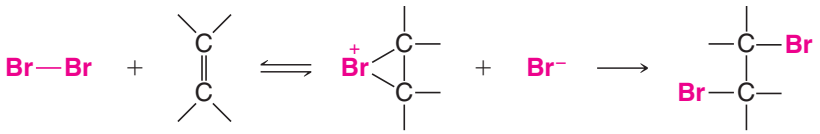
- In general, NBS is a good reagent to use for allylic bromination.



THE CHEMISTRY OF . . .

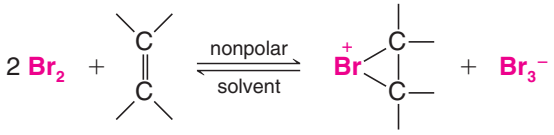
Allylic Bromination

Why, we might ask, does a low concentration of bromine favor allylic substitution over addition? To understand this, we must recall the mechanism for addition and notice that in the first step only one atom of the bromine molecule becomes attached to the alkene *in a reversible process*. The other atom (now a bromide anion) becomes attached in the second step:

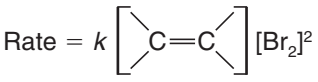


With a low concentration of bromine initially, the concentration of the bromonium ion and bromide anion after the first step will also be low. Consequently, the probability of a bromide anion finding a bromonium ion in its vicinity for the second step is also low, and hence the overall rate of addition is slow and allylic substitution competes successfully.

The use of a nonpolar solvent also slows addition. Since there are no polar molecules to solvate (and thus stabilize) the bromide ion formed in the first step, the bromide ion uses a bromine molecule as a substitute:



This means that in a nonpolar solvent the rate equation is second order with respect to bromine,



and that the low bromine concentration has an even more pronounced effect in slowing the rate of addition.

Understanding why a high temperature favors allylic substitution over addition requires a consideration of the effect of entropy changes on equilibria (Section 3.10). The addition reaction, because it combines two molecules into one, has a substantial negative entropy change. At low temperatures, the $T\Delta S°$ term in $\Delta G° = \Delta H° - T\Delta S°$ is not large enough to offset the favorable $\Delta H°$ term. But as the temperature is increased, the $T\Delta S°$ term becomes more significant, $\Delta G°$ becomes more positive, and the equilibrium becomes more unfavorable.

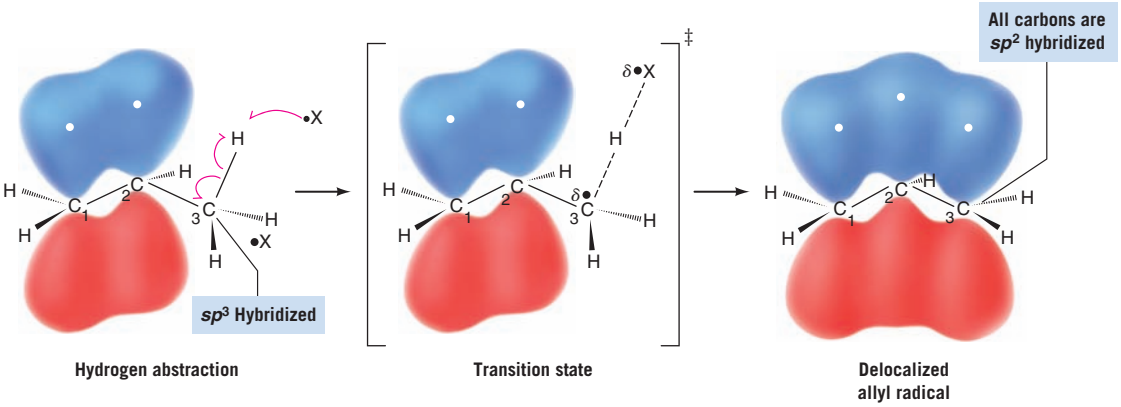
13.3 *The Stability of the Allyl Radical*

An explanation of the stability of the allyl radical can be approached in two ways: in terms of molecular orbital theory and in terms of resonance theory (Section 1.8). As we shall see soon, both approaches give us equivalent descriptions of the allyl radical. The molecular orbital approach is easier to visualize, so we shall begin with it. (As preparation for this section, it may help the reader to review the molecular orbital theory given in Sections 1.11 and 1.13.)

13.3A Molecular Orbital Description of the Allyl Radical

As an allylic hydrogen atom is abstracted from propene (see the following diagram), the sp^3-hybridized carbon atom of the methyl group changes its hybridization state to sp^2 (see Section 10.7). The p orbital of this new sp^2-hybridized carbon atom overlaps with the p orbital of the central carbon atom.

- In the allyl radical three p orbitals overlap to form a set of π molecular orbitals that encompass all three carbon atoms.
- The new p orbital of the allyl radical is said to be *conjugated* with those of the double bond, and the allyl radical is said to be a *conjugated unsaturated system*.

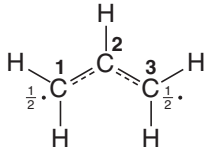


- The unpaired electron of the allyl radical and the two electrons of the π bond are **delocalized** over all three carbon atoms.

Delocalization of the unpaired electron accounts for the greater stability of the allyl radical when compared to primary, secondary, and tertiary radicals. Although some delocalization occurs in primary, secondary, and tertiary radicals, delocalization is not as effective because it occurs only through hyperconjugation (Section 6.11B) with σ bonds.

The diagram in Fig. 13.2 illustrates how the three p orbitals of the allyl radical combine to form three π molecular orbitals. (*Remember*: The number of molecular orbitals that results always equals the number of atomic orbitals that combine; see Section 1.11.) The bonding π molecular orbital is of lowest energy; it encompasses all three carbon atoms and is occupied by two spin-paired electrons. This bonding π orbital is the result of having p orbitals with lobes of the same sign overlap between adjacent carbon atoms. This type of overlap, as we recall, increases the π-electron density in the regions between the atoms where it is needed for bonding. The nonbonding π orbital is occupied by one unpaired electron, and it has a node at the central carbon atom. This node means that the unpaired electron is located in the vicinity of carbon atoms 1 and 3 only. The antibonding π molecular orbital results when orbital lobes of opposite sign overlap between adjacent carbon atoms: Such overlap means that in the antibonding π orbital there is a node between each pair of carbon atoms. This antibonding orbital of the allyl radical is of highest energy and is empty in the ground state of the radical.

We can illustrate the picture of the allyl radical given by molecular orbital theory with the following structure:



We indicate with dashed lines that both carbon–carbon bonds are partial double bonds. This accommodates one of the things that molecular orbital theory tells us: *that there is a π bond encompassing all three atoms*. We also place the symbol $\frac{1}{2}$ beside the C1 and C3 atoms. This denotes a second thing molecular orbital theory tells us: *that electron density from the unpaired electron is equal in the vicinity of C1 and C3*. Finally, implicit in the molecular

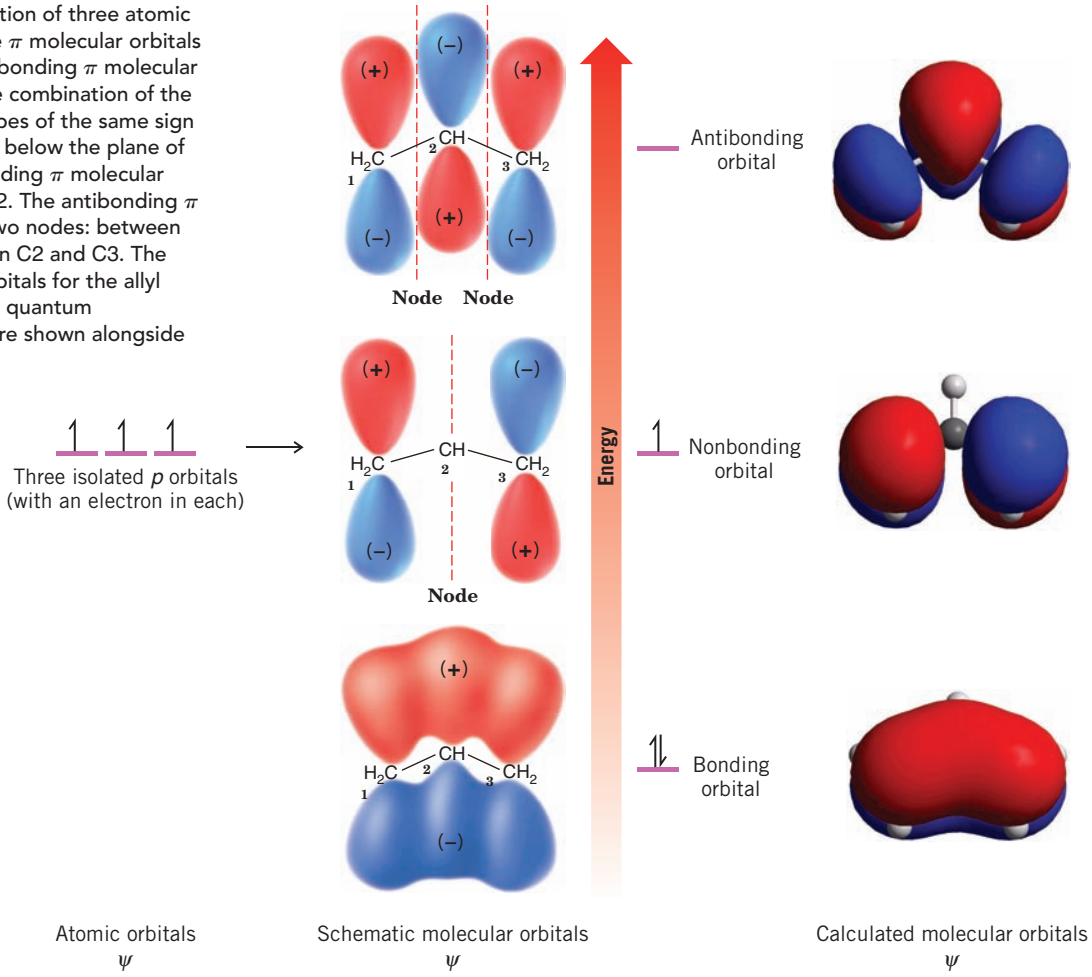


Figure 13.2 Combination of three atomic *p* orbitals to form three π molecular orbitals in the allyl radical. The bonding π molecular orbital is formed by the combination of the three *p* orbitals with lobes of the same sign overlapping above and below the plane of the atoms. The nonbonding π molecular orbital has a node at C2. The antibonding π molecular orbital has two nodes: between C1 and C2 and between C2 and C3. The shapes of molecular orbitals for the allyl radical calculated using quantum mechanical principles are shown alongside the schematic orbitals.

orbital picture of the allyl radical is this: The two ends of the allyl radical are *equivalent*. This aspect of the molecular orbital description is also implicit in the formula just given.

13.3B Resonance Description of the Allyl Radical

In Section 13.2A we wrote the structure of the allyl radical as **A**:

A

However, we might just as well have written the equivalent structure, **B**:

B

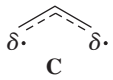
In writing structure **B**, we do not mean to imply that we have simply taken structure **A** and turned it over. What we have done is move the electrons in the following way:

We have not moved the nuclei.

Resonance theory (Section 1.8) tells us that whenever we can write two structures for a chemical entity ***that differ only in the positions of the electrons***, the entity cannot be represented by either structure alone but is a *hybrid* of both. We can represent the hybrid in two ways. We can write both structures **A** and **B** and connect them with a double-headed arrow, the special arrow we use to indicate that they are resonance structures:

A **B**

Or we can write a single structure, **C**, that blends the features of both resonance structures:



C

We see, then, that resonance theory gives us exactly the same picture of the allyl radical that we obtained from molecular orbital theory. Structure **C** describes the carbon–carbon bonds of the allyl radical as partial double bonds. The resonance structures **A** and **B** also tell us that the unpaired electron is associated only with the C1 and C3 atoms. We indicate this in structure **C** by placing a δ beside C1 and C3.[†] Because resonance structures **A** and **B** are equivalent, the electron density from the unpaired electron is shared equally by C1 and C3.

Another rule in resonance theory is the following:

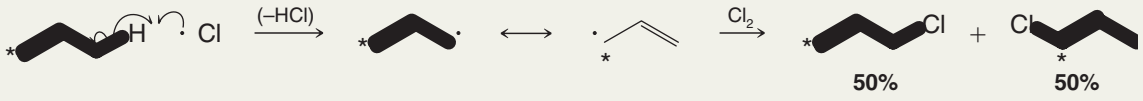
- Whenever equivalent resonance structures can be written for a chemical species, the chemical species is much more stable than any resonance structure (when taken alone) would indicate.

If we were to examine either **A** or **B** alone, we might decide incorrectly that it resembled a primary radical. Thus, we might estimate the stability of the allyl radical as approximately that of a primary radical. In doing so, we would greatly underestimate the stability of the allyl radical. Resonance theory tells us, however, that since **A** and **B** are *equivalent resonance structures*, the allyl radical should be much more stable than either, that is, much more stable than a primary radical. This correlates with what experiments have shown to be true: **The allyl radical is even more stable than a tertiary radical**.

Solved Problem 13.2

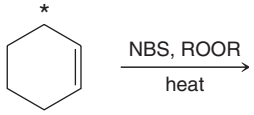
Subjecting propene labeled with ^{13}C at carbon 1 to allylic chlorination (see below) leads to a 50 : 50 mixture of 1-chloropropene labeled at C1 and at C3. Write a mechanism that explains this result. (An asterisk * next to a carbon atom indicates that the carbon atom is ^{13}C.)

STRATEGY AND ANSWER We recall (Section 13.2A) that the mechanism for allylic chlorination involves the formation of a resonance-stabilized radical created by having a chlorine atom abstract an allylic hydrogen atom. Because the radical formed in this case is a hybrid of two structures (which are equivalent except for the position of the label), it can react with Cl_2 at either end to give a 50 : 50 mixture of the differently labeled products.



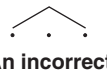
Review Problem 13.1

Consider the allylic bromination of cyclohexene labeled at C3 with ^{13}C. Neglecting stereoisomers, what products would you expect from this reaction?



(* = ^{13}C-labeled position)

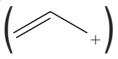
[†]A resonance structure such as the one shown below would indicate that an unpaired electron is associated with C2. This structure is not a proper resonance structure because resonance theory dictates that *all resonance structures must have the same number of unpaired electrons* (see Section 13.5A).



An incorrect resonance structure

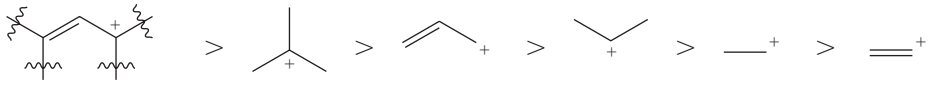
13.4 The Allyl Cation

Carbocations can be allylic as well.

- The **allyl (propenyl) cation**  is even more stable than a secondary carbocation and is almost as stable as a tertiary carbocation.

In general terms, the relative order of stabilities of carbocations is that given here.

Relative Order of Carbocation Stability



Substituted allylic > 3° > Allyl > 2° > 1° > Vinyl

The molecular orbital description of the allyl cation is shown in Fig. 13.3.

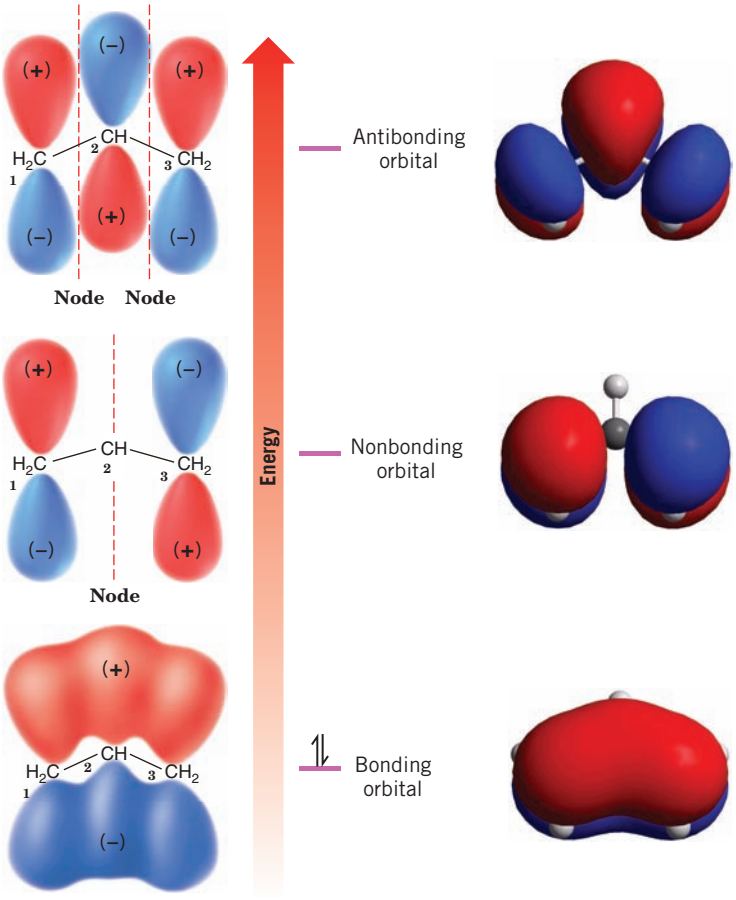
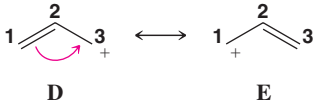


Figure 13.3 The π molecular orbitals of the allyl cation. The allyl cation, like the allyl radical (Fig. 13.2), is a conjugated unsaturated system. The shapes of molecular orbitals for the allyl cation calculated using quantum mechanical principles are shown alongside the schematic orbitals.

The bonding π molecular orbital of the allyl cation, like that of the allyl radical (Fig. 13.2), contains two spin-paired electrons. The nonbonding π molecular orbital of the allyl cation, however, is empty.

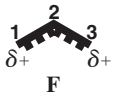
Resonance theory depicts the allyl cation as a hybrid of structures **D** and **E** represented here:



D **E**

Because **D** and **E** are *equivalent* resonance structures, resonance theory predicts that the allyl cation should be unusually stable. Since the positive charge is located on C3 in **D** and on C1 in **E**, resonance theory also tells us that the positive charge should be delocalized

over both carbon atoms. Carbon atom 2 carries none of the positive charge. The hybrid structure **F** includes charge and bond features of both **D** and **E**:



F

Solved Problem 13.3

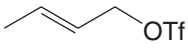
Allyl bromide (3-bromo-1-propene) forms a carbocation readily. For example, it undergoes S_N1 reactions. Explain this observation.

STRATEGY AND ANSWER Ionization of allyl bromide (at right) produces an allyl cation that is unusually stable (far more stable than a simple primary carbocation) because it is resonance stabilized.

Resonance-stabilized carbocation

Review Problem 13.2

(a) Draw resonance structures for the carbocation that could be formed from (*E*)-2-butenyl trifluoromethanesulfonate.



(b) One of the resonance structures for this carbocation should be a more important contributor to the resonance hybrid than the other. Which resonance structure would be the greater contributor?

(c) What products would you expect if this carbocation reacted with a chloride ion?

13.5 Resonance Theory Revisited

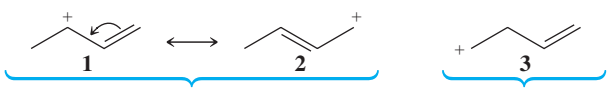
We have already used resonance theory in earlier chapters, and we have been using it extensively in this chapter because we are describing radicals and ions with delocalized electrons (and charges) in π bonds. Resonance theory is especially useful with systems like this, and we shall use it again and again in the chapters that follow. In Section 1.8 we had an introduction to resonance theory and an initial presentation of some rules for writing resonance structures. It should now be helpful, in light of our previous discussions of relative carbocation stability and radicals, and our growing understanding of conjugated systems, to review and expand on those rules as well as those for the ways in which we estimate the relative contribution a given structure will make to the overall hybrid.

Helpful Hint

Resonance is an important tool we use frequently when discussing structure and reactivity.

13.5A Rules for Writing Resonance Structures

1. **Resonance structures exist only on paper.** Although they have no real existence of their own, **resonance structures** are useful because they allow us to describe molecules, radicals, and ions for which a single Lewis structure is inadequate. Instead, we write two or more Lewis structures, calling them resonance structures or resonance contributors. We connect these structures by double-headed arrows (⟷), and we say that the hybrid of all of them represents the real molecule, radical, or ion.
2. **In writing resonance structures, we are only allowed to move electrons.** The positions of the nuclei of the atoms must remain the same in all of the structures. Structure **3** is not a resonance structure for the allylic cation, for example, because in order to form it we would have to move a hydrogen atom and this is not permitted:

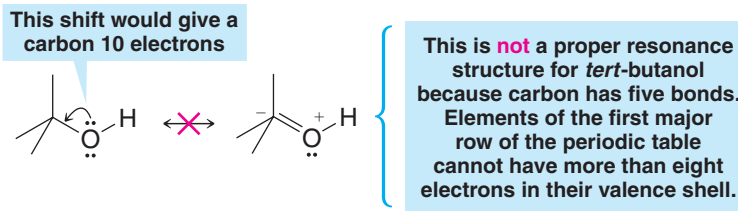


These are resonance structures for the allylic cation formed when 1,3-butadiene accepts a proton.

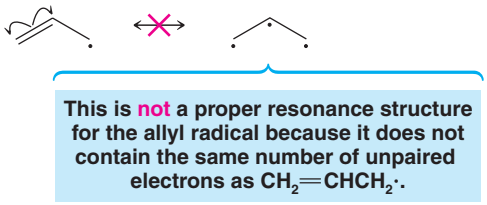
This is not a proper resonance structure for the allylic cation because a hydrogen atom has been moved.

Generally speaking, when we move electrons we move only those of π bonds (as in the example above) and those of lone pairs.

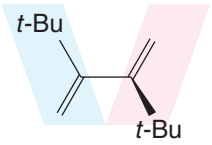
3. **All of the structures must be proper Lewis structures.** We should not write structures in which carbon has five bonds, for example:



4. **All resonance structures must have the same number of unpaired electrons.** The structure on the right is not a proper resonance structure for the allyl radical because it contains three unpaired electrons whereas the allyl radical contains only one:

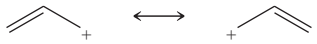


5. **All atoms that are part of the delocalized π-electron system must lie in a plane or be nearly planar.** For example, 2,3-di-*tert*-butyl-1,3-butadiene behaves like a *nonconjugated* diene because the large *tert*-butyl groups twist the structure and prevent the double bonds from lying in the same plane. Because they are not in the same plane, the *p* orbitals at C2 and C3 do not overlap and delocalization (and therefore resonance) is prevented:



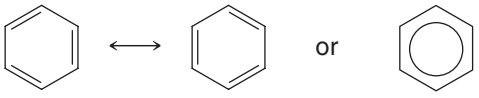
2,3-Di-*tert*-butyl-1,3-butadiene

6. **The energy of the actual molecule is lower than the energy that might be estimated for any contributing structure.** The actual allyl cation, for example, is more stable than either resonance structure **4** or **5** taken separately would indicate. Structures **4** and **5** resemble primary carbocations and yet the allyl cation is more stable (has lower energy) than a secondary carbocation. Chemists often call this kind of stabilization *resonance stabilization*:



4 **5**

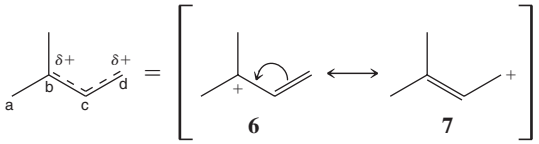
In Chapter 14 we shall find that benzene is highly resonance stabilized because it is a hybrid of the two equivalent forms that follow:



Resonance structures for benzene **Representation of hybrid**

7. **Equivalent resonance structures make equal contributions to the hybrid, and a system described by them has a large resonance stabilization.** Structures **4** and **5** above make equal contributions to the allylic cation because they are equivalent. They also make a large stabilizing contribution and account for allylic cations being unusually stable. The same can be said about the contributions made by the equivalent structures **A** and **B** (Section 13.3B) for the allyl radical.

8. The more stable a structure is (when taken by itself), the greater is its contribution to the hybrid. Structures that are not equivalent do not make equal contributions. For example, the following cation is a hybrid of structures **6** and **7**. Structure **6** makes a greater contribution than **7** because structure **6** is a more stable tertiary carbocation while structure **7** is a primary cation:

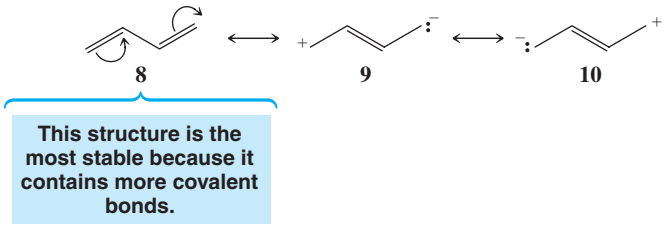


That **6** makes a larger contribution means that the partial positive charge on carbon b of the hybrid will be larger than the partial positive charge on carbon d. It also means that the bond between carbon atoms c and d will be more like a double bond than the bond between carbon atoms b and c.

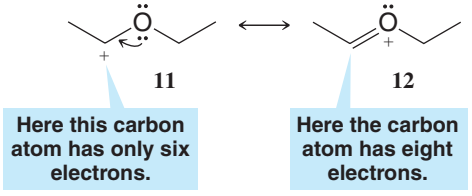
13.5B Estimating the Relative Stability of Resonance Structures

The following rules will help us in making decisions about the relative stabilities of resonance structures.

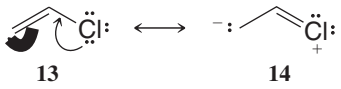
a. The more covalent bonds a structure has, the more stable it is. This is exactly what we would expect because we know that forming a covalent bond lowers the energy of atoms. This means that of the following structures for 1,3-butadiene, **8** is by far the most stable and makes by far the largest contribution because it contains one more bond. (It is also more stable for the reason given under rule **c**.)



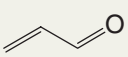
b. Structures in which all of the atoms have a complete valence shell of electrons (i.e., the noble gas structure) are especially stable and make large contributions to the hybrid. Again, this is what we would expect from what we know about bonding. This means, for example, that **12** makes a larger stabilizing contribution to the cation below than **11** because all of the atoms of **12** have a complete valence shell. (Notice too that **12** has more covalent bonds than **11**; see rule **a**.)



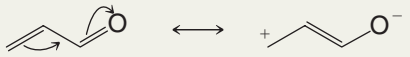
c. Charge separation decreases stability. Separating opposite charges requires energy. Therefore, structures in which opposite charges are separated have greater energy (lower stability) than those that have no charge separation. This means that of the following two structures for vinyl chloride, structure **13** makes a larger contribution because it does not have separated charges. (This does not mean that structure **14** does not contribute to the hybrid; it just means that the contribution made by **14** is smaller.)



Solved Problem 13.4

Write resonance structures for  and tell which structure would be the greater contributor to the resonance hybrid.

STRATEGY AND ANSWER We write the structure for the molecule and then move the electron pairs as shown below. Then we examine the two structures. The second structure contains separated charges (which would make it less stable) and the first structure contains more bonds (which would make it more stable). Both factors tell us that the first structure is more stable. Consequently, it should be the greater contributor to the hybrid.

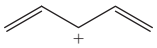


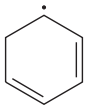
More bonds **Separated charges**

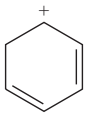
Review Problem 13.3

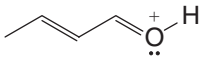
Write the important resonance structures for each of the following:

(a) 

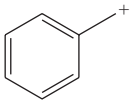
(b) 

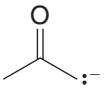
(c) 

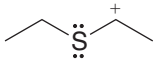
(d) 

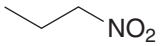
(e) 

(f) $CH_2{=}CH{-}Br$

(g) 

(h) 

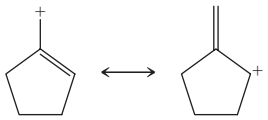
(i) 

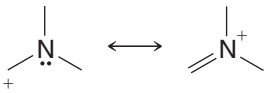
(j) 

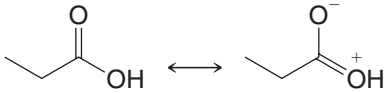
Review Problem 13.4

From each set of resonance structures that follow, designate the one that would contribute most to the hybrid and explain your choice:

(a) 

(b) 

(c) 

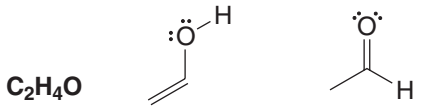
(d) 

(e) 

(f) $:NH_2{-}C{\equiv}N: \longleftrightarrow {}^{+}NH_2{=}C{=}N:^{-}$

Review Problem 13.5

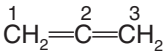
The following enol (an alk*ene*-alch*ool*) and keto (a *ket*one) forms of C_2H_4O differ in the positions for their electrons, but they are not resonance structures. Explain why they are not.

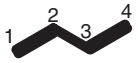


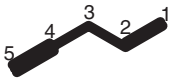
13.6 Alkadienes and Polyunsaturated Hydrocarbons

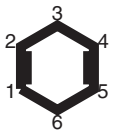
Many hydrocarbons are known that contain more than one double or triple bond. A hydrocarbon that contains two double bonds is called an **alkadiene**; one that contains three double bonds is called an **alkatriene**, and so on. Colloquially, these compounds are often referred to simply as dienes or trienes. A hydrocarbon with two triple bonds is called an **alkadiyne**, and a hydrocarbon with a double and triple bond is called an **alkenyne**.

The following examples of polyunsaturated hydrocarbons illustrate how specific compounds are named. Recall from IUPAC rules (Sections 4.5 and 4.6) that the numerical locants for double and triple bonds can be placed at the beginning of the name or immediately preceding the respective suffix. We provide examples of both styles.







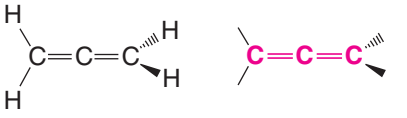


The multiple bonds of polyunsaturated compounds are classified as being **cumulated, conjugated**, or **isolated**.

- The double bonds of a 1,2-diene (such as 1,2-propadiene, also called allene) are said to be **cumulated** because one carbon (the central carbon) participates in two double bonds.

Hydrocarbons whose molecules have cumulated double bonds are called **cumulenes**. The name **allene** (Section 5.18) is also used as a class name for molecules with two cumulated double bonds:

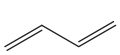
Cumulated double bonds



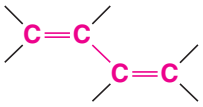
An example of a conjugated diene is 1,3-butadiene.

- In **conjugated** polyenes the double and single bonds *alternate* along the chain:

Conjugated double bonds



1,3-Butadiene



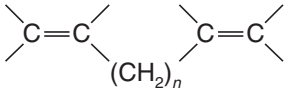
A conjugated diene

(2*E*,4*E*,6*E*)-Octa-2,4,6-triene is an example of a conjugated alkatriene.

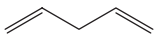
- If one or more saturated carbon atoms intervene between the double bonds of an alkadiene, the double bonds are said to be **isolated**.

An example of an isolated diene is 1,4-pentadiene:

Isolated double bonds



An isolated diene ($n \neq 0$)



1,4-Pentadiene

Review Problem 13.6

(a) Which other compounds in Section 13.6 are conjugated dienes?

(b) Which other compounds are isolated dienes?

(c) Which compound is an isolated enyne?

In Chapter 5 we saw that appropriately substituted cumulated dienes (allenes) give rise to chiral molecules. Cumulated dienes have had some commercial importance, and cumulated double bonds are occasionally found in naturally occurring molecules. In general, cumulated dienes are less stable than isolated dienes.

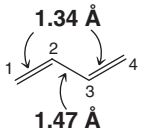
The double bonds of isolated dienes behave just as their name suggests—as isolated "enes." They undergo all of the reactions of alkenes, and, except for the fact that they are capable of reacting twice, their behavior is not unusual. Conjugated dienes are far more interesting because we find that their double bonds interact with each other. This interaction leads to unexpected properties and reactions. We shall therefore consider the chemistry of conjugated dienes in detail.

13.7 1,3-Butadiene: Electron Delocalization

13.7A Bond Lengths of 1,3-Butadiene

The carbon–carbon bond lengths of 1,3-butadiene have been determined and are shown here:

Double bonds are shorter than single bonds



The C1—C2 bond and the C3—C4 bond are (within experimental error) the same length as the carbon–carbon double bond of ethene. The central bond of 1,3-butadiene (1.47 Å), however, is considerably shorter than the single bond of ethane (1.54 Å).

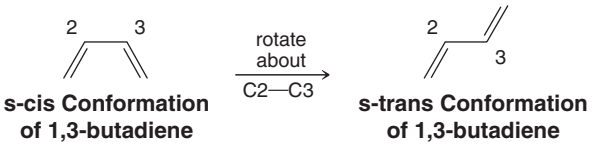
This should not be surprising. All of the carbon atoms of 1,3-butadiene are sp^2 hybridized and, as a result, the central bond of butadiene results from overlapping sp^2 orbitals. And, as we know, a sigma bond that is sp^3–sp^3 is *longer*. There is, in fact, a steady decrease in bond length of carbon–carbon single bonds as the hybridization state of the bonded atoms changes from sp^3 to sp (Table 13.1).

TABLE 13.1 Carbon–Carbon Single-Bond Lengths and Hybridization State

Compound	Hybridization State	Bond Length (Å)
$H_3C—CH_3$	sp^3–sp^3	1.54
$CH_2=CH—CH_3$	sp^2–sp^3	1.50
$CH_2=CH—CH=CH_2$	sp^2–sp^2	1.47
$HC\equiv C—CH_3$	sp–sp^3	1.46
$HC\equiv C—CH=CH_2$	sp–sp^2	1.43
$HC\equiv C—C\equiv CH$	sp–sp	1.37

13.7B Conformations of 1,3-Butadiene

There are two possible planar conformations of 1,3-butadiene: the s-cis and the s-trans conformations.

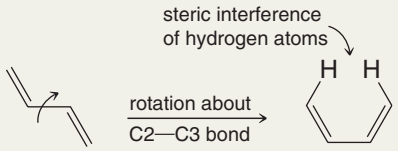


These are not true cis and trans forms since the s-cis and s-trans conformations of 1,3-butadiene can be interconverted through rotation about the single bond (hence the prefix s). The s-trans conformation is the predominant one at room temperature. We shall see that the s-cis conformation of 1,3-butadiene and other 1,3-conjugated alkenes is necessary for the Diels–Alder reaction (Section 13.11).

Solved Problem 13.5

Provide an explanation for the fact that many more molecules are in the s-trans conformation of 1,3-butadiene at equilibrium.

STRATEGY AND ANSWER The s-cis conformation of 1,3-butadiene is less stable, and therefore less populated, than the s-trans conformer because it has steric interference between the hydrogen atoms at carbons 1 and 4. Interference of this kind does not exist in the s-trans conformation, and therefore, the s-trans conformation is more stable and more populated at equilibrium.



13.7C Molecular Orbitals of 1,3-Butadiene

The central carbon atoms of 1,3-butadiene (Fig. 13.4) are close enough for overlap to occur between the *p* orbitals of C2 and C3. This overlap is not as great as that between the orbitals of C1 and C2 (or those of C3 and C4). The C2–C3 orbital overlap, however, gives the central bond partial double-bond character and allows the four π electrons of 1,3-butadiene to be delocalized over all four atoms.

Figure 13.5 shows how the four *p* orbitals of 1,3-butadiene combine to form a set of four π molecular orbitals.

- Two of the π molecular orbitals of 1,3-butadiene are bonding molecular orbitals. In the ground state these orbitals hold the four π electrons with two spin-paired electrons in each.
- The other two π molecular orbitals are antibonding molecular orbitals. In the ground state these orbitals are unoccupied.

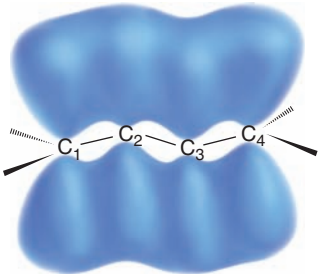


Figure 13.4 The *p* orbitals of 1,3-butadiene. (See Fig. 13.5 for the shapes of calculated molecular orbitals for 1,3-butadiene.)

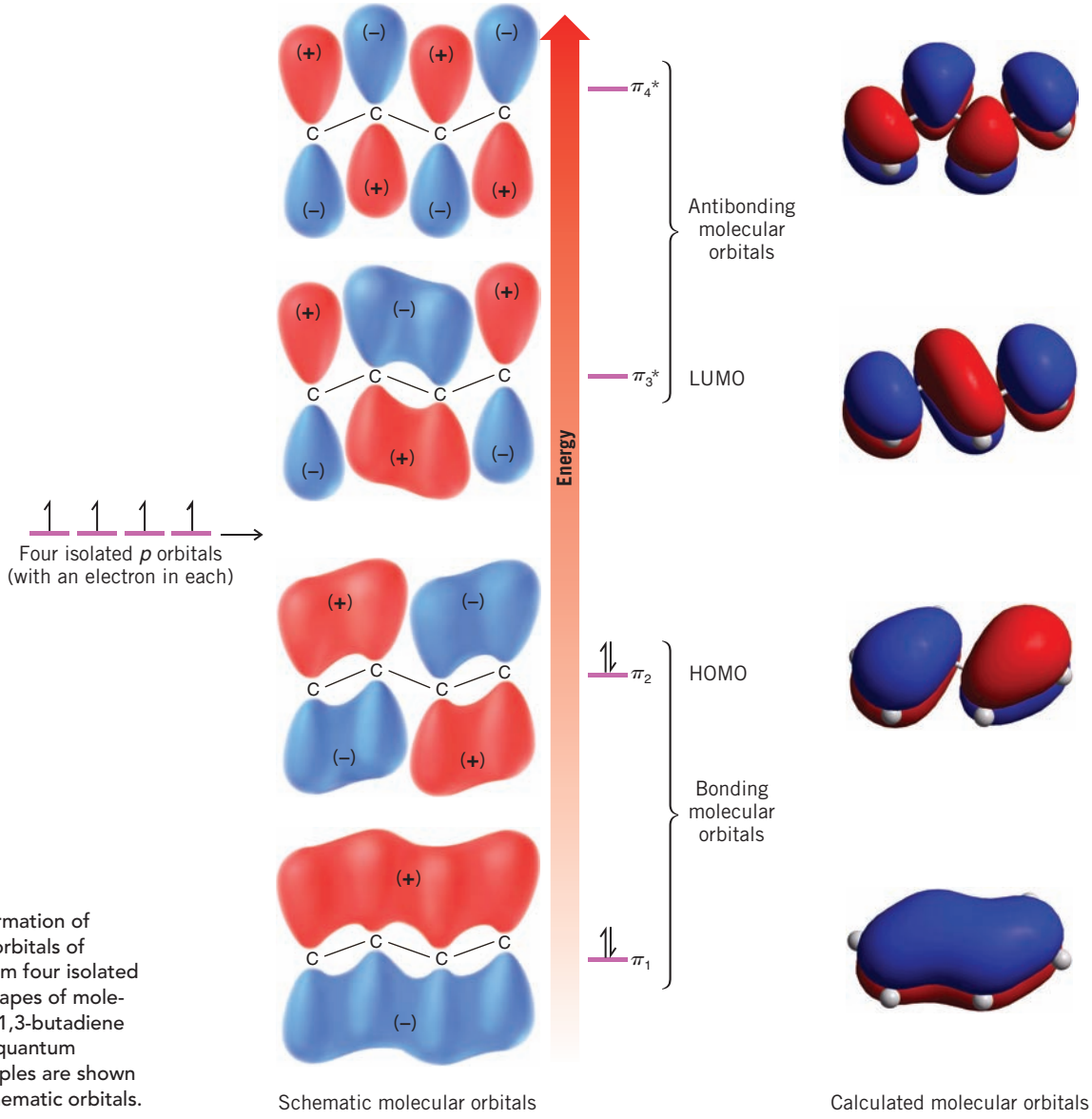


Figure 13.5 Formation of the π molecular orbitals of 1,3-butadiene from four isolated *p* orbitals. The shapes of molecular orbitals for 1,3-butadiene calculated using quantum mechanical principles are shown alongside the schematic orbitals.

An electron can be excited from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) when 1,3-butadiene absorbs light with a wavelength of 217 nm. (We shall study the absorption of light by unsaturated molecules in Section 13.9.)

- The delocalized bonding that we have just described for 1,3-butadiene is characteristic of all conjugated polyenes.

13.8 *The Stability of Conjugated Dienes*

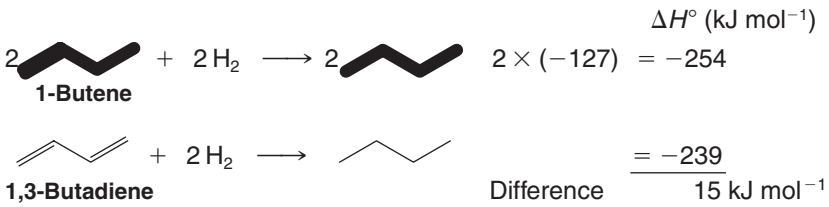
- Conjugated alkadienes are thermodynamically more stable than isomeric isolated alkadienes.

Two examples of this extra stability of conjugated dienes can be seen in an analysis of the heats of hydrogenation given in Table 13.2.

TABLE 13.2 Heats of Hydrogenation of Alkenes and Alkadienes

Compound	H_2 (mol)	$\Delta H°$ (kJ mol^{-1})
1-Butene	1	−127
1-Pentene	1	−126
trans-2-Pentene	1	−115
1,3-Butadiene	2	−239
trans-1,3-Pentadiene	2	−226
1,4-Pentadiene	2	−254
1,5-Hexadiene	2	−253

In itself, 1,3-butadiene cannot be compared directly with an isolated diene of the same chain length. However, a comparison can be made between the heat of hydrogenation of 1,3-butadiene and that obtained when two molar equivalents of 1-butene are hydrogenated:



Because 1-butene has a monosubstituted double bond like those in 1,3-butadiene, we might expect hydrogenation of 1,3-butadiene to liberate the same amount of heat (254 kJ mol^{-1}) as two molar equivalents of 1-butene. We find, however, that 1,3-butadiene liberates only 239 kJ mol^{-1}, 15 kJ mol^{-1} *less* than expected. We conclude, therefore, that conjugation imparts some extra stability to the conjugated system (Fig. 13.6).

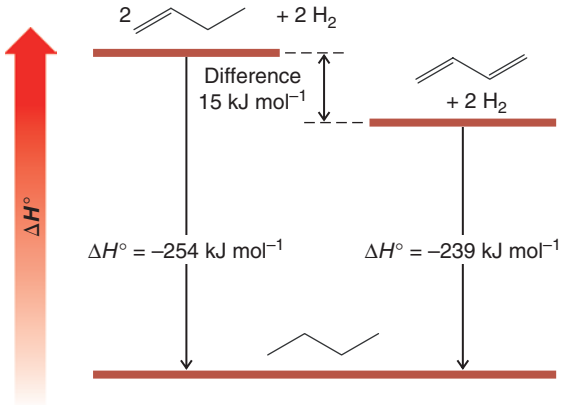
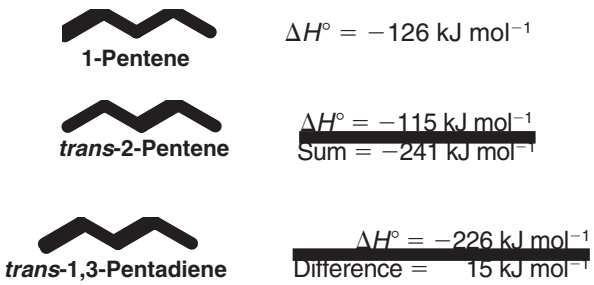


Figure 13.6 Heats of hydrogenation of 2 mol of 1-butene and 1 mol of 1,3-butadiene.

An assessment of the stabilization that conjugation provides *trans*-1,3-pentadiene can be made by comparing the heat of hydrogenation of *trans*-1,3-pentadiene to the sum of the heats of hydrogenation of 1-pentene and *trans*-2-pentene. This way we are comparing double bonds of comparable types:



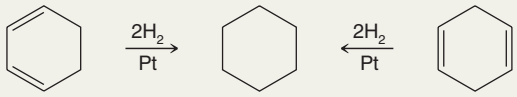
We see from these calculations that conjugation affords *trans*-1,3-pentadiene an extra stability of 15 kJ mol^{-1}, a value that is equivalent, to two significant figures, to the one we obtained for 1,3-butadiene (15 kJ mol^{-1}).

When calculations like these are carried out for other conjugated dienes, similar results are obtained; *conjugated dienes are found to be more stable than isolated dienes*. The question, then, is this: What is the source of the extra stability associated with conjugated dienes? There are two factors that contribute. The extra stability of conjugated dienes arises in part from the stronger central bond that they contain and, in part, from the additional delocalization of the π electrons that occurs in conjugated dienes.

Solved Problem 13.6

Which diene would you expect to be more stable: 1,3-cyclohexadiene or 1,4-cyclohexadiene? Why? What experiment could you carry out to confirm your answer?

STRATEGY AND ANSWER 1,3-Cyclohexadiene is conjugated, and on that basis we would expect it to be more stable. We could determine the heats of hydrogenation of the two compounds, and since on hydrogenation each compound yields the same product, the diene with the smaller heat of hydrogenation would be the more stable one.



1,3-Cyclohexadiene (a conjugated diene) **Cyclohexane** **1,4-Cyclohexadiene (an isolated diene)**

13.9 Ultraviolet–Visible Spectroscopy

The extra stability of conjugated dienes when compared to corresponding unconjugated dienes can also be seen in data from **ultraviolet–visible (UV–Vis) spectroscopy**. When electromagnetic radiation in the UV and visible regions passes through a compound containing multiple bonds, a portion of the radiation is usually absorbed by the compound. Just how much radiation is absorbed depends on the wavelength of the radiation and the structure of the compound.

- The absorption of UV–Vis radiation is caused by transfer of energy from the radiation beam to electrons that can be excited to higher energy orbitals.

In Section 13.9C we shall return to discuss specifically how data from UV–Vis spectroscopy demonstrate the additional stability of conjugated dienes. First, in Section 13.9A we briefly review the properties of electromagnetic radiation, and then in Section 13.9B we look at how data from a UV–Vis spectrophotometer are obtained.

13.9A The Electromagnetic Spectrum

According to quantum mechanics, electromagnetic radiation has a dual and seemingly contradictory nature.

- Electromagnetic radiation can be described as a wave occurring simultaneously in electrical and magnetic fields. It can also be described as if it consisted of particles called quanta or photons.

Different experiments disclose these two different aspects of electromagnetic radiation. They are not seen together in the same experiment.

- A wave is usually described in terms of its **wavelength** (λ) or its **frequency** (ν).

A simple wave is shown in Fig. 13.7. The distance between consecutive crests (or troughs) is the wavelength. The number of full cycles of the wave that pass a given point each second, as the wave moves through space, is called the *frequency* and is measured in cycles per second (cps), or **hertz (Hz)**.*

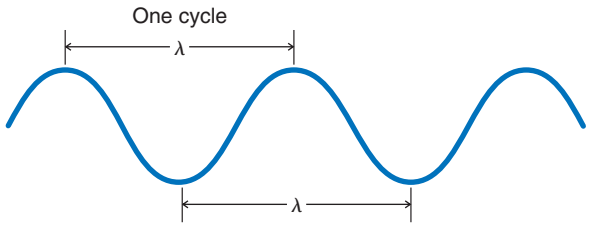


Figure 13.7 A simple wave and its wavelength, λ.

All electromagnetic radiation travels through a vacuum at the same velocity. This velocity (c), called the velocity of light, is 2.99792458×10^8 m s^{-1} and relates to wavelength and frequency as $c = \lambda\nu$. The wavelengths of electromagnetic radiation are expressed either in meters (m), millimeters (1 mm = 10^{-3} m), micrometers (1 μm = 10^{-6} m), or nanometers (1 nm = 10^{-9} m). [An older term for micrometer is *micron* (abbreviated μ) and an older term for nanometer is *millimicron*.]

The energy of a quantum of electromagnetic energy is directly related to its frequency:

$$E = h\nu$$

where h = Planck's constant, 6.63×10^{-34} J s

ν = frequency (Hz)

The higher the frequency (ν) of radiation, the greater is its energy.

X-Rays, for example, are much more energetic than rays of visible light. The frequencies of X-rays are on the order of 10^{19} Hz, while those of visible light are on the order of 10^{15} Hz.

Since $\nu = c/\lambda$, the energy of electromagnetic radiation is inversely proportional to its wavelength:

$$E = \frac{hc}{\lambda}$$

where c = velocity of light

The shorter the wavelength (λ) of radiation, the greater is its energy.

X-Rays have wavelengths on the order of 0.1 nm and are very energetic, whereas visible light has wavelengths between 400 and 750 nm and is, therefore, of lower energy than X-rays.†

It may be helpful to point out, too, that for visible light, wavelengths (and thus frequencies) are related to what we perceive as colors. The light that we call red light has a wavelength of approximately 650 nm. The light we call violet light has a wavelength of approximately 400 nm. All of the other colors of the visible spectrum (the rainbow) lie in between these wavelengths.

*The term hertz (after the German physicist H. R. Hertz), abbreviated Hz, is used in place of the older term *cycles per second* (cps). Frequency of electromagnetic radiation is also sometimes expressed in *wavenumbers*, that is, the number of waves per centimeter.

†A convenient formula that relates wavelength (in nm) to the energy of electromagnetic radiation is the following:

$$E \text{ (in kJ mol}^{-1}) = \frac{1.20 \times 10^{-9} \text{ kJ mol}^{-1}}{\text{wavelength in nanometers}}$$

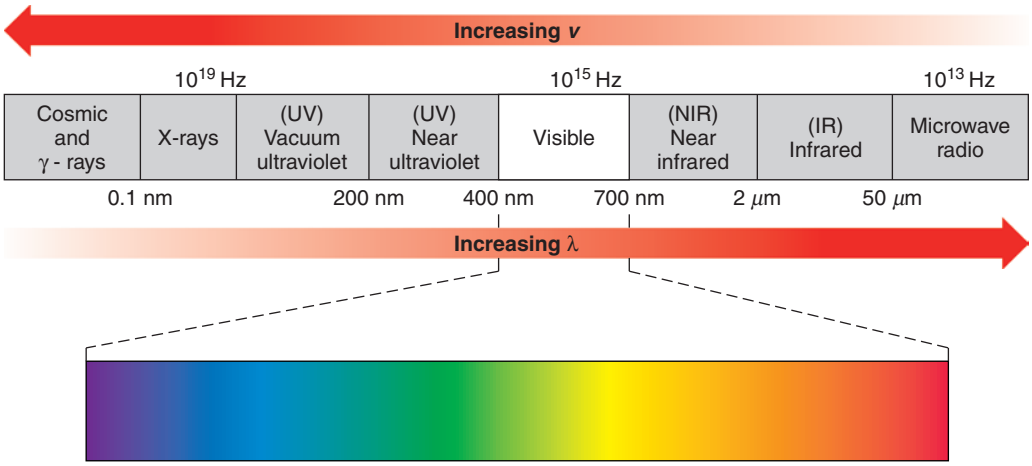


Figure 13.8 The electromagnetic spectrum.

The different regions of the **electromagnetic spectrum** are shown in Fig. 13.8. Nearly every portion of the electromagnetic spectrum from the region of X-rays to that of microwaves and radio waves has been used in elucidating structures of atoms and molecules. Although techniques differ according to the portion of the electromagnetic spectrum in which we are working, there is a consistency and unity of basic principles.

13.9B UV–Vis Spectrophotometers

- A UV–Vis spectrophotometer (Fig. 13.9) measures the amount of light absorbed by a sample at each wavelength of the UV and visible regions of the electromagnetic spectrum.

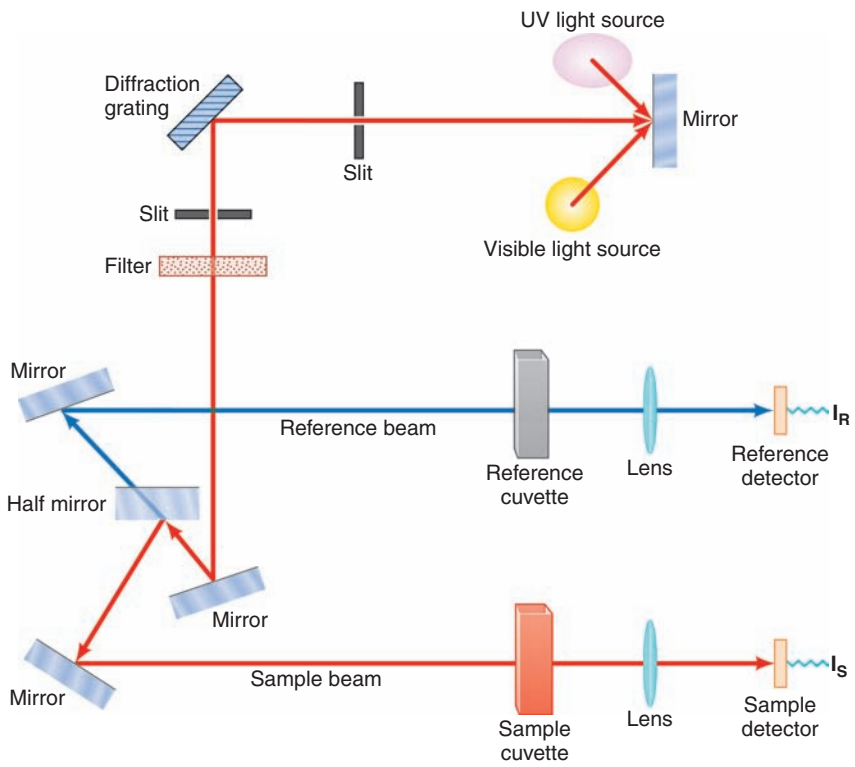


Figure 13.9 A diagram of a UV–Vis spectrophotometer. (Courtesy William Reusch, www.cem.msu.edu/~reusch. © 1999)

UV and visible radiation are of higher energy (shorter wavelength) than infrared radiation (used in IR spectroscopy) and radio frequency radiation (used in NMR) but not as energetic as X-radiation (Fig. 13.8).

In a standard UV–Vis spectrophotometer (Fig. 13.9) a beam of light is split; one half of the beam (the sample beam) is directed through a transparent cell containing a solution of the compound being analyzed, and one half (the reference beam) is directed through an identical cell that does not contain the compound but contains the solvent. Solvents are chosen to be transparent in the region of the spectrum being used for analysis. The instrument is designed so that it can make a comparison of the intensities of the two beams as it scans over the desired region of wavelengths. If the compound absorbs light at a particular wavelength, the intensity of the sample beam (I_S) will be less than that of the reference beam (I_R). The absorbance at a particular wavelength is defined by the equation $A_\lambda = \log(I_R/I_S)$.

- Data from a UV–Vis spectrophotometer are presented as an **absorption spectrum**, which is a graph of wavelength (λ) versus sample absorbance (A) at each wavelength in the spectral region of interest.

(In diode-array UV–Vis spectrophotometers the absorption of all wavelengths of light in the region of analysis is measured simultaneously by an array of photodiodes. The absorption of the solvent is measured over all wavelengths of interest first, and then the absorption of the sample is recorded over the same range. Data from the solvent are electronically subtracted from the data for the sample. The difference is then displayed as the absorption spectrum for the sample.)

A typical UV absorption spectrum, that of 2,5-dimethyl-2,4-hexadiene, is given in Fig. 13.10. It shows a broad absorption band in the region between 210 and 260 nm, with the maximum absorption at 242.5 nm.

- The wavelength of maximum absorption in a given spectrum is usually reported in the chemical literature as λ_{max}.

In addition to reporting the wavelength of maximum absorption (λ_{max}), chemists often report another quantity called the molar absorptivity, ε. (In older literature, the molar absorptivity, ε, is often referred to as the molar extinction coefficient.)

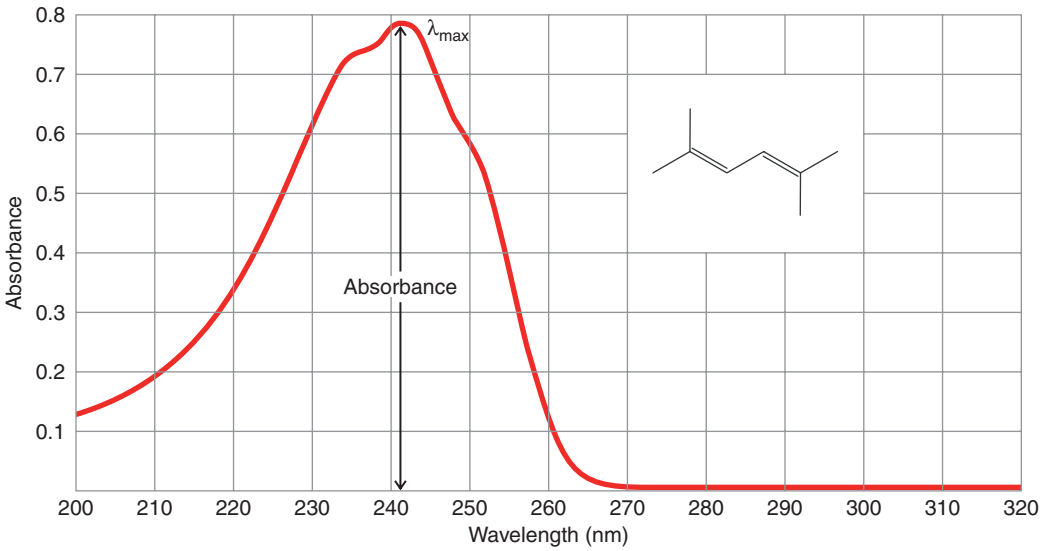


Figure 13.10 The UV absorption spectrum of 2,5-dimethyl-2,4-hexadiene in methanol at a concentration of 5.95×10^{-5} *M* in a 1.00-cm cell.

- The **molar absorptivity** (ε, in units of M^{-1} cm^{-1}) indicates the intensity of the absorbance for a sample at a given wavelength. It is a proportionality constant that relates absorbance to molar concentration of the sample (M) and the path length (l, in cm) of light through the sample.
- The equation that relates absorbance (A) to concentration (C) and path length (l) via molar absorptivity (ε) is called **Beer's law**.

$$A = \varepsilon \times C \times l \quad \text{or} \quad \varepsilon = \frac{A}{C \times l} \qquad \textbf{Beer's law}$$

For 2,5-dimethyl-2,4-hexadiene dissolved in methanol the molar absorptivity at the wavelength of maximum absorbance (242.5 nm) is 13,100 M^{-1} cm^{-1}. In the chemical literature this would be reported as

$$\text{2,5-Dimethyl-2,4-hexadiene, } \lambda_{max}^{methanol}\ 242.5\ \text{nm} \qquad (\varepsilon = 13{,}100)$$

13.9C Absorption Maxima for Nonconjugated and Conjugated Dienes

As we noted earlier, when compounds absorb light in the UV and visible regions, electrons are excited from lower electronic energy levels to higher ones. For this reason, visible and UV spectra are often called **electronic spectra**. The absorption spectrum of 2,5-dimethyl-2,4-hexadiene is a typical electronic spectrum because the absorption band (or peak) is very broad. Most absorption bands in the visible and UV region are broad because each electronic energy level has associated with it vibrational and rotational levels. Thus, electron transitions may occur from any of several vibrational and rotational states of one electronic level to any of several vibrational and rotational states of a higher level.

- Alkenes and nonconjugated dienes usually have absorption maxima (λ_{max}) below 200 nm.

Ethene, for example, gives an absorption maximum at 171 nm; 1,4-pentadiene gives an absorption maximum at 178 nm. These absorptions occur at wavelengths that are out of the range of operation of most ultraviolet–visible spectrometers because they occur where the oxygen in air also absorbs. Special air-free techniques must be employed in measuring them.

Helpful Hint

UV–Vis spectroscopic evidence for conjugated π-electron systems.

- Compounds containing *conjugated* multiple bonds have absorption maxima (λ_{max}) at wavelengths longer than 200 nm.

1,3-Butadiene, for example, absorbs at 217 nm. This longer wavelength absorption by conjugated dienes is a direct consequence of conjugation.

We can understand how conjugation of multiple bonds brings about absorption of light at longer wavelengths if we examine Fig. 13.11.

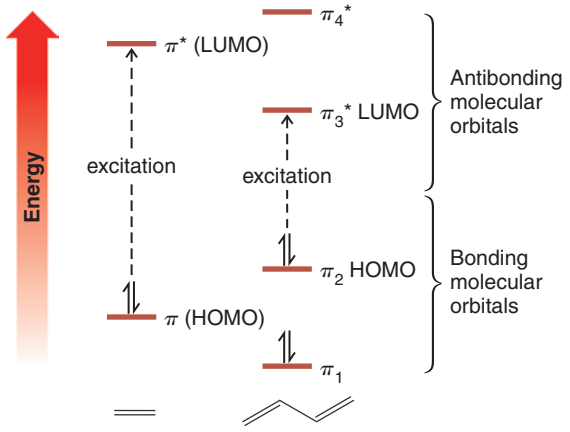


Figure 13.11 The relative energies of the π molecular orbitals of ethene and 1,3-butadiene (Section 13.7C).

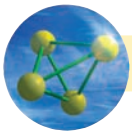
- When a molecule absorbs light at its longest wavelength, an electron is excited from its **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**.
- For most alkenes and alkadienes the HOMO is a bonding π orbital and the LUMO is an antibonding π^* orbital.

The wavelength of the absorption maximum is determined by the difference in energy between these two levels. The energy gap between the HOMO and LUMO of ethene is greater than that between the corresponding orbitals of 1,3-butadiene. Thus, the $\pi \longrightarrow \pi^*$ electron excitation of ethene requires absorption of light of greater energy (shorter wavelength) than the corresponding $\pi_2 \longrightarrow \pi_3^*$ excitation in 1,3-butadiene. The energy difference between the HOMOs and the LUMOs of the two compounds is reflected in their absorption spectra. Ethene has its λ_{max} at 171 nm; 1,3-butadiene has a λ_{max} at 217 nm.

The narrower gap between the HOMO and the LUMO in 1,3-butadiene results from the conjugation of the double bonds. Molecular orbital calculations indicate that a much larger gap should occur in isolated alkadienes. This is borne out experimentally. Isolated alkadienes give absorption spectra similar to those of alkenes. Their λ_{max} are at shorter wavelengths, usually below 200 nm. As we mentioned, 1,4-pentadiene has its λ_{max} at 178 nm.

Conjugated alkatrienes absorb at longer wavelengths than conjugated alkadienes, and this too can be accounted for in molecular orbital calculations. The energy gap between the HOMO and the LUMO of an alkatriene is even smaller than that of an alkadiene.

- In general, *the greater the number of conjugated multiple bonds in a molecule, the longer will be its* λ_{max}.

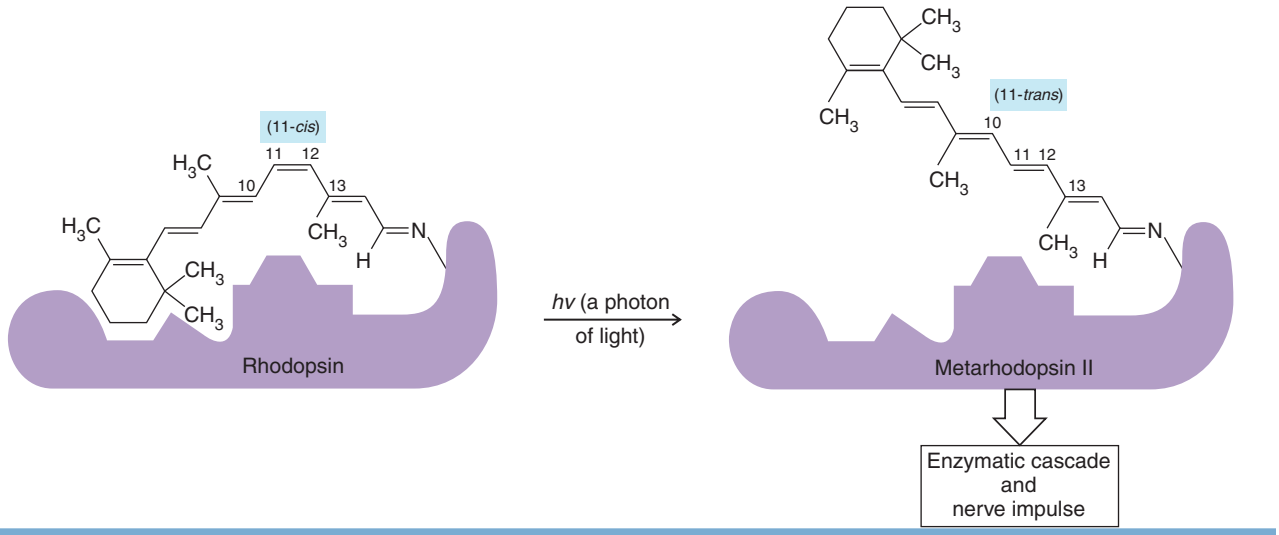


THE CHEMISTRY OF . . .

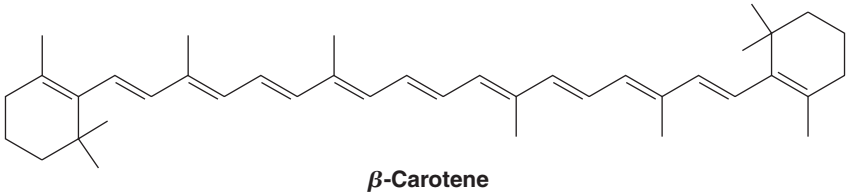
The Photochemistry of Vision

The chemical changes that occur when light impinges on the retina of the eye involve several of the phenomena that we have studied. Central to an understanding of the visual process at the molecular level are two phenomena in particular: the absorption of light by conjugated polyenes and the interconversion of cis–trans isomers. The conjugated polyene, derived from a compound called retinal, is a part of a molecule called rhodopsin.

When rhodopsin absorbs a photon of light, the 11-*cis*-retinal chromophore isomerizes to the all-trans form, causing the cyclohexene ring of the chromophore to swing into a different orientation. The first photo-product is an intermediate called bathorhodopsin, which through a series of steps becomes metarhodopsin II, shown below. It is believed that repositioning of the retinal cyclohexene ring, through the 11-cis to all-trans isomerization, causes further conformational changes in the protein that ultimately initiate a cascade of enzymatic reactions and transmission of a neural signal to the brain.

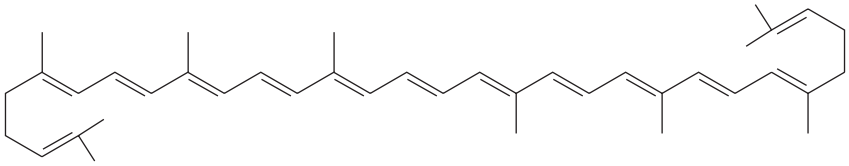


Polyenes with eight or more conjugated double bonds absorb light in the visible region of the spectrum. For example, β-carotene, a precursor of vitamin A and a compound that imparts its orange color to carrots, has 11 conjugated double bonds; β-carotene has an absorption maximum at 497 nm, well into the visible region. Light of 497 nm has a blue-green color; this is the light that is absorbed by β-carotene. We perceive the complementary color of blue green, which is red orange.



β-Carotene

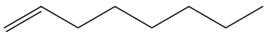
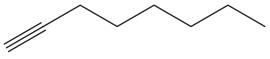
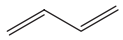
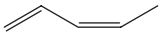
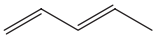
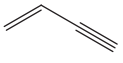
Lycopene, a compound partly responsible for the red color of tomatoes, also has 11 conjugated double bonds. Lycopene has an absorption maximum at 505 nm where it absorbs intensely. (Approximately 0.02 g of lycopene can be isolated from 1 kg of fresh, ripe tomatoes.)



Lycopene

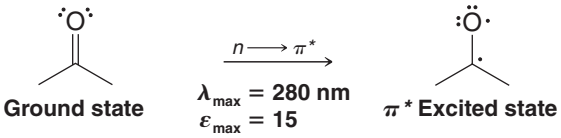
Table 13.3 gives the values of λ_{max} for a number of unsaturated compounds.

TABLE 13.3 Long-Wavelength Absorption Maxima of Unsaturated Hydrocarbons

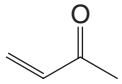
Compound	Structure	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})
Ethene	$CH_2{=}CH_2$	171	15,530
trans-3-Hexene		184	10,000
Cyclohexene		182	7,600
1-Octene		177	12,600
1-Octyne		185	2,000
1,3-Butadiene		217	21,000
cis-1,3-Pentadiene		223	22,600
trans-1,3-Pentadiene		223.5	23,000
But-1-en-3-yne		228	7,800
1,4-Pentadiene		178	17,000
1,3-Cyclopentadiene		239	3,400
1,3-Cyclohexadiene		256	8,000
trans-1,3,5-Hexatriene		274	50,000

Compounds with carbon–oxygen double bonds also absorb light in the UV region. Acetone, for example, has a broad absorption peak at 280 nm that corresponds to the excitation of an electron from one of the unshared pairs (a nonbonding or "*n*" electron) to the π^* orbital of the carbon–oxygen double bond:

Acetone



Compounds in which the carbon–oxygen double bond is conjugated with a carbon–carbon double bond have absorption maxima corresponding to $n \longrightarrow \pi^*$ excitations and $\pi \longrightarrow \pi^*$ excitations. The $n \longrightarrow \pi^*$ absorption maxima occur at longer wavelengths but are much weaker (i.e., have smaller molar absorptivity (ε) values):



$n \longrightarrow \pi^*$ $\lambda_{max} = 324$ nm, $\varepsilon_{max} = 24$
$\pi \longrightarrow \pi^*$ $\lambda_{max} = 219$ nm, $\varepsilon_{max} = 3600$

13.9D Analytical Uses of UV–Vis Spectroscopy

UV–Vis spectroscopy can be used in the structure elucidation of organic molecules to indicate whether conjugation is present in a given sample. Although conjugation in a molecule may be indicated by data from IR, NMR, or mass spectrometry, UV–Vis analysis can provide corroborating information.

A more widespread use of UV–Vis spectroscopy, however, has to do with determining the concentration of an unknown sample. As mentioned in Section 13.9B, the relationship $A = \varepsilon Cl$ indicates that the amount of absorption by a sample at a certain wavelength is dependent on its concentration. This relationship is usually linear over a range of concentrations suitable for analysis. To determine the unknown concentration of a sample, a graph of absorbance versus concentration is made for a set of standards of known concentrations. The wavelength used for analysis is usually the λ_{max} of the sample. The concentration of the sample is obtained by measuring its absorbance and determining the corresponding value of concentration from the graph of known concentrations. Quantitative analysis using UV–Vis spectroscopy is routinely used in biochemical studies to measure the rates of enzymatic reactions. The concentration of a species involved in the reaction (as related to its UV–Vis absorbance) is plotted versus time to determine the rate of reaction. UV–Vis spectroscopy is also used in environmental chemistry to determine the concentration of various metal ions (sometimes involving absorption spectra for organic complexes with the metal) and as a detection method in high-performance liquid chromatography (HPLC).

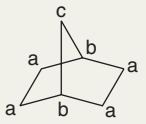
Solved Problem 13.7

Two isomeric compounds, **A** and **B**, have the molecular formula C_7H_{12}. Compound **A** shows no absorption in the UV–visible region. The ^{13}C NMR spectrum of **A** shows only three signals. Compound **B** shows a UV–visible peak in the region of 180 nm, its ^{13}C NMR spectrum shows four signals, and its DEPT ^{13}C NMR data show that none of its carbon atoms is a methyl group. On catalytic hydrogenation with excess hydrogen, **B** is converted to heptane. Propose structures for **A** and **B**.

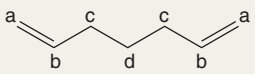
(Continues on the next page)

STRATEGY AND ANSWER On the basis of their molecular formulas, both compounds have an index of hydrogen deficiency (Section 4.17) equal to 2. Therefore on this basis alone, each could contain two double bonds, one ring and one double bond, two rings, or a triple bond. Consider **A** first. The fact that **A** does not absorb in the UV–visible region suggests that it does not have any double bonds; therefore, it must contain two rings. A compound with two rings that would give only three signals in its ^{13}C spectrum is bicyclo[2.2.1]heptane (because it has only three distinct types of carbon atoms).

Now consider **B**. The fact that **B** is converted to heptane on catalytic hydrogenation suggests that **B** is a heptadiene or a heptyne with an unbranched chain. UV–visible absorption in the 180-nm region suggests that **B** does not contain conjugated π bonds. Given that the DEPT ^{13}C data for **B** shows the absence of any methyl groups, and only four ^{13}C signals in total, **B** must be 1,6-hexadiene.



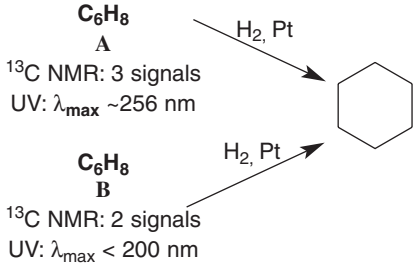
A
Bicyclo[2.2.1]heptane (three ^{13}C signals)



B
1,6-Hexadiene (four ^{13}C signals, none comes from a methyl group)

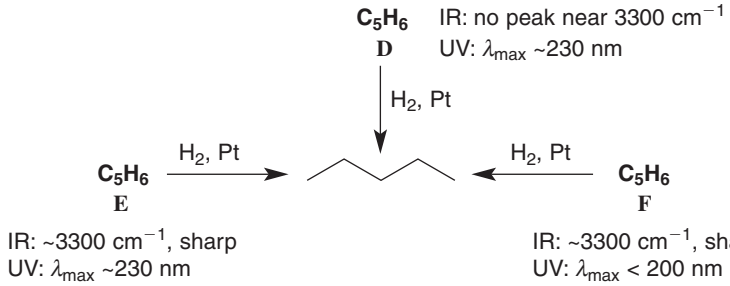
Review Problem 13.7

Two compounds, **A** and **B**, have the same molecular formula, C_6H_8. Both **A** and **B** react with two molar equivalents of hydrogen in the presence of platinum to yield cyclohexane. Compound **A** shows three signals in its broadband decoupled ^{13}C NMR spectrum. Compound **B** shows only two ^{13}C NMR signals. Compound **A** shows an absorption maximum at 256 nm, whereas **B** shows no absorption maximum at wavelengths longer than 200 nm. What are the structures of **A** and **B**?



Review Problem 13.8

Propose structures for **D, E**, and **F**.

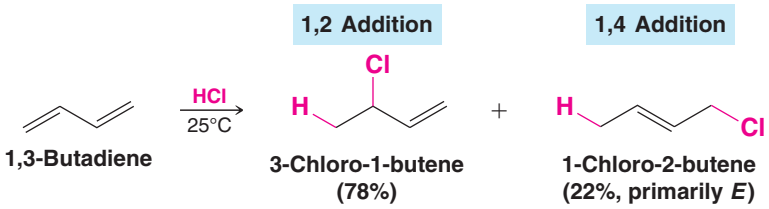


13.10 *Electrophilic Attack on Conjugated Dienes: 1,4 Addition*

Not only are conjugated dienes somewhat more stable than nonconjugated dienes, they also display special behavior when they react with electrophilic reagents.

- Conjugated dienes undergo both 1,2 and 1,4 addition through an allylic intermediate that is common to both.

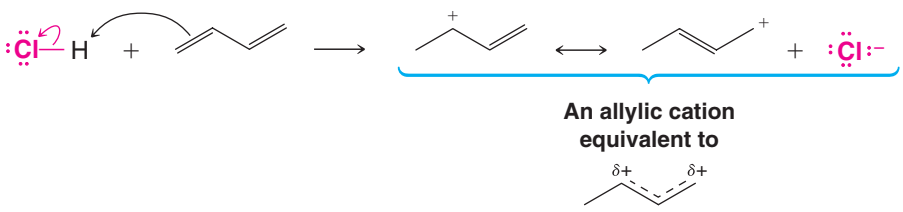
For example, 1,3-butadiene reacts with one molar equivalent of hydrogen chloride to produce two products, 3-chloro-1-butene and 1-chloro-2-butene:



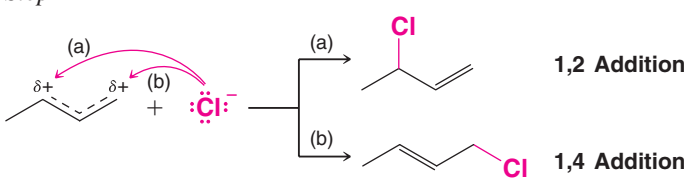
If only the first product (3-chloro-1-butene) were formed, we would not be particularly surprised. We would conclude that hydrogen chloride had added to one double bond of 1,3-butadiene in the usual way. It is the second product, 1-chloro-2-butene, that is initially surprising. Its double bond is between the central atoms, and the elements of hydrogen chloride have added to the C1 and C4 atoms.

To understand how both 1,2- and 1,4-addition products result from reaction of 1,3-butadiene with HCL, consider the following mechanism.

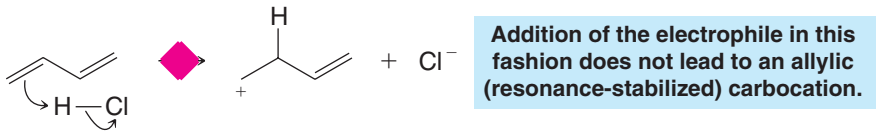
Step 1



Step 2



In step 1 a proton adds to one of the terminal carbon atoms of 1,3-butadiene to form, as usual, the more stable carbocation, in this case a resonance-stabilized allylic cation. Addition to one of the inner carbon atoms would have produced a much less stable primary cation, one that could not be stabilized by resonance:



In step 2 a chloride ion forms a bond to one of the carbon atoms of the allylic cation that bears a partial positive charge. Reaction at one carbon atom results in the 1,2-addition product; reaction at the other gives the 1,4-addition product.

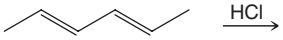
Note that the designations 1,2 and 1,4 only coincidentally relate to the IUPAC numbering of carbon atoms in this example.

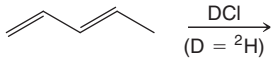
- Chemists typically use 1,2 and 1,4 to refer to modes of addition to any conjugated diene system, regardless of where the conjugated double bonds are in the overall molecule.

Thus, addition reactions of 2,4-hexadiene would still involve references to 1,2 and 1,4 modes of addition.

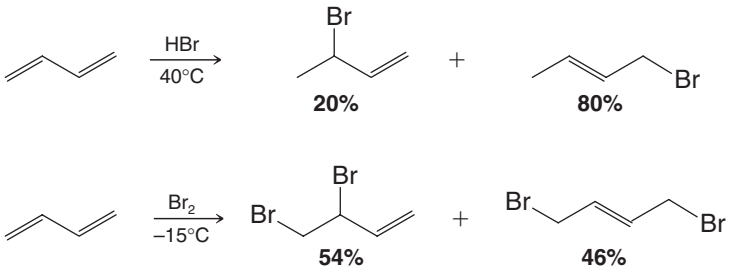
Review Problem 13.9

Predict the products of the following reactions.

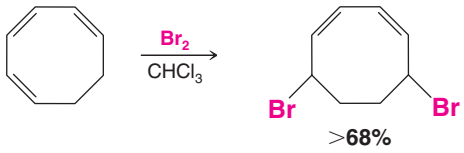
(a) 

(b) 

1,3-Butadiene shows 1,4-addition reactions with electrophilic reagents other than hydrogen chloride. Two examples are shown here, the addition of hydrogen bromide (in the absence of peroxides) and the addition of bromine:



Reactions of this type are quite general with other conjugated dienes. Conjugated trienes often show 1,6 addition. An example is the 1,6 addition of bromine to 1,3,5-cyclooctatriene:



13.10A Kinetic Control versus Thermodynamic Control of a Chemical Reaction

The addition of hydrogen bromide to 1,3-butadiene allows the illustration of another important aspect of reactivity—the way temperature affects product distribution in a reaction that can take multiple paths. In general:

- The favored products in a reaction at *lower temperature* are those formed by the pathway having the smallest energy of activation barrier. In this case the reaction is said to be under **kinetic (or rate) control**, and the predominant products are called the **kinetic products**.
- The favored products at *higher temperature* in a *reversible* reaction are those that are most stable. In this case the reaction is said to be under **thermodynamic (or equilibrium) control**, and the predominant products are called the **thermodynamic (or equilibrium) products**.

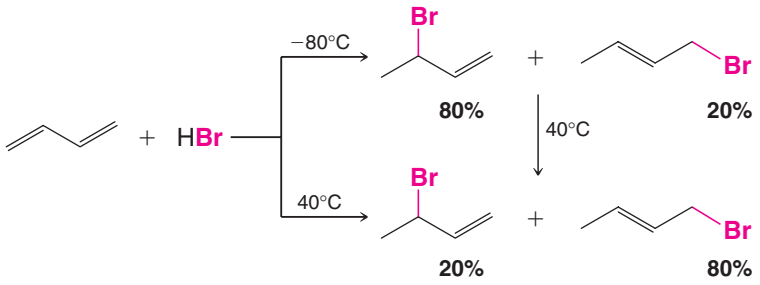
Let's consider specific reaction conditions for the ionic addition of hydrogen bromide to 1,3-butadiene.

Case 1. When 1,3-butadiene and hydrogen bromide react at low temperature (−80°C), the major product is formed by 1,2 addition. We obtain 80% of the 1,2 product and 20% of the 1,4 product.

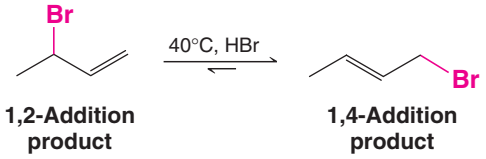
Case 2. When 1,3-butadiene and hydrogen bromide react at high temperature (40°C), the major product is formed by 1,4 addition. We obtain about 20% of the 1,2 product and about 80% of the 1,4 product.

Case 3. When the product mixture from the low temperature reaction is warmed to the higher temperature, the product distribution becomes the same as when the reaction was carried out at high temperature, that is, the 1,4 product predominates.

We summarize these scenarios here:



Furthermore, when a pure sample of 3-bromo-1-butene (the predominant product at low temperature) is subjected to the high temperature reaction conditions, an equilibrium mixture results in which the 1,4 addition product predominates.



Because this equilibrium favors the 1,4-addition product, *that product must be more stable*.

The reactions of hydrogen bromide with 1,3-butadiene serve as a striking illustration of the way that the outcome of a chemical reaction can be determined, in one instance, by relative rates of competing reactions and, in another, by the relative stabilities of the final products. At the lower temperature, the relative amounts of the products of the addition are determined by the relative rates at which the two additions occur; 1,2 addition occurs faster so the 1,2-addition product is the major product. At the higher temperature, the relative amounts of the products are determined by the position of an equilibrium. The 1,4-addition product is the more stable, so it is the major product.

This behavior of 1,3-butadiene and hydrogen bromide can be more fully understood if we examine the diagram shown in Fig. 13.12.

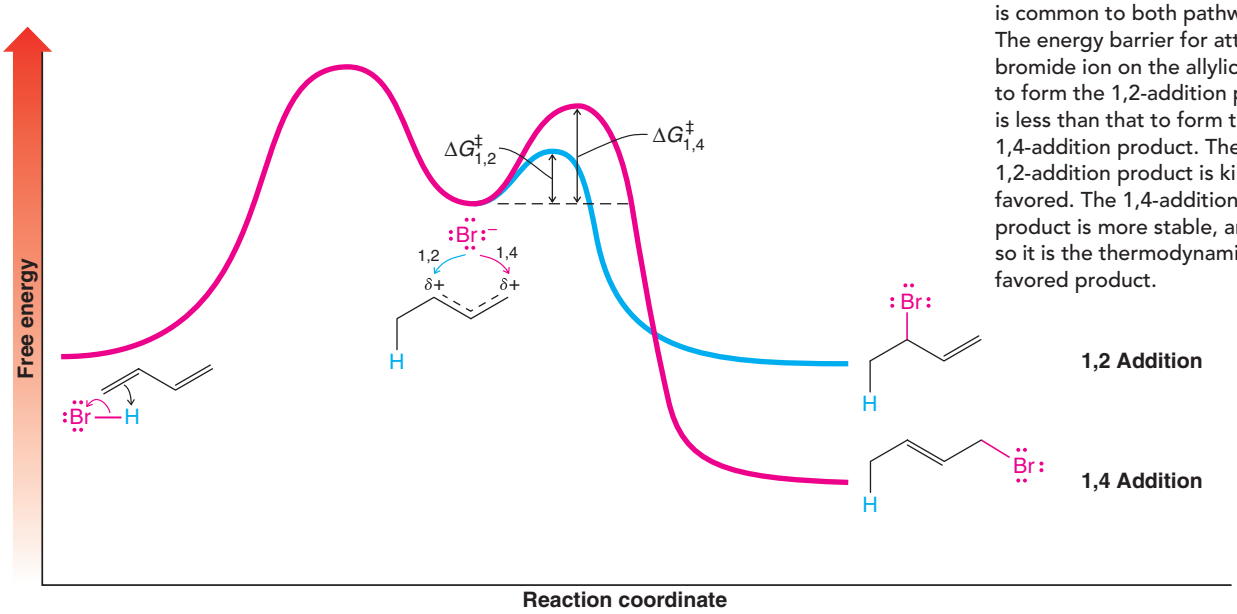
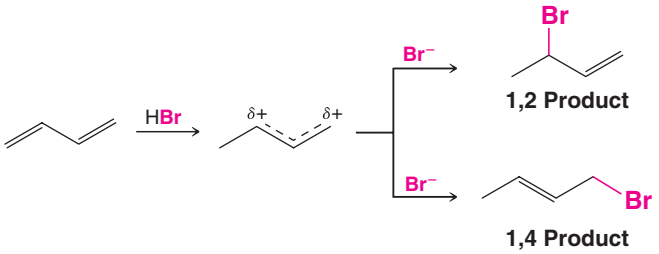


Figure 13.12 A schematic free-energy versus reaction coordinate diagram for the 1,2 and 1,4 addition of HBr to 1,3-butadiene. An allylic carbocation is common to both pathways. The energy barrier for attack of bromide ion on the allylic cation to form the 1,2-addition product is less than that to form the 1,4-addition product. The 1,2-addition product is kinetically favored. The 1,4-addition product is more stable, and so it is the thermodynamically favored product.

- The step that determines the overall outcome of this reaction is the step in which the hybrid allylic cation combines with a bromide ion.



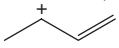
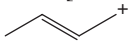
The reaction of the bromide anion with the allylic cation determines the regioselectivity of the reaction.

We see in Fig. 13.12 that the free energy of activation leading to the 1,2-addition product is less than the free energy of activation leading to the 1,4-addition product, even though the 1,4 product is more stable.

- At **low temperature**, the fraction of collisions capable of surmounting the higher energy barrier leading to formation of the 1,4 product is smaller than the fraction that can cross the barrier leading to the 1,2 product.
- At low temperature, formation of the 1,2 and 1,4 products is essentially *irreversible* because there is not enough energy for either product to cross back over the barrier to reform the allylic cation. Thus, the 1,2 product predominates at lower temperature because it is formed faster and it is not formed reversibly. It is the **kinetic product** of this reaction.
- At **higher temperature**, collisions between the intermediate ions are sufficiently energetic to allow rapid formation of *both* the 1,2 and 1,4 products. *But*, there is also sufficient energy for both products to revert to the allylic carbocation.
- Because the 1,2 product has a smaller energy barrier for conversion back to the allylic cation than does the 1,4 product, more of the 1,2 product reverts to the allylic cation than does the 1,4 product. But since both the 1,4 and the 1,2 products readily form from the allylic cation at high temperature, eventually this equilibrium leads to a preponderance of the 1,4 product because it is more stable. The 1,4 product is the **thermodynamic** or **equilibrium product** of this reaction.

Before we leave this subject, one final point should be made. This example clearly demonstrates that predictions of relative reaction rates made on the basis of product stabilities alone can be wrong. This is not always the case, however. For many reactions in which a common intermediate leads to two or more products, the most stable product is formed fastest.

Review Problem 13.10

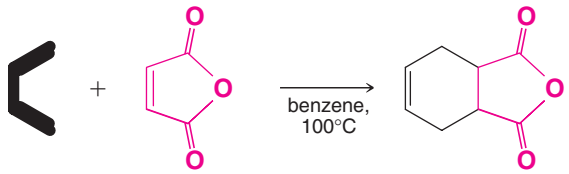
(a) Suggest a structural explanation for the fact that the 1,2-addition reaction of 1,3-butadiene and hydrogen bromide occurs faster than 1,4 addition? [*Hint*: Consider the relative contributions that the two forms  and  make to the resonance hybrid of the allylic cation.]

(b) How can you account for the fact that the 1,4-addition product is more stable?

13.11 *The Diels–Alder Reaction: A 1,4-Cycloaddition Reaction of Dienes*

In 1928 two German chemists, Otto Diels and Kurt Alder, developed a **1,4-cycloaddition** reaction of dienes that has since come to bear their names. The reaction proved to be one of such great versatility and synthetic utility that Diels and Alder were awarded the Nobel Prize in Chemistry in 1950.

An example of the Diels–Alder reaction is the reaction that takes place when 1,3-butadiene and maleic anhydride are heated together at 100°C. The product is obtained in quantitative yield:



1,3-Butadiene (diene) + **Maleic anhydride (dienophile)** → **Adduct (100%)**

- In general terms, the **Diels–Alder reaction** is one between a conjugated **diene** (a 4π-electron system) and a compound containing a double bond (a 2π-electron system) called a **dienophile** (diene + *philein*, Greek: to love). The product of a Diels–Alder reaction is often called an **adduct**.

Helpful Hint

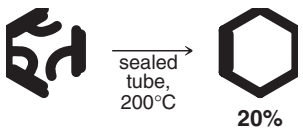
The Diels–Alder reaction is a very useful synthetic tool for preparing cyclohexene rings.

In the Diels–Alder reaction, two new σ bonds are formed at the expense of two π bonds of the diene and dienophile. The adduct contains a new six-membered ring with a double bond. Since σ bonds are usually stronger than π bonds, formation of the adduct is usually favored energetically, *but most Diels–Alder reactions are reversible*.

We can account for all of the bond changes in a Diels–Alder reaction by using curved arrows in the following way:

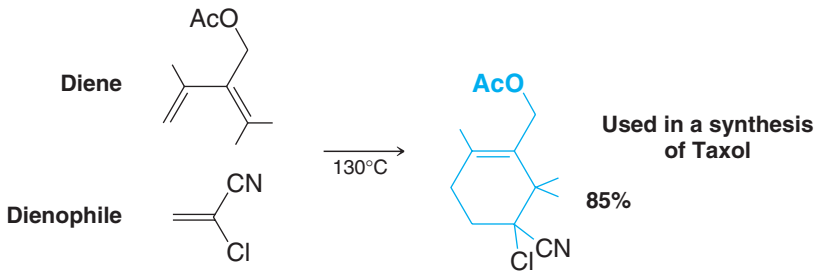
Diene **Dienophile** **Adduct**

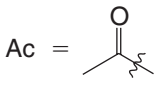
The simplest example of a Diels–Alder reaction is the one that takes place between 1,3-butadiene and ethene. This reaction, however, takes place much more slowly than the reaction of butadiene with maleic anhydride and also must be carried out under pressure:



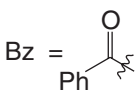
20%

Another example is the preparation of an intermediate in the synthesis of the anticancer drug Taxol (paclitaxel) by K. C. Nicolaou (Scripps Research Institute and the University of California, San Diego):

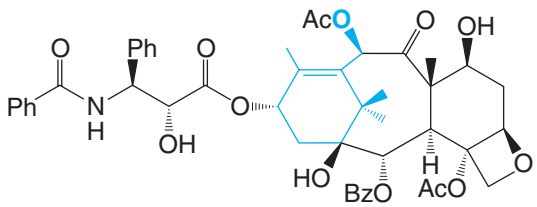




(acetyl)



(benzoyl)



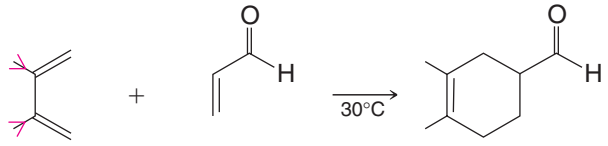
Taxol (blue atoms derived from the Diels–Alder adduct above)

13.11A Factors Favoring the Diels–Alder Reaction

Alder originally stated that the Diels–Alder reaction is favored by the presence of electron-withdrawing groups in the dienophile and by electron-releasing groups in the diene. Maleic anhydride, a very potent dienophile, has two electron-withdrawing carbonyl groups on carbon atoms adjacent to the double bond.

The helpful effect of electron-releasing groups in the diene can also be demonstrated; 2,3-dimethyl-1,3-butadiene, for example, is nearly five times as reactive in Diels–Alder reactions as is 1,3-butadiene. The methyl groups inductively release electron density, just as alkyl groups do when stabilizing a carbocation (though no carbocations are involved here). When 2,3-dimethyl-1,3-butadiene reacts with propenal (acrolein) at only 30°C, the adduct is obtained in quantitative yield:

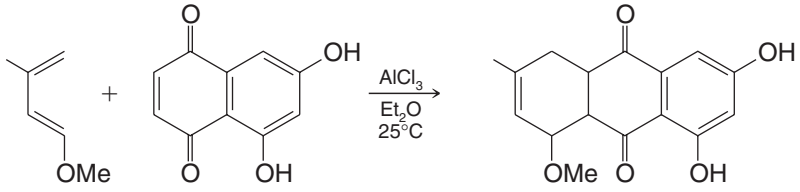
The methyl groups donate electron density.



2,3-Dimethyl-1,3-butadiene **Propenal** **100%**

Research (by C. K. Bradsher of Duke University) has shown that the locations of electron-withdrawing and electron-releasing groups in the dienophile and diene can be reversed without reducing the yields of the adducts. Dienes with electron-withdrawing groups have been found to react readily with dienophiles containing electron-releasing groups.

Besides the use of dienes and dienophiles that have complementary electron-releasing and electron-donating properties, other factors found to enhance the rate of Diels–Alder reactions include high temperature and high pressure. Another widely used method is the use of Lewis acid catalysts. The following reaction is one of many examples where Diels–Alder adducts form readily at ambient temperature in the presence of a Lewis acid catalyst. (In Section 13.11C we see how Lewis acids can be used with chiral ligands to induce asymmetry in the reaction products.)

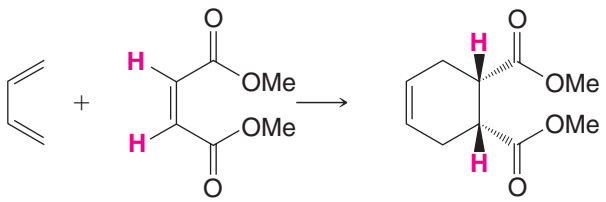


80%

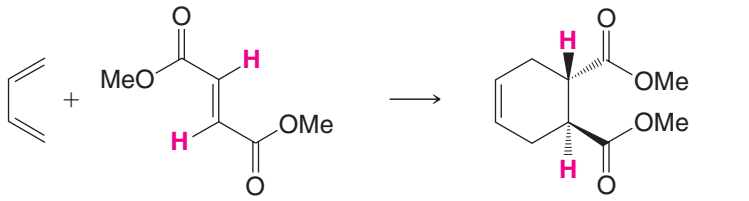
13.11B Stereochemistry of the Diels–Alder Reaction

Now let us consider some stereochemical aspects of the Diels–Alder reaction. The following factors are among the reasons why Diels–Alder reactions are so extraordinarily useful in synthesis.

1. **The Diels–Alder reaction is stereospecific: The reaction is a syn addition, and the configuration of the dienophile is *retained* in the product.** Two examples that illustrate this aspect of the reaction are shown here:



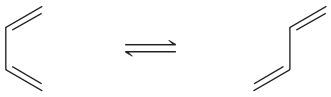
Dimethyl maleate (a *cis*-dienophile) **Dimethyl cyclohex-4-ene-*cis*-1,2-dicarboxylate**



Dimethyl fumarate (a *trans*-dienophile) **Dimethyl cyclohex-4-ene-*trans*-1,2-dicarboxylate**

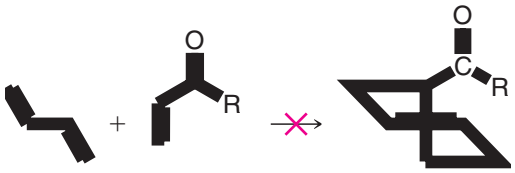
In the first example, a dienophile with cis ester groups reacts with 1,3-butadiene to give an adduct with cis ester groups. In the second example just the reverse is true. A *trans*-dienophile gives a trans adduct.

2. The diene, of necessity, reacts in the s-cis rather than in the s-trans conformation:



s-cis Conformation **s-trans Conformation**

Reaction in the s-trans conformation would, if it occurred, produce a six-membered ring with a highly strained trans double bond. This course of the Diels–Alder reaction has never been observed.

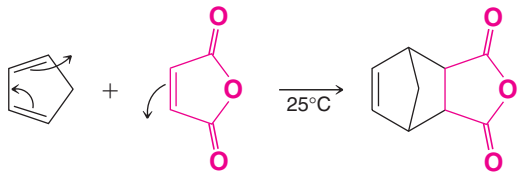


Highly strained

Helpful Hint

Use handheld molecular models to investigate the strained nature of hypothetical *trans*-cyclohexene.

Cyclic dienes in which the double bonds are held in the s-cis conformation are usually highly reactive in the Diels–Alder reaction. Cyclopentadiene, for example, reacts with maleic anhydride at room temperature to give the following adduct in quantitative yield:



Cyclopentadiene is so reactive that on standing at room temperature it slowly undergoes a Diels–Alder reaction with itself:

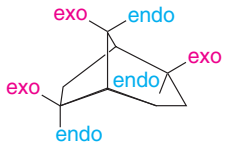
Dicyclopentadiene

The reaction is reversible, however. When dicyclopentadiene is distilled, it dissociates (is "cracked") into two molar equivalents of cyclopentadiene.

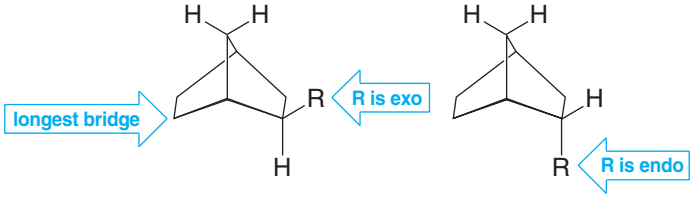
The reactions of cyclopentadiene illustrate a third stereochemical characteristic of the Diels–Alder reaction.

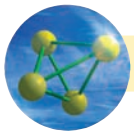
Helpful Hint

In general, the exo substituent is always on the side anti to the *longer* bridge of a bicyclic structure (exo, outside; endo, inside). For example,



3. **The Diels–Alder reaction occurs primarily in an endo rather than an exo fashion when the reaction is kinetically controlled** (see Problem 13.42). **Endo** and **exo** are terms used to designate the stereochemistry of bridged rings such as bicyclo[2.2.1]heptane. The point of reference is the longest bridge. A group that is anti to the longest bridge (the two-carbon bridge) is said to be exo; if it is on the same side, it is endo:

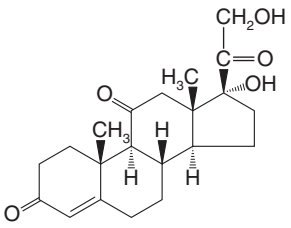




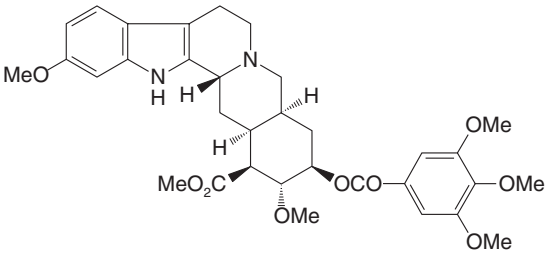
THE CHEMISTRY OF . . .

Molecules with the Nobel Prize in Their Synthetic Lineage

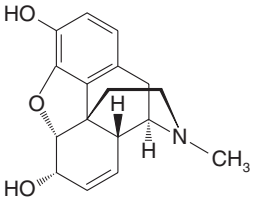
Many organic molecules from among the great targets for synthesis have the Diels–Alder reaction in their synthetic lineage. As we have learned, from acyclic precursors the Diels–Alder reaction can form a six-membered ring, with as many as four new chirality centers created in a single stereospecific step. It also produces a double bond that can be used to introduce other functionalities. The great utility of the Diels–Alder reaction earned Otto Diels and Kurt Alder the Nobel Prize in Chemistry in 1950 for developing the reaction that bears their names.



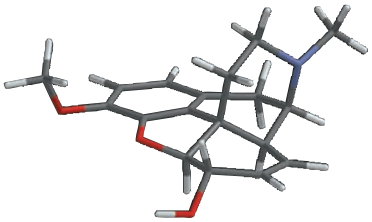
Cortisone



Reserpine



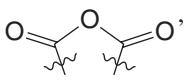
Morphine



Morphine, the synthesis of which involved the Diels–Alder reaction.

Molecules that have been synthesized using the Diels–Alder reaction (and the chemists who led the work) include morphine (above, and shown as a model), the hypnotic sedative used after many surgical procedures (M. Gates); reserpine (above), a clinically used antihypertensive agent (R. B. Woodward); cholesterol, precursor of all steroids in the body, and cortisone (also above), the anti-inflammatory agent (both by R. B. Woodward); prostaglandins $F_{2\alpha}$ and E_2 (Section 13.11C), members of a family of hormones that mediate blood pressure, smooth muscle contraction, and inflammation (E. J. Corey); vitamin B_{12} (Section 7.16A), used in the production of blood and nerve cells (A. Eschenmoser and R. B. Woodward); and Taxol (chemical name paclitaxel, Section 13.11), a potent cancer chemotherapy agent (K. C. Nicolaou). This list alone is a veritable litany of monumental synthetic accomplishments, yet there are many other molecules that have also succumbed to synthesis using the Diels–Alder reaction. It could be said that all of these molecules have a certain sense of "Nobel-ity" in their heritage.

13.11C Molecular Orbital Considerations That Favor an Endo Transition State

In the Diels–Alder reaction of cyclopentadiene with maleic anhydride the major product is the one in which the anhydride group,  , has assumed the endo configuration. This favored endo stereochemistry seems to arise from favorable interactions between the π electrons of the developing double bond in the diene and the π electrons of unsaturated groups of the dienophile. In Fig. 13.13 we can see that when the two molecules approach each other in the endo orientation, as shown, orbitals in the LUMO of maleic anhydride and the HOMO of cyclopentadiene can interact at the carbons where the new σ bonds will form (the interaction of these orbitals is indicated by purple in Fig. 13.13*b*). We can also see that this same orientation of approach (endo) has overlap between the LUMO lobes at the carbonyl groups of maleic anhydride and the HOMO lobes in cyclopentadiene above them (the interaction of these orbitals is indicated by green). This so-called secondary orbital interaction is also favorable, and it leads to a preference for endo approach of the dienophile, such that the unsaturated groups of the dienophile are tucked in and under the diene, rather than out and away in the exo orientation.

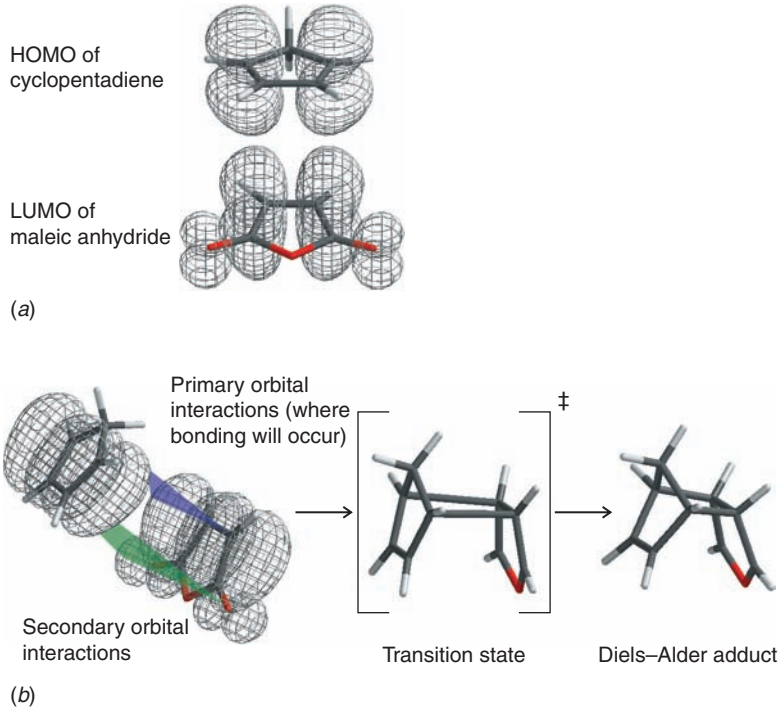


Figure 13.13 Diels–Alder reaction of cyclopentadiene and maleic anhydride. *(a)* When the highest occupied molecular orbital (HOMO) of the diene (cyclopentadiene) interacts with the lowest unoccupied molecular orbital (LUMO) of the dienophile (maleic anhydride), favorable secondary orbital interactions occur involving orbitals of the dienophile. *(b)* This interaction is indicated by the purple plane. Favorable overlap of secondary orbitals (indicated by the green plane) leads to a preference for the endo transition state shown.

The transition state for the endo product is thus of lower energy because of the favorable orbital interactions described above, and therefore the endo form is the kinetic (and major) product of this Diels–Alder reaction. The exo form is the thermodynamic product

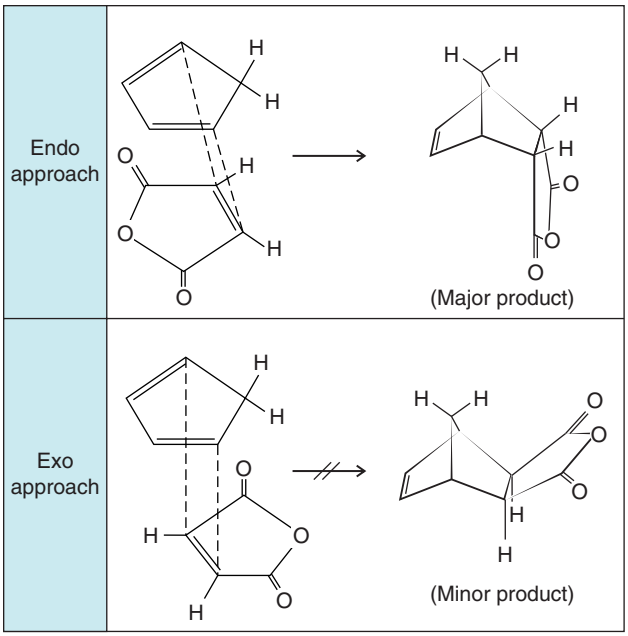


Figure 13.14 Endo and exo product formation in the Diels–Alder reaction of cyclopentadiene and maleic anhydride.

because steric interactions are fewer in the exo adduct than in the endo adduct (Fig. 13.14). Thus, the exo adduct is more stable overall, but it is not the major product because it is formed more slowly.

Here we summarize some key points.

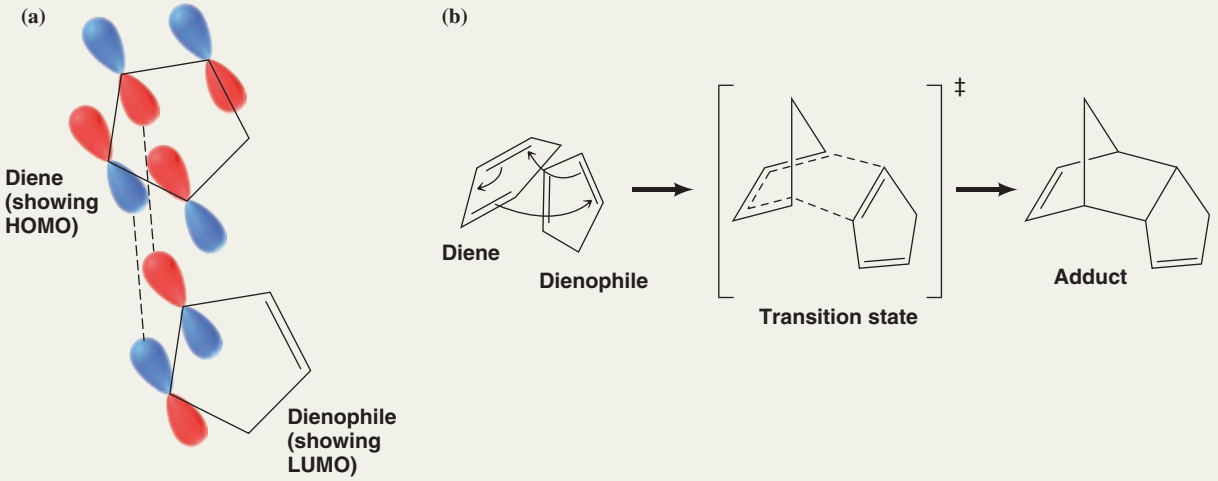
- The Diels–Alder reaction is a stereospecific syn addition. The configuration of the dienophile is retained in the product.
- The Diels–Alder reaction is stereoselective for endo addition when the reaction is under kinetic control.

Even though the Diels–Alder reaction results in formation of predominantly one stereoisomeric form (endo with retention of the original dienophile configuration), the product is nevertheless formed as a racemic mixture. The reason for this is that either face of the diene can interact with the dienophile. When the dienophile bonds with one face of the diene, the product is formed as one enantiomer, and when the dienophile bonds at the other face of the diene, the product is the other enantiomer. In the absence of chiral influences, both faces of the diene are equally likely to be attacked.

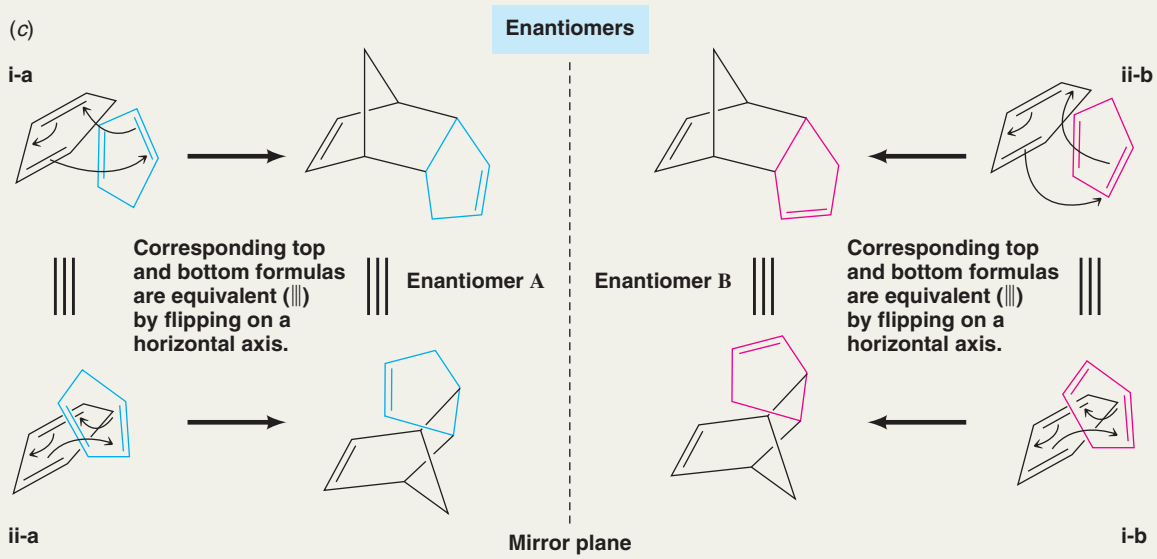
Solved Problem 13.8

The dimerization of cyclopentadiene occurs primarily through an endo transition state, as is typical for Diels–Alder reactions. **(a)** In the reactants, draw red and blue shaded lobes for the orbitals that have favorable secondary interactions in the diene and dienophile, causing the preference for an endo transition state. **(b)** Using bond-line formulas, draw curved arrows to show the flow of electrons that leads to product formation, and draw a three-dimensional formula for the product. **(c)** The reaction produces a racemic mixture. Show how the reactants align in three dimensions to form each enantiomer.

STRATEGY AND ANSWER **(a)** In the HOMO of the diene, the red and blue lobes underneath the ring have favorable same-phase interactions with the diene's LUMO. The indicated red and blue lobes in this diagram are not the ones involved in bond formation, however. They are the ones involved in secondary orbital interactions. **(b)** Two π electrons of the dienophile and all four of the π electrons of the diene interact through a cyclic transition state to form the Diels-Alder adduct shown.



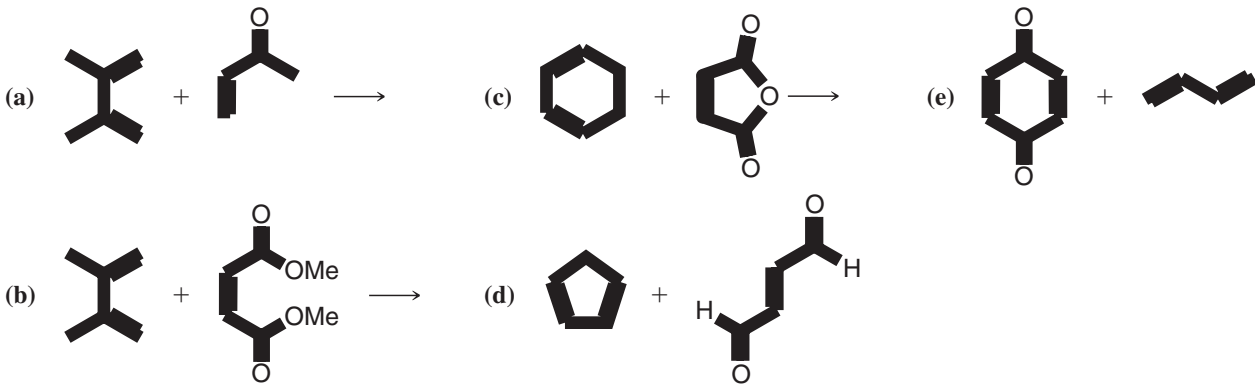
(c) Formation of the enantiomers can be shown in two ways. Compare the labeled formulas below with the following information. (i) Enantiomer **A** is formed if the dienophile approaches from below the diene and with its CH_2 group toward us (i–a). Enantiomer **B** is formed if the dienophile approaches with its CH_2 group toward us and from above (i–b). (ii) Alternatively, enantiomer **A** forms if the cyclopentadiene dienophile aligns above the diene but with its CH_2 group projecting behind the page (ii–a). Enantiomer **B** forms if the dienophile aligns below the diene but with its CH_2 group projecting behind the page (ii–b).



In doing this analysis it is interesting to note its binary nature. Changing one parameter at a time (e.g., top or bottom approach but keeping the dienophile in the same CH_2 orientation, or changing the CH_2 orientation but keeping the top or bottom approach the same) gives the two enantiomers. On the other hand, changing both of these parameters at the same time leads to just one of the enantiomers. The situation is analogous to interchanging either one or two groups at a chirality center. One interchange produces an enantiomer. Two interchanges returns the original compound.

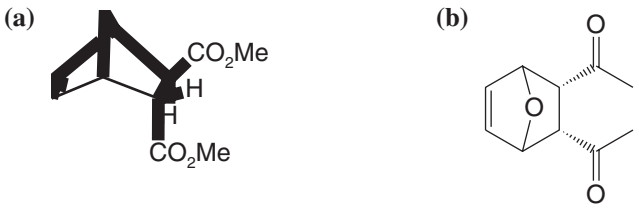
Review Problem 13.11

What products would you expect from the following reactions?

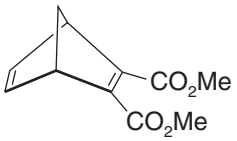


Review Problem 13.12

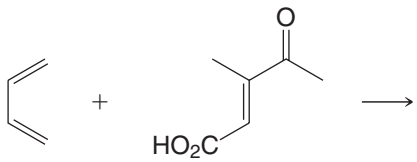
Which diene and dienophile would you employ to synthesize the following compounds?



Review Problem 13.13 Diels–Alder reactions also take place with triple-bonded (acetylenic) dienophiles. Which diene and which dienophile would you use to prepare the following?



Review Problem 13.14 1,3-Butadiene and the dienophile shown below were used by A. Eschenmoser in his synthesis of vitamin B_{12} with R. B. Woodward. Draw the structure of the enantiomeric Diels–Alder adducts that would form in this reaction and the two transition states that lead to them.



Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

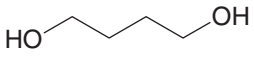
Problems

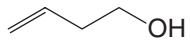
Note to Instructors: Many of the homework problems are available for assignment via *Wiley PLUS*, an online teaching and learning solution.

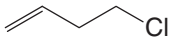
CONJUGATED SYSTEMS

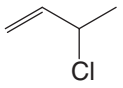
13.15 Provide the reagents needed to synthesize 1,3-butadiene starting from

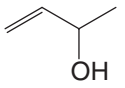
(a) 1,4-Dibromobutane

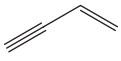
(b) 

(c) 

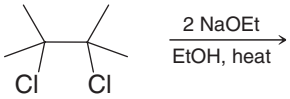
(d) 

(e) 

(f) 

(g) 

13.16 What product would you expect from the following reaction?



13.17 What products would you expect from the reaction of 1 mol of 1,3-butadiene and each of the following reagents? (If no reaction would occur, you should indicate that as well.)

(a) 1 mol of Cl_2

(b) 2 mol of Cl_2

(c) 2 mol of Br_2

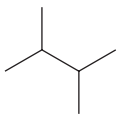
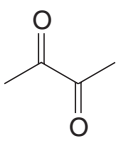
(d) 2 mol of H_2, Ni

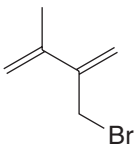
(e) 1 mol of Cl_2 in H_2O

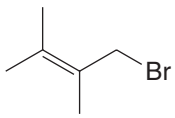
(f) Hot $KMnO_4$ (excess)

(g) H_2O, cat. H_2SO_4

13.18 Provide the reagents necessary to transform 2,3-dimethyl-1,3-butadiene into each of the following compounds.

(a) 
(b) 

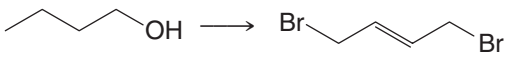
(c) 

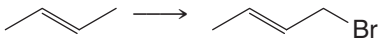
(d) 

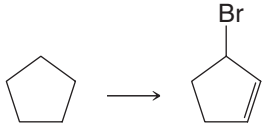
13.19 Provide the reagents necessary for each of the following transformations. In some cases several steps may be necessary.

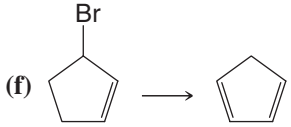
(a) 1-Butene ⟶ 1,3-butadiene

(b) 1-Pentene ⟶ 1,3-pentadiene

(c) 

(d) 

(e) 

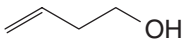
(f) 

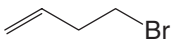
13.20 Conjugated dienes react with radicals by both 1,2 and 1,4 addition. Write a detailed mechanism to account for this fact using the peroxide-promoted addition of one molar equivalent of HBr to 1,3-butadiene as an illustration.

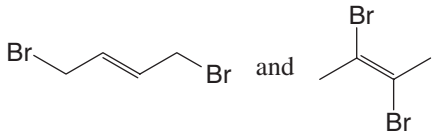
13.21 UV–Vis, IR, NMR, and mass spectrometry are spectroscopic tools we use to obtain structural information about compounds. For each pair of compounds below, describe at least one aspect from each of two spectroscopic methods (UV–Vis, IR, NMR, or mass spectrometry) that would distinguish one compound in a pair from the other.

(a) 1,3-Butadiene and 1-butyne

(b) 1,3-Butadiene and butane

(c) Butane and 

(d) 1,3-Butadiene and 

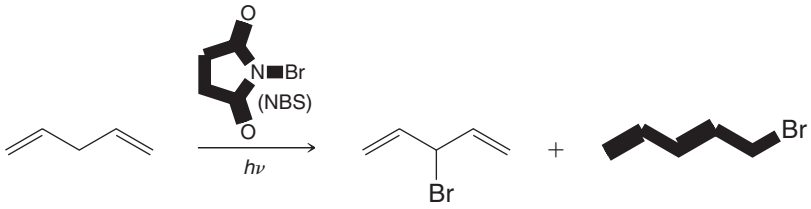
(e) 

13.22 When 2-methyl-1,3-butadiene (isoprene) undergoes a 1,4 addition of hydrogen chloride, the major product that is formed is 1-chloro-3-methyl-2-butene. Little or no 1-chloro-2-methyl-2-butene is formed. How can you explain this?

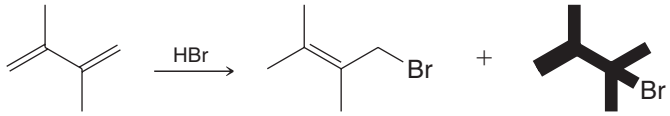
13.23 When 1-pentene reacts with *N*-bromosuccinimide (NBS), two products with the formula C_5H_9Br are obtained. What are these products and how are they formed?

13.24 **(a)** The hydrogen atoms attached to C3 of 1,4-pentadiene are unusually susceptible to abstraction by radicals. How can you account for this? **(b)** Can you provide an explanation for the fact that the protons attached to C3 of 1,4-pentadiene are more acidic than the methyl hydrogen atoms of propene?

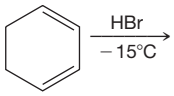
13.25 Provide a mechanism that explains formation of the following products. Include all intermediates, formal charges, and arrows showing electron flow.

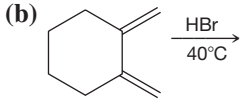


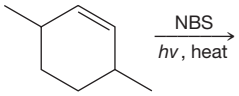
13.26 Provide a mechanism for the following reaction. Draw a reaction energy coordinate diagram that illustrates the kinetic and thermodynamic pathways for this reaction.



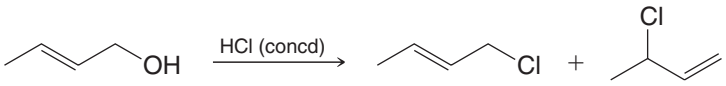
13.27 Predict the products of the following reactions.

(a) 

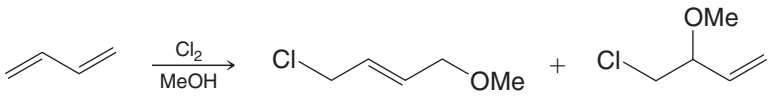
(b) 

(c) 

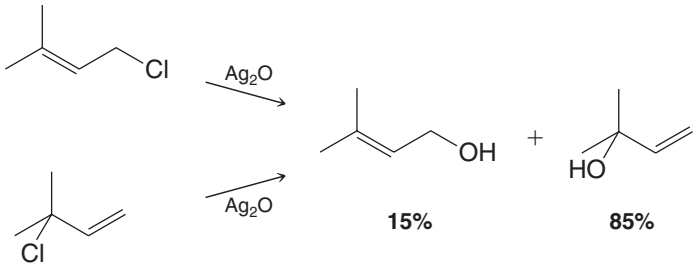
13.28 Provide a mechanism that explains formation of the following products.



13.29 Provide a mechanism that explains formation of the following products.



13.30 Treating either 1-chloro-3-methyl-2-butene or 3-chloro-3-methyl-1-butene with Ag_2O in water gives (in addition to AgCl) the following mixture of alcohol products.



(a) Write a mechanism that accounts for the formation of these products.

(b) What might explain the relative proportions of the two alkenes that are formed?

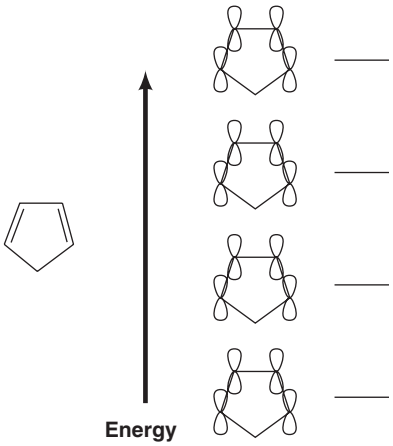
13.31 Dehydrohalogenation of 1,2-dihalides (with the elimination of two molar equivalents of HX) normally leads to an alkyne rather than to a conjugated diene. However, when 1,2-dibromocyclohexane is dehydrohalogenated, 1,3-cyclohexadiene is produced and not cyclohexyne. What factor accounts for this?

13.32 The heat of hydrogenation of allene is 298 kJ mol^{-1}, whereas that of propyne is 290 kJ mol^{-1}. **(a)** Which compound is more stable? **(b)** Treating allene with a strong base causes it to isomerize to propyne. Explain.

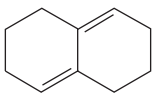
13.33 Although both 1-bromobutane and 4-bromo-1-butene are primary halides, the latter undergoes elimination more rapidly. How can this behavior be explained?

DIELS–ALDER REACTIONS

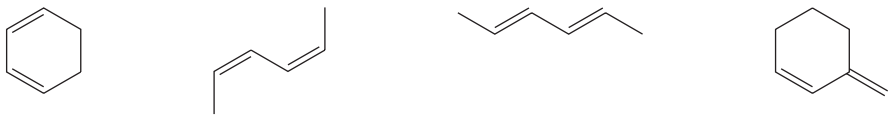
13.34 Complete the following molecular orbital description for the ground state of cyclopentadiene. Shade the appropriate lobes to indicate phase signs in each molecular orbital according to increasing energy of the molecular orbitals. Label the HOMO and LUMO orbitals, and place the appropriate number of electrons in each level, using a straight single-barbed arrow to represent each electron.



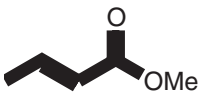
13.35 Why does the molecule shown below, although a conjugated diene, fail to undergo a Diels–Alder reaction?

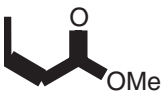


13.36 Rank the following dienes in order of increasing reactivity in a Diels–Alder reaction (1 = least reactive, 4 = most reactive). Briefly explain your ranking.



13.37 Give the structures of the products that would be formed when 1,3-butadiene reacts with each of the following:

(a) 

(b) 

(c) 

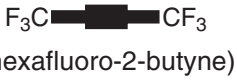
(d) 

13.38 Cyclopentadiene undergoes a Diels–Alder reaction with ethene at 160–180°C. Write the structure of the product of this reaction.

13.39 Acetylenic compounds may be used as dienophiles in the Diels–Alder reaction (see Review Problem 13.13). Write structures for the adducts that you expect from the reaction of 1,3-butadiene with

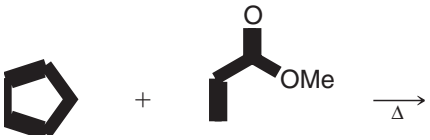
(a) 

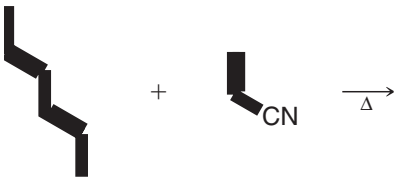
(dimethyl acetylenedicarboxylate)

(b) 

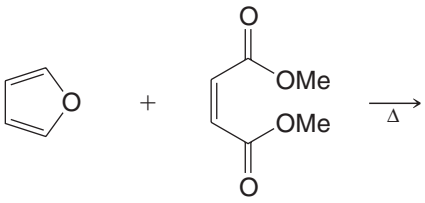
(hexafluoro-2-butyne)

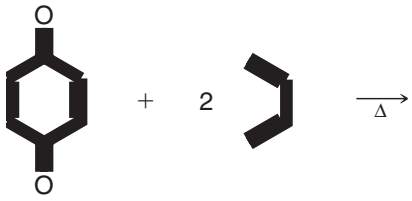
13.40 Predict the products of the following reactions.

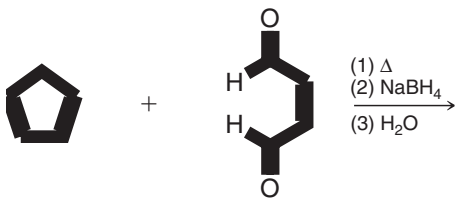
(a) 

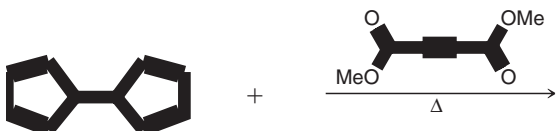
(b) 

(c) 

(d) 

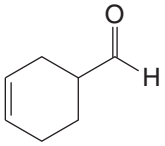
(e) 

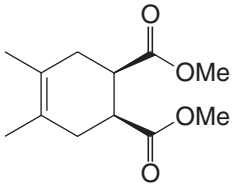
(f) 

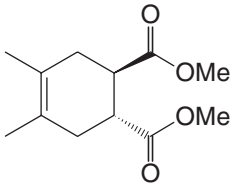
(g) 

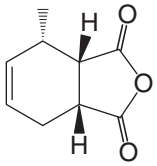
(h) 

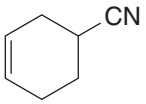
13.41 Which diene and dienophile would you employ in a synthesis of each of the following?

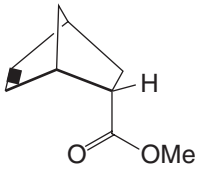
(a) 

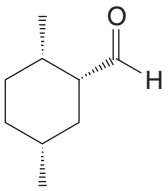
(b) 

(c) 

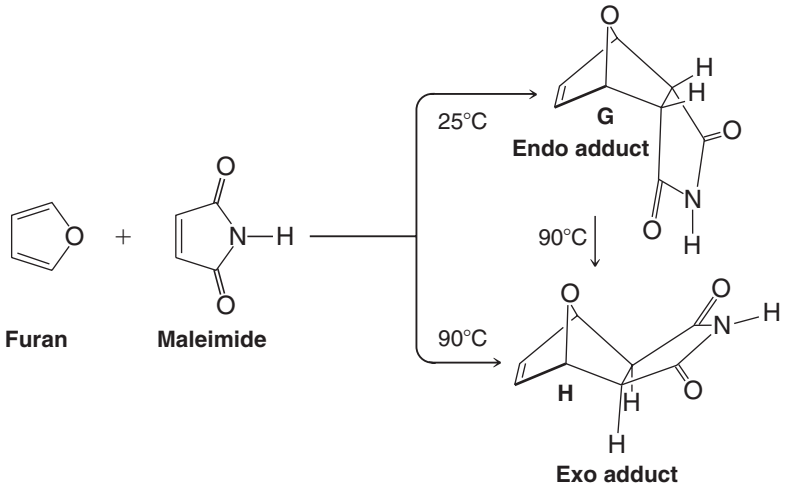
(d) 

(e) 

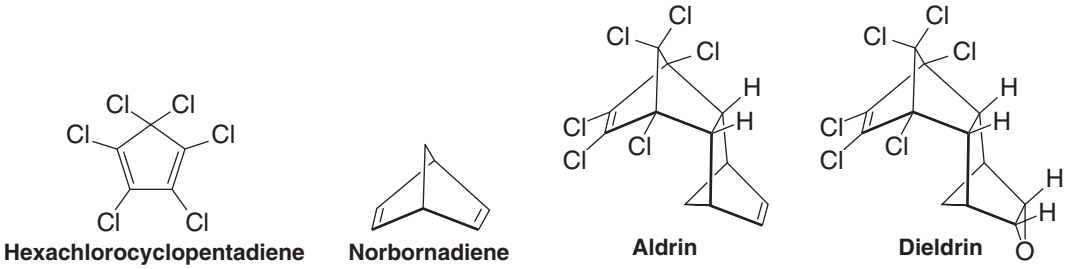
(f) 

(g) 

13.42 When furan and maleimide undergo a Diels–Alder reaction at 25°C, the major product is the endo adduct **G**. When the reaction is carried out at 90°C, however, the major product is the exo isomer **H**. The endo adduct isomerizes to the exo adduct when it is heated to 90°C. Propose an explanation that will account for these results.

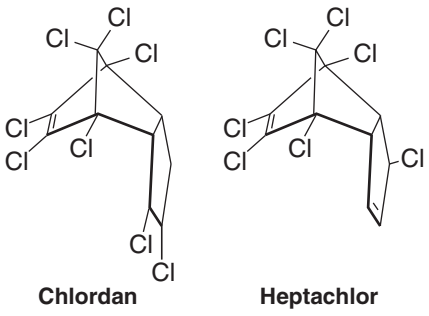


13.43 Two controversial "hard" insecticides are aldrin and dieldrin. [The Environmental Protection Agency (EPA) halted the use of these insecticides because of possible harmful side effects and because they are not biodegradable.] The commercial synthesis of aldrin began with hexachlorocyclopentadiene and norbornadiene. Dieldrin was synthesized from aldrin. Show how these syntheses might have been carried out.

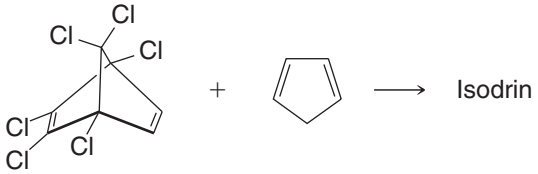


13.44 **(a)** Norbornadiene for the aldrin synthesis (Problem 13.43) can be prepared from cyclopentadiene and acetylene. Show the reaction involved. **(b)** It can also be prepared by allowing cyclopentadiene to react with vinyl chloride and treating the product with a base. Outline this synthesis.

13.45 Two other hard insecticides (see Problem 13.43) are chlordan and heptachlor. Show how they could be synthized from cyclopentadiene and hexachlorocyclopentadiene.

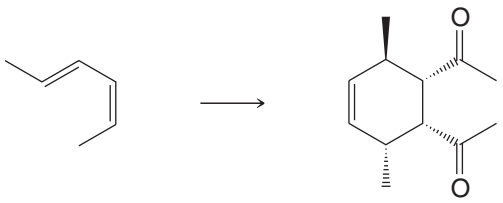


13.46 Isodrin, an isomer of aldrin, is obtained when cyclopentadiene reacts with the hexachloronorbornadiene, shown here. Propose a structure for isodrin.

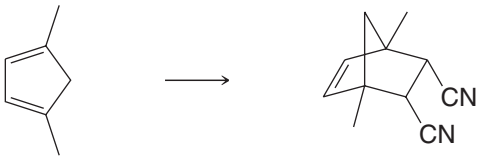


13.47 Provide the reagents necessary to achieve the following synthetic transformations. More than one step may be required.

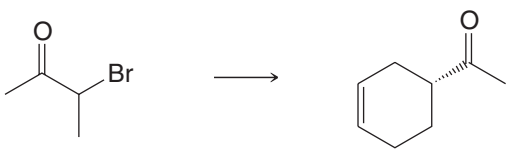
(a)



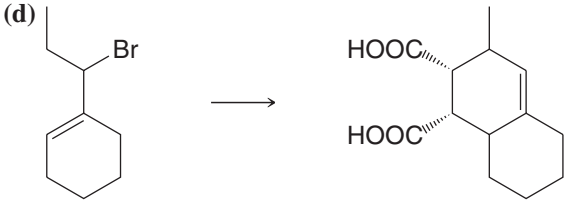
(b)



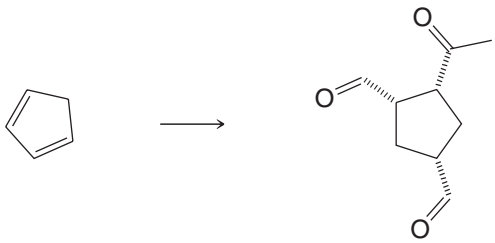
(c)



(d)

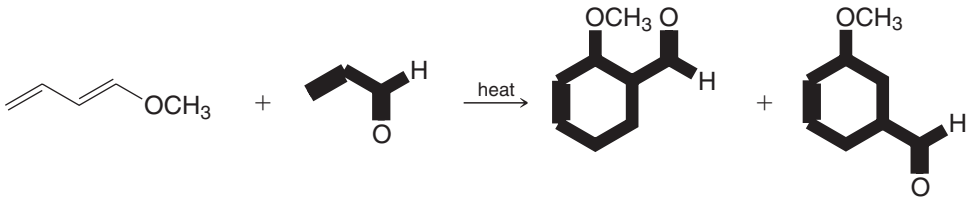


(e)



Challenge Problems

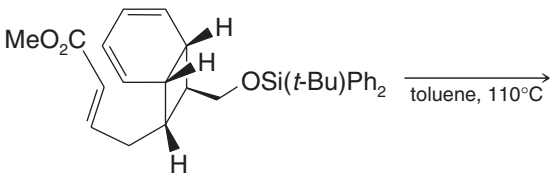
13.48 Explain the product distribution below based on the polarity of the diene and dienophile, as predicted by contributing resonance structures for each.



Major **Minor**

13.49 Mixing furan (Problem 13.42) with maleic anhydride in diethyl ether yields a crystalline solid with a melting point of 125°C. When melting of this compound takes place, however, one can notice that the melt evolves a gas. If the melt is allowed to resolidify, one finds that it no longer melts at 125°C but instead it melts at 56°C. Consult an appropriate chemistry handbook and provide an explanation for what is taking place.

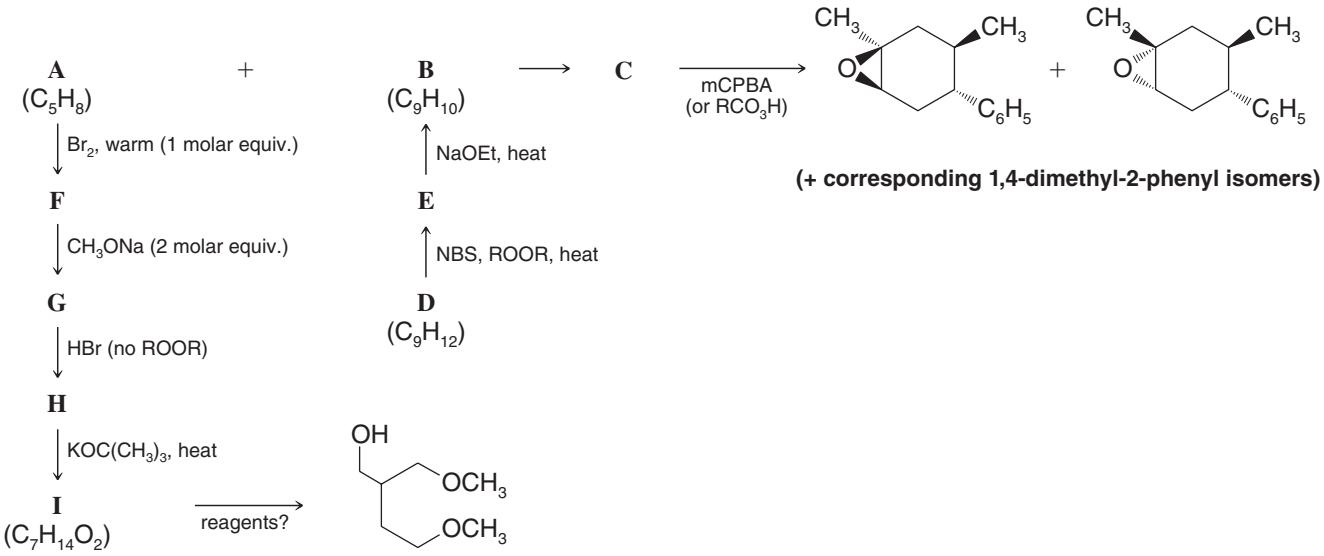
13.50 Draw the structure of the product from the following reaction (formed during a synthesis of one of the endiandric acids by K. C. Nicolaou):



13.51 Draw all of the contributing resonance structures and the resonance hybrid for the carbocation that would result from ionization of bromine from 5-bromo-1,3-pentadiene. Open the computer molecular model at the book's website depicting a map of electrostatic potential for the pentadienyl carbocation. Based on the model, which is the most important contributing resonance structure for this cation? Is this consistent with what you would have predicted based on your knowledge of relative carbocation stabilities? Why or why not?

Learning Group Problems

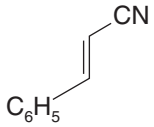
1. Elucidate the structures of compounds **A** through **I** in the following "road map" problem. Specify any missing reagents.



(+ corresponding 1,4-dimethyl-2-phenyl isomers)

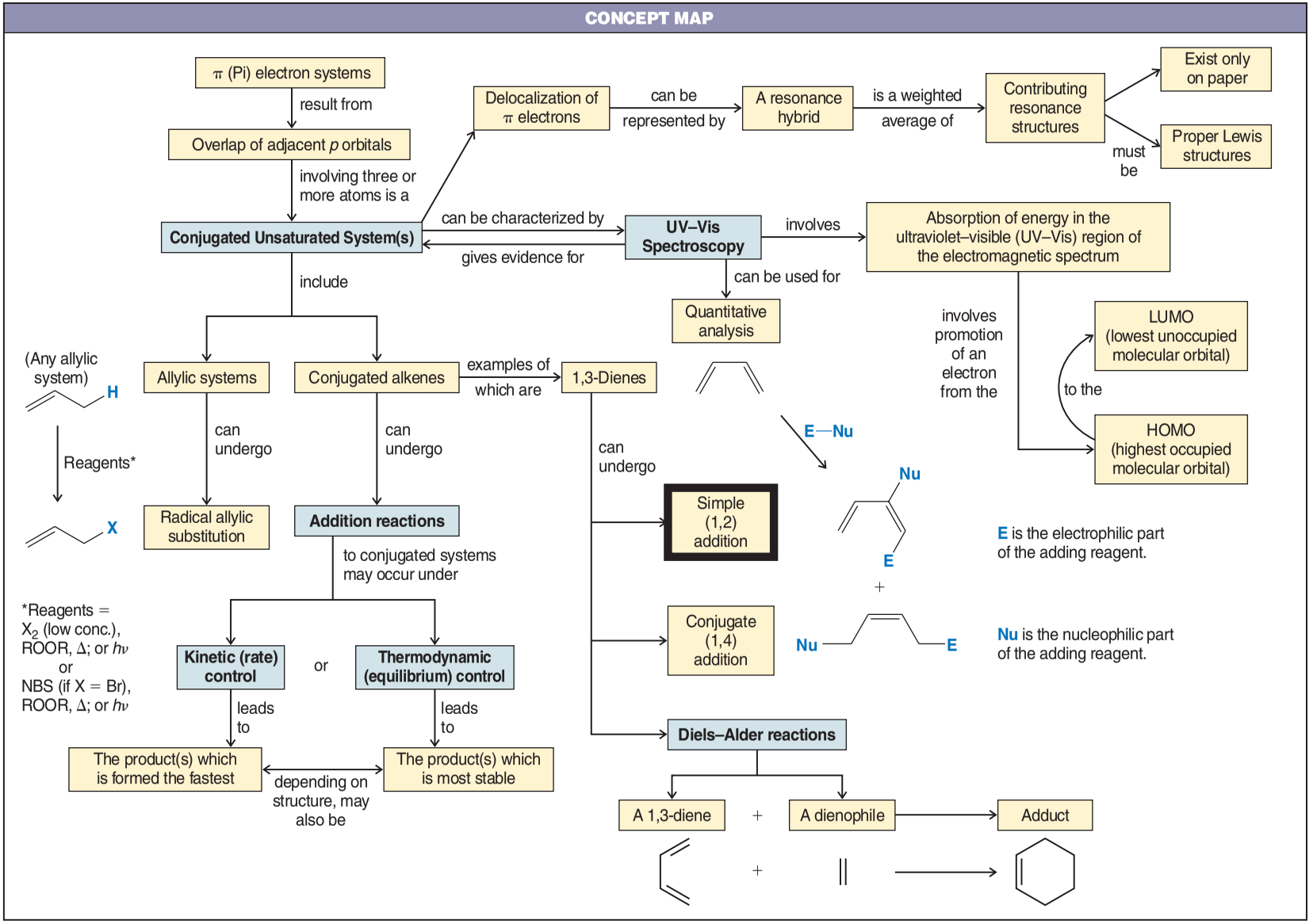
2. **(a)** Write reactions to show how you could convert 2-methyl-2-butene into 2-methyl-1,3-butadiene.

(b) Write reactions to show how you could convert ethylbenzene into the following compound:



(c) Write structures for the various Diels–Alder adduct(s) that could result on reaction of 2-methyl-1,3-butadiene with the compound shown in part (b).

CONCEPT MAP

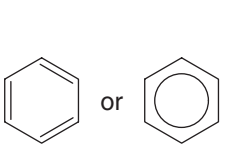


14

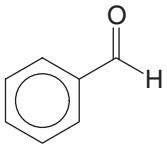
Aromatic Compounds

In ordinary conversation, the word "aromatic" conjures pleasant associations—the odor of freshly prepared coffee, or of a cinnamon bun. Similar associations occurred early in the history of organic chemistry, when pleasantly "aromatic" compounds were isolated from natural oils produced by plants. As the structures of these compounds were elucidated, a number of them were found to contain a highly unsaturated six-carbon structural unit that is also found in benzene. This special ring structure became known as a benzene ring, and the aromatic compounds containing a benzene ring became part of a larger family of compounds now classified as aromatic on the basis of their electronic structure rather than their odor.

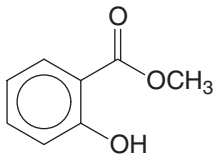
The following are a few examples of aromatic compounds including benzene itself. In these formulas we foreshadow our discussion of the special properties of the benzene ring by using a circle in a hexagon to depict the six π electrons and six-membered ring of these compounds, whereas heretofore we have shown benzene rings only as indicated in the left-hand formula for benzene below.



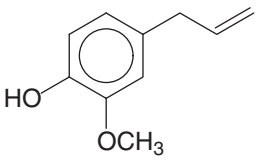
Benzene



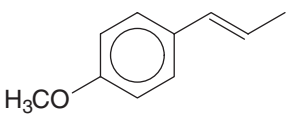
Benzaldehyde
(in oil of almonds)



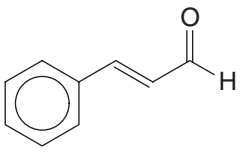
Methyl salicylate
(in oil of wintergreen)



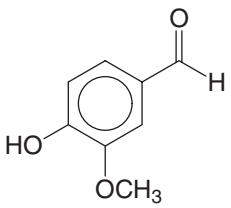
Eugenol
(in oil of cloves)



Anethole
(in oil of anise)

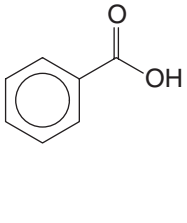


Cinnamaldehyde
(in oil of cinnamon)

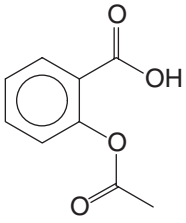


Vanillin
(in oil of vanilla)

As time passed, chemists found or synthesized many compounds with benzene rings that had no odor, such as benzoic acid and acetylsalicylic acid (aspirin).



Benzoic acid



Acetylsalicylic acid (aspirin)

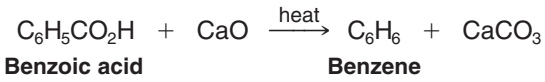
14.1 *The Discovery of Benzene*

In this chapter we shall discuss in detail the structural principles that underlie how the term "aromatic" is used today. We will also see how the structure of benzene proved so elusive. Even though benzene was discovered in 1825, it was not until the development of quantum mechanics in the 1920s that a reasonably clear understanding of its structure emerged.

- As we have seen above, two formula types are commonly used to depict benzene rings. The traditional bond-line representation allows easier depiction of mechanisms involving the π electrons, as we shall need to do in upcoming chapters, whereas the circle in the hexagon notation better suggests the structure and properties of benzene rings.

The study of the class of compounds that organic chemists call aromatic compounds (Section 2.1D) began with the discovery in 1825 of a new hydrocarbon by the English chemist Michael Faraday (Royal Institution). Faraday called this new hydrocarbon "bicarburet of hydrogen"; we now call it benzene. Faraday isolated benzene from a compressed illuminating gas that had been made by pyrolyzing whale oil.

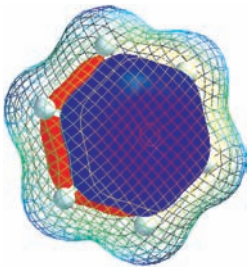
In 1834 the German chemist Eilhardt Mitscherlich (University of Berlin) synthesized benzene by heating benzoic acid with calcium oxide. Using vapor density measurements, Mitscherlich further showed that benzene has the molecular formula C_6H_6:



Benzoic acid **Benzene**

The molecular formula itself was surprising. Benzene has *only as many hydrogen atoms as it has carbon atoms*. Most compounds that were known then had a far greater proportion of hydrogen atoms, usually twice as many. Benzene, having the formula of C_6H_6, should be a highly unsaturated compound because it has an index of hydrogen deficiency equal to 4. Eventually, chemists began to recognize that benzene was a member of a new class of organic compounds with unusual and interesting properties. **As we shall see in Section 14.3, benzene does not show the behavior expected of a highly unsaturated compound**.

During the latter part of the nineteenth century the Kekulé–Couper–Butlerov theory of valence was systematically applied to all known organic compounds. One result of this effort was the placing of organic compounds in either of two broad categories; compounds were classified as being either **aliphatic** or **aromatic**. To be classified as aliphatic meant then that the chemical behavior of a compound was "fatlike." (Now it means that the compound reacts like an alkane, an alkene, an alkyne, or one of their derivatives.) To be classified as aromatic meant then that the compound had a low hydrogen-to-carbon ratio and that it was "fragrant." Most of the early aromatic compounds were obtained from balsams, resins, or essential oils.



One of the π molecular orbitals of benzene, seen through a mesh representation of its electrostatic potential at its van der Waals surface.

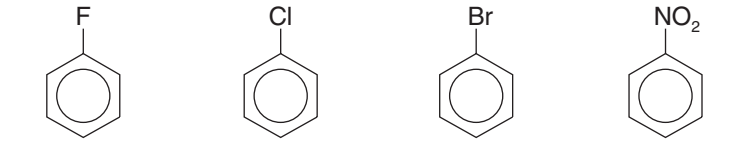
Kekulé was the first to recognize that these early aromatic compounds all contain a six-carbon unit and that they retain this six-carbon unit through most chemical transformations and degradations. Benzene was eventually recognized as being the parent compound of this new series.

14.2 Nomenclature of Benzene Derivatives

Two systems are used in naming monosubstituted benzenes.

- In many simple compounds, *benzene* is the parent name and the substituent is simply indicated by a prefix.

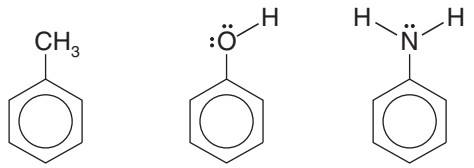
We have, for example,



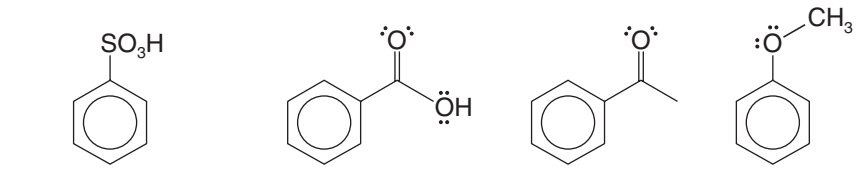
Fluorobenzene **Chlorobenzene** **Bromobenzene** **Nitrobenzene**

- For other simple and common compounds, the substituent and the benzene ring taken together may form a commonly accepted parent name.

Methylbenzene is usually called *toluene*, hydroxybenzene is almost always called *phenol*, and aminobenzene is almost always called *aniline*. These and other examples are indicated here:



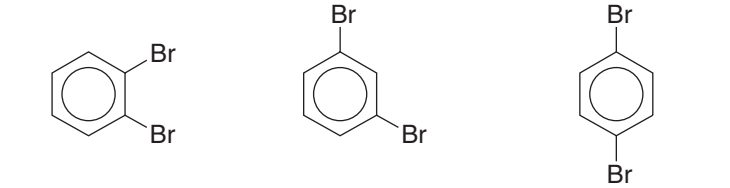
Toluene **Phenol** **Aniline**



Benzenesulfonic acid **Benzoic acid** **Acetophenone** **Anisole**

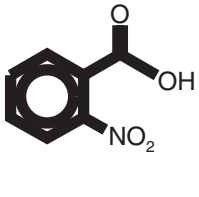
- When two substituents are present, their relative positions are indicated by the prefixes ***ortho-, meta-***, and ***para-*** (abbreviated ***o-, m-***, and ***p-***) or by the use of numbers.

For the dibromobenzenes we have

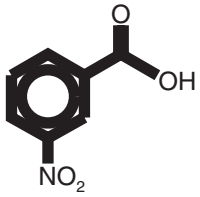


1,2-Dibromobenzene (*o*-dibromobenzene) ortho **1,3-Dibromobenzene (*m*-dibromobenzene) meta** **1,4-Dibromobenzene (*p*-dibromobenzene) para**

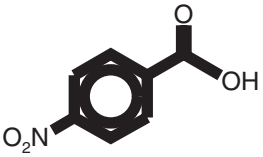
and for the nitrobenzoic acids



2-Nitrobenzoic acid (*o*-nitrobenzoic acid)

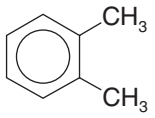


3-Nitrobenzoic acid (*m*-nitrobenzoic acid)

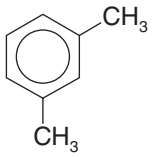


4-Nitrobenzoic acid (*p*-nitrobenzoic acid)

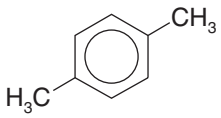
The dimethylbenzenes are often called *xylenes*:



1,2-Dimethylbenzene (*o*-xylene)



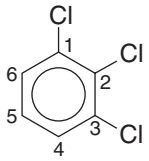
1,3-Dimethylbenzene (*m*-xylene)



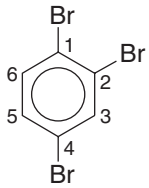
1,4-Dimethylbenzene (*p*-xylene)

- If more than two groups are present on the benzene ring, their positions must be indicated by the use of *numbers*.

As examples, consider the following two compounds:

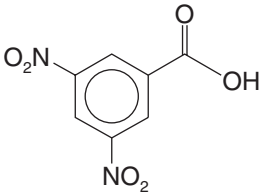


1,2,3-Trichlorobenzene

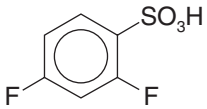


1,2,4-Tribromobenzene (*not* 1,3,4-tribromobenzene)

- The benzene ring is numbered so as to give ***the lowest possible numbers to the substituents***.
- When more than two substituents are present and the substituents are different, they are listed in alphabetical order.
- When a substituent is one that together with the benzene ring gives a new base name, that substituent is assumed to be in position 1 and the new parent name is used.



3,5-Dinitrobenzoic acid



2,4-Difluorobenzenesulfonic acid

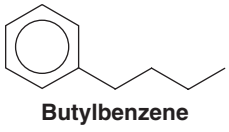
- When the C_6H_5— group is named as a substituent, it is called a **phenyl** group. The phenyl group is often abbreviated as C_6H_5—, Ph—, or φ—.

Helpful Hint

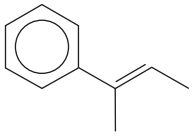
Note the abbreviations for common aromatic groups.

A hydrocarbon composed of one saturated chain and one benzene ring is usually named as a derivative of the larger structural unit. However, if the chain is unsaturated, the

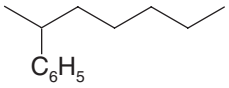
compound may be named as a derivative of that chain, regardless of ring size. The following are examples:



Butylbenzene

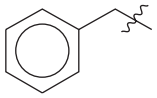


(*E*)-2-Phenyl-2-butene

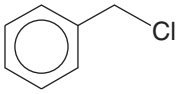


2-Phenylheptane

- **Benzyl** is an alternative name for the phenylmethyl group. It is sometimes abbreviated Bn.



The benzyl group (the phenylmethyl group)

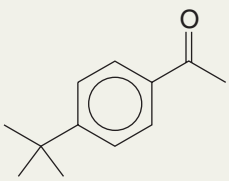


Benzyl chloride (phenylmethyl chloride or BnCl)

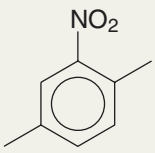
Solved Problem 14.1

Provide a name for each of the following compounds.

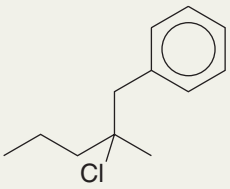
(a)



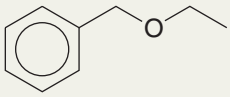
(b)



(c)



(d)

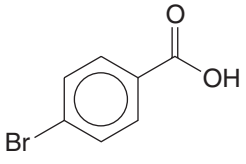


STRATEGY AND ANSWER In each compound we look first to see if a commonly named unit containing a benzene ring is present. If not, we consider whether the compound can be named as a simple derivative of benzene, or if the compound incorporates the benzene ring as a phenyl or benzyl group. In (a) we recognize the common structural unit of acetophenone, and find a *tert*-butyl group in the para position. The name is thus *p*-*tert*-butylacetophenone or 4-*tert*-butylacetophenone. Compound (b), having three substituents on the ring, must have its substituents named in alphabetical order and their positions numbered. The name is 1,4-dimethyl-2-nitrobenzene. In (c) there would appear to be a benzyl group, but the benzene ring can be considered a substituent on the alkyl chain, so it is called phenyl in this case. The name is 2-chloro-2-methyl-1-phenylpentane. Because (d) contains an ether functional group, we name it according to the groups bonded to the ether oxygen. The name is benzyl ethyl ether, or ethyl phenylmethyl ether.

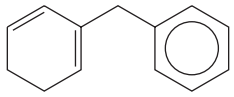
Review Problem 14.1

Provide a name for each of the following compounds.

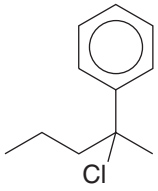
(a)



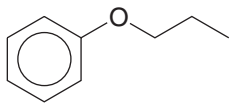
(b)



(c)



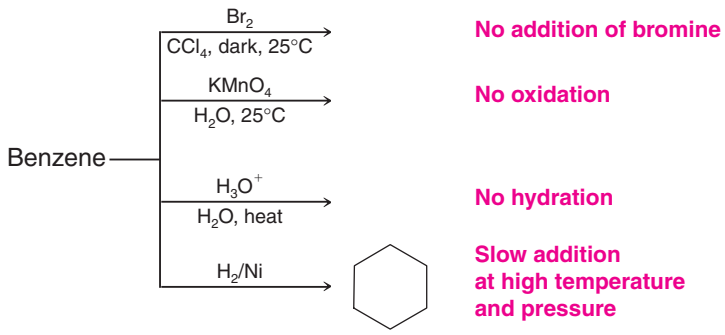
(d)



14.3 Reactions of Benzene

In the mid-nineteenth century, benzene presented chemists with a real puzzle. They knew from its formula (Section 14.1) that benzene was highly unsaturated, and they expected it to react accordingly. They expected it to react like an alkene by decolorizing bromine in carbon tetrachloride through *addition of bromine*. They expected that it would change the color of aqueous potassium permanganate by being *oxidized*, that it would *add hydrogen* rapidly in the presence of a metal catalyst, and that it would *add water* in the presence of strong acids.

Benzene does none of these. When benzene is treated with bromine in the dark or with aqueous potassium permanganate or with dilute acids, none of the expected reactions occurs. Benzene does add hydrogen in the presence of finely divided nickel, but only at high temperatures and under high pressures:



Benzene *does* react with bromine but only in the presence of a Lewis acid catalyst such as ferric bromide. Most surprisingly, however, it reacts not by addition but by *substitution*—**benzene substitution**.

Substitution

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

Substitution is observed.

Addition

$$C_6H_6 + Br_2 \not\longrightarrow C_6H_6Br_2 + C_6H_6Br_4 + C_6H_6Br_6$$

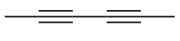
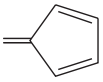
Addition is not observed.

When benzene reacts with bromine, *only one monobromobenzene* is formed. That is, only one compound with the formula C_6H_5Br is found among the products. Similarly, when benzene is chlorinated, *only one monochlorobenzene* results.

Two possible explanations can be given for these observations. The first is that only one of the six hydrogen atoms in benzene is reactive toward these reagents. The second is that all six hydrogen atoms in benzene are equivalent, and replacing any one of them with a substituent results in the same product. As we shall see, the second explanation is correct.

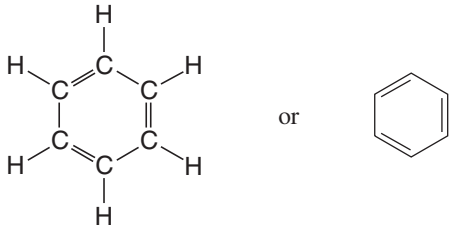
Review Problem 14.2

Listed below are four compounds that have the molecular formula C_6H_6. Which of these compounds would yield only one monosubstitution product, if, for example, one hydrogen were replaced by bromine?

(a)  **(b)**  **(c)**  **(d)** 

14.4 The Kekulé Structure for Benzene

In 1865, August Kekulé, the originator of the structural theory (Section 1.3), proposed the first definite structure for benzene,* a structure that is still used today (although as we shall soon see, we give it a meaning different from the meaning Kekulé gave it). Kekulé suggested that the carbon atoms of benzene are in a ring, that they are bonded to each other by alternating single and double bonds, and that one hydrogen atom is attached to each carbon atom. This structure satisfied the requirements of the structural theory that carbon atoms form four bonds and that all the hydrogen atoms of benzene are equivalent:



The Kekulé formula for benzene

A problem soon arose with the **Kekulé structure**, however. The Kekulé structure predicts that there should be two different 1,2-dibromobenzenes, but there are not. In one of these hypothetical compounds (below), the carbon atoms that bear the bromines would be separated by a single bond, and in the other they would be separated by a double bond.

These 1,2-dibromobenzenes do not exist as isomers.

- *Only one 1,2-dibromobenzene has ever been found, however.*

To accommodate this objection, Kekulé proposed that the two forms of benzene (and of benzene derivatives) are in a state of equilibrium and that this equilibrium is so rapidly established that it prevents isolation of the separate compounds. Thus, the two 1,2-dibromobenzenes would also be rapidly equilibrated, and this would explain why chemists had not been able to isolate the two forms:

There is no such equilibrium between benzene ring bond isomers.

- We now know that this proposal was also incorrect and that *no such equilibrium exists*.

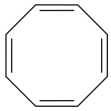
Nonetheless, the Kekulé formulation of benzene's structure was an important step forward and, for very practical reasons, it is still used today. We understand its meaning differently, however.

The tendency of benzene to react by substitution rather than addition gave rise to another concept of aromaticity. For a compound to be called aromatic meant, experimentally, that it gave substitution reactions rather than addition reactions even though it was highly unsaturated.

Before 1900, chemists assumed that the ring of alternating single and double bonds was the structural feature that gave rise to the aromatic properties. Since benzene and benzene derivatives (i.e., compounds with six-membered rings) were the only aromatic compounds

*In 1861 the Austrian chemist Johann Josef Loschmidt represented the benzene ring with a circle, but he made no attempt to indicate how the carbon atoms were actually arranged in the ring.

known, chemists naturally sought other examples. The compound cyclooctatetraene seemed to be a likely candidate:



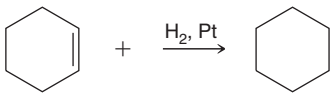
Cyclooctatetraene

In 1911, Richard Willstätter succeeded in synthesizing cyclooctatetraene. Willstätter found, however, that it is not at all like benzene. Cyclooctatetraene reacts with bromine by addition, it adds hydrogen readily, it is oxidized by solutions of potassium permanganate, and thus it is clearly *not aromatic*. While these findings must have been a keen disappointment to Willstätter, they were very significant for what they did not prove. Chemists, as a result, had to look deeper to discover the origin of benzene's aromaticity.

14.5 The Thermodynamic Stability of Benzene

We have seen that benzene shows unusual behavior by undergoing substitution reactions when, on the basis of its Kekulé structure, we should expect it to undergo addition. Benzene is unusual in another sense: It is *more stable thermodynamically* than the Kekulé structure suggests. To see how, consider the following thermochemical results.

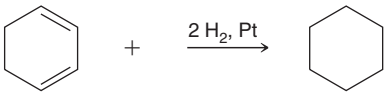
Cyclohexene, a six-membered ring containing one double bond, can be hydrogenated easily to cyclohexane. When the ΔH° for this reaction is measured, it is found to be -120 kJ mol^{-1}, very much like that of any similarly substituted alkene:



Cyclohexene **Cyclohexane**

$\Delta H^\circ = -120$ kJ mol^{-1}

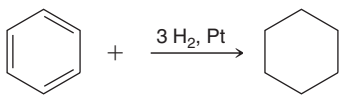
We would expect that hydrogenation of 1,3-cyclohexadiene would liberate roughly twice as much heat and thus have a ΔH° equal to about -240 kJ mol^{-1}. When this experiment is done, the result is $\Delta H^\circ = -232$ kJ mol^{-1}. This result is quite close to what we calculated, and the difference can be explained by taking into account the fact that compounds containing conjugated double bonds are usually somewhat more stable than those that contain isolated double bonds (Section 13.8):



1,3-Cyclohexadiene **Cyclohexane**

Calculated
$\Delta H^\circ = 2 \times (-120) = -240$ kJ mol^{-1}
Observed
$\Delta H^\circ = -232$ kJ mol^{-1}

If we extend this kind of thinking, and if benzene is simply 1,3,5-cyclohexatriene, we would predict benzene to liberate approximately 360 kJ mol^{-1} [$3 \times (-120)$] when it is hydrogenated. When the experiment is actually done, the result is surprisingly different. The reaction is exothermic, but only by 208 kJ mol^{-1}:



Benzene **Cyclohexane**

Calculated $\Delta H^\circ = 3 \times (-120)$	$= -360$ kJ mol^{-1}
Observed ΔH°	$= -208$ kJ mol^{-1}
Difference	$= 152$ kJ mol^{-1}

When these results are represented as in Fig. 14.1, it becomes clear that benzene is much more stable than we calculated it to be. Indeed, it is more stable than the hypothetical 1,3,5-cyclohexatriene by 152 kJ mol^{-1}. This difference between the amount of heat actually released and that calculated on the basis of the Kekulé structure is now called the **resonance energy** of the compound.

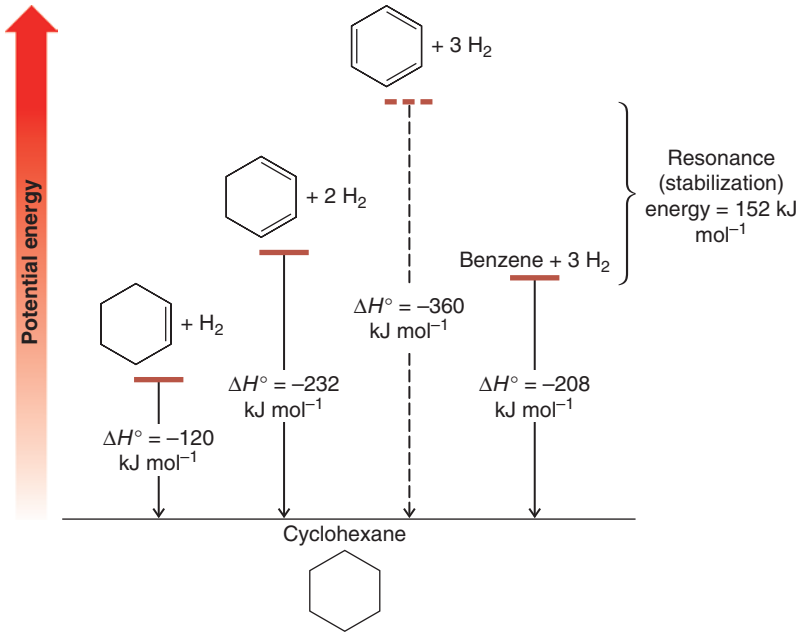


Figure 14.1 Relative stabilities of cyclohexene, 1,3-cyclohexadiene, 1,3,5-cyclohexatriene (hypothetical), and benzene.

14.6 *Modern Theories of the Structure of Benzene*

It was not until the development of quantum mechanics in the 1920s that the unusual behavior and stability of benzene began to be understood. Quantum mechanics, as we have seen, produced two ways of viewing bonds in molecules: resonance theory and molecular orbital theory. We now look at both of these as they apply to benzene.

14.6A The Resonance Explanation of the Structure of Benzene

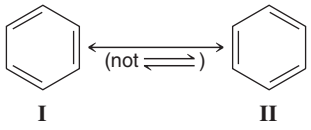
A basic postulate of resonance theory (Sections 1.8 and 13.5) is that whenever two or more Lewis structures can be written for a molecule that *differ only in the positions of their electrons*, none of the structures will be in complete accord with the compound's chemical and physical properties. If we recognize this, we can now understand the true nature of the two Kekulé structures (**I** and **II**) for benzene.

- Kekulé structures **I** and **II** below differ only in the positions of their electrons; they do not represent two separate molecules in equilibrium as Kekulé had proposed.

Instead, structures **I** and **II** are the closest we can get to a structure for benzene within the limitations of its molecular formula, the classic rules of valence, and the fact that the six hydrogen atoms are chemically equivalent. The problem with the Kekulé structures is that they are Lewis structures, and Lewis structures portray electrons in localized distributions. (With benzene, as we shall see, the electrons are delocalized.) Resonance theory, fortunately, does not stop with telling us when to expect this kind of trouble; it also gives us a way out.

- According to resonance theory, we consider Kekulé structures **I** and **II** below as *resonance contributors* to the real structure of benzene, and we relate them to each other with one double-headed, double-barbed arrow (not two separate arrows, which we reserve for equilibria).

Resonance contributors, we emphasize again, are not in equilibrium. They are not structures of real molecules. They are the closest we can get if we are bound by simple rules of valence, but they are very useful in helping us visualize the actual molecule as a hybrid:



Look at the structures carefully. All of the single bonds in structure **I** are double bonds in structure **II**.

- A hybrid (average) of Kekulé structures **I** and **II** would have neither pure single bonds nor pure double bonds between the carbons. The bond order would be between that of a single and a double bond.

Experimental evidence bears this out. Spectroscopic measurements show that the molecule of benzene is planar and that all of its carbon–carbon bonds are of equal length. Moreover, the carbon–carbon bond lengths in benzene (Fig. 14.2) are 1.39 Å, a value in between that for a carbon–carbon single bond between sp^2-hybridized atoms (1.47 Å) (see Table 13.1) and that for a carbon–carbon double bond (1.34 Å).

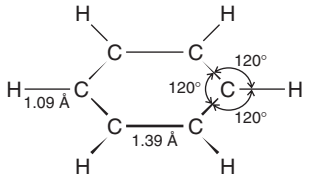


Figure 14.2 Bond lengths and angles in benzene. (Only the σ bonds are shown.)

- The hybrid structure of benzene is represented by inscribing a circle inside the hexagon as shown in formula **III** below.

III

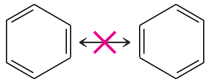
There are times when an accounting of the π electron pairs must be made, however, and for these purposes we use either Kekulé structure **I** or **II**. We do this simply because the electron pairs and total π electron count is obvious in a Kekulé structure, whereas the number of π electron pairs represented by a circle can be ambiguous. As we shall see later in this chapter, there are systems having different ring sizes and different numbers of delocalized π electrons that can also be represented by a circle. In benzene, however, the circle is understood to represent six π electrons that are delocalized around the six carbons of the ring.

- An actual molecule of benzene (depicted by the resonance hybrid **III**) is more stable than either contributing resonance structure because more than one equivalent resonance structure can be drawn for benzene (**I** and **II** above).

The difference in energy between hypothetical 1,3,5-cyclohexatriene (which if it existed would have higher energy) and benzene is called *resonance energy*, and it is an indication of the extra stability of benzene due to electron delocalization.

Review Problem 14.3

If benzene were 1,3,5-cyclohexatriene, the carbon–carbon bonds would be alternately long and short as indicated in the following structures. However, to consider the structures here as resonance contributors (or to connect them by a double-headed arrow) violates a basic principle of resonance theory. Explain.



14.6B The Molecular Orbital Explanation of the Structure of Benzene

The fact that the bond angles of the carbon atoms in the benzene ring are all 120° strongly suggests that the carbon atoms are sp^2 hybridized. If we accept this suggestion and construct a planar six-membered ring from sp^2 carbon atoms, representations like those shown

in Figs. 14.3*a* and *b* emerge. In these models, each carbon is sp^2 hybridized and has a *p* orbital available for overlap with *p* orbitals of its neighboring carbons. If we consider favorable overlap of these *p* orbitals all around the ring, the result is the model shown in Fig. 14.3*c*.

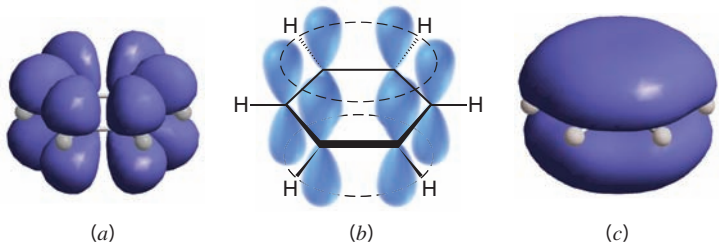


Figure 14.3 (*a*) Six sp^2-hybridized carbon atoms joined in a ring (each carbon also bears a hydrogen atom). Each carbon has a *p* orbital with lobes above and below the plane of the ring. (*b*) A stylized depiction of the *p* orbitals in (a). (*c*) Overlap of the *p* orbitals around the ring results in a molecular orbital encompassing the top and bottom faces of the ring. (Differences in the mathematical phase of the orbital lobes are not shown in these representations.)

- As we recall from the principles of quantum mechanics (Section 1.11), the number of molecular orbitals in a molecule is the same as the number of atomic orbitals from which they are derived, and each orbital can accommodate a maximum of two electrons if their spins are opposed.

If we consider only the *p* atomic orbitals contributed by the carbon atoms of benzene, there should be six π molecular orbitals. These orbitals are shown in Fig. 14.4.

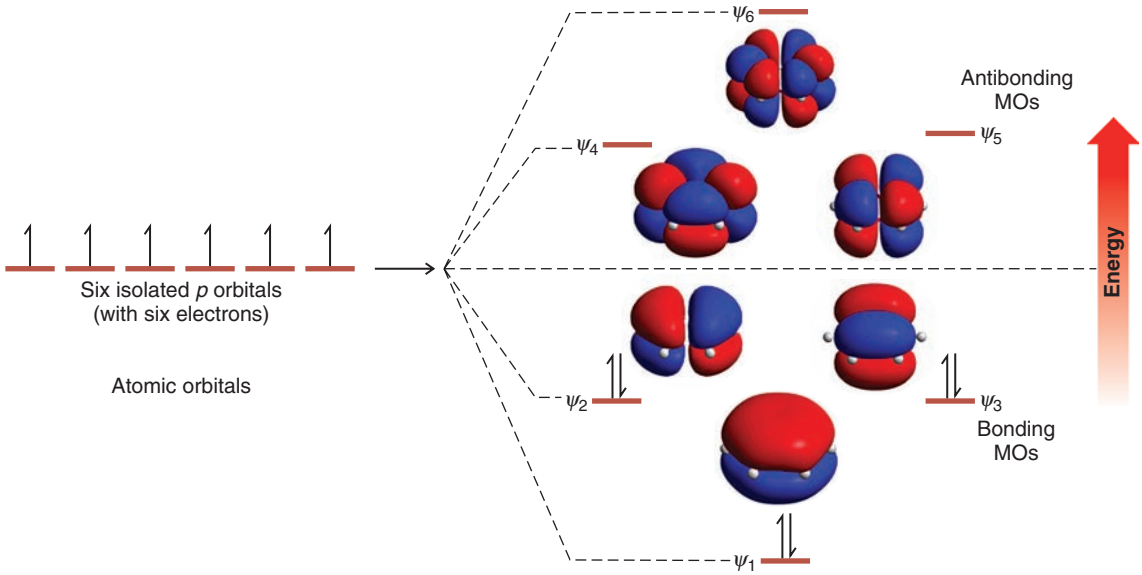


Figure 14.4 How six *p* atomic orbitals (one from each carbon of the benzene ring) combine to form six π molecular orbitals. Three of the molecular orbitals have energies lower than that of an isolated *p* orbital; these are the bonding molecular orbitals. Three of the molecular orbitals have energies higher than that of an isolated *p* orbital; these are the antibonding molecular orbitals. Orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate; the same is true of orbitals ψ_4 and ψ_5.

The electronic configuration of the ground state of benzene is obtained by adding the six π electrons to the π molecular orbitals shown in Fig. 14.4, starting with the orbitals of lowest energy. The lowest energy π molecular orbital in benzene has overlap of *p* orbitals with the same mathematical phase sign all around the top and bottom faces of the ring. In this orbital there are no nodal planes (changes in orbital phase sign) perpendicular to the atoms of the ring. The orbitals of next higher energy each have one nodal plane. (In general, each set of higher energy π molecular orbitals has an additional nodal plane.) Each of these orbitals is filled with a pair of electrons, as well. These orbitals are of equal energy

(degenerate) because they both have one nodal plane. Together, these three orbitals comprise the bonding π molecular orbitals of benzene. The next higher energy set of π molecular orbitals each has two nodal planes, and the highest energy π molecular orbital of benzene has three nodal planes. These three orbitals are the antibonding π molecular orbitals of benzene, and they are unoccupied in the ground state. Benzene is said to have a closed bonding shell of delocalized π electrons because all of its bonding orbitals are filled with electrons that have their spins paired, and no electrons are found in antibonding orbitals. This closed bonding shell accounts, in part, for the stability of benzene.

Having considered the molecular orbitals of benzene, it is now useful to view an electrostatic potential map of the van der Waals surface for benzene, also calculated from quantum mechanical principles (Fig. 14.5). We can see that this representation is consistent with our understanding that the π electrons of benzene are not localized but are evenly distributed around the top face and bottom face (not shown) of the carbon ring in benzene.

It is interesting to note the recent discovery that crystalline benzene involves perpendicular interactions between benzene rings, so that the relatively positive periphery of one molecule associates with the relatively negative faces of the benzene molecules aligned above and below it.

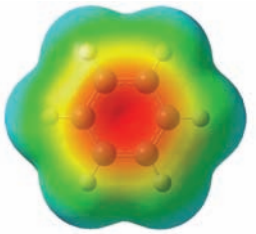


Figure 14.5 Electrostatic potential map of benzene.

14.7 Hückel's Rule: The 4n + 2 π Electron Rule

In 1931 the German physicist Erich Hückel carried out a series of mathematical calculations based on the kind of theory that we have just described. **Hückel's rule** is concerned with compounds containing **one planar ring in which each atom has a *p* orbital** as in benzene. His calculations show that planar monocyclic rings containing $4n + 2$ π electrons, where $n = 0, 1, 2, 3$, and so on (i.e., rings containing 2, 6, 10, 14, . . . , etc., π electrons), have closed shells of delocalized electrons like benzene and should have substantial resonance energies.

- In other words, Hückel's rule states that **planar monocyclic rings with 2, 6, 10, 14, . . . , delocalized electrons should be aromatic**.

14.7A How to Diagram the Relative Energies of π Molecular Orbitals in Monocyclic Systems Based on Hückel's Rule

There is a simple way to make a diagram of the relative energies of orbitals in monocyclic conjugated systems based on Hückel's calculations. To do so, we use the following procedure.

1. We start by drawing a polygon corresponding to the number of carbons in the ring, *placing a corner of the polygon at the bottom.*
2. Next we surround the polygon with a circle that touches each corner of the polygon.
3. At the points where the polygon touches the circle, we draw short horizontal lines outside the circle. The height of each line represents the relative energy of each π molecular orbital.
4. Next we draw a dashed horizontal line across and halfway up the circle. The energies of bonding π molecular orbitals are below this line. The energies of antibonding π molecular orbitals are above, and those for nonbonding orbitals are at the level of the dashed line.
5. Based on the number of π electrons in the ring, we then place electron arrows on the lines corresponding to the respective orbitals, beginning at the lowest energy level and working upward. In doing so, we fill degenerate orbitals each with one electron first, then add to each unpaired electron another with opposite spin if it is available.

Applying this method to benzene, for example (Fig. 14.6), furnishes the same energy levels that we saw earlier in Fig. 14.4, energy levels that were based on quantum mechanical calculations.

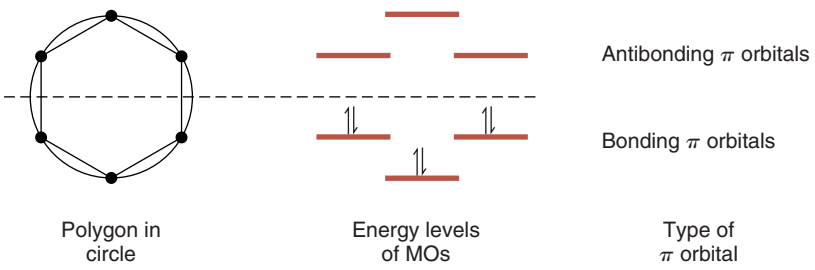


Figure 14.6 The polygon-and-circle method for deriving the relative energies of the π molecular orbitals of benzene. A horizontal line halfway up the circle divides the bonding orbitals from the antibonding orbitals. If an orbital falls on this line, it is a nonbonding orbital. This method was developed by C. A. Coulson (of Oxford University).

We can now understand why cyclooctatetraene is not aromatic. Cyclooctatetraene has a total of eight π electrons. Eight is not a Hückel number; it is a *4n number*, not a *4n + 2 number*. Using the polygon-and-circle method (Fig. 14.7), we find that cyclooctatetraene, if it were planar, *would not* have a closed shell of π electrons like benzene; it would have an unpaired electron in each of two nonbonding orbitals. Molecules with unpaired electrons (radicals) are *not* unusually stable; they are typically highly reactive and unstable. A planar form of cyclooctatetraene, therefore, should not be at all like benzene and should not be aromatic.

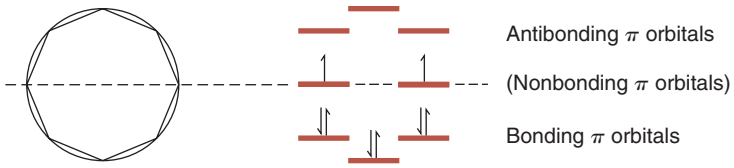
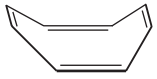


Figure 14.7 The π molecular orbitals that cyclooctatetraene would have if it were planar. Notice that, unlike benzene, this molecule is predicted to have two nonbonding orbitals, and because it has eight π electrons, it would have an unpaired electron in each of the two nonbonding orbitals (Hund's rule, Section 1.10). Such a system would not be expected to be aromatic.

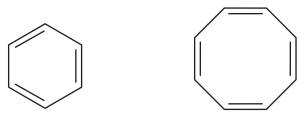
Because cyclooctatetraene does not gain stability by becoming planar, it assumes the tub shape shown below. (In Section 14.7E we shall see that cyclooctatetraene would actually lose stability by becoming planar.) The bonds of cyclooctatetraene are known to be alternately long and short; X-ray studies indicate that they are 1.48 and 1.34 Å, respectively.



14.7B The Annulenes

The word **annulene** is incorporated into the class name for monocyclic compounds that can be represented by structures having alternating single and double bonds. The ring size of an annulene is indicated by a number in brackets. Thus, benzene is [6]annulene and cyclooctatetraene is [8]annulene.

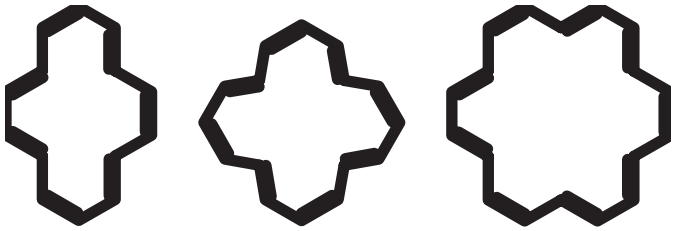
- Hückel's rule predicts that annulenes will be aromatic if their molecules have $4n + 2$ π electrons and have a planar carbon skeleton:



Benzene ([6]annulene) **Cyclooctatetraene ([8]annulene)**

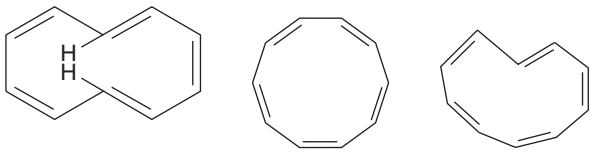
Before 1960 the only annulenes that were available to test Hückel's predictions were benzene and cyclooctatetraene. During the 1960s, and largely as a result of research by F. Sondheimer, a number of large-ring annulenes were synthesized, and the predictions of Hückel's rule were verified.

Consider the [14], [16], [18], [20], [22], and [24]annulenes as examples. Of these, *as Hückel's rule predicts*, the [14], [18], and [22]annulenes ($4n + 2$ when $n = 3, 4, 5$, respectively) have been found to be aromatic. The [16]annulene and the [24]annulene are not aromatic; they are *antiaromatic* (see Section 14.7E). They are $4n$ compounds, not $4n + 2$ compounds:



[14]Annulene (aromatic) **[16]Annulene (antiaromatic)** **[18]Annulene (aromatic)**

Examples of [10] and [12]annulenes have also been synthesized and none is aromatic. We would not expect [12]annulenes to be aromatic since they have 12 π electrons and do not obey Hückel's rule. The following [10]annulenes would be expected to be aromatic on the basis of electron count, but their rings are not planar.



4 **5** **6**

[10]Annulenes
None is aromatic because none is planar.

The [10]annulene **4** has two trans double bonds. Its bond angles are approximately 120°; therefore, it has no appreciable angle strain. The carbon atoms of its ring, however, are prevented from becoming coplanar because the two hydrogen atoms in the center of the ring interfere with each other. Because the ring is not planar, the *p* orbitals of the carbon atoms are not parallel and, therefore, cannot overlap effectively around the ring to form the π molecular orbitals of an aromatic system.

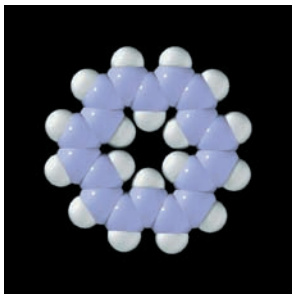
The [10]annulene with all cis double bonds (**5**) would, if it were planar, have considerable angle strain because the internal bond angles would be 144°. Consequently, any stability this isomer gained by becoming planar in order to become aromatic would be more than offset by the destabilizing effect of the increased angle strain. A similar problem of a large angle strain associated with a planar form prevents molecules of the [10]annulene isomer with one trans double bond (**6**) from being aromatic.

After many unsuccessful attempts over many years, in 1965 [4]annulene (or cyclobutadiene) was synthesized by R. Pettit and co-workers at the University of Texas, Austin. Cyclobutadiene is a $4n$ molecule, not a $4n + 2$ molecule, and, as we would expect, it is a highly unstable compound and *it is antiaromatic* (see Section 14.7E):

Cyclobutadiene or [4]annulene (antiaromatic)

Helpful Hint

These names are often used for conjugated rings of 10 or more carbon atoms, but they are seldom used for benzene and cyclooctatetraene.

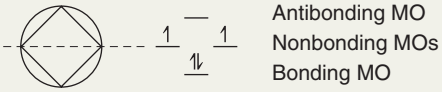


[18]Annulene.

Solved Problem 14.2

Using the polygon-and-circle method to outline the molecular orbitals of cyclobutadiene, explain why cyclobutadiene is not aromatic.

STRATEGY AND ANSWER We inscribe a square inside a circle with one corner at the bottom.



We see that cyclobutadiene, according to this model, would have have an unpaired electron in each of its two nonbonding molecular orbitals. We would, therefore, not expect cyclobutadiene to be aromatic.

14.7C NMR Spectroscopy: Evidence for Electron Delocalization in Aromatic Compounds

The ^{1}H NMR spectrum of benzene consists of a single unsplit signal at δ 7.27. That only a single unsplit signal is observed is further proof that all of the hydrogens of benzene are equivalent. That the signal occurs at relatively high frequency is, as we shall see, compelling evidence for the assertion that the π electrons of benzene are delocalized.

We learned in Section 9.6 that circulations of σ electrons of C—H bonds cause the protons of alkanes to be *shielded* from the applied magnetic field of an NMR spectrometer and, consequently, these protons absorb at lower frequency. We shall now explain the high frequency absorption of benzene protons on the basis of *deshielding caused by circulation of the π electrons of benzene*, and this explanation, as you will see, requires that the π electrons be delocalized.

When benzene molecules are placed in the powerful magnetic field of the NMR spectrometer, electrons circulate in the direction shown in Fig. 14.8; by doing so, they generate a **ring current**. (If you have studied physics, you will understand why the electrons circulate in this way.)

- The circulation of π electrons in benzene creates an induced magnetic field that, *at the position of the protons, reinforces the applied magnetic field*. This reinforcement causes the protons to be strongly *deshielded* and to have a relatively high frequency ($\delta \sim 7$) absorption.

By "deshielded" we mean that the protons sense the sum of the two fields, and, therefore, the net magnetic field strength is greater than it would have been in the absence of the induced field. This strong deshielding, which we attribute to a ring current created by the *delocalized* π electrons, explains why aromatic protons absorb at relatively high frequency.

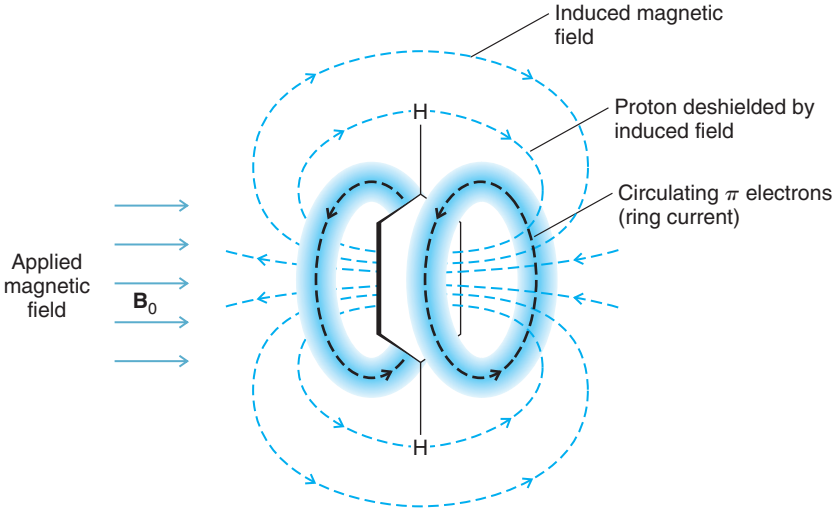


Figure 14.8 The induced magnetic field of the π electrons of benzene deshields the benzene protons. Deshielding occurs because at the location of the protons the induced field is in the same direction as the applied field.

The deshielding of external aromatic protons that results from the ring current is one of the best pieces of physical evidence that we have for π-electron delocalization in aromatic rings. In fact, relatively high frequency proton absorption is often used as a criterion for assessing aromaticity in newly synthesized conjugated cyclic compounds.

Not all aromatic protons have high frequency absorptions, however. The internal protons of large-ring aromatic compounds that have hydrogens in the center of the ring (in the π-electron cavity) absorb at unusually low frequency because they are highly shielded by the opposing induced magnetic field in the center of the ring (see Fig. 14.8). An example is [18]annulene (Fig. 14.9). The internal protons of [18]annulene absorb far upfield at δ −3.0, above the signal for tetramethylsilane (TMS); the external protons, on the other hand, absorb far downfield at δ 9.3. Considering that [18]annulene has $4n + 2$ π electrons, this evidence provides strong support for π-electron delocalization as a criterion for aromaticity and for the predictive power of Hückel's rule.

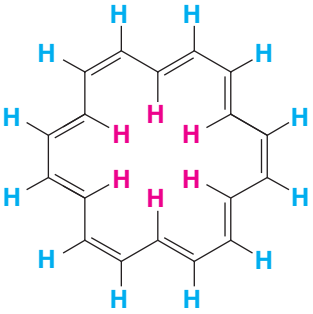
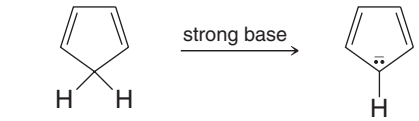


Figure 14.9 [18]Annulene. The internal protons (red) are highly shielded and absorb at δ −3.0. The external protons (blue) are highly deshielded and absorb at δ 9.3.

14.7D Aromatic Ions

In addition to the neutral molecules that we have discussed so far, there are a number of monocyclic species that bear either a positive or a negative charge. Some of these ions show unexpected stabilities that suggest that they are **aromatic ions**. Hückel's rule is helpful in accounting for the properties of these ions as well. We shall consider two examples: the cyclopentadienyl anion and the cycloheptatrienyl cation.

Cyclopentadiene is not aromatic; however, it is unusually acidic for a hydrocarbon. (The pK_a for cyclopentadiene is 16 and, by contrast, the pK_a for cycloheptatriene is 36.) Because of its acidity, cyclopentadiene can be converted to its anion by treatment with moderately strong bases. The cyclopentadienyl anion, moreover, is unusually stable, and NMR spectroscopy shows that all five hydrogen atoms in the cyclopentadienyl anion are equivalent and absorb downfield.



The orbital structure of cyclopentadiene (Fig. 14.10) shows why cyclopentadiene, itself, is not aromatic. Not only does it not have the proper number of π electrons, but the π electrons cannot be delocalized about the entire ring because of the intervening sp^3-hybridized —CH_2— group with no available p orbital.

On the other hand, if the —CH_2— carbon atom becomes sp^2 hybridized after it loses a proton (Fig. 14.10), the two electrons left behind can occupy the new p orbital that is produced. Moreover, this new p orbital can overlap with the p orbitals on either side of it and

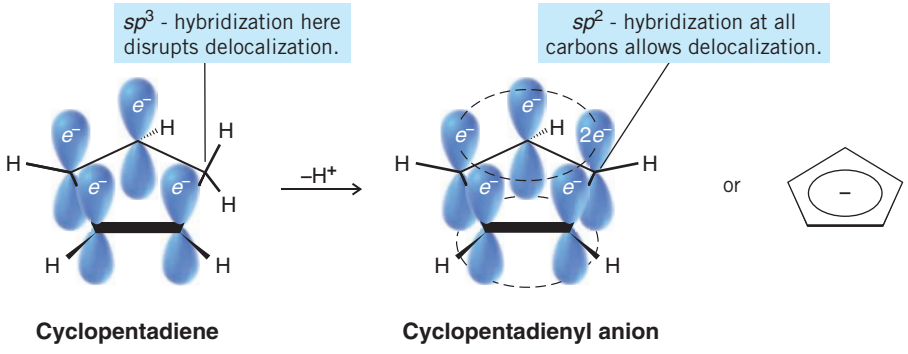


Figure 14.10 Cyclopentadiene is not aromatic because it has only four π electrons and the sp^3-hybridized carbon prevents complete delocalization around the ring. Removal of a proton produces the cyclopentadienyl anion, which is aromatic because it has 6 π electrons and all of its carbon atoms have a p orbital.

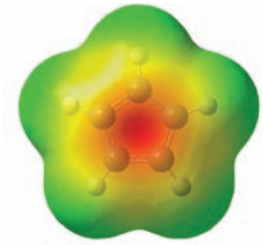


Figure 14.11 An electrostatic potential map of the cyclopentadienyl anion. The ion is negatively charged overall, of course, but regions with greatest negative potential are shown in red, and regions with least negative potential are in blue. The concentration of negative potential in the center of the top face and bottom face (not shown) indicates that the extra electron of the ion is involved in the aromatic π-electron system.

give rise to a ring with *six* delocalized π electrons. Because the electrons are delocalized, all of the hydrogen atoms are equivalent, and this agrees with what NMR spectroscopy tells us. A calculated electrostatic potential map for cyclopentadienyl anion (Fig. 14.11) also shows the symmetrical distribution of negative charge within the ring, and the overall symmetry of the ring structure.

Six, the number of π electrons in the cyclopentadienyl anion is, of course, a Hückel number ($4n + 2$, where $n = 1$).

- The cyclopentadienyl anion is, therefore, an **aromatic anion**, and the unusual acidity of cyclopentadiene is a result of the unusual stability of its anion.

Cycloheptatriene (Fig. 14.12) (a compound with the common name tropylidene) has six π electrons. However, the six π electrons of cycloheptatriene cannot be fully delocalized because of the presence of the $-CH_2-$ group, a group that does not have an available *p* orbital (Fig. 14.12).

When cycloheptatriene is treated with a reagent that can abstract a hydride ion, it is converted to the cycloheptatrienyl (or tropylium) cation. The loss of a hydride ion from cycloheptatriene occurs with unexpected ease, and the cycloheptatrienyl cation is found to be unusually stable. The NMR spectrum of the cycloheptatrienyl cation indicates that all seven hydrogen atoms are equivalent. If we look closely at Fig. 14.12, we see how we can account for these observations.

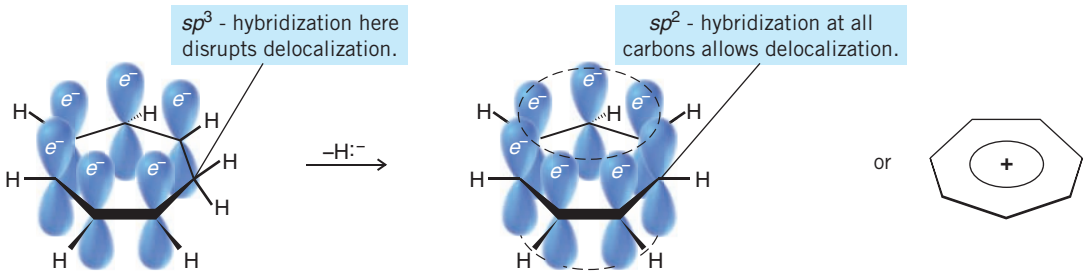


Figure 14.12 Cycloheptatriene is not aromatic, even though it has six π electrons, because it has an sp^3-hybridized carbon that prevents delocalization around the ring. Removal of a hydride ($H:^-$) produces the cycloheptatrienyl cation, which is aromatic because all of its carbon atoms now have a *p* orbital, and it still has 6 π electrons.

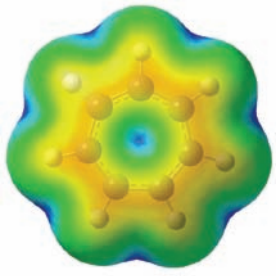
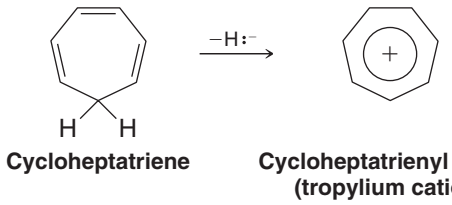


Figure 14.13 An electrostatic potential map of the tropylium cation. The ion is positive overall, of course, but a region of relatively greater negative electrostatic potential can clearly be seen around the top face (and bottom face, though not shown) of the ring where electrons are involved in the π system of the aromatic ring.



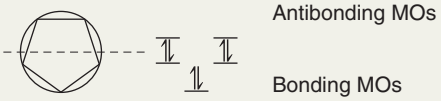
As a hydride ion is removed from the $-CH_2-$ group of cycloheptatriene, a vacant *p* orbital is created, and the carbon atom becomes sp^2 hybridized. The cation that results has seven overlapping *p* orbitals containing *six* delocalized π electrons. The cycloheptatrienyl cation is, therefore, an aromatic cation, and all of its hydrogen atoms should be equivalent; again, this is exactly what we find experimentally.

The calculated electrostatic potential map for cycloheptatrienyl (tropylium) cation (Fig. 14.13) also shows the symmetry of this ion. Electrostatic potential from the π electrons involved in the aromatic system is indicated by the yellow-orange color that is evenly distributed around the top face (and bottom face, though not shown) of the carbon framework. The entire ion is positive, of course, and the region of greatest positive potential is indicated by blue around the periphery of the ion.

Solved Problem 14.3

Apply the polygon-and-circle method to explain why the cyclopentadienyl anion is aromatic.

STRATEGY AND ANSWER We inscribe a pentagon inside a circle with one corner at the bottom and find that the energy levels of the molecular orbitals are such that three molecular orbitals are bonding and two are antibonding:



Cyclopentadienyl anion has six π electrons, which is a Hückel number, and they fill all the bonding orbitals. There are no unpaired electrons and no electrons in antibonding orbitals. This is what we would expect of an aromatic ion.

Review Problem 14.4

Apply the polygon-and-circle method to cyclopentadienyl cation and explain whether it would be aromatic or not.

Cyclopentadienyl cation

Review Problem 14.5

Apply the polygon-and-circle method to the cycloheptatrienyl anion and cation and explain whether each would be aromatic or not.

(a)

Cycloheptatrienyl anion

(b)

Cycloheptatrienyl cation

Review Problem 14.6

1,3,5-Cycloheptatriene is even less acidic than 1,3,5-heptatriene. Explain how this experimental observation might help to confirm your answer to part (b) of the previous problem.

Review Problem 14.7

When 1,3,5-cycloheptatriene reacts with one molar equivalent of bromine at 0°C, it undergoes 1,6 addition. (**a**) Write the structure of this product. (**b**) On heating, this 1,6-addition product loses HBr readily to form a compound with the molecular formula C_7H_7Br, called *tropylium bromide*. Tropylium bromide is insoluble in nonpolar solvents but is soluble in water; it has an unexpectedly high melting (mp 203°C), and when treated with silver nitrate, an aqueous solution of tropylium bromide gives a precipitate of AgBr. What do these experimental results suggest about the bonding in tropylium bromide?

14.7E Aromatic, Antiaromatic, and Nonaromatic Compounds

- An aromatic compound has its π electrons *delocalized* over the entire ring and it is *stabilized* by the π-electron delocalization.

As we have seen, a good way to determine whether the π electrons of a cyclic system are delocalized is through the use of NMR spectroscopy. It provides direct physical evidence of whether or not the π electrons are delocalized.

But what do we mean by saying that a compound is stabilized by π-electron delocalization? We have an idea of what this means from our comparison of the heat of hydrogenation of benzene and that calculated for the hypothetical 1,3,5-cyclohexatriene. We saw that benzene—in which the π electrons are delocalized—is much more stable than 1,3,5-cyclohexatriene (a model in which the π electrons are not delocalized). We call the energy difference between them the resonance energy (delocalization energy) or stabilization energy.

In order to make similar comparisons for other aromatic compounds, we need to choose proper models. But what should these models be?

One way to evaluate whether a cyclic compound is stabilized by delocalization of π electrons through its ring is to compare it with an open-chain compound having the same number of π electrons. This approach is particularly useful because it furnishes us with models not only for annulenes but for aromatic cations and anions, as well. (Corrections need to be made, of course, when the cyclic system is strained.)

To use this approach we do the following:

1. We take as our model a linear chain of sp^2-hybridized atoms having the same number of π electrons as our cyclic compound.
2. Then we imagine removing a hydrogen atom from each end of the chain and joining the ends to form a ring.
   - If, based on sound calculations or experiments, the ring has *lower* π-electron energy, then the ring is aromatic.
   - If the ring and the chain have the *same* π-electron energy, then the ring is nonaromatic.
   - If the ring has *greater* π-electron energy than the open chain, then the ring is **antiaromatic**.

The actual calculations and experiments used in determining π-electron energies are beyond our scope, but we can study four examples that illustrate how this approach has been used.

Cyclobutadiene For cyclobutadiene we consider the change in π-electron energy for the following *hypothetical* transformation:

1,3-Butadiene
4 π electrons

Cyclobutadiene
4 π electrons (antiaromatic)

Calculations indicate and experiments appear to confirm that the π-electron energy of cyclobutadiene is higher than that of its open-chain counterpart. Thus cyclobutadiene is classified as antiaromatic.

Benzene Here our comparison is based on the following hypothetical transformation:

1,3,5-Hexatriene
6 π electrons

Benzene
6 π electrons (aromatic)

Calculations indicate and experiments confirm that benzene has a much lower π-electron energy than 1,3,5-hexatriene. Benzene is classified as being aromatic on the basis of this comparison as well.

Cyclopentadienyl Anion Here we use a linear anion for our hypothetical transformation:

6 π electrons — Cyclopentadienyl anion, 6 π electrons (aromatic)

Both calculations and experiments confirm that the cyclic anion has a lower π-electron energy than its open-chain counterpart. Therefore the cyclopentadienyl anion is classified as aromatic.

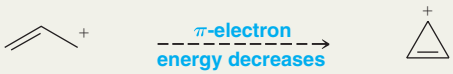
Cyclooctatetraene For cyclooctatetraene we consider the following hypothetical transformation:

8 π electrons — Hypothetical planar cyclooctatetraene, 8 π electrons (antiaromatic)

Here calculations and experiments indicate that a planar cyclooctatetraene would have higher π-electron energy than the open-chain octatetraene. Therefore, a planar form of cyclooctatetraene would, if it existed, be *antiaromatic*. As we saw earlier, cyclooctatetraene is not planar and behaves like a simple cyclic polyene.

Solved Problem 14.4

Calculations indicate that the π-electron energy decreases for the hypothetical transformation from the allyl cation to the cyclopropenyl cation below. What does this indicate about the possible aromaticity of the cyclopropenyl cation



STRATEGY AND ANSWER Because the π-electron energy of the cyclic cation is less than that of the allyl cation, we can conclude that the cyclopropenyl cation would be aromatic. (See Review Problem 14.9 for more information on this cation.)

Review Problem 14.8

The cyclopentadienyl cation is apparently *antiaromatic*. Explain what this means in terms of the π-electron energies of a cyclic and an open-chain compound.

Review Problem 14.9

In 1967 R. Breslow (of Columbia University) and co-workers showed that adding $SbCl_5$ to a solution of 3-chlorocyclopropene in CH_2Cl_2 caused the precipitation of a white solid with the composition $C_3H_3^+SbCl_6^-$. NMR spectroscopy of a solution of this salt showed that all of its hydrogen atoms were equivalent. (**a**) What new aromatic ion had Breslow and co-workers prepared? (**b**) How many ^{13}C NMR signals would you predict for this ion?

14.8 Other Aromatic Compounds

14.8A Benzenoid Aromatic Compounds

In addition to those that we have seen so far, there are many other examples of aromatic compounds. Representatives of one broad class of **benzenoid aromatic compounds**, called **polycyclic aromatic hydrocarbons (PAH)**, are illustrated in Fig. 14.14.

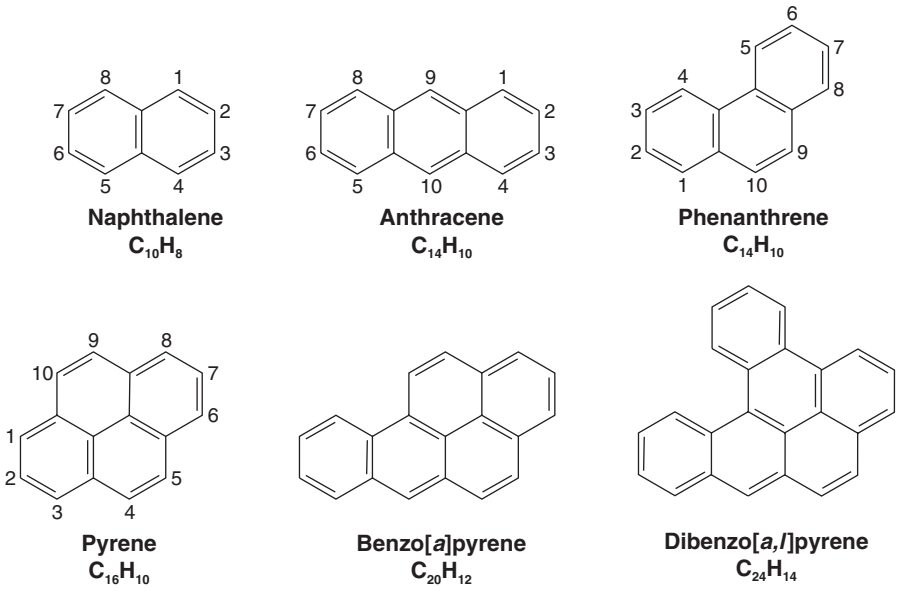


Figure 14.14 Benzenoid aromatic hydrocarbons. Some polycyclic aromatic hydrocarbons (PAHs), such as dibenzo[*a,l*]pyrene, are carcinogenic. (See "The Chemistry of . . . Epoxides, Carcinogens, and Biological Oxidation" in Section 11.14.)

- Benzenoid polycyclic aromatic hydrocarbons consist of molecules having two or more benzene rings *fused* together.

A close look at one example, naphthalene, will illustrate what we mean by this.

According to resonance theory, a molecule of naphthalene can be considered to be a hybrid of three Kekulé structures. One of these Kekulé structures, the most important one, is shown in Fig. 14.15. There are two carbon atoms in naphthalene (C4a and C8a) that are common to both rings. These two atoms are said to be at the points of *ring fusion*. They direct all of their bonds toward other carbon atoms and do not bear hydrogen atoms.

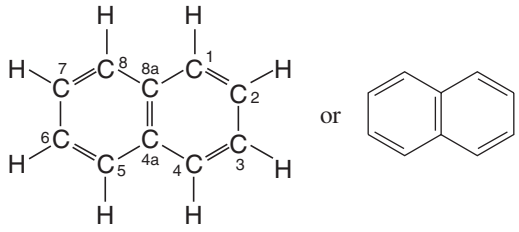
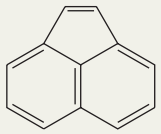


Figure 14.15 One Kekulé structure for naphthalene.

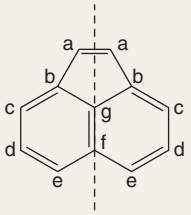
Solved Problem 14.5

How many ^{13}C NMR signals would you expect for acenaphthylene?



Acenaphthylene

STRATEGY AND ANSWER Acenaphthylene has a plane of symmetry which makes the five carbon atoms on the left (a–e, at right) equivalent to those on the right. Carbon atoms f and g are unique. Consequently, acenaphthylene should give seven ^{13}C NMR signals.



Acenaphthylene

How many ^{13}C NMR signals would you predict for (**a**) naphthalene, (**b**) anthracene, (**c**) phenanthrene, and (**d**) pyrene?

Review Problem 14.10

Molecular orbital calculations for naphthalene begin with the model shown in Fig. 14.16. The *p* orbitals overlap around the periphery of both rings and across the points of ring fusion.

When molecular orbital calculations are carried out for naphthalene using the model shown in Fig. 14.16, the results of the calculations correlate well with our experimental knowledge of naphthalene. The calculations indicate that delocalization of the 10 π electrons over the two rings produces a structure with considerably lower energy than that calculated for any individual Kekulé structure. Naphthalene, consequently, has a substantial resonance energy. Based on what we know about benzene, moreover, naphthalene's tendency to react by substitution rather than addition and to show other properties associated with aromatic compounds is understandable.

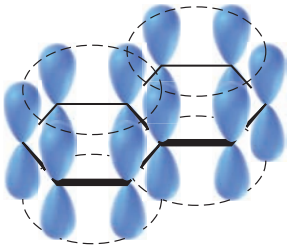


Figure 14.16 The stylized *p* orbitals of naphthalene.

Anthracene and phenanthrene (Fig. 14.14) are isomers. In anthracene the three rings are fused in a linear way, and in phenanthrene they are fused so as to produce an angular molecule. Both of these molecules also show large resonance energies and chemical properties typical of aromatic compounds.

Pyrene (Fig. 14.17) is also aromatic. Pyrene itself has been known for a long time; a pyrene derivative, however, has been the object of research that shows another interesting application of Hückel's rule.

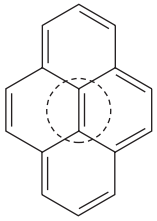
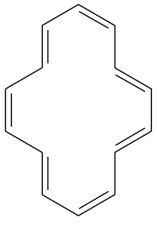
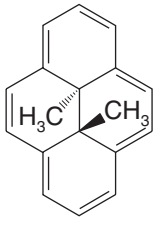


Figure 14.17 One Kekulé structure for pyrene. The internal double bond is enclosed in a dotted circle for emphasis.

To understand this particular research, we need to pay special attention to the Kekulé structure for pyrene (Fig. 14.17). The total number of π electrons in pyrene is 16 (8 double bonds = 16 π electrons). Sixteen is a non-Hückel number, but **Hückel's rule is intended to be applied only to monocyclic compounds** and pyrene is clearly tetracyclic. If we disregard the internal double bond of pyrene, however, and look only at the periphery, we see that the periphery is a planar ring with 14 π electrons. The periphery is, in fact, very much like that of [14]annulene. Fourteen *is* a Hückel number ($4n + 2$, where $n = 3$), and one might then predict that the periphery of pyrene would be aromatic by itself, in the absence of the internal double bond.



[14]Annulene



***trans*-15,16-Dimethyldihydropyrene**

This prediction was confirmed when V. Boekelheide (University of Oregon) synthesized *trans*-15,16-dimethyldihydropyrene and showed that it is aromatic.

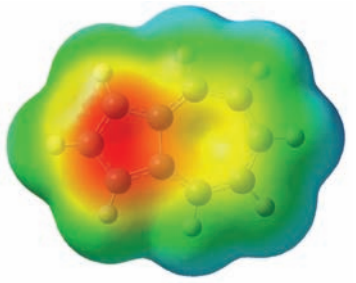
Review Problem 14.11

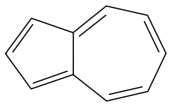
In addition to a signal downfield, the ^{1}H NMR spectrum of *trans*-15,16-dimethyldihydropyrene has a signal far upfield at δ −4.2. Account for the presence of this upfield signal.

14.8B Nonbenzenoid Aromatic Compounds

Naphthalene, phenanthrene, and anthracene are examples of *benzenoid* aromatic compounds. On the other hand, the cyclopentadienyl anion, the cycloheptatrienyl cation, *trans*-15,16-dimethyldihydropyrene, and the aromatic annulenes (except for [6]annulene) are classified as **nonbenzenoid aromatic compounds**.

Another example of a *nonbenzenoid* aromatic hydrocarbon is the compound azulene. Azulene has a resonance energy of 205 kJ mol^{-1}. There is substantial separation of charge between the rings in azulene, as is indicated by the electrostatic potential map for azulene shown in Fig. 14.18. Factors related to aromaticity account for this property of azulene (see Review Problem 14.12).





Azulene

Figure 14.18 A calculated electrostatic potential map for azulene. (Red areas are more negative and blue areas are less negative.)

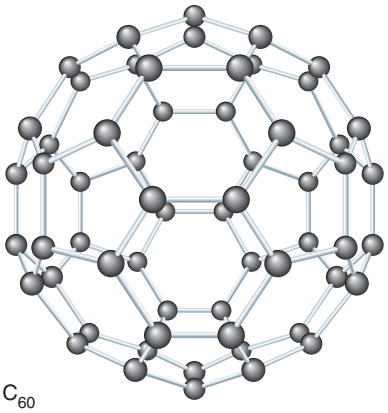
Review Problem 14.12

Azulene has an appreciable dipole moment. Write resonance structures for azulene that explain this dipole moment and that help explain its aromaticity.

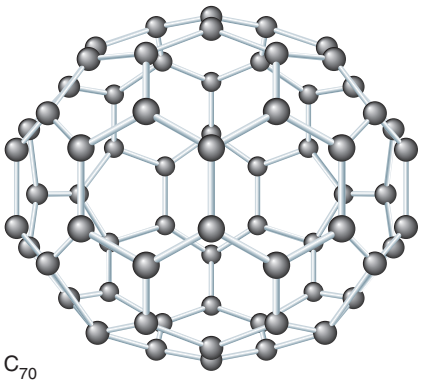
14.8C Fullerenes

In 1990 W. Krätschmer (Max Planck Institute, Heidelberg), D. Huffman (University of Arizona), and their co-workers described the first practical synthesis of C_{60}, a molecule shaped like a soccer ball and called buckminsterfullerene. Formed by the resistive heating of graphite in an inert atmosphere, C_{60} is a member of an exciting new group of aromatic compounds called **fullerenes**. Fullerenes are cagelike molecules with the geometry of a truncated icosahedron or geodesic dome, named after the architect Buckminster Fuller, renowned for his development of structures with geodesic domes. The structure of C_{60} and its existence had been established five years earlier, by H. W. Kroto (University of Sussex), R. E. Smalley and R. F. Curl (Rice University), and their co-workers. Kroto, Curl, and Smalley had found both C_{60} and C_{70} (Fig. 14.19) as highly stable components

The Nobel Prize in Chemistry was awarded in 1996 to Professors Curl, Kroto, and Smalley for their discovery of fullerenes.



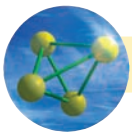
C_{60}



C_{70}

Figure 14.19 The structures of C_{60} and C_{70}. Reprinted with permission from Diederic, F., and Whetten, R. L. Accounts of Chemical Research, **Vol. 25**, pp. 119-126, 1992. Copyright 1992 by American Chemical Society.

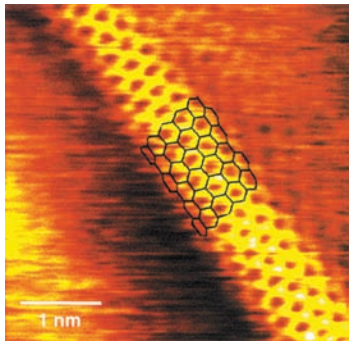
of a mixture of carbon clusters formed by laser-vaporizing graphite. Since 1990 chemists have synthesized many other higher and lower fullerenes and have begun exploring their interesting chemistry.



THE CHEMISTRY OF . . .

Nanotubes

Nanotubes are a relatively new class of carbon-based materials related to buckminsterfullerenes. A **nanotube** is a structure that looks as though it were formed by rolling a sheet of graphitelike carbon (a flat network of fused benzene rings resembling chicken wire) into the shape of a tube and capping each end with half of a buckyball. Nanotubes are very tough—about 100 times as strong as steel. Besides their potential as strengtheners for new composite materials, some nanotubes have been shown to act as electrical conductors or semiconductors depending on their precise form. They are also being used as probe tips for analysis of DNA and proteins by atomic force microscopy (AFM). Many other applications have been envisioned for them as well, including use as molecular-size test tubes or capsules for drug delivery.



A network of benzene rings, highlighted in black on this scanning tunneling microscopy (STM) image, comprise the wall of a nanotube.

Like a geodesic dome, a fullerene is composed of a network of pentagons and hexagons. To close into a spheroid, a fullerene must have exactly 12 five-membered faces, but the number of six-membered faces can vary widely. The structure of C_{60} has 20 hexagonal faces; C_{70} has 25. Each carbon of a fullerene is sp^2 hybridized and forms σ bonds to three other carbon atoms. The remaining electron at each carbon is delocalized into a system of molecular orbitals that gives the whole molecule aromatic character.

The chemistry of fullerenes is proving to be even more fascinating than their synthesis. Fullerenes have a high electron affinity and readily accept electrons from alkali metals to produce a new metallic phase—a "buckide" salt. One such salt, K_3C_{60}, is a stable metallic crystal consisting of a face-centered-cubic structure of "buckyballs" with a potassium ion in between; it becomes a superconductor when cooled below 18 K. Fullerenes have even been synthesized that have metal atoms in the interior of the carbon atom cage.

14.9 Heterocyclic Aromatic Compounds

Almost all of the cyclic molecules that we have discussed so far have had rings composed solely of carbon atoms. However, in many cyclic compounds an element other than carbon is present in the ring.

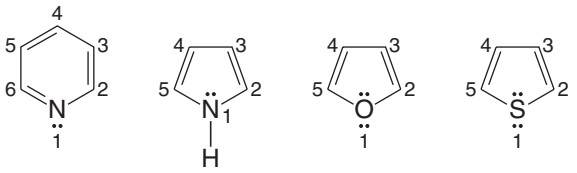
- Cyclic compounds that include an element other than carbon are called **heterocyclic compounds**.

Heterocyclic molecules are quite commonly encountered in nature. For this reason, and because some of these molecules are aromatic, we shall now describe a few examples of **heterocyclic aromatic compounds**.

Heterocyclic compounds containing nitrogen, oxygen, or sulfur are by far the most common. Four important examples are given here in their Kekulé forms. *These four compounds are all aromatic*:
Observe the following:

- Pyridine is electronically related to benzene.

- Pyrrole, furan, and thiophene are related to the cyclopentadienyl anion.



The nitrogen atoms in molecules of both pyridine and pyrrole are sp^2 hybridized. In pyridine (Fig. 14.20) the sp^2-hybridized nitrogen donates one bonding electron to the π system. This electron, together with one from each of the five carbon atoms, gives pyridine a sextet of electrons like benzene. The two unshared electrons of the nitrogen of pyridine are in an sp^2 orbital that lies in the same plane as the atoms of the ring. This sp^2 orbital does not overlap with the p orbitals of the ring (it is, therefore, said to be *orthogonal* to the p orbitals). The unshared pair on nitrogen is not a part of the π system, and these electrons confer on pyridine the properties of a weak base.

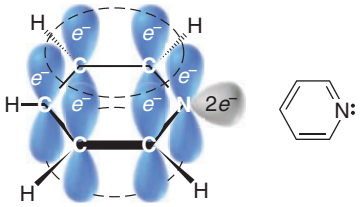


Figure 14.20 Pyridine is aromatic and weakly basic. Its nitrogen atom has an unshared electron pair in an sp^2 orbital (shown in gray) that is not part of the aromatic system.

In pyrrole (Fig. 14.21) the electrons are arranged differently. Because only four π electrons are contributed by the carbon atoms of the pyrrole ring, the sp^2-hybridized nitrogen must contribute two electrons to give an aromatic sextet. Because these electrons are a part of the aromatic sextet, they are not available for donation to a proton. Thus, in aqueous solution, pyrrole is not appreciably basic.

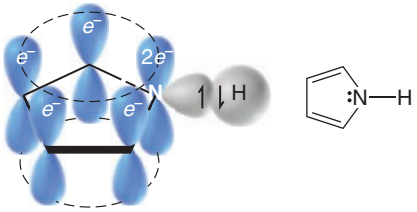
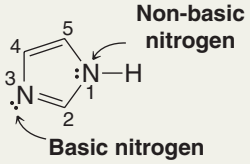


Figure 14.21 Pyrrole is aromatic but not basic. It does not have any unshared electron pairs. The electron pair on nitrogen is part of the aromatic system.

Solved Problem 14.6

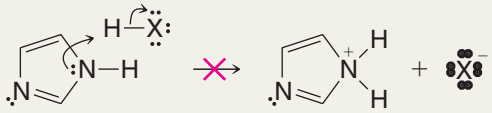
Imidazole (at right) has two nitrogens. N3 is relatively basic (like the nitrogen of pyridine). N1 is relatively nonbasic (like the nitrogen of pyrrole).
Explain the different basicities of these two nitrogens.



STRATEGY AND ANSWER When imidazole accepts a proton at N3 the electron pair that accepts the proton is not a part of the π system of six electrons that makes imidazole aromatic. Consequently, the conjugate base that is formed is still aromatic (it is an aromatic cation) and retains its resonance energy of stabilization.

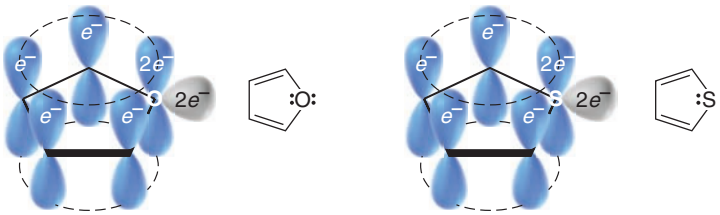
(Aromatic) (Aromatic)

On the other hand, if imidazole were to accept a proton at N1 the resulting ion (which is not formed) would **not** be aromatic and would have much greater potential energy (its resonance stabilization would be lost). Hence, N1 is not appreciably basic.



(Aromatic) 6 π electrons (Non-aromatic) 4 π electrons

Furan and thiophene are structurally quite similar to pyrrole. The oxygen atom in furan and the sulfur atom in thiophene are sp^2 hybridized. In both compounds the p orbital of the heteroatom donates two electrons to the π system. The oxygen and sulfur atoms of furan and thiophene carry an unshared pair of electrons in an sp^2 orbital (Fig. 14.22) that is orthogonal to the π system.



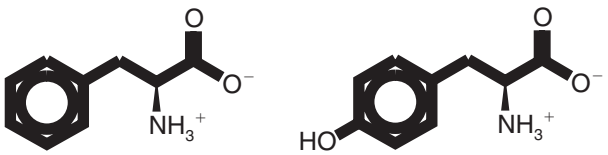
Furan Thiophene

Figure 14.22 Furan and thiophene are aromatic. In each case, the heteroatom provides a pair of electrons to the aromatic system, but each also has an unshared electron pair in an sp^2 orbital that is not part of the aromatic system.

14.10 Aromatic Compounds in Biochemistry

Compounds with aromatic rings occupy numerous and important positions in reactions that occur in living systems. It would be impossible to describe them all in this chapter. We shall, however, point out a few examples now and we shall see others later.

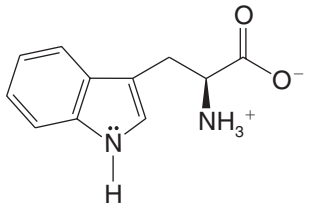
Two amino acids necessary for protein synthesis contain the benzene ring:



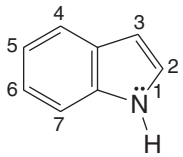
Phenylalanine Tyrosine

Dairy products, beans, fish, meat, and poultry are dietary sources of the essential amino acids.

A third aromatic amino acid, tryptophan, contains a benzene ring fused to a pyrrole ring. (This aromatic ring system is called an indole system, see Section 20.1B.)



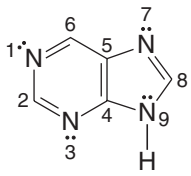
Tryptophan



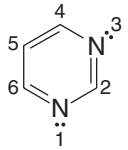
Indole

It appears that humans, because of the course of evolution, do not have the biochemical ability to synthesize the benzene ring. As a result, phenylalanine and tryptophan derivatives are essential in the human diet. Because tyrosine can be synthesized from phenylalanine in a reaction catalyzed by an enzyme known as *phenylalanine hydroxylase*, it is not essential in the diet as long as phenylalanine is present.

Heterocyclic aromatic compounds are also present in many biochemical systems. Derivatives of purine and pyrimidine are essential parts of DNA and RNA:



Purine



Pyrimidine

DNA is the molecule responsible for the storage of genetic information, and RNA is prominently involved in the synthesis of enzymes and other proteins (Chapter 25).

Review Problem 14.13

(**a**) The —SH group is sometimes called the *mercapto group*. 6-Mercaptopurine is used in the treatment of acute leukemia. Write its structure. (**b**) Allopurinol, a compound used to treat gout, is 6-hydroxypurine. Write its structure.

Nicotinamide adenine dinucleotide, one of the most important coenzymes (Section 24.9) in biological oxidations and reductions, includes both a pyridine derivative (nicotinamide) and a purine derivative (adenine) in its structure. Its formula is shown in Fig. 14.23 as NAD^+, the oxidized form that contains the pyridinium aromatic ring. The reduced form of the coenzyme is NADH, in which the pyridine ring is no longer aromatic due to presence of an additional hydrogen and two electrons in the ring.

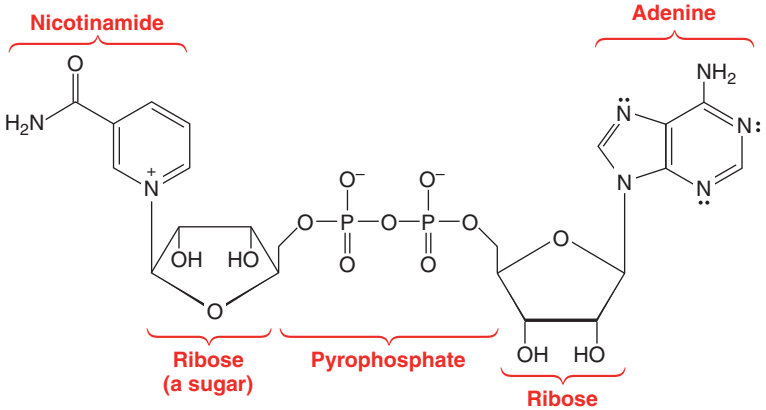


Figure 14.23 Nicotinamide adenine dinucleotide (NAD^+).

A key role of NAD^+ in metabolism is to serve as a coenzyme for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in glycolysis, the pathway by which glucose is broken down for energy production. In the reaction catalyzed by GAPDH (Fig. 14.24), the aldehyde group of glyceraldehyde-3-phosphate (GAP) is oxidized to a carboxyl group (incorporated as a phosphoric anhydride) in 1,3-bisphosphoglycerate (1,3-BPG). Concurrently, the aromatic pyridinium ring of NAD^+ is reduced to its higher energy form, NADH. One of the ways the chemical energy stored in the nonaromatic ring of NADH is used is in the mitochondria for the production of ATP, where cytochrome electron transport and oxidative phosphorylation take place. There, release of chemical energy from NADH by oxidation to the more stable aromatic form NAD^+ (and a proton) is coupled with the pumping of protons across the inner mitochondrial membrane. An electrochemical gradient is created across the mitochondrial membrane, which drives the synthesis of ATP by the enzyme ATP synthase.

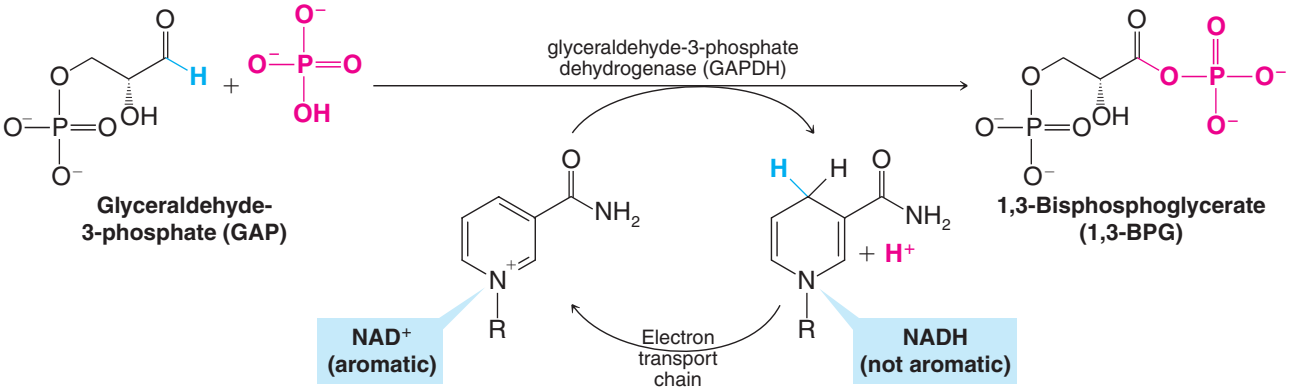
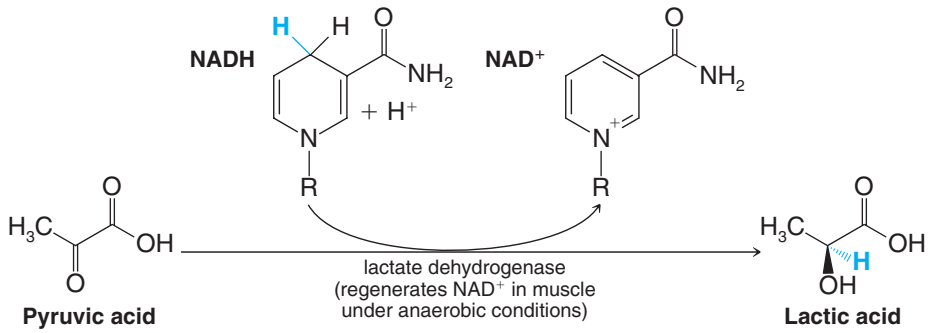


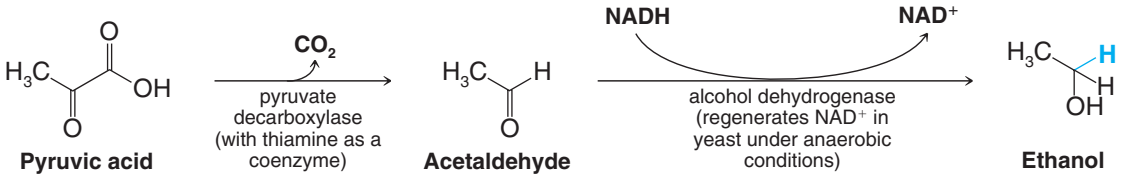
Figure 14.24 NAD^+, as the coenzyme in glyceraldehyde-3-phosphate dehydrogenase (GAPDH), is used to oxidize glyceraldehyde-3-phosphate (GAP) to 1,3-bisphosphoglycerate during the degradation of glucose in glycolysis. One of the ways that NADH can be reoxidized to NAD^+ is by the electron transport chain in mitochondria, where, under aerobic conditions, rearomatization of NADH helps to drive ATP synthesis.

The chemical energy stored in NADH is used to bring about many other essential biochemical reactions as well. NADH is part of an enzyme called lactate dehydrogenase that reduces the ketone group of pyruvic acid to the alcohol group of lactic acid. Here, the nonaromatic ring of NADH is converted to the aromatic ring of NAD^+. This process is important in muscles operating under oxygen-depleted conditions (anaerobic metabolism), where reduction of pyruvic acid to lactic acid by NADH serves to regenerate NAD^+ that is needed to continue glycolytic synthesis of ATP:

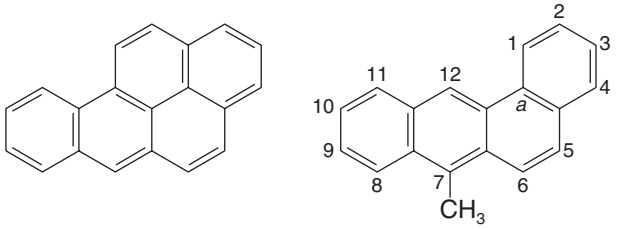


Yeasts growing under anaerobic conditions (fermentation) also have a pathway for regenerating NAD^+ from NADH. Under oxygen-deprived conditions, yeasts convert pyruvic acid

to acetaldehyde by decarboxylation (CO_2 is released, (see "The Chemistry of … Thiamine" in *WileyPLUS*); then NADH in alcohol dehydrogenase reduces acetaldehyde to ethanol. As in oxygen-starved muscles, this pathway occurs for the purpose of regenerating NAD^+ needed to continue glycolytic ATP synthesis:



Although many aromatic compounds are essential to life, others are hazardous. Many are quite toxic, and several benzenoid compounds, including benzene itself, are **carcinogenic.** Two other examples are benzo[*a*]pyrene and 7-methylbenz[*a*]anthracene:



Helpful Hint

The mechanism for the carcinogenic effects of compounds like benzo[a]pyrene was discussed in "The Chemistry of . . . Epoxides, Carcinogens, and Biological Oxidation" in Section 11.14.

The hydrocarbon benzo[*a*]pyrene has been found in cigarette smoke and in the exhaust from automobiles. It is also formed in the incomplete combustion of any fossil fuel. It is found on charcoal-broiled steaks and exudes from asphalt streets on a hot summer day. Benzo[*a*]pyrene is so carcinogenic that one can induce skin cancers in mice with almost total certainty simply by shaving an area of the body of the mouse and applying a coating of benzo[*a*]pyrene.

14.11 Spectroscopy of Aromatic Compounds

14.11A ^{1}H NMR Spectra

- The ring hydrogens of benzene derivatives absorb downfield in the region between δ 6.0 and δ 9.5.

In Section 14.7C we found that absorption takes place far downfield because a ring current generated in the benzene ring creates a magnetic field, called "the induced field," which reinforces the applied magnetic field at the position of the protons of the ring. This reinforcement causes the protons of benzene to be highly deshielded.

We also learned in Section 14.7C that internal hydrogens of large-ring aromatic compounds such as [18]annulene, because of their position, are highly shielded by this induced field. They therefore absorb at unusually low frequency, often at negative delta values.

14.11B ^{13}C NMR Spectra

- The carbon atoms of benzene rings generally absorb in the δ 100–170 region of ^{13}C NMR spectra.

Figure 14.25 gives the broadband proton-decoupled ^{13}C NMR spectrum of 4-*N*,*N*-diethylaminobenzaldehyde and permits an exercise in making ^{13}C assignments of a compound with both aromatic and aliphatic carbon atoms.

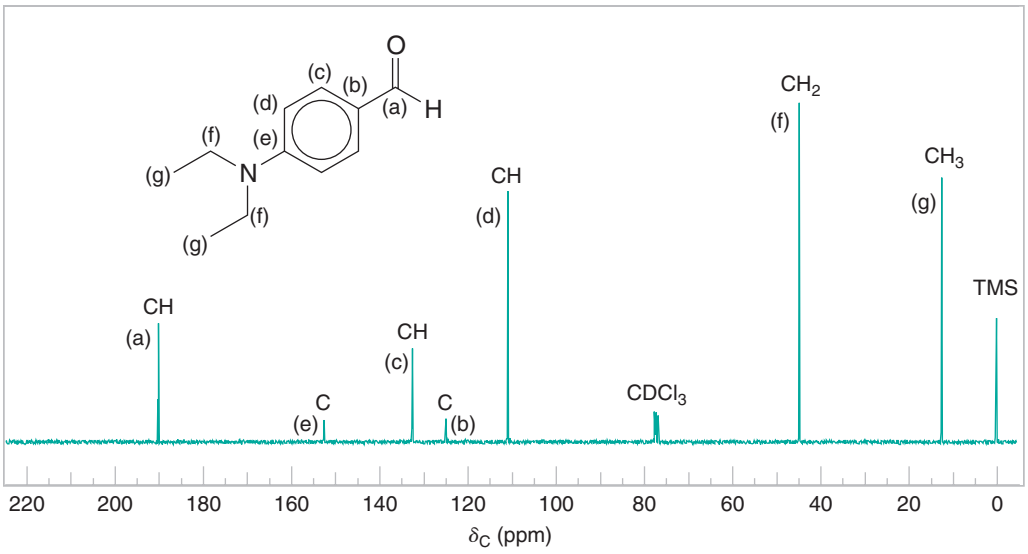
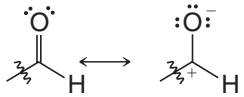


Figure 14.25 The broadband proton-decoupled ^{13}C NMR spectrum of 4-*N*,*N*-diethylaminobenzaldehyde. DEPT information and carbon assignments are shown by each peak.

The DEPT spectra (not given to save space) show that the signal at δ 45 arises from a CH_2 group and the one at δ 13 arises from a CH_3 group. This allows us to assign these two signals immediately to the two carbons of the equivalent ethyl groups.

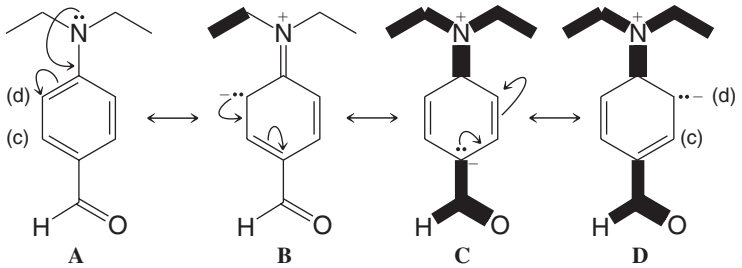
The signals at δ 126 and δ 153 appear in the DEPT spectra as carbon atoms that do not bear hydrogen atoms and are assigned to carbons b and e (see Fig. 14.25). The greater electronegativity of nitrogen (when compared to carbon) causes the signal from e to be further downfield (at δ 153). The signal at δ 190 appears as a CH group in the DEPT spectra and arises from the carbon of the aldehyde group. Its chemical shift is the most downfield of all the peaks because of the great electronegativity of its oxygen and because the second resonance structure below contributes to the hybrid. Both factors cause the electron density at this carbon to be very low, and, therefore, this carbon is strongly deshielded.



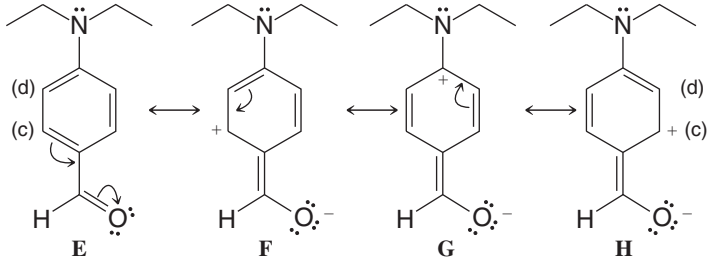
Resonance contributors for an aldehyde group

This leaves the signals at δ 112 and δ 133 and the two sets of carbon atoms of the benzene ring labeled c and d to be accounted for. Both signals are indicated as CH groups in the DEPT spectra. But which signal belongs to which set of carbon atoms? Here we find another interesting application of resonance theory.

If we write resonance structures **A–D** involving the unshared electron pair of the amino group, we see that contributions made by **B** and **D** increase the electron density at the set of carbon atoms labeled d:



On the other hand, writing structures **E–H** involving the aldehyde group shows us that contributions made by **F** and **H** decrease the electron density at the set of carbon atoms labeled c:



(Other resonance structures are possible but are not pertinent to the argument here.)

Increasing the electron density at a carbon should increase its shielding and should shift its signal upfield. Therefore, we assign the signal at δ 112 to the set of carbon atoms labeled d. Conversely, decreasing the electron density at a carbon should shift its signal downfield, so we assign the signal at δ 133 to the set labeled c.

Carbon-13 spectroscopy can be especially useful in recognizing a compound with a high degree of symmetry. The following Solved Problem illustrates one such application.

Solved Problem 14.7

The broadband proton-decoupled ^{13}C spectrum given in Fig. 14.26 is of a tribromobenzene ($C_6H_3Br_3$). Which tribromobenzene is it?

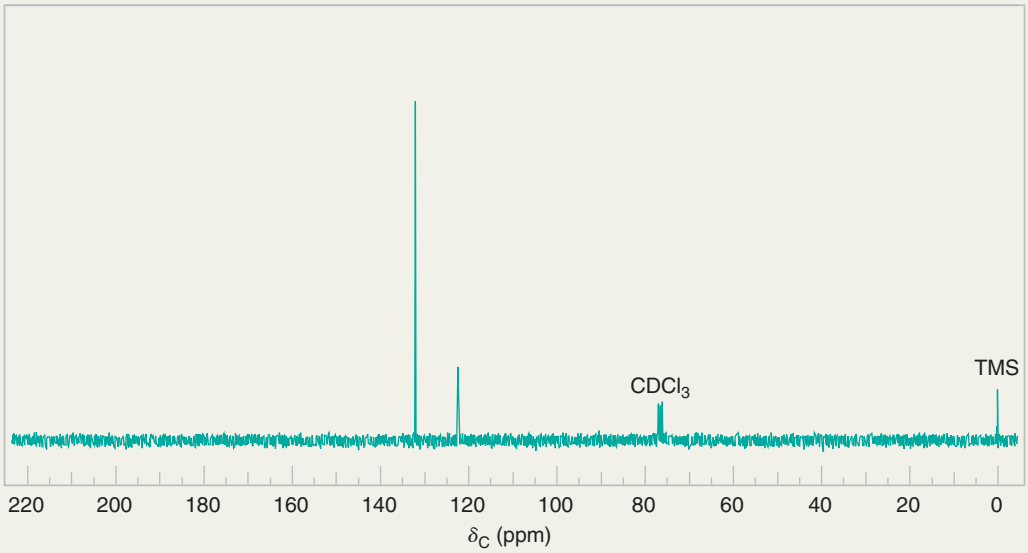
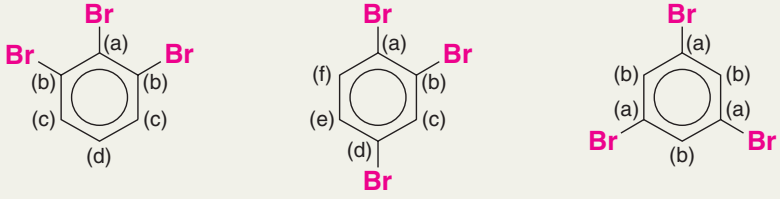


Figure 14.26 The broadband proton-decoupled ^{13}C NMR spectrum of a tribromobenzene.

ANSWER There are three possible tribromobenzenes:



1,2,3-Tribromobenzene **1,2,4-Tribromobenzene** **1,3,5-Tribromobenzene**

Our spectrum (Fig. 14.26) consists of only two signals, indicating that only two different types of carbon atoms are present in the compound. Only 1,3,5-tribromobenzene has a degree of symmetry such that it would give only two signals, and, therefore, it is the correct answer. 1,2,3-Tribromobenzene would give four ^{13}C signals and 1,2,4-tribromobenzene would give six.

Explain how ^{13}C NMR spectroscopy could be used to distinguish the *ortho*-, *meta*-, and *para*-dibromobenzene isomers one from another.

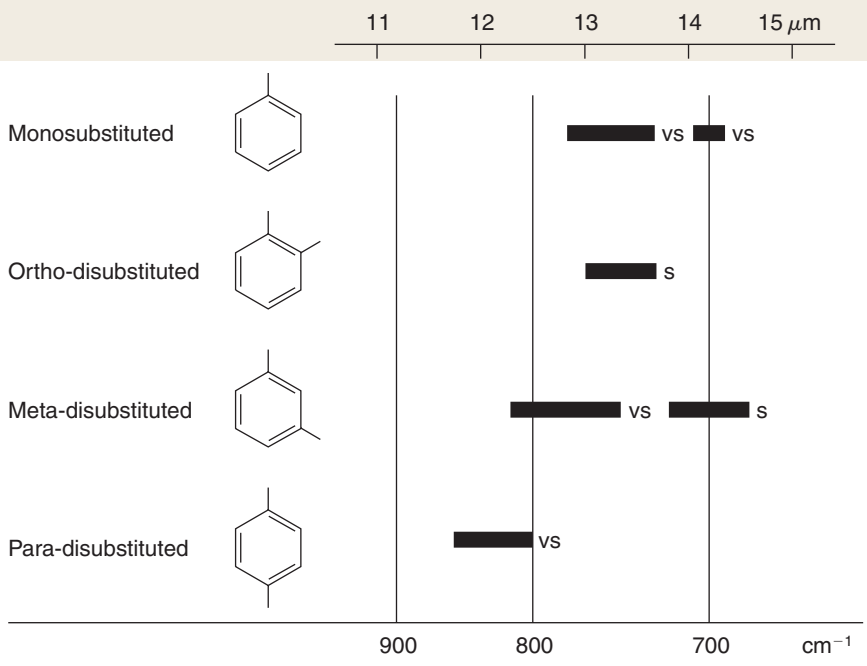
Review Problem 14.14

14.11C Infrared Spectra of Substituted Benzenes

Benzene derivatives give characteristic C—H stretching peaks near 3030 cm^{-1} (Table 2.7). Stretching motions of the benzene ring can give as many as four bands in the 1450–1600-cm^{-1} region, with two peaks near 1500 and 1600 cm^{-1} being stronger.

Absorption peaks in the 680–860-cm^{-1} region from out-of-plane C—H bending can often (but not always) be used to characterize the substitution patterns of benzene compounds (Table 14.1). **Monosubstituted benzenes** give two very strong peaks, between 690 and 710 cm^{-1} and between 730 and 770 cm^{-1}.

TABLE 14.1 Infrared Absorptions in the 680–860-cm^{-1} Region[a]



[a]s, strong; vs, very strong.

Ortho-disubstituted benzenes show a strong absorption peak between 735 and 770 cm^{-1} that arises from bending motions of the C—H bonds. **Meta-disubstituted benzenes** show two peaks: one strong peak between 680 and 725 cm^{-1} and one very strong peak between 750 and 810 cm^{-1}. **Para-disubstituted benzenes** give a single very strong absorption between 800 and 860 cm^{-1}.

Review Problem 14.15

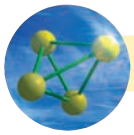
Four benzenoid compounds, all with the formula C_7H_7Br, gave the following IR peaks in the 680–860-cm^{-1} region:

A, 740 cm^{-1} (strong)
B, 800 cm^{-1} (very strong)
C, 680 cm^{-1} (strong) and 760 cm^{-1} (very strong)
D, 693 cm^{-1} (very strong) and 765 cm^{-1} (very strong)

Propose structures for **A, B, C,** and **D.**

14.11D Ultraviolet–Visible Spectra of Aromatic Compounds

The conjugated π electrons of a benzene ring give characteristic ultraviolet absorptions that indicate the presence of a benzene ring in an unknown compound. One absorption band of moderate intensity occurs near 205 nm and another, less intense band appears in the 250–275-nm range. Conjugation outside the benzene ring leads to absorptions at other wavelengths.



THE CHEMISTRY OF . . .

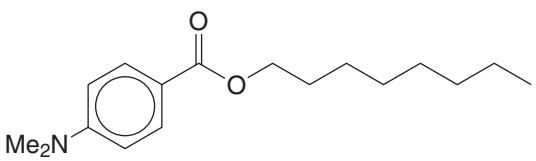
Sunscreens (Catching the Sun's Rays and What Happens to Them)

The use of sunscreens in recent years has increased due to heightened concern over the risk of skin cancer and other conditions caused by exposure to UV radiation. In DNA, for example, UV radiation can cause adjacent thymine bases to form mutagenic dimers. Sunscreens afford protection from UV radiation because they contain aromatic molecules that absorb energy in the UV region of the electromagnetic spectrum. Absorption of UV radiation by these molecules promotes π and nonbonding electrons to higher energy levels (Section 13.9C), after which the energy is dissipated by relaxation through molecular vibration. In essence, the UV radiation is converted to heat (IR radiation).

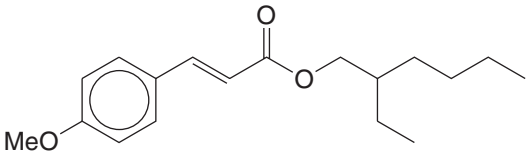
A UV-A and UV-B sunscreen product whose active ingredients are octyl 4-methoxycinnamate and 2-hydroxy-4-methoxybenzophenone (oxybenzone).

Sunscreens are classified according to the portion of the UV spectrum where their maximum absorption occurs. Three regions of the UV spectrum are typically discussed. The region from 320 to 400 nm is called UV-A, the region from 280 to 320 nm is called UV-B, and the region from 100 to 280 nm is called UV-C. The UV-C region is potentially the most dangerous because it encompasses the shortest UV wavelengths and is therefore of the highest energy. However, ozone and other components in Earth's atmosphere absorb UV-C wavelengths, and thus we are protected from radiation in this part of the spectrum so long as Earth's atmosphere is not compromised further by ozone-depleting pollutants. Most of the UV-A and some of the UV-B radiation passes through the atmosphere to reach us, and it is against these regions of the spectrum that sunscreens are formulated. Tanning and sunburn are caused by UV-B radiation. Risk of skin cancer is primarily associated with UV-B radiation, although some UV-A wavelengths may be important as well.

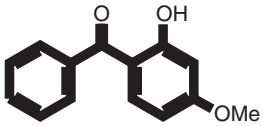
The specific range of protection provided by a sunscreen depends on the structure of its UV-absorbing groups. Most sunscreens have structures derived from the following parent compounds: *p*-aminobenzoic acid (PABA), cinnamic acid (3-phenylpropenoic acid), benzophenone (diphenyl ketone), and salicylic acid (*o*-hydroxybenzoic acid). The structures and λ_{max} for a few of the most common sunscreen agents are given below. The common theme among them is an aromatic core in conjugation with other functional groups.



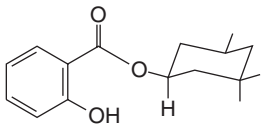
Octyl 4-*N,N*-dimethylaminobenzoate (Padimate O), λ_{max} 310 nm



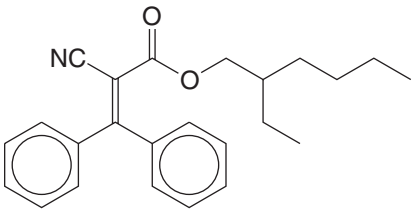
2-Ethylhexyl 4-methoxycinnamate (Parsol MCX), λ_{max} 310 nm



2-Hydroxy-4-methoxybenzophenone (Oxybenzone), λ_{max} 288 and 325 nm



Homomenthyl salicylate (Homosalate), λ_{max} 309 nm



2-Ethylhexyl 2-cyano-3,3-diphenylacrylate (Octocrylene), λ_{max} 310 nm

14.11E Mass Spectra of Aromatic Compounds

The major ion in the mass spectrum of an alkyl-substituted benzene is often *m/z* 91 ($C_6H_5CH_2^+$), resulting from cleavage between the first and second carbons of the alkyl chain attached to the ring. The ion presumably originates as a benzylic cation that rearranges to a tropylium cation ($C_7H_7^+$, Section 14.7D). Another ion frequently seen in mass spectra of monoalkylbenzene compounds is *m/z* 77, corresponding to $C_6H_5^+$.

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via *Wiley PLUS*, an online teaching and learning solution.

NOMENCLATURE

14.16 Write structural formulas for each of the following:

(a) 3-Nitrobenzoic acid
(b) *p*-Bromotoluene
(c) *o*-Dibromobenzene
(d) *m*-Dinitrobenzene
(e) 3,5-Dinitrophenol
(f) *p*-Nitrobenzoic acid
(g) 3-Chloro-1-ethoxybenzene
(h) *p*-Chlorobenzenesulfonic acid
(i) Methyl *p*-toluenesulfonate
(j) Benzyl bromide
(k) *p*-Nitroaniline
(l) *o*-Xylene
(m) *tert*-Butylbenzene
(n) *p*-Methylphenol
(o) *p*-Bromoacetophenone
(p) 3-Phenylcyclohexanol
(q) 2-Methyl-3-phenyl-1-butanol
(r) *o*-Chloroanisole

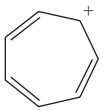
14.17 Write structural formulas and give acceptable names for all representatives of the following:

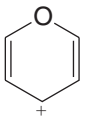
(a) Tribromobenzenes
(b) Dichlorophenols
(c) Nitroanilines
(d) Methylbenzenesulfonic acids
(e) Isomers of $C_6H_5—C_4H_9$

AROMATICITY

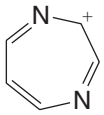
14.18 Which of the following molecules would you expect to be aromatic?

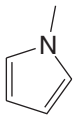
(a) 

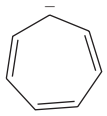
(b) 

(c) 

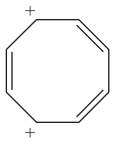
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

(j) 

(k) 

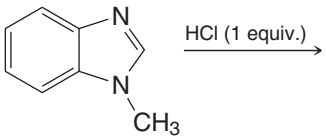
(l) 

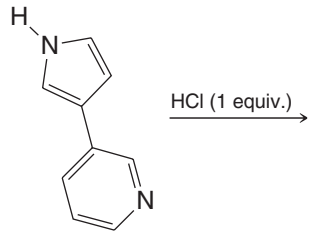
14.19 Use the polygon-and-circle method to draw an orbital diagram for each of the following compounds.

(a) 

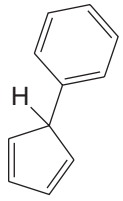
(b) 

14.20 Write the structure of the product formed when each of the following compounds reacts with one molar equivalent of HCl.

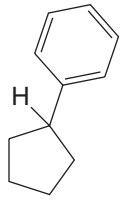
(a) 

(b) 

14.21 Which of the hydrogen atoms shown below is more acidic? Explain your answer.

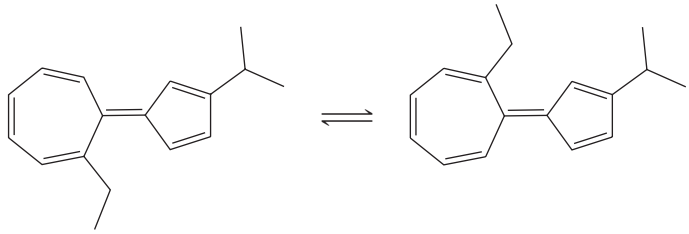


A

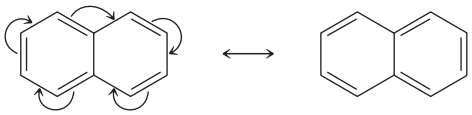


B

14.22 The rings below are joined by a double bond that undergoes cis–trans isomerization much more readily than the bond of a typical alkene. Provide an explanation.



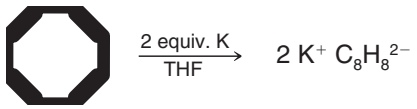
14.23 Although Hückel's rule (Section 14.7) strictly applies only to monocyclic compounds, it does appear to have application to certain bicyclic compounds, if one assumes use of resonance structures involving only the perimeter double bonds, as shown with one resonance contributor for naphthalene below.



Both naphthalene (Section 14.8A) and azulene (Section 14.8B) have 10 π electrons and are aromatic. Pentalene (below) is apparently antiaromatic and is unstable even at $-100°C$. Heptalene has been made but it adds bromine, it reacts with acids, and it is not planar. Is Hückel's rule applicable to these compounds? If so, explain their lack of aromaticity.

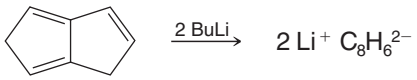
Pentalene **Heptalene**

14.24 **(a)** In 1960 T. Katz (Columbia University) showed that cyclooctatetraene adds two electrons when treated with potassium metal and forms a stable, planar dianion, $C_8H_8^{2-}$ (as the dipotassium salt):



Use the molecular orbital diagram given in Fig. 14.7 and explain this result.

(b) In 1964 Katz also showed that removing two protons from the compound below (using butyllithium as the base) leads to the formation of a stable dianion with the formula $C_8H_6^{2-}$ (as the dilithium salt).



Propose a reasonable structure for the product and explain why it is stable.

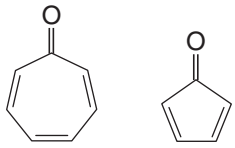
14.25 Although none of the [10]annulenes given in Section 14.7B is aromatic, the following 10 π-electron system is aromatic:

What factor makes this possible?

14.26 Cycloheptatrienone (**I**) is very stable. Cyclopentadienone (**II**) by contrast is quite unstable and rapidly undergoes a Diels–Alder reaction with itself.

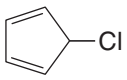
(a) Propose an explanation for the different stabilities of these two compounds.

(b) Write the structure of the Diels–Alder adduct of cyclopentadienone.



I **II**

14.27 5-Chloro-1,3-cyclopentadiene (below) undergoes S_N1 solvolysis in the presence of silver ion extremely slowly even though the chlorine is doubly allylic and allylic halides normally ionize readily (Section 15.15). Provide an explanation for this behavior.



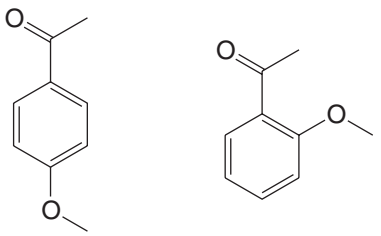
14.28 Explain the following: (**a**) Cyclononatetraenyl anion is planar (in spite of the angle strain involved) and appears to be aromatic. (**b**) Although [16]annulene is not aromatic, it adds two electrons readily to form an aromatic dianion.

14.29 Furan possesses less aromatic character than benzene as measured by their resonance energies (96 kJ mol^{-1} for furan; 151 kJ mol^{-1} for benzene). What reaction have we studied earlier that shows that furan is less aromatic than benzene and can react in a way characteristic of some dienes?

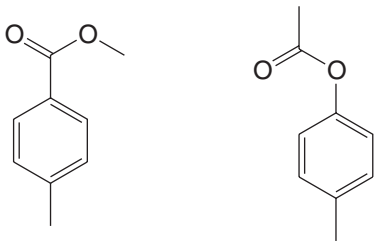
SPECTROSCOPY AND STRUCTURE ELUCIDATION

14.30 For each of the pairs below, predict specific aspects in their ^{1}H NMR spectra that would allow you to distinguish one compound from the other.

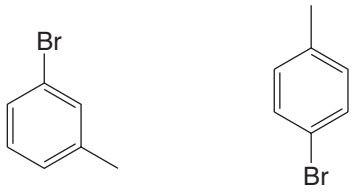
(a)



(b)



(c)



14.31 Assign structures to each of the compounds **A, B,** and **C** whose ^{1}H NMR spectra are shown in Fig. 14.27.

14.32 The ^{1}H NMR spectrum of cyclooctatetraene consists of a single line located at δ 5.78. What does the location of this signal suggest about electron delocalization in cyclooctatetraene?

14.33 Give a structure for compound **F** that is consistent with the ^{1}H NMR and IR spectra in Fig. 14.28.

14.34 A compound (**L**) with the molecular formula C_9H_{10} reacts with bromine in carbon tetrachloride and gives an IR absorption spectrum that includes the following absorption peaks: 3035 cm^{-1}(m), 3020 cm^{-1}(m), 2925 cm^{-1}(m), 2853 cm^{-1}(w), 1640 cm^{-1}(m), 990 cm^{-1}(s), 915 cm^{-1}(s), 740 cm^{-1}(s), 695 cm^{-1}(s). The ^{1}H NMR spectrum of **L** consists of:

Doublet δ 3.1 (2H)	Multiplet δ 5.1	Multiplet δ 7.1 (5H)
Multiplet δ 4.8	Multiplet δ 5.8	

The UV spectrum shows a maximum at 255 nm. Propose a structure for compound **L** and make assignments for each of the IR peaks.

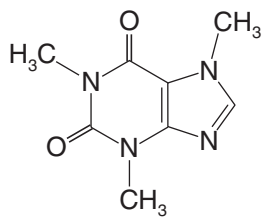
14.35 Compound **M** has the molecular formula C_9H_{12}. The ^{1}H NMR spectrum of **M** is given in Fig. 14.29 and the IR spectrum in Fig. 14.30. Propose a structure for **M**.

14.36 A compound (**N**) with the molecular formula $C_9H_{10}O$ reacts with osmium tetroxide. The ^{1}H NMR spectrum of **N** is shown in Fig. 14.31 and the IR spectrum of **N** is shown in Fig. 14.32. Propose a structure for **N**.

14.37 The IR and ^{1}H NMR spectra for compound **X** (C_8H_{10}) are given in Fig. 14.33. Propose a structure for compound **X**.

14.38 The IR and ^{1}H NMR spectra of compound **Y** ($C_9H_{12}O$) are given in Fig. 14.34. Propose a structure for **Y**.

14.39 **(a)** How many signals would you expect to find in the ^{1}H NMR spectrum of caffeine?



Caffeine

(b) What characteristic peaks would you expect to find in the IR spectrum of caffeine?

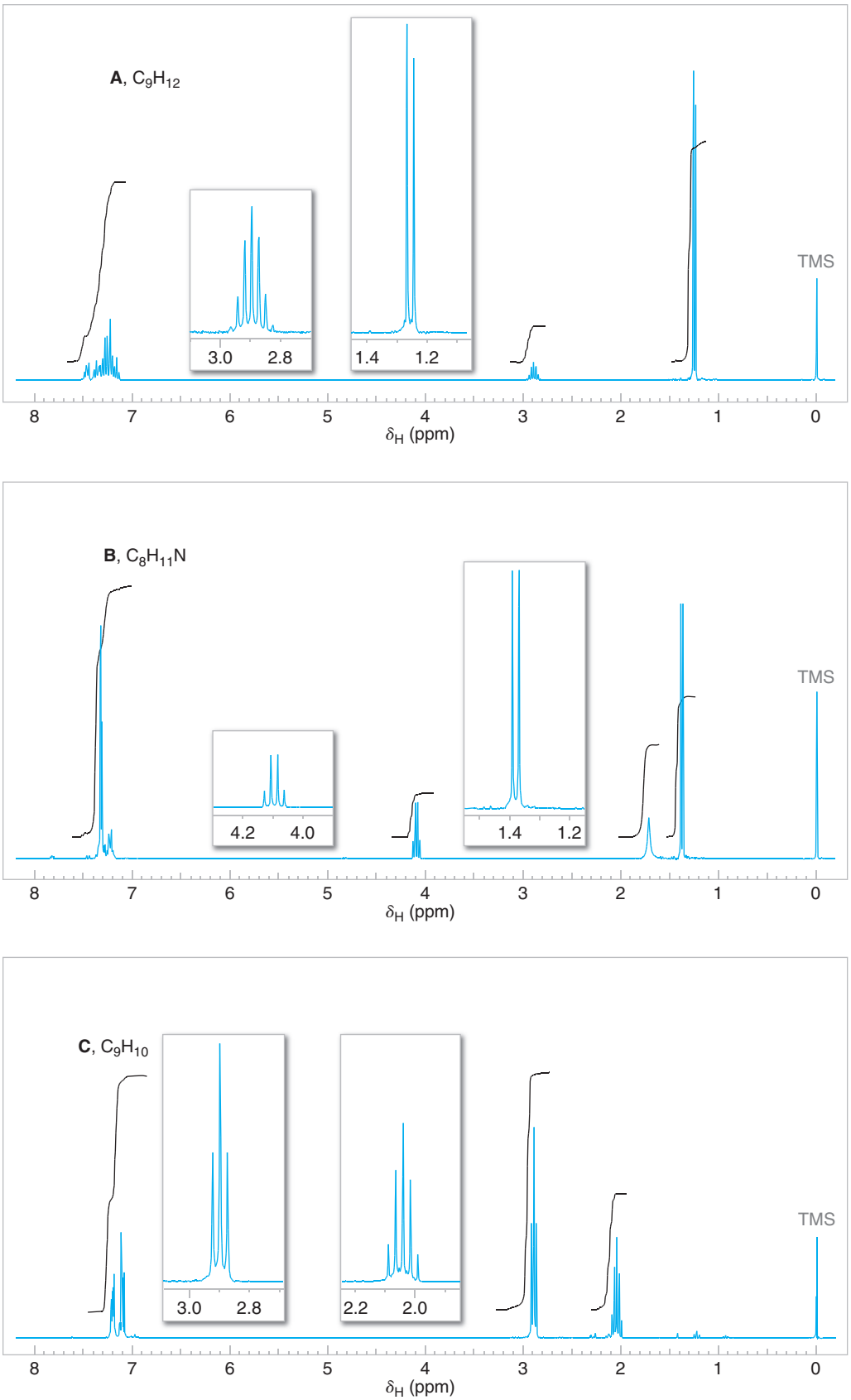
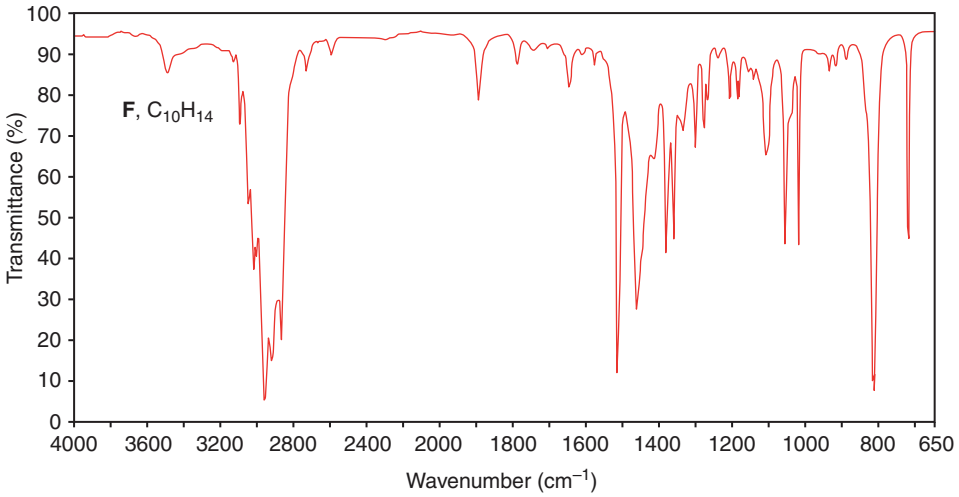


Figure 14.27 The 300-MHz ^{1}H NMR spectra for Problem 14.31. Expansions of the signals are shown in the offset plots.



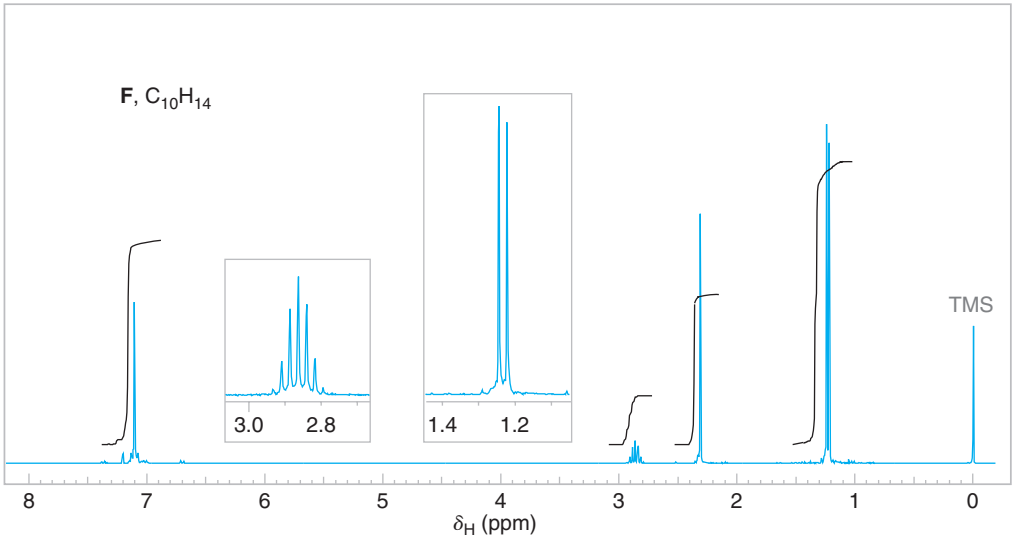


Figure 14.28 The 300-MHz ^{1}H NMR and IR spectra of compound **F**, Problem 14.33. Expansions of the signals are shown in the offset plots. IR spectra, SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, September 24, 2009)

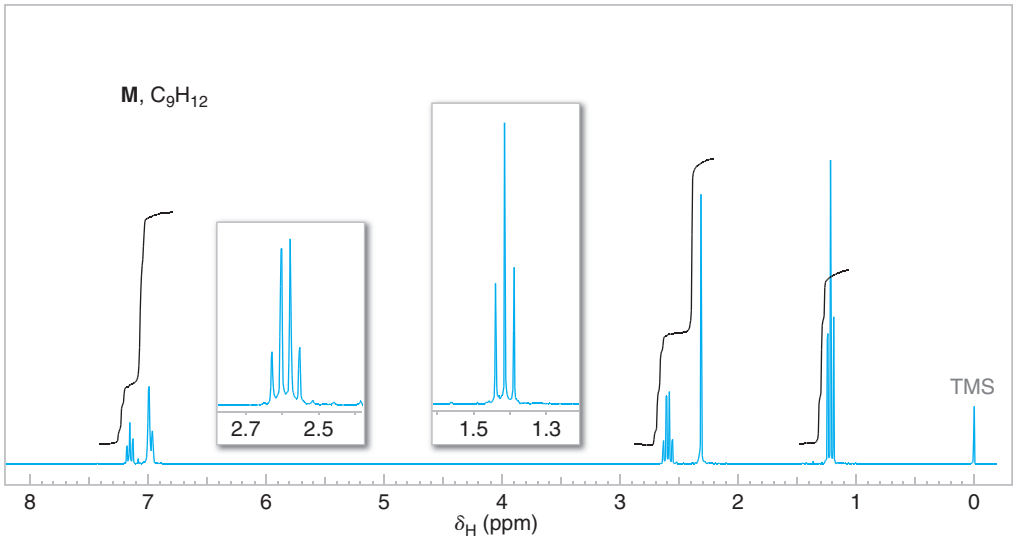


Figure 14.29 The 300-MHz ^{1}H NMR spectrum of compound **M**, Problem 14.35. Expansions of the signals are shown in the offset plots.

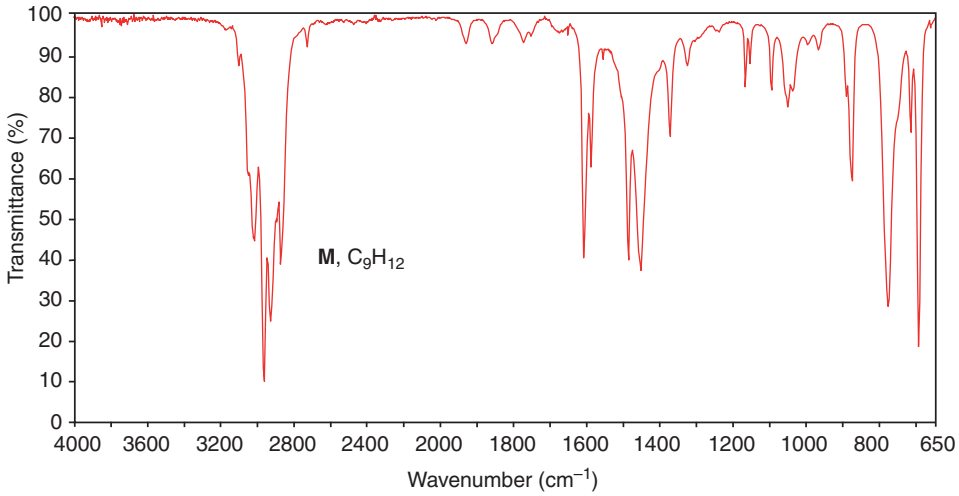


Figure 14.30 The IR spectrum of compound **M**, Problem 14.35.

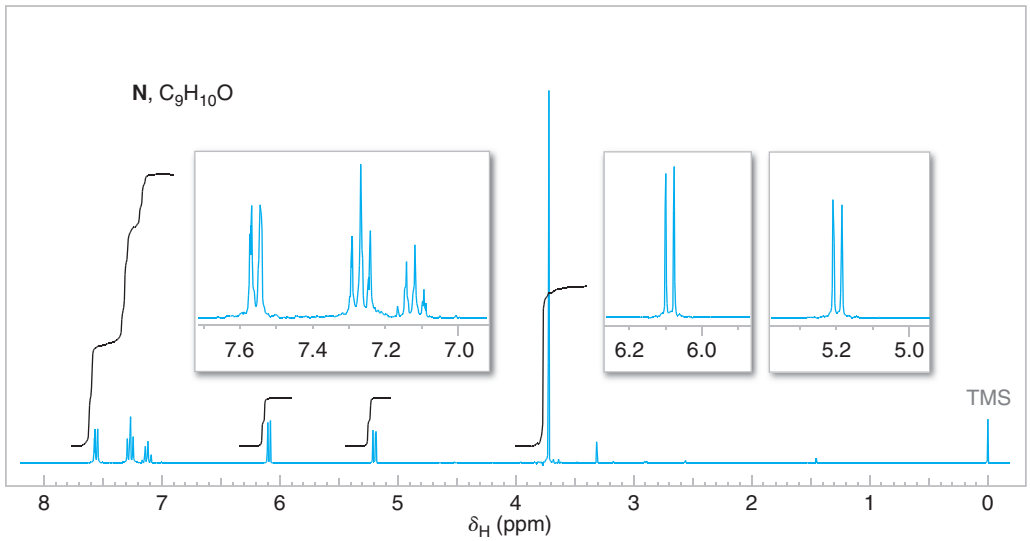


Figure 14.31 The 300-MHz ^{1}H NMR spectrum of compound **N**, Problem 14.36. Expansions of the signals are shown in the offset plots.

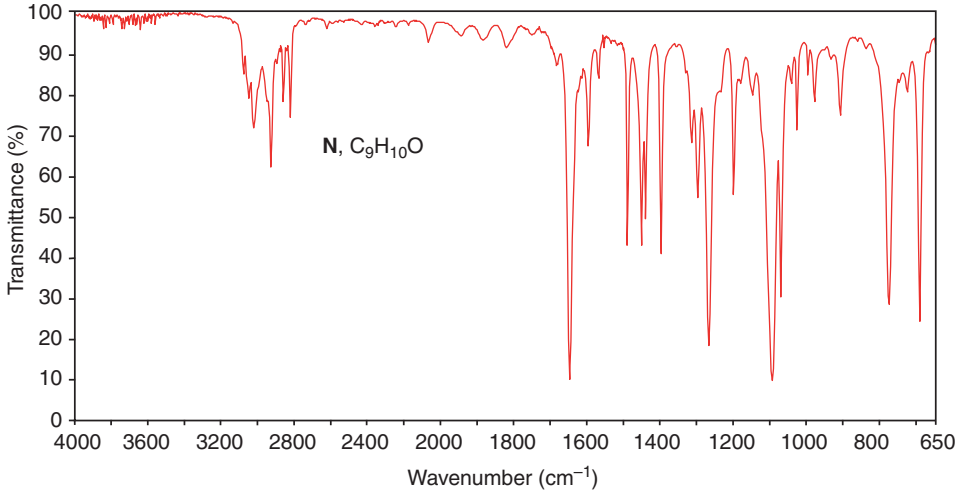
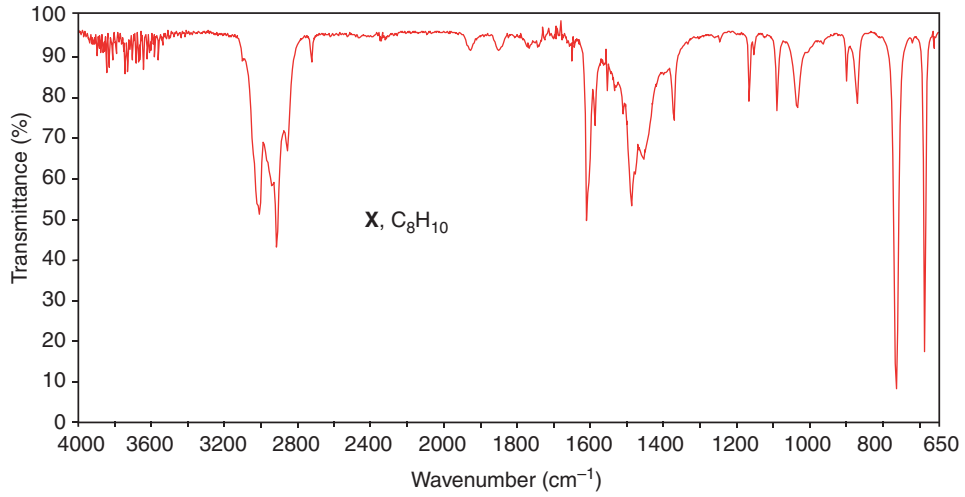


Figure 14.32 The IR spectrum of compound **N**, Problem 14.36.



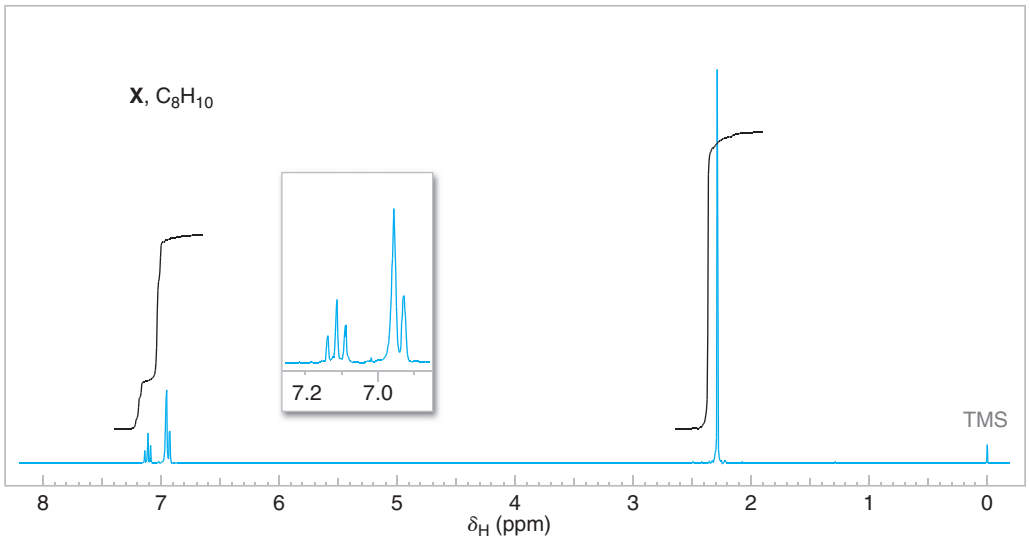


Figure 14.33 The IR and 300-MHz ^{1}H NMR spectra of compound **X**, Problem 14.37. Expansions of the signals are shown in the offset plots.

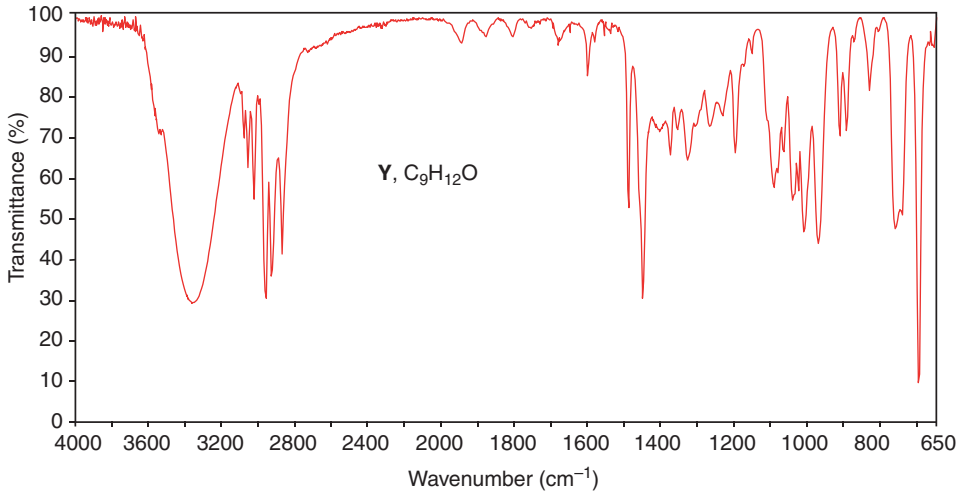


Figure 14.34 The IR and 300-MHz ^{1}H NMR spectra (next page) of compound **Y**, Problem 14.38. Expansions of the signals are shown in the offset plots.

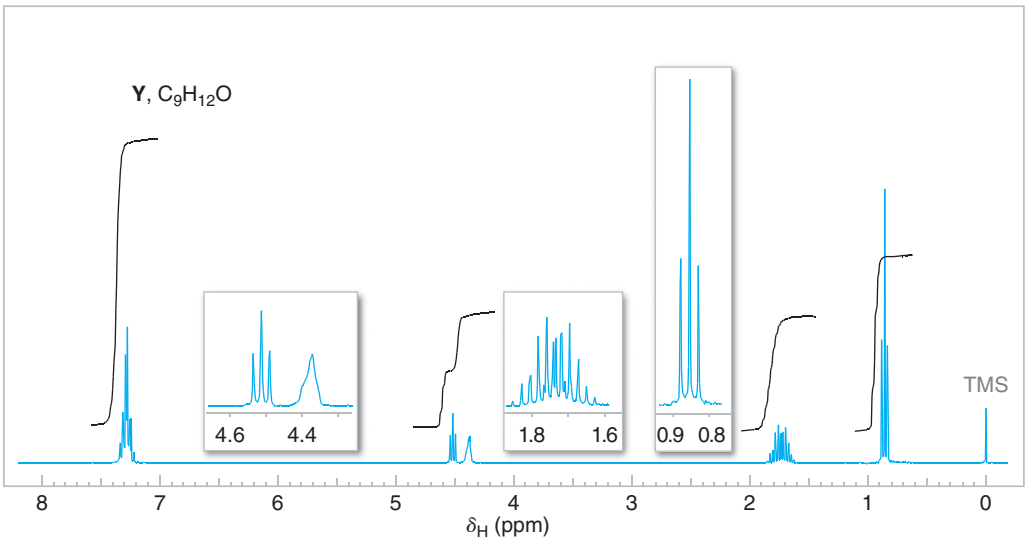
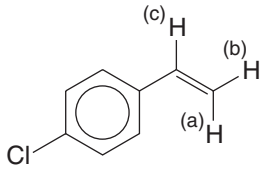


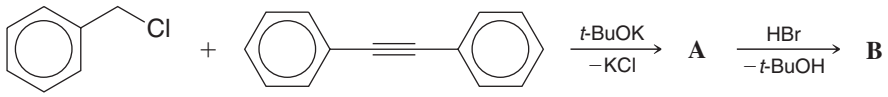
Figure 14.34 *(Continued)*

Challenge Problems

14.40 Given the following information, predict the appearance of the ^{1}H NMR spectrum arising from the vinyl hydrogen atoms of *p*-chlorostyrene. Deshielding by the induced magnetic field of the ring is greatest at proton c (δ 6.7) and is least at proton b (δ 5.3). The chemical shift of a is about δ 5.7. The coupling constants have the following approximate magnitudes: $J_{ac} \cong 18$ Hz, $J_{bc} \cong 11$ Hz, and $J_{ab} \cong 2$ Hz. (These coupling constants are typical of those given by vinylic systems: Coupling constants for trans hydrogen atoms are larger than those for cis hydrogen atoms, and coupling constants for geminal vinylic hydrogen atoms are very small.)



14.41 Consider these reactions:



The intermediate **A** is a covalently bonded compound that has typical ^{1}H NMR signals for aromatic ring hydrogens and only one additional signal at δ 1.21, with an area ratio of 5:3, respectively. Final product **B** is ionic and has only aromatic hydrogen signals.

What are the structures of **A** and **B**?

14.42 The final product of this sequence, **D**, is an orange, crystalline solid melting at 174°C and having molecular weight 186:

$$\text{Cyclopentadiene} + \text{Na} \longrightarrow \mathbf{C} + \mathbf{H_2}$$
$$2\,\mathbf{C} + \text{FeCl}_2 \longrightarrow \mathbf{D} + 2\,\text{NaCl}$$

In its ^{1}H and ^{13}C NMR spectra, product **D** shows only one kind of hydrogen and only one kind of carbon, respectively.

Draw the structure of **C** and make a structural suggestion as to how the high degree of symmetry of **D** can be explained. (**D** belongs to a group of compounds named after something you might get at a deli for lunch.)

14.43 Compound **E** has the spectral features given below. What is its structure?

MS (*m/z*): $M^{+\cdot}$ 202

IR (cm^{-1}): 3030–3080, 2150 (very weak), 1600, 1490, 760, and 690

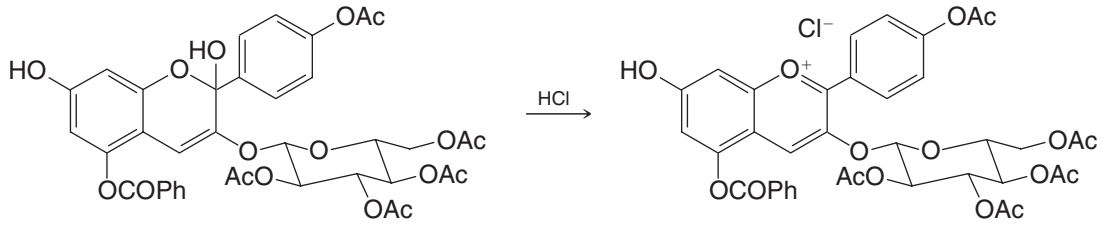
^{1}H **NMR** (δ): narrow multiplet centered at 7.34

UV (nm): 287 (ϵ = 25,000), 305 (ϵ = 36,000), and 326 (ϵ = 33,000)

14.44 Draw all of the π molecular orbitals for (3*E*)-1,3,5-hexatriene, order them from lowest to highest in energy, and indicate the number of electrons that would be found in each in the ground state for the molecule. After doing so, open the computer molecular model for (3*E*)-1,3,5-hexatriene and display the calculated molecular orbitals. How well does the appearance and sequence of the orbitals you drew (e.g., number of nodes, overall symmetry of each, etc.) compare with the orbitals in the calculated model? Are the same orbitals populated with electrons in your analysis as in the calculated model?

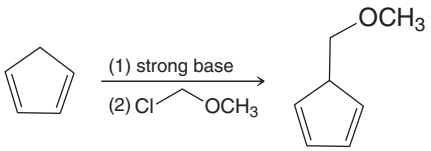
Learning Group Problems

1. Write mechanism arrows for the following step in the chemical synthesis by A. Robertson and R. Robinson (*J. Chem. Soc*. **1928**, 1455–1472) of callistephin chloride, a red flower pigment from the purple-red aster. Explain why this transformation is a reasonable process.

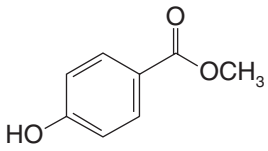


Callistephin chloride

2. The following reaction sequence was used by E. J. Corey (*J. Am. Chem. Soc*. **1969**, *91*, 5675–5677) at the beginning of a synthesis of prostaglandin $F_{2\alpha}$ and prostaglandin E_2. Explain what is involved in this reaction and why it is a reasonable process.



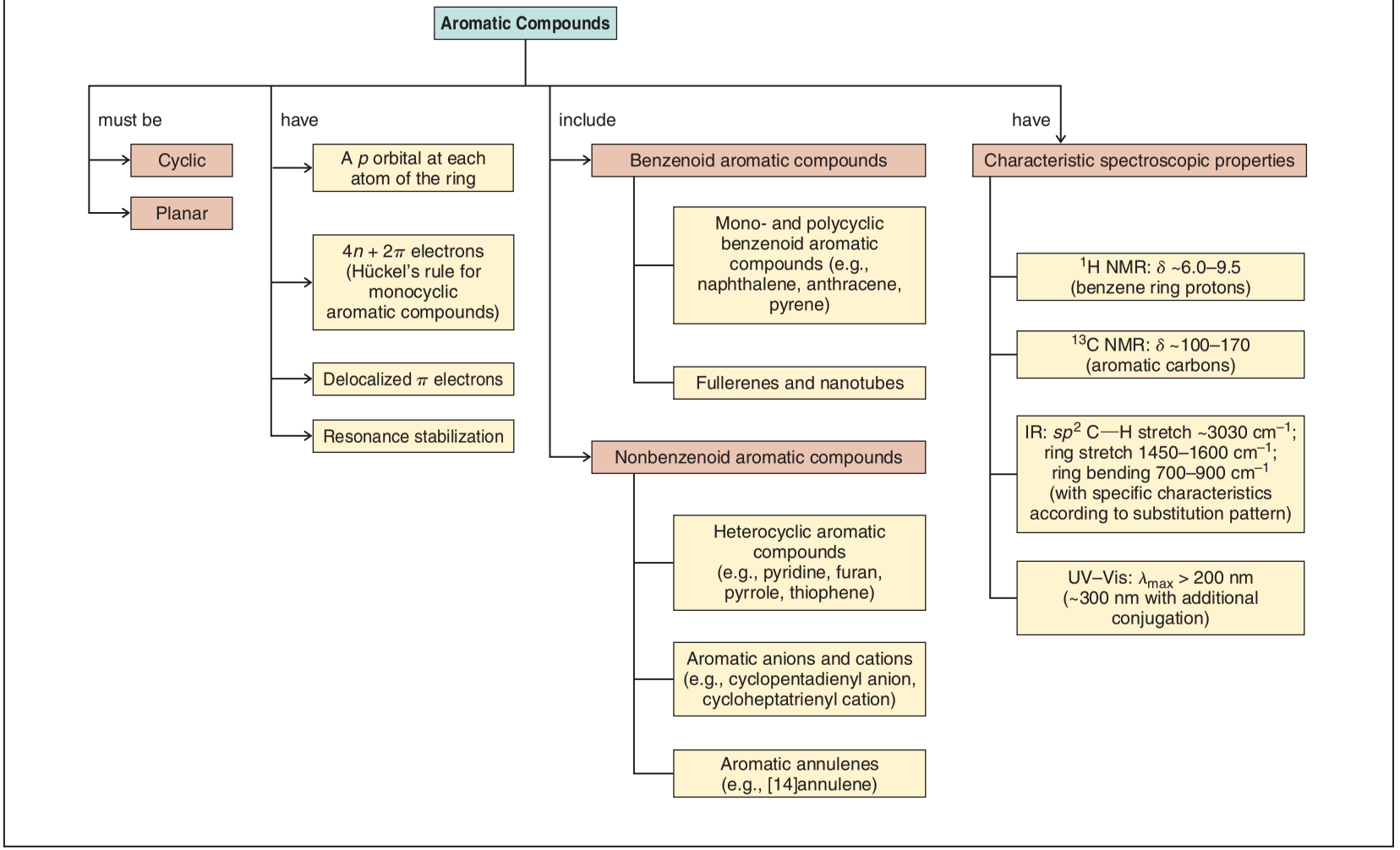
3. The ^{1}H NMR signals for the aromatic hydrogens of methyl *p*-hydroxybenzoate appear as two doublets at approximately 7.05 and 8.04 ppm (δ). Assign these two doublets to the respective hydrogens that produce each signal. Justify your assignments using arguments of relative electron density based on contributing resonance structures.



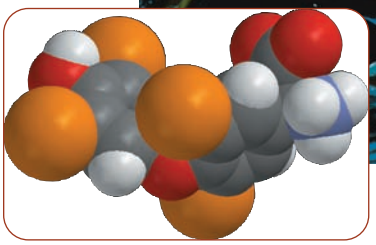
4. Draw the structure of adenine, a heterocyclic aromatic compound incorporated in the structure of DNA. Identify the nonbonding electron pairs that are *not* part of the aromatic system in the rings of adenine. Which nitrogen atoms in the rings would you expect to be more basic and which should be less basic?

5. Draw structures of the nicotinamide ring in NADH and NAD^+. In the transformation of NADH to NAD^+, in what form must a hydrogen be transferred in order to produce the aromatic pyridinium ion in NAD^+?

CONCEPT MAP



15 Reactions of Aromatic Compounds

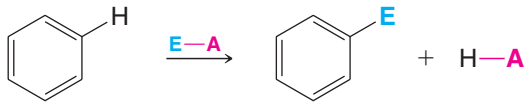


Thyroxine

Thyroxine (see the model above) is an aromatic compound and a key hormone that raises metabolic rate. Low levels of thyroxine (hypothyroidism) can lead to obesity, lethargy, and an enlarged thyroid gland (goiter). The thyroid gland makes thyroxine from iodine and tyrosine, which are two essential components of our diet. Most of us obtain iodine from iodized salt, but iodine is also found in products derived from seaweed, like the kelp shown above. An abnormal level of thyroxine is a relatively common malady, however. Fortunately, low levels of thyroxine are easily corrected by hormone supplements. After we study a new class of reaction in this chapter called electrophilic aromatic substitution, we shall return to see how that reaction is related to thyroxine in "The Chemistry of . . . Iodine Incorporation in Thyroxine Biosynthesis."

15.1 Electrophilic Aromatic Substitution Reactions

Some of the most important reactions of aromatic compounds are those in which an electrophile replaces one of the hydrogen atoms of the ring.



(E—A is an electrophilic reactant)

These reactions, called **electrophilic aromatic substitutions (EAS)**, allow the direct introduction of groups onto aromatic rings such as benzene, and they provide synthetic routes to many important compounds. Figure 15.1 outlines five different types of electrophilic aromatic substitutions that we will study in this chapter, including carbon–carbon bond-forming reactions and halogenations.

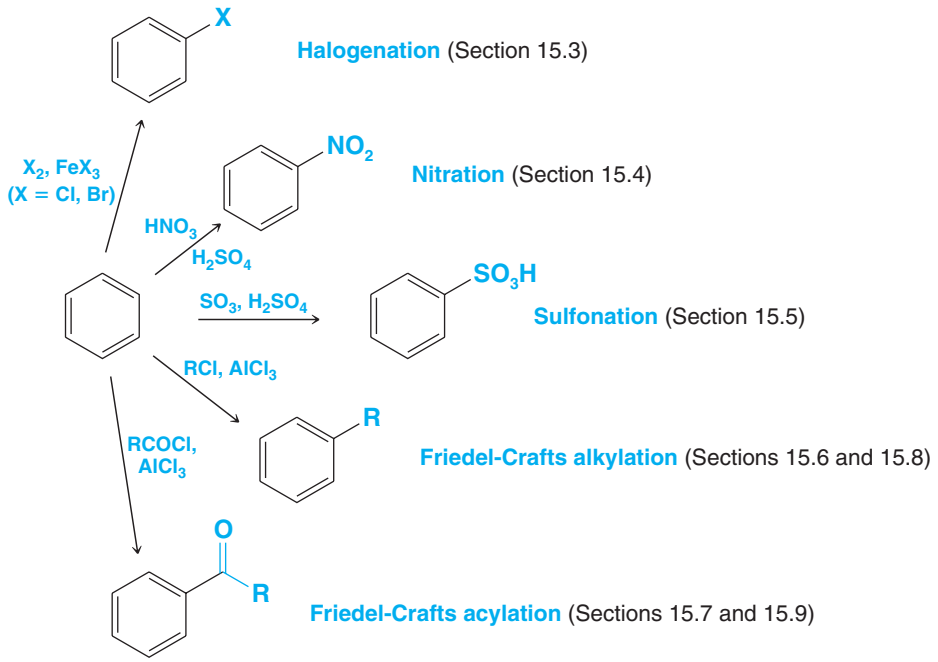
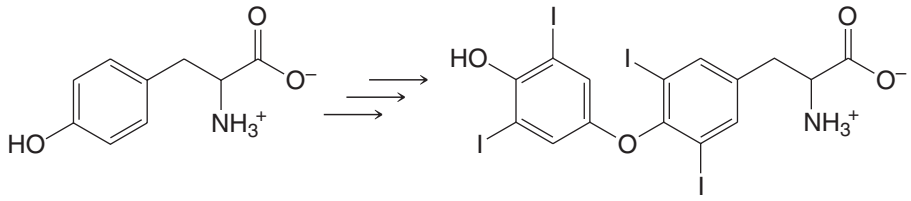


Figure 15.1 Electrophilic aromatic substitution reactions.

A noteworthy example of electrophilic aromatic substitution in nature, as mentioned above, is biosynthesis of the thyroid hormone thyroxine, where iodine is incorporated into benzene rings that are derived from tyrosine.



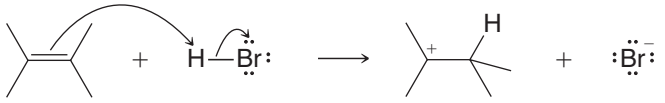
Tyrosine
(a dietary amino acid)

Thyroxine
(a thyroid hormone)

In the next section we shall learn the general mechanism for the way an electrophile reacts with a benzene ring. Then in Sections 15.3–15.7 we shall see specific examples of electrophiles and how each is formed in a reaction mixture.

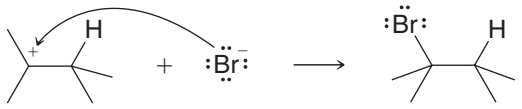
15.2 A General Mechanism for Electrophilic Aromatic Substitution

The π electrons of benzene react with strong electrophiles. In this respect, benzene has something in common with alkenes. When an alkene reacts with an electrophile, as in the addition of HBr (Section 8.2), electrons from the alkene π bond react with the electrophile, leading to a carbocation intermediate.



Alkene **Electrophile** **Carbocation**

The carbocation formed from the alkene then reacts with the nucleophilic bromide ion to form the addition product.



Carbocation **Addition product**

The similarity of benzene reactivity with that of an alkene ends, however, at the carbocation stage, prior to nucleophilic attack. As we saw in Chapter 14, benzene's closed shell of six π electrons give it special stability.

- Although benzene is susceptible to electrophilic attack, it undergoes *substitution reactions* rather than *addition reactions*.

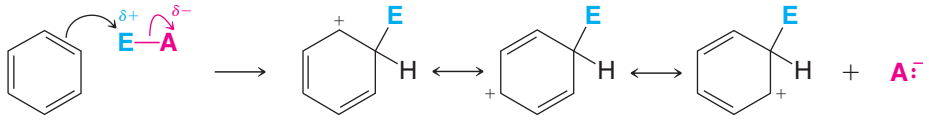
Substitution reactions allow the aromatic sextet of π electrons in benzene to be regenerated after attack by the electrophile. We can see how this happens if we examine a general mechanism for electrophilic aromatic substitution.

Experimental evidence indicates that electrophiles attack the π system of benzene to form a ***nonaromatic cyclohexadienyl carbocation*** known as an **arenium ion**. In showing this step, it is convenient to use Kekulé structures, because these make it much easier to keep track of the π electrons:

Helpful Hint

Resonance structures (like those used here for the arenium ion) will be important for our study of electrophilic aromatic substitution.

Step 1



Arenium ion
(a delocalized cyclohexadienyl cation)

- In step 1 the electrophile takes two electrons of the six-electron π system to form a σ bond to one carbon atom of the benzene ring.

Formation of this bond interrupts the cyclic system of π electrons, because in the formation of the arenium ion the carbon that forms a bond to the electrophile becomes sp^3 hybridized and, therefore, no longer has an available p orbital. Now only five carbon atoms of the ring are sp^2 hybridized and still have p orbitals. The four π electrons of the arenium ion are delocalized through these five p orbitals. A calculated electrostatic potential map for the arenium ion formed by electrophilic addition of bromine to benzene indicates that positive charge is distributed in the arenium ion ring (Fig. 15.2), just as was shown in the contributing resonance structures.

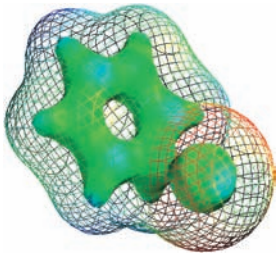
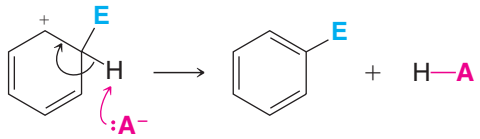


Figure 15.2 A calculated structure for the arenium ion intermediate formed by electrophilic addition of bromine to benzene (Section 15.3). The electrostatic potential map for the principal location of bonding electrons (indicated by the solid surface) shows that positive charge (blue) resides primarily at the ortho and para carbons relative to the carbon where the electrophile has bonded. This distribution of charge is consistent with the resonance model for an arenium ion. (The van der Waals surface is indicated by the wire mesh.)

- In step 2 a proton is removed from the carbon atom of the arenium ion that bears the electrophile, restoring aromaticity to the ring.

Step 2



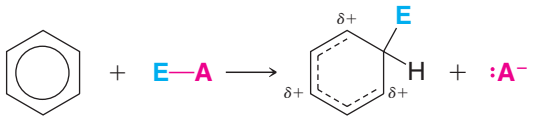
The two electrons that bonded the proton to the ring become a part of the π system. The carbon atom that bears the electrophile becomes sp^2 hybridized again, and a benzene derivative with six fully delocalized π electrons is formed. (The proton is removed by any of the bases present, for example, by the anion derived from the electrophile.)

Review Problem 15.1

Show how loss of a proton can be represented using each of the three resonance structures for the arenium ion and show how each representation leads to the formation of a benzene ring with three alternating double bonds (i.e., six fully delocalized π electrons).

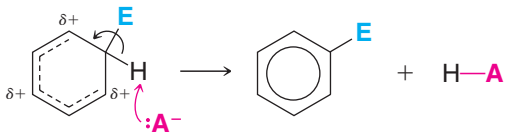
Kekulé structures are more appropriate for writing mechanisms such as electrophilic aromatic substitution because they permit the use of resonance theory, which, as we shall soon see, is invaluable as an aid to our understanding. If, for brevity, however, we wish to show the mechanism using the hybrid formula for benzene we can do it in the following way. We draw the arenium ion as a delocalized cyclohexadienyl cation:

Step 1



Arenium ion

Step 2



Helpful Hint

In our color scheme for chemical formulas, blue generally indicates groups that are electrophilic or have electron-withdrawing character. Red indicates groups that are or become Lewis bases, or have electron-donating character.

There is firm experimental evidence that the arenium ion is a true *intermediate* in electrophilic substitution reactions. It is not a transition state. This means that in a free-energy diagram (Fig. 15.3) the arenium ion lies in an energy valley between two transition states.

The free energy of activation for step 1, $\Delta G^{\ddagger}_{(1)}$, has been shown to be much greater than the free energy of activation for step 2, $\Delta G^{\ddagger}_{(2)}$. This is consistent with what we would expect.

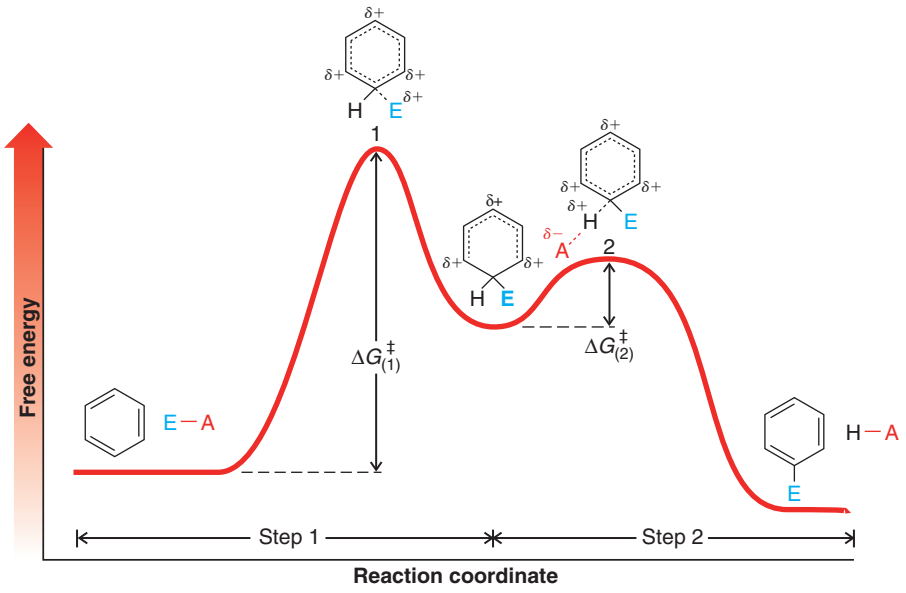
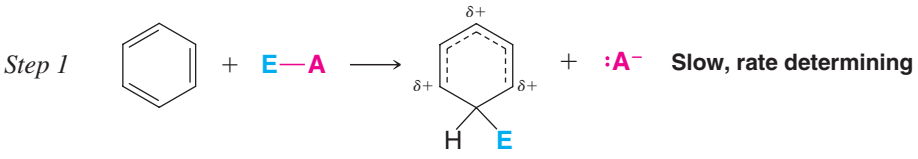
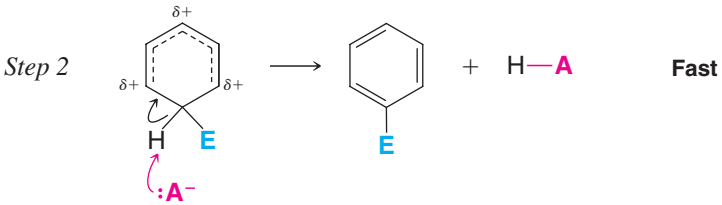


Figure 15.3 The free-energy diagram for an electrophilic aromatic substitution reaction. The arenium ion is a true intermediate lying between transition states 1 and 2. In transition state 1 the bond between the electrophile and one carbon atom of the benzene ring is only partially formed. In transition state 2 the bond between the same benzene carbon atom and its hydrogen atom is partially broken. The bond between the hydrogen atom and the conjugate base is partially formed.

The reaction leading from benzene and an electrophile to the arenium ion is highly endothermic, because the aromatic stability of the benzene ring is lost. The reaction leading from the arenium ion to the substituted benzene, by contrast, is highly exothermic because it restores aromaticity to the system.

Of the following two steps, step 1 (the formation of the arenium ion) is usually the rate-determining step in electrophilic aromatic substitution because of its higher free energy of activation:

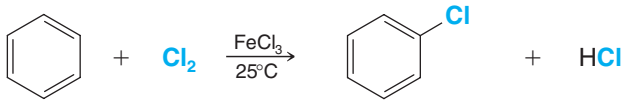




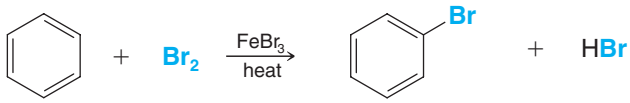
Step 2, the removal of a proton, occurs rapidly relative to step 1 and has no effect on the overall rate of reaction.

15.3 Halogenation of Benzene

Benzene reacts with bromine and chlorine in the presence of Lewis acids to give halogenated substitution products in good yield.



Chlorobenzene (90%)



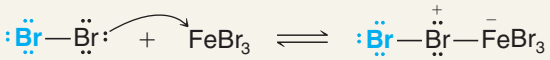
Bromobenzene (75%)

The Lewis acids typically used are aluminum chloride ($AlCl_3$) and iron chloride ($FeCl_3$) for chlorination, and iron bromide ($FeBr_3$) for bromination. The purpose of the Lewis acid is to make the halogen a stronger electrophile. A mechanism for electrophilic aromatic bromination is shown here.

A MECHANISM FOR THE REACTION

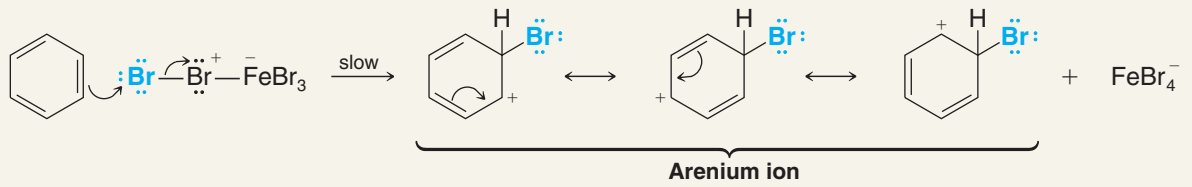
Electrophilic Aromatic Bromination

Step 1



Bromine combines with $FeBr_3$ to form a complex.

Step 2

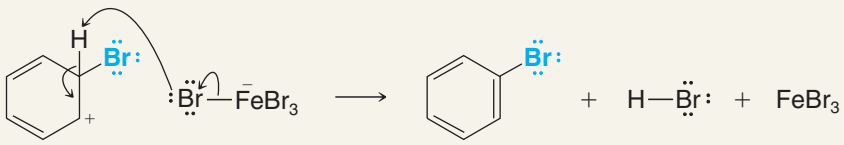


Helpful Hint

An electrostatic potential map for this arenium ion is shown in Fig. 15.2.

The benzene ring donates an electron pair to the terminal bromine, forming the arenium ion and neutralizing the formal positive charge on the other bromine.

Step 3

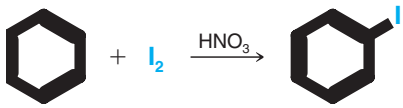


A proton is removed from the arenium ion to form bromobenzene and regenerate the catalyst.

The mechanism of the chlorination of benzene in the presence of ferric chloride is analogous to the one for bromination.

Fluorine reacts so rapidly with benzene that aromatic fluorination requires special conditions and special types of apparatus. Even then, it is difficult to limit the reaction to monofluorination. Fluorobenzene can be made, however, by an indirect method that we shall see in Section 20.7D.

Iodine, on the other hand, is so unreactive that a special technique has to be used to effect direct iodination; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid:

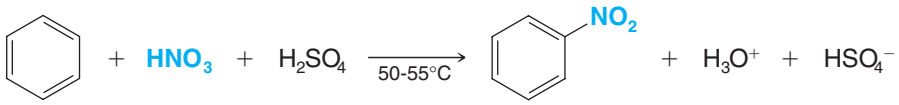


86%

Biochemical iodination, as in the biosynthesis of thyroxine, occurs with enzymatic catalysis. Thyroxine biosynthesis is discussed further in "The Chemistry of . . . Iodine Incorporation in Thyroxine Biosynthesis" box in Section 15.11E.

15.4 Nitration of Benzene

Benzene undergoes nitration on reaction with a mixture of concentrated nitric acid and concentrated sulfuric acid.



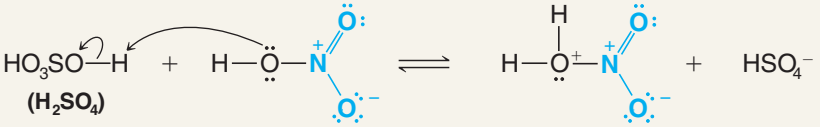
85%

Concentrated sulfuric acid increases the rate of the reaction by increasing the concentration of the electrophile, the nitronium ion (NO_2^+), as shown in the first two steps of the following mechanism.

A MECHANISM FOR THE REACTION

Nitration of Benzene

Step 1

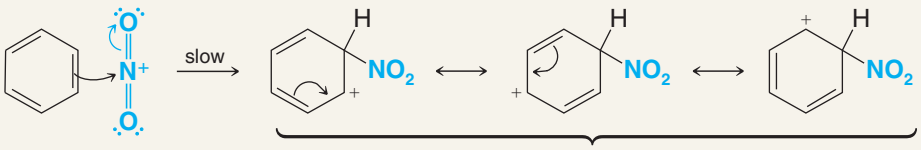


In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.

Step 2

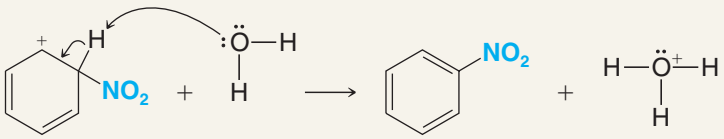
Now that it is protonated, nitric acid can dissociate to form a nitronium ion.

Step 3



The nitronium ion is the electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.

Step 4



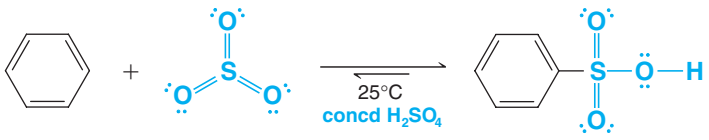
The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

Review Problem 15.2

Given that the pK_a of H_2SO_4 is -9 and that of HNO_3 is -1.4, explain why nitration occurs more rapidly in a mixture of concentrated nitric and sulfuric acids than in concentrated nitric acid alone.

15.5 *Sulfonation of Benzene*

Benzene reacts with fuming sulfuric acid at room temperature to produce benzenesulfonic acid. Fuming sulfuric acid is sulfuric acid that contains added sulfur trioxide (SO_3). Sulfonation also takes place in concentrated sulfuric acid alone, but more slowly. Under either condition, the electrophile appears to be sulfur trioxide.



In concentrated sulfuric acid, sulfur trioxide is produced in an equilibrium in which H_2SO_4 acts as both an acid and a base (see step 1 of the following mechanism).

A MECHANISM FOR THE REACTION

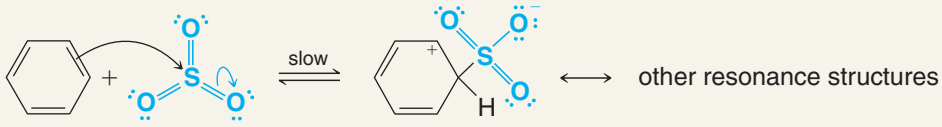
Sulfonation of Benzene

Step 1

$$2\,H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$$

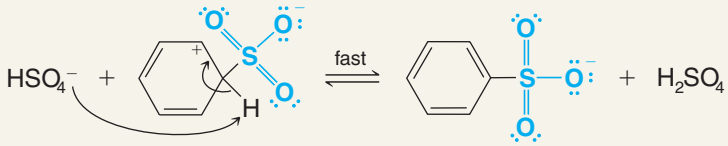
This equilibrium produces SO_3 in concentrated H_2SO_4.

Step 2



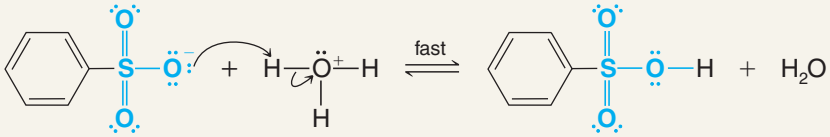
SO_3 is the electrophile that reacts with benzene to form an arenium ion.

Step 3



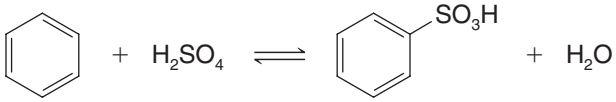
A proton is removed from the arenium ion to form the benzenesulfonate ion.

Step 4



The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

All of the steps in sulfonation are equilibria, which means that the overall reaction is reversible. The position of equilibrium can be influenced by the conditions we employ.



- If we want to sulfonate the ring (install a sulfonic acid group), we use concentrated sulfuric acid or—better yet—fuming sulfuric acid. Under these conditions the position of equilibrium lies appreciably to the right, and we obtain benzenesulfonic acid in good yield.
- If we want to desulfonate the ring (**remove** a sulfonic acid group), we employ dilute sulfuric acid and usually pass steam through the mixture. Under these conditions—with a high concentration of water—the equilibrium lies appreciably to the left and desulfonation occurs.

We shall see later that sulfonation and desulfonation reactions are often used in synthetic work.

- We sometimes install a sulfonate group **as a protecting group**, to temporarily block its position from electrophilic aromatic substitution, or **as a directing group, to influence the position** of another substitution relative to it (Section 15.10). When it is no longer needed we remove the sulfonate group.

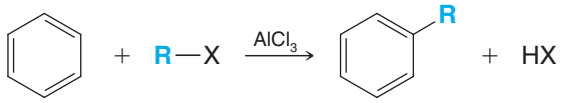
Helpful Hint

Sulfonation–desulfonation is a useful tool in syntheses involving electrophilic aromatic substitution.

15.6 *Friedel–Crafts Alkylation*

Charles Friedel, a French chemist, and his American collaborator, James M. Crafts, discovered new methods for the preparation of alkylbenzenes (ArR) and acylbenzenes (ArCOR) in 1877. These reactions are now called the Friedel–Crafts alkylation and acylation reactions. We shall study the Friedel–Crafts alkylation reaction here and take up the Friedel–Crafts acylation reaction in Section 15.7.

- The following is a general equation for a **Friedel–Crafts alkylation** reaction:



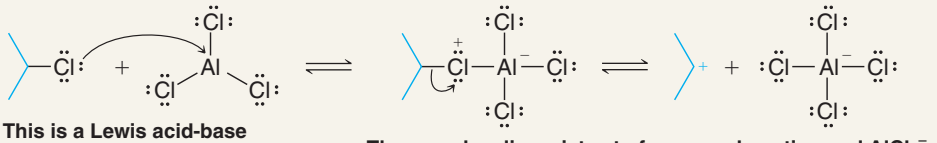
- The mechanism for the reaction starts with the formation of a carbocation.
- The carbocation then acts as an electrophile and attacks the benzene ring to form an arenium ion.
- The arenium ion then loses a proton.

This mechanism is illustrated below using 2-chloropropane and benzene.

A MECHANISM FOR THE REACTION

Friedel–Crafts alkylation

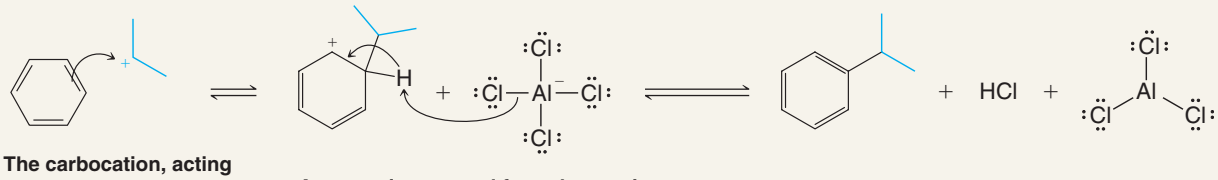
Step 1



This is a Lewis acid-base reaction (see Section 3).

The complex dissociates to form a carbocation and $AlCl_4^-$.

Step 2



The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.

A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

- When R — X is a primary halide, a simple carbocation probably does not form. Instead, the aluminum chloride forms a complex with the alkyl halide, and this complex acts as the electrophile.

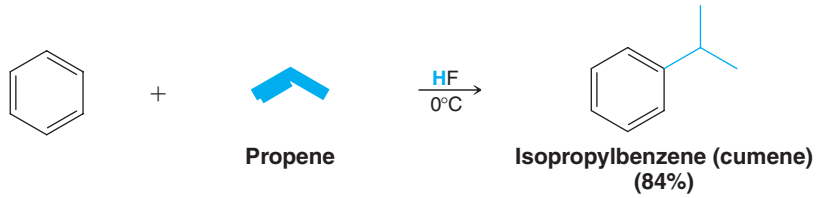
The complex is one in which the carbon–halogen bond is nearly broken—and one in which the carbon atom has a considerable positive charge:

$$\overset{\delta+}{R}CH_2 \text{ ---- } \ddot{Cl}:Al\,Cl_3^{\delta-}$$

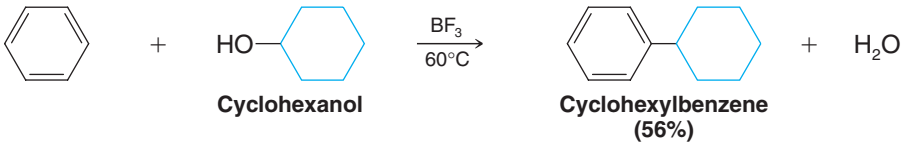
Even though this complex is not a simple carbocation, it acts as if it were and it transfers a positive alkyl group to the aromatic ring.

- These complexes react so much like carbocations that they also undergo typical carbocation rearrangements (Section 15.8).
- Friedel–Crafts alkylations are not restricted to the use of alkyl halides and aluminum chloride. Other pairs of reagents that form carbocations (or species like carbocations) may be used in Friedel–Crafts alkylations as well.

These possibilities include the use of a mixture of an alkene and an acid:



A mixture of an alcohol and an acid may also be used:



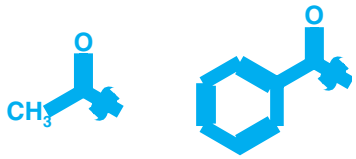
There are several important limitations of the Friedel–Crafts reaction. These are discussed in Section 15.8.

Review Problem 15.3

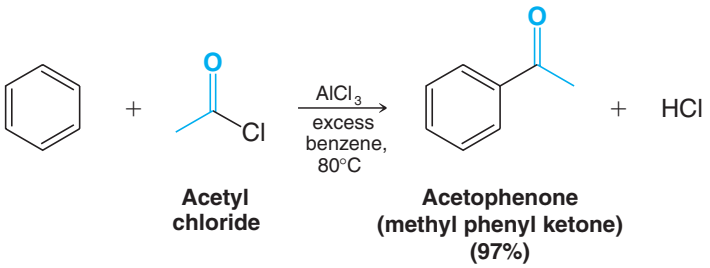
Outline all steps in a reasonable mechanism for the formation of isopropylbenzene from propene and benzene in liquid HF (just shown). Your mechanism must account for the product being isopropylbenzene, not propylbenzene.

15.7 Friedel–Crafts Acylation

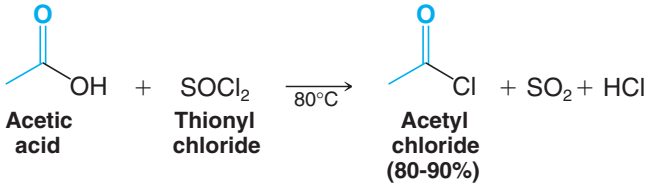
The  group is called an **acyl group**, and a reaction whereby an acyl group is introduced into a compound is called an **acylation** reaction. Two common acyl groups are the acetyl group and the benzoyl group. (The benzoyl group should not be confused with the benzyl group, $-CH_2C_6H_5$; see Section 14.2.)

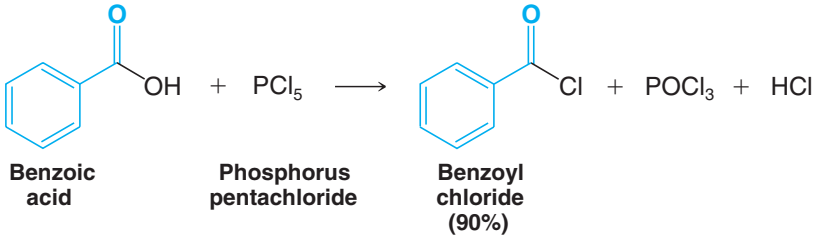


The **Friedel–Crafts acylation** reaction is often carried out by treating the aromatic compound with an **acyl halide** (often an acyl chloride). Unless the aromatic compound is one that is highly reactive, the reaction requires the addition of at least one equivalent of a Lewis acid (such as $AlCl_3$) as well. The product of the reaction is an aryl ketone:

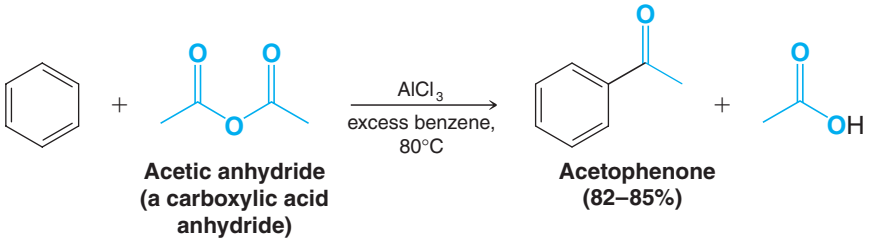


Acyl chlorides, also called **acid chlorides**, are easily prepared (Section 18.5) by treating carboxylic acids with thionyl chloride ($SOCl_2$) or phosphorus pentachloride (PCl_5):

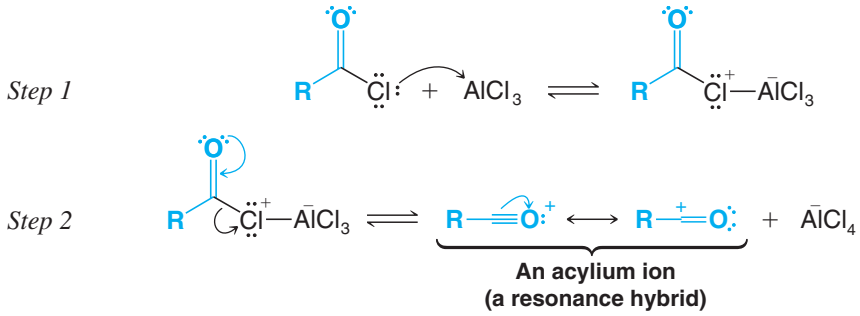




Friedel–Crafts acylations can also be carried out using carboxylic acid anhydrides. For example,



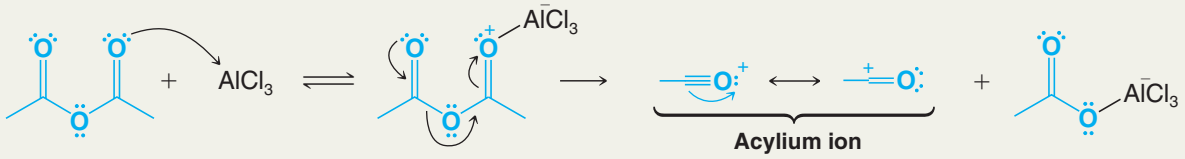
In most Friedel–Crafts acylations the electrophile appears to be an **acylium ion** formed from an acyl halide in the following way:



Solved Problem 15.1

Show how an acylium ion could be formed from acetic anhydride in the presence of $AlCl_3$.

STRATEGY AND ANSWER We recognize that $AlCl_3$ is a Lewis acid and that an acid anhydride, because it has multiple unshared electron pairs, is a Lewis base. A reasonable mechanism starts with a Lewis acid–base reaction and proceeds to form an acylium ion in the following way.

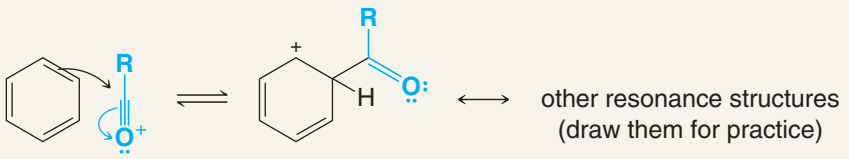


The remaining steps in the Friedel–Crafts acylation of benzene are the following:

A MECHANISM FOR THE REACTION

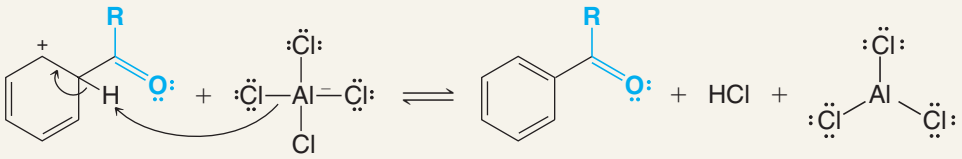
Friedel–Crafts Acylation

Step 3



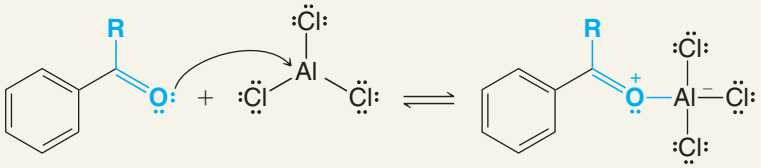
The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

Step 4



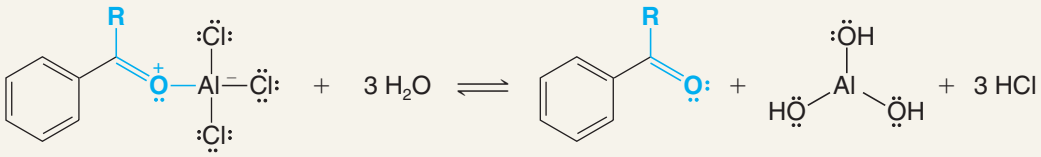
A proton is removed from the arenium ion, forming the aryl ketone.

Step 5



The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

Step 6



Treating the complex with water liberates the ketone and hydrolyzes the Lewis acid.

Several important synthetic applications of the Friedel–Crafts reaction are given in Section 15.9.

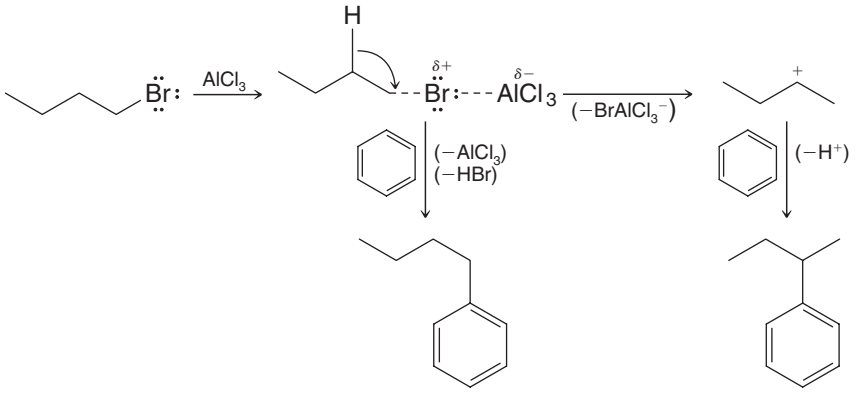
15.8 *Limitations of Friedel–Crafts Reactions*

Several restrictions limit the usefulness of Friedel–Crafts reactions:

1. **When the carbocation formed from an alkyl halide, alkene, or alcohol can rearrange to one or more carbocations that are more stable, it usually does so, and the major products obtained from the reaction are usually those from the more stable carbocations.**

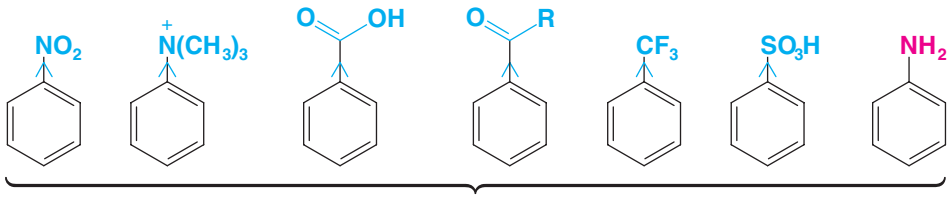
   When benzene is alkylated with butyl bromide, for example, some of the developing butyl cations rearrange by a hydride shift. Some of the developing 1° carbocations (see following reactions) become more stable 2° carbocations.

Then benzene reacts with both kinds of carbocations to form both butylbenzene and *sec*-butylbenzene:



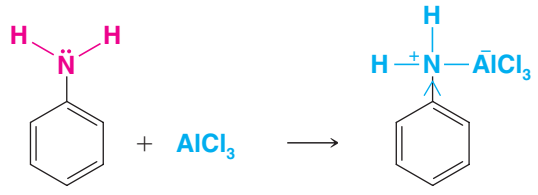
Butylbenzene (32–36% of mixture) **sec-Butylbenzene (64–68% of mixture)**

2. **Friedel–Crafts reactions usually give poor yields when powerful electron-withdrawing groups** (Section 15.11) **are present on the aromatic ring or when the ring bears an** —NH_2, —NHR, **or** —NR_2 **group**. This applies to both alkylations and acylations.



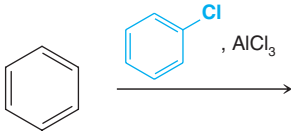
These usually give poor yields in Friedel-Crafts reactions.

We shall learn in Section 15.10 that groups present on an aromatic ring can have a large effect on the reactivity of the ring toward electrophilic aromatic substitution. **Electron-withdrawing groups make the ring less reactive by making it electron deficient**. Any substituent more electron withdrawing (or deactivating) than a halogen, that is, **any meta-directing group** (Section 15.11C), **makes an aromatic ring too electron deficient to undergo a Friedel–Crafts reaction**. The amino groups, —NH_2, —NHR, and —NR_2, are changed into powerful electron-withdrawing groups by the Lewis acids used to catalyze Friedel–Crafts reactions. For example,

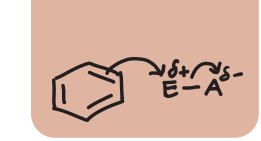


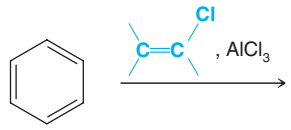
Does not undergo a Friedel-Crafts reaction

3. **Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily** (see Section 6.14A):



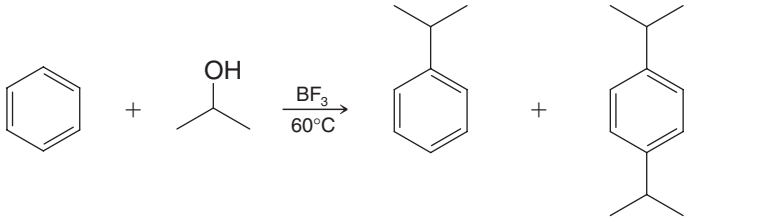
No Friedel-Crafts reaction because the halide is aryl





No Friedel-Crafts reaction because the halide is vinylic

4. **Polyalkylations often occur.** Alkyl groups are electron-releasing groups, and once one is introduced into the benzene ring, it activates the ring toward further substitution (see Section 15.10):



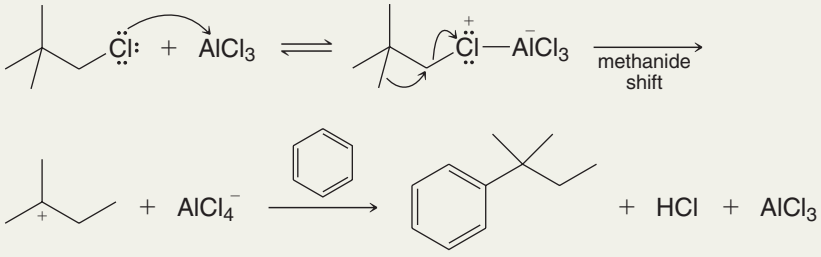
Isopropylbenzene (24%) **p-Diisopropylbenzene (14%)**

Polyacylations are not a problem in Friedel–Crafts acylations, however. The acyl group (RCO—) by itself is an electron-withdrawing group, and when it forms a complex with $AlCl_3$ in the last step of the reaction (Section 15.7), it is made even more electron withdrawing. This strongly inhibits further substitution and makes monoacylation easy.

Solved Problem 15.2

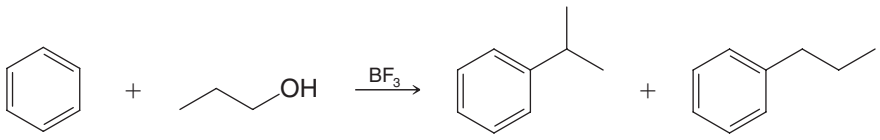
When benzene reacts with 1-chloro-2,2-dimethylpropane (neopentyl chloride) in the presence of aluminum chloride, the major product is 2-methyl-2-phenylbutane, not 2,2-dimethyl-1-phenylpropane (neopentylbenzene). Explain this result.

STRATEGY AND ANSWER The carbocation formed by direct reaction of $AlCl_3$ with 1-chloro-2,2-dimethylpropane would be a primary carbocation; however, it rearranges to the more stable tertiary carbocation before it can react with the benzene ring.



Review Problem 15.4

Provide a mechanism that accounts for the following result.

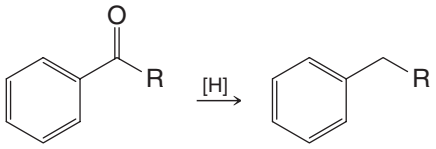


15.9 Synthetic Applications of Friedel–Crafts Acylations: The Clemmensen Reduction

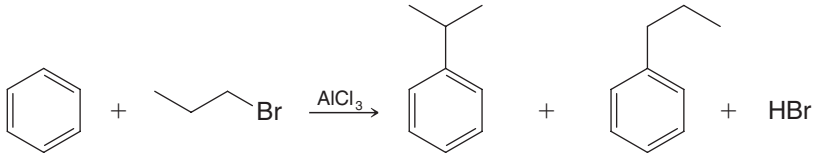
- Rearrangements of the carbon chain do not occur in Friedel–Crafts acylations.

The acylium ion, because it is stabilized by resonance, is more stable than most other carbocations. Thus, there is no driving force for a rearrangement. Because rearrangements do not occur, Friedel–Crafts acylations followed by reduction of the carbonyl group to a CH_2 group often give us much better routes to unbranched alkylbenzenes than do Friedel–Crafts alkylations.

- The carbonyl group of an aryl ketone can be reduced to a CH_2 group.

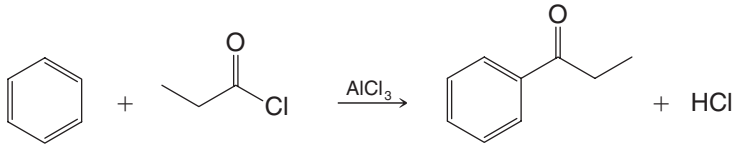


As an example, let us consider the problem of synthesizing propylbenzene. If we attempt this synthesis through a Friedel–Crafts alkylation, a rearrangement occurs and the major product is isopropylbenzene (see also Review Problem 15.4):



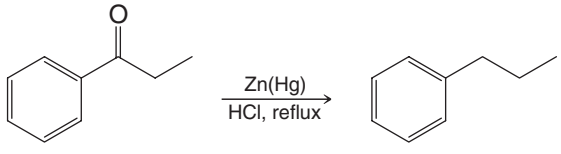
Isopropylbenzene (major product) **Propylbenzene (minor product)**

By contrast, the Friedel–Crafts acylation of benzene with propanoyl chloride produces a ketone with an unrearranged carbon chain in excellent yield:



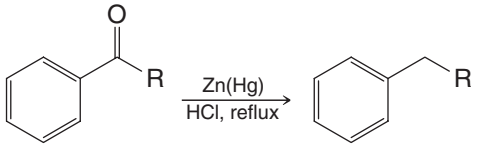
Propanoyl chloride **Ethyl phenyl ketone (90%)**

This ketone can then be reduced to propylbenzene by several methods. One general method—called the **Clemmensen reduction**—consists of refluxing the ketone with hydrochloric acid containing amalgamated zinc. [*Caution*: As we shall discuss later (Section 20.4B), zinc and hydrochloric acid will also reduce nitro groups to amino groups.]



Ethyl phenyl ketone **Propylbenzene (80%)**

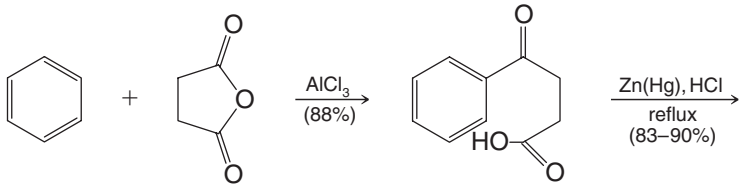
In general,



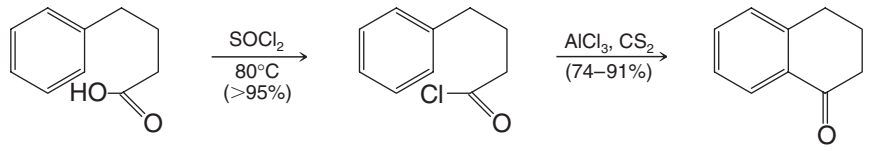
Helpful Hint

Friedel–Crafts acylation followed by ketone reduction is the synthetic equivalent of Friedel–Crafts alkylation.

When cyclic anhydrides are used as one component, the Friedel–Crafts acylation provides a means of adding a new ring to an aromatic compound. One illustration is shown here. Note that only the ketone is reduced in the Clemmensen reduction step. The carboxylic acid is unaffected:



Benzene (excess) + **Succinic anhydride** → **3-Benzoylpropanoic acid**



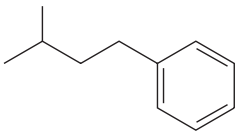
4-Phenylbutanoic acid → **4-Phenylbutanoyl chloride** → ***α*-Tetralone**

Review Problem 15.5

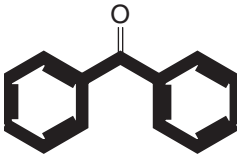
Starting with benzene and the appropriate acyl chloride or acid anhydride, outline a synthesis of each of the following:

(a) Butylbenzene

(b)

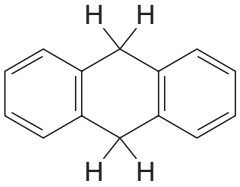


(c)



Benzophenone

(d)



9,10-Dihydroanthracene

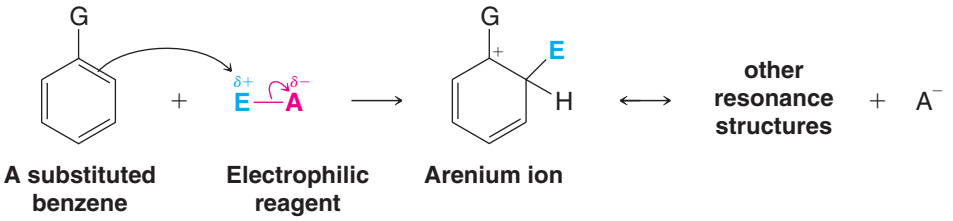
15.10 *Substituents Can Affect Both the Reactivity of the Ring and the Orientation of the Incoming Group*

A substituent group already present on a benzene ring can affect both the **reactivity** of the ring toward electrophilic substitution and the **orientation** that the incoming group takes on the ring.

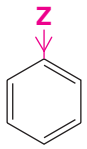
- A substituent can make the ring **more reactive** than benzene (i.e., it can make the compound react faster than benzene reacts). Such a group is called an **activating group**.
- A substituent can make the ring **less reactive** than benzene (i.e., it can make the compound react more slowly than benzene reacts). Such groups are called **deactivating groups**.

15.10A How Do Substituents Affect Reactivity?

Recall from Fig. 15.3 and Section 15.2 that the slow step in electrophilic aromatic substitution, the step that determines the overall rate of reaction, is the first step. In this step an electron-seeking reagent reacts by accepting an electron pair from the benzene ring.

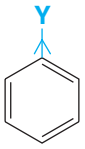


If a substituent that is already present on the ring makes the ring more electron rich by donating electrons to it, then the ring will be more reactive toward the electrophile and the reaction will take place faster.



If Z donates electrons the ring is more electron rich and it reacts faster with an electrophile.

On the other hand, if the substituent on the ring withdraws electrons, the ring will be electron poor and an electrophile will react with the ring more slowly.

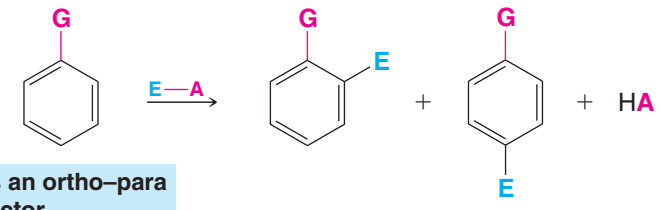


If Y withdraws electrons the ring is electron poor and it reacts more slowly with an electrophile.

15.10B Ortho–Para-Directing Groups and Meta-Directing Groups

A substituent on the ring can also affect the **orientation** that the incoming group takes when it replaces a hydrogen atom on the ring. Substituents fall into two general classes:

- **Ortho–para directors** predominantly direct the incoming group to a position ortho or para to itself.

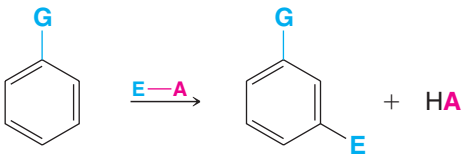


G is an ortho–para director.

Ortho product

Para product

- **Meta directors** predominantly direct the incoming group to a position meta to itself.



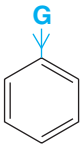
G is a meta director.

Meta product

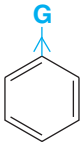
15.10C Electron-Donating and Electron-Withdrawing Substituents

Whether a substituent is an activating group or a deactivating group, and whether it is an ortho–para director or a meta director, depends largely on whether the substituent donates electrons to the ring or whether it withdraws electrons.

- All electron-donating groups are activating groups and all are ortho–para directors.
- With the exception of halogen substituents, all electron-withdrawing groups are deactivating groups and all are meta directors.
- Halogen substituents are weakly deactivating groups and are ortho–para directors.



If G donates electrons the ring is activated; it reacts faster, and at an ortho or para position.



If G withdraws electrons the ring is deactivated; it reacts more slowly, and at a meta position (except when G is a halogen).

15.10D Groups: Ortho–Para Directors

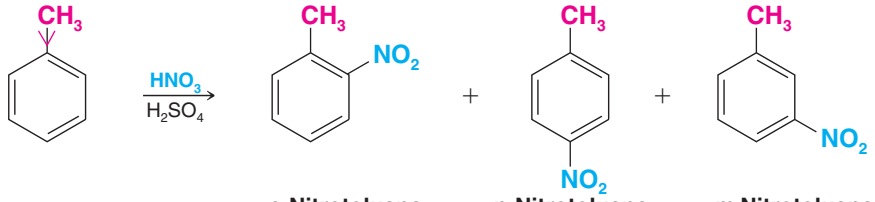
- Alkyl substituents are electron-donating groups and they are **activating** groups. They are also **ortho–para directors**.

Toluene, for example, reacts considerably faster than benzene in all electrophilic substitutions:

Toluene is more reactive than benzene toward electrophilic substitution.

We observe the greater reactivity of toluene in several ways. We find, for example, that with toluene, milder conditions—lower temperatures and lower concentrations of the electrophile—can be used in electrophilic substitutions than with benzene. We also find that under the same conditions toluene reacts faster than benzene. In nitration, for example, toluene reacts 25 times as fast as benzene.

We find, moreover, that when toluene undergoes electrophilic substitution, most of the substitution takes place at its ortho and para positions. When we nitrate toluene with nitric and sulfuric acids, we get mononitrotoluenes in the following relative proportions:



***o*-Nitrotoluene (59%)** + ***p*-Nitrotoluene (37%)** + ***m*-Nitrotoluene (4%)**

Of the mononitrotoluenes obtained from the reaction, 96% (59% + 37%) have the nitro group in an ortho or para position. Only 4% have the nitro group in a meta position.

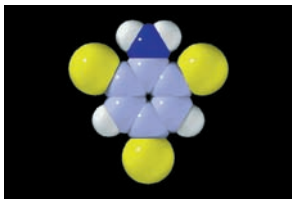
Explain how the percentages just given show that the methyl group exerts an ortho–para directive effect by considering the percentages that would be obtained if the methyl group had no effect on the orientation of the incoming electrophile.

Review Problem 15.6

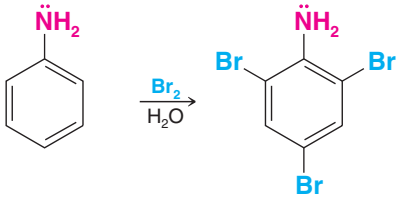
Predominant substitution of toluene at the ortho and para positions is not restricted to nitration reactions. The same behavior is observed in halogenation, sulfonation, and so forth.

- Groups that have an unshared electron pair on the atom attached to the aromatic ring, such as amino, hydroxyl, alkoxyl, and amides or esters with the oxygen or nitrogen directly bonded to the ring, are powerful activating groups and are strong ortho–para directors.

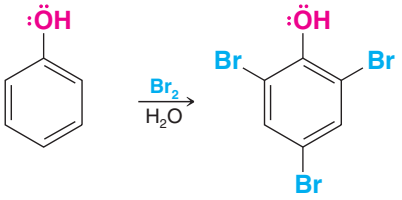
Phenol and aniline react with bromine in water (no catalyst is required) at room temperature to produce compounds in which both of the ortho positions and the para position become substituted.



2,4,6-Tribromoaniline



2,4,6-Tribromoaniline
(~100%)

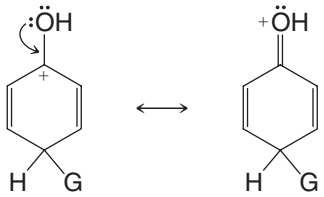


2,4,6-Tribromophenol
(~100%)

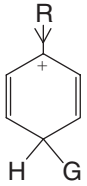
- In general, substituent groups with unshared electron pairs on the atom adjacent to the benzene ring (e.g., hydroxyl, amino) are stronger activating groups than groups without unshared electron pairs (i.e., alkyl groups).
- Contribution of electron density to the benzene ring through resonance is generally stronger than through an inductive effect.

As a corollary, even though amides and esters have an unshared electron pair on the atom adjacent to the ring, their activating effect is diminished because the carbonyl group provides a resonance structure where electron density is directed away from the benzene ring. This makes amides and esters less activating than groups where the only resonance possibilities involve donation of electron density toward the benzene ring.

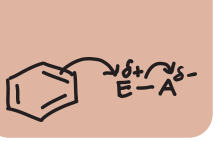
Examples of arenium ion stabilization by resonance and inductive effects

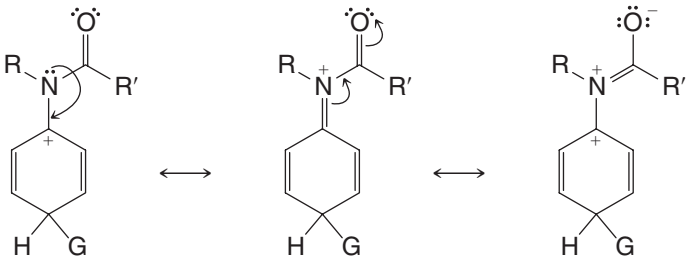


Electron donation through resonance



Electron donation through the inductive effect



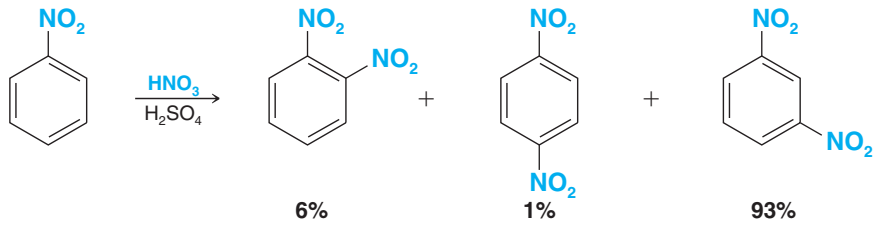


Electron donation to the ring by resonance is reduced when there is an alternative resonance pathway away from the ring.

15.10E Deactivating Groups: Meta Directors

- The nitro group is a very strong **deactivating group** and, because of the combined electronegativities of the nitrogen and oxygen atoms, it is a powerful electron-withdrawing group.

Nitrobenzene undergoes nitration at a rate only 10^{-4} times that of benzene. The nitro group is a **meta director**. When nitrobenzene is nitrated with nitric and sulfuric acids, 93% of the substitution occurs at the meta position:



- The carboxyl group (—CO_2H), the sulfonic acid group (—SO_3H), and the trifluoromethyl group (—CF_3) are also deactivating groups; they are also meta directors.

15.10F Halo Substituents: Deactivating Ortho–Para Directors

- The chloro and bromo groups are ortho–para directors. However, even though they contain unshared electron pairs, they are deactivating toward electrophilic aromatic substitution because of the electronegative effect of the halogens.

Chlorobenzene and bromobenzene, for example, undergo nitration at a rate approximately 30 times slower than benzene. The relative percentages of monosubstituted products that are obtained when chlorobenzene is chlorinated, brominated, nitrated, or sulfonated are shown in Table 15.1.

TABLE 15.1 Electrophilic Substitutions of Chlorobenzene

Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

Similar results are obtained from electrophilic substitutions of bromobenzene.

15.10G Classification of Substituents

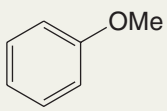
A summary of the effects of some substituents on reactivity and orientation is provided in Table 15.2.

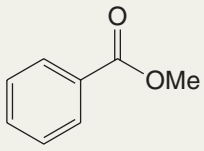
TABLE 15.2 Effect of Substituents on Electrophilic Aromatic Substitution

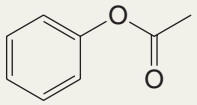
Ortho–Para Directors	Meta Directors
Strongly Activating —$\ddot{N}H_2$, —$\ddot{N}HR$, —$\ddot{N}R_2$ —$\ddot{O}H$, —$\ddot{O}:^-$	**Moderately Deactivating** —C≡N —SO_3H
Moderately Activating —NH—C(=O)—R —O—C(=O)—R, —O—R	—C(=O)—OH, —C(=O)—OR —C(=O)—H, —C(=O)—R
Weakly Activating —R (alkyl) —C_6H_5 (phenyl)	**Strongly Deactivating** —NO_2 —NR_3^+ —CF_3, —CCl_3
Weakly Deactivating —$\ddot{F}:$, —$\ddot{Cl}:$, —$\ddot{Br}:$, —$\ddot{I}:$	

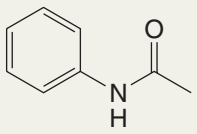
Solved Problem 15.3

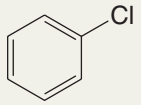
Label each of the following aromatic rings as activated or deactivated based on the substituent attached, and state whether the group is an ortho–para or meta director.

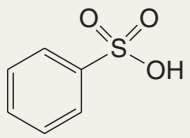
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

STRATEGY AND ANSWER If a substituent donates electron density it will activate the ring and cause ortho and para substitution. If a substituent withdraws electron density it will deactivate the ring and cause meta substitution (except for halogens, which are electron withdrawing but cause ortho–para substitution). (a) Activated; an ether is an ortho–para director; (b) deactivated; the ester carbonyl is a meta director; (c) activated; the single-bonded oxygen of the ester is directly bonded to the ring, and therefore it is an ortho–para director; (d) activated; the amide nitrogen is an ortho–para director; (e) deactivated; however, the halogen is ortho–para director through resonance; (f) deactivated; the sulfonate group is a meta director.

Review Problem 15.7

Predict the major products formed when:

(a) Toluene is sulfonated.

(b) Benzoic acid is nitrated.

(c) Nitrobenzene is brominated.

(d) Isopropylbenzene reacts with acetyl chloride and $AlCl_3$.

If the major products would be a mixture of ortho and para isomers, you should so state.

15.11 How Substituents Affect Electrophilic Aromatic Substitution: A Closer Look

15.11A Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

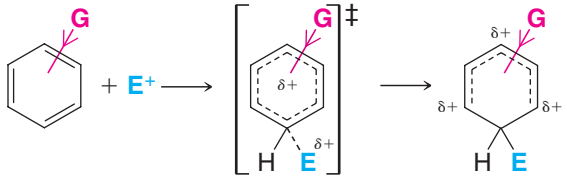
- We can account for relative reaction rates by examining the transition state for the rate-determining steps.

We know that any factor that increases the energy of the transition state relative to that of the reactants decreases the relative rate of the reaction. It does this because it increases the free energy of activation of the reaction. In the same way, any factor that decreases the energy of the transition state relative to that of the reactants lowers the free energy of activation and increases the relative rate of the reaction.

The rate-determining step in electrophilic substitutions of substituted benzenes is the step that results in the formation of the arenium ion. We can write the formula for a substituted benzene in a generalized way if we use the letter G to represent any ring substituent, including hydrogen.

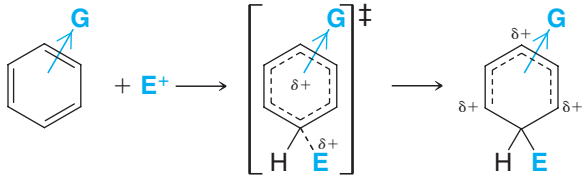
When we examine this step for a large number of reactions, we find that the relative rates of the reactions depend on whether G **withdraws** or **releases** electrons.

- If G is an electron-releasing group (relative to hydrogen), the reaction occurs faster than the corresponding reaction of benzene.
- If G is an electron-withdrawing group, the reaction is slower than that of benzene:



G releases electrons. Transition state is stabilized. Arenium ion is stabilized.

When G is electron donating, the reaction is faster.



G withdraws electrons. Transition state is destabilized. Arenium ion is destabilized.

When G is electron withdrawing, the reaction is slower.

It appears, then, that the substituent (G) must affect the stability of the transition state relative to that of the reactants. Electron-releasing groups apparently make the transition state more stable, whereas electron-withdrawing groups make it less stable. That this is so is entirely reasonable, because the transition state resembles the arenium ion, and the arenium ion is a delocalized *carbocation*.

This effect illustrates another application of the Hammond–Leffler postulate (Section 6.13A). The arenium ion is a high-energy intermediate, and the step that leads to it is a *highly endothermic step*. Thus, according to the Hammond–Leffler postulate, there should be a strong resemblance between the arenium ion itself and the transition state leading to it.

Since the arenium ion is positively charged, we would expect an electron-releasing group to stabilize the arenium ion *and the transition state leading to it* , for the transition state is a developing delocalized carbocation. We can make the same kind of arguments about the effect of electron-withdrawing groups. An electron-withdrawing group should make the arenium ion *less stable*, and in a corresponding way it should make the transition state leading to the arenium ion *less stable*.

Figure 15.4 shows how the electron-withdrawing and electron-releasing abilities of substituents affect the relative free energies of activation of electrophilic aromatic substitution reactions.

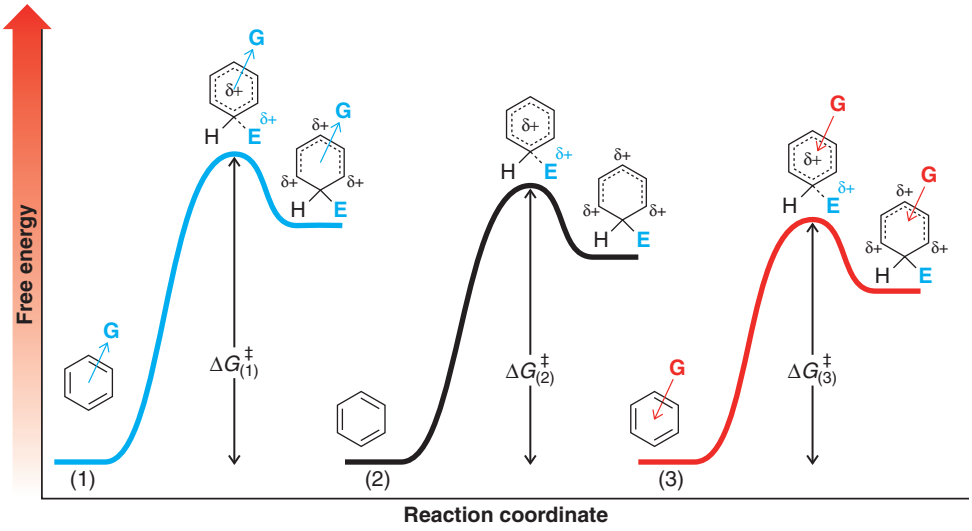


Figure 15.4 A comparison of free-energy profiles for arenium ion formation in a ring with an electron-withdrawing substituent (≻ G), no substituent, and an electon-donating substituent (≺ G). In (1) (blue energy profile), the electron-withdrawing group G raises the transition state energy. The energy of activation barrier is the highest, and therefore the reaction is the slowest. Reaction (2), with no substituent, serves as a reference for comparison. In (3) (red energy profile), an electron-donating group G stabilizes the transition state. The energy of activation barrier is lowest, and therefore the reaction is the fastest.

Calculated electrostatic potential maps for two arenium ions comparing the charge-stabilizing effect of an electron-donating methyl group with the charge-destabilizing effect of an electron-withdrawing trifluoromethyl group are shown in Fig. 15.5. The arenium ion at the left (Fig. 15.5*a*) is that from electrophilic addition of bromine to methylbenzene (toluene) at the para position. The arenium ion at the right (Fig. 15.5*b*) is that from electrophilic addition of bromine to trifluoromethylbenzene at the meta position. Notice that the atoms of the ring in Fig. 15.5*a* have much less blue color associated with them, showing that they are much less positive and that the ring is stabilized.

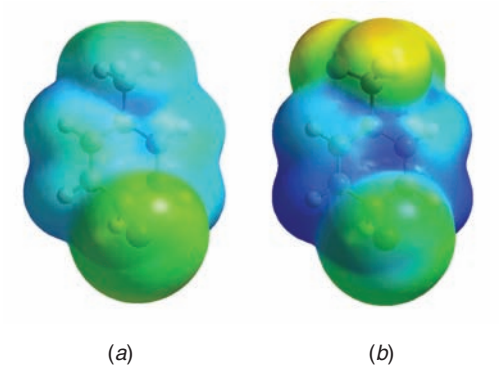
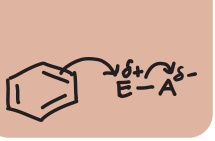


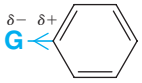
Figure 15.5 Calculated electrostatic potential maps for the arenium ions from electrophilic addition of bromine to *(a)* methylbenzene (toluene) and *(b)* trifluoromethylbenzene. The positive charge in the arenium ion ring of methylbenzene *(a)* is delocalized by the electron-releasing ability of the methyl group, whereas the positive charge in the arenium ion of trifluoromethylbenzene *(b)* is enhanced by the electron-withdrawing effect of the trifluoromethyl group. (The electrostatic potential maps for the two structures use the same color scale with respect to potential so that they can be directly compared.)

15.11B Inductive and Resonance Effects: Theory of Orientation

We can account for the electron-withdrawing and electron-releasing properties of groups on the basis of two factors: *inductive effects* and *resonance effects*. We shall also see that these two factors determine orientation in aromatic substitution reactions.

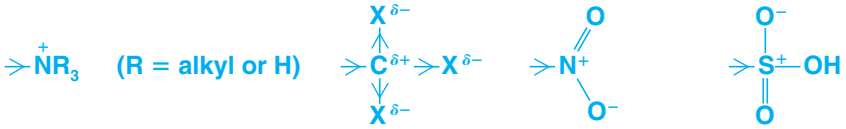


Inductive Effects The **inductive effect** of a substituent G arises from the electrostatic interaction of the polarized bond to G with the developing positive charge in the ring as it is attacked by an electrophile. If, for example, G is a more electronegative atom (or group) than carbon, then the ring will be at the positive end of the dipole:



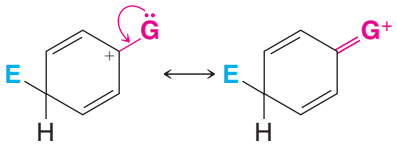
(e.g., G = F, Cl, or Br)

Attack by an electrophile will be slowed because this will lead to an additional full positive charge on the ring. The halogens are all more electronegative than carbon and exert an electron-withdrawing inductive effect. Other groups have an electron-withdrawing inductive effect because the atom directly attached to the ring bears a full or partial positive charge. Examples are the following:



Electron-withdrawing groups with a full or partial charge on the atom attached to the ring

Resonance Effects The **resonance effect** of a substituent G refers to the possibility that the presence of G may increase or decrease the resonance stabilization of the intermediate arenium ion. The G substituent may, for example, cause one of the three contributors to the resonance hybrid for the arenium ion to be better or worse than the case when G is hydrogen. Moreover, when G is an atom bearing one or more nonbonding electron pairs, it may lend extra stability to the arenium ion by providing a *fourth* resonance contributor in which the positive charge resides on G:



This electron-donating resonance effect applies with decreasing strength in the following order:

This is also the order of the activating ability of these groups.

- Amino groups are highly activating, hydroxyl and alkoxyl groups are somewhat less activating, and halogen substituents are weakly deactivating.

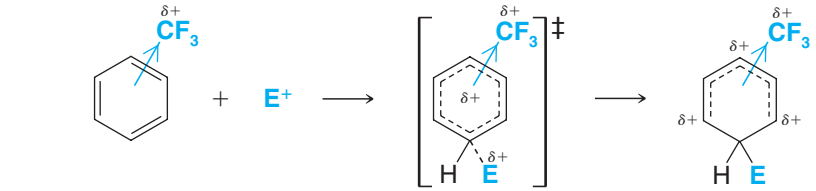
When X = F, this order can be related to the electronegativity of the atoms with the nonbonding pair. The more electronegative the atom is, the less able it is to accept the positive charge (fluorine is the most electronegative, nitrogen the least). When X = Cl, Br, or I, the relatively poor electron-donating ability of the halogens by resonance is understandable on a different basis. These atoms (Cl, Br, and I) are all larger than carbon, and, therefore, the orbitals that contain the nonbonding pairs are further from the nucleus and do not overlap well with the 2*p* orbital of carbon. (This is a general phenomenon: Resonance effects are not transmitted well between atoms of different rows in the periodic table.)

15.11C Meta-Directing Groups

- All meta-directing groups have either a partial positive charge or a full positive charge on the atom directly attached to the ring.

As a typical example let us consider the trifluoromethyl group. The trifluoromethyl group, because of the three highly electronegative fluorine atoms, is strongly electron withdrawing. It is a strong deactivating group and a powerful meta director in electrophilic aromatic substitution reactions. We can account for both of these characteristics of the trifluoromethyl group in the following way.

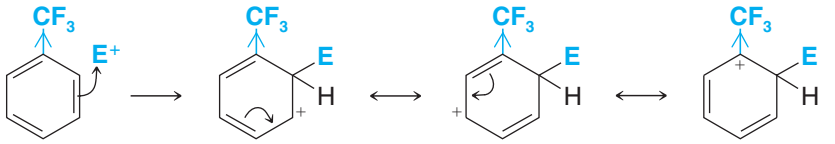
The trifluoromethyl group affects the rate of reaction by causing the transition state leading to the arenium ion to be highly unstable. It does this by withdrawing electrons from the developing carbocation, thus increasing the positive charge on the ring:



Trifluoromethylbenzene **Transition state** **Arenium ion**

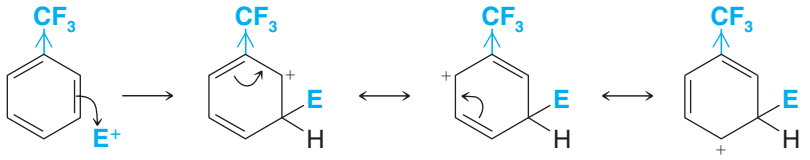
We can understand how the trifluoromethyl group affects *orientation* in electrophilic aromatic substitution if we examine the resonance structures for the arenium ion that would be formed when an electrophile attacks the ortho, meta, and para positions of trifluoromethylbenzene.

Ortho Attack

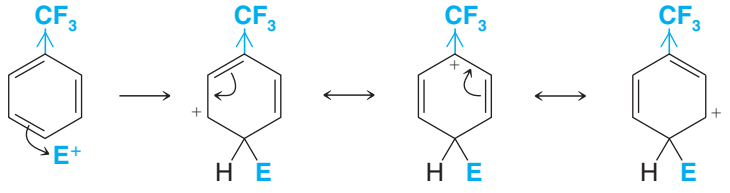


Highly unstable contributor

Meta Attack



Para Attack

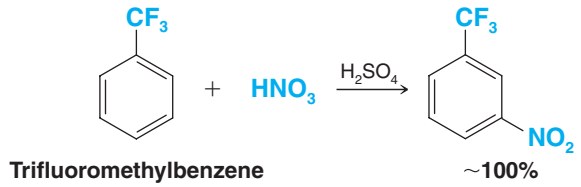


Highly unstable contributor

- The arenium ion arising from ortho and para attack each has *one contributing structure that is highly unstable relative to all the others because the positive charge is located on the ring carbon that bears the electron-withdrawing group.*

- The arenium ion arising from meta attack has *no* such highly unstable resonance structure.
- By the usual reasoning we would also expect the transition state leading to the meta-substituted arenium ion to be the least unstable and, therefore, that meta attack would be favored.

This is exactly what we find experimentally. The trifluoromethyl group is a powerful meta director:



Trifluoromethylbenzene **~100%**

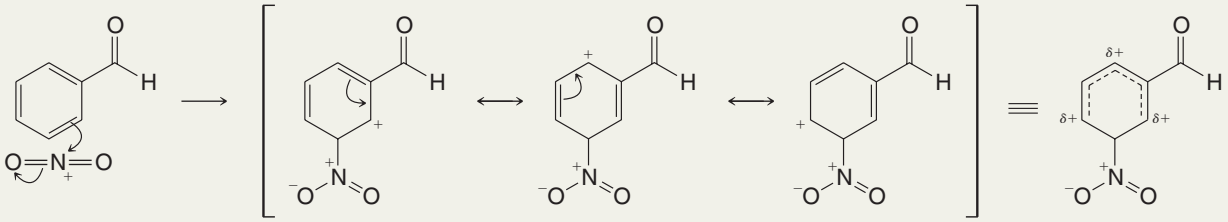
Bear in mind, however, that meta substitution is favored only in the sense that *it is the least unfavorable of three unfavorable pathways*. The free energy of activation for substitution at the meta position of trifluoromethylbenzene is less than that for attack at an ortho or para position, but it is still far greater than that for an attack on benzene. Substitution occurs at the meta position of trifluoromethylbenzene faster than substitution takes place at the ortho and para positions, but it occurs much more slowly than it does with benzene.

- The nitro group, the carboxyl group, and other meta-directing groups (see Table 15.2) are all powerful electron-withdrawing groups and act in a similar way.

Solved Problem 15.4

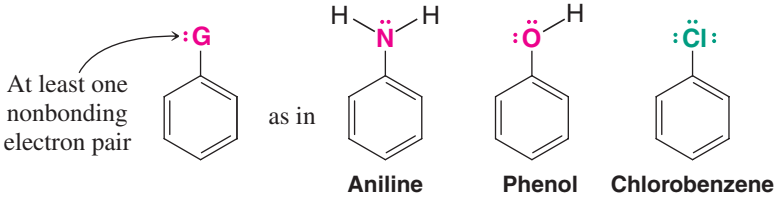
Write contributing resonance structures and the resonance hybrid for the arenium ion formed when benzaldehyde undergoes nitration at the meta position.

STRATEGY AND ANSWER



15.11D Ortho–Para-Directing Groups

Except for the alkyl and phenyl substituents, all of the ortho–para-directing groups in Table 15.2 are of the following general type:



Aniline **Phenol** **Chlorobenzene**

This structural feature—an unshared electron pair on the atom adjacent to the ring—determines the orientation and influences reactivity in electrophilic substitution reactions.

The *directive effect* of groups with an unshared pair is predominantly caused by an electron-releasing resonance effect. The resonance effect, moreover, operates primarily in the arenium ion and, consequently, in the transition state leading to it.

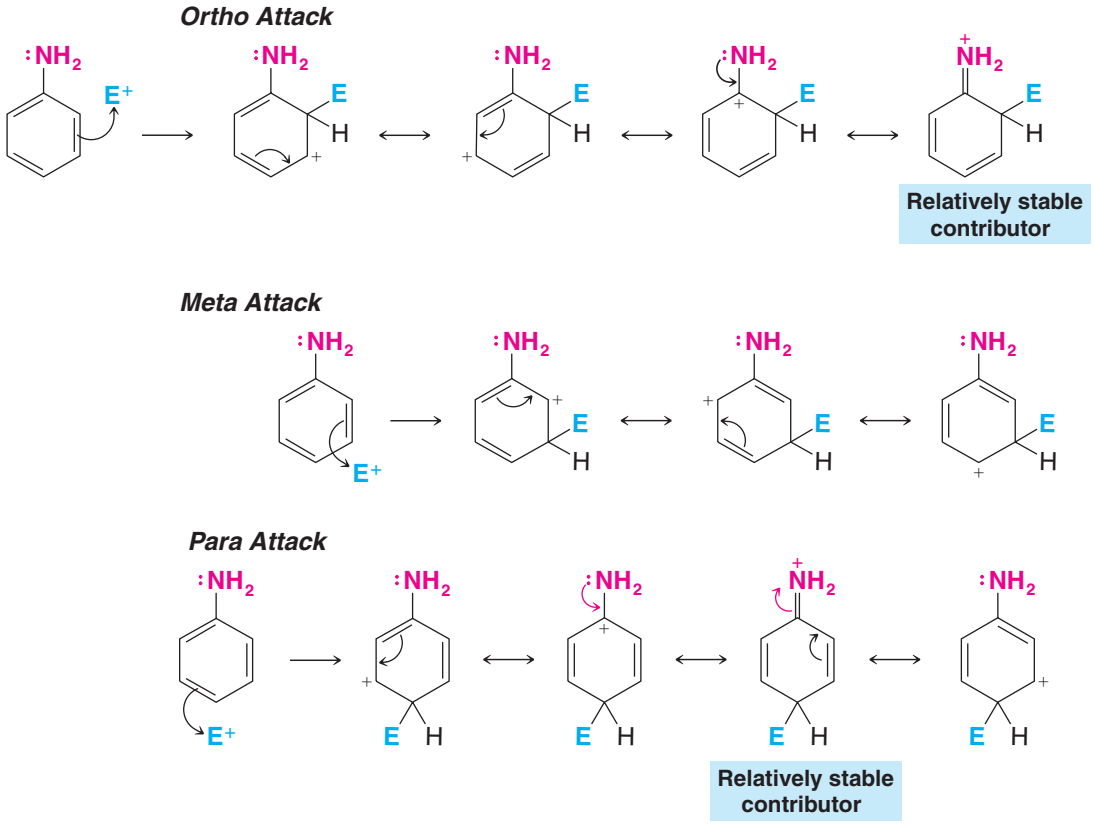
Except for the halogens, the primary effect of these groups on relative reactivity of the benzene ring is also caused by an electron-releasing resonance effect. And, again, this effect operates primarily in the transition state leading to the arenium ion.

In order to understand these resonance effects, let us begin by recalling the effect of the amino group on electrophilic aromatic substitution reactions. The amino group is not only a powerful activating group, it is also a powerful ortho–para director. We saw earlier (Section 15.10D) that aniline reacts with bromine in aqueous solution at room temperature and in the absence of a catalyst to yield a product in which both ortho positions and the para position are substituted.

The inductive effect of the amino group makes it slightly electron withdrawing. Nitrogen, as we know, is more electronegative than carbon. The difference between the electronegativities of nitrogen and carbon in aniline is not large, however, because the carbon of the benzene ring is sp^2 hybridized and so it is somewhat more electronegative than it would be if it were sp^3 hybridized.

- The resonance effect of the amino group is far more important than its inductive effect in electrophilic aromatic substitution, and this resonance effect makes the amino group electron releasing.

We can understand this effect if we write the resonance structures for the arenium ions that would arise from ortho, meta, and para attack on aniline:



Four reasonable resonance structures can be written for the arenium ions resulting from ortho and para attack, whereas only three can be written for the arenium ion that results from meta attack. This, in itself, suggests that the ortho- and para-substituted arenium ions should be more stable. Of greater importance, however, are the relatively stable structures that contribute to the hybrid for the ortho- and para-substituted arenium ions. In these structures, nonbonding pairs of electrons from nitrogen form an additional covalent bond to the carbon of the ring. This extra bond—and the fact that every atom in each of these structures has a complete outer octet of electrons—makes these structures the most stable of all of the contributors. Because

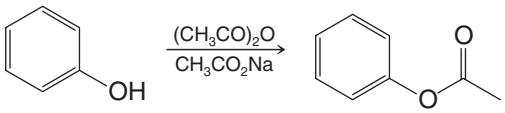
these structures are unusually stable, they make a large—*and stabilizing*—contribution to the hybrid. This means, of course, that the ortho- and para-substituted arenium ions themselves are considerably more stable than the arenium ion that results from the meta attack. The transition states leading to the ortho- and para-substituted arenium ions occur at unusually low free energies. As a result, electrophiles react at the ortho and para positions very rapidly.

Review Problem 15.8

Use resonance theory to explain why the hydroxyl group of phenol is an activating group and an ortho–para director. Illustrate your explanation by showing the arenium ions formed when phenol reacts with a Br^+ ion at the ortho, meta, and para positions.

Review Problem 15.9

Phenol reacts with acetic anhydride in the presence of sodium acetate to produce the ester phenyl acetate:



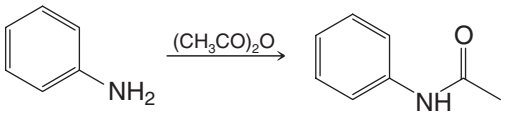
Phenol **Phenyl acetate**

The $CH_3COO—$ group of phenyl acetate, like the $—OH$ group of phenol (Review Problem 15.8), is an ortho–para director.

(a) What structural feature of the $CH_3COO—$ group explains this?

(b) Phenyl acetate, although undergoing reaction at the ortho and para positions, is less reactive toward electrophilic aromatic substitution than phenol. Use resonance theory to explain why this is so.

(c) Aniline is often so highly reactive toward electrophilic substitution that undesirable reactions take place (see Section 15.14A). One way to avoid these undesirable reactions is to convert aniline to acetanilide (below) by treating aniline with acetyl chloride or acetic anhydride:



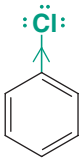
Aniline **Acetanilide**

What kind of directive effect would you expect the acetamido group ($CH_3CONH—$) to have?

(d) Explain why it is much less activating than the amino group, $—NH_2$.

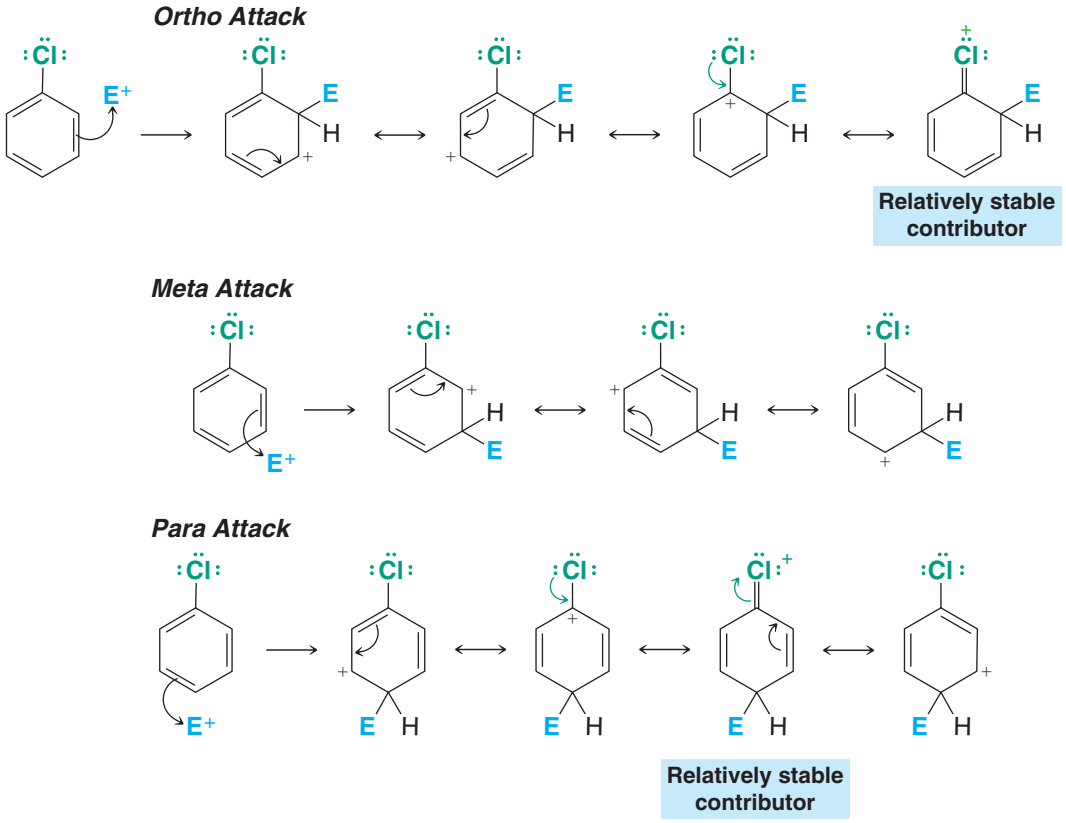
The directive and reactivity effects of halo substituents may, at first, seem to be contradictory. *The halo groups are the only ortho–para directors* (in Table 15.2) *that are deactivating groups*. [Because of this behavior we have color coded halogen substituents green rather than red (electron donating) or blue (electron withdrawing).] All other deactivating groups are meta directors. We can readily account for the behavior of halo substituents, however, if we assume that their electron-withdrawing inductive effect influences *reactivity* and their electron-donating resonance effect governs *orientation*.

Let us apply these assumptions specifically to chlorobenzene. The chlorine atom is highly electronegative. Thus, we would expect a chlorine atom to withdraw electrons from the benzene ring and thereby deactivate it:



The inductive effect of the chlorine atom deactivates the ring.

On the other hand, when electrophilic attack does take place, the chlorine atom stabilizes the arenium ions resulting from ortho and para attack relative to that from meta attack. The chlorine atom does this in the same way as amino groups and hydroxyl groups do—***by donating an unshared pair of electrons***. These electrons give rise to relatively stable resonance structures contributing to the hybrids for the ortho- and para-substituted arenium ions.



What we have said about chlorobenzene is also true of bromobenzene.

We can summarize the inductive and resonance effects of halo substituents in the following way.

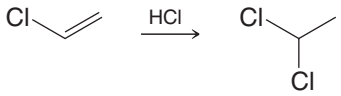
- Through their electron-withdrawing inductive effect, halo groups make the ring more electron deficient than that of benzene. This causes the free energy of activation for any electrophilic aromatic substitution reaction to be greater than that for benzene, and, therefore, halo groups are deactivating.
- Through their electron-donating resonance effect, however, halo substituents cause the free energies of activation leading to ortho and para substitution to be lower than the free energy of activation leading to meta substitution. This makes halo substituents ortho–para directors.

You may have noticed an apparent contradiction between the rationale offered for the unusual effects of the halogens and that offered earlier for amino or hydroxyl groups. That is, oxygen is *more* electronegative than chlorine or bromine (and especially iodine). Yet the hydroxyl group is an activating group, whereas halogens are deactivating groups. An explanation for this can be obtained if we consider the relative stabilizing contributions made to the transition state leading to the arenium ion by resonance structures involving a group —G (—G = —$\ddot{N}H_2$, —$\ddot{O}$—H, —$\ddot{F}$:, —$\ddot{C}l$:, —$\ddot{B}r$:, —$\ddot{I}$:) that is directly attached to the benzene ring in which $\ddot{G}$ donates an electron pair. If —$\ddot{G}$ is —$\ddot{O}$H or —$\ddot{N}H_2$, these resonance structures arise because of the overlap of a 2*p* orbital of carbon with that of oxygen or nitrogen. Such overlap is favorable because the atoms are almost the same size. With

chlorine, however, donation of an electron pair to the benzene ring requires overlap of a carbon 2*p* orbital with a chlorine 3*p* orbital. Such overlap is less effective; the chlorine atom is much larger and its 3*p* orbital is much further from its nucleus. With bromine and iodine, overlap is even less effective. Justification for this explanation can be found in the observation that fluorobenzene (G = —F:) is the most reactive halobenzene in spite of the high electronegativity of fluorine and the fact that —F: is the most powerful ortho–para director of the halogens. With fluorine, donation of an electron pair arises from overlap of a 2*p* orbital of fluorine with a 2*p* orbital of carbon (as with —NH_2 and —OH). This overlap is effective because the orbitals of =C< and —F: are of the same relative size.

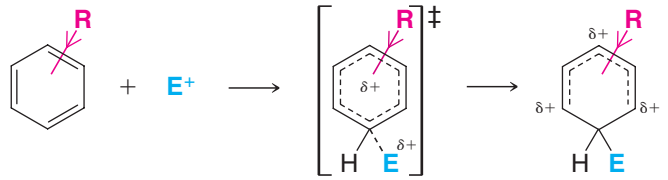
Review Problem 15.10

Chloroethene adds hydrogen chloride more slowly than ethene, and the product is 1,1-dichloroethane. How can you explain this using resonance and inductive effects?



15.11E Ortho–Para Direction and Reactivity of Alkylbenzenes

Alkyl groups are better electron-releasing groups than hydrogen. Because of this, they can activate a benzene ring toward electrophilic substitution by stabilizing the transition state leading to the arenium ion:



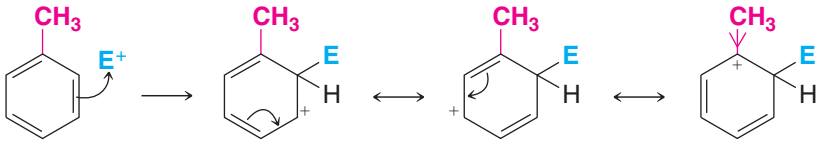
Transition state is stabilized. **Arenium ion is stabilized.**

For an alkylbenzene the free energy of activation of the step leading to the arenium ion (just shown) is lower than that for benzene, and alkylbenzenes react faster.

Alkyl groups are ortho–para directors. We can also account for this property of alkyl groups on the basis of their ability to release electrons—an effect that is particularly important when the alkyl group is attached directly to a carbon that bears a positive charge. (Recall the ability of alkyl groups to stabilize carbocations that we discussed in Section 6.11 and in Fig. 6.8.)

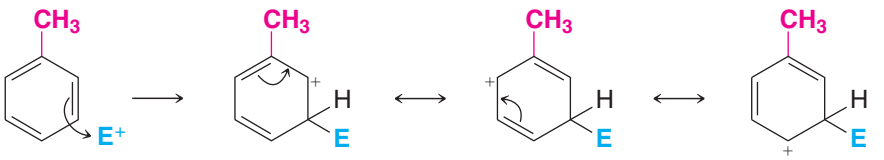
If, for example, we write resonance structures for the arenium ions formed when toluene undergoes electrophilic substitution, we get the results shown below:

Ortho Attack

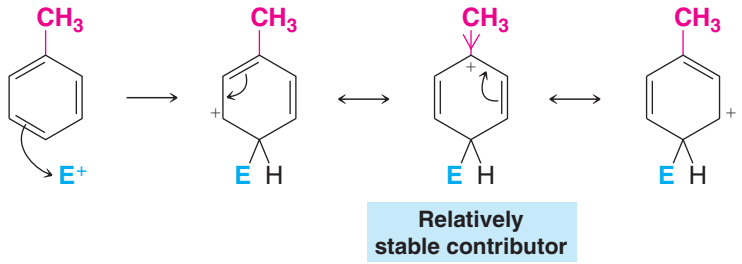


Relatively stable contributor

Meta Attack



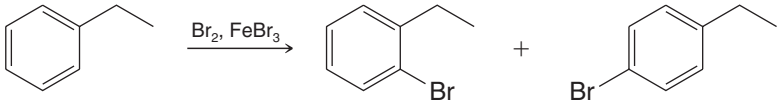
Para Attack



In ortho attack and para attack we find that we can write resonance structures in which the methyl group is directly attached to a positively charged carbon of the ring. These structures are more *stable* relative to any of the others because in them the stabilizing influence of the methyl group (by electron release) is most effective. These structures, therefore, make a large (stabilizing) contribution to the overall hybrid for ortho- and para-substituted arenium ions. No such relatively stable structure contributes to the hybrid for the meta-substituted arenium ion, and as a result it is less stable than the ortho- or para-substituted arenium ions. Since the ortho- and para-substituted arenium ions are more stable, the transition states leading to them occur at lower energy and ortho and para substitutions take place most rapidly.

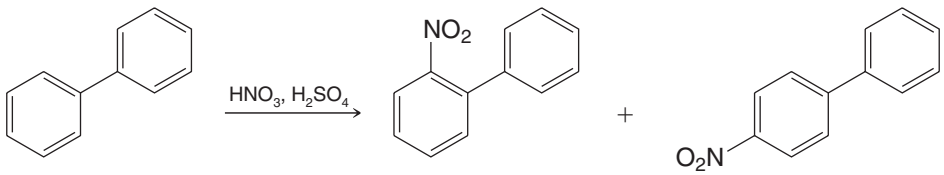
Review Problem 15.11

Write resonance structures for the arenium ions formed when ethylbenzene reacts with a Br^+ ion (as formed from $Br_2/FeBr_3$) to produce the following ortho and para products.



Review Problem 15.12

Provide a mechanism for the following reaction and explain why it occurs faster than nitration of benzene.

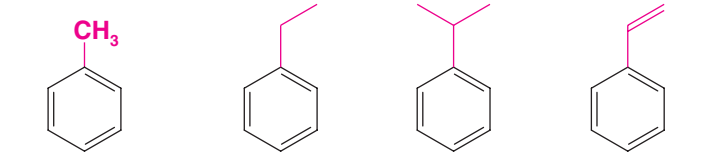


15.11F Summary of Substituent Effects on Orientation and Reactivity

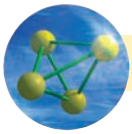
With a theoretical understanding now in hand of substituent effects on orientation and reactivity, we refer you back to Table 15.2 for a summary of specific groups and their effects.

15.12 *Reactions of the Side Chain of Alkylbenzenes*

Hydrocarbons that consist of both aliphatic and aromatic groups are also known as **arenes**. Toluene, ethylbenzene, and isopropylbenzene are **alkylbenzenes**:



Phenylethene, usually called styrene, is an example of an **alkenylbenzene**. The aliphatic portion of these compounds is commonly called the **side chain**.



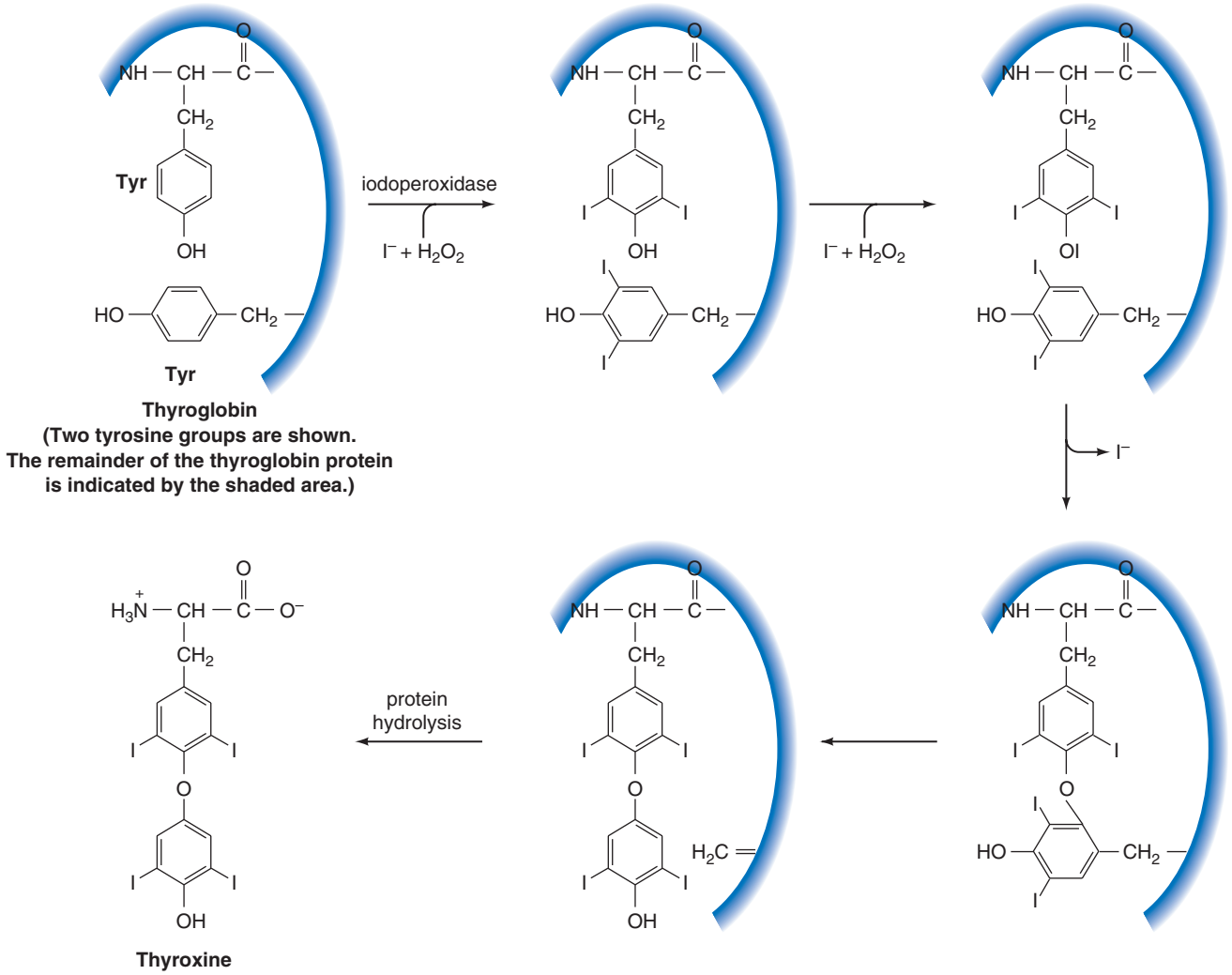
THE CHEMISTRY OF . . .

Iodine Incorporation in Thyroxine Biosynthesis

The biosynthesis of thyroxine involves introduction of iodine atoms into tyrosine units of thyroglobin. This process occurs by a biochemical version of electrophilic aromatic substitution. An iodoperoxidase enzyme catalyzes the reaction between iodide anions and hydrogen peroxide to generate an electrophilic form of iodine (presumably a species like I—OH). Nucleophilic attack by the aromatic ring of tyrosine on the electrophilic iodine leads to incorporation of iodine at the 3 and 5 positions of the tyrosine rings in thyroglobulin. These are the positions ortho to the phenol hydroxyl group, precisely where we would expect electrophilic aromatic substitution to occur in tyrosine. (Substitution para to the hydroxyl cannot occur in tyrosine because that position is blocked, and substitution ortho to the alkyl group is less favored than ortho to the hydroxyl.) Electrophilic iodine is also involved in the coupling of two tyrosine units necessary to complete biosynthesis of thyroxine.

Electrophilic aromatic substitution also plays a role in the 1927 laboratory synthesis of thyroxine by C. Harington and G. Barger. Their synthesis helped prove the structure of this important hormone by comparison of the synthetic material with natural thyroxine. Harington and Barger used electrophilic aromatic substitution to introduce the iodine atoms at the ortho positions in the phenol ring of thyroxine. They used a different reaction, however, to introduce the iodine atoms in the other ring of thyroxine (*nucleophilic* aromatic substitution—a reaction we shall study in Chapter 21.)

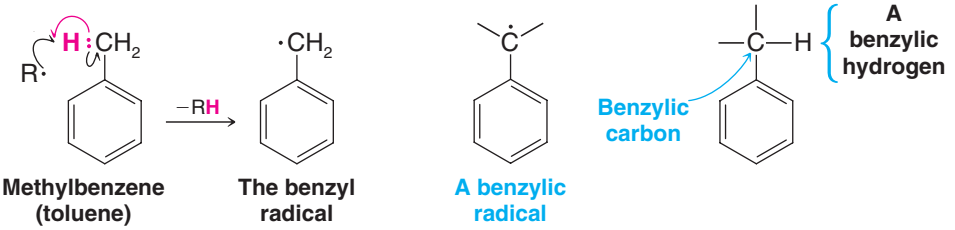
(Figure below adapted with permission of John Wiley & Sons, Inc. from Voet, D. and Voet, J. G., *Biochemistry*, 2nd edition. © 1995 Voet D. and Voet, J. G.)



The biosynthesis of thyroxine in the thyroid gland through the iodination, rearrangement, and hydrolysis (proteolysis) of thyroglobin Tyr residues. The relatively scarce I^- is actively sequestered by the thyroid gland.

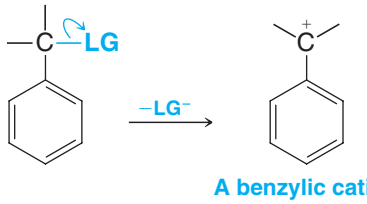
15.12A Benzylic Radicals and Cations

Hydrogen abstraction from the methyl group of methylbenzene (toluene) produces a radical called the **benzyl radical**:

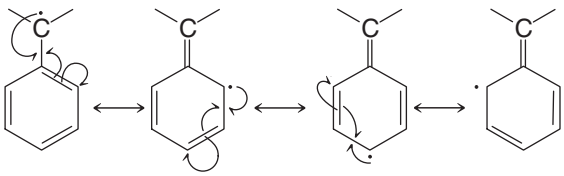


The name benzyl radical is used as a specific name for the radical produced in this reaction. The general name **benzylic radical** applies to all radicals that have an unpaired electron on the side-chain carbon atom that is directly attached to the benzene ring. The hydrogen atoms of the carbon atom directly attached to the benzene ring are called **benzylic hydrogen atoms**. A group bonded at a benzylic position is called a **benzylic substituent**.

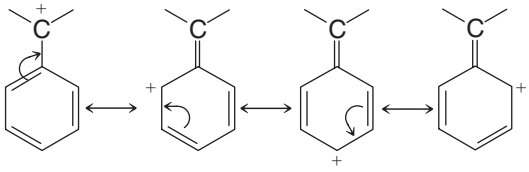
Departure of a leaving group (LG) from a benzylic position produces a **benzylic cation**:



Benzylic radicals and benzylic cations are *conjugated unsaturated systems* and *both are unusually stable*. They have approximately the same stabilities as allylic radicals and cations. This exceptional stability of benzylic radicals and cations can be explained by resonance theory. In the case of each entity, resonance structures can be written that place either the unpaired electron (in the case of the radical) or the positive charge (in the case of the cation) on an ortho or para carbon of the ring (see the following structures). Thus resonance delocalizes the unpaired electron or the charge, and this delocalization causes the radical or cation to be highly stabilized.



Benzylic radicals are stabilized by resonance.



Benzylic cations are stabilized by resonance.

Calculated structures for the benzyl radical and benzyl cation are presented in Fig. 15.6. These structures show the presence at their ortho and para carbons of unpaired electron density in the radical and positive charge in the cation, consistent with the resonance structures above.

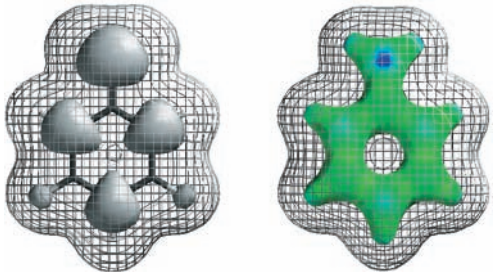
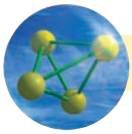


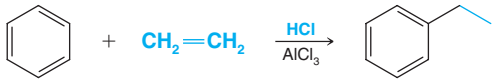
Figure 15.6 The gray lobes in the calculated structure for the benzyl radical *(left)* show the location of density from the unpaired electron. This model indicates that the unpaired electron resides primarily at the benzylic, ortho, and para carbons, which is consistent with the resonance model for the benzylic radical discussed earlier. The calculated electrostatic potential map for the bonding electrons in the benzyl cation *(right)* indicates that positive charge (blue regions) resides primarily at the benzylic, ortho, and para carbons, which is consistent with the resonance model for the benzylic cation. The van der Waals surface of both structures is represented by the wire mesh.



THE CHEMISTRY OF . . .

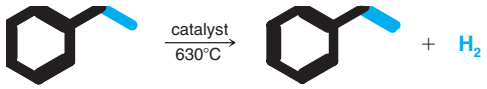
Industrial Styrene Synthesis

Styrene is one of the most important industrial chemicals—more than 11 billion pounds is produced each year. The starting material for a major commercial synthesis of styrene is ethylbenzene, produced by Friedel–Crafts alkylation of benzene:



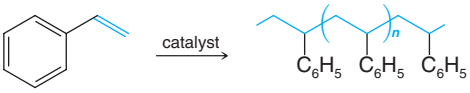
Ethylbenzene

Ethylbenzene is then dehydrogenated in the presence of a catalyst (zinc oxide or chromium oxide) to produce styrene.



Styrene (90–92% yield)

Most styrene is polymerized (Special Topic A) to the familiar plastic, polystyrene:



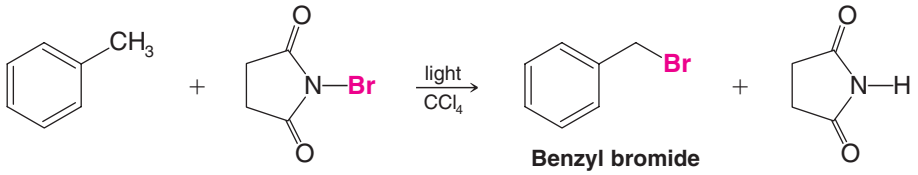
Polystyrene

15.12B Halogenation of the Side Chain: Benzylic Radicals

We have already seen that we can substitute bromine and chlorine for hydrogen atoms on the *ring* of toluene and other alkylaromatic compounds using electrophilic aromatic substitution reactions. Chlorine and bromine can also be made to replace hydrogen atoms that are on a *benzylic* carbon, such as the methyl group of toluene.

- Benzylic halogenation is carried out ***in the absence of Lewis acids*** **and under conditions that favor the formation of radicals**.

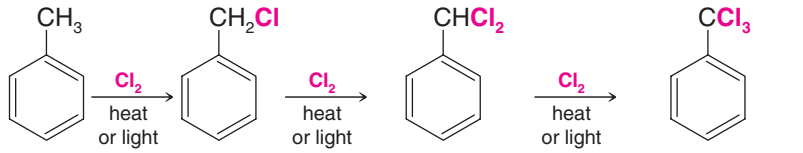
When toluene reacts with *N*-bromosuccinimide (NBS) in the presence of light, for example, the major product is benzyl bromide. *N*-Bromosuccinimide furnishes a low concentration of Br_2, and the reaction is analogous to that for allylic bromination that we studied in Section 13.2B.



NBS

Benzyl bromide (α-bromotoluene) (64%)

Side-chain chlorination of toluene takes place in the gas phase at 400–600°C or in the presence of UV light. When an excess of chlorine is used, multiple chlorinations of the side chain occur:



Benzyl chloride **Dichloromethylbenzene** **Trichloromethylbenzene**

These halogenations take place through the same radical mechanism we saw for alkanes in Section 10.4. The halogens dissociate to produce halogen atoms and then the halogen atoms initiate chain reactions by abstracting hydrogens of the methyl group.

Benzylic halogenations are similar to allylic halogenations (Section 13.2) in that they involve the formation of *unusually stable radicals* (Section 15.12A).

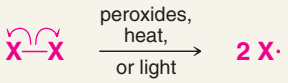
- Benzylic and allylic radicals are even more stable than tertiary radicals.

A MECHANISM FOR THE REACTION

Benzylic Halogenation

Chain Initiation

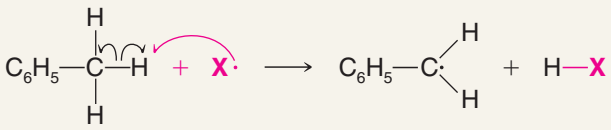
Step 1



Peroxides, heat, or light cause halogen molecules to cleave into radicals.

Chain Propagation

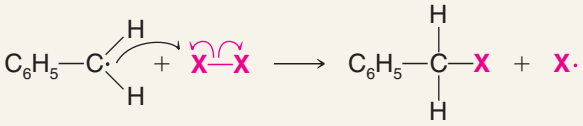
Step 2



Benzyl radical

A halogen radical abstracts a benzylic hydrogen atom, forming a benzylic radical and a molecule of the hydrogen halide.

Step 3

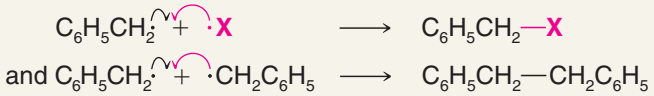


Benzyl radical **Benzyl halide**

The benzylic radical reacts with a halogen molecule to form the benzylic halide product and a halogen radical that propagates the chain.

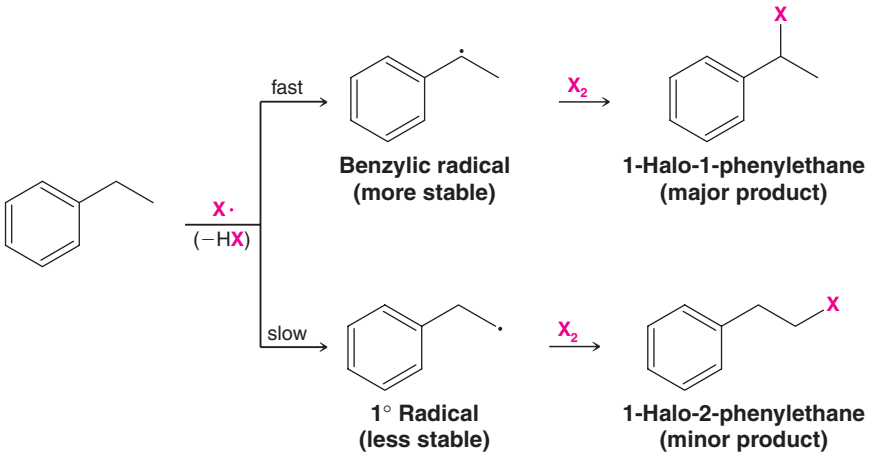
Chain Termination

Step 4



Various radical coupling reactions terminate the chain.

The greater stability of benzylic radicals accounts for the fact that when ethylbenzene is halogenated, the major product is the 1-halo-1-phenylethane. The benzylic radical is formed much faster than the 1° radical:



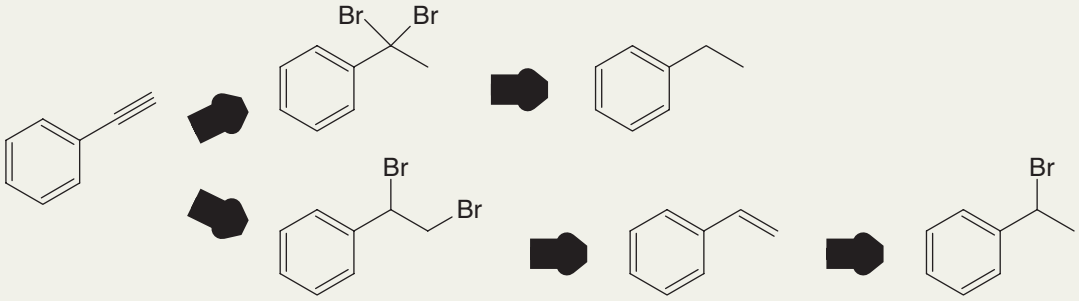
Review Problem 15.13

When propylbenzene reacts with chlorine in the presence of UV radiation, the major product is 1-chloro-1-phenylpropane. Both 2-chloro-1-phenylpropane and 3-chloro-1-phenylpropane are minor products. Write the structure of the radical leading to each product and account for the fact that 1-chloro-1-phenylpropane is the major product.

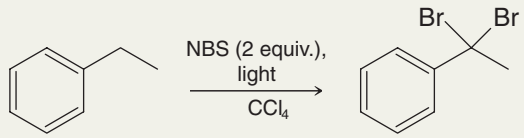
Solved Problem 15.5

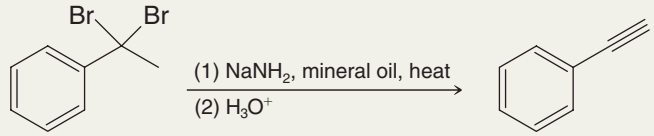
ILLUSTRATING A MULTISTEP SYNTHESIS Show how phenylacetylene ($C_6H_5C{\equiv}CH$) could be synthesized from ethylbenzene (phenylethane). Begin by writing a retrosynthetic analysis, and then write reactions needed for the synthesis.

ANSWER Working backward, that is, using *retrosynthetic analysis*, we find that we can easily envision two syntheses of phenylacetylene. We can make phenylacetylene by dehydrohalogenation of 1,1-dibromo-1-phenylethane, which could have been prepared by allowing ethylbenzene (phenylethane) to react with 2 mol of NBS. Alternatively, we can prepare phenylacetylene from 1,2-dibromo-1-phenylethane, which could be prepared from styrene (phenylethene). Styrene can be made from 1-bromo-1-phenylethane, which can be made from ethylbenzene.

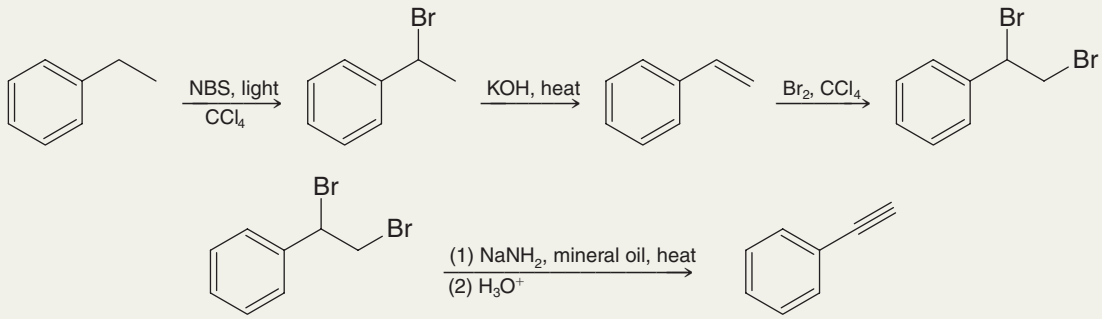


Following are the synthetic reactions we need for the two retrosynthetic analyses above:





or



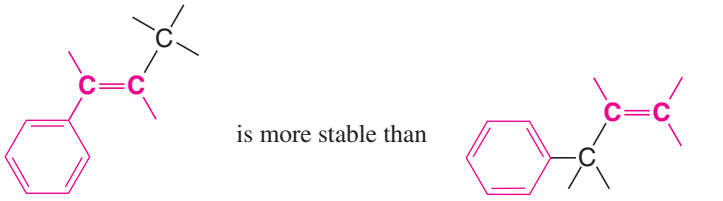
Review Problem 15.14

Show how the following compounds could be synthesized from phenylacetylene ($C_6H_5C{\equiv}CH$): **(a)** 1-phenylpropyne, **(b)** 1-phenyl-1-butyne, **(c)** (*Z*)-1-phenylpropene, and **(d)** (*E*)-1-phenylpropene. Begin each synthesis by writing a retrosynthetic analysis.

15.13 *Alkenylbenzenes*

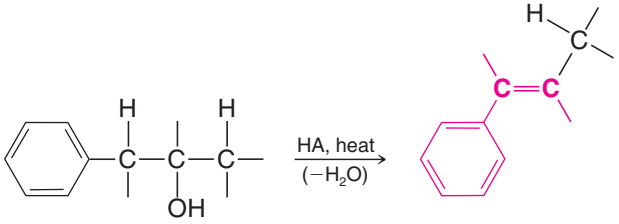
15.13A Stability of Conjugated Alkenylbenzenes

- Alkenylbenzenes that have their side-chain double bond conjugated with the benzene ring are more stable than those that do not:



Conjugated system **Nonconjugated system**

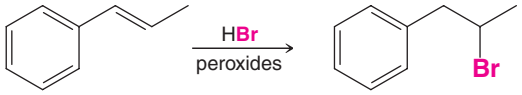
Part of the evidence for this comes from acid-catalyzed alcohol dehydrations, which are known to yield the most stable alkene (Section 7.8A). For example, dehydration of an alcohol such as the one that follows yields exclusively the conjugated system:



Because conjugation always lowers the energy of an unsaturated system by allowing the π electrons to be delocalized, this behavior is just what we would expect.

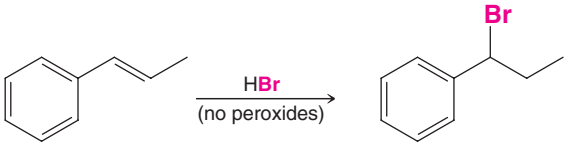
15.13B Additions to the Double Bond of Alkenylbenzenes

In the presence of peroxides, hydrogen bromide adds to the double bond of 1-phenylpropene to give 2-bromo-1-phenylpropane as the major product:



1-Phenylpropene **2-Bromo-1-phenylpropane**

In the absence of peroxides, HBr adds in just the opposite way:



1-Phenylpropene **1-Bromo-1-phenylpropane**

The addition of hydrogen bromide to 1-phenylpropene proceeds through a benzylic radical in the presence of peroxides and through a benzylic cation in their absence (see Review Problem 15.15 and Section 10.9).

Review Problem 15.15

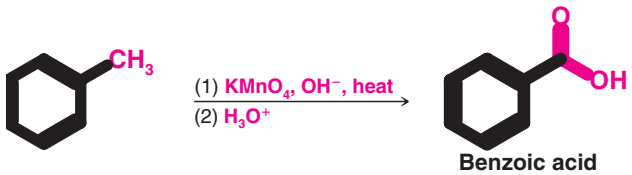
Write mechanisms for the reactions whereby HBr adds to 1-phenylpropene **(a)** in the presence of peroxides and **(b)** in the absence of peroxides. In each case account for the regiochemistry of the addition (i.e., explain why the major product is 2-bromo-1-phenylpropane when peroxides are present and why it is 1-bromo-1-phenylpropane when peroxides are absent).

(a) What would you expect to be the major product when 1-phenylpropene reacts with HCl?
(b) What product would you expect when it is subjected to oxymercuration–demercuration?

Review Problem 15.16

15.13C Oxidation of the Side Chain

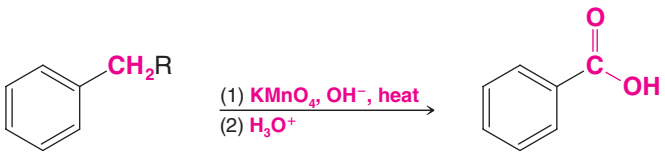
Strong oxidizing agents oxidize toluene to benzoic acid. The oxidation can be carried out by the action of hot alkaline potassium permanganate. This method gives benzoic acid in almost quantitative yield:



Benzoic acid (~100%)

An important characteristic of side-chain oxidations is that oxidation takes place initially at the benzylic carbon.

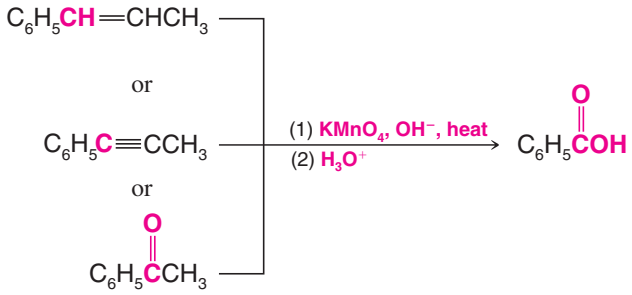
- Alkylbenzenes with alkyl groups longer than methyl are ultimately degraded to benzoic acids:



An alkylbenzene **Benzoic acid**

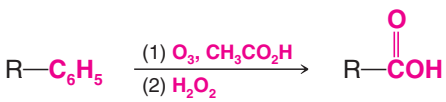
Side-chain oxidations are similar to benzylic halogenations, because in the first step the oxidizing agent abstracts a benzylic hydrogen. Once oxidation is begun at the benzylic carbon, it continues at that site. Ultimately, the oxidizing agent oxidizes the benzylic carbon to a carboxyl group, and, in the process, it cleaves off the remaining carbon atoms of the side chain. (*tert*-Butylbenzene is resistant to side-chain oxidation. Why?)

- Side-chain oxidation is not restricted to alkyl groups. Alkenyl, alkynyl, and acyl groups are also oxidized by hot alkaline potassium permanganate.



15.13D Oxidation of the Benzene Ring

The benzene ring carbon where an alkyl group is bonded can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide.

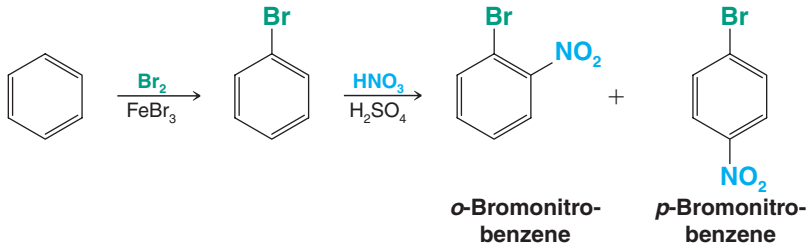


15.14 *Synthetic Applications*

The substitution reactions of aromatic rings and the reactions of the side chains of alkyl- and alkenylbenzenes, when taken together, offer us a powerful set of reactions for organic synthesis. By using these reactions skillfully, we shall be able to synthesize a large number of benzene derivatives.

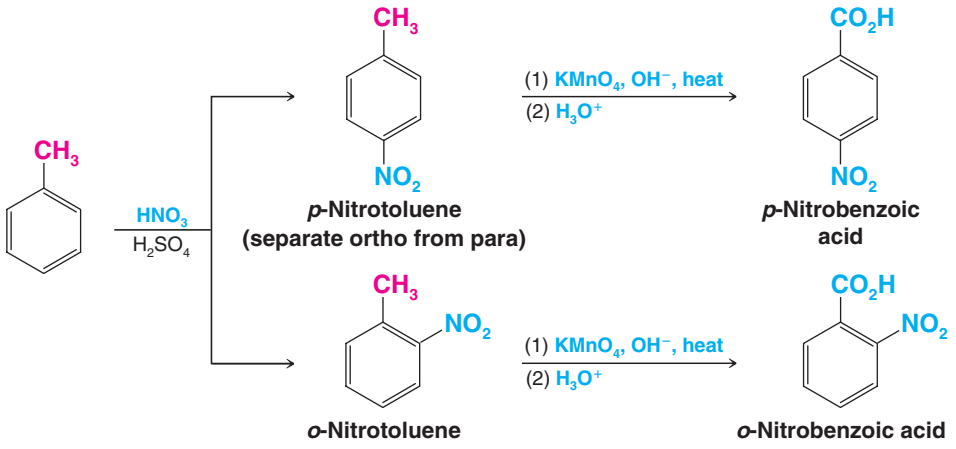
- Part of the skill in planning a synthesis is deciding in what order to carry out the reactions.

Let us suppose, for example, that we want to synthesize *o*-bromonitrobenzene. We can see very quickly that we should introduce the bromine into the ring first because it is an ortho–para director:

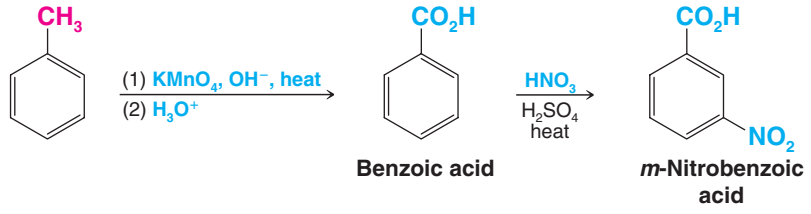


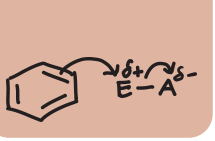
The ortho and para products can be separated by various methods because they have different physical properties. However, had we introduced the nitro group first, we would have obtained *m*-bromonitrobenzene as the major product.

Other examples in which choosing the proper order for the reactions is important are the syntheses of the *ortho*-, *meta*-, and *para*-nitrobenzoic acids. Because the methyl group of toluene is an electron-donating group (shown in red below), we can synthesize the *ortho*- and *para*-nitrobenzoic acids from toluene by nitrating it, separating the *ortho*- and *para*-nitrotoluenes, and then oxidizing the methyl groups to carboxyl groups:



We can synthesize *m*-nitrobenzoic acid by reversing the order of the reactions. We oxidize the methyl group to a carboxylic acid, then use the carboxyl as an electron-withdrawing group (shown in blue) to direct nitration to the meta position.

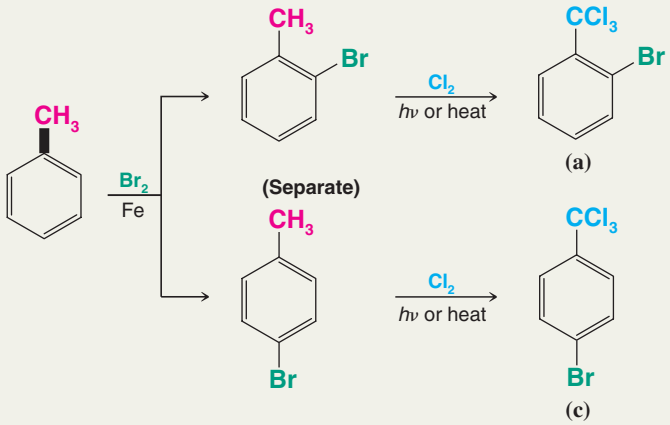




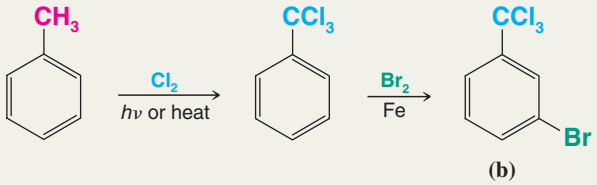
Solved Problem 15.6

Starting with toluene, outline a synthesis of **(a)** 1-bromo-2-trichloromethylbenzene, **(b)** 1-bromo-3-trichloromethylbenzene, and **(c)** 1-bromo-4-trichloromethylbenzene.

ANSWER Compounds (a) and (c) can be obtained by ring bromination of toluene followed by chlorination of the side chain using three molar equivalents of chlorine:

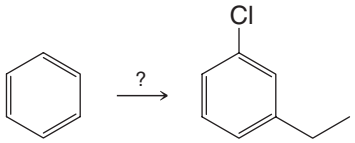


To make compound (b), we reverse the order of the reactions. By converting the side chain to a $—CCl_3$ group first, we create a meta director, which causes the bromine to enter the desired position:



Review Problem 15.17

Suppose you needed to synthesize *m*-chloroethylbenzene from benzene.



You could begin by chlorinating benzene and then follow with a Friedel–Crafts alkylation using chloroethane and $AlCl_3$, or you could begin with a Friedel–Crafts alkylation followed by chlorination. Neither method will give the desired product, however.

(a) Why will neither method give the desired product?

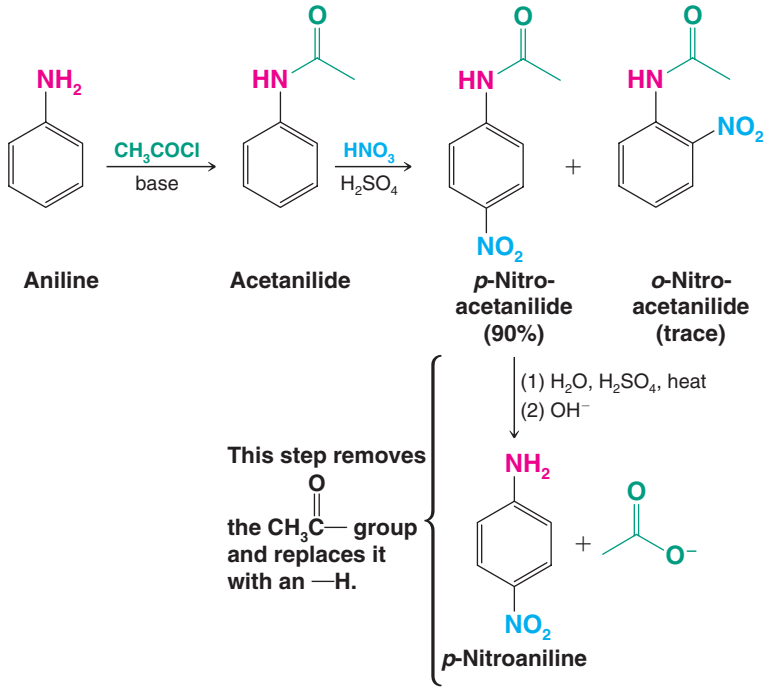
(b) There is a three-step method that will work if the steps are done in the right order. What is this method?

15.14A Use of Protecting and Blocking Groups

- Very powerful activating groups such as amino groups and hydroxyl groups cause the benzene ring to be so reactive that undesirable reactions may take place.

Some reagents used for electrophilic substitution reactions, such as nitric acid, are also strong *oxidizing agents*. Both electrophiles and oxidizing agents seek electrons. Thus, amino groups and hydroxyl groups not only activate the ring toward electrophilic substitution but also activate it toward oxidation. Nitration of aniline, for example, results in considerable destruction of the benzene ring because it is oxidized by the nitric acid. Direct nitration of aniline, consequently, is not a satisfactory method for the preparation of *o*- and *p*-nitroaniline.

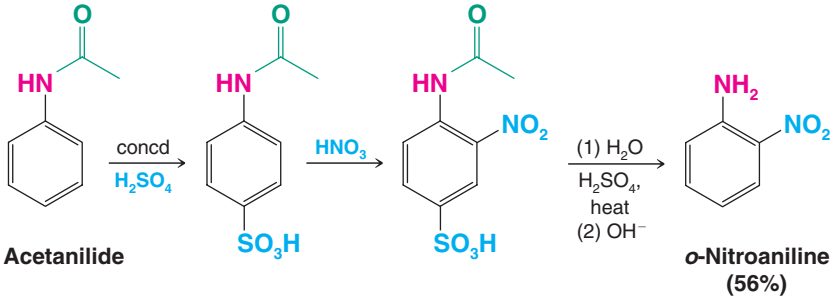
Treating aniline with acetyl chloride, CH_3COCl, or acetic anhydride, $(CH_3CO)_2O$, converts the amino group of aniline to an amide, (specifically an acetamido group, $—NHCOCH_3$), forming acetanilide. An amide group is only moderately activating, and it does not make the ring highly susceptible to oxidation during nitration (see Review Problem 15.9). Thus, with the amino group of aniline blocked in acetanilide, direct nitration becomes possible:



Nitration of acetanilide gives *p*-nitroacetanilide in excellent yield with only a trace of the ortho isomer. Acidic hydrolysis of *p*-nitroacetanilide (Section 18.8F) removes the acetyl group and gives *p*-nitroaniline, also in good yield.

Suppose, however, that we need *o*-nitroaniline. The synthesis that we just outlined would obviously not be a satisfactory method, for only a trace of *o*-nitroacetanilide is obtained in the nitration reaction. (The acetamido group is purely a para director in many reactions. Bromination of acetanilide, for example, gives *p*-bromoacetanilide almost exclusively.)

We can synthesize *o*-nitroaniline, however, through the reactions that follow:

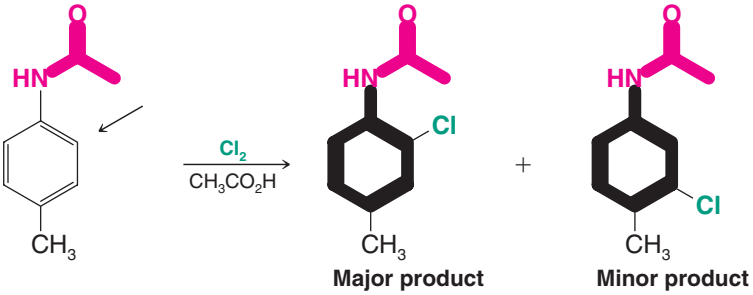


Here we see how a sulfonic acid group can be used as a "blocking group." We can remove the sulfonic acid group by desulfonation at a later stage. In this example, the reagent used for desulfonation (dilute H_2SO_4) also conveniently removes the acetyl group that we employed to "protect" the benzene ring from oxidation by nitric acid.

15.14B Orientation in Disubstituted Benzenes

- When two different groups are present on a benzene ring, the more powerful activating group (Table 15.2) generally determines the outcome of the reaction.

Let us consider, as an example, the orientation of electrophilic substitution of *p*-methylacetanilide. The amide group is a much stronger activating group than the methyl group. The following example shows that the amide group determines the outcome of the reaction. Substitution occurs primarily at the position ortho to the amide group:

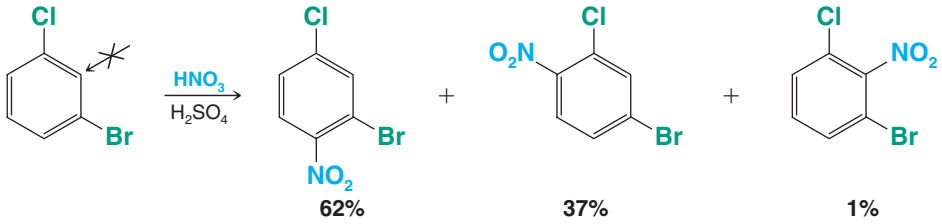


- An ortho–para director takes precedence over a meta director in determining the position of substitution because all ortho–para-directing groups are more activating than meta directors.

Steric effects are also important in aromatic substitutions.

- Substitution does not occur to an appreciable extent between meta substituents if another position is open.

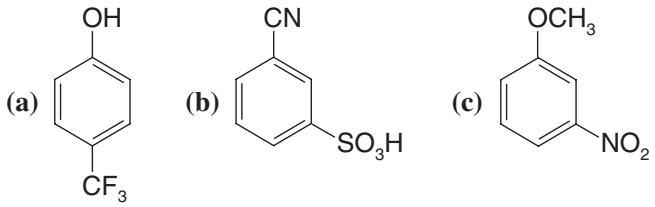
A good example of this effect can be seen in the nitration of *m*-bromochlorobenzene:



Only 1% of the mononitro product has the nitro group between the bromine and chlorine.

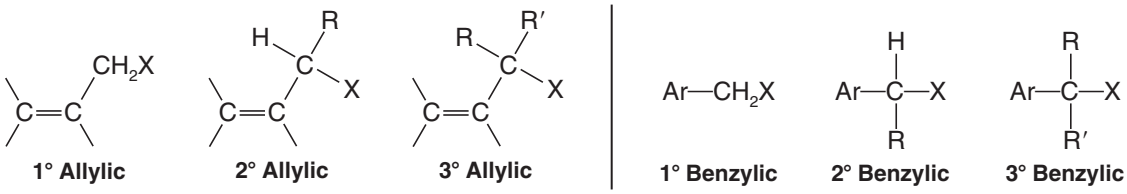
Review Problem 15.18

Predict the major product (or products) that would be obtained when each of the following compounds is nitrated:



15.15 *Allylic and Benzylic Halides in Nucleophilic Substitution Reactions*

Allylic and benzylic halides can be classified in the same way that we have classified other organic halides:



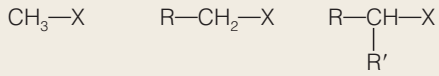
All of these compounds undergo nucleophilic substitution reactions. As with other tertiary halides (Section 6.13A), the steric hindrance associated with having three bulky groups on the carbon bearing the halogen prevents tertiary allylic and tertiary benzylic halides from reacting by an S_N2 mechanism. They react with nucleophiles only by an S_N1 mechanism.

Primary and secondary allylic and benzylic halides can react either by an S_N2 mechanism or by an S_N1 mechanism in ordinary nonacidic solvents. We would expect these halides to react by an S_N2 mechanism because they are structurally similar to primary and secondary alkyl halides. (Having only one or two groups attached to the carbon bearing the halogen does not prevent S_N2 attack.) But primary and secondary allylic and benzylic halides can also react by an S_N1 mechanism because they can form relatively stable **allylic carbocations** and **benzylic carbocations**, and in this regard they differ from primary and secondary alkyl halides.*

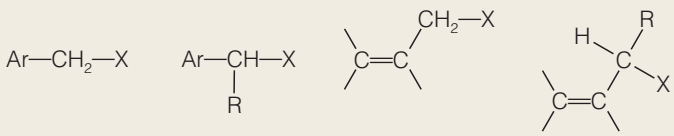
- Overall we can summarize the effect of structure on the reactivity of alkyl, allylic, and benzylic halides in the ways shown in Table 15.3.

TABLE 15.3 A Summary of Alkyl, Allylic, and Benzylic Halides in S_N Reactions

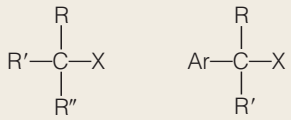
These halides give mainly S_N2 reactions.

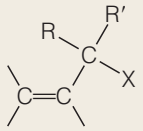


These halides may give either S_N1 or S_N2 reactions.



These halides give mainly S_N1 reactions.

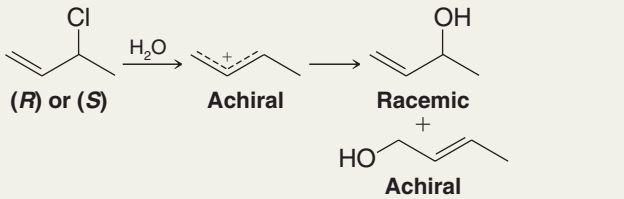




Solved Problem 15.7

When either enantiomer of 3-chloro-1-butene [(*R*) or (*S*)] is subjected to hydrolysis, the products of the reaction are optically inactive. Explain these results.

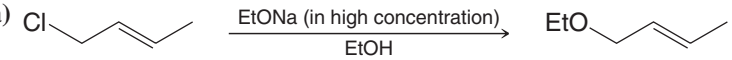
ANSWER The solvolysis reaction is S_N1. The intermediate allylic cation is achiral and therefore reacts with water to give the enantiomeric 3-buten-2-ols in equal amounts and to give some of the achiral 2-buten-1-ol:



Review Problem 15.19

Account for the following observations with mechanistic explanations.

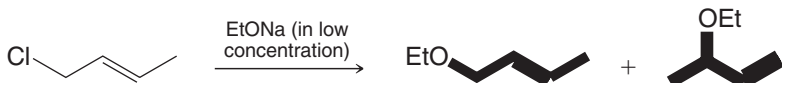
(a)



At high concentration of ethoxide, the rate depends on both the allylic halide and ethoxide concentrations.

*There is some dispute as to whether 2° alkyl halides react by an S_N1 mechanism to any appreciable extent in ordinary nonacidic solvents such as mixtures of water and alcohol or acetone, but it is clear that reaction by an S_N2 mechanism is, for all practical purposes, the more important pathway.

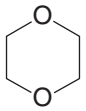
(b)



At low concentration of ethoxide, the rate depends only on the allylic halide concentration.

Review Problem 15.20

1-Chloro-3-methyl-2-butene undergoes hydrolysis in a mixture of water and dioxane at a rate that is more than a thousand times that of 1-chloro-2-butene. **(a)** What factor accounts for the difference in reactivity? **(b)** What products would you expect to obtain? [Dioxane is a cyclic ether (below) that is miscible with water in all proportions and is a useful cosolvent for conducting reactions like these. Dioxane is carcinogenic (i.e., cancer causing), however, and like most ethers, it tends to form peroxides.]



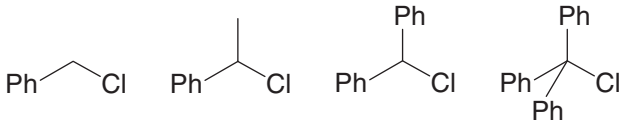
Dioxane

Review Problem 15.21

Primary halides of the type $ROCH_2X$ apparently undergo S_N1-type reactions, whereas most primary halides do not. Can you propose a resonance explanation for the ability of halides of the type $ROCH_2X$ to undergo S_N1 reactions?

Review Problem 15.22

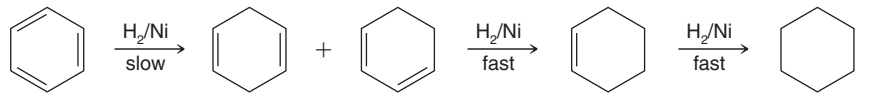
The following chlorides (Ph = phenyl) undergo solvolysis in ethanol at the relative rates given in parentheses. How can you explain these results?



(0.08) **(1)** **(300)** **(3×10^6)**

15.16 *Reduction of Aromatic Compounds*

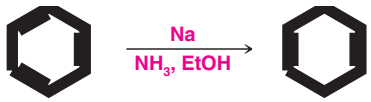
Hydrogenation of benzene under pressure using a metal catalyst such as nickel results in the addition of three molar equivalents of hydrogen and the formation of cyclohexane (Section 14.3). The intermediate cyclohexadienes and cyclohexene cannot be isolated because these undergo catalytic hydrogenation faster than benzene does.



Benzene **Cyclohexadienes** **Cyclohexene** **Cyclohexane**

15.16A The Birch Reduction

Benzene can be reduced to 1,4-cyclohexadiene by treating it with an alkali metal (sodium, lithium, or potassium) in a mixture of liquid ammonia and an alcohol. This reaction is called the **Birch reduction**, after A. J. Birch, the Australian chemist who developed it.

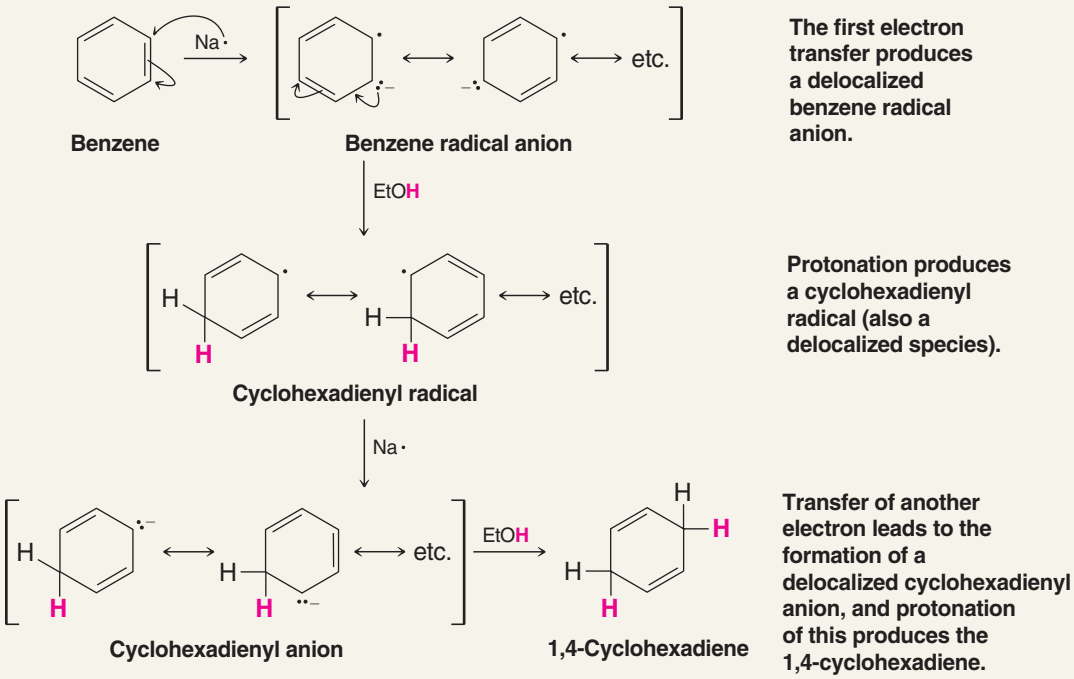


Benzene **1,4-Cyclohexadiene**

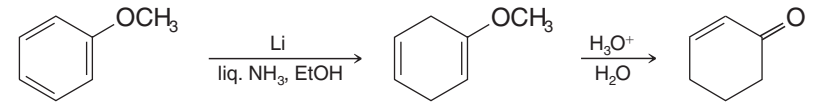
The Birch reduction is a dissolving metal reduction, and the mechanism for it resembles the mechanism for the reduction of alkynes that we studied in Section 7.15B. A sequence of electron transfers from the alkali metal and proton transfers from the alcohol takes place, leading to a 1,4-cyclohexadiene. The reason for formation of a 1,4-cyclohexadiene in preference to the more stable conjugated 1,3-cyclohexadiene is not understood.

A MECHANISM FOR THE REACTION

Birch Reduction

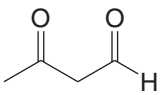
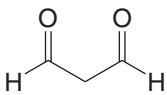


Substituent groups on the benzene ring influence the course of the reaction. Birch reduction of methoxybenzene (anisole) leads to the formation of 1-methoxy-1,4-cyclohexadiene, a compound that can be hydrolyzed by dilute acid to 2-cyclohexenone. This method provides a useful synthesis of 2-cyclohexenones:



Methoxybenzene (anisole) → **1-Methoxy-1,4-cyclohexadiene (84%)** → **2-Cyclohexenone**

Review Problem 15.23

Birch reduction of toluene leads to a product with the molecular formula C_7H_{10}. On ozonolysis followed by reduction with dimethyl sulfide, the product is transformed into  and  . What is the structure of the Birch reduction product?

Key Terms and Concepts

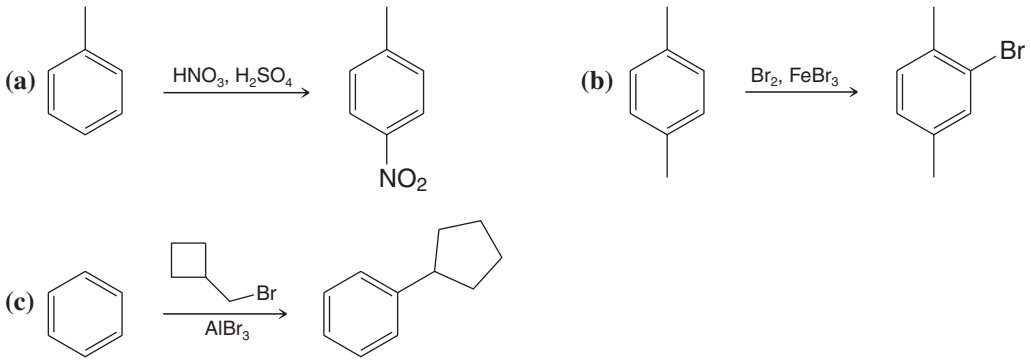
The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

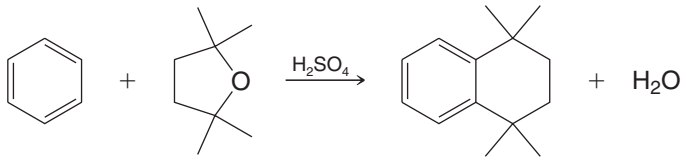
Note to Instructors: Many of the homework problems are available for assignment via *Wiley PLUS*, an online teaching and learning solution.

MECHANISMS

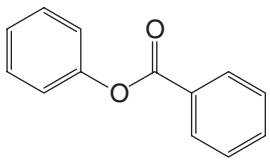
15.24 Provide a detailed mechanism for each of the following reactions. Include contributing resonance structures and the resonance hybrid for the arenium ion intermediates.



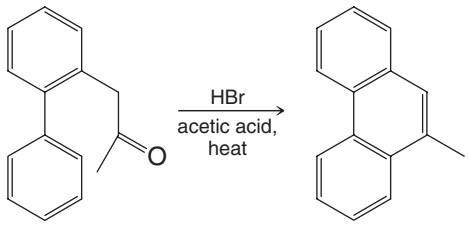
15.25 Provide a detailed mechanism for the following reaction.



15.26 One ring of phenyl benzoate undergoes electrophilic aromatic substitution much more readily than the other. **(a)** Which one is it? **(b)** Explain your answer.



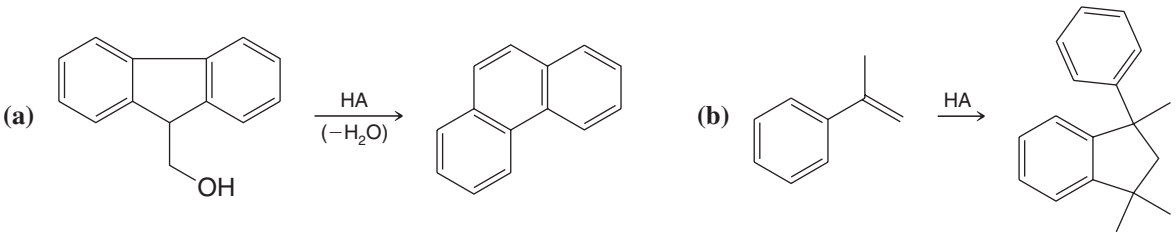
15.27 Many polycyclic aromatic compounds have been synthesized by a cyclization reaction known as the **Bradsher reaction** or **aromatic cyclodehydration**. This method can be illustrated by the following synthesis of 9-methylphenanthrene:



9-Methylphenanthrene

An arenium ion is an intermediate in this reaction, and the last step involves the dehydration of an alcohol. Propose a plausible mechanism for this example of the Bradsher reaction.

15.28 Write mechanisms that account for the products of the following reactions:



15.29 The addition of a hydrogen halide (hydrogen bromide or hydrogen chloride) to 1-phenyl-1,3-butadiene produces (only) 1-phenyl-3-halo-1-butene. **(a)** Write a mechanism that accounts for the formation of this product. **(b)** Is this 1,4 addition or 1,2 addition to the butadiene system? **(c)** Is the product of the reaction consistent with the formation of the most stable intermediate carbocation? **(d)** Does the reaction appear to be under kinetic control or equilibrium control? Explain.

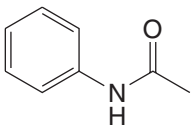
REACTIONS AND SYNTHESIS

15.30 Predict the major product (or products) formed when each of the following reacts with Cl_2 and $FeCl_3$:

(a) Ethylbenzene
(b) Anisole (methoxybenzene)
(c) Fluorobenzene
(d) Benzoic acid
(e) Nitrobenzene
(f) Chlorobenzene
(g) Biphenyl ($C_6H_5—C_6H_5$)
(h) Ethyl phenyl ether

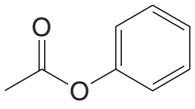
15.31 Predict the major product (or products) formed when each of the following reacts with a mixture of concentrated HNO_3 and H_2SO_4.

(a)



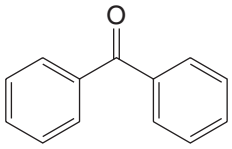
Acetanilide

(b)



Phenyl acetate

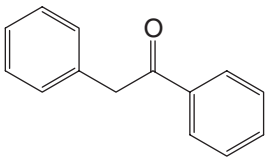
(c) 4-Chlorobenzoic acid
(d) 3-Chlorobenzoic acid
(e)



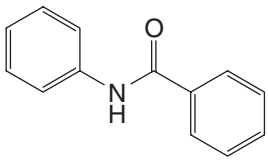
Benzophenone

15.32 What monobromination product (or products) would you expect to obtain when the following compounds undergo ring bromination with Br_2 and $FeBr_3$?

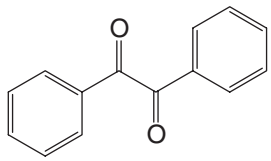
(a)



(b)

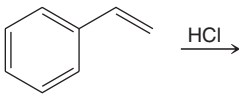


(c)



15.33 Predict the major products of the following reactions:

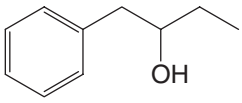
(a)



Styrene

(b) 2-Bromo-1-phenylpropane $\xrightarrow{\text{EtONa}}$

(c)



$\xrightarrow{\text{HA, heat}}$

(d) Product of (c) + HBr $\xrightarrow{\text{peroxides}}$

(e) Product of (c) + H_2O $\xrightarrow[\text{heat}]{\text{HA}}$

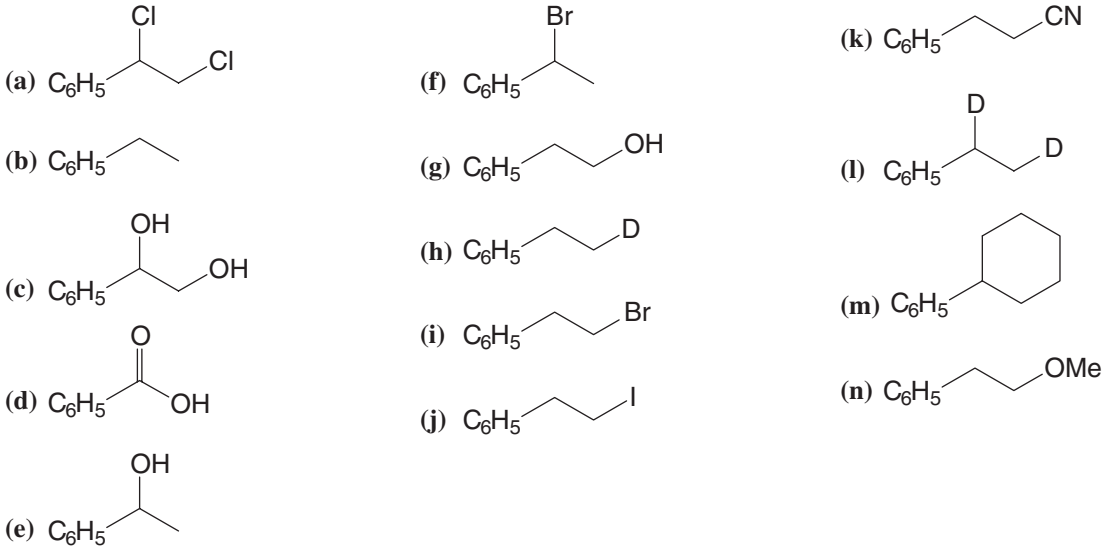
(f) Product of (c) + H_2 (1 molar equivalent) $\xrightarrow[25°C]{\text{Pt}}$

(g) Product of (f) $\xrightarrow[(2)\ H_3O^+]{(1)\ KMnO_4,\ OH^-,\ \text{heat}}$

15.34 Starting with benzene, outline a synthesis of each of the following:

(a) Isopropylbenzene
(b) *tert*-Butylbenzene
(c) Propylbenzene
(d) Butylbenzene
(e) 1-*tert*-Butyl-4-chlorobenzene
(f) 1-Phenylcyclopentene
(g) *trans*-2-Phenylcyclopentanol
(h) *m*-Dinitrobenzene
(i) *m*-Bromonitrobenzene
(j) *p*-Bromonitrobenzene
(k) *p*-Chlorobenzenesulfonic acid
(l) *o*-Chloronitrobenzene
(m) *m*-Nitrobenzenesulfonic acid

15.35 Starting with styrene, outline a synthesis of each of the following:



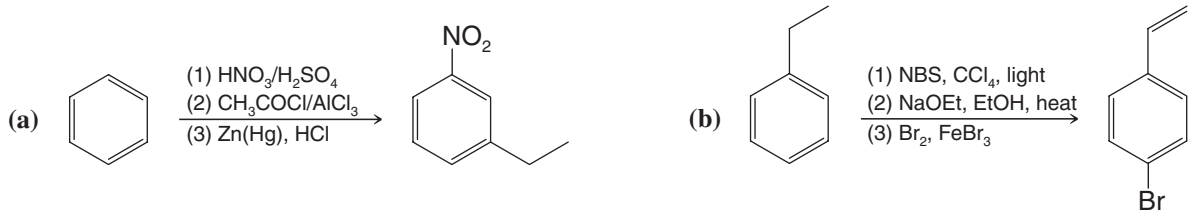
15.36 Starting with toluene, outline a synthesis of each of the following:

(a) *m*-Chlorobenzoic acid
(b) *p*-Methylacetophenone
(c) 2-Bromo-4-nitrotoluene
(d) *p*-Bromobenzoic acid
(e) 1-Chloro-3-trichloromethylbenzene
(f) *p*-Isopropyltoluene (*p*-cymene)
(g) 1-Cyclohexyl-4-methylbenzene
(h) 2,4,6-Trinitrotoluene (TNT)
(i) 4-Chloro-2-nitrobenzoic acid
(j) 1-Butyl-4-methylbenzene

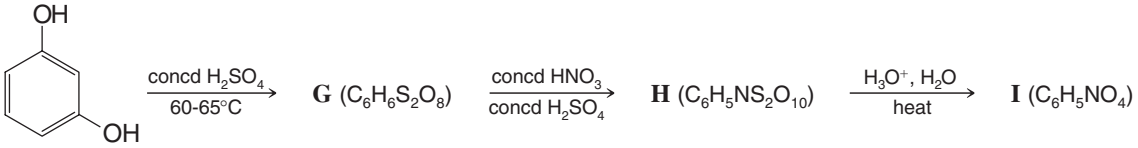
15.37 Starting with aniline, outline a synthesis of each of the following:

(a) *p*-Bromoaniline
(b) *o*-Bromoaniline
(c) 2-Bromo-4-nitroaniline
(d) 4-Bromo-2-nitroaniline
(e) 2,4,6-Tribromoaniline

15.38 Both of the following syntheses will fail. Explain what is wrong with each one.

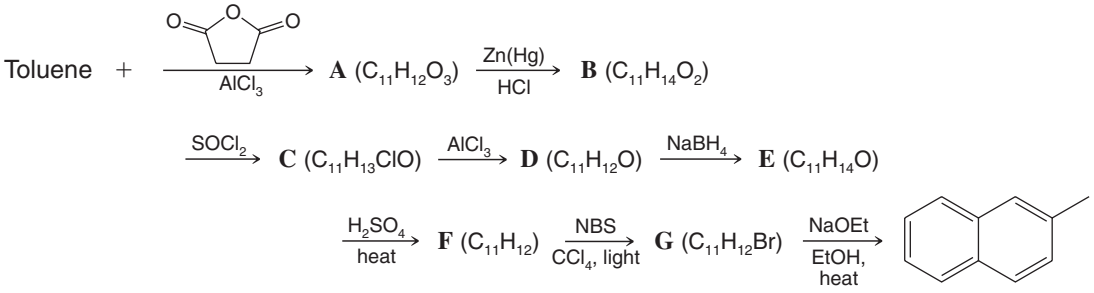


15.39 Propose structures for compounds **G–I:**

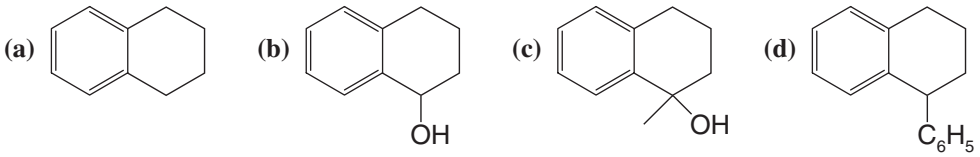


15.40 2,6-Dichlorophenol has been isolated from the females of two species of ticks (*Amblyomma americanum* and *A. maculatum*), where it apparently serves as a sex attractant. Each female tick yields about 5 ng of 2,6-dichlorophenol. Assume that you need larger quantities than this and outline a synthesis of 2,6-dichlorophenol from phenol. [*Hint*: When phenol is sulfonated at 100°C, the product is chiefly *p*-hydroxybenzenesulfonic acid.]

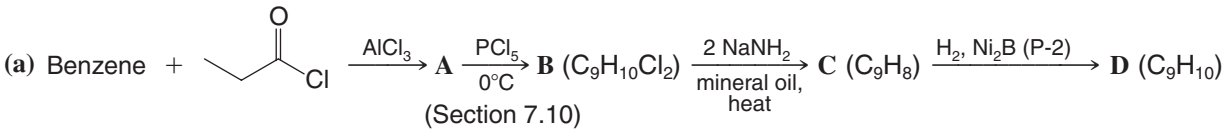
15.41 2-Methylnaphthalene can be synthesized from toluene through the following sequence of reactions. Write the structure of each intermediate.



15.42 Show how you might synthesize each of the following starting with α-tetralone (Section 15.9):



15.43 Give structures (including stereochemistry where appropriate) for compounds **A–G:**



[*Hint*: The ^{1}H NMR spectrum of compound **C** consists of a multiplet at δ 7.20 (5H) and a singlet at δ 2.0 (3H).]

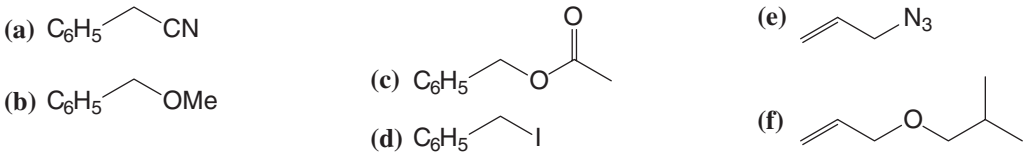
(b) **C** $\xrightarrow[\text{(2) } NH_4Cl \text{ (Section 7.15B)}]{\text{(1) Li, } EtNH_2}$ **E** (C_9H_{10})

(c) **D** $\xrightarrow[CCl_4,\ 2\text{–}5°C]{Br_2}$ **F** + enantiomer (major products)

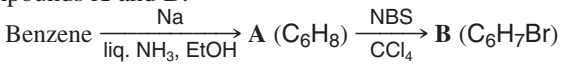
(d) **E** $\xrightarrow[CCl_4,\ 2\text{–}5°C]{Br_2}$ **G** + enantiomer (major products)

GENERAL PROBLEMS

15.44 Show how you might synthesize each of the following compounds starting with either benzyl bromide or allyl bromide:

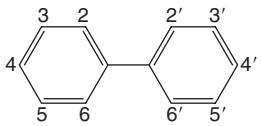


15.45 Provide structures for compounds **A** and **B**:



15.46 Ring nitration of a dimethylbenzene (a xylene) results in the formation of only one dimethylnitrobenzene. Which dimethylbenzene isomer was the reactant?

15.47 The compound phenylbenzene ($C_6H_5—C_6H_5$) is called *biphenyl*, and the ring carbons are numbered in the following manner:



Use models to answer the following questions about substituted biphenyls. **(a)** When certain large groups occupy three or four of the *ortho* positions (e.g., 2, 6, 2′, and 6′), the substituted biphenyl may exist in enantiomeric forms. An example of a biphenyl that exists in enantiomeric forms is the compound in which the following substituents are present: 2-NO_2, 6-CO_2H, 2′-NO_2, 6′-CO_2H. What factors account for this? **(b)** Would you expect a biphenyl with 2-Br, 6-CO_2H, 2′-CO_2H, 6′-H to exist in enantiomeric forms? **(c)** The biphenyl with 2-NO_2, 6-NO_2, 2′-CO_2H, 6′-Br cannot be resolved into enantiomeric forms. Explain.

15.48 Treating cyclohexene with acetyl chloride and $AlCl_3$ leads to the formation of a product with the molecular formula $C_8H_{13}ClO$. Treating this product with a base leads to the formation of 1-acetylcyclohexene. Propose mechanisms for both steps of this sequence of reactions.

15.49 The *tert*-butyl group can be used as a blocking group in certain syntheses of aromatic compounds. **(a)** How would you introduce a *tert*-butyl group? **(b)** How would you remove it? **(c)** What advantage might a *tert*-butyl group have over a $-SO_3H$ group as a blocking group?

15.50 When toluene is sulfonated (concentrated H_2SO_4) at room temperature, predominantly (about 95% of the total) ortho and para substitution occurs. If elevated temperatures (150–200°C) and longer reaction times are employed, meta (chiefly) and para substitution account for some 95% of the products. Account for these differences in terms of kinetic and thermodynamic pathways. [*Hint: m*-Toluenesulfonic acid is the most stable isomer.]

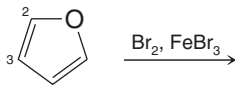
15.51 A C—D bond is harder to break than a C—H bond, and, consequently, reactions in which C—D bonds are broken proceed more slowly than reactions in which C—H bonds are broken. What mechanistic information comes from the observation that perdeuterated benzene, C_6D_6, is nitrated at the same rate as normal benzene, C_6H_6?

15.52 Heating 1,1,1-triphenylmethanol with ethanol containing a trace of a strong acid causes the formation of 1-ethoxy-1,1,1-triphenylmethane. Write a plausible mechanism that accounts for the formation of this product.

15.53 **(a)** Which of the following halides would you expect to be most reactive in an S_N2 reaction? **(b)** In an S_N1 reaction? Explain your answers.

Challenge Problems

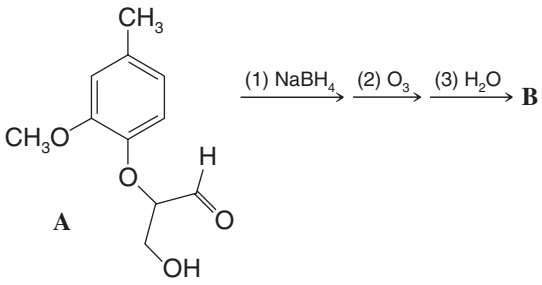
15.54 Furan undergoes electrophilic aromatic substitution. Use resonance structures for possible arenium ion intermediates to predict whether furan is likely to undergo bromination more rapidly at C2 or at C3.



Furan

15.55 Acetanilide was subjected to the following sequence of reactions: (1) concd H_2SO_4; (2) HNO_3, heat; (3) H_2O, H_2SO_4, heat, then OH^-. The ^{13}C NMR spectrum of the final product gives six signals. Write the structure of the final product.

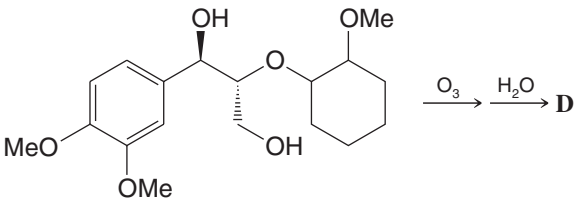
15.56 The lignins are macromolecules that are major components of the many types of wood, where they bind cellulose fibers together in these natural composites. The lignins are built up out of a variety of small molecules (most having phenylpropane skeletons). These precursor molecules are covalently connected in varying ways, and this gives the lignins great complexity. To explain the formation of compound **B** below as one of many products obtained when lignins are ozonized, lignin model compound **A** was treated as shown. Use the following information to determine the structure of **B**.



A

To make **B** volatile enough for GC/MS (gas chromatography–mass spectrometry, Section 9.19), it was first converted to its tris(*O*-trimethylsilyl) derivative, which had M^+ 308 *m/z*. ["Tris" means that three of the indicated complex groups named (e.g., trimethylsilyl groups here) are present. The capital, italicized *O* means these are attached to oxygen atoms of the parent compound, taking the place of hydrogen atoms. Similarly, the prefix "bis" indicates the presence of two complex groups subsequently named, and "tetrakis" (used in the problem below), means four.] The IR spectrum of **B** had a broad absorption at 3400 cm^{-1}, and its ^1H NMR spectrum showed a single multiplet at δ 3.6. What is the structure of **B**?

15.57 When compound **C**, which is often used to model a more frequently occurring unit in lignins, was ozonized, product **D** was obtained. In a variety of ways it has been established that the stereochemistry of the three-carbon side chain of such lignin units remains largely if not completely unchanged during oxidations like this.

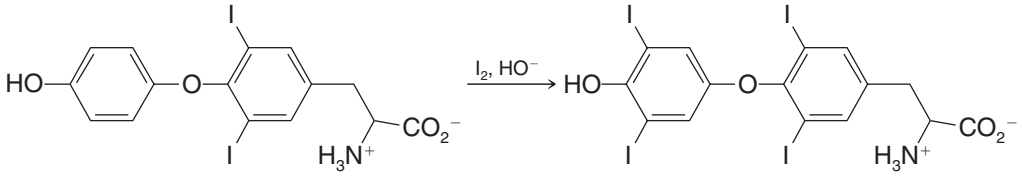


C

For GC/MS, **D** was converted to its tetrakis(*O*-trimethylsilyl) derivative, which had M^+ 424 *m/z*. The IR spectrum of **D** had bands at 3000 cm^{-1} (broad, strong) and 1710 cm^{-1} (strong). Its ^1H NMR spectrum had peaks at δ 3.7 (multiplet, 3H) and δ 4.2 (doublet, 1H) after treatment with D_2O. Its DEPT ^{13}C NMR spectra had peaks at δ 64 (CH_2), δ 75 (CH), δ 82 (CH), and δ 177 (C). What is the structure of **D**, including its stereochemistry?

Learning Group Problems

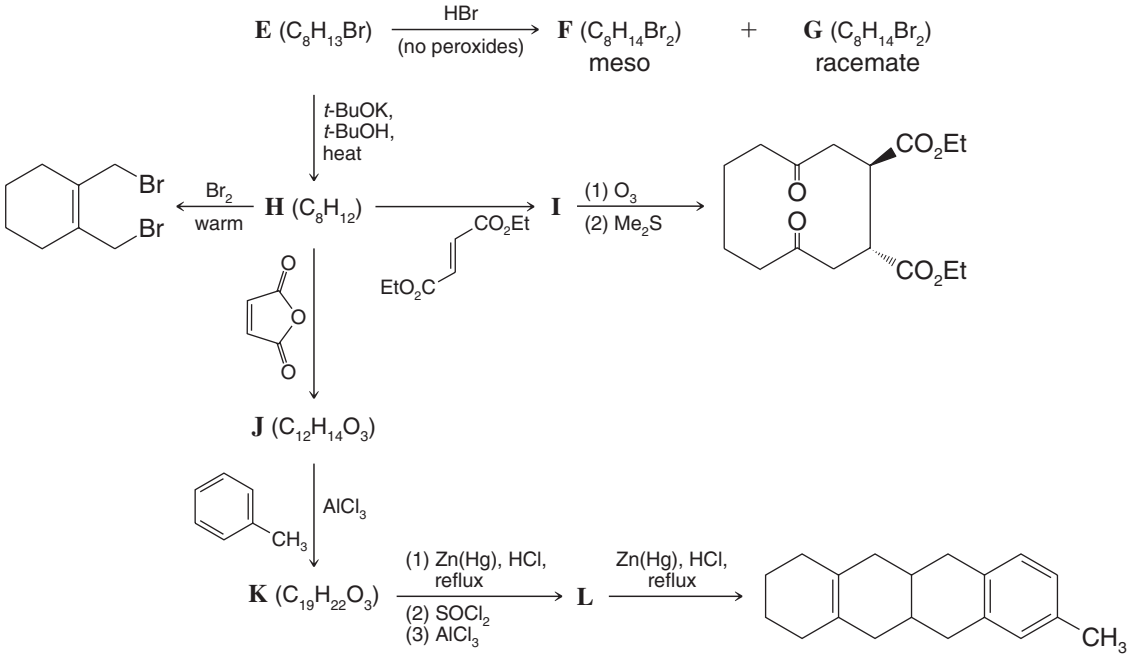
1. The structure of thyroxine, a thyroid hormone that helps to regulate metabolic rate, was determined in part by comparison with a synthetic compound believed to have the same structure as natural thyroxine. The final step in the laboratory synthesis of thyroxine by Harington and Barger, shown below, involves an electrophilic aromatic substitution. Draw a detailed mechanism for this step and explain why the iodine substitutions occur ortho to the phenolic hydroxyl and not ortho to the oxygen of the aryl ether. [One reason iodine is required in our diet (e.g., in iodized salt), of course, is for the biosynthesis of thyroxine.]



Thyroxine

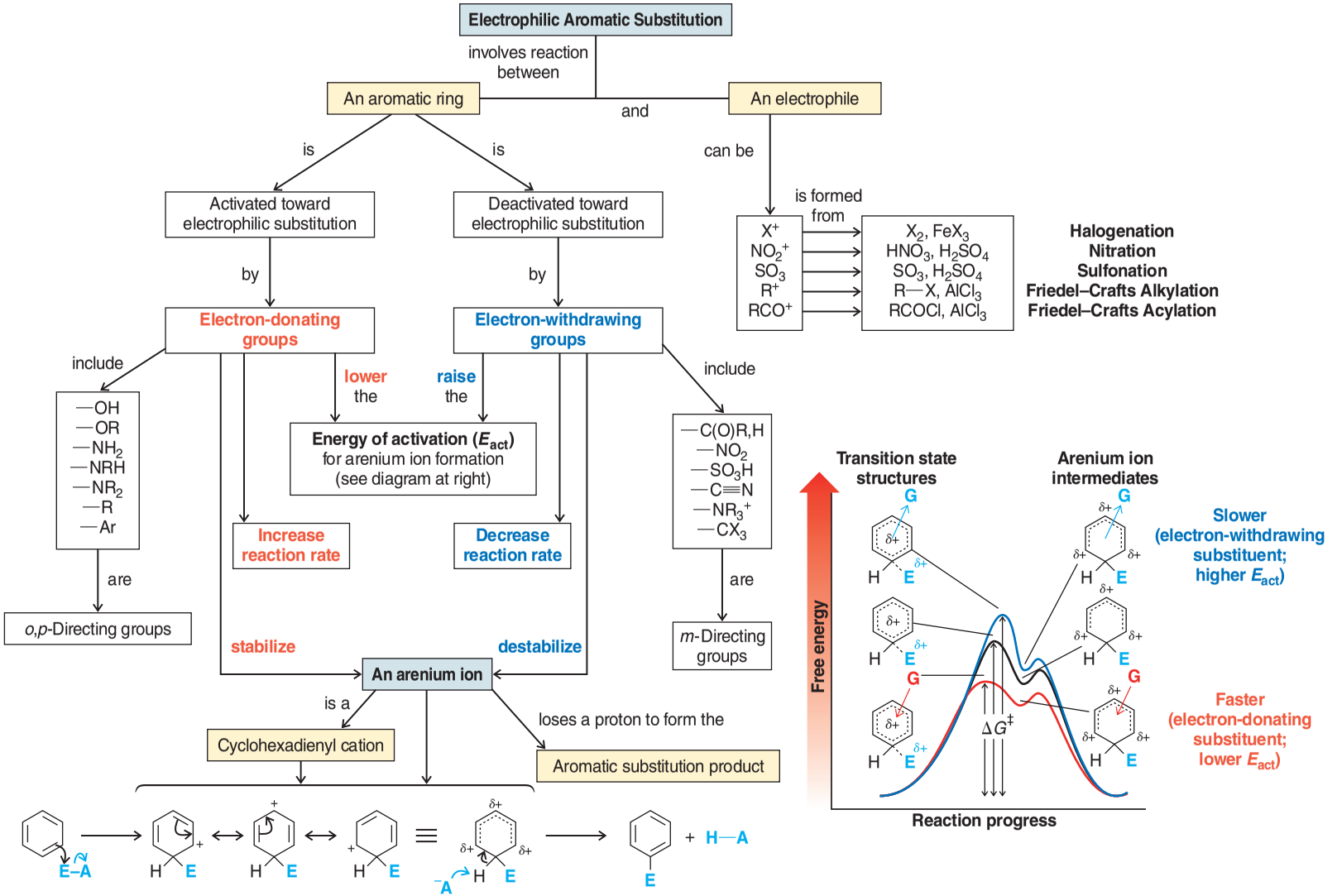
2. Synthesize 2-chloro-4-nitrobenzoic acid from toluene and any other reagents necessary. Begin by writing a retrosynthetic analysis.

3. Deduce the structures of compounds **E–L** in the roadmap below.



CONCEPT MAP

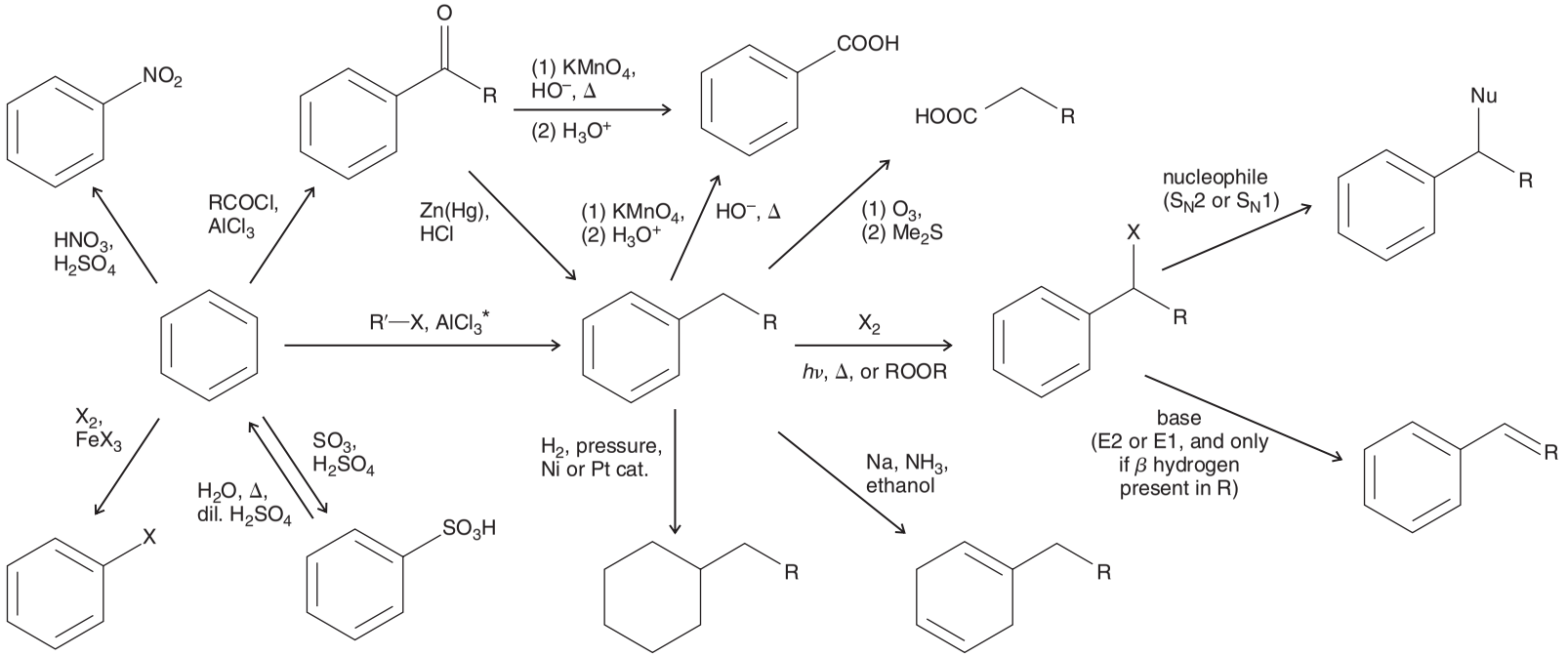
Summary of Mechanisms



CONCEPT MAP

Some Synthetic Connections of Benzene and Aryl Derivatives

- Nitration
- Halogenation
- Sulfonation/desulfonation
- Friedel–Crafts alkylation
- Friedel–Crafts acylation
- Clemmensen reduction
- Side-chain oxidation
- Ring oxidation
- Catalytic hydrogenation of ring
- Birch reduction
- Benzylic radical halogenation
- Benzylic substitution/elimination



*In the Friedel–Crafts alkylation example shown here, R' is a primary alkyl halide. If carbocation rearrangements are likely, then Friedel–Crafts acylation followed by Clemmensen reduction should be used to incorporate a primary alkyl group.