16

In the 19th and early-20th centuries, benzene was used as an aftershave lotion because of its pleasant smell and as a solvent to decaffeinate coffee beans. Neither is a good idea. © Niday Picture Library/Alamy

Chemistry of Benzene: Electrophilic Aromatic Substitution

16.1 Electrophilic Aromatic Substitution Reactions: Bromination
16.2 Other Aromatic Substitutions
16.3 Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction
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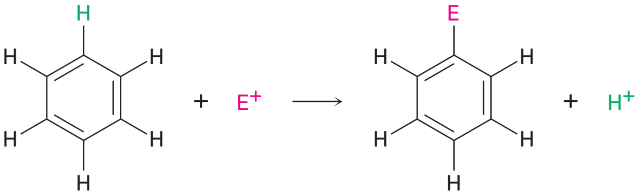
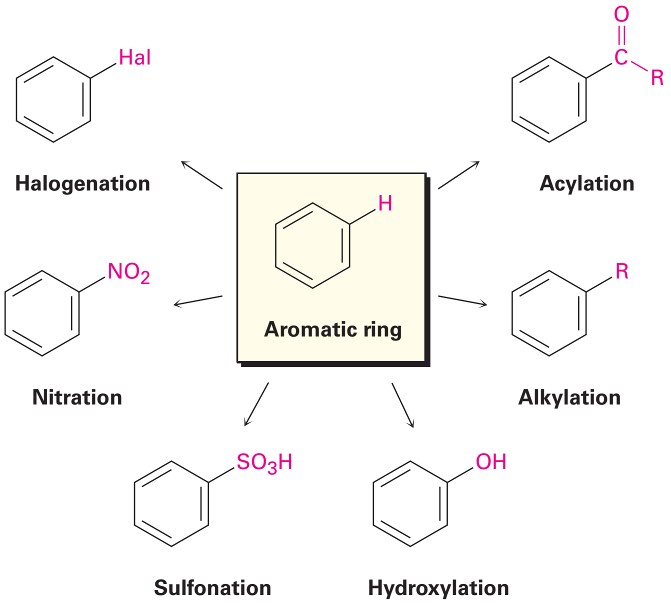
A Deeper Look—Combinatorial Chemistry

In the preceding chapter, we looked at *aromaticity*—the stability associated with benzene and related compounds that contain a cyclic conjugated system of $4n + 2$ π electrons. In this chapter, we'll look at some of the unique reactions that aromatic molecules undergo.

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**, in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.



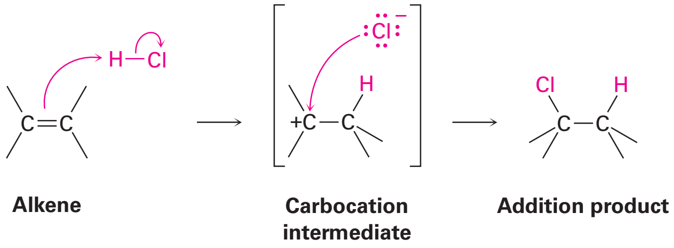
Many different substituents can be introduced onto an aromatic ring through electrophilic substitution reactions. To list some possibilities, an aromatic ring can be substituted by a halogen (—Cl, —Br, I), a nitro group ($-NO_2$), a sulfonic acid group ($-SO_3H$), a hydroxyl group (—OH), an alkyl group (—R), or an acyl group (—COR). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.



Why This Chapter? This chapter continues the coverage of aromatic molecules begun in the preceding chapter, but we'll shift focus to concentrate on reactions, looking at the relationship between aromatic structure and reactivity. This relationship is critical to an understanding of how many biological molecules and pharmaceutical agents are synthesized and why they behave as they do.

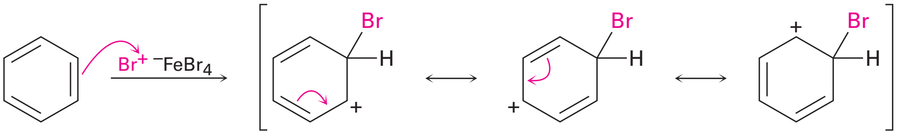
16.1 Electrophilic Aromatic Substitution Reactions: Bromination

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall what we said in Chapter 7 about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the π electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl^- ion to yield the addition product.



An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes are. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed. The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give an $FeBr_4^-Br^+$ species that reacts as if it were Br^+. The polarized Br_2 molecule then reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate that is doubly allylic **(Section 11.5)** and has three resonance forms.

$$Br{-}Br \; + \; FeBr_3 \longrightarrow Br^+ \; {}^-FeBr_4$$



Although more stable than a typical alkyl carbocation because of resonance, the intermediate in electrophilic aromatic substitution is nevertheless much less stable than the starting benzene ring itself, with its 150 kJ/mol (36 kcal/mol) of aromatic stability. Thus, the reaction of an electrophile with a benzene ring is endergonic, has a substantial activation energy, and is rather slow. **Figure 16.1** shows an energy diagram comparing the reaction of an electrophile with an alkene and with benzene. The benzene reaction is slower (higher $\Delta G^\ddagger$) because the starting material is more stable.

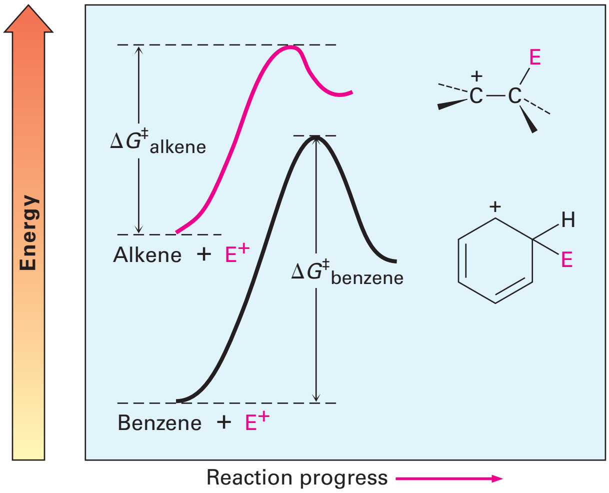


Figure 16.1 A comparison of the reactions of an electrophile (E^+) with an alkene and with benzene: $\Delta G^\ddagger_{alkene} < \Delta G^\ddagger_{benzene}$. The benzene reaction is slower than the alkene reaction because of the stability of the aromatic ring.

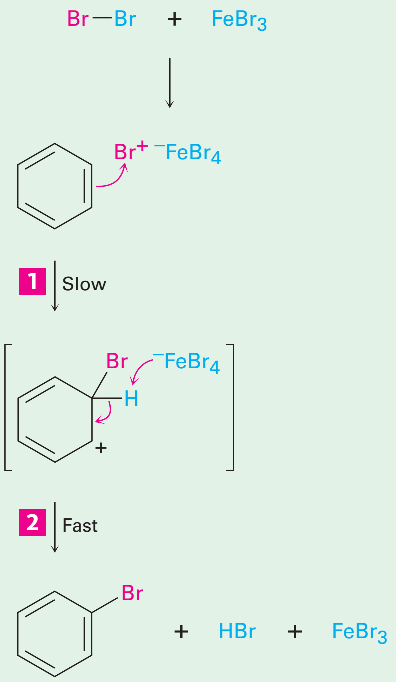
Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon to give a substitution product. Note that this loss of H^+ is similar to what occurs in the second step of an E1 reaction **(Section 11.10)**. The net effect of reaction of Br_2 with benzene is the substitution of H^+ by Br^+ by the overall mechanism shown in **Figure 16.2**.

Figure 16.2 | **MECHANISM**

The mechanism of the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.

1 An electron pair from the benzene ring attacks the positively polarized bromine, forming a new C–Br bond and leaving a nonaromatic carbocation intermediate.

2 A base removes H^+ from the carbocation intermediate, and the neutral substitution product forms as two electrons from the C–H bond move to re-form the aromatic ring.



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Why does the reaction of Br_2 with benzene take a different course than its reaction with an alkene? The answer is straightforward. If *addition* occurred, the 150 kJ/mol stabilization energy of the aromatic ring would be lost and the overall reaction would be endergonic. When *substitution* occurs, though, the stability of the aromatic ring is retained and the reaction is exergonic. An energy diagram for the overall process is shown in **Figure 16.3**.

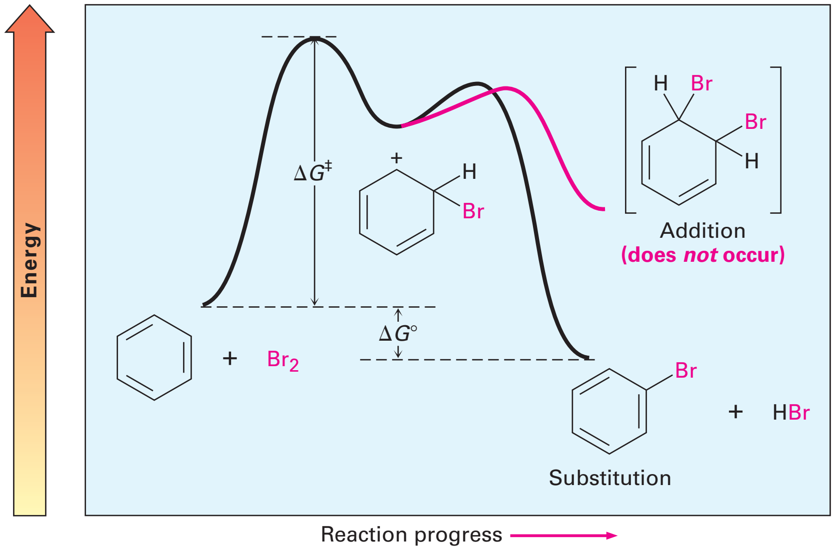


Figure 16.3 An energy diagram for the electrophilic bromination of benzene. Because the stability of the aromatic ring is retained, the overall process is exergonic.

Problem 16.1

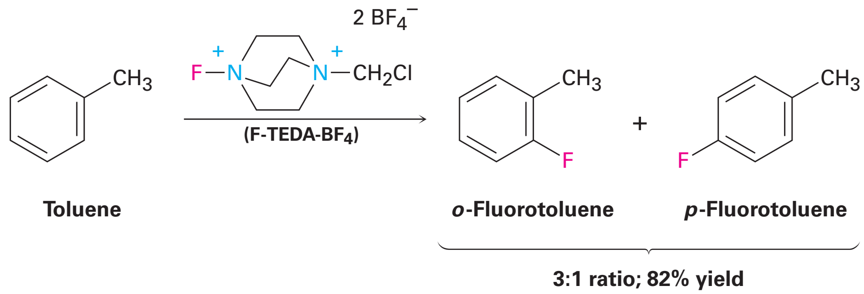
Monobromination of toluene gives a mixture of three bromotoluene products. Draw and name them.

16.2 Other Aromatic Substitutions

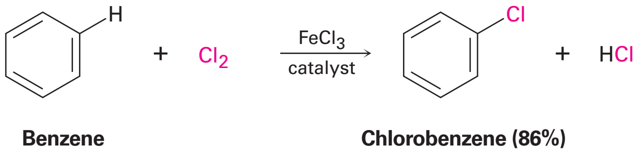
There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

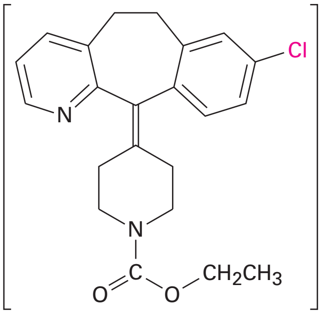
Aromatic Fluorination, Chlorination, and Iodination

Chlorine and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of monofluoroaromatic products are obtained by direct fluorination. Instead, other sources of "F^+" are used in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF_4 and is sold under the name Selectfluor.



Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with Br_2 and $FeBr_3$. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.

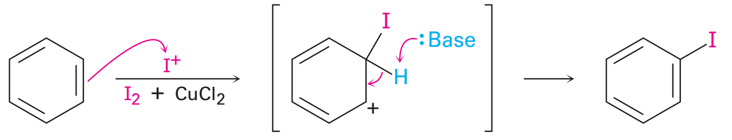




Loratadine

Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as $CuCl_2$ must be added to the reaction. These substances accelerate the iodination reaction by oxidizing I_2 to a more powerful electrophilic species that reacts as if it were I^+. The aromatic ring then reacts with I^+ in the typical way, yielding a substitution product.

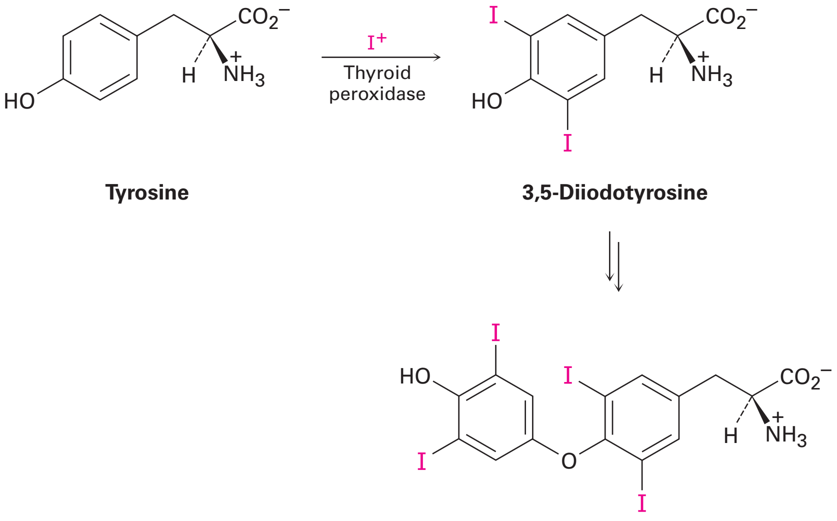
$$I_2 + 2\,Cu^{2+} \longrightarrow 2\,I^+ + 2\,Cu^+$$



Benzene

Iodobenzene (65%)

Electrophilic aromatic halogenations also occur in the biosynthesis of many naturally occurring molecules, particularly those produced by marine organisms. In humans, the best-known example occurs in the thyroid gland during the biosynthesis of thyroxine, a thyroid hormone involved in regulating growth and metabolism. The amino acid tyrosine is first iodinated by thyroid peroxidase, and two of the iodinated tyrosine molecules then couple. The electrophilic iodinating agent is an I^+ species, perhaps hypoiodous acid (HIO), that is formed from iodide ion by oxidation with H_2O_2.



Tyrosine

3,5-Diiodotyrosine

Thyroxine
(a thyroid hormone)

Aromatic Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2^+, which is formed from HNO_3 by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+ from this intermediate gives the neutral substitution product, nitrobenzene **(Figure 16.4)**.

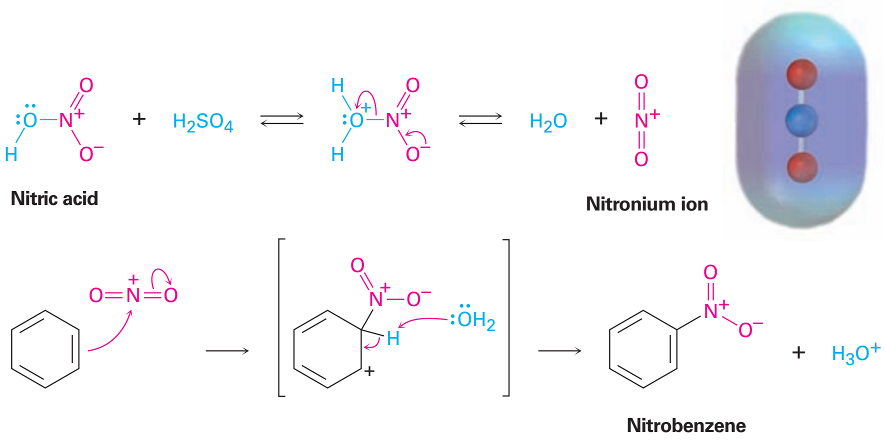
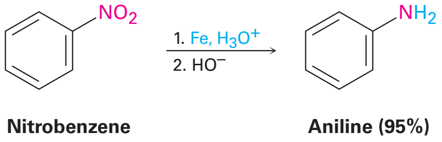


Figure 16.4 The mechanism of electrophilic nitration of an aromatic ring. An electrostatic potential map of the reactive electrophile $NO_2{}^+$ shows that the **nitrogen atom is most positive**.

Electrophilic nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be reduced by reagents such as iron, tin, or $SnCl_2$ to yield an *arylamine,* $ArNH_2$. Attachment of an amino group to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents. We'll discuss this reduction and other reactions of aromatic nitrogen compounds in Chapter 24.



Aromatic Sulfonation

Aromatic rings can be sulfonated by reaction with fuming sulfuric acid, a mixture of H_2SO_4 and SO_3. The reactive electrophile is either $HSO_3{}^+$ or neutral SO_3, depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration **(Figure 16.5)**. Note, however, that the sulfonation reaction is readily reversible; it can occur either forward or backward, depending on the reaction conditions. Sulfonation is favored in strong acid, but desulfonation is favored in hot, dilute aqueous acid.

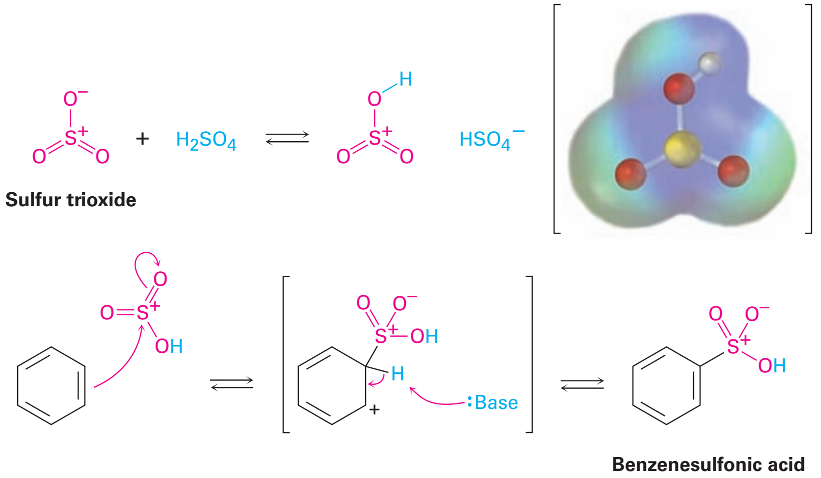
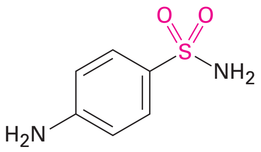


Figure 16.5 The mechanism of electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile $HOSO_2{}^+$ shows that **sulfur and hydrogen are the most positive atoms**.

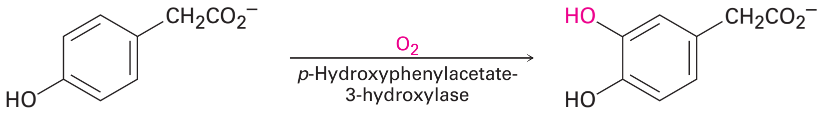
Aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. Although largely replaced today by more effective agents, sulfa drugs are still used in the treatment of meningitis and urinary tract infections. These drugs are prepared commercially by a process that involves aromatic sulfonation as the key step.



Sulfanilamide (an antibiotic)

Aromatic Hydroxylation

Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a *phenol*) is difficult and rarely done in the laboratory but occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4-dihydroxyphenylacetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



***p*-Hydroxyphenylacetate** **3,4-Dihydroxyphenylacetate**

By analogy with other electrophilic aromatic substitutions, you might expect that an electrophilic oxygen species acting as an "OH^+ equivalent" is needed for the hydroxylation reaction. That is just what happens, as shown in **Figure 16.6** on the next page. Protonation of FAD hydroperoxide, RO–OH, occurs to give an intermediate that reacts as if it were HO^+ ($RO{-}OH + H^+ \rightarrow ROH + OH^+$ and carries out an electrophilic aromatic substitution reaction. The FAD hydroperoxide is itself formed by reaction of $FADH_2$ with O_2.

Problem 16.2

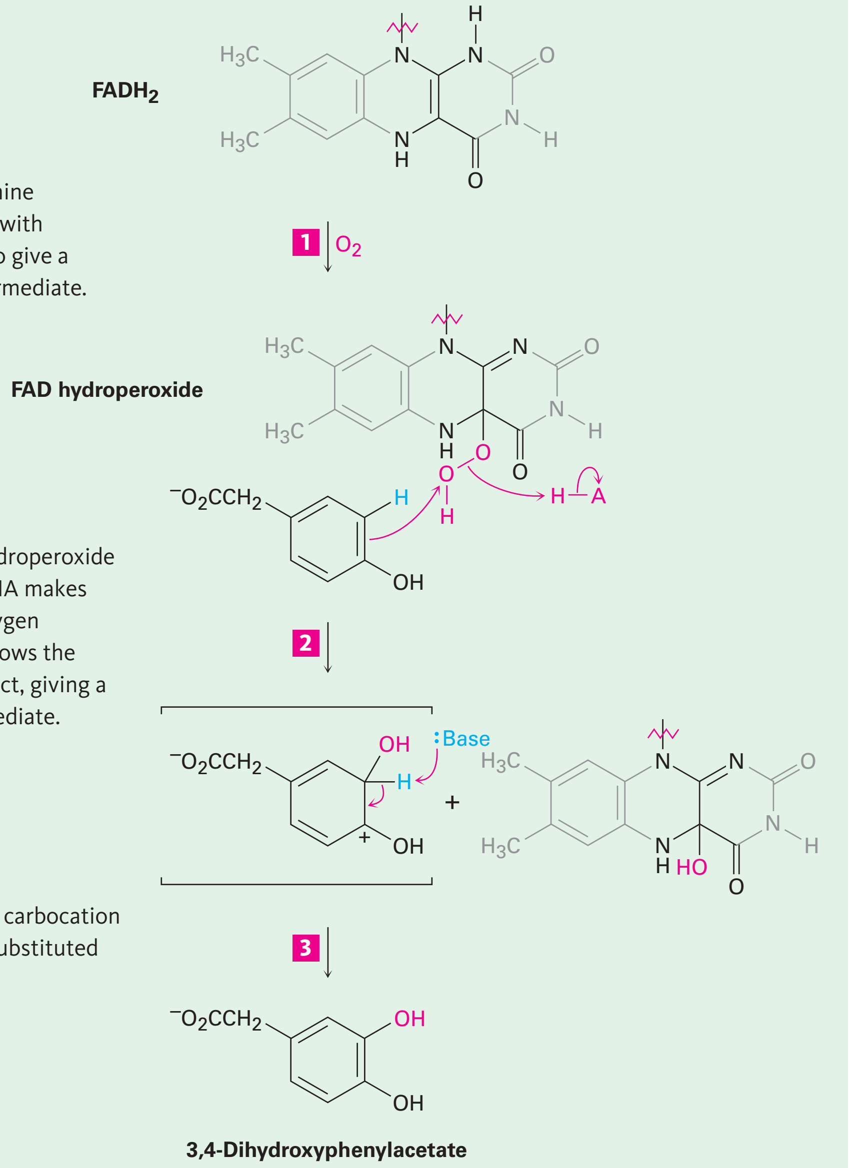
Propose a mechanism for the electrophilic fluorination of benzene with F-TEDA-BF_4.

Problem 16.3

How many products might be formed on chlorination of *o*-xylene (*o*-dimethylbenzene), *m*-xylene, and *p*-xylene?

Problem 16.4

When benzene is treated with D_2SO_4, deuterium slowly replaces all six hydrogens in the aromatic ring. Explain.



1 Reduced flavin adenine dinucleotide reacts with molecular oxygen to give a hydroperoxide intermediate.

2 Protonation of a hydroperoxide oxygen by an acid HA makes the neighboring oxygen electrophilic and allows the aromatic ring to react, giving a carbocation intermediate.

3 Loss of H^+ from the carbocation gives the hydroxy-substituted aromatic product.

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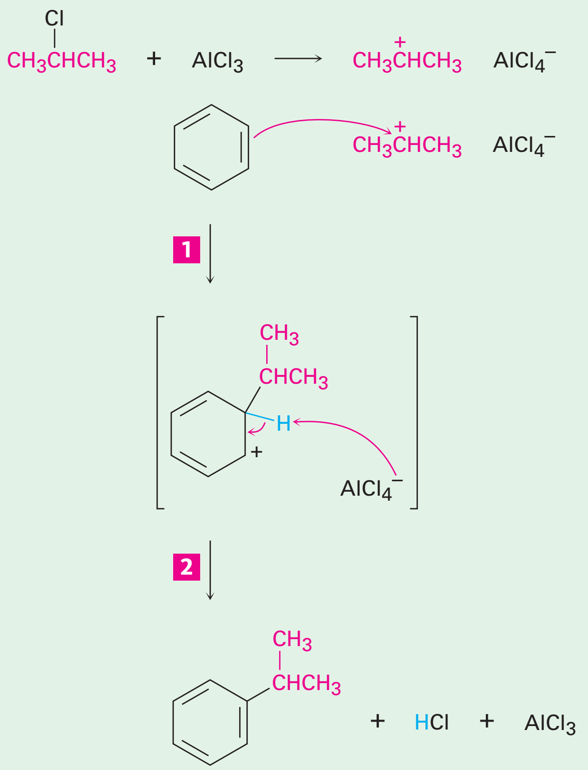
Figure 16.6 | **MECHANISM**

Mechanism of the electrophilic hydroxylation of *p*-hydroxyphenylacetate, by reaction with FAD hydroperoxide. The hydroxylating species is an "OH^+ equivalent" that arises by protonation of FAD hydroperoxide.

16.3 Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction

Among the most useful electrophilic aromatic substitution reactions in the laboratory is **alkylation**—the introduction of an alkyl group onto the benzene ring. Called the **Friedel–Crafts reaction** after its discoverers, the reaction is carried out by treating the aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R^+. Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate in much the same way that $FeBr_3$ catalyzes aromatic brominations by polarizing Br_2 **(Section 16.1)**. Loss of H^+ then completes the reaction **(Figure 16.7)**.



1 An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

2 Loss of a proton then gives the neutral alkylated substitution product.

Figure 16.7 | **MECHANISM**

Mechanism of the Friedel–Crafts alkylation reaction of benzene with 2-chloropropane to yield isopropylbenzene (cumene). The electrophile is a carbocation, generated by $AlCl_3$-assisted dissociation of an alkyl halide.

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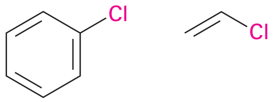
Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only *alkyl* halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.

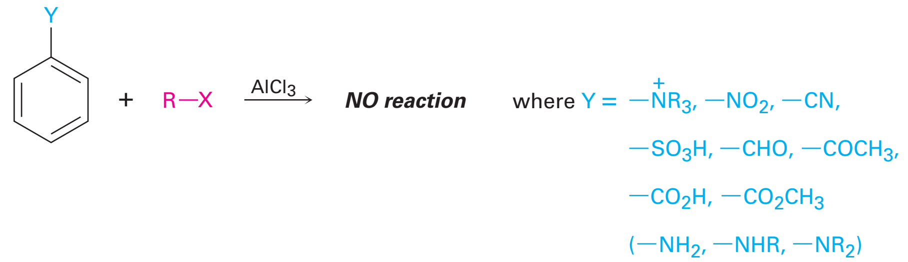
An aryl halide



A vinylic halide

Not reactive

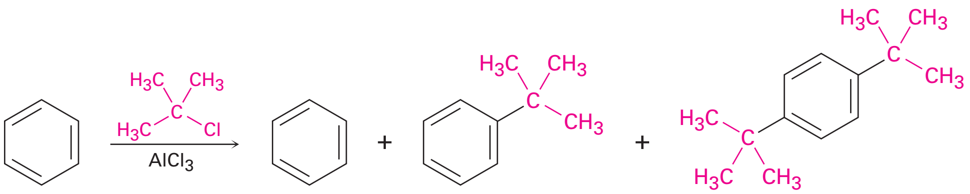
Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by a basic amino group that can be protonated. We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's subsequent reactivity toward further electrophilic substitution. Rings that contain any of the substituents listed in **Figure 16.8** do not undergo Friedel–Crafts alkylation.



where Y = $-\overset{+}{N}R_3$, $-NO_2$, $-CN$, $-SO_3H$, $-CHO$, $-COCH_3$, $-CO_2H$, $-CO_2CH_3$ ($-NH_2$, $-NHR$, $-NR_2$)

Figure 16.8 Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.

A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation*. Reaction of benzene with 1 mol equivalent of 2-chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*-butylbenzene and unreacted benzene. A high yield of monoalkylation product is obtained only when a large excess of benzene is used.

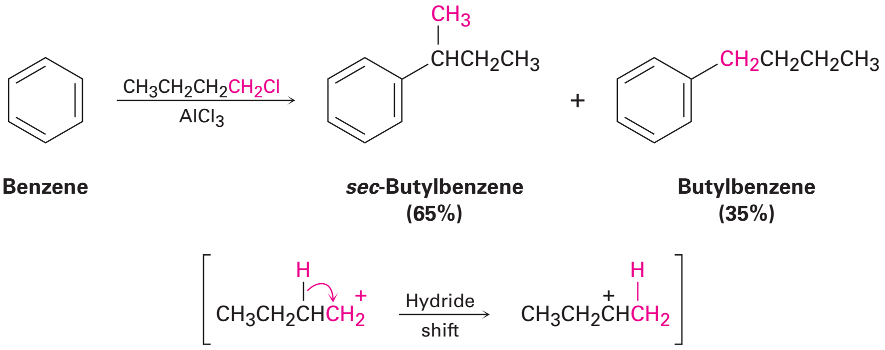


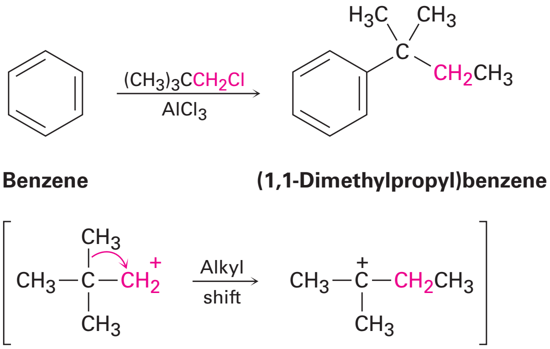
Minor product **Major product**

Yet a final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2:1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

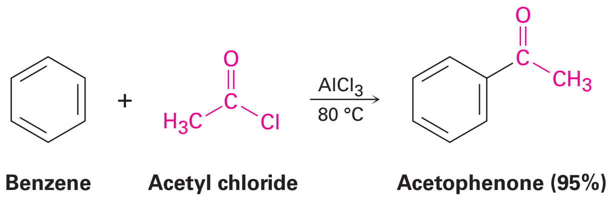
The carbocation rearrangements that accompany Friedel–Crafts reactions are like those that accompany electrophilic additions to alkenes **(Section 7.11)** and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with $AlCl_3$ rearranges to the more stable secondary butyl carbocation by shift of a hydrogen atom and its electron pair (a hydride ion, $H:^-$) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2-dimethylpropane yields

(1,1-dimethylpropyl)benzene. The initially formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.





Just as an aromatic ring is alkylated by reaction with an alkyl chloride, it is **acylated** by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$. That is, an **acyl group** (–COR; pronounced **a**-sil) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone, acetophenone.



The mechanism of the Friedel–Crafts acylation reaction is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure 16.8 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and $AlCl_3$ **(Figure 16.9)**. As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

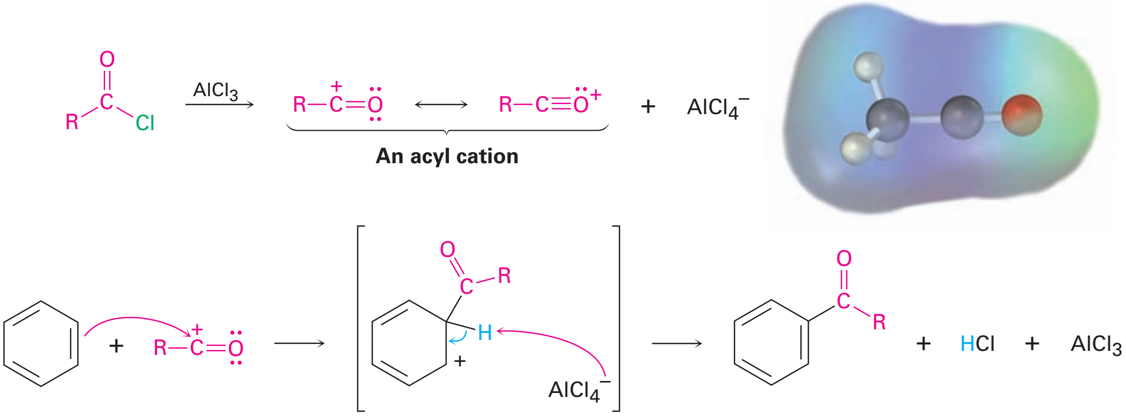
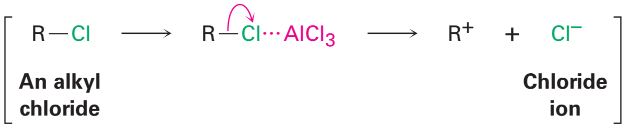
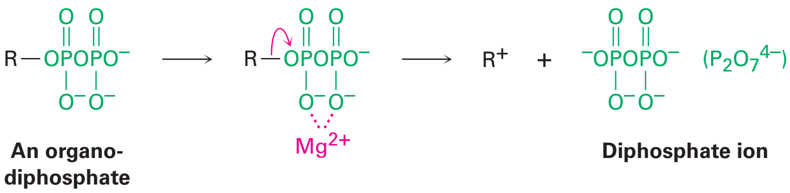


Figure 16.9 Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that **carbon is the most positive atom**.

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the nonacylated starting material. We'll account for this reactivity difference in the next section.

Aromatic alkylations occur in numerous biological pathways, although there is of course no $AlCl_3$ present in living systems to catalyze the reaction. Instead, the carbocation electrophile is typically formed by dissociation of an organodiphosphate, as we saw in **Section 11.6**. The dissociation is usually assisted by complexation to a divalent metal cation such as Mg^{2+} just as dissociation of an alkyl chloride is assisted by $AlCl_3$.





An example of a biological Friedel–Crafts reaction occurs during the biosynthesis of phylloquinone, or vitamin K_1, the human blood-clotting factor. Phylloquinone is formed by reaction of 1,4-dihydroxynaphthoic acid with phytyl diphosphate. Phytyl diphosphate first dissociates to a resonance-stabilized allylic carbocation, which then substitutes onto the aromatic ring in the typical way. Several further transformations lead to phylloquinone **(Figure 16.10)**.

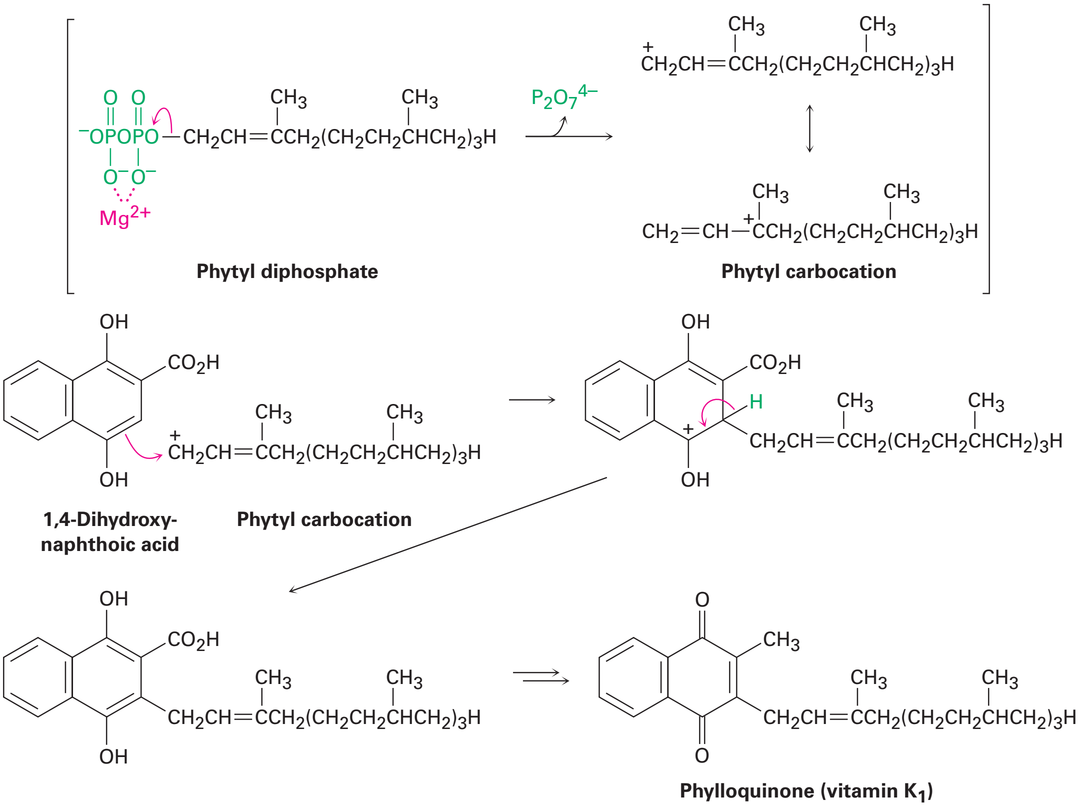


Figure 16.10 Biosynthesis of phylloquinone (vitamin K_1) from 1,4-dihydroxynaphthoic acid. The key step that joins the 20-carbon phytyl side chain to the aromatic ring is a Friedel–Crafts-like electrophilic substitution reaction with a diphosphate ion as the leaving group.

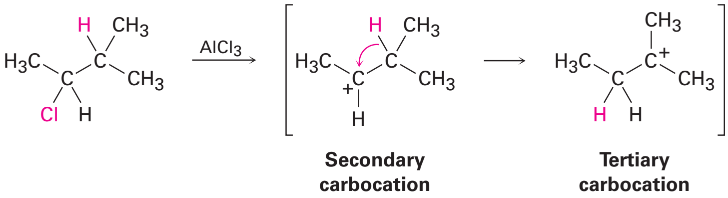
Predicting the Product of a Carbocation Rearrangement

Worked Example 16.1

The Friedel–Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of $AlCl_3$ occurs with a carbocation rearrangement. What is the structure of the product?

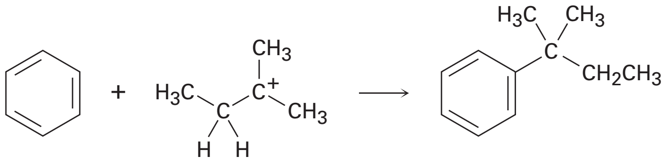
Strategy

A Friedel–Crafts reaction involves initial formation of a carbocation, which can rearrange by either a hydride shift or an alkyl shift to give a more stable carbocation. Draw the initial carbocation, assess its stability, and see if the shift of a hydride ion or an alkyl group from a neighboring carbon will result in increased stability. In the present instance, the initial carbocation is a secondary one that can rearrange to a more stable tertiary one by a hydride shift.



Use this more stable tertiary carbocation to complete the Friedel–Crafts reaction.

Solution



Problem 16.5

Which of the following alkyl halides would you expect to undergo Friedel–Crafts reaction with rearrangement and which without? Explain.

(a) CH_3CH_2Cl **(b)** $CH_3CH_2CH(Cl)CH_3$ **(c)** $CH_3CH_2CH_2Cl$
(d) $(CH_3)_3CCH_2Cl$ **(e)** Chlorocyclohexane

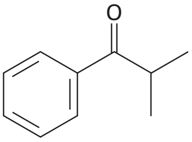
Problem 16.6

What is the major monosubstitution product from the Friedel–Crafts reaction of benzene with 1-chloro-2-methylpropane in the presence of $AlCl_3$?

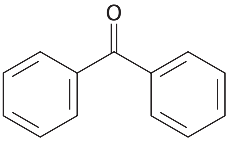
Problem 16.7

Identify the carboxylic acid chloride that might be used in a Friedel–Crafts acylation reaction to prepare each of the following acylbenzenes:

(a)



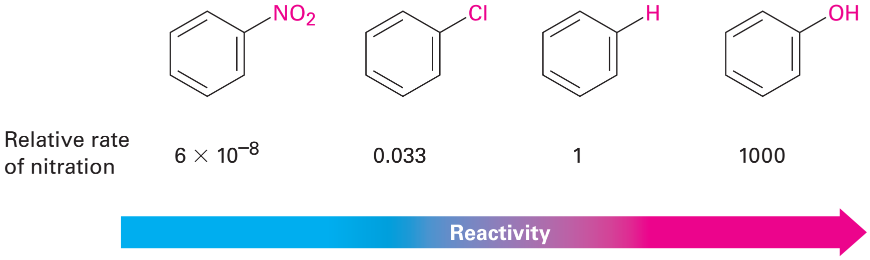
(b)



16.4 Substituent Effects in Substituted Aromatic Rings

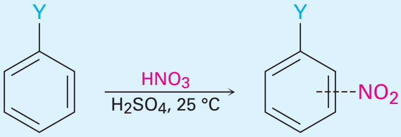
Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? A substituent already present on the ring has two effects.

- **Substituents affect the *reactivity* of the aromatic ring.** Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an –OH substituent makes the ring 1000 times more reactive than benzene, while an $-NO_2$ substituent makes the ring more than 10 million times less reactive.



- **Substituents affect the *orientation* of the reaction.** The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent already present on the benzene ring determines the position of the second substitution. An −OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as −CHO directs substitution primarily toward the meta position. Table 16.1 lists experimental results for the nitration of some substituted benzenes.

Table 16.1 Orientation of Nitration in Substituted Benzenes



	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				**Ortho- and para-directing deactivators**			
$-\overset{+}{N}(CH_3)_3$	2	87	11	−F	13	1	86
$-NO_2$	7	91	2	−Cl	35	1	64
$-CO_2H$	22	76	2	−Br	43	1	56
−CN	17	81	2	−I	45	1	54
$-CO_2CH_3$	28	66	6	**Ortho- and para-directing activators**			
$-COCH_3$	26	72	2	$-CH_3$	63	3	34
−CHO	19	72	9	−OH	50	0	50
				$-NHCOCH_3$	19	2	79

Substituents can be classified into three groups, as shown in **Figure 16.11**: *ortho- and para-directing activators, ortho- and para-directing deactivators,* and *meta-directing deactivators*. There are no meta-directing activators. Notice how the directing effect of a group correlates with its reactivity. All meta-directing groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

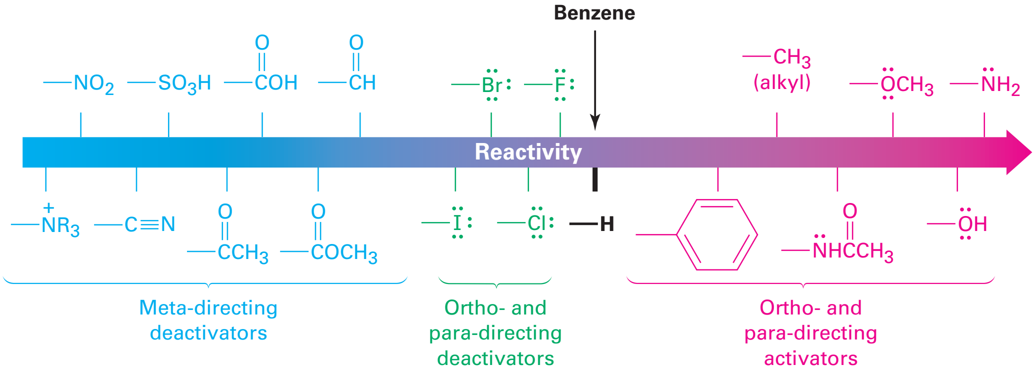


Figure 16.11 Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing.

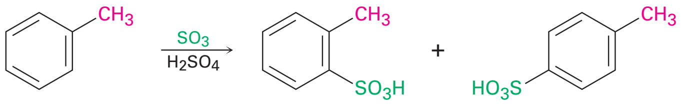
Worked Example 16.2 Predicting the Product of an Electrophilic Aromatic Substitution Reaction

Predict the major product of the sulfonation of toluene.

Strategy

Identify the substituent present on the ring, and decide whether it is ortho- and para-directing or meta-directing. According to Figure 16.11, an alkyl substituent is ortho- and para-directing, so sulfonation of toluene will give primarily a mixture of *o*-toluenesulfonic acid and *p*-toluenesulfonic acid.

Solution



Toluene **o-Toluenesulfonic acid** **p-Toluenesulfonic acid**

Problem 16.8

Rank the compounds in each of the following groups in order of their reactivity to electrophilic substitution:

(a) Nitrobenzene, phenol, toluene, benzene
(b) Phenol, benzene, chlorobenzene, benzoic acid
(c) Benzene, bromobenzene, benzaldehyde, aniline

Problem 16.9

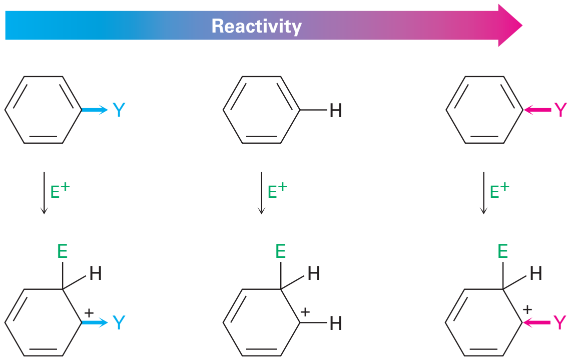
Predict the major products of the following reactions:

(a) Nitration of bromobenzene **(b)** Bromination of nitrobenzene
(c) Chlorination of phenol **(d)** Bromination of aniline

16.5 An Explanation of Substituent Effects

Activation and Deactivation of Aromatic Rings

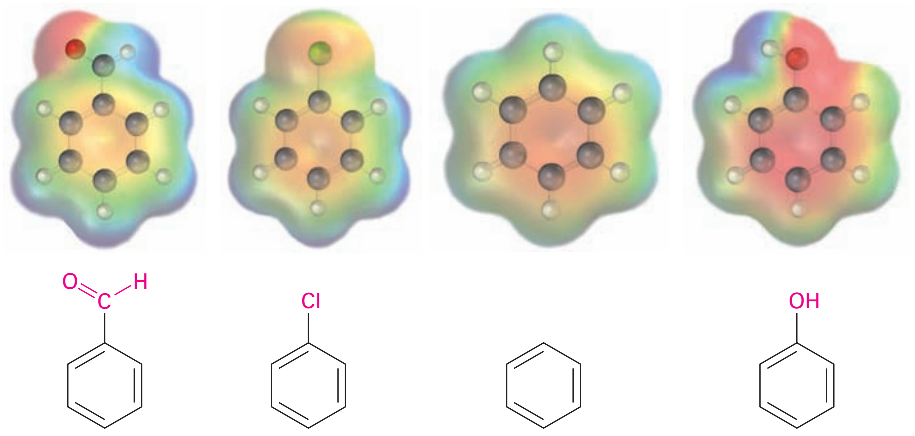
What makes a group either activating or deactivating? The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

Y donates electrons; carbocation intermediate is more stable, and ring is more reactive.

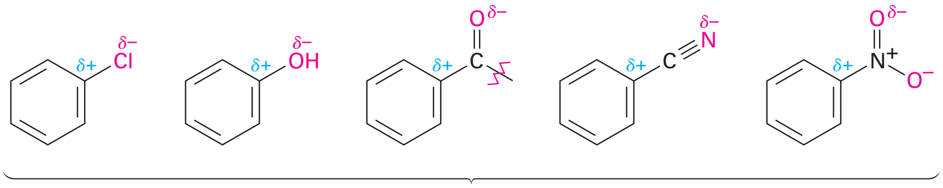
Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. As shown in **Figure 16.12**, the ring is more positive (yellow-green) when an electron-withdrawing group such as −CHO or −Cl is present and more negative (red) when an electron-donating group such as −OH is present.



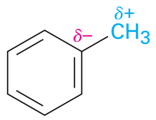
Benzaldehyde **Chlorobenzene** **Benzene** **Phenol**

Figure 16.12 Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group (−CHO or −Cl) makes the ring more **electron-poor**, while an electron-donating group (−OH) makes the ring more **electron-rich**.

The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive effects* and *resonance effects*. As we saw in **Section 2.1**, an **inductive effect** is the withdrawal or donation of electrons through a σ bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the σ bond linking the substituent to a benzene ring. The effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes **(Section 7.6)** and carbocations **(Section 7.9)**.

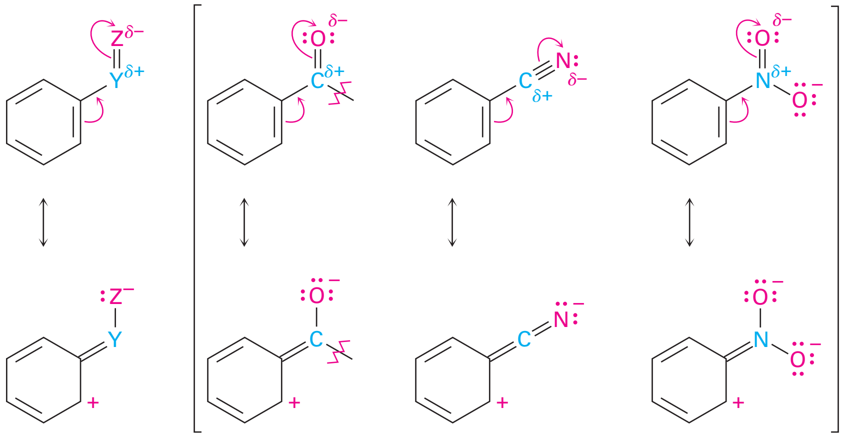


Inductive electron withdrawal



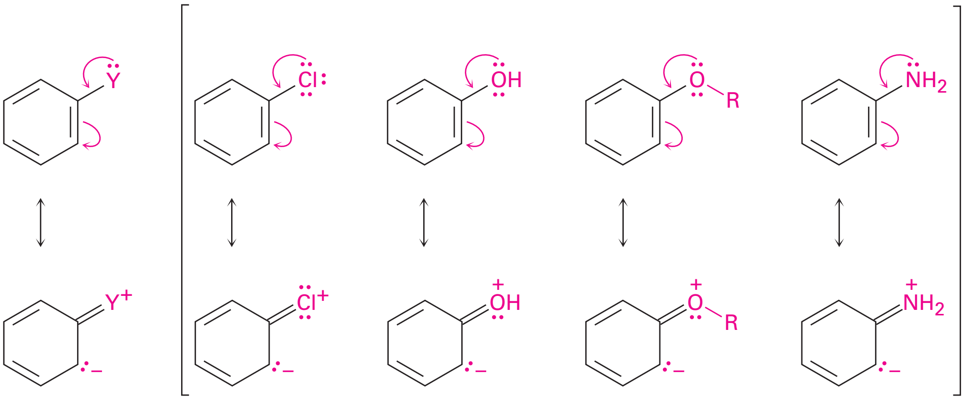
Inductive electron donation

A **resonance effect** is the withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The π electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electron-withdrawing resonance effect have the general structure —Y=Z, where the Z atom is more electronegative than Y.



Resonance electron-withdrawing group

Conversely, halogen, hydroxyl, alkoxyl (—OR), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge in the ring. Substituents with an electron-donating resonance effect have the general structure $-\ddot{Y}$, where the Y atom has a lone pair of electrons available for donation to the ring.

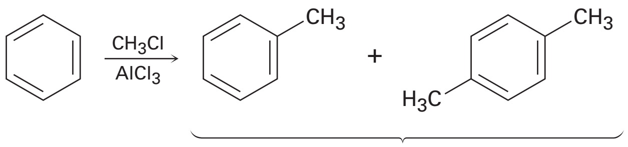


Resonance electron-donating group

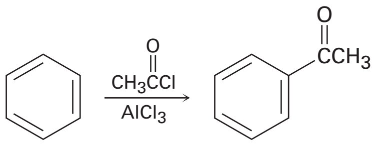
One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxyl, and amino substituents, for instance, have electron-withdrawing inductive effects because of the electronegativity of the −X, −O, or −N atom bonded to the aromatic ring but have electron-donating resonance effects because of the lone-pair electrons on those −X, −O, or −N atoms. When the two effects act in opposite directions, the stronger effect dominates. Thus, hydroxyl, alkoxyl, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Halogens, however, are deactivators because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect.

Problem 16.10

Use Figure 16.11 to explain why Friedel–Crafts alkylations often give polysubstitution but Friedel–Crafts acylations do not.



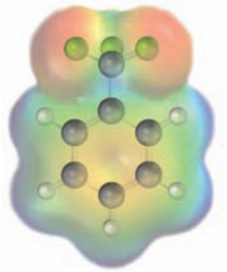
(Product mixture)



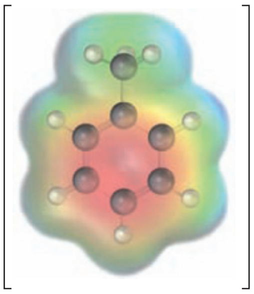
(Sole product)

Problem 16.11

An electrostatic potential map of (trifluoromethyl)benzene, $C_6H_5CF_3$, is shown. Would you expect (trifluoromethyl)benzene to be more reactive or less reactive than toluene toward electrophilic substitution? Explain.



(Trifluoromethyl)benzene



Toluene

Ortho- and Para-Directing Activators: Alkyl Groups

Inductive and resonance effects account not only for reactivity but also for the orientation of electrophilic aromatic substitutions. Take alkyl groups, for instance, which have an electron-donating inductive effect and are ortho and para directors. The results of toluene nitration are shown in **Figure 16.13**.

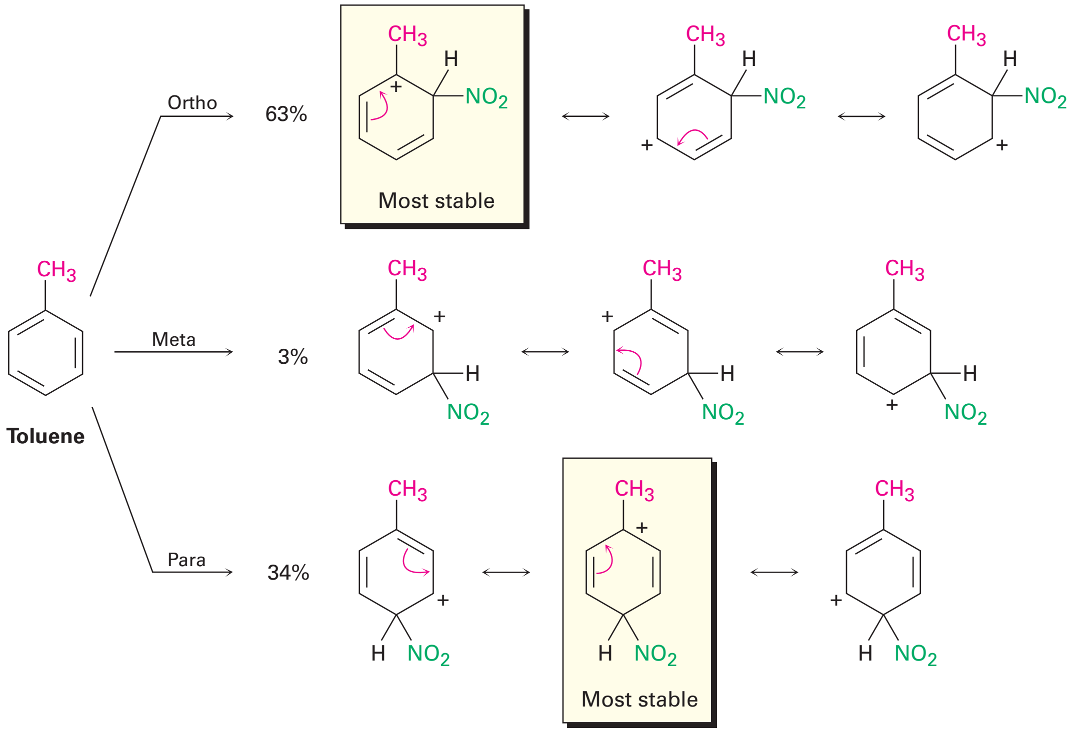


Figure 16.13 Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in Figure 16.13. Although all three intermediates are resonance-stabilized, the ortho and para intermediates are more stabilized than the meta intermediate. For both the ortho and para reactions, but not for the meta reaction, a resonance form places the positive charge directly on the methyl-substituted carbon, where it is in a tertiary position and can be stabilized by the electron-donating inductive effect of the methyl group. The ortho and para intermediates are thus lower in energy than the meta intermediate and form faster.

Ortho- and Para-Directing Activators: OH and NH_2

Hydroxyl, alkoxyl, and amino groups are also ortho–para activators, but for a different reason than for alkyl groups. As described earlier in this section, hydroxyl, alkoxyl, and amino groups have a strong, electron-donating resonance effect that outweighs a weaker electron-withdrawing inductive effect. When phenol is nitrated, for instance, reaction can occur either ortho, meta, or para to the –OH group, giving the carbocation intermediates shown in **Figure 16.14**. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. The intermediate from meta reaction has no such stabilization.

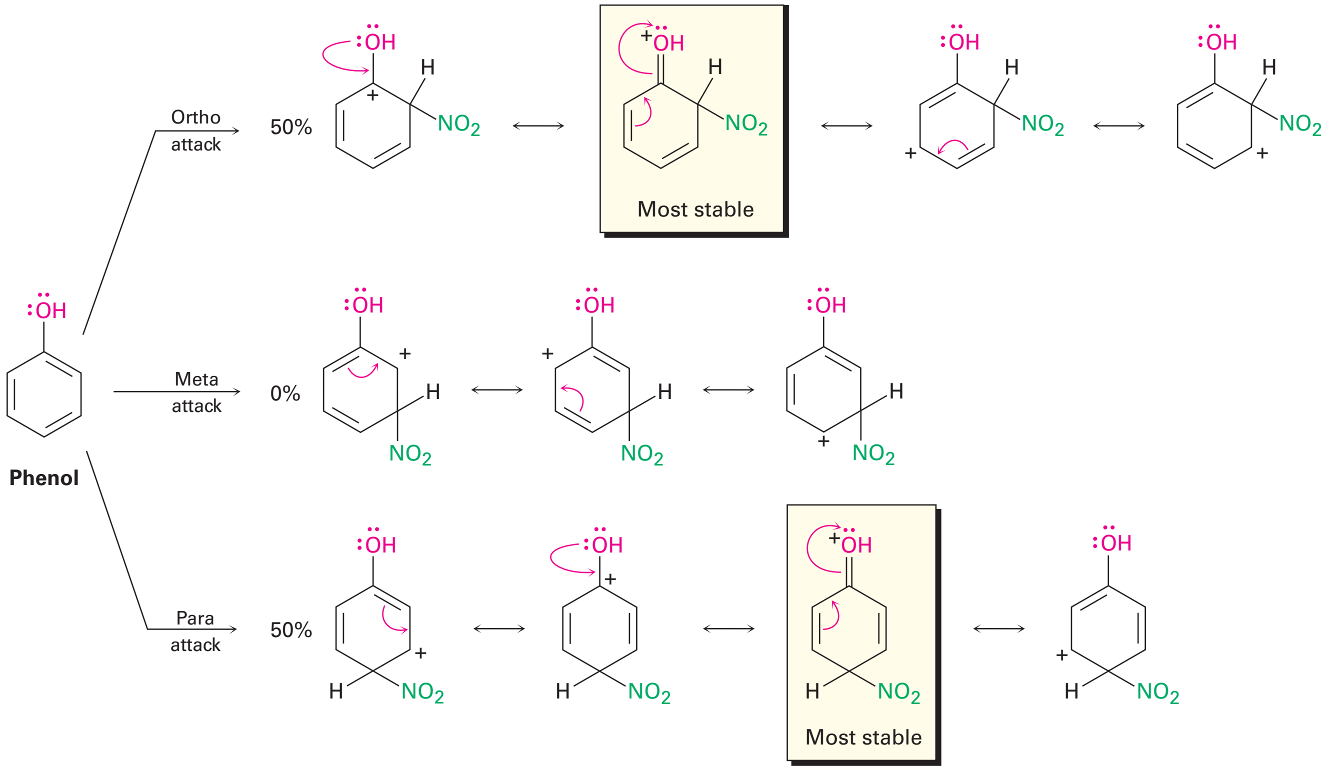
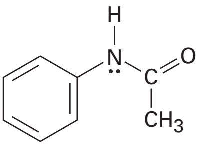


Figure 16.14 Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that involves electron donation from the oxygen atom.

Problem 16.12

Acetanilide is less reactive than aniline toward electrophilic substitution. Explain.



Acetanilide

Ortho- and Para-Directing Deactivators: Halogens

Halogens are deactivating because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect. Although weak, that electron-donating resonance effect is nevertheless felt only at the ortho and para positions and not at the meta position **(Figure 16.15)**. Thus, a halogen substituent can stabilize the positive charge of the carbocation intermediates from ortho and para reaction in the same way that hydroxyl and amino substituents can. The meta intermediate, however, has no such stabilization and is therefore formed more slowly.

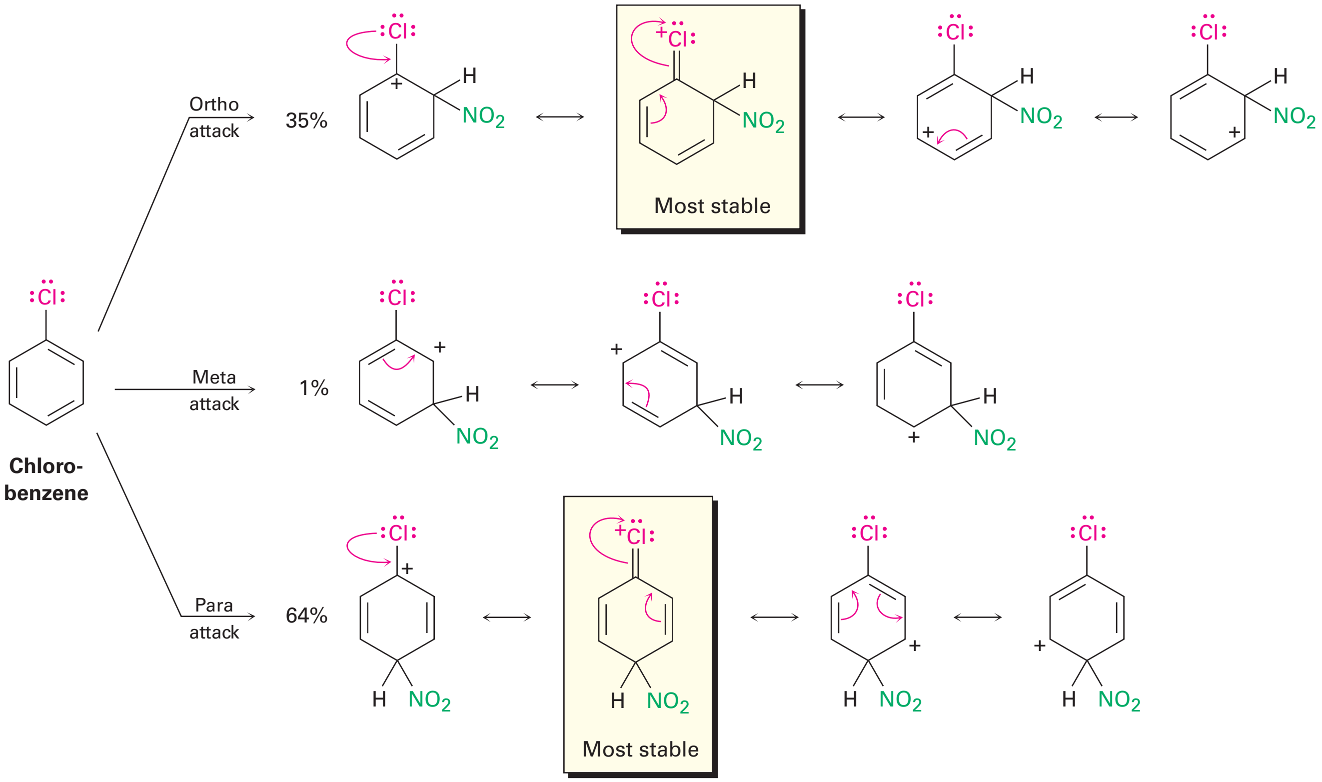


Figure 16.15 Carbocation intermediates in the nitration of chlorobenzene. The ortho and para intermediates are more stable than the meta intermediate because of electron donation of the halogen lone-pair electrons.

Note again that halogens, hydroxyl, alkoxyl, and amino groups all withdraw electrons inductively but donate electrons by resonance. Halogens have a stronger electron-withdrawing inductive effect but a weaker electron-donating resonance effect and are thus deactivators. Hydroxyl, alkoxyl, and amino groups have a weaker electron-withdrawing inductive effect but a stronger electron-donating resonance effect and are thus activators. All are ortho and para directors, however, because of the lone pair of electrons on the atom bonded to the aromatic ring.

Meta-Directing Deactivators

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the nitration of benzaldehyde, for instance **(Figure 16.16)**. Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, but the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the C=O group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

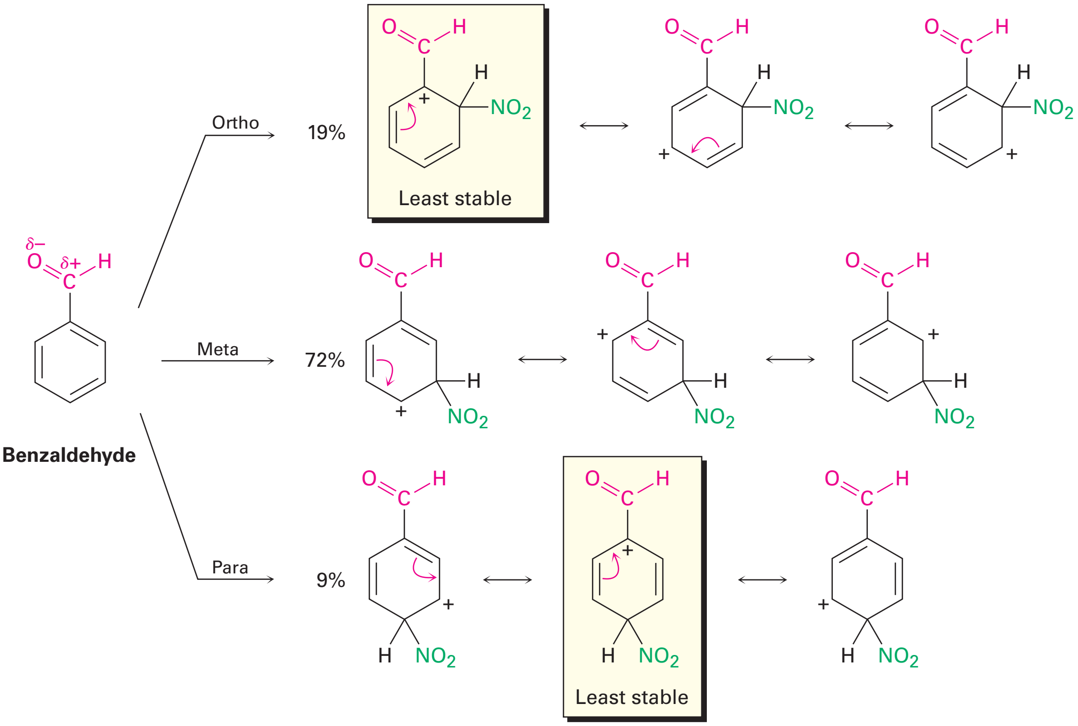


Figure 16.16 Carbocation intermediates in the nitration of benzaldehyde. The ortho and para intermediates are less stable than the meta intermediate. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom ($\delta+$) directly attached to the ring will make one of the resonance forms of the ortho and para intermediates unfavorable and will thus act as a meta director.

Problem 16.13

Draw resonance structures for the intermediates from reaction of an electrophile at the ortho, meta, and para positions of nitrobenzene. Which intermediates are most stable?

A Summary of Substituent Effects in Aromatic Substitution

A summary of the activating and directing effects of substituents in electrophilic aromatic substitution is shown in Table 16.2.

Key **IDEAS**

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

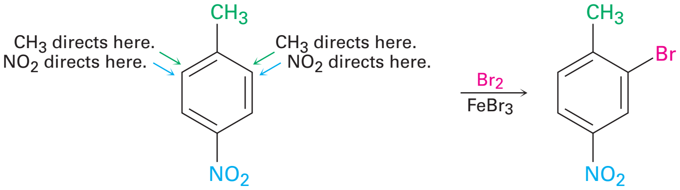
Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

16.6 Trisubstituted Benzenes: Additivity of Effects

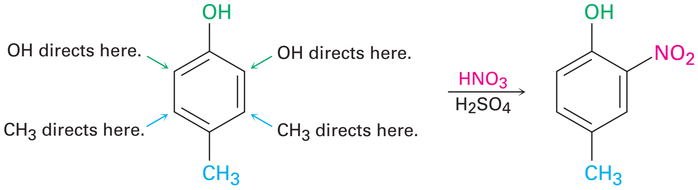
Electrophilic substitution of a disubstituted benzene ring is governed by the same resonance and inductive effects that affect monosubstituted rings. The only difference is that it's necessary to consider the additive effects of two different groups. In practice, this isn't as difficult as it sounds; three rules are usually sufficient.

1. If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.



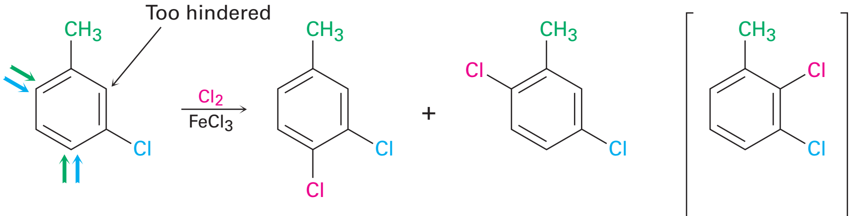
***p*-Nitrotoluene** **2-Bromo-4-nitrotoluene**

2. If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products are often formed. For example, bromination of *p*-methylphenol yields primarily 2-bromo-4-methylphenol because $-OH$ is a more powerful activator than $-CH_3$.



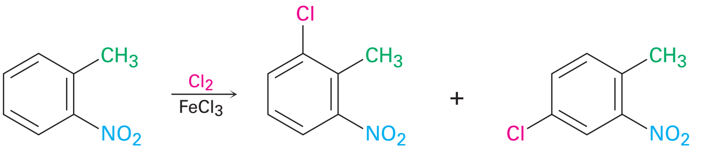
***p*-Methylphenol** **4-Methyl-2-nitrophenol**

3. Further substitution rarely occurs between the two groups in a meta-disubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as by substitution of an ortho-disubstituted compound.



***m*-Chlorotoluene** **3,4-Dichlorotoluene** **2,5-Dichlorotoluene** ***Not* formed**

But:



***o*-Nitrotoluene** **2-Chloro-6-nitrotoluene** **4-Chloro-2-nitrotoluene**

Predicting the Product of Substitution on a Disubstituted Benzene

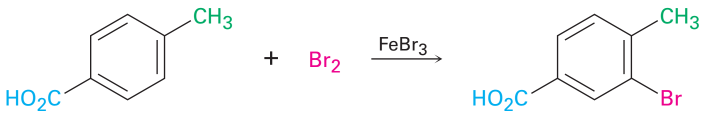
Worked Example
16.3

What product would you expect from bromination of *p*-methylbenzoic acid?

Strategy

Identify the two substituents present on the ring, decide the directing effect of each and, if necessary, decide which substituent is the stronger activator. In the present case, the carboxyl group ($-CO_2H$) is a meta director and the methyl group is an ortho and para director. Both groups direct bromination to the position next to the methyl group, yielding 3-bromo-4-methylbenzoic acid.

Solution

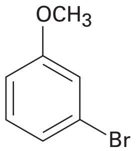


***p*-Methylbenzoic acid** **3-Bromo-4-methylbenzoic acid**

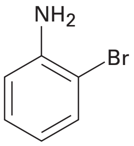
Problem 16.14

At what position would you expect electrophilic substitution to occur in each of the following substances?

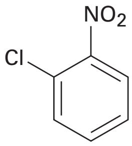
(a)



(b)



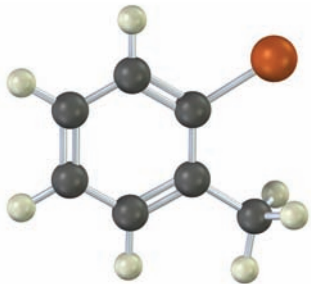
(c)



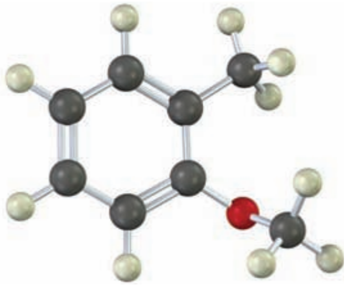
Problem 16.15

Show the major product(s) from reaction of the following substances with (1) CH_3CH_2Cl, $AlCl_3$ and (2) HNO_3, H_2SO_4:

(a)

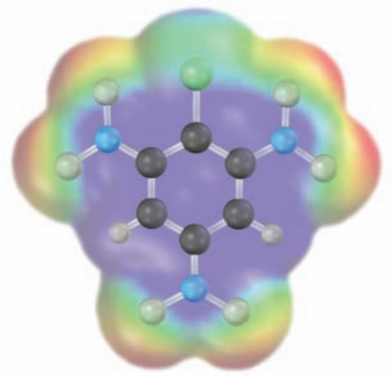


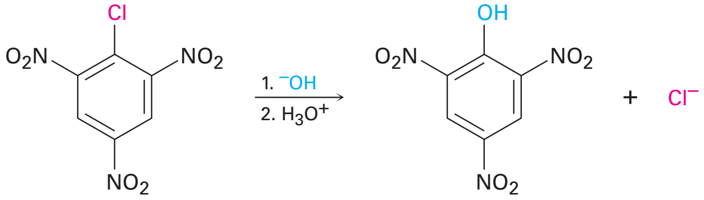
(b)



16.7 Nucleophilic Aromatic Substitution

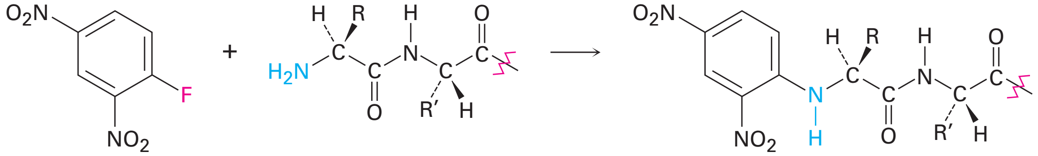
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. The nucleophile OH^- has substituted for Cl^-.





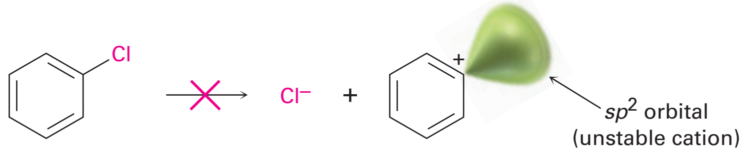
2,4,6-Trinitrochlorobenzene **2,4,6-Trinitrophenol (100%)**

Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent,* to attach a "label" to the terminal NH_2 group of the amino acid at one end of the protein chain.

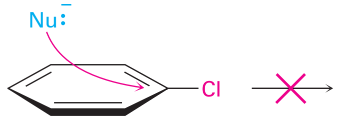


2,4-Dinitrofluorobenzene **A protein** **A labeled protein**

Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides discussed in Chapter 11, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through the aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction.

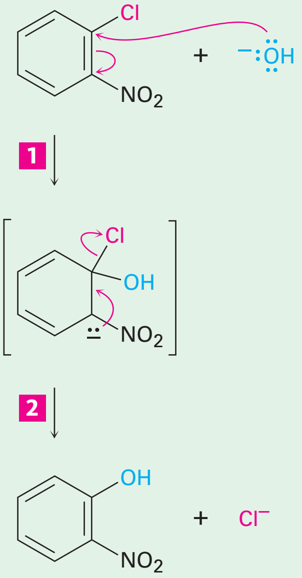
Nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in **Figure 16.17**. The nucleophile first adds to the electron-deficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a Meisenheimer complex after its discoverer. Halide ion is then eliminated.

Figure 16.17 | **MECHANISM**

Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance-stabilized carbanion intermediate.

1 Nucleophilic addition of hydroxide ion to the electron-poor aromatic ring takes place, yielding a stabilized carbanion intermediate.

2 The carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.



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Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance **(Figure 16.18)**. A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH⁻.

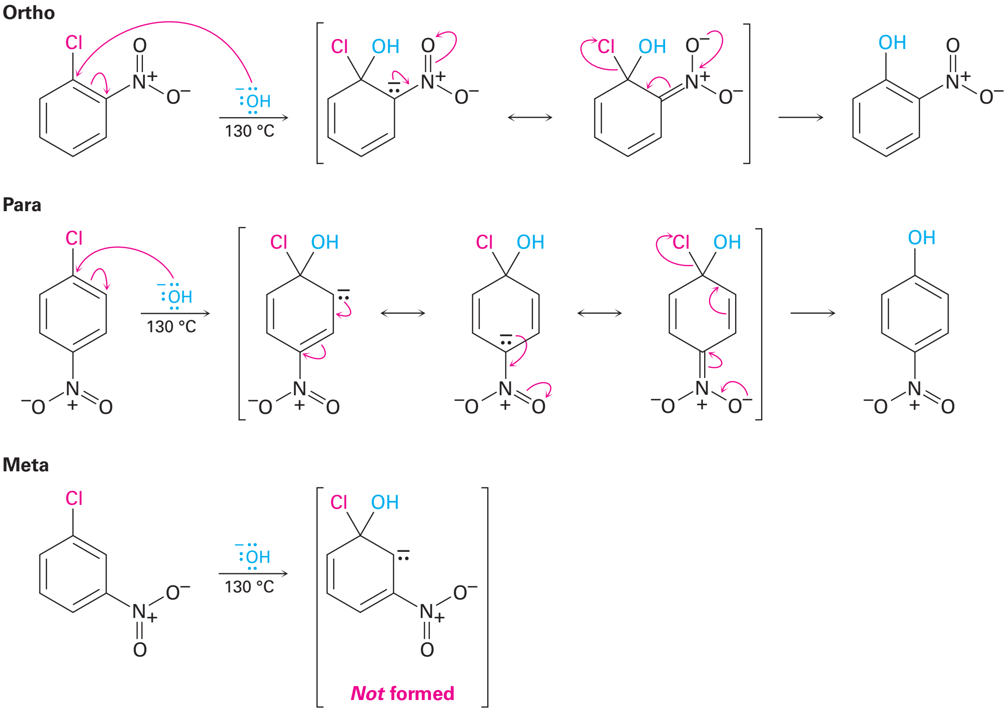
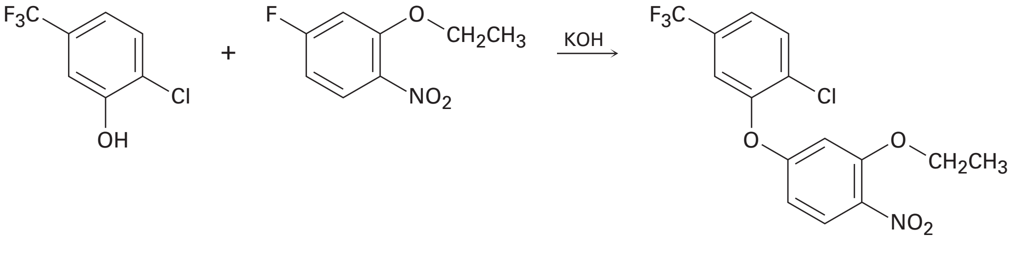


Figure 16.18 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that *deactivate* rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) *activate* them for nucleophilic substitution. What's more, these groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

Problem 16.16

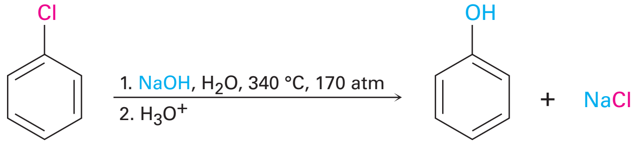
The herbicide oxyfluorfen can be prepared by reaction between a phenol and an aryl fluoride. Propose a mechanism.



Oxyfluorfen

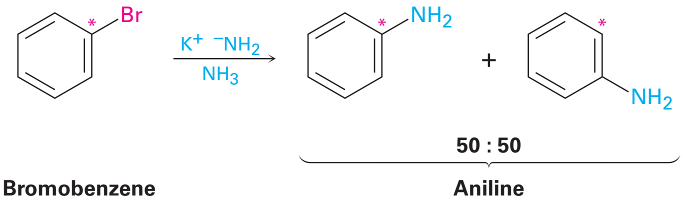
16.8 Benzyne

Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. Chemists at the Dow Chemical Company discovered in 1928 that phenol could be prepared on a large industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340 °C under 170 atm pressure.

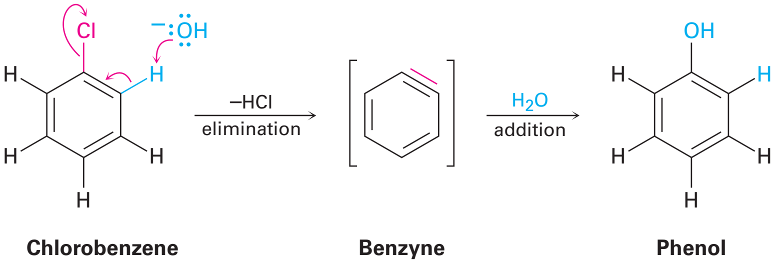


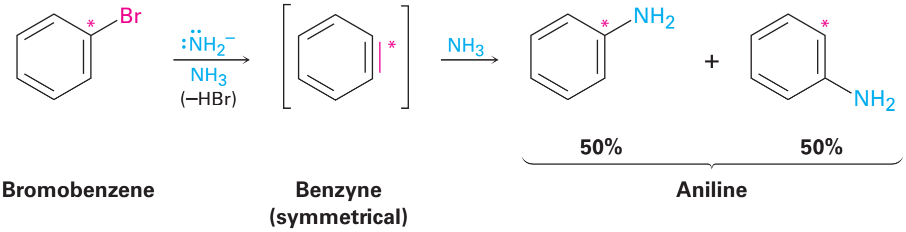
Chlorobenzene **Phenol**

A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH_2) in liquid NH_3 solvent, for instance, gives aniline. Curiously, though, when bromobenzene labeled with radioactive ^{14}C at the C1 position is used, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.



Further mechanistic evidence comes from trapping experiments. When bromobenzene is treated with KNH_2 in the presence of a conjugated diene, such as furan, a Diels–Alder reaction **(Section 14.4)** occurs, implying that the symmetrical intermediate is a **benzyne**, formed by elimination of HBr from bromobenzene. Benzyne is too reactive to be isolated as a pure compound but, in the presence of water, addition occurs to give the phenol. In the presence of a diene, Diels–Alder cycloaddition takes place.





The electronic structure of benzyne, shown in **Figure 16.19**, is that of a highly distorted alkyne. Although a typical alkyne triple bond uses *sp*-hybridized carbon atoms, the benzyne triple bond uses sp^2-hybridized carbons. Furthermore, a typical alkyne triple bond has two mutually perpendicular π bonds formed by *p–p* overlap, but the benzyne triple bond has one π bond formed by *p–p* overlap and one π bond formed by sp^2–sp^2 overlap. The latter π bond is in the plane of the ring and is very weak.

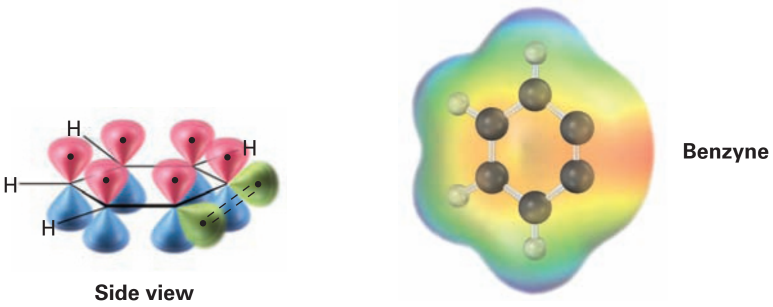


Figure 16.19 An orbital picture and electrostatic potential map of benzyne. The benzyne carbons are sp^2-hybridized, and the "third" bond results from weak overlap of two adjacent sp^2 orbitals.

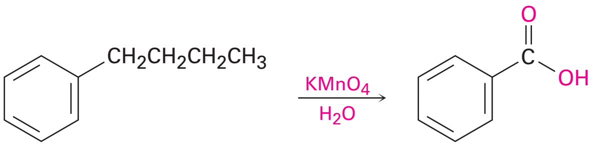
Problem 16.17

Treatment of *p*-bromotoluene with NaOH at 300 °C yields a mixture of *two* products, but treatment of *m*-bromotoluene with NaOH yields a mixture of *three* products. Explain.

16.9 Oxidation of Aromatic Compounds

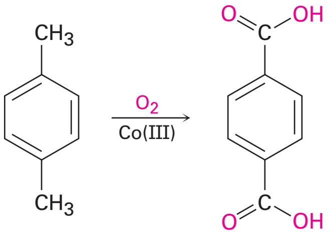
Oxidation of Alkyl Side Chains

Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as $KMnO_4$ and $Na_2Cr_2O_7$, reagents that will cleave alkene carbon–carbon bonds **(Section 8.8)**. It turns out, however, that the presence of the aromatic ring has a dramatic effect on alkyl side chains. Alkyl side chains react rapidly with oxidizing agents and are converted into carboxyl groups, $-CO_2H$.The net effect is conversion of an alkylbenzene into a benzoic acid, Ar–R → $Ar-CO_2H$. Butylbenzene is oxidized by aqueous $KMnO_4$ to give benzoic acid, for instance.



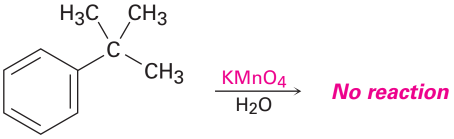
Butylbenzene **Benzoic acid (85%)**

A similar oxidation is employed industrially for the preparation of the terephthalic acid used in the production of polyester fibers. Worldwide, approximately 20 million tons per year of terephthalic acid is produced by oxidation of *p*-xylene, using air as the oxidant and Co(III) salts as catalyst.



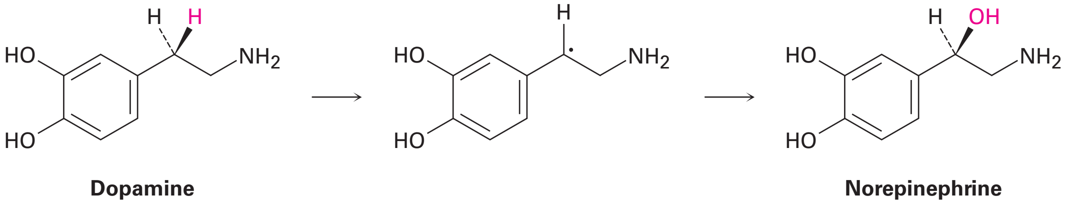
***p*-Xylene** **Terephthalic acid**

The mechanism of side-chain oxidation is complex and involves reaction of C–H bonds at the position next to the aromatic ring to form intermediate benzylic radicals. *tert*-Butylbenzene has no benzylic hydrogens, however, and is therefore inert.



***tert*-Butylbenzene**

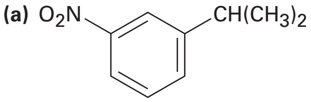
Analogous side-chain oxidations occur in various biosynthetic pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine β-monooxygenase and occurs by a radical mechanism. A copper–oxygen species in the enzyme first abstracts the *pro*-R benzylic hydrogen to give a radical, and a hydroxyl is then transferred from copper to carbon.



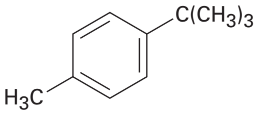
Problem 16.18

What aromatic products would you obtain from the $KMnO_4$ oxidation of the following substances?

(a)

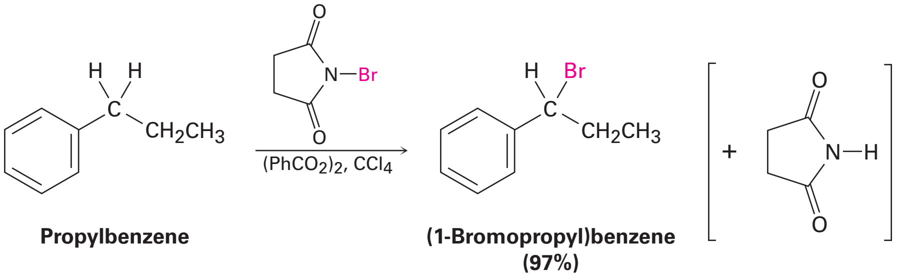


(b)

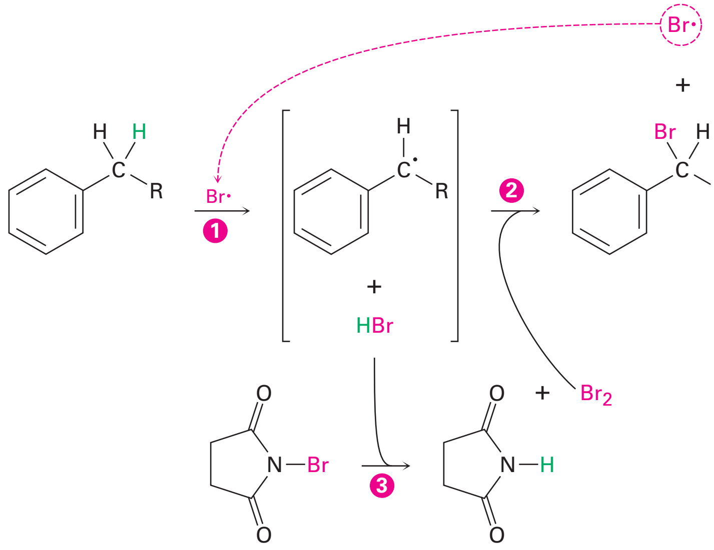


Bromination of Alkylbenzene Side Chains

Side-chain bromination at the benzylic position occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS). For example, propylbenzene gives (1-bromopropyl)benzene in 97% yield on reaction with NBS in the presence of benzoyl peroxide, $(PhCO_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position next to the aromatic ring and does not give a mixture of products.



The mechanism of benzylic bromination is similar to that discussed in **Section 10.3** for allylic bromination of alkenes. Abstraction of a benzylic hydrogen atom first generates an intermediate benzylic radical, which then reacts with Br_2 in step 2 to yield product and a Br• radical that cycles back into the reaction to carry on the chain. The Br_2 necessary for reaction with the benzylic radical is produced in step 3 by a concurrent reaction of HBr with NBS.



Reaction occurs exclusively at the benzylic position because the benzylic radical intermediate is stabilized by resonance. **Figure 16.20** shows how the benzyl radical is stabilized by overlap of its *p* orbital with the ring π electron system.

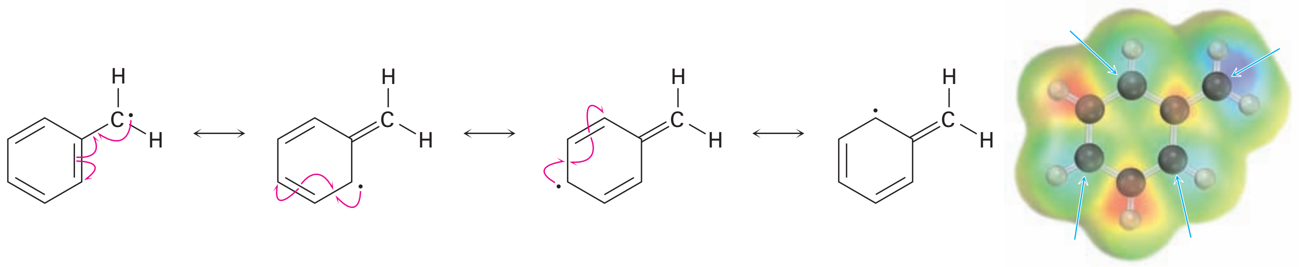


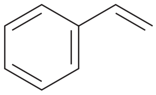
Figure 16.20 A resonance-stabilized benzylic radical. The spin-density surface shows that the **unpaired electron** is shared by the ortho and para carbons of the ring.

Problem 16.19

Refer to Table 6.3 on page 204 for a quantitative idea of the stability of a benzyl radical. How much more stable (in kJ/mol) is the benzyl radical than a primary alkyl radical? How does a benzyl radical compare in stability to an allyl radical?

Problem 16.20

Styrene, the simplest alkenylbenzene, is prepared commercially for use in plastics manufacture by catalytic dehydrogenation of ethylbenzene. How might you prepare styrene from benzene using reactions you've studied?

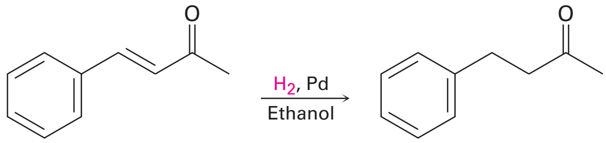


Styrene

16.10 Reduction of Aromatic Compounds

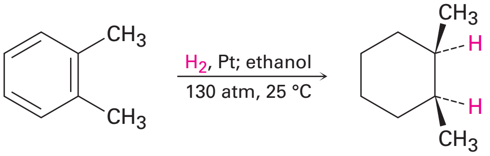
Catalytic Hydrogenation of Aromatic Rings

Just as aromatic rings are generally inert to oxidation, they're also inert to catalytic hydrogenation under conditions that reduce typical alkene double bonds. As a result, it's possible to reduce an alkene double bond selectively in the presence of an aromatic ring. For example, 4-phenyl-3-buten-2-one is reduced to 4-phenyl-2-butanone using a palladium catalyst at room temperature and atmospheric pressure. Neither the benzene ring nor the ketone carbonyl group is affected.

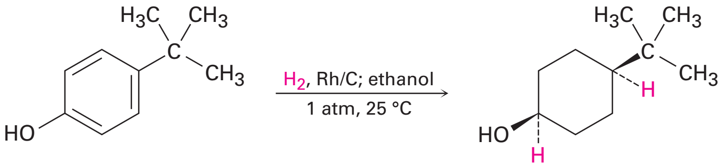


4-Phenyl-3-buten-2-one **4-Phenyl-2-butanone (100%)**

To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at several hundred atmospheres pressure or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For example, *o*-xylene yields 1,2-dimethylcyclohexane, and 4-*tert*-butylphenol gives 4-*tert*-butylcyclohexanol.



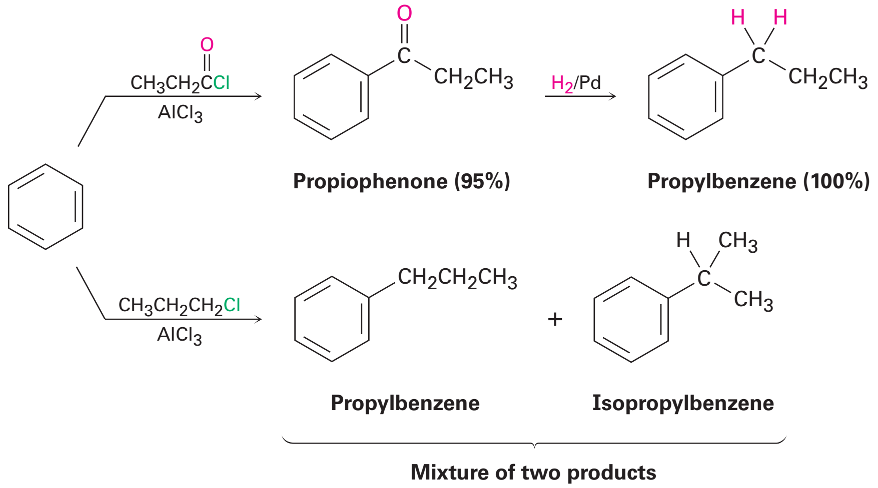
***o*-Xylene** ***cis*-1,2-Dimethylcyclohexane**



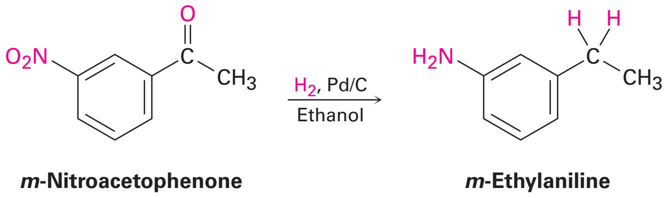
4-*tert*-Butylphenol ***cis*-4-*tert*-Butylcyclohexane**

Reduction of Aryl Alkyl Ketones

In the same way that an aromatic ring activates a neighboring (benzylic) C–H toward oxidation, it also activates a benzylic carbonyl group toward reduction. Thus, an aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst. Propiophenone, for instance, is reduced to propylbenzene by catalytic hydrogenation. Since the net effect of Friedel–Crafts acylation followed by reduction is the preparation of a primary alkylbenzene, this two-step sequence of reactions makes it possible to circumvent the carbocation rearrangement problems associated with direct Friedel–Crafts alkylation using a primary alkyl halide **(Section 16.3)**.



The conversion of a carbonyl group into a methylene group (C=O → CH_2) by catalytic hydrogenation is limited to aryl alkyl ketones; dialkyl ketones are not reduced under these conditions. Furthermore, the catalytic reduction of aryl alkyl ketones is not compatible with the presence of a nitro substituent on the aromatic ring because a nitro group is reduced to an amino group under the reaction conditions. We'll see a more general method for reducing ketone carbonyl groups to yield alkanes in **Section 19.9**.



Problem 16.21

How would you prepare diphenylmethane, $(Ph)_2CH_2$, from benzene and an acid chloride?

16.11 Synthesis of Polysubstituted Benzenes

One of the surest ways to learn organic chemistry is to work synthesis problems. The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of a great many organic reactions. Not only must you know *which* reactions to use, you must also know *when* to use them because the order in which reactions are carried out is often critical to the success of the overall scheme.

The ability to plan a sequence of reactions in the right order is particularly important in the synthesis of substituted aromatic rings, where the introduction of a new substituent is strongly affected by the directing effects of other substituents. Planning syntheses of substituted aromatic compounds is therefore a good way to gain confidence in using the many reactions learned in the past few chapters.

During our previous discussion of strategies for working synthesis problems in **Section 9.9**, we said that it's usually best to work a problem backward, or *retrosynthetically*. Look at the target molecule and ask yourself, "What is an immediate precursor of this compound?" Choose a likely answer and continue working backward, one step at a time, until you arrive at a simple starting material. Let's try some examples.

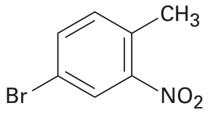
Synthesizing a Polysubstituted Benzene

Worked Example 16.4

Synthesize 4-bromo-2-nitrotoluene from benzene.

Strategy

Draw the target molecule, identify the substituents, and recall how each group can be introduced separately. Then plan retrosynthetically.

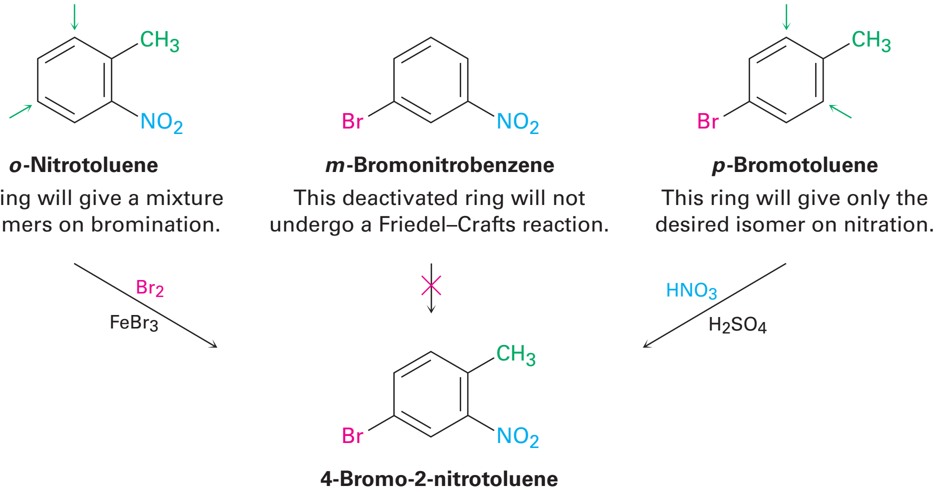


4-Bromo-2-nitrotoluene

The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $Br_2/FeBr_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $CH_3Cl/AlCl_3$, and a nitro group can be introduced by nitration with HNO_3/H_2SO_4.

Solution

Ask yourself, "What is an immediate precursor of the target?" The final step will involve introduction of one of three groups—bromine, methyl, or nitro—so we have to consider three possibilities. Of the three, the bromination of *o*-nitrotoluene could be used because the activating methyl group would dominate the deactivating nitro group and direct bromination to the right position. Unfortunately, a mixture of product isomers would be formed. A Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on a nitro-substituted (strongly deactivated) benzene. The best precursor of the desired product is probably *p*-bromotoluene, which can be nitrated ortho to the activating methyl group to give a single product.



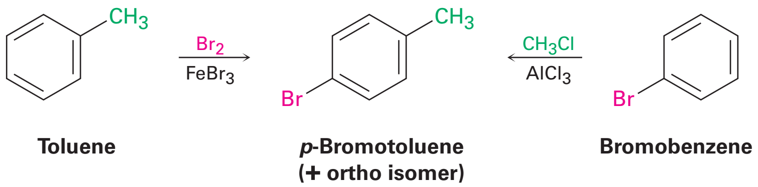
***o*-Nitrotoluene**
This ring will give a mixture of isomers on bromination.

***m*-Bromonitrobenzene**
This deactivated ring will not undergo a Friedel–Crafts reaction.

***p*-Bromotoluene**
This ring will give only the desired isomer on nitration.

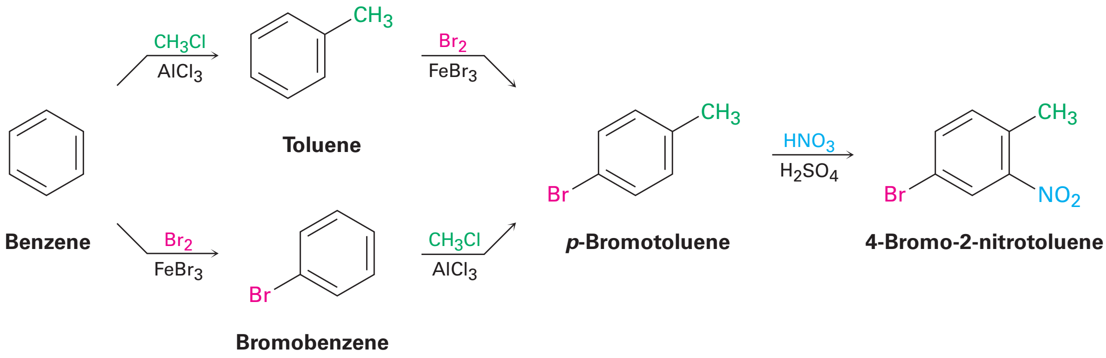
4-Bromo-2-nitrotoluene

Next ask, “What is an immediate precursor of *p*-bromotoluene?” Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts methylation and obtain a mixture of ortho and para products. Both answers are satisfactory, although both would also lead unavoidably to a product mixture that would have to be separated.



“What is an immediate precursor of toluene?” Benzene, which could be methylated in a Friedel–Crafts reaction. Alternatively, “What is an immediate precursor of bromobenzene?” Benzene, which could be brominated.

The retrosynthetic analysis has provided two valid routes from benzene to 4-bromo-2-nitrotoluene.

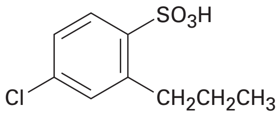


Worked Example 16.5 Synthesizing a Polysubstituted Benzene

Synthesize 4-chloro-2-propylbenzenesulfonic acid from benzene.

Strategy

Draw the target molecule, identify its substituents, and recall how each of the three can be introduced. Then plan retrosynthetically.

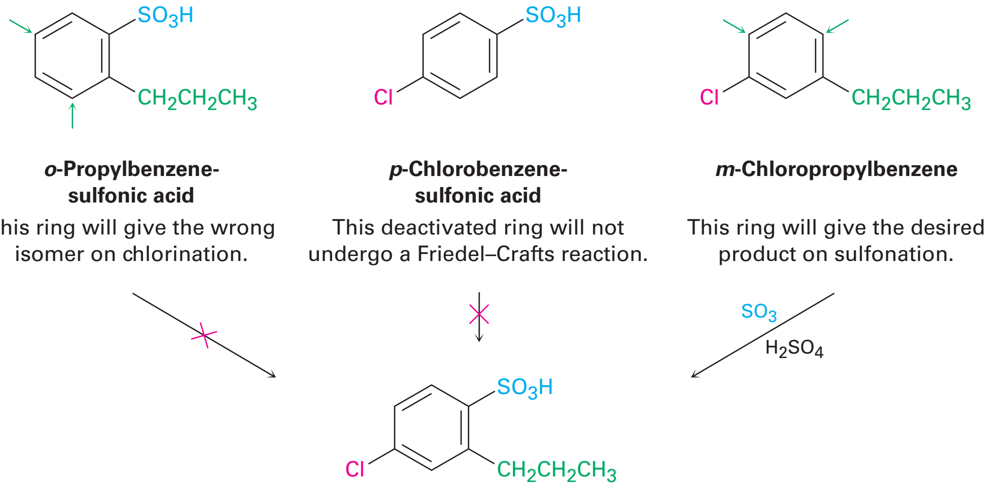


4-Chloro-2-propylbenzenesulfonic acid

The three substituents on the ring are a chlorine, a propyl group, and a sulfonic acid group. A chlorine can be introduced by chlorination with $Cl_2/FeCl_3$, a propyl group can be introduced by Friedel–Crafts acylation with $CH_3CH_2COCl/AlCl_3$ followed by reduction with H_2/Pd, and a sulfonic acid group can be introduced by sulfonation with SO_3/H_2SO_4.

Solution

"What is an immediate precursor of the target?" The final step will involve introduction of one of three groups—chlorine, propyl, or sulfonic acid—so we have to consider three possibilities. Of the three, the chlorination of *o*-propylbenzenesulfonic acid can't be used because the reaction would occur at the wrong position. Similarly, a Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on sulfonic acid-substituted (strongly deactivated) benzenes. Thus, the immediate precursor of the desired product is probably *m*-chloropropylbenzene, which can be sulfonated to give a mixture of product isomers that must then be separated.



***o*-Propylbenzene-sulfonic acid**

This ring will give the wrong isomer on chlorination.

***p*-Chlorobenzene-sulfonic acid**

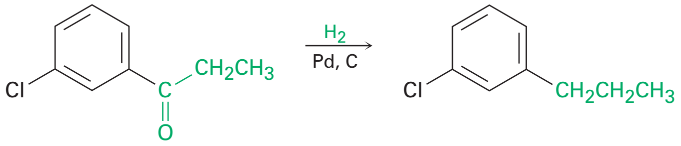
This deactivated ring will not undergo a Friedel–Crafts reaction.

***m*-Chloropropylbenzene**

This ring will give the desired product on sulfonation.

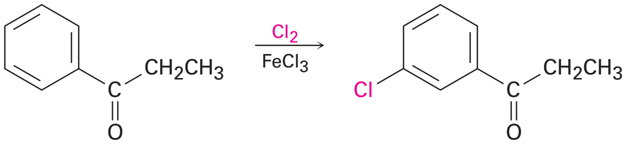
4-Chloro-2-propylbenzenesulfonic acid

"What is an immediate precursor of *m*-chloropropylbenzene?" Because the two substituents have a meta relationship, the first substituent placed on the ring must be a meta director so that the second substitution will take place at the proper position. Furthermore, because primary alkyl groups such as propyl can't be introduced directly by Friedel–Crafts alkylation, the precursor of *m*-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced.



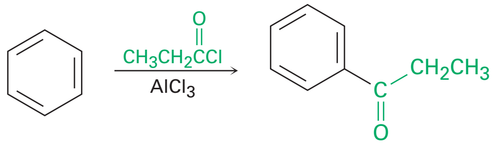
***m*-Chloropropiophenone** ***m*-Chloropropylbenzene**

"What is an immediate precursor of *m*-chloropropiophenone?" Propiophenone, which could be chlorinated in the meta position.



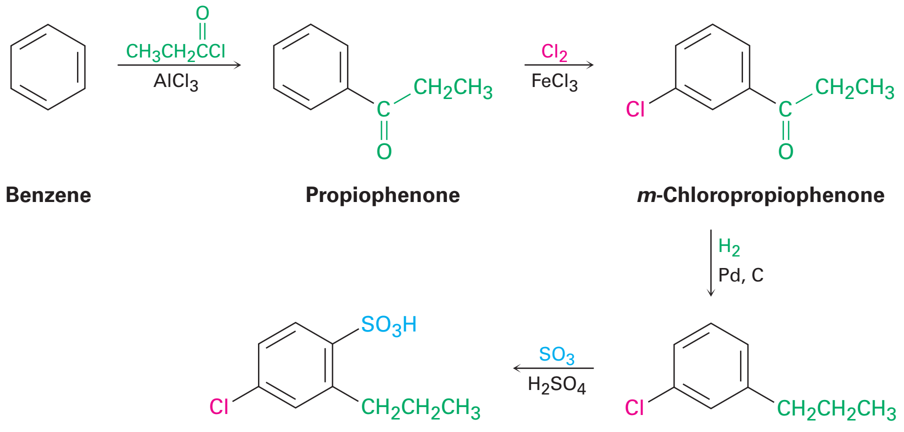
Propiophenone ***m*-Chloropropiophenone**

"What is an immediate precursor of propiophenone?" Benzene, which could undergo Friedel–Crafts acylation with propanoyl chloride and $AlCl_3$.



Benzene **Propiophenone**

The final synthesis is a four-step route from benzene:



Benzene **Propiophenone** ***m*-Chloropropiophenone**

4-Chloro-2-propylbenzenesulfonic acid ***m*-Chloropropylbenzene**

Planning an organic synthesis has been compared with playing chess. There are no tricks; all that's required is a knowledge of the allowable moves (the organic reactions) and the discipline to plan ahead, carefully evaluating the consequences of each move. Practicing may not be easy, but it's a great way to learn organic chemistry.

Problem 16.22

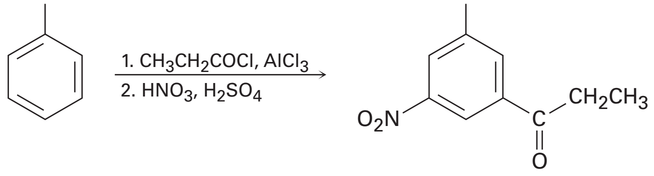
How might you synthesize the following substances from benzene?

(a) *m*-Chloronitrobenzene **(b)** *m*-Chloroethylbenzene
(c) 4-Chloro-1-nitro-2-propylbenzene **(d)** 3-Bromo-2-methylbenzenesulfonic acid

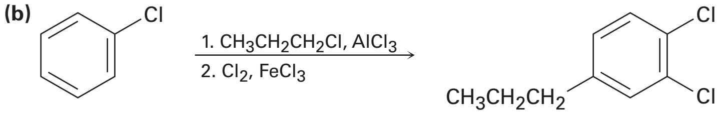
Problem 16.23

In planning a synthesis, it's as important to know what not to do as to know what to do. As written, the following reaction schemes have flaws in them. What is wrong with each?

(a)

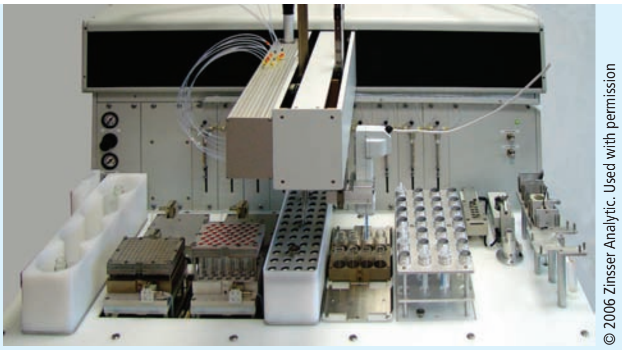


(b)



A DEEPER LOOK

Combinatorial Chemistry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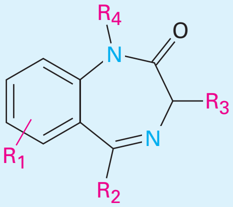
Organic chemistry by robot means no spilled flasks!

Traditionally, organic compounds have been synthesized one at a time. This works well for preparing large amounts of a few substances, but it doesn't work so well for preparing small amounts of a great many substances. This latter goal is particularly important in the pharmaceutical industry, where vast numbers of structurally similar compounds must be screened to find the optimum drug candidate.

To speed the process of drug discovery, *combinatorial chemistry* has been developed to prepare what are called *combinatorial libraries,* in which anywhere from a few dozen to several hundred thousand substances are prepared simultaneously. Among the early successes of combinatorial chemistry is the development of a benzodiazepine library, a class of aromatic compounds much used as antianxiety agents.



Benzodiazepine library (R_1–R_4 are various organic substituents)

Two main approaches to combinatorial chemistry are used—*parallel synthesis* and *split synthesis*. In parallel synthesis, each compound is prepared independently. Typically, a reactant is first linked to the surface of polymer beads, which are then placed into small wells on a 96-well glass plate. Programmable robotic instruments add different sequences of building blocks to the different wells, thereby making 96 different products. When the reaction sequences are complete, the polymer beads are washed and their products are released.

In split synthesis, the initial reactant is again linked to the surface of polymer beads, which are then divided into several groups. A different building block is added to each group of beads, the different groups are combined, and the reassembled mix is again split to form new groups. Another building block is added to each group, the groups are again combined and redivided, and the process continues. If, for example, the beads are divided into four groups at each step, the number of compounds increases in the progression 4 → 16 → 64 → 256. After 10 steps, more than 1 million compounds have been prepared **(Figure 16.21)**.

(continued)

(continued)

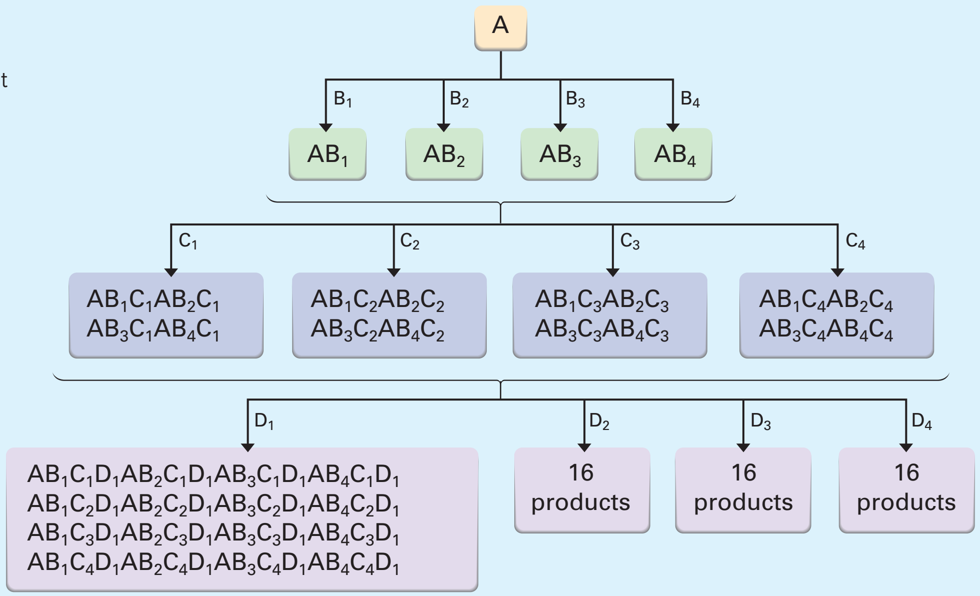


Figure 16.21 The results of split combinatorial synthesis. Assuming that 4 different building blocks are used at each step, 64 compounds result after 3 steps, and more than one million compounds result after 10 steps.

Of course, with so many different final products mixed together, the problem is to identify them. What structure is linked to what bead? Several approaches to this problem have been developed, all of which involve the attachment of encoding labels to each polymer bead to keep track of the chemistry each has undergone. Encoding labels used thus far have included proteins, nucleic acids, halogenated aromatic compounds, and even computer chips.

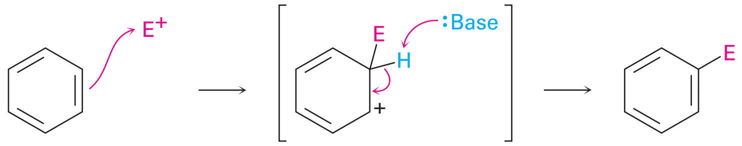
Summary

Key words

acyl group, 577
acylation, 577
alkylation, 575
benzyne, 595
electrophilic aromatic substitution, 566
Friedel–Crafts reaction, 575
inductive effect, 583
nucleophilic aromatic substitution, 592
resonance effect, 584

We've continued the coverage of aromatic molecules in this chapter, shifting focus to concentrate on reactions. In particular, we've looked at the relationship between aromatic structure and reactivity, a relationship critical to understanding how numerous biological molecules and pharmaceutical agents are synthesized and why they behave as they do.

An **electrophilic aromatic substitution reaction** takes place in two steps—initial reaction of an electrophile, E^+, with the aromatic ring, followed by loss of H^+ from the resonance-stabilized carbocation intermediate to regenerate the aromatic ring.



Many variations of the reaction can be carried out, including halogenation, nitration, and sulfonation. **Friedel–Crafts alkylation** and **acylation** reactions, which involve reaction of an aromatic ring with carbocation electrophiles, are particularly useful. They are limited, however, by the fact that the aromatic ring must be at least as reactive as a halobenzene. In addition, polyalkylation and carbocation rearrangements often occur in Friedel–Crafts alkylation.

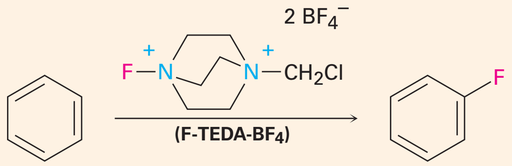
Substituents on the benzene ring affect both the reactivity of the ring toward further substitution and the orientation of that substitution. Groups can be classified as ortho- and para-directing activators, ortho- and para-directing deactivators, or meta-directing deactivators. Substituents influence aromatic rings by a combination of resonance and inductive effects. **Resonance effects** are transmitted through π bonds; **inductive effects** are transmitted through σ bonds.

Halobenzenes undergo **nucleophilic aromatic substitution** through either of two mechanisms. If the halobenzene has a strongly electron-withdrawing substituent in the ortho or para position, substitution occurs by addition of a nucleophile to the ring, followed by elimination of halide from the intermediate anion. If the halobenzene is not activated by an electron-withdrawing substituent, substitution can occur by elimination of HX to give a **benzyne**, followed by addition of a nucleophile.

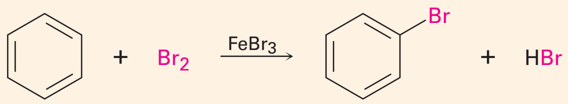
The benzylic position of an alkylbenzene can be brominated by reaction with *N*-bromosuccinimide, and the entire side chain can be degraded to a carboxyl group by oxidation with aqueous $KMnO_4$. Aromatic rings can also be reduced to cyclohexanes by hydrogenation over a platinum or rhodium catalyst, and aryl alkyl ketones are reduced to alkylbenzenes by hydrogenation over a platinum catalyst.

Summary of Reactions

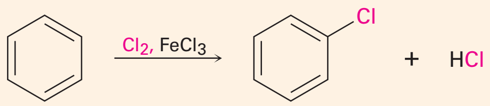
1. Electrophilic aromatic substitution
   (a) Fluorination (Section 16.2)



   (b) Bromination (Section 16.1)

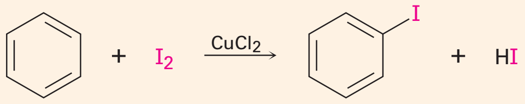


   (c) Chlorination (Section 16.2)

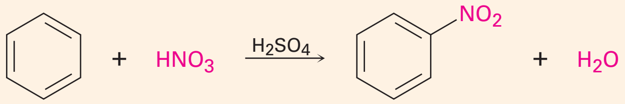


(continued)

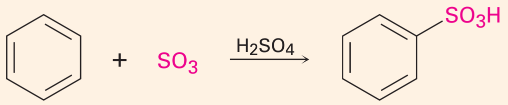
(d) Iodination (Section 16.2)



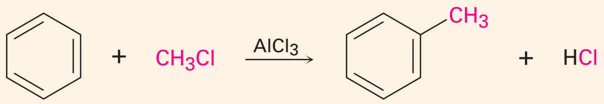
(e) Nitration (Section 16.2)



(f) Sulfonation (Section 16.2)

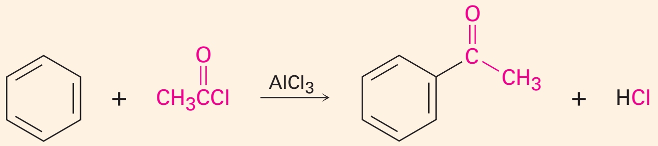


(g) Friedel–Crafts alkylation (Section 16.3)

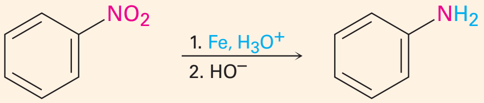


Aromatic ring.	Must be at least as reactive as a halobenzene.
Alkyl halide.	Primary alkyl halides undergo carbocation rearrangement.

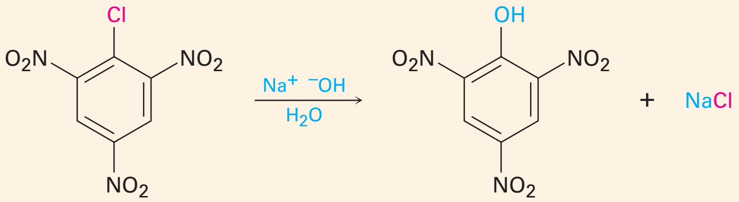
(h) Friedel–Crafts acylation (Section 16.3)



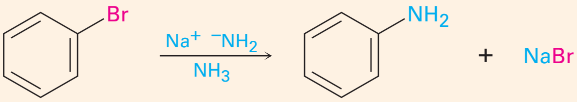
2. Reduction of aromatic nitro groups (Section 16.2)



3. Nucleophilic aromatic substitution
   (a) By addition to activated aryl halides (Section 16.7)

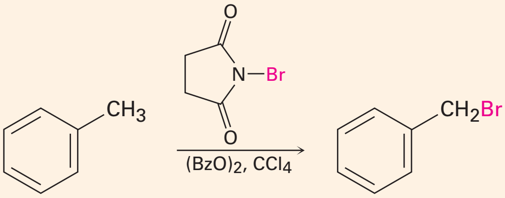


(b) By formation of benzyne intermediate from unactivated aryl halide (Section 16.8)

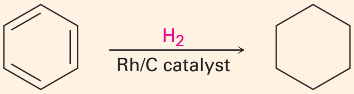


4. Oxidation of alkylbenzene side chain (Section 16.9)

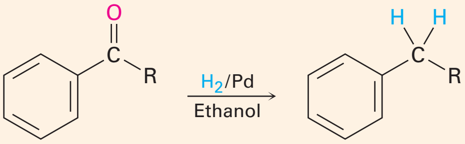
5. Benzylic bromination of alkylbenzene side chain (Section 16.9)



6. Catalytic hydrogenation of aromatic ring (Section 16.10)



7. Reduction of aryl alkyl ketones (Section 16.10)



Exercises

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

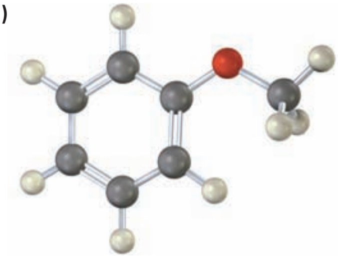
▲ denotes problems linked to the Key Ideas in this chapter.

Visualizing Chemistry

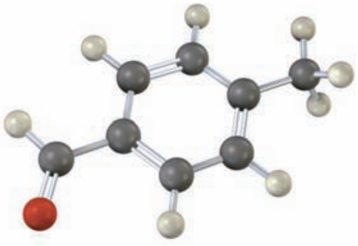
(Problems 16.1–16.23 appear within the chapter.)

16.24 Draw the product from reaction of each of the following substances with (1) Br_2, $FeBr_3$ and (2) CH_3COCl, $AlCl_3$.

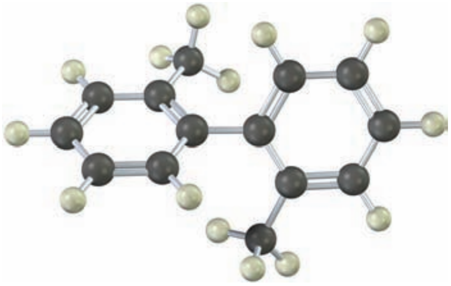
(a)



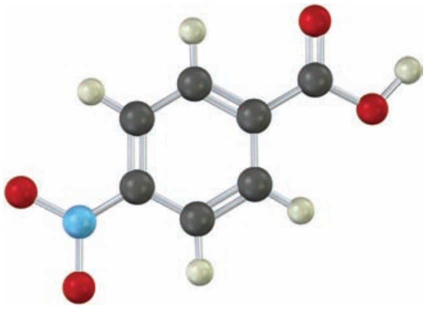
(b)



16.25 The following molecular model of a dimethyl-substituted biphenyl represents the lowest-energy conformation of the molecule. Why are the two benzene rings tilted at a 63° angle to each other rather than being in the same plane so that their *p* orbitals can overlap? Why doesn't complete rotation around the single bond joining the two rings occur?

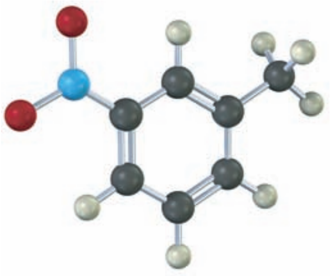


16.26 How would you synthesize the following compound starting from benzene? More than one step is needed.



▲ Problems linked to Key Ideas in this chapter

16.27 The following compound can't be synthesized using the methods discussed in this chapter. Why not?



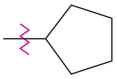
Additional Problems

Reactivity and Orientation of Electrophilic Substitutions

16.28 Identify each of the following groups as an activator or deactivator and as an *o,p*-director or *m*-director:

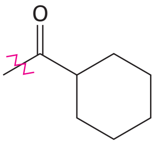
(a) $-N(CH_3)_2$

(b)



(c) $-OCH_2CH_3$

(d)



16.29 Predict the major product(s) of nitration of the following substances. Which react faster than benzene, and which slower?

(a) Bromobenzene **(b)** Benzonitrile **(c)** Benzoic acid
(d) Nitrobenzene **(e)** Benzenesulfonic acid **(f)** Methoxybenzene

16.30 ▲ Rank the compounds in each group according to their reactivity toward electrophilic substitution.

(a) Chlorobenzene, *o*-dichlorobenzene, benzene
(b) *p*-Bromonitrobenzene, nitrobenzene, phenol
(c) Fluorobenzene, benzaldehyde, *o*-xylene
(d) Benzonitrile, *p*-methylbenzonitrile, *p*-methoxybenzonitrile

16.31 ▲ Predict the major monoalkylation products you would expect to obtain from reaction of the following substances with chloromethane and $AlCl_3$:

(a) Bromobenzene **(b)** *m*-Bromophenol
(c) *p*-Chloroaniline **(d)** 2,4-Dichloronitrobenzene
(e) 2,4-Dichlorophenol **(f)** Benzoic acid
(g) *p*-Methylbenzenesulfonic acid **(h)** 2,5-Dibromotoluene

16.32 Name and draw the major product(s) of electrophilic chlorination of the following compounds:

(a) *m*-Nitrophenol **(b)** *o*-Xylene
(c) *p*-Nitrobenzoic acid **(d)** *p*-Bromobenzenesulfonic acid

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▲ Problems linked to Key Ideas in this chapter

16.33 Predict the major product(s) you would obtain from sulfonation of the following compounds:

(a) Fluorobenzene **(b)** *m*-Bromophenol

(c) *m*-Dichlorobenzene **(d)** 2,4-Dibromophenol

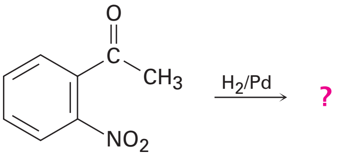
16.34 Rank the following aromatic compounds in the expected order of their reactivity toward Friedel–Crafts alkylation. Which compounds are unreactive?

(a) Bromobenzene **(b)** Toluene **(c)** Phenol

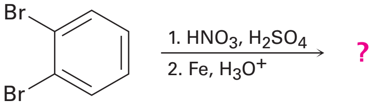
(d) Aniline **(e)** Nitrobenzene **(f)** *p*-Bromotoluene

16.35 What product(s) would you expect to obtain from the following reactions?

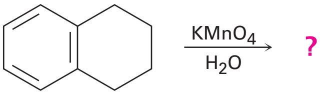
(a)



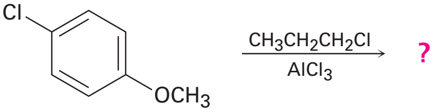
(b)



(c)

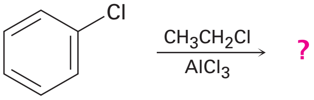


(d)



16.36 Predict the major product(s) of the following reactions:

(a)



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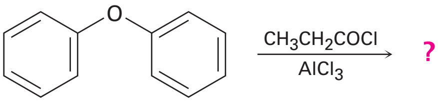

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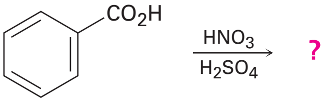
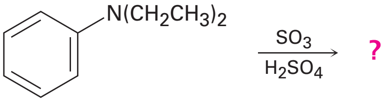


(d)



Mechanisms of Electrophilic Substitutions

16.37 Aromatic iodination can be carried out with a number of reagents, including iodine monochloride, ICl. What is the direction of polarization of ICl? Propose a mechanism for the iodination of an aromatic ring with ICl.

16.38 The sulfonation of an aromatic ring with SO_3 and H_2SO_4 is reversible. That is, heating benzenesulfonic acid with H_2SO_4 yields benzene. Show the mechanism of the desulfonation reaction. What is the electrophile?

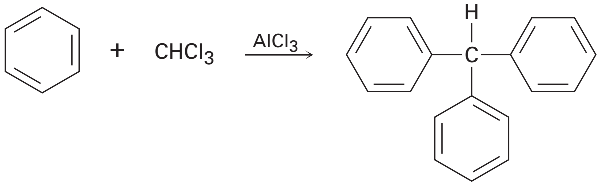
16.39 The carbocation electrophile in a Friedel–Crafts reaction can be generated in ways other than by reaction of an alkyl chloride with $AlCl_3$. For example, reaction of benzene with 2-methylpropene in the presence of H_3PO_4 yields *tert*-butylbenzene. Propose a mechanism for this reaction.

16.40 The *N*,*N*,*N*-trimethylammonium group, $-\overset{+}{N}(CH_3)_3$, is one of the few groups that is a meta-directing deactivator yet has no electron-withdrawing resonance effect. Explain.

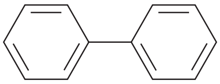
▲ Problems linked to Key Ideas in this chapter

16.41 The nitroso group, $-N{=}O$, is one of the few nonhalogens that is an ortho- and para-directing deactivator. Explain by drawing resonance structures of the carbocation intermediates in ortho, meta, and para electrophilic reaction on nitrosobenzene, $C_6H_5N{=}O$.

16.42 Triphenylmethane can be prepared by reaction of benzene and chloroform in the presence of $AlCl_3$. Propose a mechanism for the reaction.

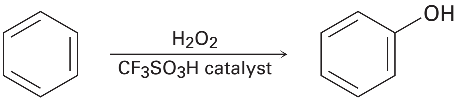


16.43 Using resonance structures of the intermediates, explain why bromination of biphenyl occurs at ortho and para positions rather than at meta.



Biphenyl

16.44 Benzene and alkyl-substituted benzenes can be hydroxylated by reaction with H_2O_2 in the presence of an acidic catalyst. What is the structure of the reactive electrophile? Propose a mechanism for the reaction.



Organic Synthesis

16.45 How would you synthesize the following substances starting from benzene or phenol? Assume that ortho- and para-substitution products can be separated.

(a) *o*-Bromobenzoic acid **(b)** *p*-Methoxytoluene
(c) 2,4,6-Trinitrobenzoic acid **(d)** *m*-Bromoaniline

16.46 Starting with benzene as your only source of aromatic compounds, how would you synthesize the following substances? Assume that you can separate ortho and para isomers if necessary.

(a) *p*-Chloroacetophenone **(b)** *m*-Bromonitrobenzene
(c) *o*-Bromobenzenesulfonic acid **(d)** *m*-Chlorobenzenesulfonic acid

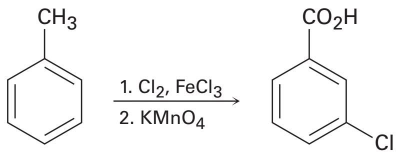
16.47 Starting with either benzene or toluene, how would you synthesize the following substances? Assume that ortho and para isomers can be separated.

(a) 2-Bromo-4-nitrotoluene **(b)** 1,3,5-Trinitrobenzene
(c) 2,4,6-Tribromoaniline **(d)** *m*-Fluorobenzoic acid

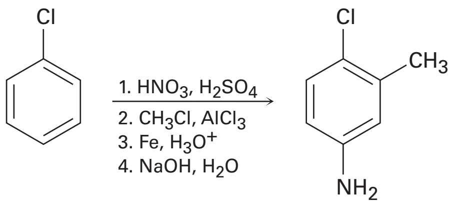
▲ Problems linked to Key Ideas in this chapter

16.48 As written, the following syntheses have flaws. What is wrong with each?

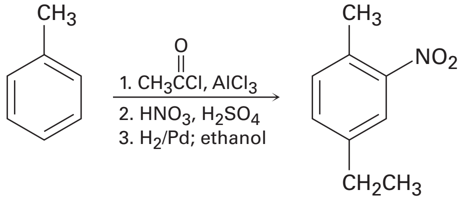
(a)



(b)

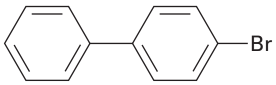


(c)



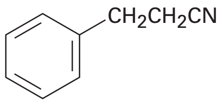
General Problems

16.49 ▲ At what position and on what ring do you expect nitration of 4-bromobiphenyl to occur? Explain, using resonance structures of the potential intermediates.

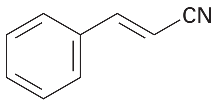


4-Bromobiphenyl

16.50 ▲ Electrophilic substitution on 3-phenylpropanenitrile occurs at the ortho and para positions, but reaction with 3-phenylpropenenitrile occurs at the meta position. Explain, using resonance structures of the intermediates.

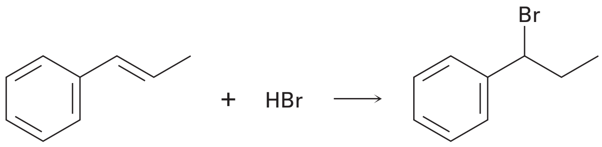


3-Phenylpropanenitrile



3-Phenylpropenenitrile

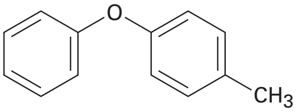
16.51 Addition of HBr to 1-phenylpropene yields only (1-bromopropyl)benzene. Propose a mechanism for the reaction, and explain why none of the other regioisomer is produced.



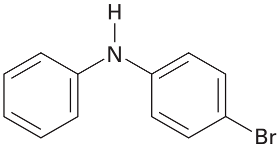
▲ Problems linked to Key Ideas in this chapter

16.52 At what position, and on what ring, would you expect the following substances to undergo electrophilic substitution?

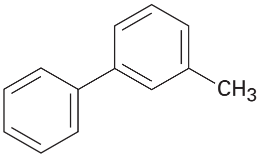
(a)



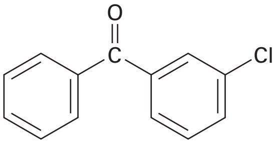
(b)



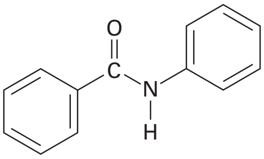
(c)



(d)



16.53 At what position, and on what ring, would you expect bromination of benzanilide to occur? Explain by drawing resonance structures of theintermediates.

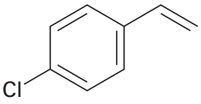


Benzanilide

16.54 Would you expect the Friedel–Crafts reaction of benzene with (*R*)-2-chlorobutane to yield optically active or racemic product? Explain.

16.55 How would you synthesize the following substances starting from benzene?

(a)



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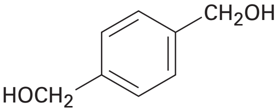
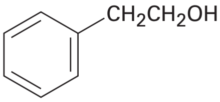
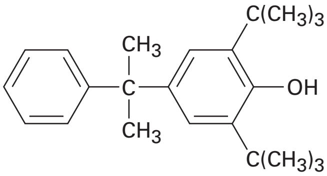


(c)



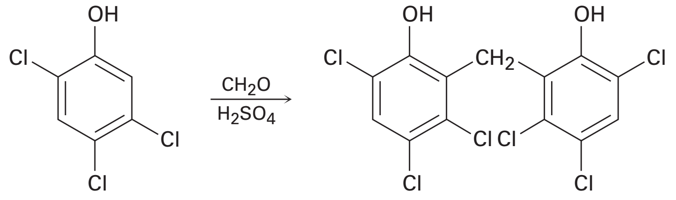
16.56 The compound MON-0585 is a nontoxic, biodegradable larvicide that is highly selective against mosquito larvae. Synthesize MON-0585 using either benzene or phenol as a source of the aromatic rings.



MON-0585

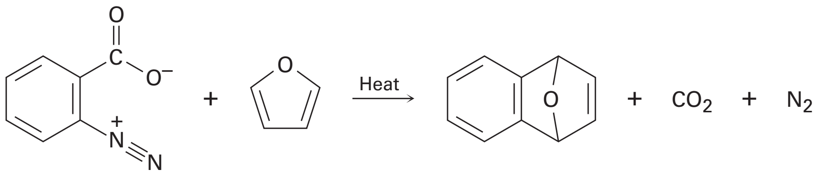
▲ Problems linked to Key Ideas in this chapter

16.57 Hexachlorophene, a substance used in the manufacture of germicidal soaps, is prepared by reaction of 2,4,5-trichlorophenol with formaldehyde in the presence of concentrated sulfuric acid. Propose a mechanism for the reaction.



Hexachlorophene

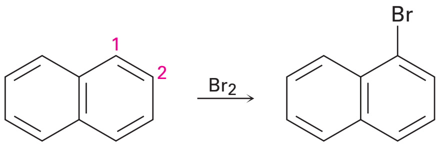
16.58 Benzenediazonium carboxylate decomposes when heated to yield N_2, CO_2, and a reactive substance that can't be isolated. When benzenediazonium carboxylate is heated in the presence of furan, the following reaction is observed:



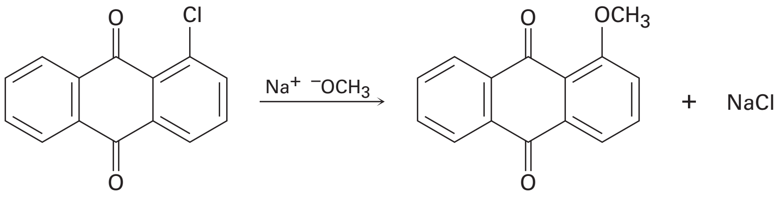
What intermediate is involved in this reaction? Propose a mechanism for its formation.

16.59 Phenylboronic acid, $C_6H_5B(OH)_2$, is nitrated to give 15% ortho-substitution product and 85% meta. Explain the meta-directing effect of the $-B(OH)_2$ group.

16.60 Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic substitution at C1 rather than C2.



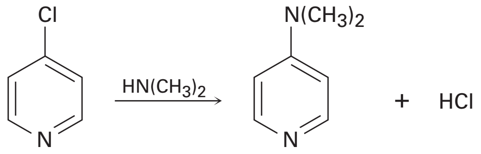
16.61 Propose a mechanism for the reaction of 1-chloroanthraquinone with methoxide ion to give the substitution product 1-methoxyanthraquinone. Use curved arrows to show the electron flow in each step.



1-Chloroanthraquinone **1-Methoxyanthraquinone**

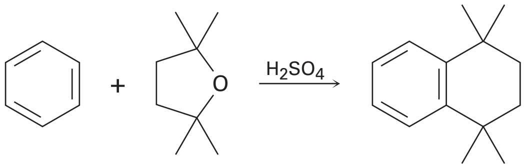
▲ Problems linked to Key Ideas in this chapter

16.62 4-Chloropyridine undergoes reaction with dimethylamine to yield 4-dimethylaminopyridine. Propose a mechanism for the reaction.

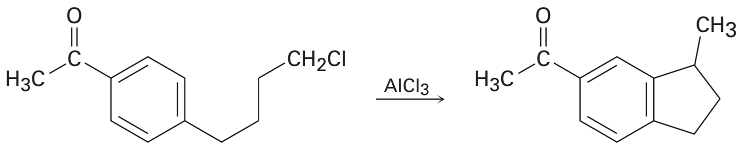


16.63 *p*-Bromotoluene reacts with potassium amide to give a mixture of *m*- and *p*-methylaniline. Explain.

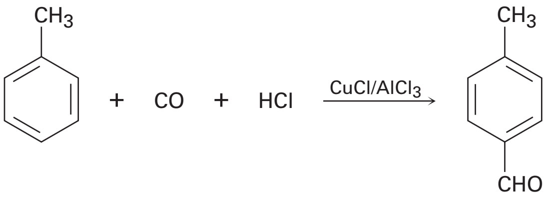
16.64 Propose a mechanism to account for the reaction of benzene with 2,2,5,5-tetramethyltetrahydrofuran.



16.65 Propose a mechanism to account for the following reaction:



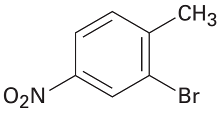
16.66 In the *Gatterman–Koch reaction,* a formyl group (−CHO) is introduced directly onto a benzene ring. For example, reaction of toluene with CO and HCl in the presence of mixed CuCl/AlCl$_3$ gives p-methylbenzaldehyde. Propose a mechanism.



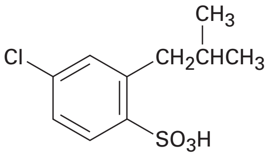
16.67 Treatment of *p-tert*-butylphenol with a strong acid such as H_2SO_4 yields phenol and 2-methylpropene. Propose a mechanism.

16.68 How would you synthesize the following compounds from benzene? Assume that ortho and para isomers can be separated.

(a)

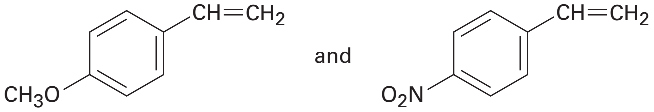


(b)

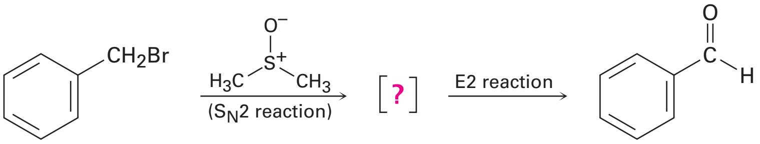


▲ Problems linked to Key Ideas in this chapter

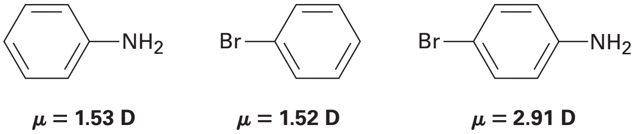
16.69 You know the mechanism of HBr addition to alkenes, and you know the effects of various substituent groups on aromatic substitution. Use this knowledge to predict which of the following two alkenes reacts faster with HBr. Explain your answer by drawing resonance structures of the carbocation intermediates.



16.70 Benzyl bromide is converted into benzaldehyde by heating in dimethyl sulfoxide. Propose a structure for the intermediate, and show the mechanisms of the two steps in the reaction.

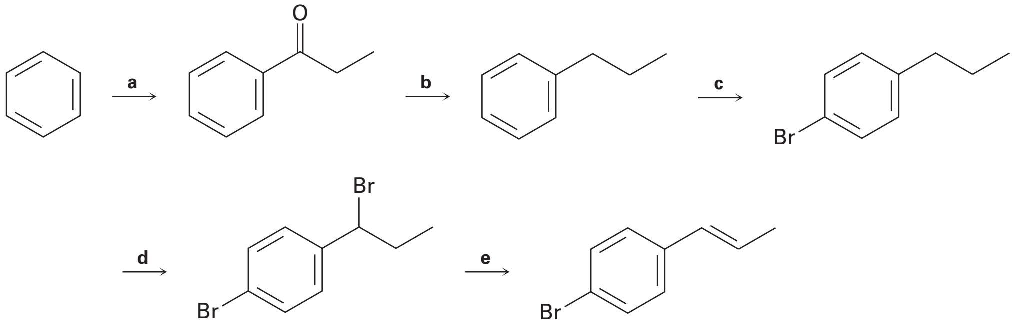


16.71 Use your knowledge of directing effects, along with the following data, to deduce the directions of the dipole moments in aniline and bromobenzene.



▲ Problems linked to Key Ideas in this chapter

16.72 Identify the reagents represented by the letters **a–e** in the following scheme:



16.73 Phenols (ArOH) are relatively acidic, and the presence of a substituent group on the aromatic ring has a large effect. The pK_a of unsubstituted phenol, for example, is 9.89, while that of *p*-nitrophenol is 7.15. Draw resonance structures of the corresponding phenoxide anions and explain the data.

16.74 Would you expect *p*-methylphenol to be more acidic or less acidic than unsubstituted phenol? Explain. (See Problem 16.73.)

▲ Problems linked to Key Ideas in this chapter

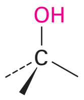
The phenol resveratrol, found in the skin of red grapes, is under investigation for its potential anti-cancer, antiarthritis, and hypoglycemic properties. Image copyright ArtKolo, 2010. Used under license from Shutterstock.com

17

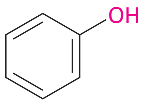
Alcohols and Phenols

17.1 Naming Alcohols and Phenols
17.2 Properties of Alcohols and Phenols
17.3 Preparation of Alcohols: A Review
17.4 Alcohols from Carbonyl Compounds: Reduction
17.5 Alcohols from Carbonyl Compounds: Grignard Reaction
17.6 Reactions of Alcohols
17.7 Oxidation of Alcohols
17.8 Protection of Alcohols
17.9 Phenols and Their Uses
17.10 Reactions of Phenols
17.11 Spectroscopy of Alcohols and Phenols
A Deeper Look—Ethanol: Chemical, Drug, Poison

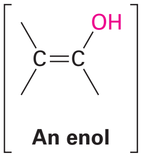
Alcohols and **phenols** can be thought of as organic derivatives of water in which one of the water hydrogens is replaced by an organic group: H–O–H versus R–O–H and Ar–O–H. In practice, the group name *alcohol* is restricted to compounds that have their –OH group bonded to a saturated, sp^3-hybridized carbon atom, while compounds with their –OH group bonded to a vinylic, sp^2-hybridized carbon are called *enols*. We'll look at enols in Chapter 22.



An alcohol



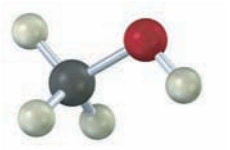
A phenol



An enol

Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 40 million metric tons (13 billion gallons) of methanol is manufactured worldwide each year, most of it by catalytic reduction of carbon monoxide with hydrogen gas. Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).

$$CO \quad + \quad 2\ H_2 \xrightarrow[\text{Zinc oxide/chromia catalyst}]{400\ °C} CH_3OH$$



Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Today, approximately 55 million metric tons (18 billion gallons) of ethanol is produced worldwide each year, most of it by fermentation of corn, barley, sorghum, and other plant sources. Essentially the entire amount is used for automobile fuel.

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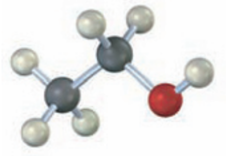
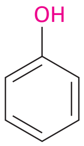
Ethanol for industrial use as a solvent or chemical intermediate is largely obtained by acid-catalyzed hydration of ethylene at high temperature.

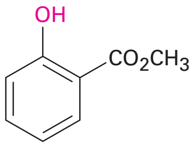
$$H_2C{=}CH_2 \xrightarrow[\substack{H_3PO_4 \\ 250\ °C}]{H_2O} CH_3CH_2OH$$



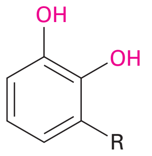
Phenols occur widely throughout nature and also serve as intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar; methyl salicylate is a flavoring agent found in oil of wintergreen; and the urushiols are the allergenic constituents of poison oak and poison ivy. Note that the word *phenol* is the name both of the specific compound (hydroxybenzene) and of a class of compounds.



Phenol (also known as carbolic acid)



Methyl salicylate

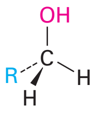


Urushiols (R = different C_{15} alkyl and alkenyl chains)

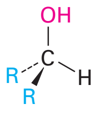
Why This Chapter? Up to this point, we've focused on developing some general ideas of organic reactivity, on looking at the chemistry of hydrocarbons and alkyl halides, and on seeing some of the tools used in structural studies. With that background, it's now time to begin a study of the oxygen-containing functional groups that lie at the heart of organic and biological chemistry. We'll look at alcohols in this chapter and then move on to carbonyl compounds in Chapters 19 through 23.

17.1 Naming Alcohols and Phenols

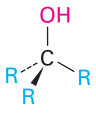
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol



A tertiary (3°) alcohol

Simple alcohols are named by the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*.

RULE 1

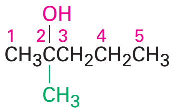
Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

RULE 2

Number the alkane chain beginning at the end nearer the hydroxyl group.

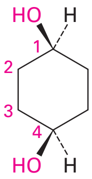
RULE 3

Number the substituents according to their position on the chain, and write the name, listing the substituents in alphabetical order and identifying the position to which the –OH is bonded. Note that in naming *cis*-1,4-cyclohexanediol, the final *-e* of cyclohexane is not deleted because the next letter, *d*, is not a vowel; that is, cyclohexanediol rather than cyclohexandiol. Also, as with alkenes **(Section 7.3)**, newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.

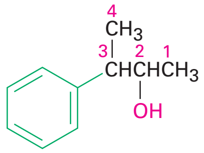


$CH_3\overset{OH}{\underset{CH_3}{C}}CH_2CH_2CH_3$

2-Methyl-2-pentanol
(New: 2-Methylpentan-2-ol)

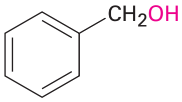


cis-1,4-Cyclohexanediol
(New: cis-Cyclohexane-1,4-diol)



3-Phenyl-2-butanol
(New: 3-Phenylbutan-2-ol)

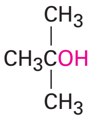
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



Benzyl alcohol
(phenylmethanol)

$H_2C{=}CHCH_2OH$

Allyl alcohol
(2-propen-1-ol)

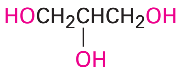


$CH_3\overset{CH_3}{\underset{CH_3}{C}}OH$

***tert*-Butyl alcohol**
(2-methyl-2-propanol)

$HOCH_2CH_2OH$

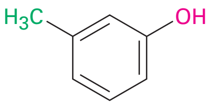
Ethylene glycol
(1,2-ethanediol)



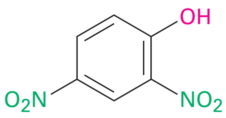
$HOCH_2\underset{OH}{CH}CH_2OH$

Glycerol
(1,2,3-propanetriol)

Phenols are named as described previously for aromatic compounds according to the rules discussed in **Section 15.1**. Note that *-phenol* is used as the parent name rather than *-benzene*.



***m*-Methylphenol**
(*m*-Cresol)

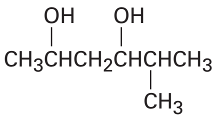


2,4-Dinitrophenol

Problem 17.1

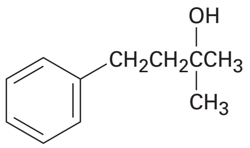
Give IUPAC names for the following compounds:

(a)

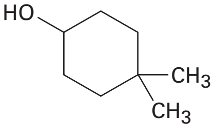


$$CH_3\overset{OH}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}H\underset{CH_3}{\underset{|}{C}}HCH_3$$

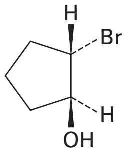
(b)



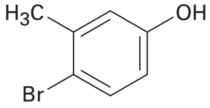
(c)



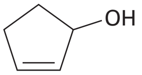
(d)



(e)



(f)



Problem 17.2

Draw structures corresponding to the following IUPAC names:

(a) (*Z*)-2-Ethyl-2-buten-1-ol
(b) 3-Cyclohexen-1-ol
(c) *trans*-3-Chlorocycloheptanol
(d) 1,4-Pentanediol
(e) 2,6-Dimethylphenol
(f) *o*-(2-Hydroxyethyl)phenol

17.2 Properties of Alcohols and Phenols

Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The R–O–H bond angle has an approximately tetrahedral value (108.5° in methanol, for instance), and the oxygen atom is sp^3-hybridized.

Also like water, alcohols and phenols have higher boiling points than might be expected because of hydrogen-bonding **(Section 2.12)**. A positively polarized –OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together **(Figure 17.1)**. These intermolecular attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. For example, 1-propanol (MW = 60), butane (MW = 58), and chloroethane (MW = 65) have similar molecular weights, yet 1-propanol boils at 97 °C, compared with −0.5 °C for the alkane and 12.5 °C for the chloroalkane.

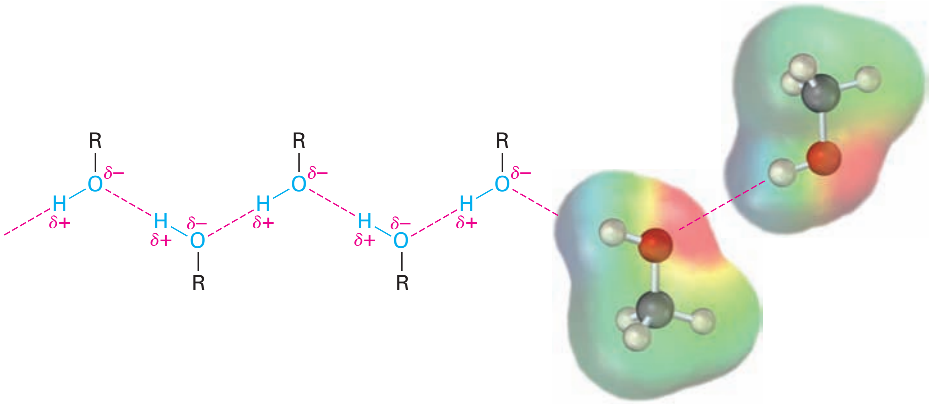
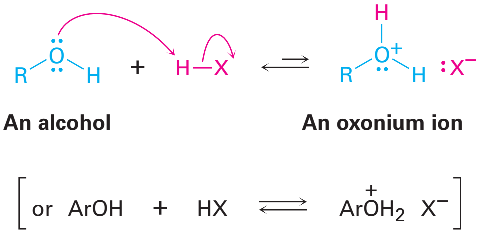


Figure 17.1 Hydrogen-bonding in alcohols and phenols. Attraction between a positively polarized OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the **positively polarized** O–H hydrogen and the **negatively polarized** oxygen.

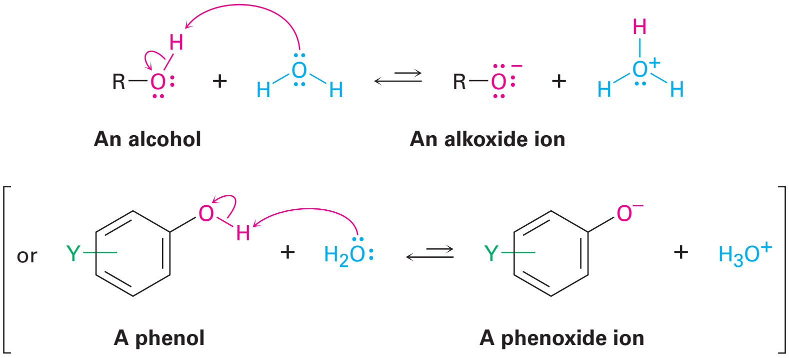
Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.


An alcohol

An oxonium ion

$$\left[\text{or } ArOH + HX \rightleftharpoons Ar\overset{+}{O}H_2 \; X^-\right]$$

As weak acids, they dissociate slightly in dilute aqueous solution by donating a proton to water, generating H_3O^+ and an **alkoxide ion, RO^-**, or a **phenoxide ion, ArO^-**.


An alcohol

An alkoxide ion

A phenol

A phenoxide ion

Recall from the earlier discussion of acidity in **Sections 2.7–2.11** that the strength of any acid HA in water can be expressed by an acidity constant, K_a.

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

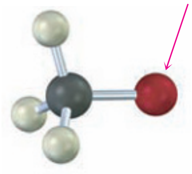
Compounds with a smaller K_a and larger pK_a are less acidic, whereas compounds with a larger K_a and smaller pK_a are more acidic. As shown by the data in Table 17.1, simple alcohols like methanol and ethanol are about as acidic as water but the more highly substituted *tert*-butyl alcohol is somewhat weaker. Substituent groups also have a significant effect: 2,2,2-trifluoroethanol is approximately 3700 times stronger than ethanol, for instance. Phenols and *thiols,* the sulfur analogs of alcohols, are substantially more acidic than water.

The effect of alkyl substitution on alcohol acidity is due primarily to solvation of the alkoxide ion formed on acid dissociation. The more readily the alkoxide ion is solvated by water, the more stable it is, the more its formation is energetically favored, and the greater the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is sterically accessible and is easily solvated by water. The oxygen

Table 17.1 Acidity Constants of Some Alcohols and Phenols

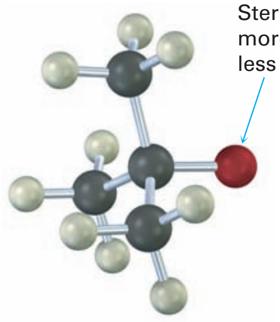
Compound	pK_a	
$(CH_3)_3COH$	18.00	Weaker acid
CH_3CH_2OH	16.00	
H_2O	15.74	
CH_3OH	15.54	
CF_3CH_2OH	12.43	
p-Aminophenol	10.46	
CH_3SH	10.3	
p-Methylphenol	10.17	
Phenol	9.89	
p-Chlorophenol	9.38	
p-Nitrophenol	7.15	Stronger acid

atom of a hindered alkoxide ion, however, such as that from *tert*-butyl alcohol, is less easily solvated and is therefore less stabilized.



Sterically accessible; less hindered and more easily solvated.

Methoxide ion, CH_3O^-
(pK_a = 15.54)

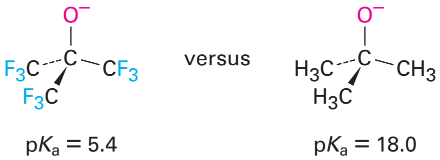


Sterically less accessible; more hindered and less easily solvated.

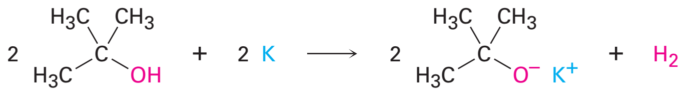
***tert*-Butoxide ion, $(CH_3)_3CO^-$**
(pK_a = 18.00)

Inductive effects **(Section 16.5)** are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for instance, stabilize an alkoxide ion by spreading out the charge over a larger volume, thus making the alcohol more acidic. Compare, for example, the acidities of ethanol (pK_a = 16.00) and 2,2,2-trifluoroethanol (pK_a = 12.43), or of *tert*-butyl alcohol (pK_a = 18.0) and nonafluoro-*tert*-butyl alcohol (pK_a = 5.4).

Electron-withdrawing groups stabilize the alkoxide ion and lower the pK_a.



Because alcohols are weak acids, they don't react with weak bases, such as amines or bicarbonate ion, and they react to only a limited extent with metal hydroxides, such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide ($NaNH_2$), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.



tert-Butyl alcohol (2-methyl-2-propanol)

Potassium _tert_-butoxide (potassium 2-methyl-2-propanolate)

$$CH_3OH + NaH \longrightarrow CH_3O^- \ Na^+ + H_2$$

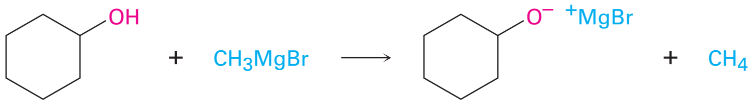
Methanol

Sodium methoxide (sodium methanolate)

$$CH_3CH_2OH + NaNH_2 \longrightarrow CH_3CH_2O^- \ Na^+ + NH_3$$

Ethanol

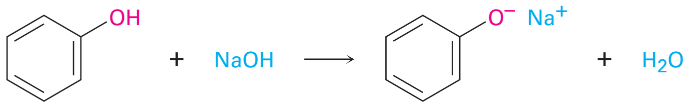
Sodium ethoxide (sodium ethanolate)



Cyclohexanol

Bromomagnesium cyclohexanolate

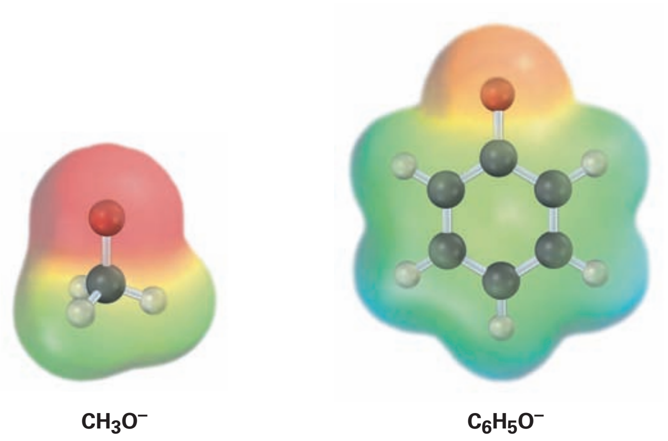
Phenols are about a million times more acidic than alcohols (Table 17.1). They are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture simply by basic extraction into aqueous solution, followed by reacidification.



Phenol

Sodium phenoxide (sodium phenolate)

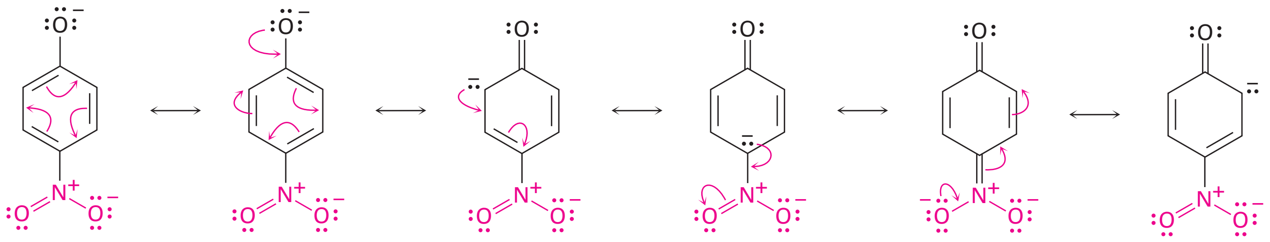
Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. Delocalization of the negative charge over the ortho and para positions of the aromatic ring results in increased stability of the phenoxide anion relative to undissociated phenol and in a consequently lower $\Delta G°$ for dissociation. **Figure 17.2** compares electrostatic potential maps of an alkoxide ion (CH_3O^-) with phenoxide ion and shows how the negative charge in phenoxide ion is delocalized from oxygen to the ring.



CH_3O^- $C_6H_5O^-$

Figure 17.2 The resonance-stabilized phenoxide ion is more stable than an alkoxide ion. Electrostatic potential maps show how the **negative charge** is concentrated on oxygen in the methoxide ion but is spread over the aromatic ring in the phenoxide ion.

Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-withdrawing or electron-donating **(Section 16.5)**. Phenols with an electron-withdrawing substituent are more acidic because these substituents delocalize the negative charge; phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge. The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.



Predicting the Relative Acidity of a Substituted Phenol

Worked Example 17.1

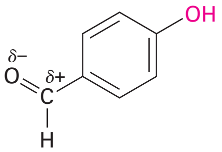
Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy

Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution

We saw in **Section 16.5** that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde is more acidic ($pK_a = 7.9$) than phenol ($pK_a = 9.89$).



***p*-Hydroxybenzaldehyde**
($pK_a = 7.9$)

Problem 17.3

The following data for isomeric four-carbon alcohols show that there is a decrease in boiling point with increasing substitution of the OH-bearing carbon. How might you account for this trend?

1-Butanol, bp 117.5 °C
2-Butanol, bp 99.5 °C
2-Methyl-2-propanol, bp 82.2 °C

Problem 17.4

Rank the following substances in order of increasing acidity:

(a) $(CH_3)_2CHOH$, $HC{\equiv}CH$, $(CF_3)_2CHOH$, CH_3OH
(b) Phenol, *p*-methylphenol, *p*-(trifluoromethyl)phenol
(c) Benzyl alcohol, phenol, *p*-hydroxybenzoic acid

Problem 17.5

p-Nitrobenzyl alcohol is more acidic than benzyl alcohol, but *p*-methoxybenzyl alcohol is less acidic. Explain.

17.3 Preparation of Alcohols: A Review

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of compounds **(Figure 17.3)**.

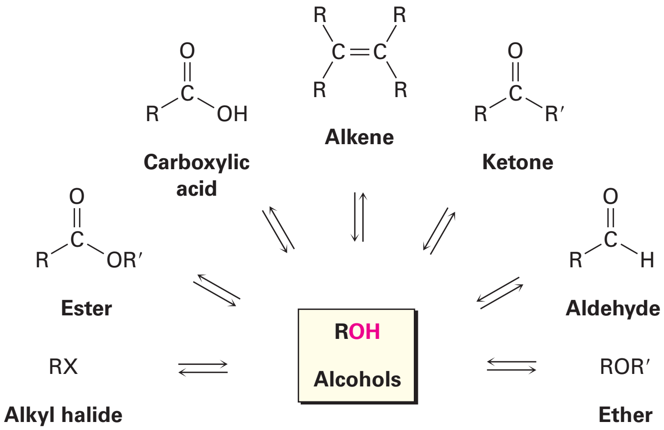
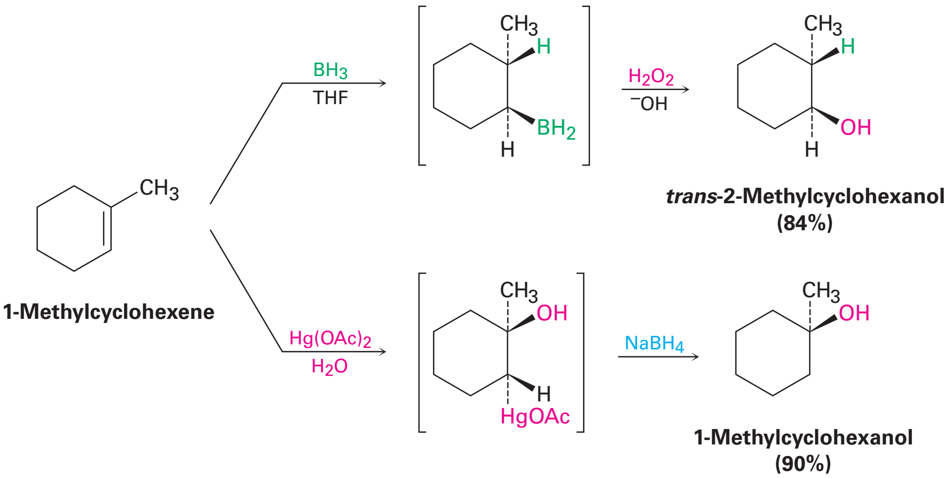


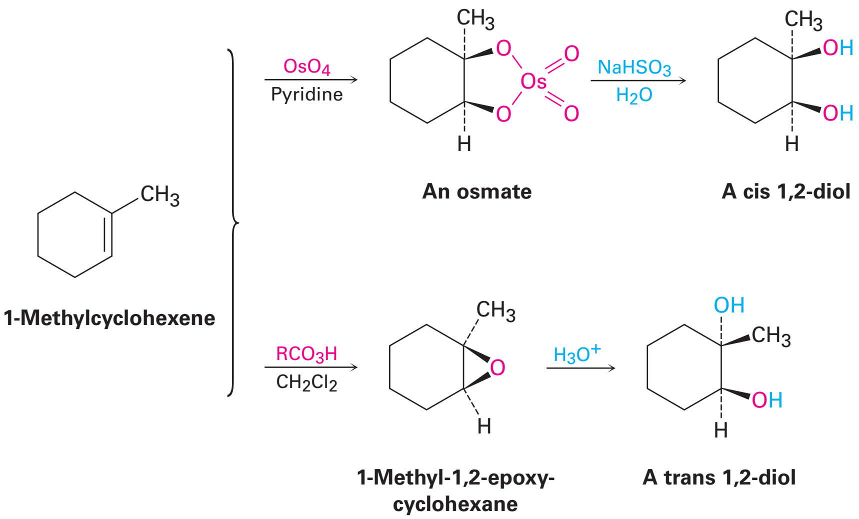
Figure 17.3 The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

We've already seen several methods of alcohol synthesis:

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration–oxidation yields the product of syn, non-Markovnikov hydration **(Section 8.5)**, whereas oxymercuration–demercuration yields the product of Markovnikov hydration **(Section 8.4)**.



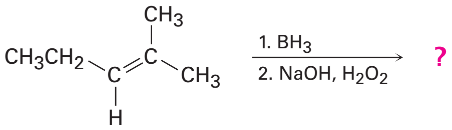
- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with $NaHSO_3$ or by acid-catalyzed hydrolysis of an epoxide **(Section 8.7)**. The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.



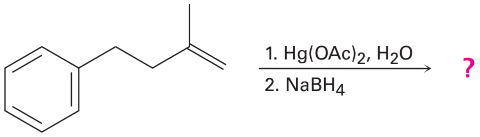
Problem 17.6

Predict the products of the following reactions:

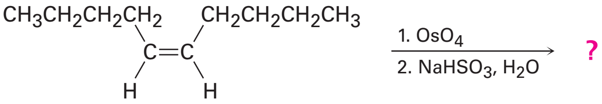
(a)



(b)

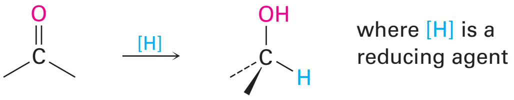


(c)



17.4 Alcohols from Carbonyl Compounds: Reduction

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane **(Section 8.6)**, reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



A carbonyl compound **An alcohol**

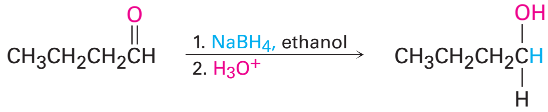
Reduction of Aldehydes and Ketones

Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.

An aldehyde **A primary alcohol** **A ketone** **A secondary alcohol**

Dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety and ease of handling. Sodium borohydride is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

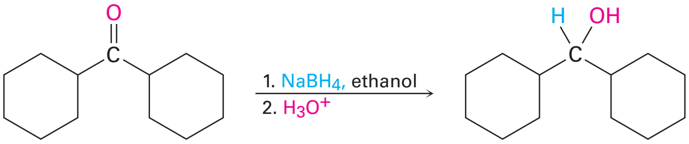
Aldehyde reduction



Butanal

1-Butanol (85%)
(a 1° alcohol)

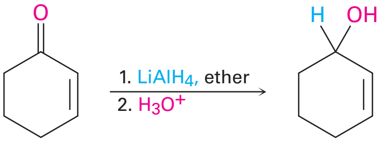
Ketone reduction



Dicyclohexyl ketone

Dicyclohexylmethanol (88%)
(a 2° alcohol)

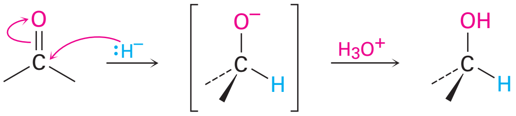
Lithium aluminum hydride, $LiAlH_4$, is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, $LiAlH_4$ is much more reactive than $NaBH_4$ but also more dangerous. It reacts violently with water and decomposes explosively when heated above 120 °C.



2-Cyclohexenone

2-Cyclohexenol (94%)

We'll defer a detailed discussion of the mechanisms of these reductions until Chapter 19. For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion (**:**H^-) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



A carbonyl compound

An alkoxide ion intermediate

An alcohol

In living organisms, aldehyde and ketone reductions are carried out by either of the coenzymes NADH (reduced nicotinamide adenine dinucleotide) or NADPH (reduced nicotinamide adenine dinucleotide phosphate). Although these biological "reagents" are much more complex structurally than $NaBH_4$ or $LiAlH_4$, the mechanisms of laboratory and biological reactions are similar. The coenzyme acts as a hydride-ion donor to give an alkoxide anion, and the intermediate anion is then protonated by acid. An example is the reduction of acetoacetyl ACP to *β*-hydroxybutyryl ACP, a step in the biological synthesis of fats **(Figure 17.4)**. Note that the *pro-R* hydrogen of NADPH is the one transferred in this example. Enzyme-catalyzed reactions usually occur with high specificity, although it's not usually possible to predict the stereochemical result before the fact.

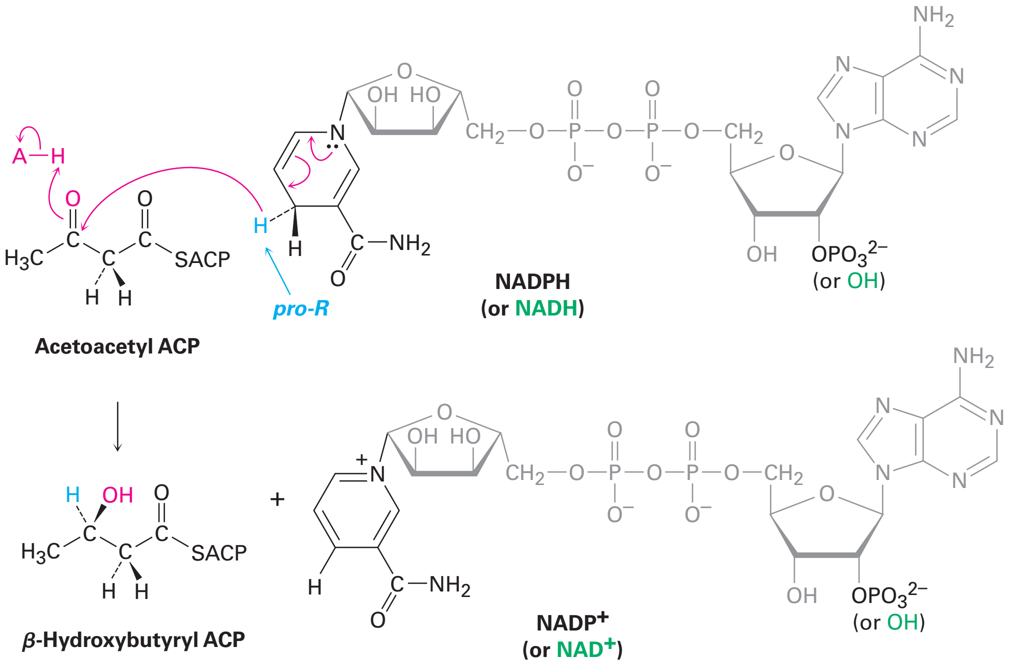
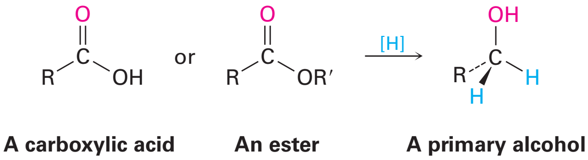


Figure 17.4 The biological reduction of a ketone (acetoacetyl ACP) to an alcohol (*β*-hydroxybutyryl ACP) by NADPH.

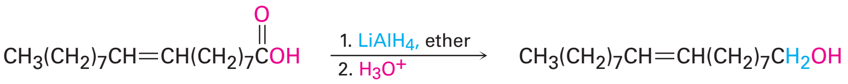
Reduction of Carboxylic Acids and Esters

Carboxylic acids and esters are reduced to give primary alcohols.



These reactions aren't as rapid as the reductions of aldehydes and ketones. $NaBH_4$ reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent $LiAlH_4$. All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions. We'll defer a discussion of the mechanisms of these reactions until Chapter 21.

Carboxylic acid reduction

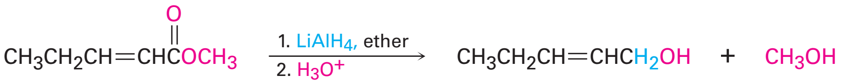


$$CH_3(CH_2)_7CH{=}CH(CH_2)_7\overset{\overset{O}{\|}}{C}OH \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

9-Octadecenoic acid
(oleic acid)

9-Octadecen-1-ol (87%)

Ester reduction



$$CH_3CH_2CH{=}CH\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3CH_2CH{=}CHCH_2OH + CH_3OH$$

Methyl 2-pentenoate

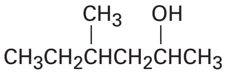
2-Penten-1-ol (91%)

Identifying a Reactant, Given the Product

Worked Example
17.2

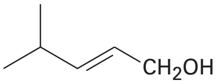
What carbonyl compounds would you reduce to obtain the following alcohols?

(a)



$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_3$$

(b)

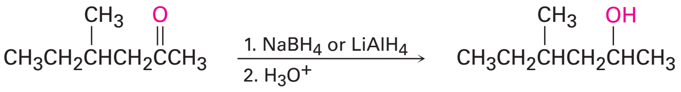


Strategy

Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

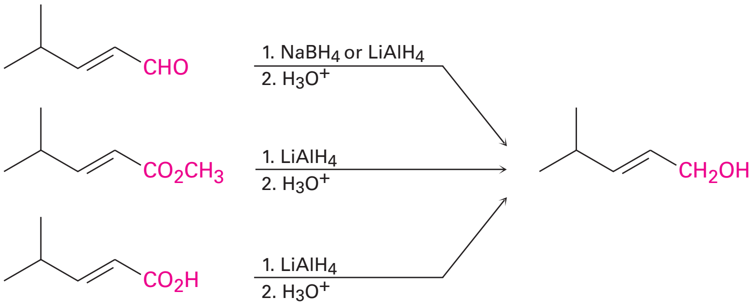
Solution

(a) The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either $NaBH_4$ or $LiAlH_4$ can be used.



$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4\ or\ LiAlH_4} CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_3$$

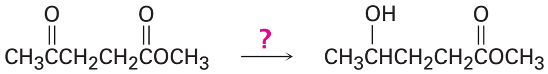
(b) The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. $LiAlH_4$ is needed for the ester and carboxylic acid reductions.



Problem 17.7

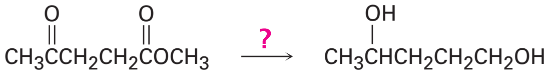
What reagent would you use to accomplish each of the following reactions?

(a)



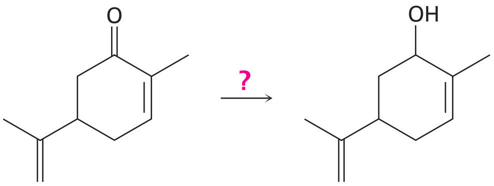
$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow{?} CH_3\overset{OH}{\overset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3}$$

(b)



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow{?} CH_3\overset{OH}{\overset{|}{C}}HCH_2CH_2CH_2OH}$$

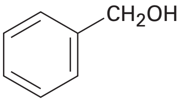
(c)



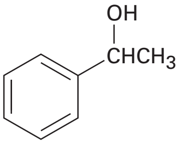
Problem 17.8

What carbonyl compounds give the following alcohols on reduction with $LiAlH_4$? Show all possibilities.

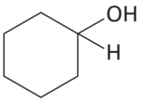
(a)



(b)



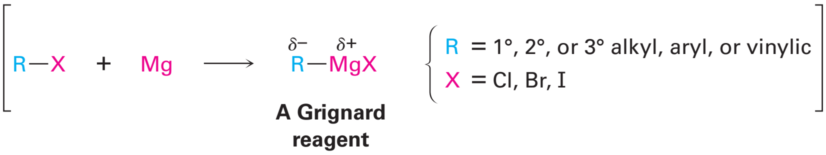
(c)

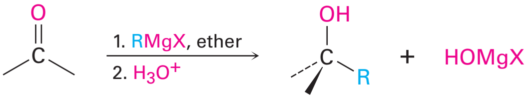


(d) $(CH_3)_2CHCH_2OH$

17.5 Alcohols from Carbonyl Compounds: Grignard Reaction

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium **(Section 10.6)**, react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the C=O bond, Grignard reaction involves addition of a carbanion nucleophile ($R:^{-}\,{}^{+}MgX$).

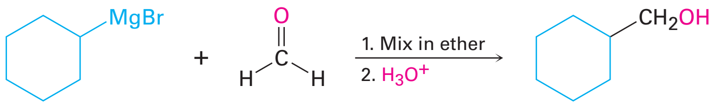




The reaction of Grignard reagents with carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth knowing about for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction *does* have an indirect biological counterpart, for we'll see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

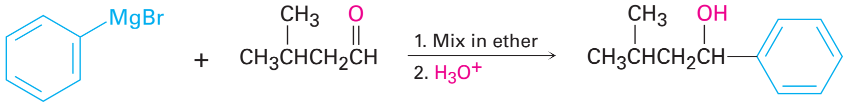
As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $H_2C{=}O$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

Formaldehyde reaction



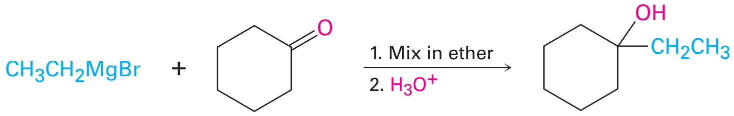
Cyclohexylmagnesium bromide **Formaldehyde** **Cyclohexylmethanol (65%) (a 1° alcohol)**

Aldehyde reaction



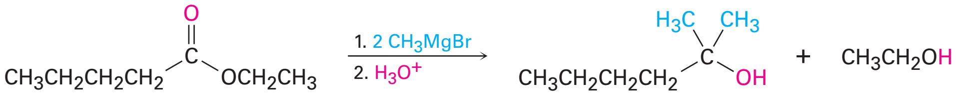
Phenylmagnesium bromide **3-Methylbutanal** **3-Methyl-1-phenyl-1-butanol (73%) (a 2° alcohol)**

Ketone reaction



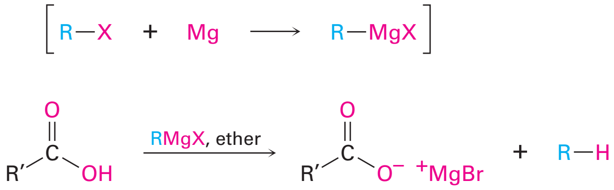
Ethylmagnesium bromide **Cyclohexanone** **1-Ethylcyclohexanol (89%) (a 3° alcohol)**

Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as $LiAlH_4$ reduction of an ester adds two hydrogens.



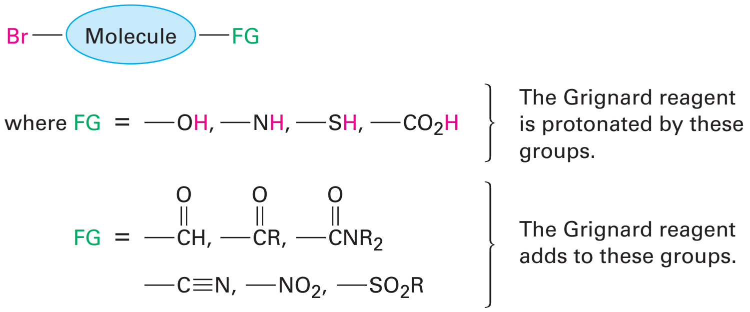
Ethyl pentanoate **2-Methyl-2-hexanol (85%) (a 3° alcohol)**

Carboxylic acids don't give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.



A carboxylic acid **A carboxylic acid salt**

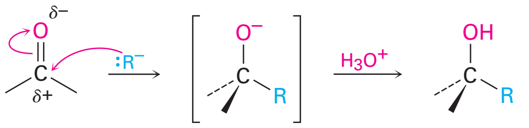
The Grignard reaction, although useful, also has limitations. One major problem is that a Grignard reagent can't be prepared from an organohalide if other reactive functional groups are present in the same molecule. For example, a compound that is both an alkyl halide and a ketone can't form a Grignard reagent because it would react with itself. Similarly, a compound that is both an alkyl halide and a carboxylic acid, an alcohol, or an amine can't form a Grignard reagent because the acidic $RCO_2\mathbf{H}$, $RO\mathbf{H}$, or $RN\mathbf{H_2}$ hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents can't be prepared from alkyl halides that contain the following functional groups (FG):



where FG = —OH, —NH, —SH, —CO_2H } The Grignard reagent is protonated by these groups.

FG = —CH(=O), —CR(=O), —CNR_2(=O), —C≡N, —NO_2, —SO_2R } The Grignard reagent adds to these groups.

As with the reduction of carbonyl compounds discussed in the previous section, we'll defer a detailed treatment of the mechanism of Grignard reactions until Chapter 19. For the moment, it's sufficient to note that Grignard reagents act as nucleophilic carbanions (:R^-) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step.



A carbonyl compound **An alkoxide ion intermediate** **An alcohol**

Worked Example 17.3

Using a Grignard Reaction to Synthesize an Alcohol

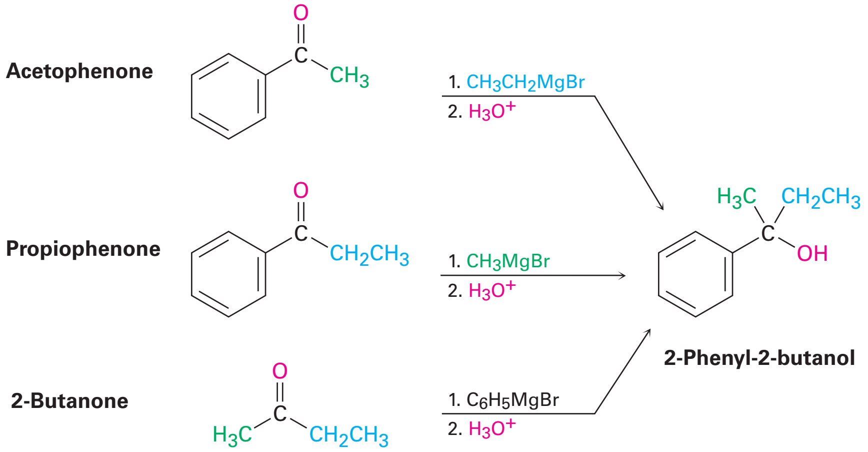
How could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2-butanol?

Strategy

Draw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone.

Solution

2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group ($-C_6H_5$) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.



Worked Example 17.4

Using a Grignard Reaction to Synthesize an Alcohol

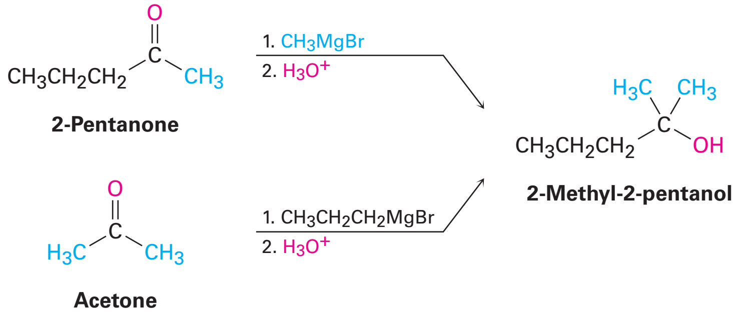
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?

Strategy

Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound might be either a ketone or an ester.

Solution

In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone.

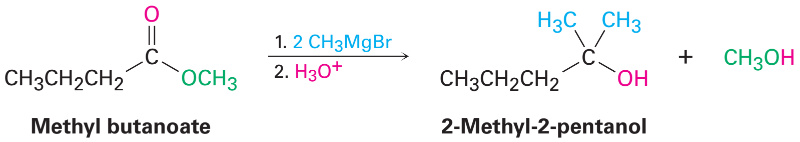


2-Pentanone

Acetone

2-Methyl-2-pentanol

Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.



Methyl butanoate

2-Methyl-2-pentanol

Problem 17.9

Show the products obtained from addition of methylmagnesium bromide to the following compounds:

(a) Cyclopentanone **(b)** Benzophenone (diphenyl ketone) **(c)** 3-Hexanone

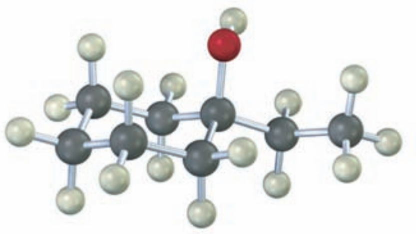
Problem 17.10

Use a Grignard reaction to prepare the following alcohols:

(a) 2-Methyl-2-propanol **(b)** 1-Methylcyclohexano **(c)** 3-Methyl-3-pentanol
(d) 2-Phenyl-2-butanol **(e)** Benzyl alcohol **(f)** 4-Methyl-1-pentanol

Problem 17.11

Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound:



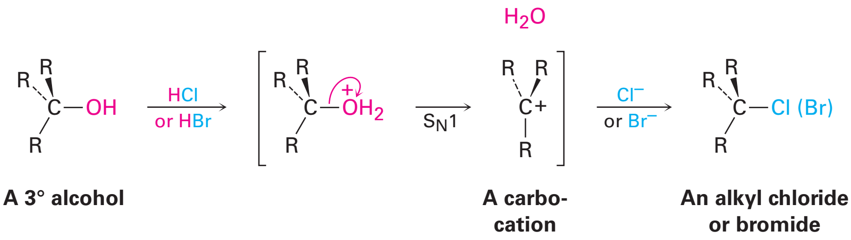
17.6 Reactions of Alcohols

We've already seen several reactions of alcohols—their conversion into alkyl halides and tosylates in **Section 10.5** and their dehydration to give alkenes in **Section 8.1**—although without mechanistic details. Let's now look at those details.

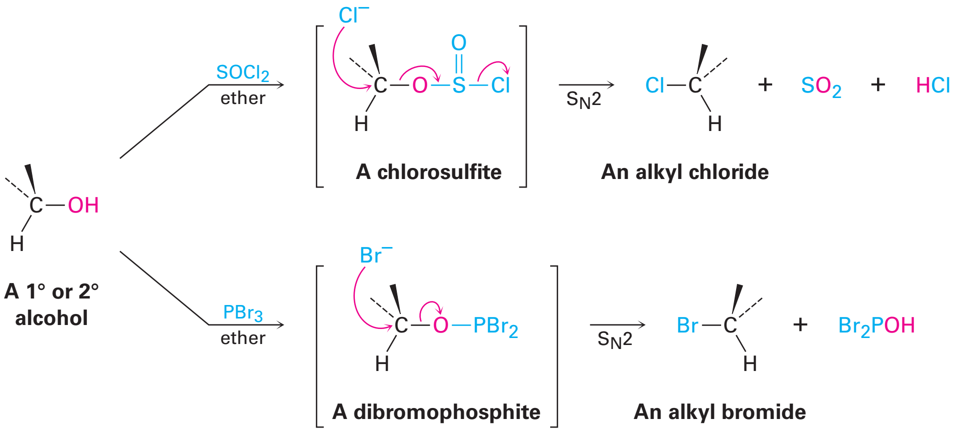
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom, water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.



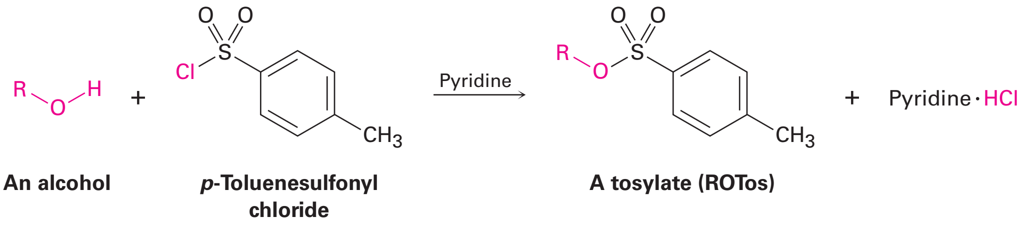
The reactions of primary and secondary alcohols with $SOCl_2$ and PBr_3 take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with $SOCl_2$ or PBr_3 converts the −OH into a much better leaving group, either a chlorosulfite (−OSOCl) or a dibromophosphite (−$OPBr_2$), that is readily expelled by backside nucleophilic substitution.



Conversion of Alcohols into Tosylates

Alcohols react with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine solution to yield alkyl tosylates, ROTos **(Section 11.1)**. Only the O−H bond of the alcohol is broken in this reaction; the C−O bond remains intact, so no change of configuration occurs if the oxygen is attached to a chirality center.

The resultant alkyl tosylates behave much like alkyl halides, undergoing both S_N1 and S_N2 substitution reactions.



One of the most important reasons for using tosylates in S_N2 reactions is stereochemical. The S_N2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry as the starting alcohol. The S_N2 reaction of an alcohol via a tosylate, however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. **Figure 17.5** shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

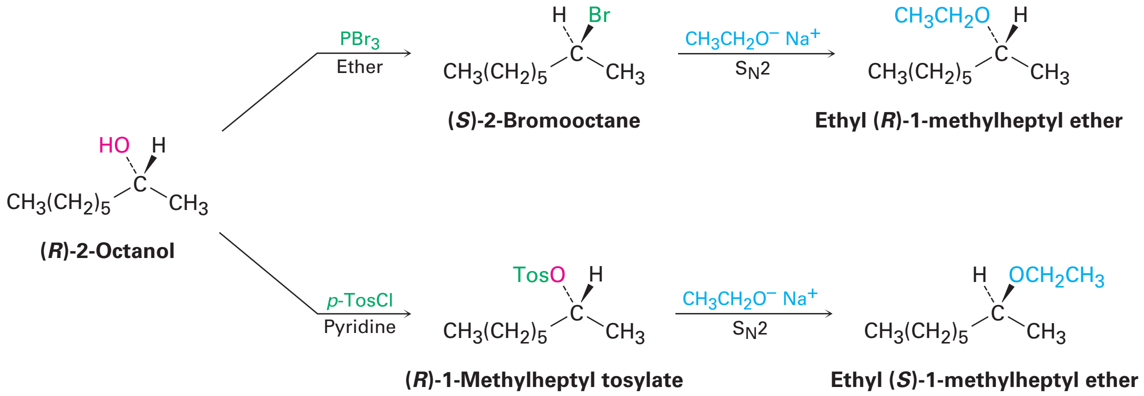
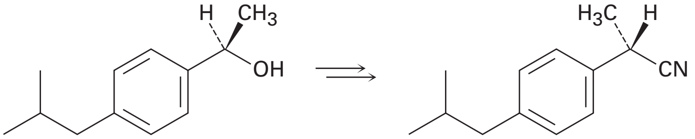


Figure 17.5 Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

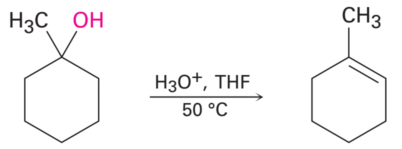
Problem 17.12

How would you carry out the following transformation, a step used in the commercial synthesis of (*S*)-ibuprofen?



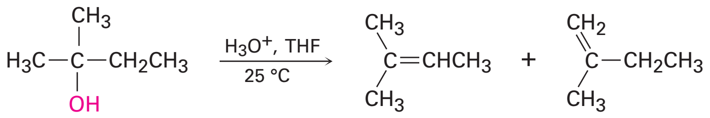
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of ways have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in **Section 8.1**. For example, treatment of 1-methylcyclohexanol with warm aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

Acid-catalyzed dehydrations usually follow Zaitsev's rule **(Section 11.7)** and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



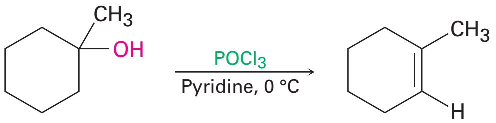
2-Methyl-2-butanol

2-Methyl-2-butene (trisubstituted)
Major product

2-Methyl-1-butene (disubstituted)
Minor product

The reaction is an E1 process **(Section 11.10)** and occurs by the three-step mechanism shown in **Figure 17.6** on the next page. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As usual for E1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates. Secondary alcohols can be made to react, but the conditions are severe (75% H_2SO_4, 100 °C) and sensitive molecules don't survive.

To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride ($POCl_3$) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



1-Methylcyclohexanol **1-Methylcyclohexene (96%)**

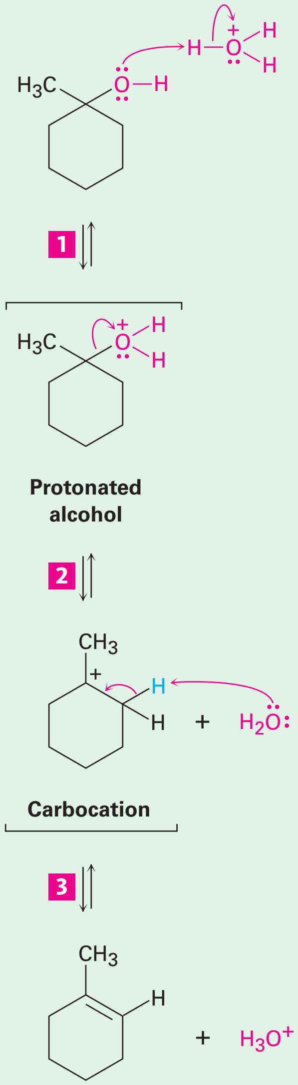
Figure 17.6 | **MECHANISM**

Mechanism of the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

1 Two electrons from the oxygen atom bond to H^+, yielding a protonated alcohol intermediate.

2 The carbon–oxygen bond breaks, and the two electrons from the bond stay with oxygen, leaving a carbocation intermediate.

3 Two electrons from a neighboring carbon–hydrogen bond form the alkene π bond, and H^+ (a proton) is eliminated.



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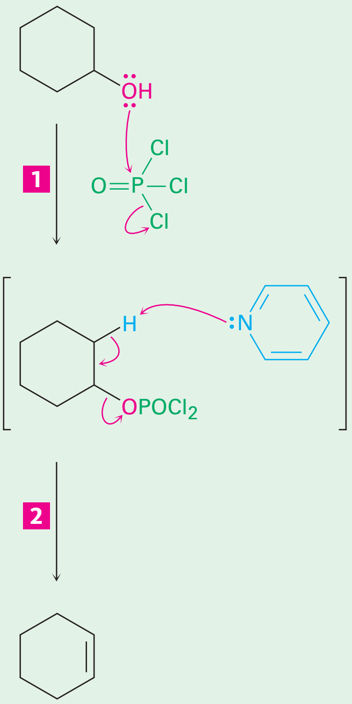
Alcohol dehydrations carried out with $POCl_3$ in pyridine take place by an E2 mechanism, as shown in **Figure 17.7**. Because hydroxide ion is a poor leaving group **(Section 11.3)**, direct E2 elimination of water from an alcohol does not occur. On reaction with $POCl_3$, however, the –OH group is converted into a dichlorophosphate ($-OPOCl_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E2 elimination step.

Figure 17.7 | **MECHANISM**

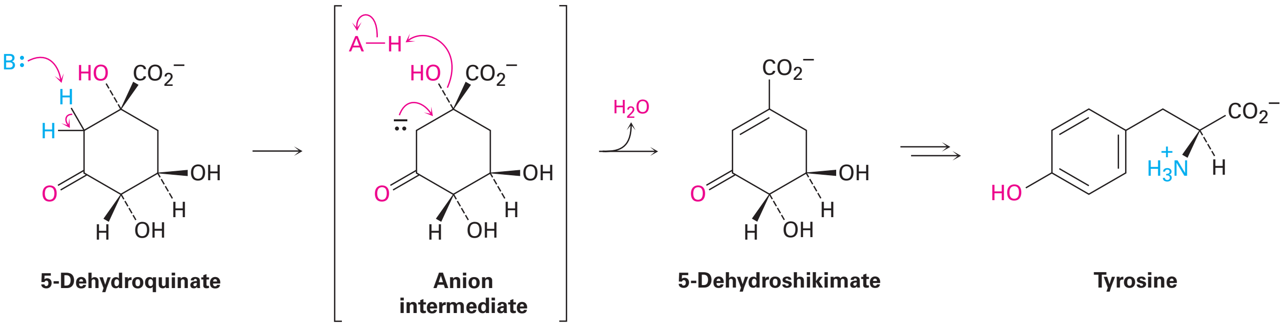
Mechanism of the dehydration of secondary and tertiary alcohols by reaction with $POCl_3$ in pyridine. The reaction is an E2 process.

1 The alcohol hydroxyl group reacts with $POCl_3$ to form a dichlorophosphate intermediate.

2 E2 elimination then occurs by the usual one-step mechanism as the amine base pyridine abstracts a proton from the neighboring carbon at the same time that the dichlorophosphate group is leaving.



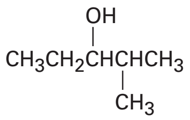
As noted previously in **Section 11.11**, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the –OH group is two carbons away from a carbonyl group. An example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base (:B) first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate then expels the –OH group with simultaneous protonation by an acid (HA) to form water.



Problem 17.13

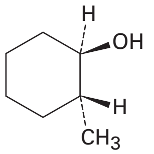
What product(s) would you expect from dehydration of the following alcohols with $POCl_3$ in pyridine? Indicate the major product in each case.

(a)

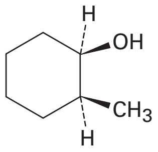


$\mathrm{CH_3CH_2\overset{OH}{C}H\underset{CH_3}{C}HCH_3}$

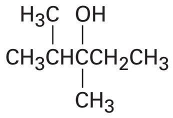
(b)



(c)

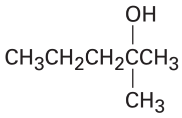


(d)



$\mathrm{CH_3\overset{H_3C}{C}H\overset{OH}{\underset{CH_3}{C}}CH_2CH_3}$

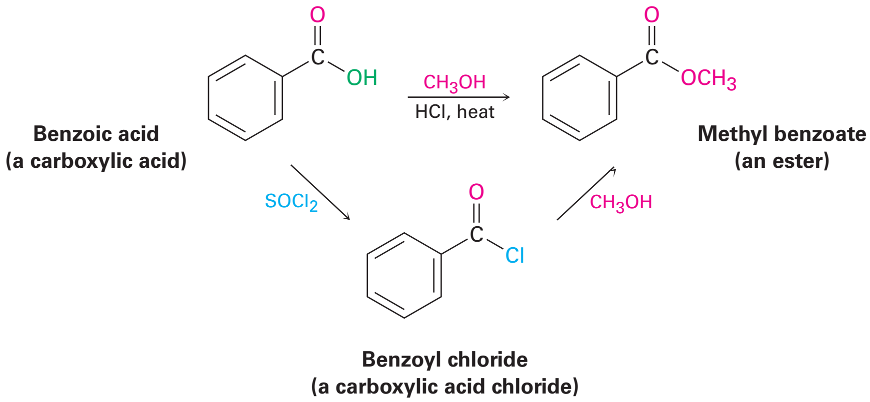
(e)



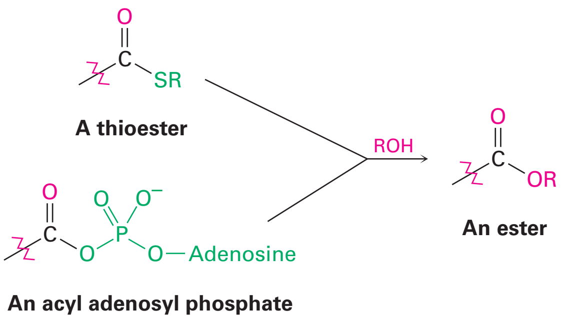
$\mathrm{CH_3CH_2CH_2\overset{OH}{\underset{CH_3}{C}}CH_3}$

Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol.

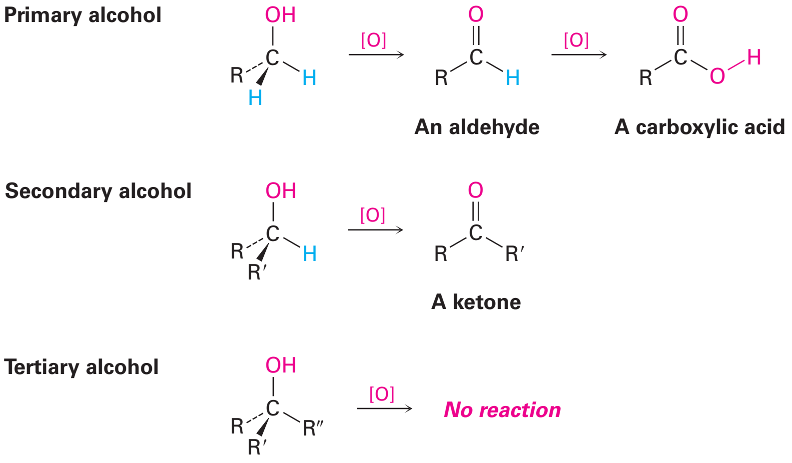


In living organisms, a similar process occurs, although a thioester or acyl adenosyl phosphate is the substrate rather than a carboxylic acid chloride. We'll look at the mechanisms of these reactions in Chapter 21.



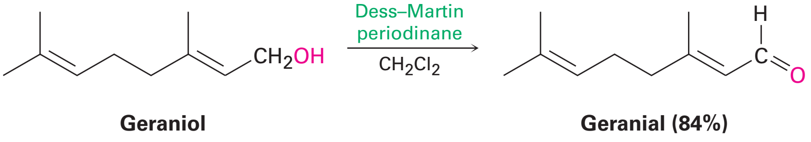
17.7 Oxidation of Alcohols

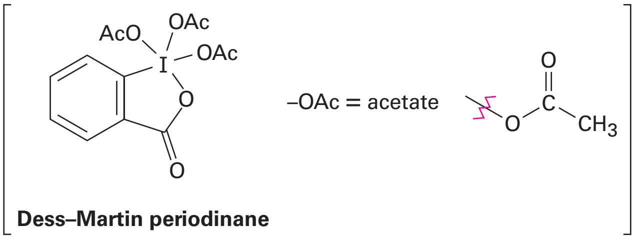
Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds—the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don’t normally react with most oxidizing agents.



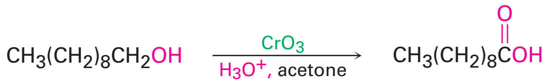
The oxidation of a primary or secondary alcohol can be accomplished by any of a large number of reagents, including $KMnO_4$, CrO_3, and $Na_2Cr_2O_7$. Which reagent is used in a specific case depends on such factors as cost, convenience, reaction yield, and alcohol sensitivity. For example, the large-scale oxidation of a simple, inexpensive alcohol such as cyclohexanol might best be done with a cheap oxidant such as $Na_2Cr_2O_7$. On the other hand, the small-scale oxidation of a delicate and expensive polyfunctional alcohol might best be done with one of several mild and high-yielding reagents, regardless of cost.

Primary alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagents chosen and the conditions used. Older methods were often based on Cr(VI) reagents such as CrO_3 or $Na_2Cr_2O_7$, but a more common current choice for preparing an aldehyde from a primary alcohol in the laboratory is to use the I(V)-containing *Dess–Martin periodinane* in dichloromethane solvent.





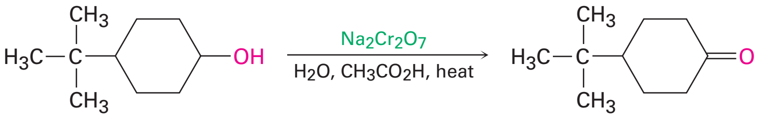
Most other commonly used oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can't usually be isolated because it is further oxidized too rapidly.



$$CH_3(CH_2)_8CH_2OH \xrightarrow[H_3O^+,\ \text{acetone}]{CrO_3} CH_3(CH_2)_8\overset{O}{\overset{\|}{C}}OH$$

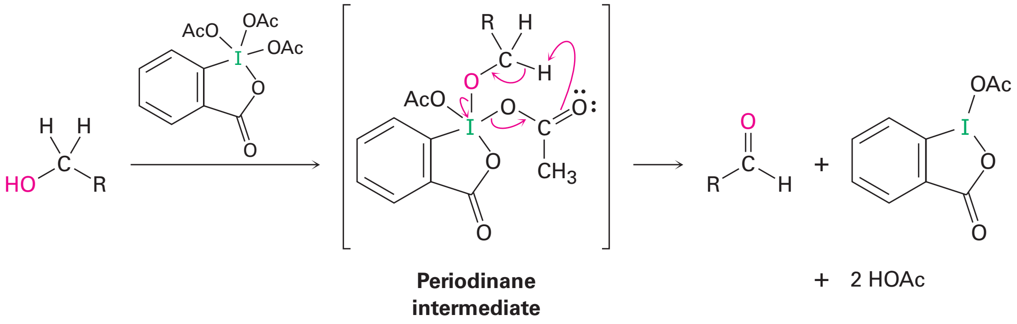
1-Decanol **Decanoic acid (93%)**

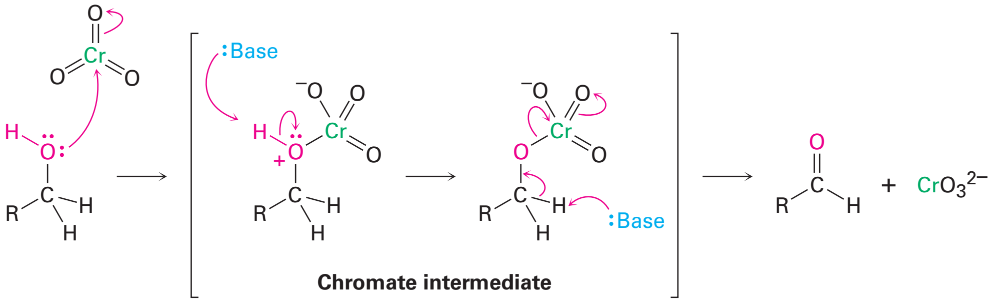
Secondary alcohols are easily oxidized to give ketones. For a sensitive or costly alcohol, the Dess–Martin procedure is often used because the reaction is nonacidic and occurs at lower temperatures. For a large-scale oxidation, however, an inexpensive reagent such as $Na_2Cr_2O_7$ in aqueous acetic acid might be used.



4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (91%)**

All these oxidations occur by a mechanism that is closely related to the E2 reaction **(Section 11.8)**. In the Dess–Martin oxidation, for instance, the first step involves a substitution reaction between the alcohol and the I(V) reagent to form a new periodinane intermediate, followed by expulsion of reduced I(III) as the leaving group. Similarly, when a Cr(VI) reagent, such as CrO_3, is the oxidant, reaction with the alcohol gives a chromate intermediate followed by expulsion of a reduced Cr(IV) species. Although we usually think of the E2 reaction as a means of generating a carbon–*carbon* double bond by elimination of a halide leaving group, the reaction is also useful for generating a carbon–*oxygen* double bond by elimination of a reduced iodine or metal as the leaving group.





Biological alcohol oxidations are the opposite of biological carbonyl reductions and are carried by the coenzymes NAD$^+$ and NADP$^+$. A base removes the –OH proton, and the alkoxide ion transfers a hydride ion to the coenzyme. An example is the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate, a step in the biological metabolism of fats **(Figure 17.8)**. Note that addition occurs exclusively on the *Re* face of the NAD$^+$ ring, adding a hydrogen with *pro-R* stereochemistry.

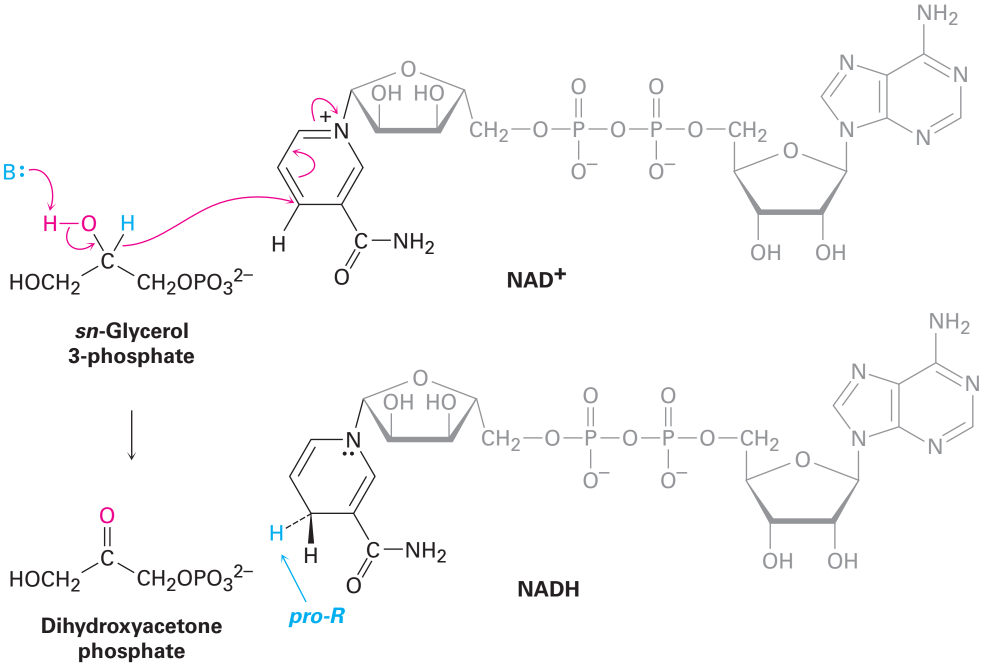
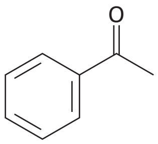


Figure 17.8 The biological oxidation of an alcohol (*sn*-glycerol 3-phosphate) to give a ketone (dihydroxyacetone phosphate). This mechanism is the exact opposite of the ketone reduction shown previously in Figure 17.4.

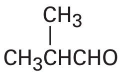
Problem 17.14

What alcohols would give the following products on oxidation?

(a)

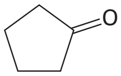


(b)



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCHO$$

(c)



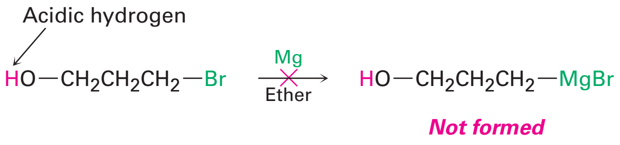
Problem 17.15

What products would you expect from oxidation of the following compounds with CrO_3 in aqueous acid? With the Dess–Martin periodinane?

(a) 1-Hexanol **(b)** 2-Hexanol **(c)** Hexanal

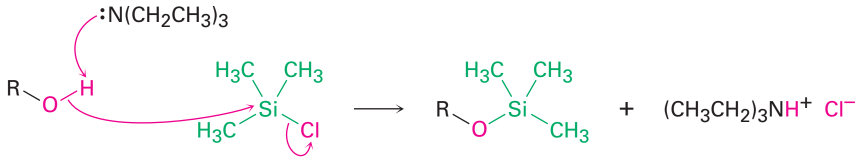
17.8 Protection of Alcohols

It often happens, particularly during the synthesis of complex molecules, that one functional group in a molecule interferes with an intended reaction on another functional group elsewhere in the same molecule. We saw earlier in this chapter, for instance, that a Grignard reagent can't be prepared from a halo alcohol because the C–Mg bond is not compatible with the presence of an acidic –OH group in the same molecule.



When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (1) introducing a **protecting group** to block the interfering function, (2) carrying out the desired reaction, and (3) removing the protecting group.

One of the more common methods of alcohol protection is by reaction with a chlorotrialkylsilane, Cl–SiR$_3$, to yield a trialkylsilyl ether, R′–O–SiR$_3$. Chlorotrimethylsilane is often used, and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.

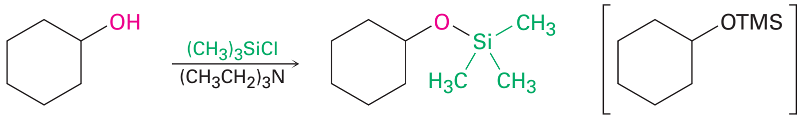


An alcohol

Chlorotrimethylsilane

A trimethylsilyl (TMS) ether

For example:

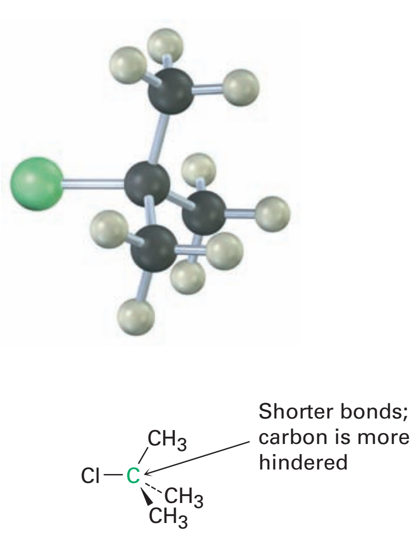


Cyclohexanol

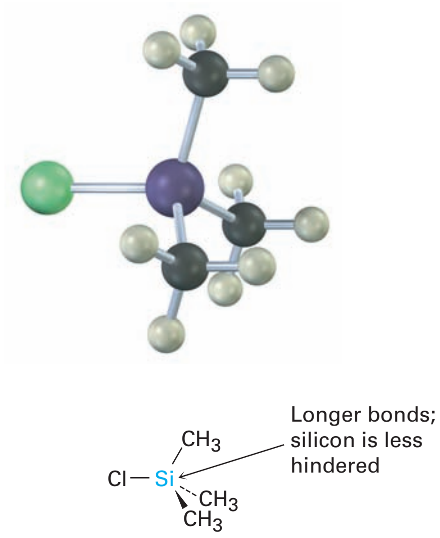
Cyclohexyl trimethylsilyl ether (94%)

The ether-forming step is an S$_N$2-like reaction of the alkoxide ion on the silicon atom, with concurrent loss of the leaving chloride anion. Unlike most

S_N2 reactions, though, this reaction takes place at a *tertiary* center—a trialkyl-substituted silicon atom. The reaction occurs because silicon, a third-row atom, is larger than carbon and forms longer bonds. The three methyl substituents attached to silicon thus offer less steric hindrance to reaction than they do in the analogous *tert*-butyl chloride.

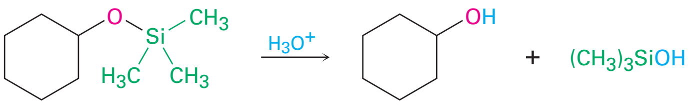


C–C bond length: 154 pm



C–Si bond length: 195 pm

Like most other ethers, which we'll study in the next chapter, TMS ethers are relatively unreactive. They have no acidic hydrogens and don't react with oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol.

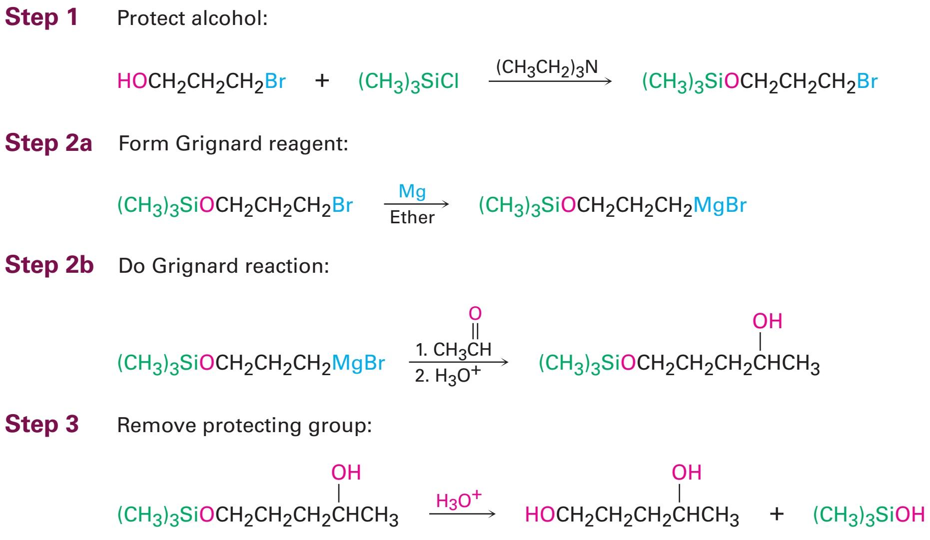


Cyclohexyl trimethylsilyl ether

Cyclohexanol

To now solve the problem posed at the beginning of this section, it's possible to use a halo alcohol in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromo-1-propanol to acetaldehyde by the route shown in **Figure 17.9**.

Figure 17.9 Use of a TMS-protected alcohol during a Grignard reaction.



Step 1 Protect alcohol:

$$HOCH_2CH_2CH_2Br + (CH_3)_3SiCl \xrightarrow{(CH_3CH_2)_3N} (CH_3)_3SiOCH_2CH_2CH_2Br$$

Step 2a Form Grignard reagent:

$$(CH_3)_3SiOCH_2CH_2CH_2Br \xrightarrow[\text{Ether}]{\text{Mg}} (CH_3)_3SiOCH_2CH_2CH_2MgBr$$

Step 2b Do Grignard reaction:

$$(CH_3)_3SiOCH_2CH_2CH_2MgBr \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3\overset{O}{\overset{\|}{C}}H} (CH_3)_3SiOCH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3$$

Step 3 Remove protecting group:

$$(CH_3)_3SiOCH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3 \xrightarrow{H_3O^+} HOCH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3 + (CH_3)_3SiOH$$

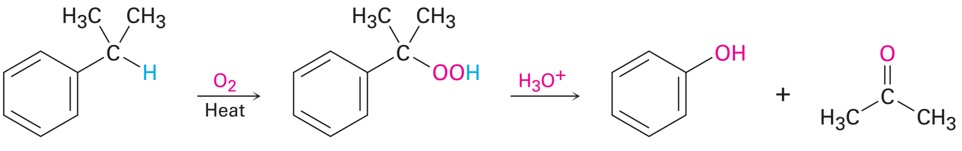
Problem 17.16

TMS ethers can be removed by treatment with fluoride ion as well as by acid-catalyzed hydrolysis. Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF. Fluorotrimethylsilane is a product.

17.9 Phenols and Their Uses

Historically, the outbreak World War I provided a stimulus for the industrial preparation of large amounts of synthetic phenol, which was needed as a raw material to manufacture the explosive, picric acid (2,4,6-trinitrophenol). Today, approximately 8 million metric tons of phenol is manufactured worldwide each year for use in such products as Bakelite resin and adhesives for binding plywood.

Phenol was manufactured for many years by the Dow process, in which chlorobenzene reacts with NaOH at high temperature and pressure **(Section 16.8)**. Now, however, an alternative synthesis from isopropylbenzene, commonly called *cumene,* is used. Cumene reacts with air at high temperature by benzylic oxidation through a radical mechanism to form cumene hydroperoxide, which is converted into phenol and acetone by treatment with acid. This is a particularly efficient process because two valuable chemicals are prepared at the same time.

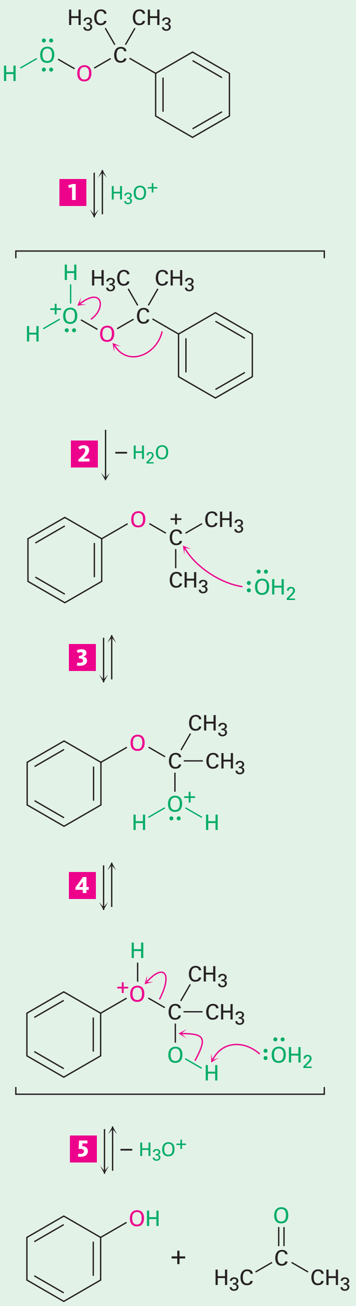


Cumene (isopropylbenzene) **Cumene hydroperoxide** **Phenol** **Acetone**

As shown in **Figure 17.10**, the reaction occurs by protonation of oxygen followed by shift of the phenyl group from carbon to oxygen with simultaneous loss of water. Readdition of water then yields an intermediate called a *hemiacetal*—a compound that contains one –OR group and one –OH group bonded to the same carbon atom—which breaks down to phenol and acetone.

Figure 17.10 | **MECHANISM**

Mechanism of the formation of phenol by acid-catalyzed rearrangement of cumene hydroperoxide.



1 Protonation of the hydroperoxy group on the terminal oxygen atom gives an oxonium ion . . .

2 . . . which undergoes rearrangement by migration of the phenyl ring from carbon to oxygen, expelling water as the leaving group and giving a carbocation.

3 Nucleophilic addition of water to the carbocation yields another oxonium ion . . .

4 . . . which rearranges by a proton shift from one oxygen to another.

5 Elimination of phenol gives acetone as co-product and regenerates the acid catalyst.

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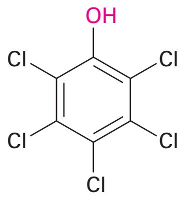
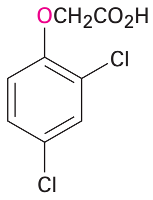
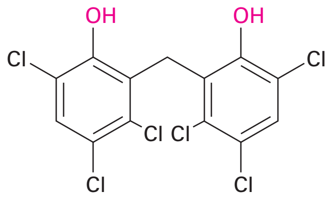
In addition to its use in making resins and adhesives, phenol is also the starting material for the synthesis of chlorinated phenols and the food preservatives BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole). Pentachlorophenol, a widely used wood preservative, is prepared by reaction of phenol with excess Cl_2. The herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) is prepared from 2,4-dichlorophenol, and the hospital antiseptic agent hexachlorophene is prepared from 2,4,5-trichlorophenol.



Pentachlorophenol (wood preservative)

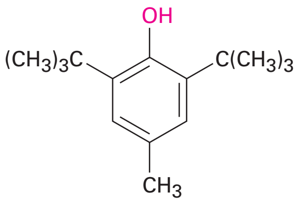


2,4-Dichlorophenoxyacetic acid, 2,4-D (herbicide)

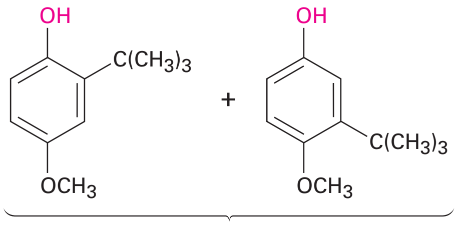


Hexachlorophene (antiseptic)

The food preservative BHT is prepared by Friedel–Crafts alkylation of *p*-methylphenol (*p*-cresol) with 2-methylpropene in the presence of acid; BHA is prepared similarly by alkylation of *p*-methoxyphenol.



BHT



BHA

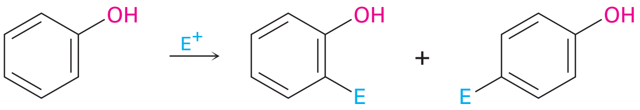
Problem 17.17

Show the mechanism of the reaction of *p*-methylphenol with 2-methylpropene and H_3PO_4 catalyst to yield the food additive BHT.

17.10 Reactions of Phenols

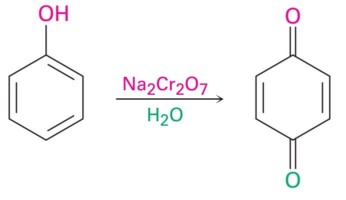
Electrophilic Aromatic Substitution Reactions

The hydroxyl group is a strongly activating, ortho- and para-directing substituent in electrophilic aromatic substitution reactions **(Section 16.4)**. As a result, phenols are highly reactive substrates for electrophilic halogenation, nitration, sulfonation, and Friedel–Crafts reactions.

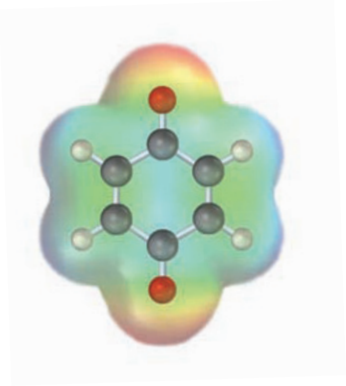


Oxidation of Phenols: Quinones

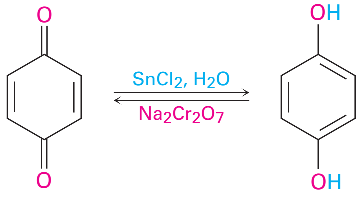
Phenols don't undergo oxidation in the same way that alcohols do because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, oxidation of a phenol yields a cyclohexa-2,5-diene-1,4-dione, or **quinone**. Many different oxidizing agents will accomplish the transformation, with $Na_2Cr_2O_7$ a common choice for simple phenols and potassium nitrosodisulfonate $[(KSO_3)_2NO]$, called Fremy's salt, used in more complex cases.



Phenol **Benzoquinone (79%)**

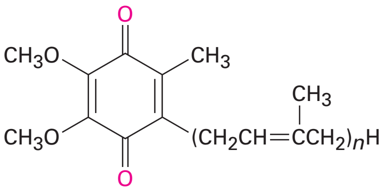


Quinones are a valuable class of compounds because of their oxidation–reduction, or *redox,* properties. They can be easily reduced to **hydroquinones** (*p*-dihydroxybenzenes) by reagents such as $NaBH_4$ and $SnCl_2$, and hydroquinones can be easily reoxidized back to quinones by $Na_2Cr_2O_7$.



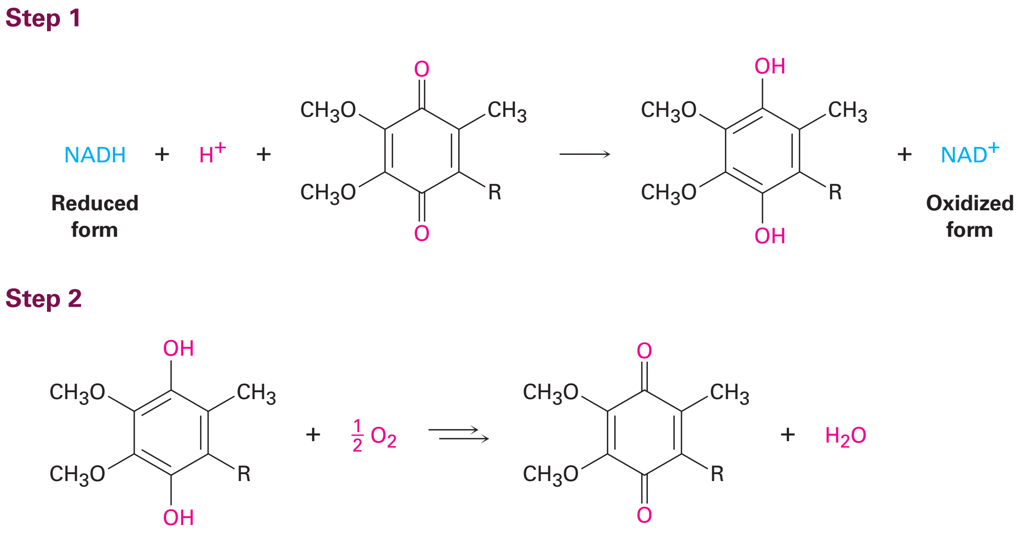
Benzoquinone **Hydroquinone**

The redox properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q,* are components of the cells of all aerobic organisms, from the simplest bacterium to humans. They are so named because of their ubiquitous occurrence in nature.



Ubiquinones (n = 1–10)

Ubiquinones function within the mitochondria of cells to mediate the respiration process in which electrons are transported from the biological reducing agent NADH to molecular oxygen. Through a complex series of steps, the ultimate result is a cycle whereby NADH is oxidized to NAD^+, O_2 is reduced to water, and energy is produced. Ubiquinone acts only as an intermediary and is itself unchanged.



Net change: $NADH + \frac{1}{2}O_2 + H^+ \longrightarrow NAD^+ + H_2O$

17.11 Spectroscopy of Alcohols and Phenols

Infrared Spectroscopy

Alcohols have a strong C–O stretching absorption near 1050 cm^{-1} and a characteristic O–H stretching absorption at 3300 to 3600 cm^{-1}. The exact position of the O–H stretch depends on the extent of hydrogen-bonding in the molecule. Unassociated alcohols show a fairly sharp absorption near 3600 cm^{-1}, whereas hydrogen-bonded alcohols show a broader absorption in the 3300 to 3400 cm^{-1} range. The hydrogen-bonded hydroxyl absorption appears at 3350 cm^{-1} in the IR spectrum of cyclohexanol **(Figure 17.11)**.

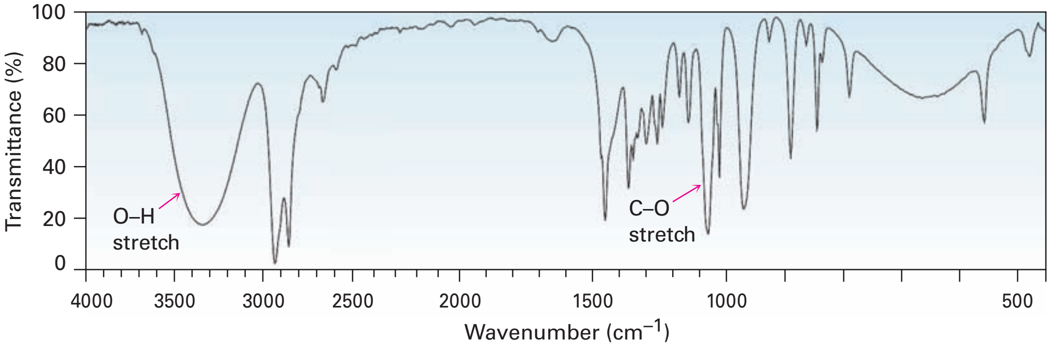


Figure 17.11 Infrared spectrum of cyclohexanol. Characteristic O–H and C–O stretching absorptions are indicated.

Phenols also show a characteristic broad IR absorption at 3500 cm^{-1} due to the –OH group, as well as the usual 1500 and 1600 cm^{-1} aromatic bands **(Figure 17.12)**. In phenol itself, the monosubstituted aromatic-ring peaks at 690 and 760 cm^{-1} are visible.

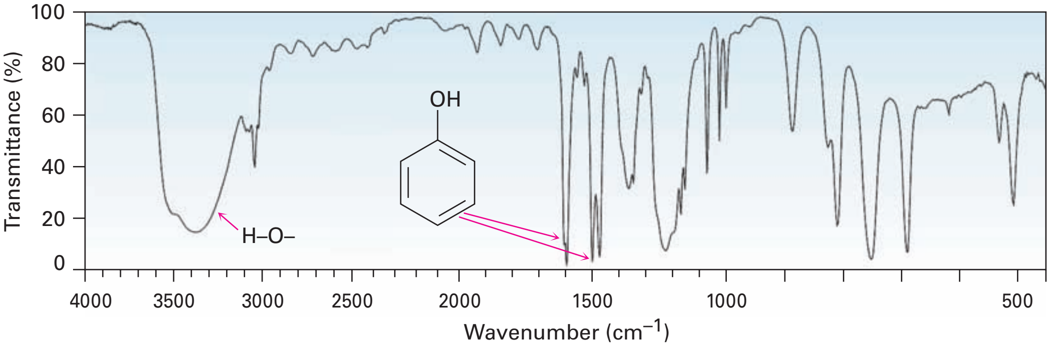
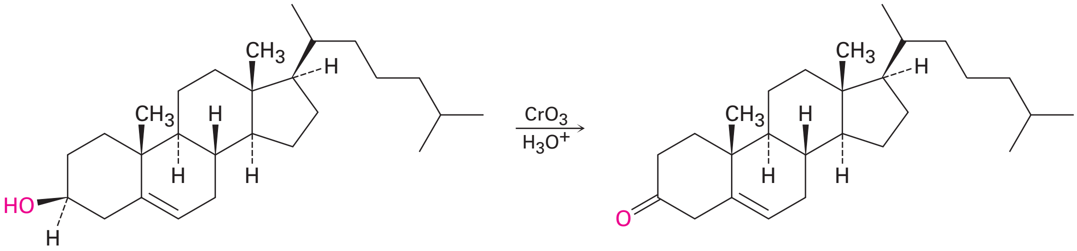


Figure 17.12 Infrared spectrum of phenol.

Problem 17.18

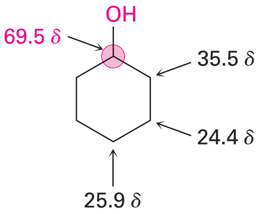
Assume that you need to prepare 5-cholesten-3-one from cholesterol. How could you use IR spectroscopy to tell whether the reaction was successful? What differences would you look for in the IR spectra of starting material and product?



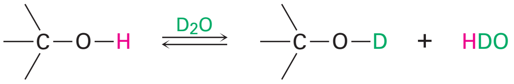
Cholesterol **5-Cholestene-3-one**

Nuclear Magnetic Resonance Spectroscopy

Carbon atoms bonded to electron-withdrawing –OH groups are deshielded and absorb at a lower field in the ^{13}C NMR spectrum than do typical alkane carbons. Most alcohol carbon absorptions fall in the range 50 to 80 δ, as the following data illustrate for cyclohexanol:



Alcohols also show characteristic absorptions in the ^{1}H NMR spectrum. Hydrogens on the oxygen-bearing carbon atom are deshielded by the electron-withdrawing effect of the nearby oxygen, and their absorptions occur in the range 3.4 to 4.5 δ. Spin–spin splitting, however, is not usually observed between the O–H proton of an alcohol and the neighboring protons on carbon. Most samples contain small amounts of acidic impurities, which catalyze an exchange of the O–H proton on a timescale so rapid that the effect of spin–spin splitting is removed. It's often possible to take advantage of this rapid proton exchange to identify the position of the O–H absorption. If a small amount of deuterated water, D_2O, is added to the NMR sample tube, the O–H proton is rapidly exchanged for deuterium and the hydroxyl absorption disappears from the spectrum.



Typical spin–spin splitting *is* observed between protons on the oxygen-bearing carbon and other neighbors. For example, the signal of the two $-CH_2O-$ protons in 1-propanol is split into a triplet by coupling with the neighboring $-CH_2-$ protons **(Figure 17.13)**.

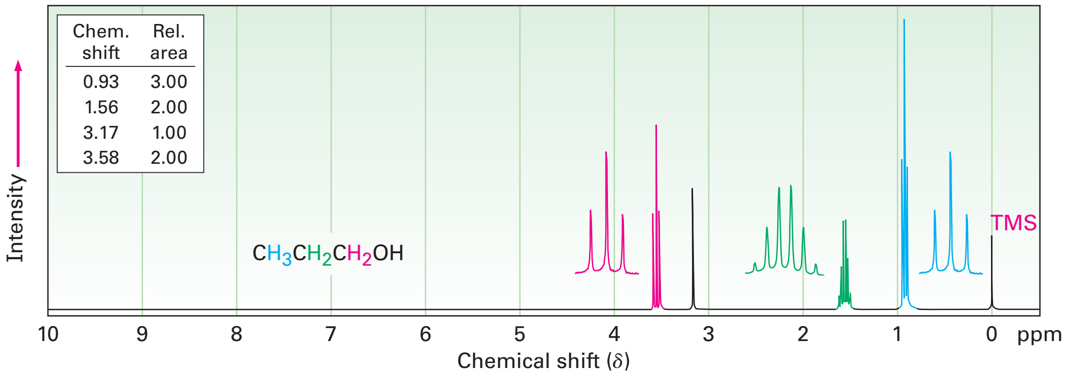


Figure 17.13 ^{1}H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ.

Phenols, like all aromatic compounds, show ^{1}H NMR absorptions near 7 to 8 δ, the expected position for aromatic-ring protons **(Section 15.7)**. In addition, phenol O–H protons absorb at 3 to 8 δ. In neither case are these absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

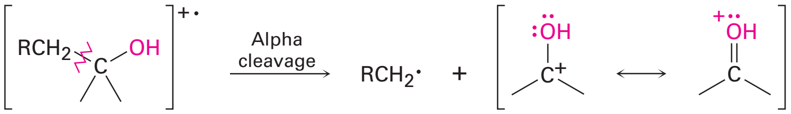
Problem 17.19

When the ^{1}H NMR spectrum of an alcohol is run in dimethyl sulfoxide (DMSO) solvent rather than in chloroform, exchange of the O–H proton is slow and spin–spin splitting is seen between the O–H proton and C–H protons on the adjacent carbon. What spin multiplicities would you expect for the hydroxyl protons in the following alcohols?

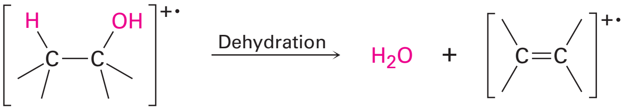
(a) 2-Methyl-2-propanol **(b)** Cyclohexanol **(c)** Ethanol
(d) 2-Propanol **(e)** Cholesterol **(f)** 1-Methylcyclohexanol

Mass Spectrometry

As noted previously in **Section 12.3**, alcohols undergo fragmentation in the mass spectrometer by two characteristic pathways, alpha cleavage and dehydration. In the alpha-cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation.



In the dehydration pathway, water is eliminated, yielding an alkene radical cation.



Both fragmentation modes are apparent in the mass spectrum of 1-butanol **(Figure 17.14)**. The peak at $m/z = 56$ is due to loss of water from the molecular ion, and the peak at $m/z = 31$ is due to an alpha cleavage.

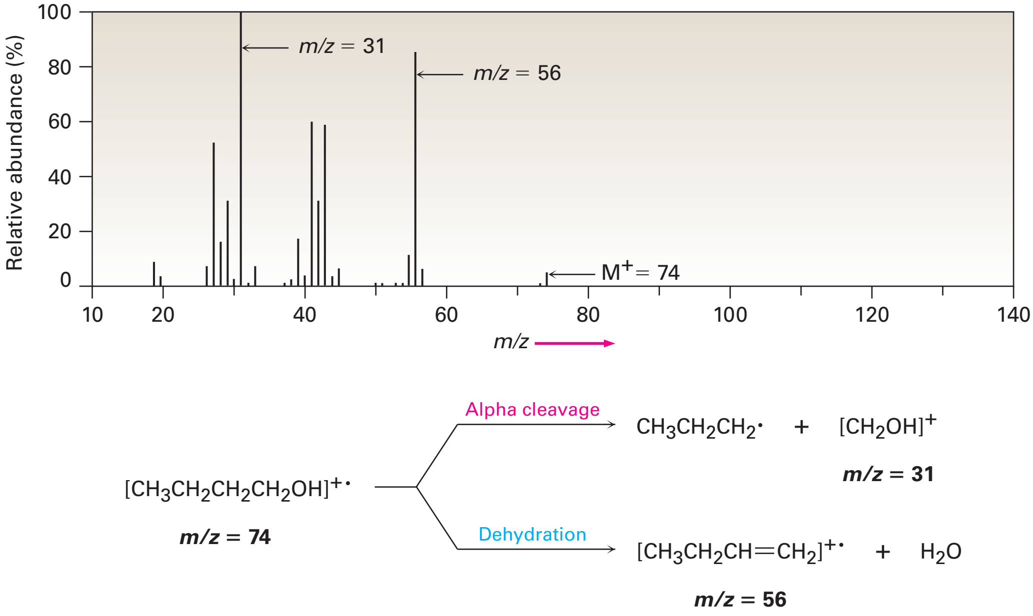


Figure 17.14 Mass spectrum of 1-butanol ($M^+ = 74$). Dehydration gives a peak at $m/z = 56$, and fragmentation by alpha cleavage gives a peak at $m/z = 31$.

A DEEPER LOOK

Ethanol: Chemical, Drug, Poison

© Bettmann/CORBIS

The Harger Drunkometer was the first breath analyzer, introduced in 1938 to help convict drunk drivers.

The production of ethanol by fermentation of grains and sugars is one of the oldest known organic reactions, going back at least 8000 years in the Middle East and perhaps as many as 9000 years in China. Fermentation is carried out by adding yeast to an aqueous sugar solution, where enzymes break down carbohydrates into ethanol and CO_2. As noted in the chapter introduction, approximately 4 billion gallons of ethanol is produced each year in the United States by fermentation, with essentially the entire amount used to make E90 automobile fuel.

$$\underset{\textbf{A carbohydrate}}{C_6H_{12}O_6} \xrightarrow{\text{Yeast}} 2\ CH_3CH_2OH + 2\ CO_2$$

Ethanol is classified medically as a central nervous system (CNS) depressant. Its effects—that is, being drunk—resemble the human response to anesthetics. There is an initial excitability and increase in sociable behavior, but this results from depression of inhibition rather than from stimulation. At a blood alcohol concentration of 0.1% to 0.3%, motor coordination is affected, accompanied by loss of balance, slurred speech, and amnesia. When blood alcohol concentration rises to 0.3% to 0.4%, nausea and loss of consciousness occur. Above 0.6%, spontaneous respiration and cardiovascular regulation are affected, ultimately leading to death. The LD_{50} of ethanol is 10.6 g/kg (Chapter 1 *A Deeper Look*).

The passage of ethanol through the body begins with its absorption in the stomach and small intestine, followed by rapid distribution to all body fluids and organs. In the pituitary gland, ethanol inhibits the production of a hormone that regulates urine flow, causing increased urine production and dehydration. In the stomach, ethanol stimulates production of acid. Throughout the body, ethanol causes blood vessels to dilate, resulting in flushing of the skin and a sensation of warmth as blood moves into capillaries beneath the surface. The result is not a warming of the body, but an increased loss of heat at the surface.

Ethanol metabolism occurs mainly in the liver and proceeds by oxidation in two steps, first to acetaldehyde (CH_3CHO) and then to acetic acid (CH_3CO_2H). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration seen in chronic alcoholics. The liver usually suffers the worst damage since it is the major site of alcohol metabolism.

Approximately 17,000 people are killed each year in the United States in alcohol-related automobile accidents. Thus, all 50 states—Massachusetts was the final holdout—have made it illegal to drive with a blood alcohol concentration (BAC) above 0.08%. Fortunately, simple tests have been devised for measuring blood alcohol concentration. The *Breathalyzer test* measures alcohol concentration in expired air by the color change that occurs when the bright orange oxidizing agent potassium dichromate ($K_2Cr_2O_7$) is reduced to blue-green chromium(III). The *Intoxilyzer* test uses IR spectroscopy to measure blood alcohol levels in expired air. Just breathe into the machine, and let the spectrum tell the tale.

Summary

In previous chapters, we focused on developing general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides and seeing some of the tools used in structural studies. With that accomplished, we have now begun in this chapter to study of the oxygen-containing functional groups that lie at the heart of organic and biological chemistry.

Alcohols are among the most versatile of all organic compounds. They occur widely in nature, are important industrially, and have an unusually rich chemistry. The most widely used methods of alcohol synthesis start with carbonyl compounds. Aldehydes, esters, and carboxylic acids are reduced by reaction with $LiAlH_4$ to give primary alcohols (RCH_2OH); ketones are reduced to yield secondary alcohols (R_2CHOH).

Alcohols are also prepared by reaction of carbonyl compounds with Grignard reagents, RMgX. Addition of a Grignard reagent to formaldehyde yields a primary alcohol, addition to an aldehyde yields a secondary alcohol, and addition to a ketone or an ester yields a tertiary alcohol. The Grignard reaction is limited by the fact that Grignard reagents can't be prepared from alkyl halides that contain reactive functional groups in the same molecule. This problem can sometimes be avoided by **protecting** the interfering functional group. Alcohols are often protected by formation of trimethylsilyl (TMS) ethers.

Alcohols undergo many reactions and can be converted into many other functional groups. They can be dehydrated to give alkenes by treatment with $POCl_3$ and can be transformed into alkyl halides by treatment with PBr_3 or $SOCl_2$. Furthermore, alcohols are weakly acidic ($pK_a \approx 16–18$) and react with strong bases and with alkali metals to form **alkoxide anions**, which are used frequently in organic synthesis. Perhaps the most important reactions of alcohols is their oxidation to carbonyl compounds. Primary alcohols yield either aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols are not normally oxidized.

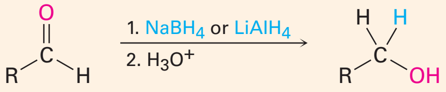
Phenols are aromatic counterparts of alcohols but are more acidic ($pK_a \approx 10$) because the corresponding **phenoxide anions** are resonance stabilized by delocalization of the negative charge into the aromatic ring. Substitution of the aromatic ring by an electron-withdrawing group increases phenol acidity, and substitution by an electron-donating group decreases acidity. Phenols can be oxidized to **quinones**, and quinones can be reduced back to **hydroquinones**.

Key words

alcohol (ROH), 620
alkoxide ion (RO^-), 624
hydroquinone, 653
phenol (ArOH), 620
phenoxide ion (ArO^-), 624
protecting group, 648
quinone, 653

Summary of Reactions

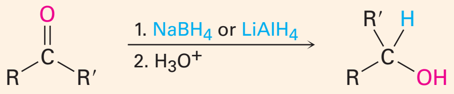
1. Synthesis of alcohols
   (a) Reduction of carbonyl compounds (Section 17.4)
      (1) Aldehydes



Primary alcohol

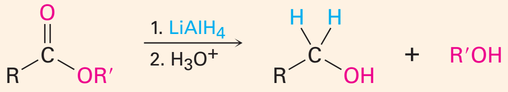
(continued)

(2) Ketones



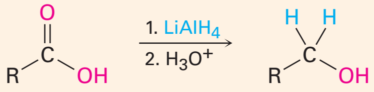
Secondary alcohol

(3) Esters



Primary alcohol

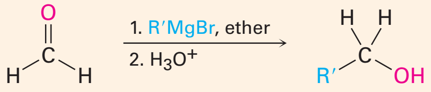
(4) Carboxylic acids



Primary alcohol

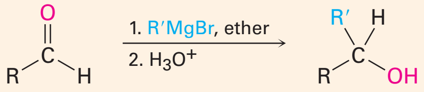
(b) Grignard addition to carbonyl compounds (Section 17.5)

(1) Formaldehyde



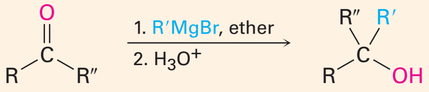
Primary alcohol

(2) Aldehydes



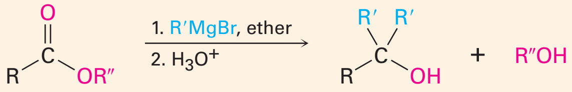
Secondary alcohol

(3) Ketones



Tertiary alcohol

(4) Esters

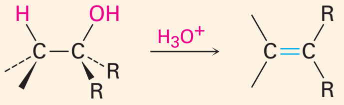


Tertiary alcohol

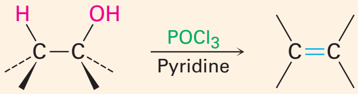
2. Reactions of alcohols

(a) Dehydration (Section 17.6)

(1) Tertiary alcohols

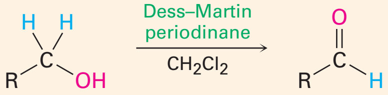


(2) Secondary and tertiary alcohols

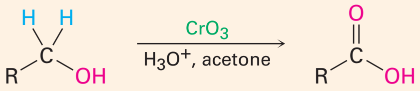


(b) Oxidation (Section 17.7)

(1) Primary alcohols

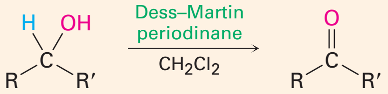


Aldehyde



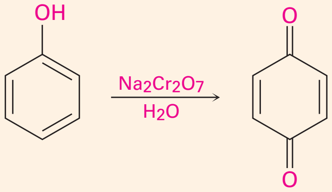
Carboxylic acid

(2) Secondary alcohols



Ketone

3. Oxidation of phenols to quinones (Section 17.10)



Exercises

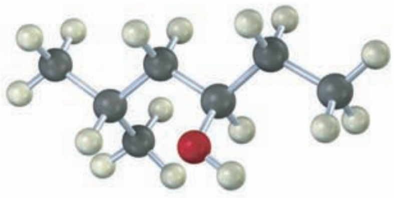
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

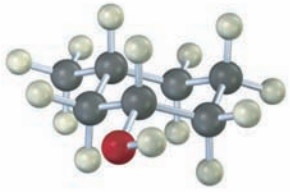
(Problems 17.1–17.19 appear within the chapter.)

17.20 Give IUPAC names for the following compounds:

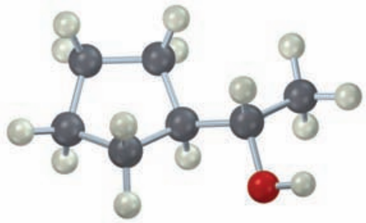
(a)



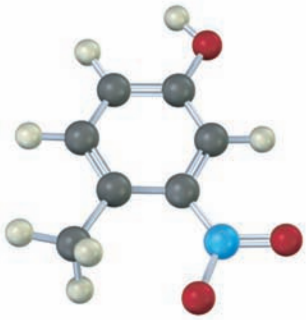
(b)



(c)

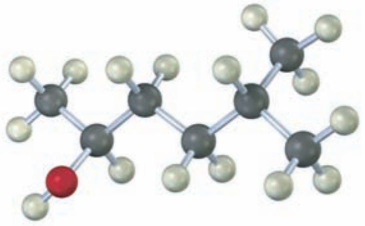


(d)

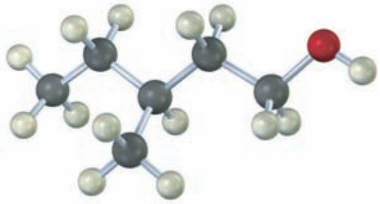


17.21 Draw the structure of the carbonyl compound(s) from which each of the following alcohols might have been prepared, and show the products you would obtain by treatment of each alcohol with (1) Na metal, (2) $SOCl_2$, and (3) Dess–Martin periodinane.

(a)



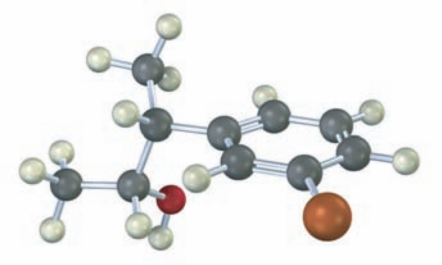
(b)



17.22 Predict the product from reaction of the following substance (reddish brown = Br) with:

(a) PBr_3 **(b)** Aqueous H_2SO_4 **(c)** $SOCl_2$

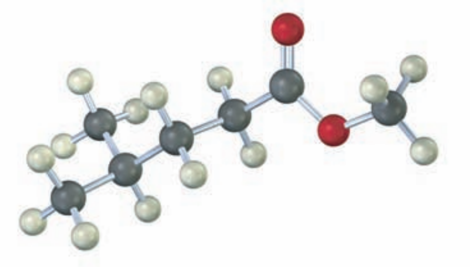
(d) Dess–Martin periodinane **(e)** Br_2, $FeBr_3$



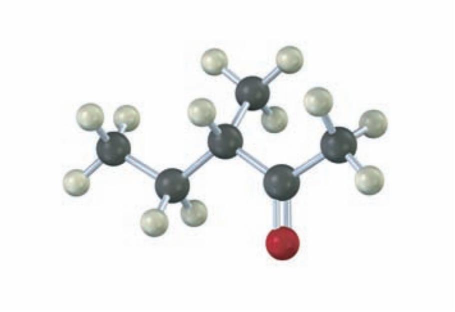
17.23 Predict the product from reaction of the following substance with:

(a) $NaBH_4$; then H_3O^+ **(b)** $LiAlH_4$; then H_3O^+

(c) 2 CH_3CH_2MgBr; then H_3O^+



17.24 Name and assign *R* or *S* stereochemistry to the product(s) you would obtain by reaction of the following substance with ethylmagnesium bromide. Is the product chiral? Is it optically active? Explain.

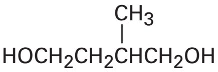


Additional Problems

Naming Alcohols

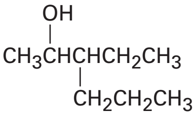
17.25 Give IUPAC names for the following compounds:

(a)



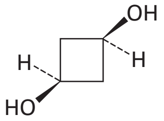
$HOCH_2CH_2\overset{\overset{CH_3}{|}}{C}HCH_2OH$

(b)

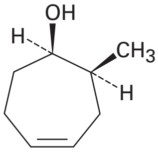


$CH_3\overset{\overset{OH}{|}}{C}H\underset{\underset{CH_2CH_2CH_3}{|}}{C}HCH_2CH_3$

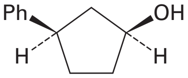
(c)



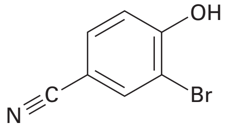
(d)



(e)



(f)

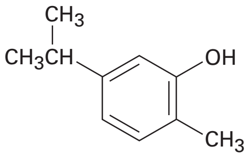


17.26 Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$.

17.27 Which of the eight alcohols you identified in Problem 17.26 react with CrO_3 in aqueous acid? Show the products you would expect from each reaction.

17.28 Named *bombykol,* the sex pheromone secreted by the female silkworm moth has the formula $C_{16}H_{28}O$ and the systematic name (10*E*,12*Z*)-10,12-hexadecadien-1-ol. Draw bombykol showing correct geometry for the two double bonds.

17.29 *Carvacrol* is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?

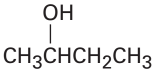


Carvacrol

Synthesizing Alcohols

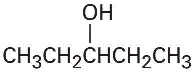
17.30 What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols?

(a)



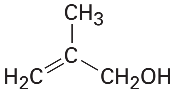
$CH_3\overset{\overset{OH}{|}}{C}HCH_2CH_3$

(b)



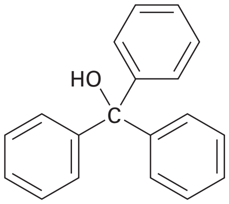
$CH_3CH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3$

(c)

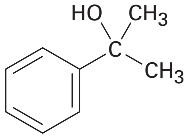


$H_2C{=}\overset{\overset{CH_3}{|}}{C}CH_2OH$

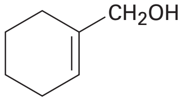
(d)



(e)

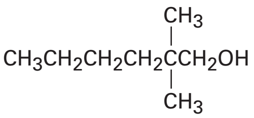


(f)



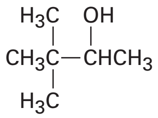
17.31 What carbonyl compounds would you reduce to prepare the following alcohols? List all possibilities.

(a)



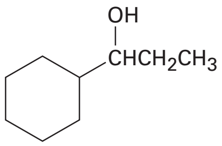
$CH_3CH_2CH_2CH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2OH$

(b)



$\overset{H_3C}{\underset{H_3C}{CH_3C}}-\overset{OH}{CHCH_3}$

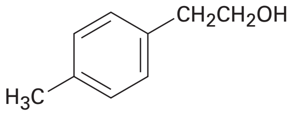
(c)



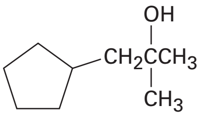
17.32 What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

(a) 2-Methyl-2-propanol
(b) 1-Ethylcyclohexanol
(c) 3-Phenyl-3-pentanol
(d) 2-Phenyl-2-pentanol

(e)

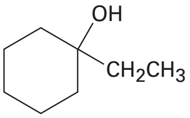


(f)

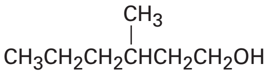


17.33 How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?

(a)

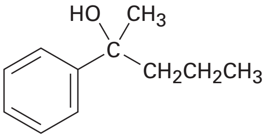


(b)

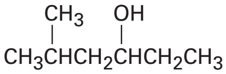


$CH_3CH_2CH_2\overset{CH_3}{C}HCH_2CH_2OH$

(c)



(d)



$CH_3\overset{CH_3}{C}HCH_2\overset{OH}{C}HCH_2CH_3$

Reactions of Alcohols

17.34 What products would you obtain from reaction of 1-pentanol with the following reagents?

(a) PBr_3
(b) $SOCl_2$
(c) CrO_3, H_2O, H_2SO_4
(d) Dess–Martin periodinane

17.35 How would you prepare the following compounds from 2-phenylethanol? More than one step may be required.

(a) Styrene ($PhCH{=}CH_2$)
(b) Phenylacetaldehyde ($PhCH_2CHO$)
(c) Phenylacetic acid ($PhCH_2CO_2H$)
(d) Benzoic acid
(e) Ethylbenzene
(f) Benzaldehyde
(g) 1-Phenylethanol
(h) 1-Bromo-2-phenylethane

17.36 How would you prepare the following compounds from 1-phenylethanol? More than one step may be required.

(a) Acetophenone ($PhCOCH_3$)
(b) Benzyl alcohol
(c) *m*-Bromobenzoic acid
(d) 2-Phenyl-2-propanol

17.37 How would you prepare the following substances from cyclopentanol? More than one step may be required.

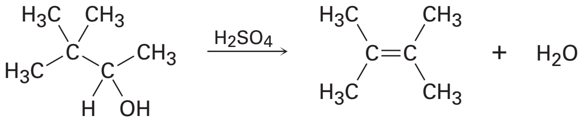
(a) Cyclopentanone **(b)** Cyclopentene
(c) 1-Methylcyclopentanol **(d)** *trans*-2-Methylcyclopentanol

17.38 What products would you expect to obtain from reaction of 1-methylcyclohexanol with the following reagents?

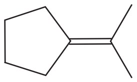
(a) HBr **(b)** NaH **(c)** H_2SO_4 **(d)** $Na_2Cr_2O_7$

Mechanisms

17.39 Evidence for the intermediate carbocations in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethyl-2-butene from 3,3-dimethyl-2-butanol.

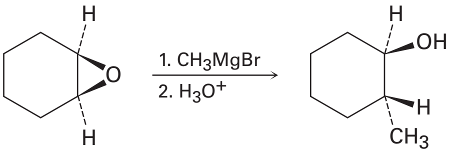


17.40 Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexene and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.



Isopropylidenecyclopentane

17.41 Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.

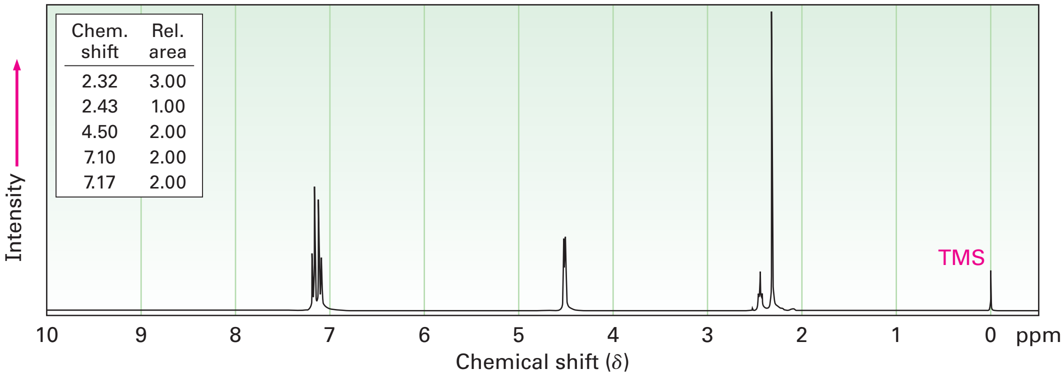


17.42 Treatment of the following epoxide with aqueous acid produces a carbocation intermediate that reacts with water to give a diol product. Show the structure of the carbocation, and propose a mechanism for the second step.

17.43 Reduction of 2-butanone with $NaBH_4$ yields 2-butanol. Is the product chiral? Is it optically active? Explain.

Spectroscopy

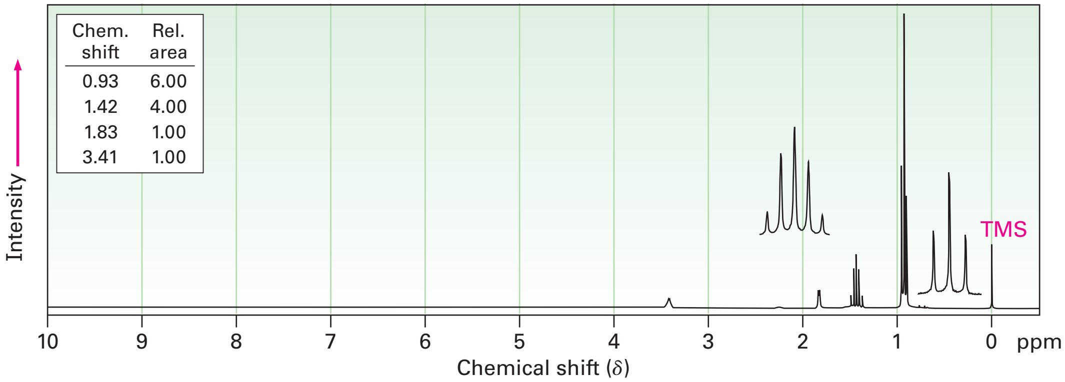
17.44 The following ^{1}H NMR spectrum is that of an alcohol, $C_8H_{10}O$. Propose a structure.



Chem. shift	Rel. area
2.32	3.00
2.43	1.00
4.50	2.00
7.10	2.00
7.17	2.00

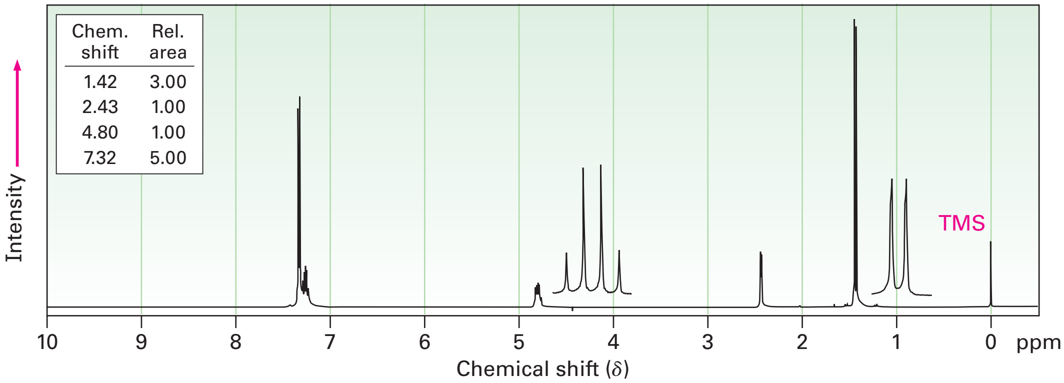
17.45 Propose structures for alcohols that have the following ^{1}H NMR spectra:

(a) $C_5H_{12}O$



Chem. shift	Rel. area
0.93	6.00
1.42	4.00
1.83	1.00
3.41	1.00

(b) $C_8H_{10}O$



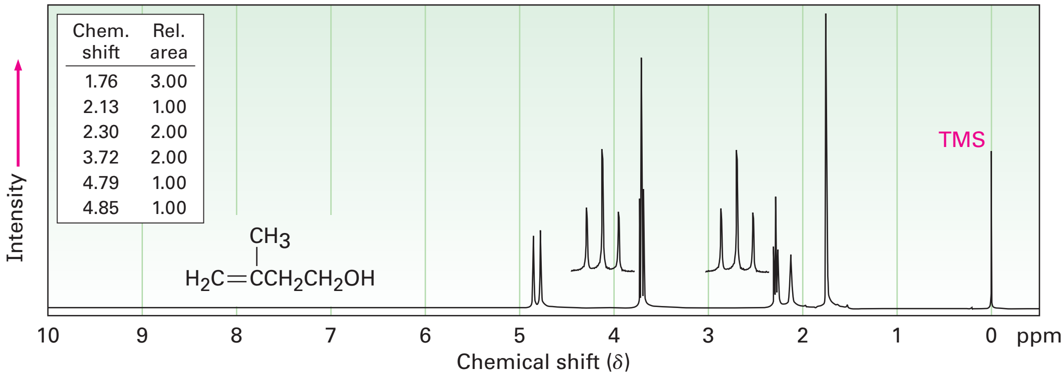
Chem. shift	Rel. area
1.42	3.00
2.43	1.00
4.80	1.00
7.32	5.00

17.46 Propose a structure consistent with the following spectral data for a compound $C_8H_{18}O_2$:

IR: 3350 cm^{-1}

^1H NMR: 1.24 δ (12 H, singlet); 1.56 δ (4 H, singlet); 1.95 δ (2 H, singlet)

17.47 The ^1H NMR spectrum shown is that of 3-methyl-3-buten-1-ol. Assign all the observed resonance peaks to specific protons, and account for the splitting patterns.



Chem. shift	Rel. area
1.76	3.00
2.13	1.00
2.30	2.00
3.72	2.00
4.79	1.00
4.85	1.00

17.48 A compound of unknown structure gave the following spectroscopic data:

Mass spectrum: $M^+ = 88.1$

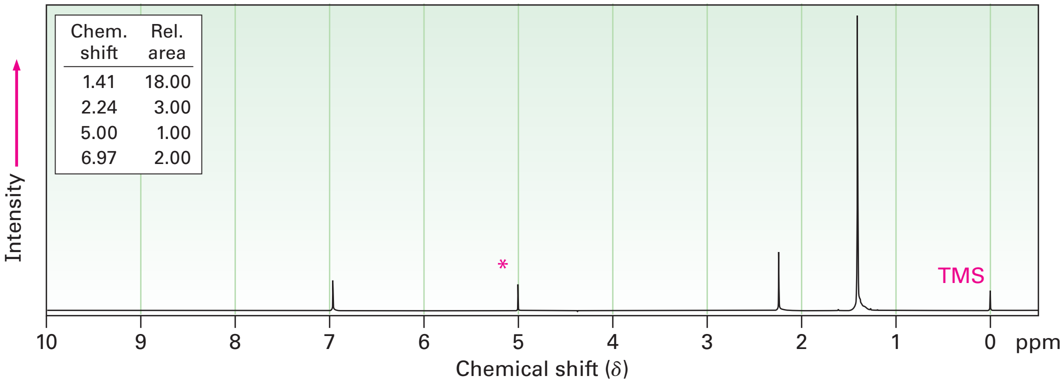
IR: 3600 cm^{-1}

^1H NMR: 1.4 δ (2 H, quartet, $J = 7$ Hz); 1.2 δ (6 H, singlet); 1.0 δ (1 H, singlet); 0.9 δ (3 H, triplet, $J = 7$ Hz)

^{13}C NMR: 74, 35, 27, 25 δ

(a) Assuming that the compound contains C and H but may or may not contain O, give three possible molecular formulas.
(b) How many protons (H) does the compound contain?
(c) What functional group(s) does the compound contain?
(d) How many carbons does the compound contain?
(e) What is the molecular formula of the compound?
(f) What is the structure of the compound?
(g) Assign the peaks in the ^1H NMR spectrum of the molecule to specific protons.

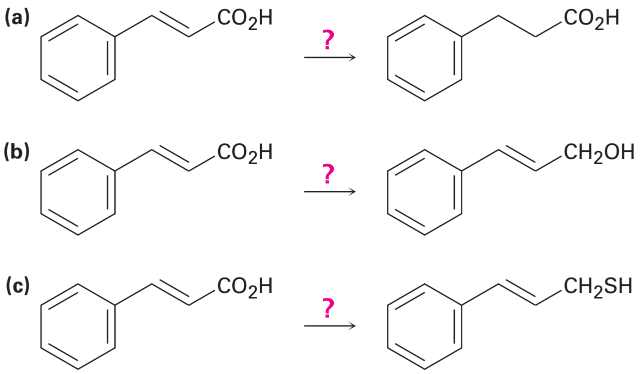
17.49 Propose a structure for a compound $C_{15}H_{24}O$ that has the following ^1H NMR spectrum. The peak marked by an asterisk disappears when D_2O is added to the sample.



Chem. shift	Rel. area
1.41	18.00
2.24	3.00
5.00	1.00
6.97	2.00

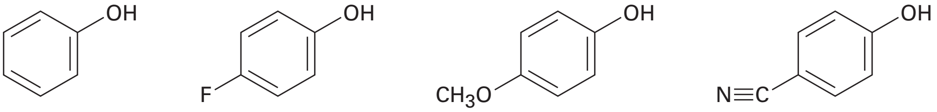
General Problems

17.50 How would you carry out the following transformations?

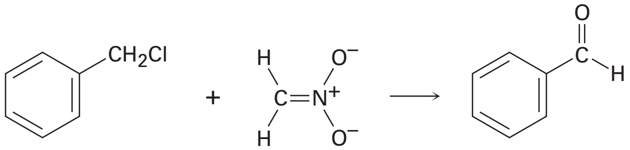


17.51 Benzoquinone is an excellent dienophile in the Diels–Alder reaction. What product would you expect from reaction of benzoquinone with 1 equivalent of 1,3-butadiene? From reaction with 2 equivalents of 1,3-butadiene?

17.52 Rank the following substituted phenols in order of increasing acidity, and explain your answer:

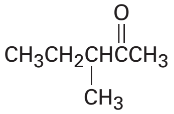


17.53 Benzyl chloride can be converted into benzaldehyde by treatment with nitromethane and base. The reaction involves initial conversion of nitromethane into its anion, followed by S_N2 reaction of the anion with benzyl chloride and subsequent E2 reaction. Write the mechanism in detail, using curved arrows to indicate the electron flow in each step.



Benzyl chloride **Nitromethane anion** **Benzaldehyde**

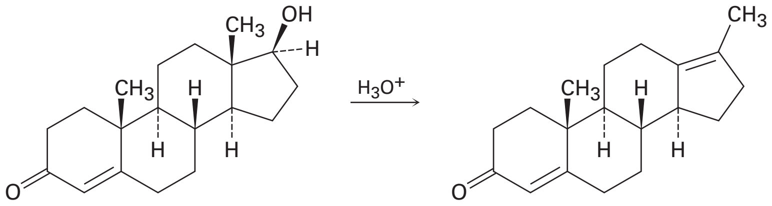
17.54 Reaction of (*S*)-3-methyl-2-pentanone with methylmagnesium bromide followed by acidification yields 2,3-dimethyl-2-pentanol. What is the stereochemistry of the product? Is the product optically active?



$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}CH_3$$

3-Methyl-2-pentanone

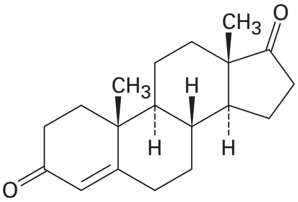
17.55 Testosterone is one of the most important male steroid hormones. When testosterone is dehydrated by treatment with acid, rearrangement occurs to yield the product shown. Propose a mechanism to account for this reaction.



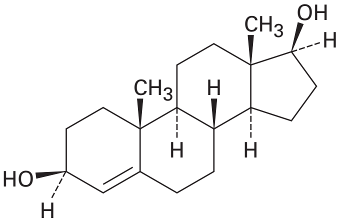
Testosterone

17.56 Starting from testosterone (Problem 17.55), how would you prepare the following substances?

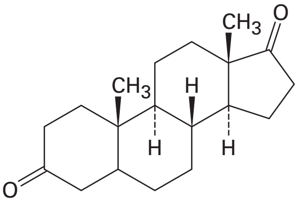
(a)



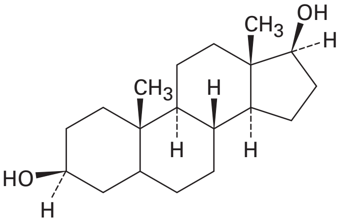
(b)



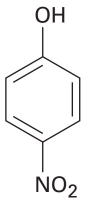
(c)



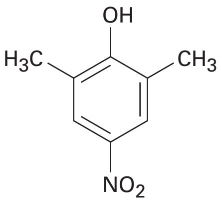
(d)



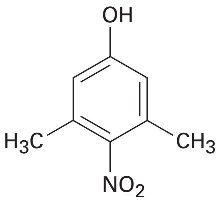
17.57 *p*-Nitrophenol and 2,6-dimethyl-4-nitrophenol both have pK_a = 7.15, but 3,5-dimethyl-4-nitrophenol has pK_a = 8.25. Why is 3,5-dimethyl-4-nitrophenol so much less acidic?



pK_a = 7.15



pK_a = 7.15



pK_a = 8.25

17.58 Compound **A**, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 25 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Write the reactions involved, and identify **A** and **B**.

17.59 Compound **A**, $C_5H_{10}O$, is one of the basic building blocks of nature. All steroids and many other naturally occurring compounds are built from compound **A**. Spectroscopic analysis of **A** yields the following information:

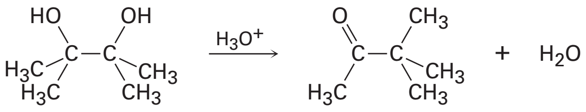
IR: 3400 cm^{-1}; 1640 cm^{-1}

^{1}H NMR: 1.63 δ (3 H, singlet); 1.70 δ (3 H, singlet); 3.83 δ (1 H, broad singlet); 4.15 δ (2 H, doublet, J = 7 Hz); 5.70 δ (1 H, triplet, J = 7 Hz)

(a) How many double bonds and/or rings does **A** have?
(b) From the IR spectrum, what is the identity of the oxygen-containing functional group?
(c) What kinds of protons are responsible for the NMR absorptions listed?
(d) Propose a structure for **A**.

17.60 Dehydration of *trans*-2-methylcyclopentanol with $POCl_3$ in pyridine yields predominantly 3-methylcyclopentene. Is the stereochemistry of this dehydration syn or anti? Can you suggest a reason for formation of the observed product? (Make molecular models!)

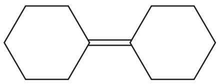
17.61 2,3-Dimethyl-2,3-butanediol has the common name *pinacol.* On heating with aqueous acid, pinacol rearranges to *pinacolone,* 3,3-dimethyl-2-butanone. Suggest a mechanism for this reaction.



Pinacol **Pinacolone**

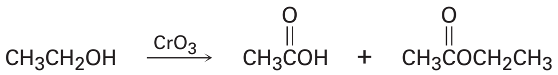
17.62 As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.

17.63 Propose a synthesis of bicyclohexylidene, starting from cyclohexanone as the only source of carbon.



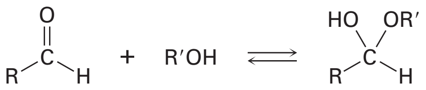
Bicyclohexylidene

17.64 A problem often encountered in the oxidation of primary alcohols to acids is that esters are sometimes produced as by-products. For example, oxidation of ethanol yields acetic acid and ethyl acetate:

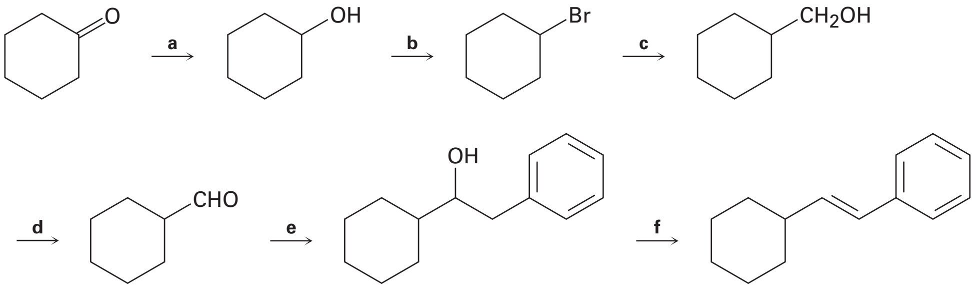


$$CH_3CH_2OH \xrightarrow{CrO_3} CH_3\overset{\overset{O}{\|}}{C}OH + CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

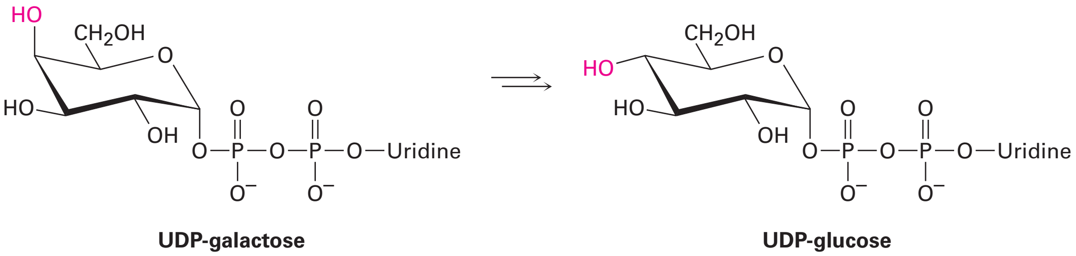
Propose a mechanism to account for the formation of ethyl acetate. Take into account the reversible reaction between aldehydes and alcohols:



17.65 Identify the reagents **a–f** in the following scheme:

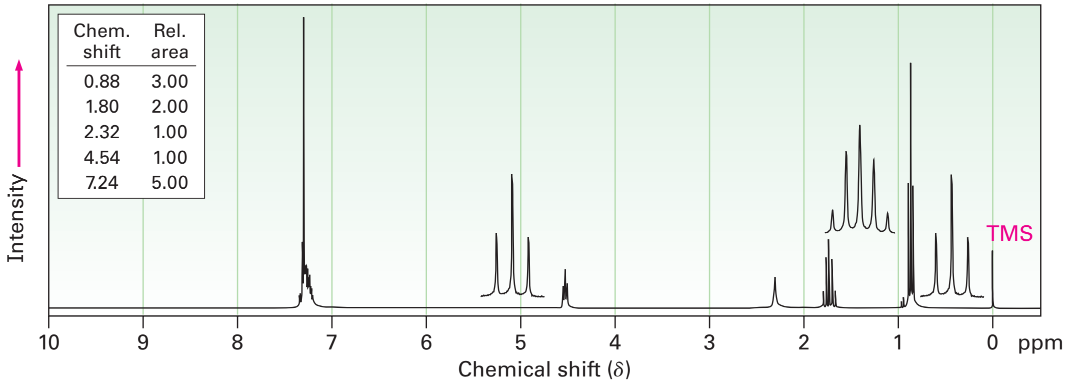


17.66 Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the isomerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The enzyme responsible for the transformation uses NAD$^+$ as cofactor. Propose a mechanism.



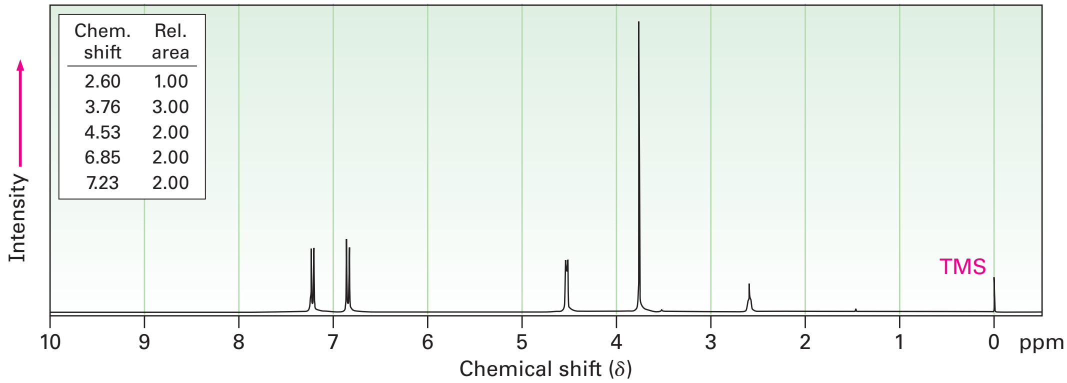
17.67 Propose structures for alcohols that have the following ^{1}H NMR spectra:

(a) $C_9H_{12}O$



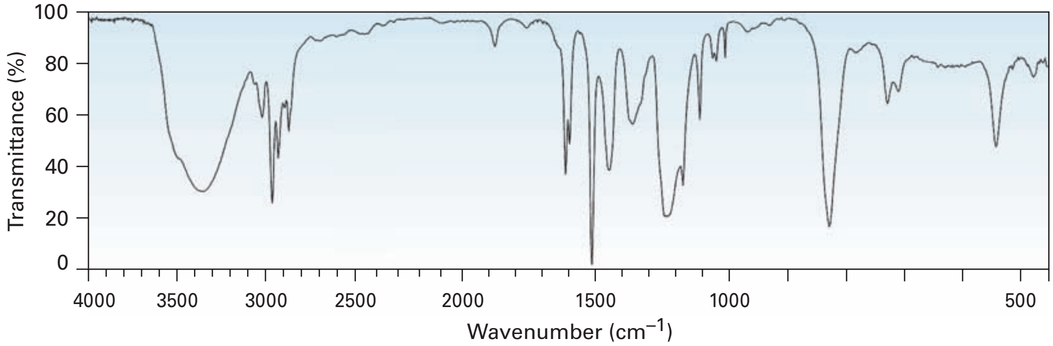
Chem. shift	Rel. area
0.88	3.00
1.80	2.00
2.32	1.00
4.54	1.00
7.24	5.00

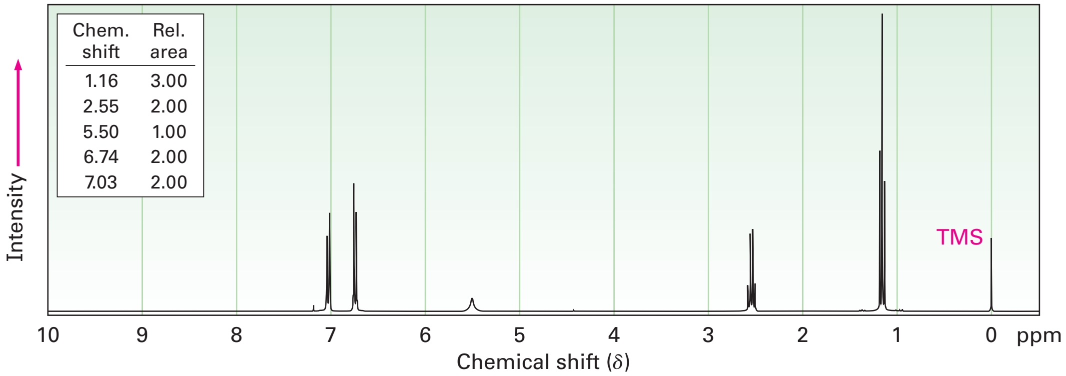
(b) $C_8H_{10}O_2$



Chem. shift	Rel. area
2.60	1.00
3.76	3.00
4.53	2.00
6.85	2.00
7.23	2.00

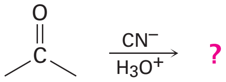
17.68 Compound **A**, $C_8H_{10}O$, has the IR and ^1H NMR spectra shown. Propose a structure consistent with the observed spectra, and assign each peak in the NMR spectrum. Note that the absorption at 5.5 δ disappears when D_2O is added.



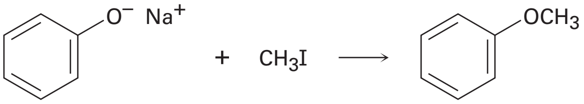


Chem. shift	Rel. area
1.16	3.00
2.55	2.00
5.50	1.00
6.74	2.00
7.03	2.00

17.69 The reduction of carbonyl compounds by reaction with hydride reagents (H**:**$^-$) and the Grignard addition by reaction with organomagnesium halides (R**:**$^-$ $^+$MgBr) are examples of *nucleophilic carbonyl addition reactions*. What analogous product do you think might result from reaction of cyanide ion with a ketone?



17.70 Ethers can be prepared by reaction of an alkoxide or phenoxide ion with a primary alkyl halide. Anisole, for instance, results from reaction of sodium phenoxide with iodomethane. What kind of reaction is occurring? Show the mechanism.



Sodium phenoxide **Anisole**

18

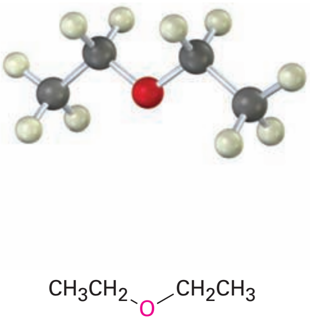
The appalling and unforgettable odor of skunks is due to a mixture of several simple thiols. Comstock Images/ Jupiterimages

Ethers and Epoxides; Thiols and Sulfides

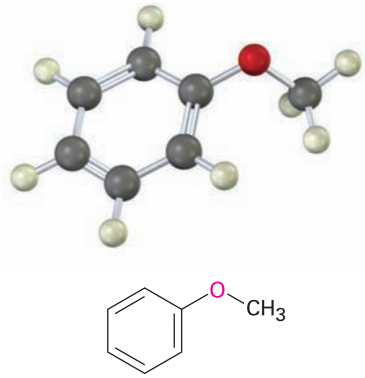
18.1 Names and Properties of Ethers
18.2 Synthesis of Ethers
18.3 Reactions of Ethers: Acidic Cleavage
18.4 Reactions of Ethers: Claisen Rearrangement
18.5 Cyclic Ethers: Epoxides
18.6 Reactions of Epoxides: Ring-Opening
18.7 Crown Ethers
18.8 Thiols and Sulfides
18.9 Spectroscopy of Ethers
A Deeper Look—Epoxy Resins and Adhesives

Ethers (R–O–R′), like the alcohols we saw in the preceding chapter, are also organic derivatives of water, but they have two organic groups bonded to the same oxygen atom rather than one. The organic groups might be alkyl, aryl, or vinylic, and the oxygen atom might be in an open chain or a ring.

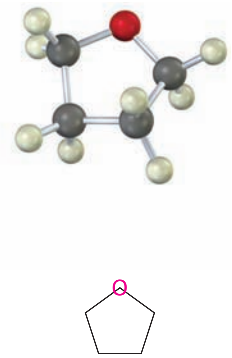
Perhaps the most well-known ether is diethyl ether, which has a long history of medicinal use as an anesthetic and industrial use as a solvent. Other useful ethers include anisole, a pleasant-smelling aromatic ether used in perfumery, and tetrahydrofuran (THF), a cyclic ether often used as a solvent.



Diethyl ether



Anisole (methyl phenyl ether)



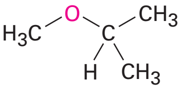
Tetrahydrofuran

Thiols (R–S–H) and **sulfides (R–S–R′)** are sulfur analogs of alcohols and ethers, respectively. Both functional groups are found in various biomolecules, although not as commonly as their oxygen-containing relatives.

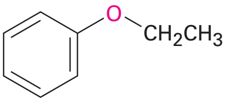
Why This Chapter? This chapter finishes the coverage of functional groups with C–O and C–S single bonds that was begun in Chapter 17. We'll focus primarily on ethers and take only a brief look at thiols and sulfides before going on to an extensive coverage of compounds with C=O double bonds in Chapters 19 through 23.

18.1 Names and Properties of Ethers

Simple ethers with no other functional groups are named by identifying the two organic substituents and adding the word *ether.*

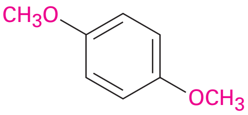


Isopropyl methyl ether

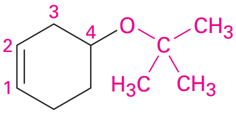


Ethyl phenyl ether

If other functional groups are present, the ether part is considered an *alkoxy* substituent. For example:

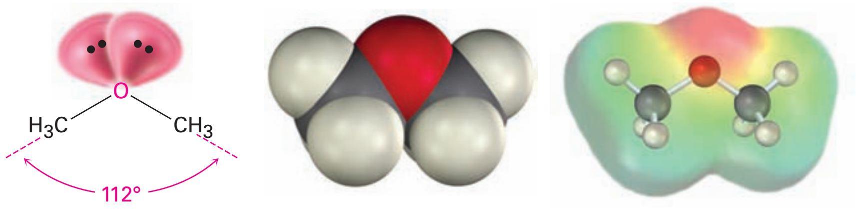


***p*-Dimethoxybenzene**



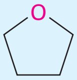
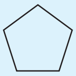
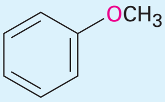
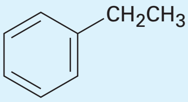
4-*tert*-Butoxy-1-cyclohexene

Like alcohols, ethers have nearly the same geometry as water. The R–O–R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is sp^3-hybridized.



The electronegative oxygen atom gives ethers a slight dipole moment, and the boiling points of ethers are often slightly higher than the boiling points of comparable alkanes. Table 18.1 compares the boiling points of some common ethers and the corresponding hydrocarbons.

Table 18.1 Comparison of Boiling Points of Ethers and Hydrocarbons

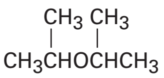
Ether	Boiling point °C	Hydrocarbon	Boiling point °C
CH_3OCH_3	−25	$CH_3CH_2CH_3$	−45
$CH_3CH_2OCH_2CH_3$	34.6	$CH_3CH_2CH_2CH_2CH_3$	36
	65		49
	158		136

Ethers are relatively stable and unreactive in many respects, but some ethers react slowly with the oxygen in air to give *peroxides,* compounds that contain an O–O bond. The peroxides from low-molecular-weight ethers such as diisopropyl ether and tetrahydrofuran are explosive and extremely dangerous, even in tiny amounts. Ethers are very useful as solvents in the laboratory, but they must always be used cautiously and should not be stored for long periods of time.

Problem 18.1

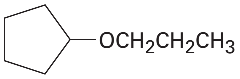
Name the following ethers:

(a)

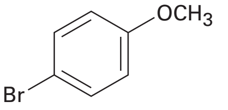


$CH_3\overset{CH_3}{\overset{|}{C}}HO\overset{CH_3}{\overset{|}{C}}HCH_3$

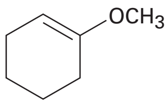
(b)



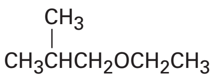
(c)



(d)



(e)

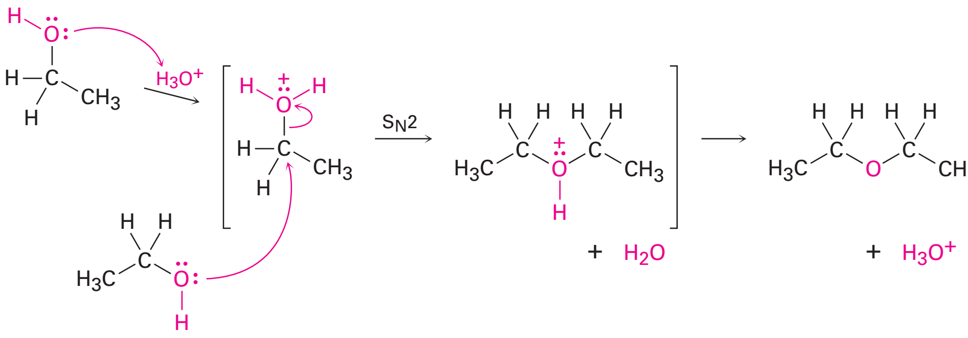


$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2OCH_2CH_3$

(f) $H_2C{=}CHCH_2OCH{=}CH_2$

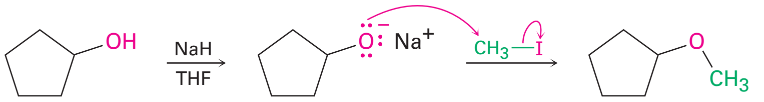
18.2 Synthesis of Ethers

Diethyl ether and other simple symmetrical ethers are prepared industrially by the sulfuric acid–catalyzed reaction of alcohols. The reaction occurs by S_N2 displacement of water from a protonated ethanol molecule by the oxygen atom of a second ethanol. Unfortunately, the method is limited to use with primary alcohols because secondary and tertiary alcohols dehydrate by an E1 mechanism to yield alkenes **(Section 17.6)**.



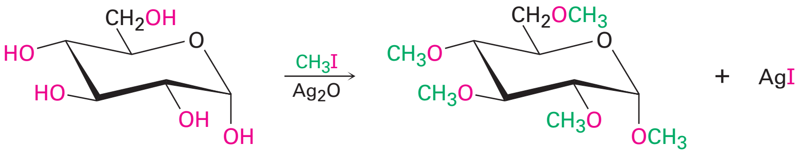
The Williamson Ether Synthesis

The most generally useful method of preparing ethers is by the *Williamson ether synthesis,* in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an S_N2 reaction. As we saw earlier in **Section 17.2**, the alkoxide ion is normally prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH.



Cyclopentanol **Alkoxide ion** **Cyclopentyl methyl ether (74%)**

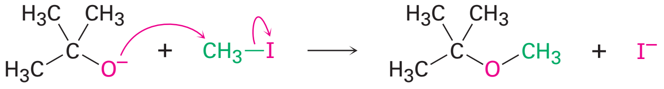
A useful variation of the Williamson synthesis involves silver oxide, Ag_2O, as a mild base rather than NaH. Under these conditions, the free alcohol reacts directly with alkyl halide, so there is no need to preform the metal alkoxide intermediate. Sugars react particularly well; glucose, for example, reacts with excess iodomethane in the presence of Ag_2O to generate a pentaether in 85% yield.



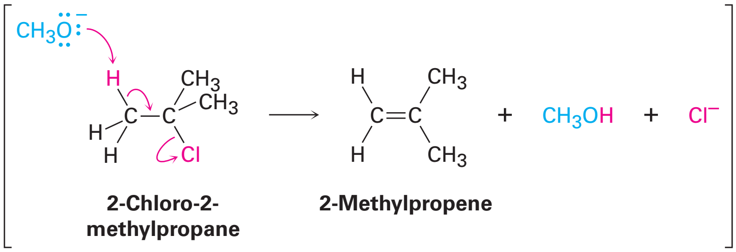
α-D-Glucose

α-D-Glucose pentamethyl ether (85%)

Because the Williamson synthesis is an S_N2 reaction, it is subject to all the usual constraints, as discussed in **Section 11.3**. Primary halides and tosylates work best because competitive E2 elimination can occur with more hindered substrates. Unsymmetrical ethers should therefore be synthesized by reaction between the more hindered alkoxide partner and less hindered halide partner rather than vice versa. For example, *tert*-butyl methyl ether, a substance used in the 1990s as an octane booster in gasoline, is best prepared by reaction of *tert*-butoxide ion with iodomethane rather than by reaction of methoxide ion with 2-chloro-2-methylpropane.



***tert*-Butoxide** **Iodomethane** ***tert*-Butyl methyl ether**



2-Chloro-2-methylpropane **2-Methylpropene**

Problem 18.2

Why do you suppose only symmetrical ethers are prepared by the sulfuric acid–catalyzed dehydration procedure? What product(s) would you expect if ethanol and 1-propanol were allowed to react together? In what ratio would the products be formed if the two alcohols were of equal reactivity?

Problem 18.3

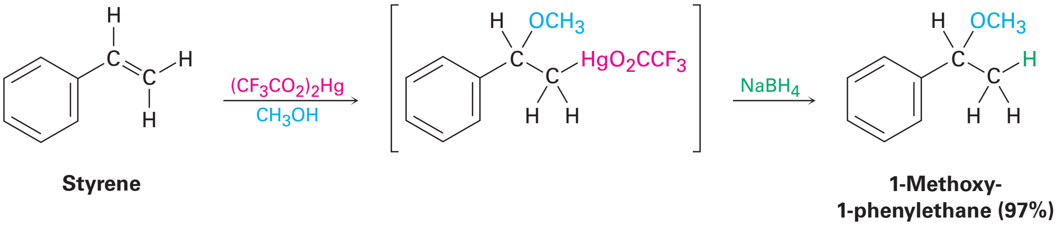
How would you prepare the following ethers using a Williamson synthesis?

(a) Methyl propyl ether **(b)** Anisole (methyl phenyl ether)

(c) Benzyl isopropyl ether **(d)** Ethyl 2,2-dimethylpropyl ether

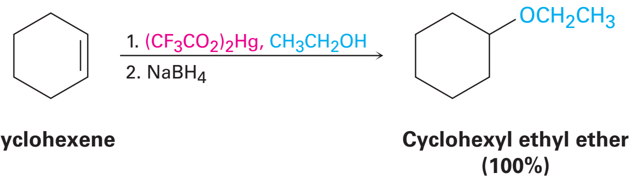
Alkoxymercuration of Alkenes

We saw in **Section 8.4** that alkenes react with water in the presence of mercuric acetate to yield a hydroxymercuration product. Subsequent treatment with $NaBH_4$ breaks the C–Hg bond and yields the alcohol. A similar **alkoxymercuration** reaction occurs when an alkene is treated with an *alcohol* in the presence of mercuric acetate or, even better, mercuric trifluoroacetate, $(CF_3CO_2)_2Hg$. Demercuration by reaction with $NaBH_4$ then yields an ether. The net result is Markovnikov addition of the alcohol to the alkene.



Styrene

1-Methoxy-1-phenylethane (97%)



Cyclohexene

Cyclohexyl ethyl ether (100%)

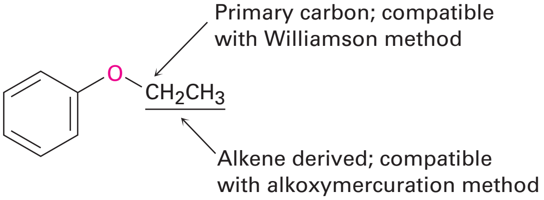
The mechanism of the alkoxymercuration reaction is similar to that described in **Section 8.4** for hydroxymercuration. The reaction is initiated by electrophilic addition of Hg^{2+} to the alkene, followed by reaction of the intermediate cation with alcohol and reduction of the C–Hg bond by $NaBH_4$. A variety of alcohols and alkenes can be used in the alkoxymercuration reaction. Primary, secondary, and even tertiary alcohols react well, but ditertiary ethers can't be prepared because of steric hindrance to reaction.

Worked Example 18.1 Synthesizing an Ether

How would you prepare ethyl phenyl ether? Use whichever method you think is more appropriate, the Williamson synthesis or the alkoxymercuration reaction.

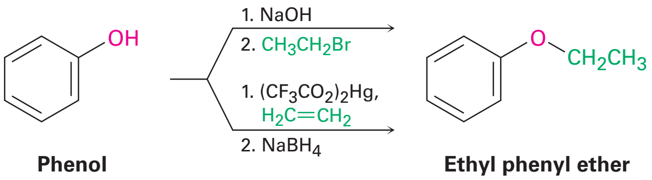
Strategy

Draw the target ether, identify the two groups attached to oxygen, and recall the limitations of the two methods for preparing ethers. The Williamson synthesis uses an S_N2 reaction and requires that one of the two groups attached to oxygen be either secondary or (preferably) primary. The alkoxymercuration reaction requires that one of the two groups come from an alkene precursor. Ethyl phenyl ether could be made by either method.



Ethyl phenyl ether

Solution



Problem 18.4

Review the mechanism of oxymercuration shown in Figure 8.3 on page 272, and then write the mechanism of the alkoxymercuration reaction of 1-methylcyclopentene with ethanol. Use curved arrows to show the electron flow in each step.

Problem 18.5

How would you prepare the following ethers? Use whichever method you think is more appropriate, the Williamson synthesis or the alkoxymercuration reaction.

(a) Butyl cyclohexyl ether
(b) Benzyl ethyl ether ($C_6H_5CH_2OCH_2CH_3$)
(c) *sec*-Butyl *tert*-butyl ether
(d) Tetrahydrofuran

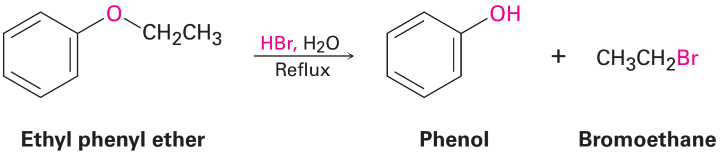
Problem 18.6

Rank the following halides in order of their reactivity in the Williamson synthesis:

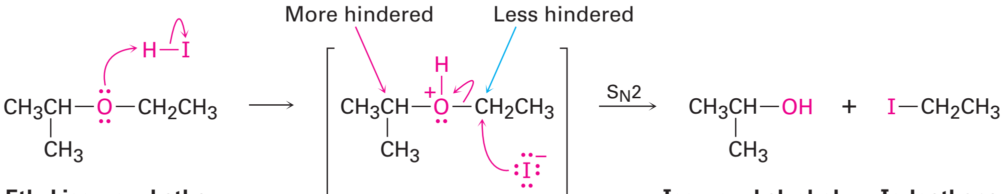
(a) Bromoethane, 2-bromopropane, bromobenzene
(b) Chloroethane, bromoethane, 1-iodopropene

18.3 Reactions of Ethers: Acidic Cleavage

Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents. Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one truly general reaction—they are cleaved by strong acids. Aqueous HBr and HI both work well, but HCl does not cleave ethers.

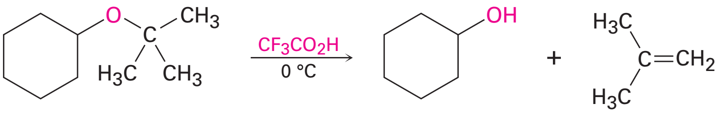


Acidic ether cleavages are typical nucleophilic substitution reactions and take place by either S_N1 or S_N2 mechanisms depending on the structure of the substrate. Ethers with only primary and secondary alkyl groups react by an S_N2 mechanism, in which I^- or Br^- attacks the protonated ether at the less hindered site. This usually results in a selective cleavage into a single alcohol and a single alkyl halide. For example, ethyl isopropyl ether yields exclusively isopropyl alcohol and iodoethane on cleavage by HI because nucleophilic attack by iodide ion occurs at the less hindered primary site rather than at the more hindered secondary site.



Ethyl isopropyl ether **Isopropyl alcohol** **Iodoethane**

Ethers with a tertiary, benzylic, or allylic group cleave by either an S_N1 or E1 mechanism because these substrates can produce stable intermediate carbocations. These reactions are often fast and take place at moderate temperatures. *tert*-Butyl ethers, for example, react by an E1 mechanism on treatment with trifluoroacetic acid at 0 °C. We'll see in **Section 26.7** that the reaction is often used in the laboratory synthesis of peptides.

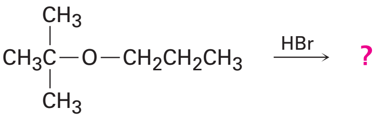


***tert*-Butyl cyclohexyl ether** **Cyclohexanol (90%)** **2-Methylpropene**

Worked Example 18.2

Predicting the Product of an Ether Cleavage Reaction

Predict the products of the following reaction:

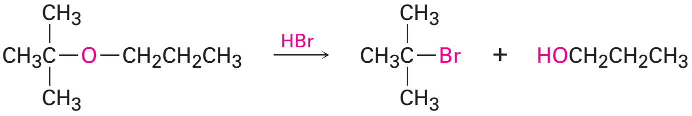


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}-O-CH_2CH_2CH_3 \xrightarrow{HBr} ?$$

Strategy

Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl groups usually undergoes cleavage by S_N2 attack of a nucleophile on the less hindered alkyl group, but an ether with a tertiary alkyl group usually undergoes cleavage by an S_N1 mechanism. In this case, an S_N1 cleavage of the tertiary C—O bond will occur, giving 1-propanol and a tertiary alkyl bromide. In addition, a competitive E1 reaction leading to alkene might occur.

Solution



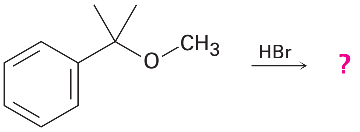
$$CH_3\overset{CH_3}{\underset{CH_3}{C}}-O-CH_2CH_2CH_3 \xrightarrow{HBr} CH_3\overset{CH_3}{\underset{CH_3}{C}}-Br + HOCH_2CH_2CH_3$$

***tert*-Butyl propyl ether** **2-Bromo-2-methylpropane** **1-Propanol**

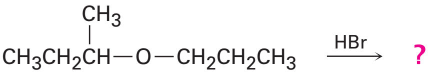
Problem 18.7

Predict the products of the following reactions:

(a)



(b)



$CH_3CH_2\overset{CH_3}{\overset{|}{C}H}—O—CH_2CH_2CH_3 \xrightarrow{HBr} ?$

Problem 18.8

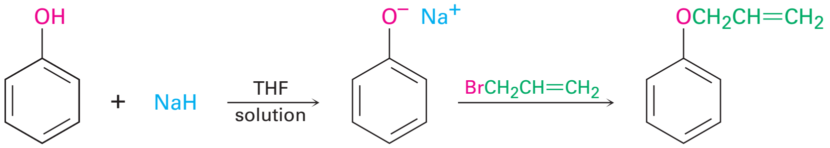
Write the mechanism of the acid-induced cleavage of *tert*-butyl cyclohexyl ether to yield cyclohexanol and 2-methylpropene.

Problem 18.9

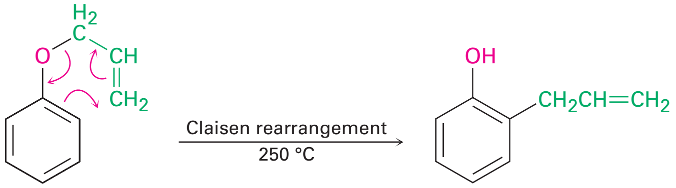
Why are HI and HBr more effective than HCl in cleaving ethers? (See **Section 11.3**.)

18.4 Reactions of Ethers: Claisen Rearrangement

Unlike the acid-induced ether cleavage reaction discussed in the previous section, which is general to all ethers, the **Claisen rearrangement** is specific to allyl aryl ethers ($H_2C{=}CHCH_2—O—Ar$) and allyl vinyl ethers ($H_2C{=}CHCH_2—O—CH{=}CH_2$). Treatment of a phenoxide ion with 3-bromopropene (allyl bromide) results in a Williamson ether synthesis and formation of an allyl aryl ether. Heating the allyl aryl ether to 200–250 °C then effects Claisen rearrangement, leading to an *o*-allylphenol. The net result is alkylation of the phenol in an ortho position.

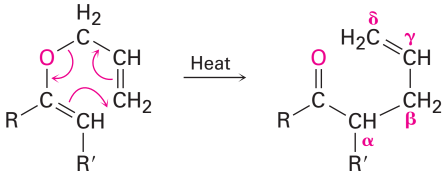


Phenol **Sodium phenoxide** **Allyl phenyl ether**



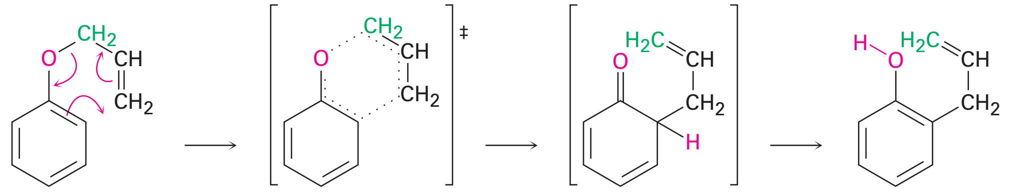
Allyl phenyl ether ***o*-Allylphenol**

A similar rearrangement takes place with allyl vinyl ethers, leading to a so-called γ,δ-unsaturated ketone or aldehyde.



An allyl vinyl ether **A γ,δ unsaturated ketone**

Like the Diels–Alder reaction discussed in **Sections 14.4 and 14.5**, the Claisen rearrangement reaction takes place in a single step through a pericyclic mechanism in which a reorganization of bonding electrons occurs through a six-membered, cyclic transition state. The 6-allyl-2,4-cyclohexadienone intermediate then isomerizes to *o*-allylphenol **(Figure 18.1)**.

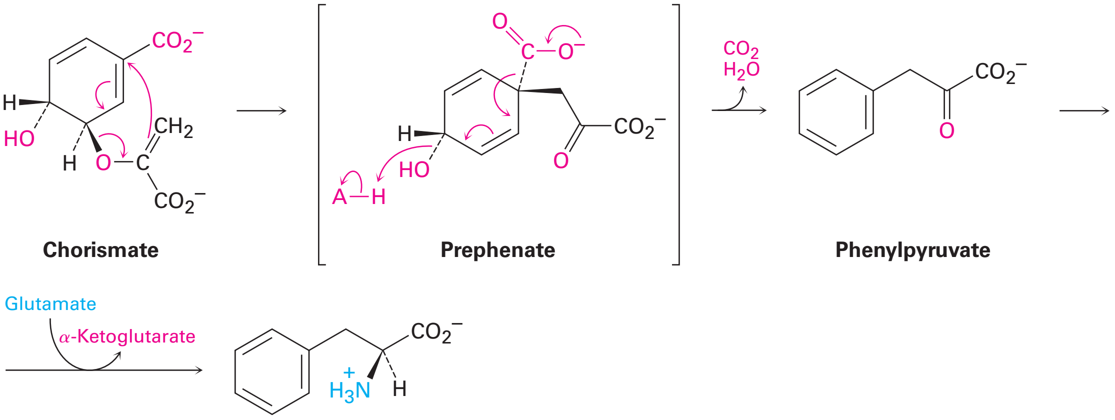


Allyl phenyl ether **Transition state** **Intermediate (6-allyl-2,4-cyclohexadienone)** ***o*-Allylphenol**

Figure 18.1 The mechanism of the Claisen rearrangement. The C—O bond-breaking and C—C bond-making occur simultaneously.

Evidence for this mechanism comes from the observation that the rearrangement takes place with an inversion of the allyl group. That is, allyl phenyl ether containing a ^{14}C label on the allyl *ether* carbon atom yields *o*-allylphenol in which the label is on the *terminal* vinylic carbon (green in Figure 18.1). We'll look at the reaction in more detail in **Section 30.8**.

Claisen rearrangements are uncommon in biological pathways, but a well-studied example does occur during biosynthesis of the amino acids phenylalanine and tyrosine. Both phenylalanine and tyrosine arise from a precursor called prephenate, which is itself formed by a biological Claisen rearrangement of the allylic vinyl ether chorismate.

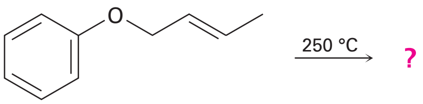


Chorismate **Prephenate** **Phenylpyruvate**

Phenylalanine

Problem 18.10

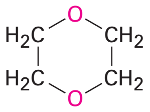
What product would you expect from Claisen rearrangement of 2-butenyl phenyl ether?



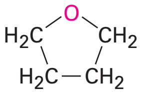
2-Butenyl phenyl ether

18.5 Cyclic Ethers: Epoxides

For the most part, cyclic ethers behave like acyclic ethers. The chemistry of the ether functional group is the same, whether it's in an open chain or in a ring. Common cyclic ethers such as tetrahydrofuran and dioxane, for example, are often used as solvents because of their inertness, yet they can be cleaved by strong acids.



1,4-Dioxane

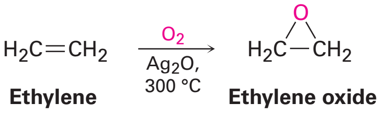


Tetrahydrofuran

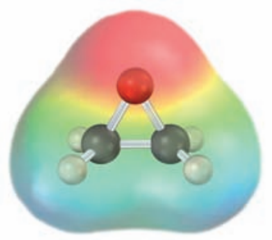
The one group of cyclic ethers that behaves differently from open-chain ethers are the three-membered-ring compounds called *epoxides,* or *oxiranes,* which we saw in **Section 8.7**. The strain of the three-membered ring gives epoxides unique chemical reactivity.

Ethylene oxide, the simplest epoxide, is an intermediate in the manufacture of both ethylene glycol, used for automobile antifreeze, and polyester polymers. Approximately 18 million metric tons of ethylene oxide is produced worldwide each year, most of it by air oxidation of ethylene over a silver oxide catalyst at 300 °C. This process is not useful for other epoxides, however, and is of little value in the laboratory.

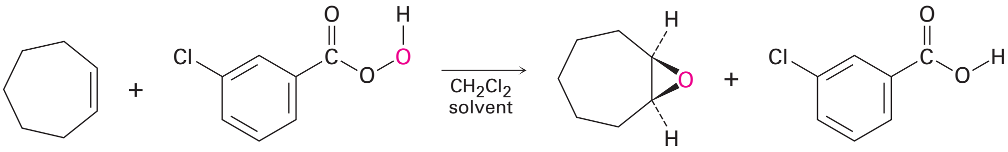
Note that the name *ethylene oxide* is not a systematic one because the *-ene* ending implies the presence of a double bond in the molecule. The name is frequently used, however, because ethylene oxide is derived *from* ethylene by addition of an oxygen atom. Other simple epoxides are named similarly. The systematic name for ethylene oxide is 1,2-epoxyethane.



Ethylene **Ethylene oxide**

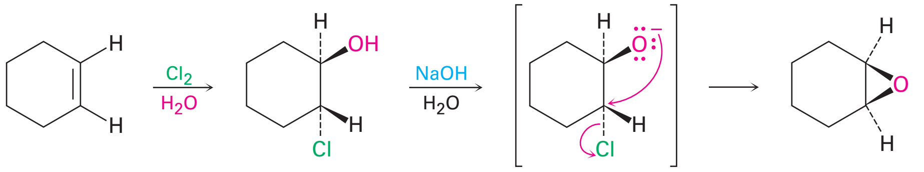


In the laboratory, as we saw in **Section 8.7**, epoxides are usually prepared by treatment of an alkene with a peroxyacid (RCO_3H), typically *m*-chloroperoxybenzoic acid.



Cycloheptene ***meta*-Chloroperoxybenzoic acid** **1,2-Epoxycycloheptane** ***meta*-Chlorobenzoic acid**

Epoxides can also be prepared from halohydrins, themselves produced by electrophilic addition of HO–X to alkenes **(Section 8.3)**. When a halohydrin is treated with base, HX is eliminated and an epoxide is produced by an *intramolecular* Williamson ether synthesis. That is, the nucleophilic alkoxide ion and the electrophilic alkyl halide are in the same molecule.



Cyclohexene **_trans_-2-Chloro-cyclohexanol** **1,2-Epoxy-cyclohexane**

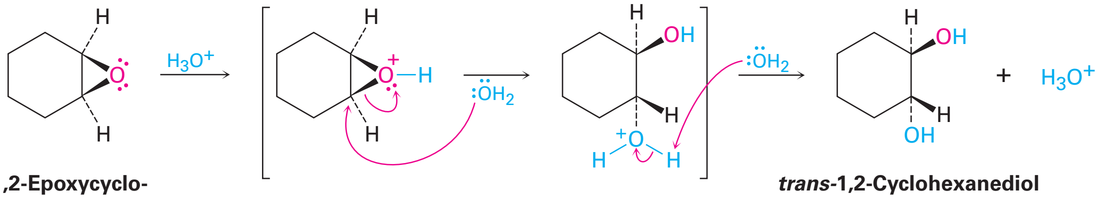
Problem 18.11

Reaction of *cis*-2-butene with *m*-chloroperoxybenzoic acid yields an epoxide different from that obtained by reaction of the trans isomer. Explain.

18.6 Reactions of Epoxides: Ring-Opening

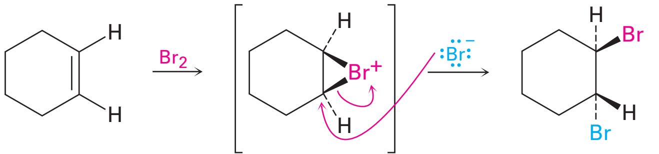
Acid-Catalyzed Epoxide Opening

Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain. As we saw in **Section 8.7**, dilute aqueous acid at room temperature is sufficient to cause the hydrolysis of epoxides to give 1,2-diols, also called *vicinal glycols*. (The word *vicinal* means "adjacent," and a *glycol* is a diol.) The epoxide cleavage takes place by S_N2-like backside attack of a nucleophile on the protonated epoxide, giving a trans-1,2-diol as product.



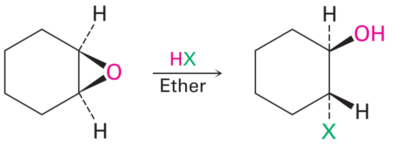
1,2-Epoxycyclo-hexane **_trans_-1,2-Cyclohexanediol (86%)**

Recall the following:



Cyclohexene **_trans_-1,2-Dibromo-cyclohexane**

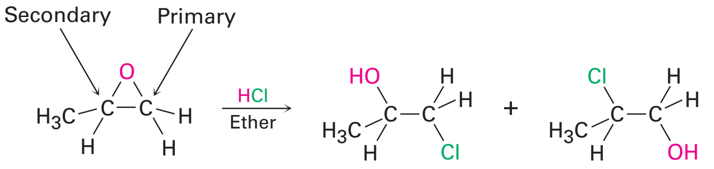
Epoxides can also be opened by reaction with acids other than H_3O^+. If anhydrous HX is used, for instance, an epoxide is converted into a trans halohydrin.



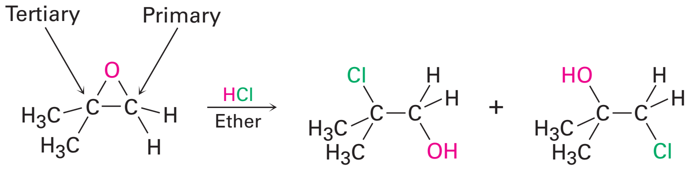
A trans 2-halocyclohexanol

where X = F, Br, Cl, or I

The regiochemistry of acid-catalyzed ring-opening depends on the epoxide's structure, and a mixture of products is often formed. When both epoxide carbon atoms are either primary or secondary, attack of the nucleophile occurs primarily at the less highly substituted site—an S_N2-like result. When one of the epoxide carbon atoms is tertiary, however, nucleophilic attack occurs primarily at the *more* highly substituted site—an S_N1-like result. Thus, 1,2-epoxypropane reacts with HCl to give primarily 1-chloro-2-propanol, but 2-methyl-1,2-epoxypropane gives 2-chloro-2-methyl-1-propanol as the major product.



1,2-Epoxypropane **1-Chloro-2-propanol (90%)** **2-Chloro-1-propanol (10%)**

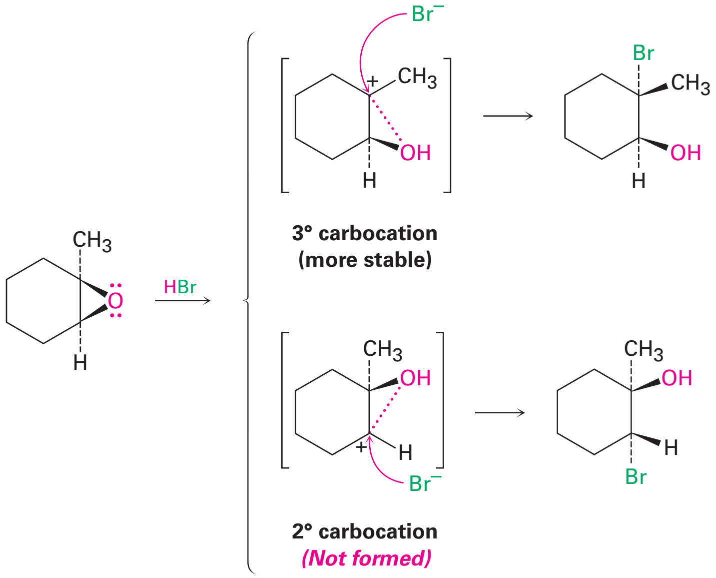


2-Methyl-1,2-epoxypropane **2-Chloro-2-methyl-1-propanol (60%)** **1-Chloro-2-methyl-2-propanol (40%)**

The mechanisms of these acid-catalyzed epoxide openings are more complex than they at first appear. They seem to be neither purely S_N1 nor S_N2 but instead to be midway between the two extremes and to have characteristics of both. Take the reaction of 1,2-epoxy-1-methylcyclohexane with HBr shown in **Figure 18.2**, for instance. The reaction yields only a single stereoisomer of 2-bromo-2-methylcyclohexanol in which the –Br and –OH groups are trans, an S_N2-like result caused by backside displacement of the epoxide oxygen. But the fact that Br^- attacks the more hindered tertiary side of the epoxide rather than the less hindered secondary side is an S_N1-like result in which the more stable, tertiary carbocation is involved.

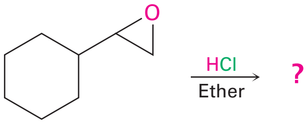
Evidently, the transition state for acid-catalyzed epoxide opening has an S_N2-like geometry but also has a large amount of S_N1-like carbocationic character. Since the positive charge in the protonated epoxide is shared by the more highly substituted carbon atom, backside attack of Br^- occurs at the more highly substituted site.

Figure 18.2 Ring-opening of 1,2-epoxy-1-methylcyclohexane with HBr. There is a high degree of S_N1-like carbocation character in the transition state, which leads to backside attack of the nucleophile at the tertiary center and to formation of a product isomer that has —Br and —OH groups trans.



Worked Example 18.3 Predicting the Product of Epoxide Ring-Opening

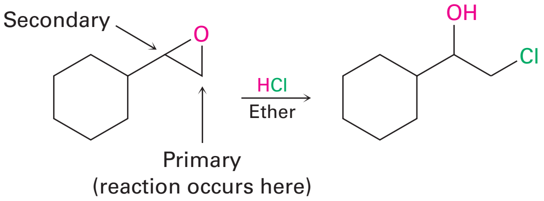
Predict the major product of the following reaction:



Strategy

Identify the substitution pattern of the two epoxide carbon atoms—in this case, one carbon is secondary and one is primary. Then recall the guidelines for epoxide cleavages. An epoxide with only primary and secondary carbons usually undergoes cleavage by S_N2-like attack of a nucleophile on the less hindered carbon, but an epoxide with a tertiary carbon atom usually undergoes cleavage by backside attack on the more hindered carbon. In this case, an S_N2 cleavage of the primary C—O epoxide bond will occur.

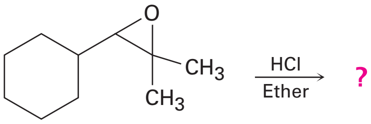
Solution



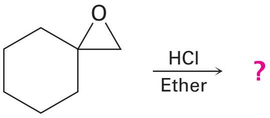
Problem 18.12

Predict the major product of each of the following reactions:

(a)



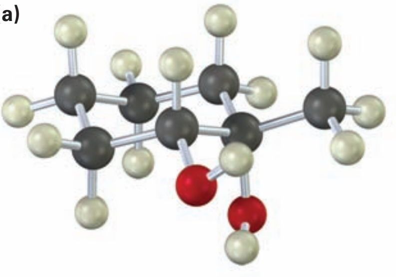
(b)



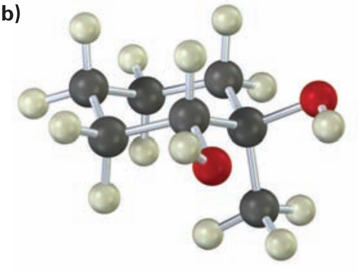
Problem 18.13

How would you prepare the following diols?

(a)

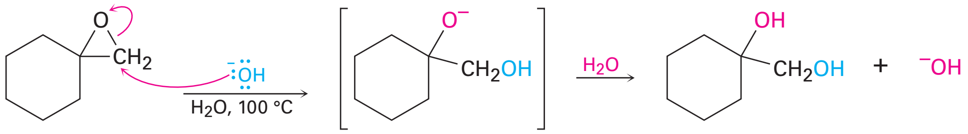


(b)



Base-Catalyzed Epoxide Opening

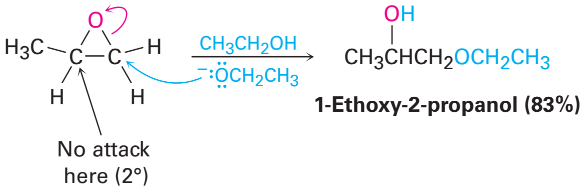
Unlike other ethers, epoxide rings can be cleaved by bases and nucleophiles as well as by acid. Although an ether oxygen is normally a poor leaving group in an S_N2 reaction **(Section 11.3)**, the strain of the three-membered ring causes epoxides to react with hydroxide ion at elevated temperatures.



Methylenecyclohexane oxide

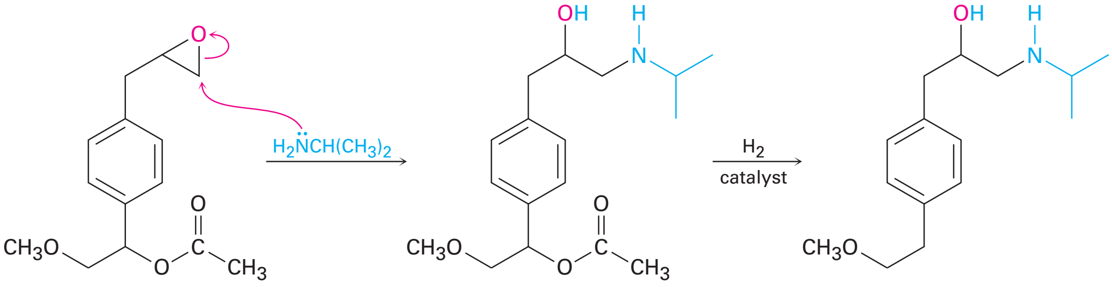
1-Hydroxymethylcyclohexanol (70%)

Base-catalyzed epoxide opening is a typical S_N2 reaction in which attack of the nucleophile takes place at the less hindered epoxide carbon. For example, 1,2-epoxypropane reacts with ethoxide ion exclusively at the less highly substituted, primary, carbon to give 1-ethoxy-2-propanol.



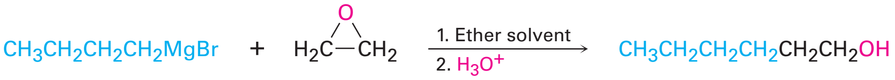
1-Ethoxy-2-propanol (83%)

Many different nucleophiles can be used for epoxide opening, including amines (RNH_2 or R_2NH) and Grignard reagents (RMgX). An example of an amine reacting with an epoxide occurs in the commercial synthesis of metoprolol, a so-called β-blocker that is used for treatment of cardiac arrhythmias, hypertension, and heart attacks. β-blockers are among the most widely prescribed drugs in the world.



Metoprolol

A similar nucleophilic ring-opening occurs when epoxides are treated with Grignard reagents. Ethylene oxide is frequently used, thereby allowing the conversion of a Grignard reagent into a primary alcohol having two more carbons than the starting alkyl halide. 1-Bromobutane, for example, is converted into 1-hexanol by reaction of its Grignard reagent with ethylene oxide.



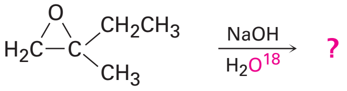
$$CH_3CH_2CH_2CH_2MgBr + H_2C\overset{O}{-}CH_2 \xrightarrow[2.\ H_3O^+]{1.\ \text{Ether solvent}} CH_3CH_2CH_2CH_2CH_2CH_2OH$$

Butylmagnesium bromide **Ethylene oxide** **1-Hexanol (62%)**

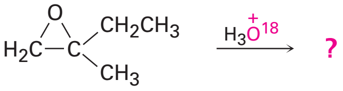
Problem 18.14

Predict the major product of the following reactions:

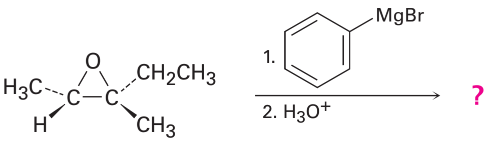
(a)



(b)

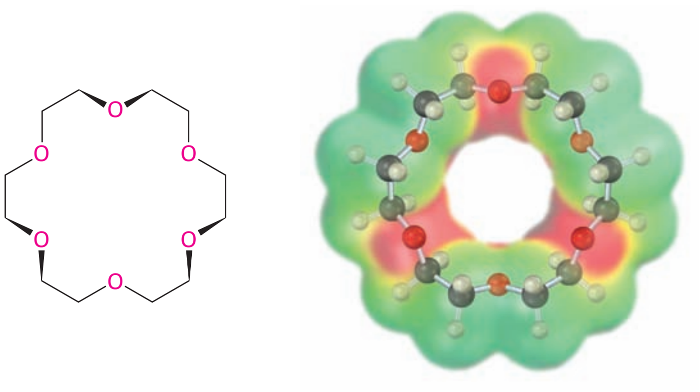


(c)



18.7 Crown Ethers

Crown ethers, discovered in the early 1960s by Charles Pedersen at the DuPont Company, are a relatively recent addition to the ether family. They are named according to the general format *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. Thus, 18-crown-6 ether is an 18-membered ring containing 6 ether oxygen atoms. Note the size and negative (red) character of the crown ether cavity in the following electrostatic potential map.



18-Crown-6 ether

The importance of crown ethers derives from their ability to sequester specific metal cations in the center of the polyether cavity. 18-Crown-6, for example, binds strongly with potassium ion. As a result, a solution of 18-crown-6 in a nonpolar organic solvent will dissolve many potassium salts. Potassium permanganate, $KMnO_4$, dissolves in toluene in the presence of 18-crown-6, for instance, and the resulting solution is a valuable reagent for oxidizing alkenes.

The effect of using a crown ether to dissolve an inorganic salt in a hydrocarbon or ether solvent is similar to the effect of dissolving the salt in a polar aprotic solvent such as DMSO, DMF, or HMPA **(Section 11.3)**. In both cases, the metal cation is strongly solvated, leaving the anion bare. Thus, the S_N2 reactivity of an anion is tremendously enhanced in the presence of a crown ether.

Problem 18.15

15-Crown-5 and 12-crown-4 ethers complex Na^+ and Li^+, respectively. Make models of these crown ethers, and compare the sizes of the cavities.

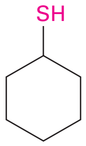
18.8 Thiols and Sulfides

Thiols

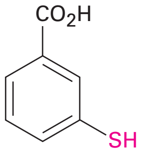
Thiols, sometimes called *mercaptans,* are sulfur analogs of alcohols. They are named by the same system used for alcohols, with the suffix -*thiol* used in place of -*ol*. The −SH group itself is referred to as a **mercapto group**. Like alcohols, thiols are weakly acidic; the pK_a of CH_3SH, for instance, is 10.3. Unlike alcohols, however, thiols don't typically form hydrogen bonds because the sulfur atom is not sufficiently electronegative.

CH_3CH_2SH

Ethanethiol



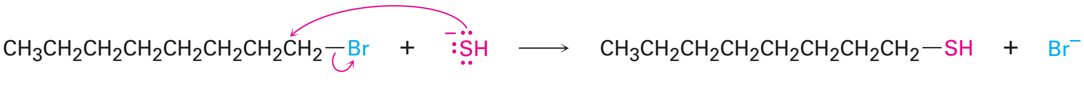
Cyclohexanethiol



***m*-Mercaptobenzoic acid**

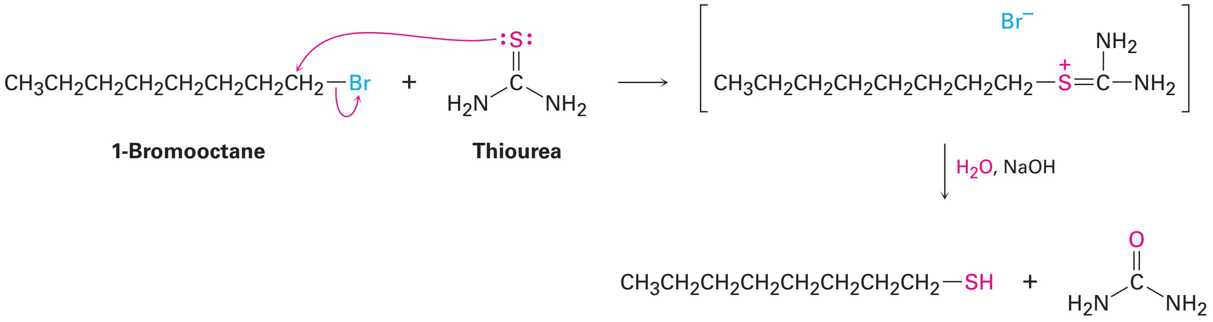
The most striking characteristic of thiols is their appalling odor. Skunk scent, for instance, is caused primarily by the simple thiols 3-methyl-1-butanethiol and 2-butene-1-thiol. Volatile thiols such as ethanethiol are also added to natural gas and liquefied propane to serve as an easily detectable warning in case of leaks.

Thiols are usually prepared from alkyl halides by S_N2 displacement with a sulfur nucleophile such as hydrosulfide anion, ^-SH.



1-Bromooctane **1-Octanethiol (83%)**

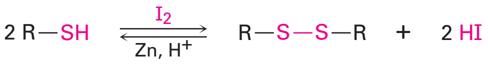
The reaction often works poorly unless an excess of the nucleophile is used because the product thiol can undergo a second S_N2 reaction with alkyl halide to give a sulfide as a by-product. To circumvent this problem, thiourea, $(NH_2)_2C{=}S$, is often used as the nucleophile in the preparation of a thiol from an alkyl halide. The reaction occurs by displacement of the halide ion to yield an intermediate alkyl isothiourea salt, which is hydrolyzed by subsequent reaction with aqueous base.



1-Bromooctane **Thiourea**

1-Octanethiol (83%) **Urea**

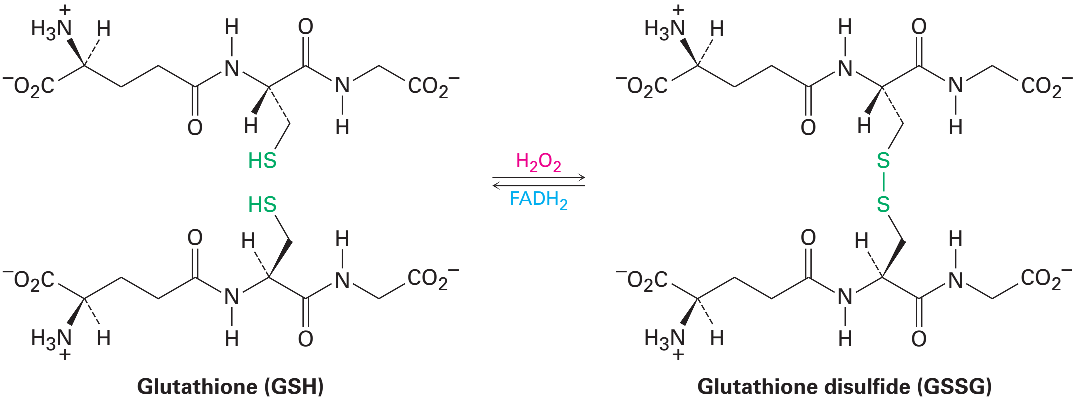
Thiols can be oxidized by Br_2 or I_2 to yield **disulfides (RSSR′)**. The reaction is easily reversed, and a disulfide can be reduced back to a thiol by treatment with zinc and acid.



$$2\,R{-}SH \underset{Zn,\,H^+}{\overset{I_2}{\rightleftharpoons}} R{-}S{-}S{-}R + 2\,HI$$

A thiol **A disulfide**

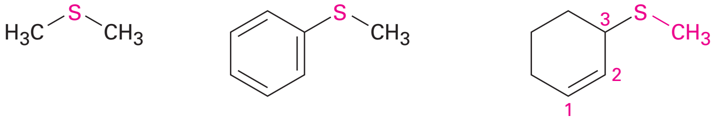
This thiol–disulfide interconversion is a key part of numerous biological processes. We'll see in Chapter 26, for instance, that disulfide formation is involved in defining the structure and three-dimensional conformations of proteins, where disulfide "bridges" often form cross-links between cysteine amino acid units in the protein chains. Disulfide formation is also involved in the process by which cells protect themselves from oxidative degradation. A cellular component called *glutathione* removes potentially harmful oxidants and is itself oxidized to glutathione disulfide in the process. Reduction back to the thiol requires the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



Glutathione (GSH) **Glutathione disulfide (GSSG)**

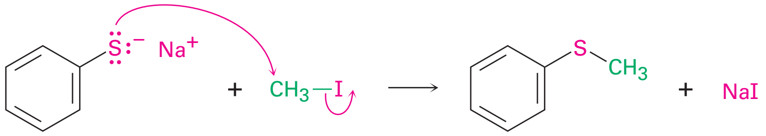
Sulfides

Sulfides are the sulfur analogs of ethers just as thiols are the sulfur analogs of alcohols. Sulfides are named by following the same rules used for ethers, with *sulfide* used in place of *ether* for simple compounds and *alkylthio* used in place of *alkoxy* for more complex substances.



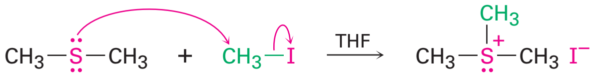
Dimethyl sulfide **Methyl phenyl sulfide** **3-(Methylthio)cyclohexene**

Treatment of a thiol with a base, such as NaH, gives the corresponding **thiolate ion (RS^-)**, which undergoes reaction with a primary or secondary alkyl halide to give a sulfide. The reaction occurs by an S_N2 mechanism, analogous to the Williamson synthesis of ethers **(Section 18.2)**.



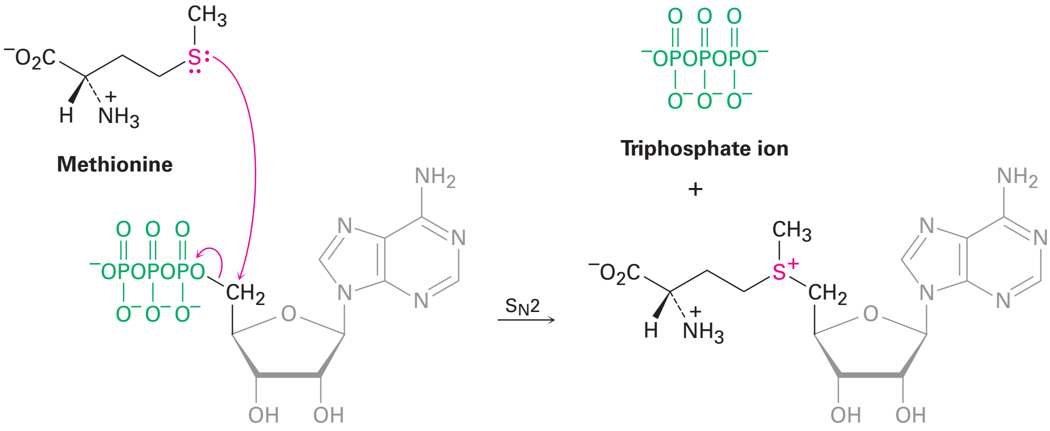
Sodium benzenethiolate **Methyl phenyl sulfide (96%)**

Despite their close structural similarity, sulfides and ethers differ substantially in their chemistry. Because the valence electrons on sulfur are farther from the nucleus and are less tightly held than those on oxygen (3*p* electrons versus 2*p* electrons), sulfur compounds are more nucleophilic than their oxygen analogs. Unlike dialkyl ethers, dialkyl sulfides react rapidly with primary alkyl halides by an S_N2 mechanism to give **sulfonium ions (R_3S^+)**.



Dimethyl sulfide **Iodomethane** **Trimethylsulfonium iodide**

The most common example of this process in living organisms is the reaction of the amino acid methionine with adenosine triphosphate (ATP; **Section 6.8**) to give *S*-adenosylmethionine. The reaction is somewhat unusual in that the biological leaving group in this S_N2 process is the *triphosphate* ion rather than the more frequently seen diphosphate ion **(Section 11.6)**.



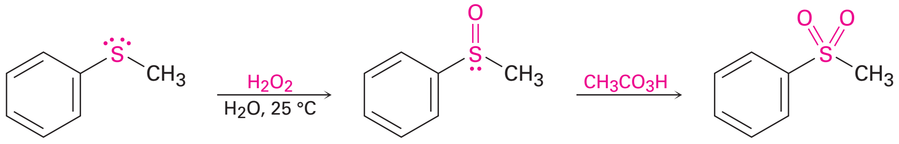
Methionine

Triphosphate ion

Adenosine triphosphate (ATP) ***S*-Adenosylmethionine**

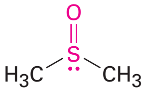
Sulfonium ions are themselves useful alkylating agents because a nucleophile can attack one of the groups bonded to the positively charged sulfur, displacing a neutral sulfide as leaving group. We saw an example in **Section 11.6** (Figure 11.16 on page 396) in which *S*-adenosylmethionine transferred a methyl group to norepinephrine to give adrenaline.

Another difference between sulfides and ethers is that sulfides are easily oxidized. Treatment of a sulfide with hydrogen peroxide, H_2O_2, at room temperature yields the corresponding **sulfoxide (R_2SO)**, and further oxidation of the sulfoxide with a peroxyacid yields a **sulfone (R_2SO_2)**.



Methyl phenyl sulfide **Methyl phenyl sulfoxide** **Methyl phenyl sulfone**

Dimethyl sulfoxide (DMSO) is a particularly well-known sulfoxide that is often used as a polar aprotic solvent. It must be handled with care, however, because it has a remarkable ability to penetrate the skin, carrying along whatever is dissolved in it.

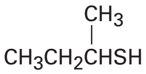


Dimethyl sulfoxide
(a polar aprotic solvent)

Problem 18.16

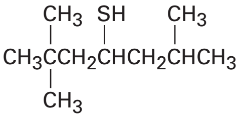
Name the following compounds:

(a)



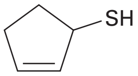
$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HSH$

(b)

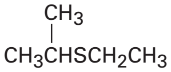


$CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{SH}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH_3$

(c)

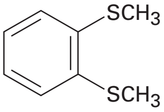


(d)

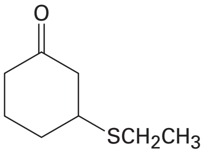


$CH_3\overset{CH_3}{\overset{|}{C}}HSCH_2CH_3$

(e)

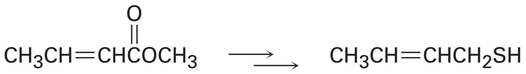


(f)



Problem 18.17

2-Butene-1-thiol is one component of skunk spray. How would you synthesize this substance from methyl 2-butenoate? From 1,3-butadiene?



$CH_3CH{=}CH\overset{O}{\overset{\|}{C}}OCH_3 \longrightarrow CH_3CH{=}CHCH_2SH$

Methyl 2-butenoate **2-Butene-1-thiol**

18.9 Spectroscopy of Ethers

Infrared Spectroscopy

Ethers are difficult to identify by IR spectroscopy. Although they show an absorption due to C–O single-bond stretching in the range 1050 to 1150 cm^{-1}, many other kinds of absorptions occur in the same range. **Figure 18.3** shows the IR spectrum of diethyl ether and identifies the C–O stretch.

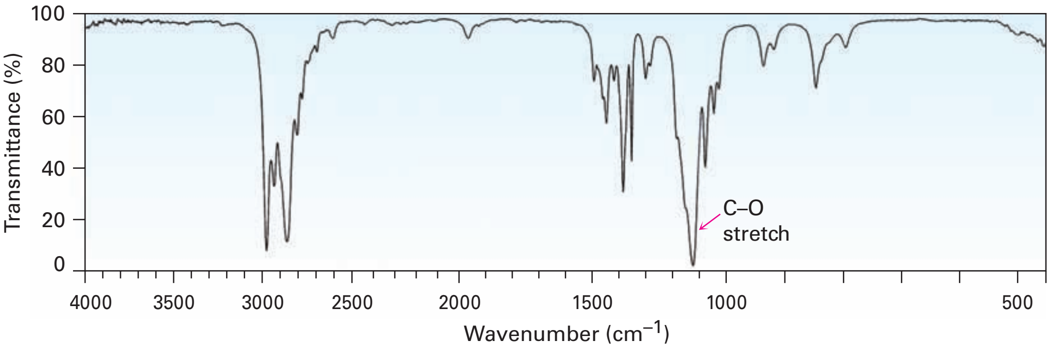
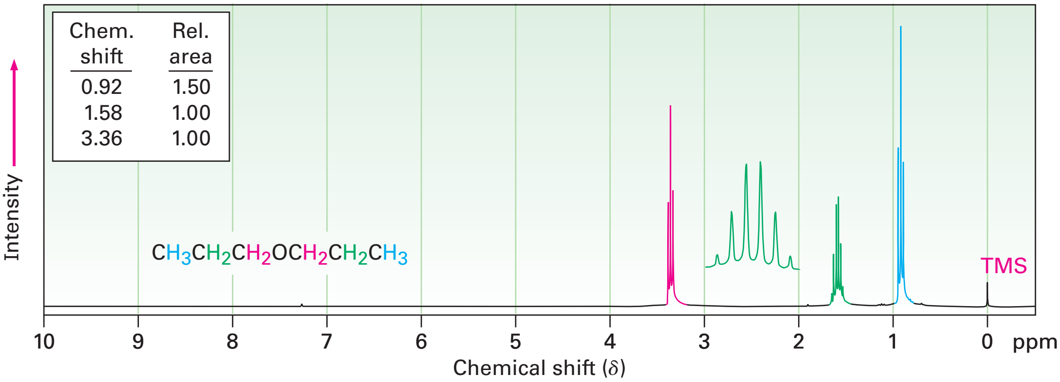


Figure 18.3 The infrared spectrum of diethyl ether, $CH_3CH_2OCH_2CH_3$.

Nuclear Magnetic Resonance Spectroscopy

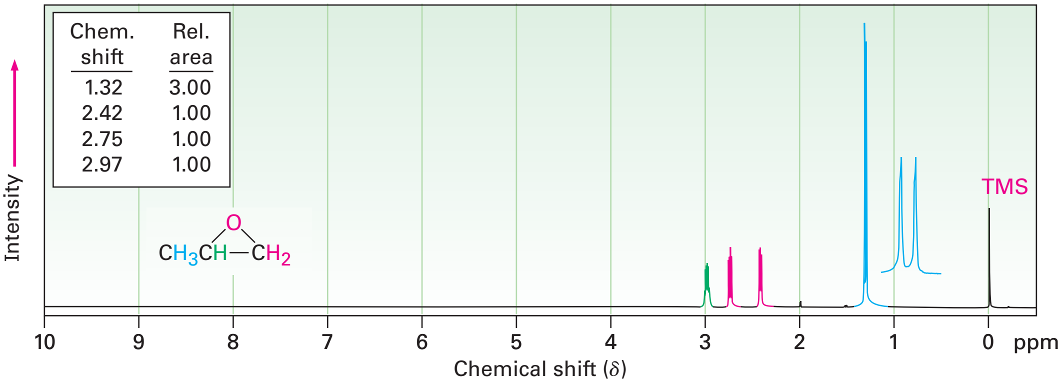
Hydrogens on carbon next to an ether oxygen are shifted downfield from the normal alkane resonance and show ^{1}H NMR absorptions in the region 3.4 to 4.5 δ. This downfield shift is clearly seen in the spectrum of dipropyl ether shown in **Figure 18.4**.



Chem. shift	Rel. area
0.92	1.50
1.58	1.00
3.36	1.00

Figure 18.4 The ^{1}H NMR spectrum of dipropyl ether. Protons on carbon next to oxygen are shifted downfield to 3.4 δ.

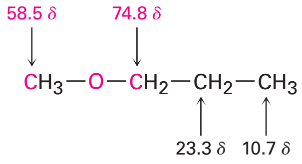
Epoxides absorb at a slightly higher field than other ethers and show characteristic resonances at 2.5 to 3.5 δ in their ^{1}H NMR spectra, as indicated for 1,2-epoxypropane in **Figure 18.5**.

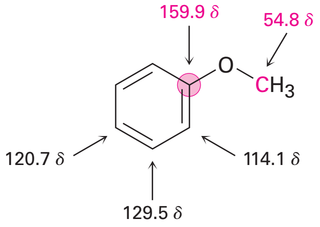


Chem. shift	Rel. area
1.32	3.00
2.42	1.00
2.75	1.00
2.97	1.00

Figure 18.5 The ^{1}H NMR spectrum of 1,2-epoxypropane.

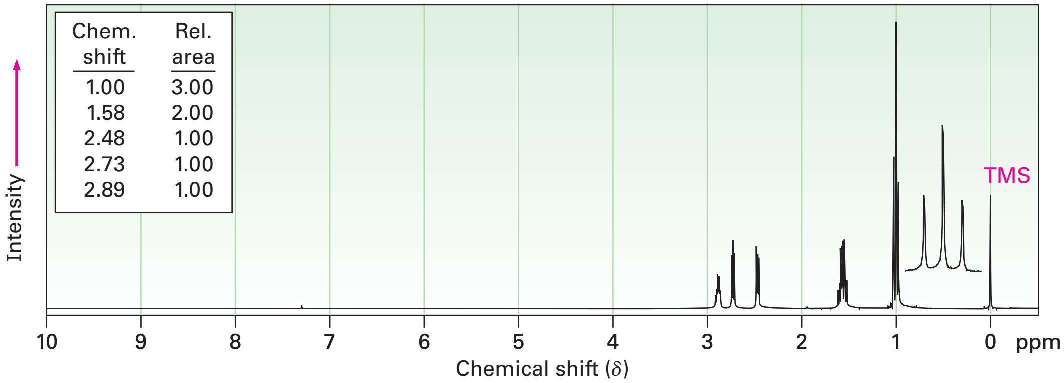
Ether carbon atoms also exhibit a downfield shift in the ^{13}C NMR spectrum, where they usually absorb in the 50 to 80 δ range. For example, the carbon atoms next to oxygen in methyl propyl ether absorb at 58.5 and 74.8 δ. Similarly, the methyl carbon in anisole absorbs at 54.8 δ.





Problem 18.18

The ^{1}H NMR spectrum shown is that of a cyclic ether with the formula C_4H_8O. Propose a structure.



Chem. shift	Rel. area
1.00	3.00
1.58	2.00
2.48	1.00
2.73	1.00
2.89	1.00

A DEEPER LOOK Epoxy Resins and Adhesives

Few nonchemists know exactly what an epoxide is, but practically everyone has used an "epoxy glue" for household repairs or an epoxy resin for a protective coating. Worldwide, approximately 15 billion dollars' worth of epoxies are used annually for a vast number of adhesive and coating applications, including many in the aerospace industry. Much of the new Boeing 787 Dreamliner, for instance, is held together with epoxy-based adhesives.

Epoxy resins and adhesives generally consist of two components that are mixed just prior to use. One component is a liquid "prepolymer," and the second is a "curing agent" that reacts with the prepolymer and causes it to solidify.

The most widely used epoxy resins and adhesives are based on a prepolymer made from bisphenol A and epichlorohydrin. On treatment with base, bisphenol A is converted into its anion, which acts as a nucleophile in an S_N2 reaction with epichlorohydrin. Each epichlorohydrin molecule can react with two molecules of bisphenol A, once by S_N2 displacement of chloride ion and once by nucleophilic opening of the epoxide ring. At the same time, each bisphenol A molecule can react with two epichlorohydrins, leading to a long polymer chain. Each end of a prepolymer chain has an unreacted epoxy group, and each chain has numerous secondary alcohol groups spaced regularly along its midsection.

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Kayaks are often made of a high-strength polymer coated with epoxy resin.

(continued)

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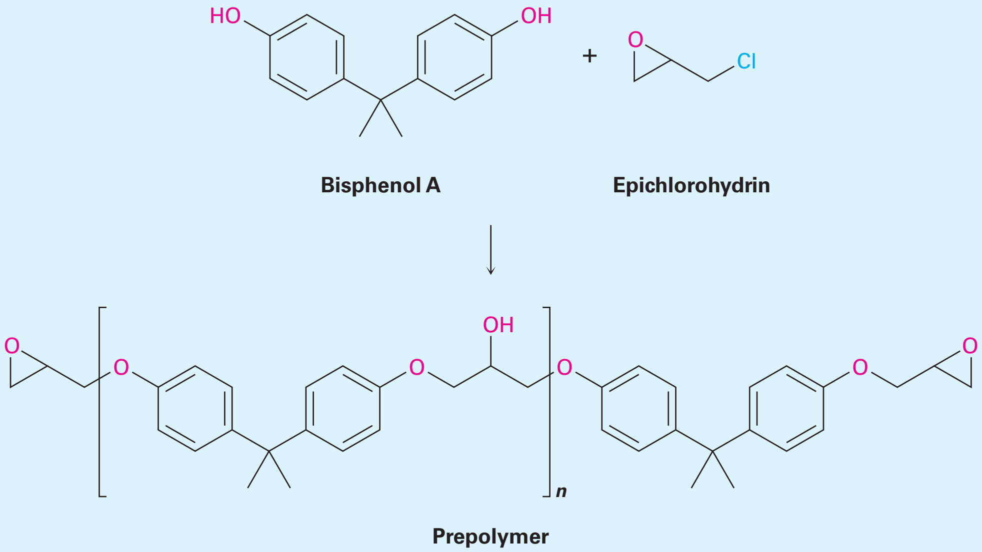
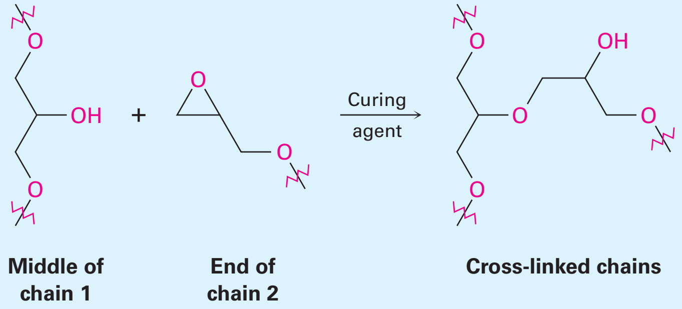


When the epoxide is to be used, a basic curing agent such as a tertiary amine, R_3N, is added to cause the individual prepolymer chains to link together. This cross-linking of chains is simply a base-catalyzed, S_N2 epoxide ring-opening of an —OH group in the middle of one chain with an epoxide group on the end of another chain. The result of such cross-linking is formation of a vast, three-dimensional tangle that has enormous strength and chemical resistance.



Key words

- alkoxymercuration, 680
- Claisen rearrangement, 683
- crown ether, 690
- disulfide (RSSR′), 692
- ether (ROR′), 676
- mercapto group (—SH), 691
- sulfide (RSR′), 676
- sulfone (R_2SO_2), 694
- sulfonium ion (R_3S^+), 694
- sulfoxide (R_2SO), 694
- thiol (RSH), 676
- thiolate ion (RS^-), 693

Summary

This chapter has finished the coverage of functional groups with C—O and C—S single bonds, focusing primarily on ethers, epoxides, thiols, and sulfides. **Ethers** are compounds that have two organic groups bonded to the same oxygen atom, ROR′. The organic groups can be alkyl, vinylic, or aryl, and the oxygen atom can be in a ring or in an open chain. Ethers are prepared by either the Williamson ether synthesis, which involves S_N2 reaction of an alkoxide ion with a primary alkyl halide, or the **alkoxymercuration** reaction, which involves Markovnikov addition of an alcohol to an alkene.

Ethers are inert to most reagents but react with strong acids to give cleavage products. Both HI and HBr are often used. The cleavage reaction takes place by an S_N2 mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen, but by an S_N1 or E1 mechanism if one of the alkyl groups bonded to oxygen is tertiary. Allyl aryl ethers and allyl vinyl ethers undergo **Claisen rearrangement** to give *o*-allylphenols and γ,δ-unsaturated ketones, respectively.

Epoxides are cyclic ethers with a three-membered, oxygen-containing ring. Because of the strain in the ring, epoxides undergo a cleavage reaction with both acids and bases. Acid-catalyzed ring-opening occurs with a regiochemistry that depends on the structure of the epoxide. Cleavage of the C–O bond at the less highly substituted site occurs if both epoxide carbons are primary or secondary, but cleavage of the C–O bond to the more highly substituted site occurs if one of the epoxide carbons is tertiary. Base-catalyzed epoxide ring-opening occurs by S_N2 reaction of a nucleophile at the less hindered epoxide carbon.

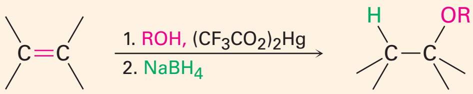
Thiols, the sulfur analogs of alcohols, are usually prepared by S_N2 reaction of an alkyl halide with thiourea. Mild oxidation of a thiol yields a **disulfide**, and mild reduction of a disulfide gives back the thiol. **Sulfides**, the sulfur analogs of ethers, are prepared by an S_N2 reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are more nucleophilic than ethers and can be alkylated by reaction with a primary alkyl halide to yield a **sulfonium ion**. Sulfides can also be oxidized to **sulfoxides** and to **sulfones**.

Summary of Reactions

1. Synthesis of ethers (Section 18.2)
   (a) Williamson ether synthesis

$$RO^- + R'CH_2X \longrightarrow ROCH_2R' + X^-$$

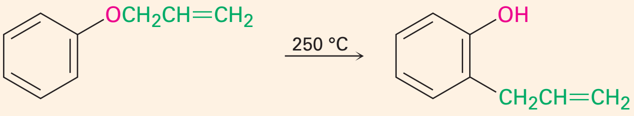
   (b) Alkoxymercuration/demercuration

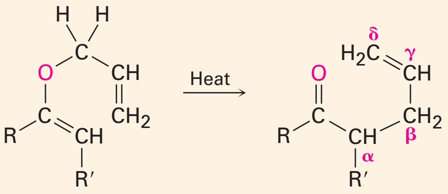


2. Reactions of ethers
   (a) Cleavage by HBr or HI (Section 18.3)

$$R{-}O{-}R' \xrightarrow[H_2O]{HX} RX + R'OH$$

   (b) Claisen rearrangement (Section 18.4)





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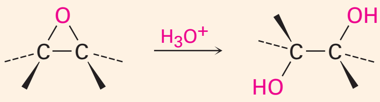
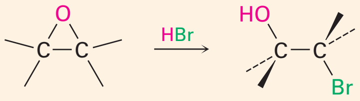
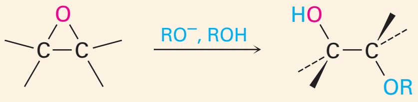
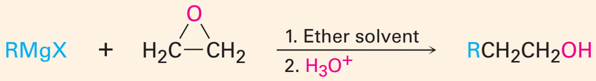
(c) Acid-catalyzed epoxide opening (Section 18.6)





(d) Base-catalyzed epoxide opening (Section 18.6)





3. Synthesis of thiols (Section 18.8)

$$RCH_2Br \xrightarrow[\text{2. } H_2O\text{, NaOH}]{\text{1. } (H_2N)_2C{=}S} RCH_2SH$$

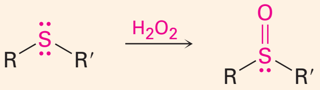
4. Oxidation of thiols to disulfides (Section 18.8)

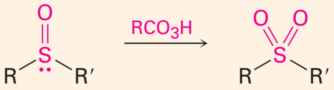
$$2\ RSH \xrightarrow{I_2,\ H_2O} RS{-}SR$$

5. Synthesis of sulfides (Section 18.8)

$$RS^- + R'CH_2Br \longrightarrow RSCH_2R' + Br^-$$

6. Oxidation of sulfides to sulfoxides and sulfones (Section 18.8)





Exercises

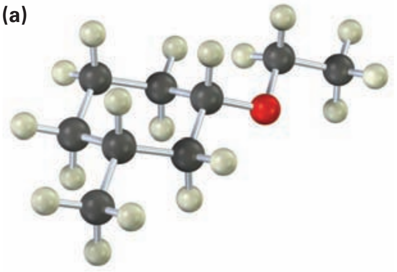
Visualizing Chemistry

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

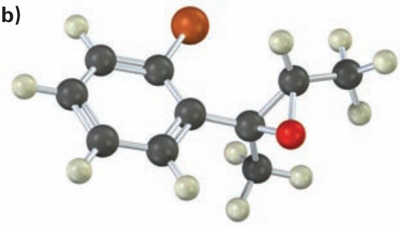
(Problems 18.1–18.18 appear within the chapter.)

18.19 Give IUPAC names for the following compounds (reddish brown = Br; yellow = S):

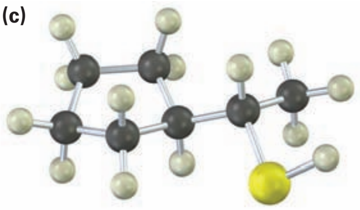
(a)



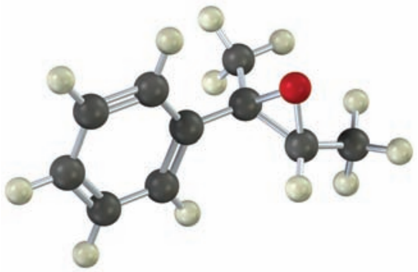
(b)



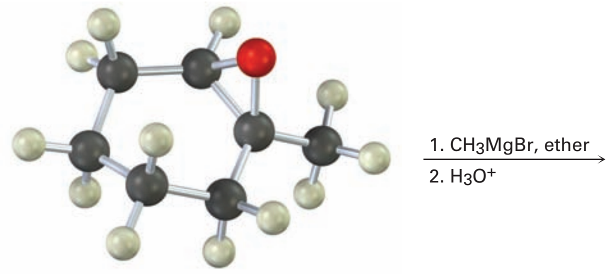
(c)



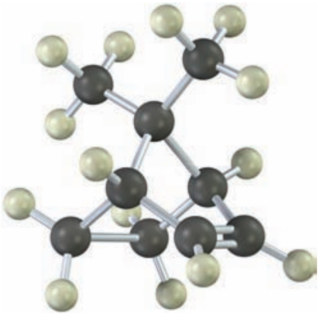
18.20 Show the product, including stereochemistry, that would result from reaction of the following epoxide with HBr:



18.21 Show the product, including stereochemistry, of the following reaction:



18.22 Treatment of the following alkene with a peroxyacid yields an epoxide different from that obtained by reaction with aqueous Br_2 followed by base treatment. Propose structures for the two epoxides, and explain the result.



Additional Problems

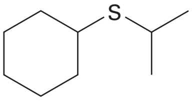
Naming Ethers

18.23 Draw structures corresponding to the following IUPAC names:

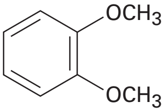
(a) Ethyl 1-ethylpropyl ether
(b) Di(*p*-chlorophenyl) ether
(c) 3,4-Dimethoxybenzoic acid
(d) Cyclopentyloxycyclohexane
(e) 4-Allyl-2-methoxyphenol (eugenol; from oil of cloves)

18.24 Give IUPAC names for the following structures:

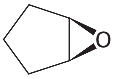
(a)



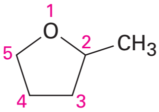
(b)



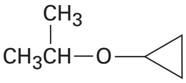
(c)



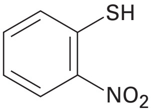
(d)



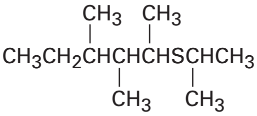
(e)



(f)

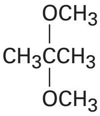


(g)



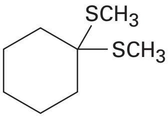
$CH_3CH_2\overset{CH_3}{CH}\underset{CH_3}{CH}\overset{CH_3}{CH}S\underset{CH_3}{CH}CH_3$

(h)



$CH_3\overset{OCH_3}{\underset{OCH_3}{C}}CH_3$

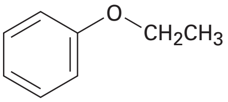
(i)



Synthesizing Ethers

18.25 How would you prepare the following ethers?

(a)



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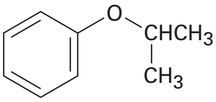

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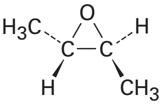

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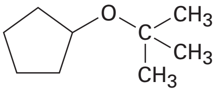

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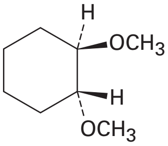

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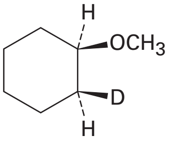
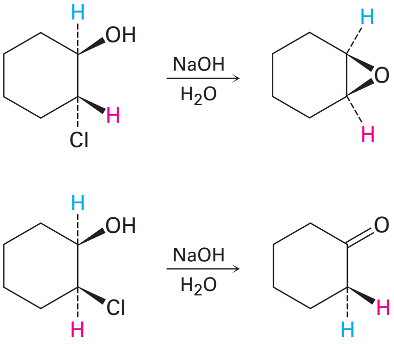


18.26 How would you prepare the following compounds from 1-phenylethanol?

(a) Methyl 1-phenylethyl ether
(b) Phenylepoxyethane
(c) *tert*-Butyl 1-phenylethyl ether
(d) 1-Phenylethanethiol

18.27 *tert*-Butyl ethers can be prepared by the reaction of an alcohol with 2-methylpropene in the presence of an acid catalyst. Propose a mechanism for this reaction.

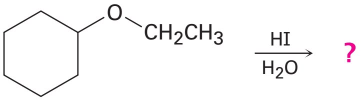
18.28 Treatment of *trans*-2-chlorocyclohexanol with NaOH yields 1,2-epoxycyclohexane, but reaction of the cis isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions, and explain why the different results are obtained.



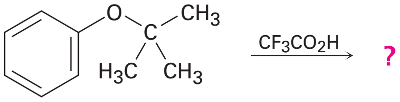
Reactions of Ethers and Epoxides

18.29 Predict the products of the following ether cleavage reactions:

(a)

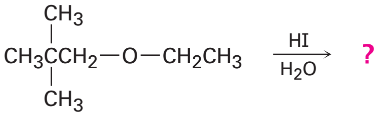


(b)



(c) $H_2C{=}CH{-}O{-}CH_2CH_3 \xrightarrow[H_2O]{HI}$?

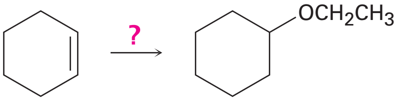
(d)



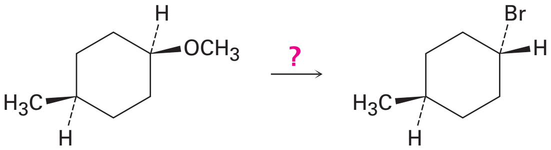
$$\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{CH_3\overset{|}{\underset{|}{C}}CH_2}}{-}O{-}CH_2CH_3 \xrightarrow[H_2O]{HI} ?$$

18.30 How would you carry out the following transformations? More than one step may be required.

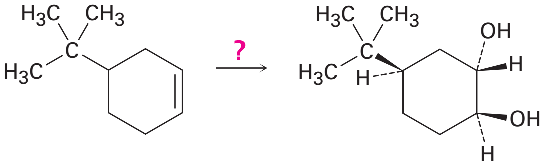
(a)



(b)

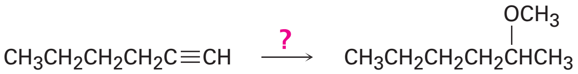


(c)



(d) $CH_3CH_2CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2OCH_3$

(e)



$$CH_3CH_2CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CH_2\overset{\displaystyle OCH_3}{\overset{|}{C}}HCH_3$$

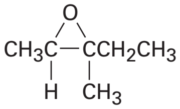
18.31 What product would you expect from cleavage of tetrahydrofuran with HI?

18.32 Write the mechanism of the hydrolysis of *cis*-5,6-epoxydecane by reaction with aqueous acid. What is the stereochemistry of the product, assuming normal backside S_N2 attack?

18.33 What is the stereochemistry of the product from acid-catalyzed hydrolysis of *trans*-5,6-epoxydecane? How does the product differ from that formed in Problem 18.32?

18.34 Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a trans-diaxial 1,2-diol. What product would you expect to obtain from acidic hydrolysis of *cis*-3-*tert*-butyl-1,2-epoxycyclohexane? (Recall that the bulky *tert*-butyl group locks the cyclohexane ring into a specific conformation.)

18.35 Imagine that you have treated (2*R*,3*R*)-2,3-epoxy-3-methylpentane with aqueous acid to carry out a ring-opening reaction.

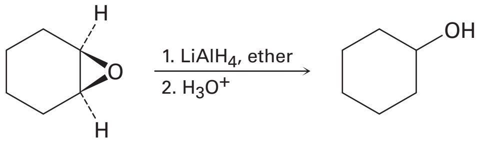


$$\overset{O}{\overbrace{\mathrm{CH_3\underset{H}{C}-\underset{CH_3}{C}CH_2CH_3}}}$$

2,3-Epoxy-3-methylpentane (no stereochemistry implied)

(a) Draw the epoxide, showing stereochemistry.
(b) Draw and name the product, showing stereochemistry.
(c) Is the product chiral? Explain.
(d) Is the product optically active? Explain.

18.36 Epoxides are reduced by treatment with lithium aluminum hydride to yield alcohols. Propose a mechanism for this reaction.



18.37 Show the structure and stereochemistry of the alcohol that would result if 1,2-epoxycyclohexane were reduced with lithium aluminum deuteride, $LiAlD_4$ (Problem 18.36).

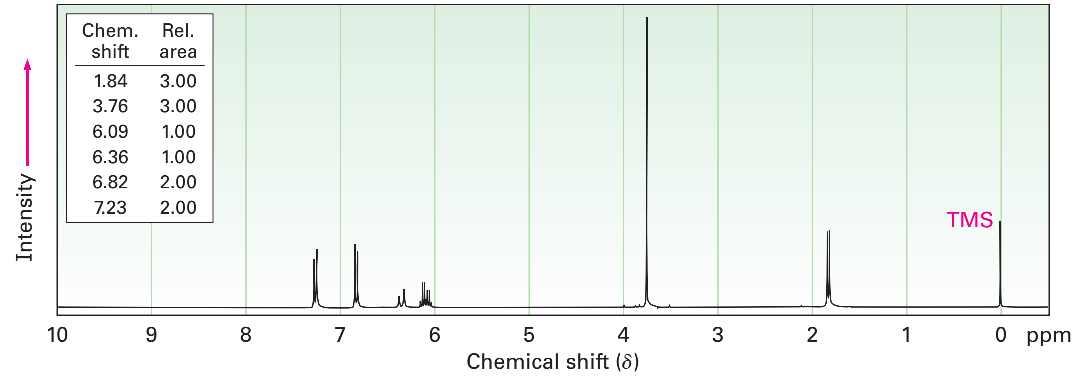
Spectroscopy

18.38 The red fox *(Vulpes vulpes)* uses a chemical communication system based on scent marks in urine. One component of fox urine is a sulfide whose mass spectrum has $M^+ = 116$. IR spectroscopy shows an intense band at 890 cm^{-1}, and ^{1}H NMR spectroscopy reveals the following peaks:

1.74 δ (3 H, singlet); 2.11 δ (3 H, singlet); 2.27 δ (2 H, triplet, $J = 4.2$ Hz); 2.57 δ (2 H, triplet, $J = 4.2$ Hz); 4.73 δ (2 H, broad)

Propose a structure consistent with these data. [*Note:* $(CH_3)_2S$ absorbs at 2.1 δ.]

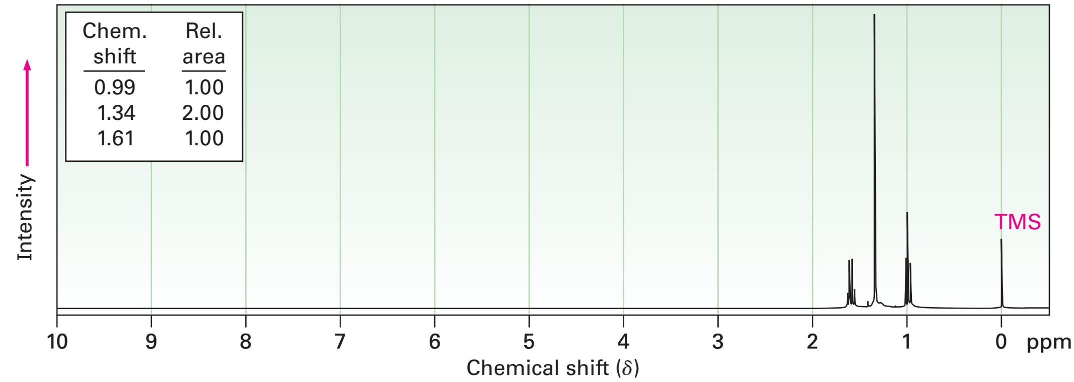
18.39 Anethole, $C_{10}H_{12}O$, a major constituent of the oil of anise, has the ^1H NMR spectrum shown. On oxidation with $Na_2Cr_2O_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.



Chem. shift	Rel. area
1.84	3.00
3.76	3.00
6.09	1.00
6.36	1.00
6.82	2.00
7.23	2.00

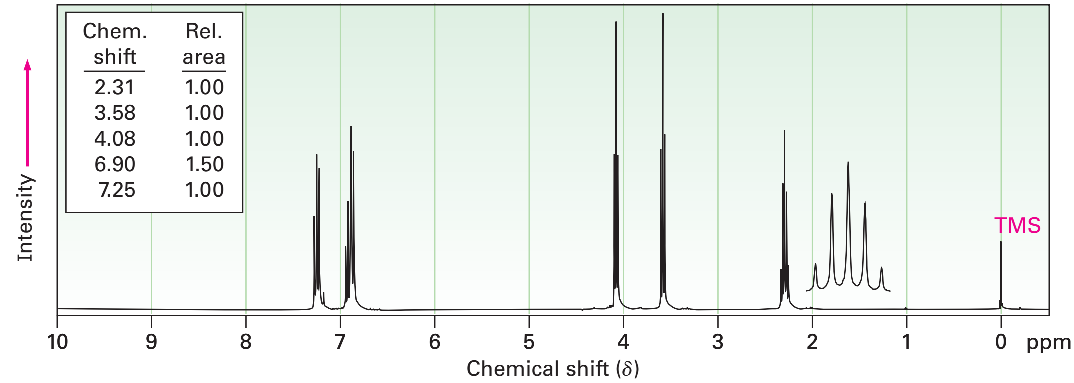
18.40 Propose structures for compounds that have the following ^1H NMR spectra:

(a) $C_5H_{12}S$ (An –SH proton absorbs near 1.6 δ.)



Chem. shift	Rel. area
0.99	1.00
1.34	2.00
1.61	1.00

(b) $C_9H_{11}BrO$

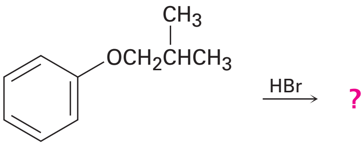


Chem. shift	Rel. area
2.31	1.00
3.58	1.00
4.08	1.00
6.90	1.50
7.25	1.00

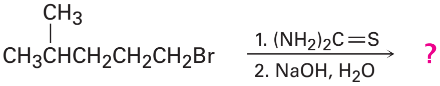
General Problems

18.41 Predict the products of the following reactions:

(a)

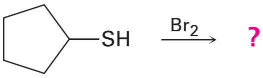


(b)

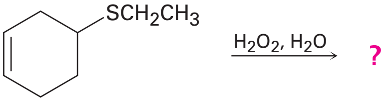


$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CH_2Br \xrightarrow[2.\ NaOH,\ H_2O]{1.\ (NH_2)_2C{=}S} ?$

(c)



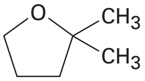
(d)



18.42 How would you synthesize anethole (Problem 18.39) from phenol?

18.43 How could you prepare benzyl phenyl ether from benzene and phenol? More than one step is required.

18.44 When 2-methyl-2,5-pentanediol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?



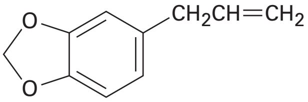
2,2-Dimethyltetrahydrofuran

18.45 Methyl aryl ethers, such as anisole, are cleaved to iodomethane and a phenoxide ion by treatment with LiI in hot DMF. Propose a mechanism for this reaction.

18.46 *Meerwein's reagent,* triethyloxonium tetrafluoroborate, is a powerful ethylating agent that converts alcohols into ethyl ethers at neutral pH. Show the reaction of Meerwein's reagent with cyclohexanol, and account for the fact that trialkyloxonium salts are much more reactive alkylating agents than alkyl iodides.

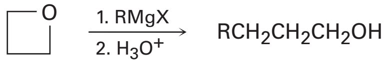
$(CH_3CH_2)_3O^+\ BF_4^-$ **Meerwein's reagent**

18.47 Safrole, a substance isolated from oil of sassafras, is used as a perfumery agent. Propose a synthesis of safrole from catechol (1,2-benzenediol).



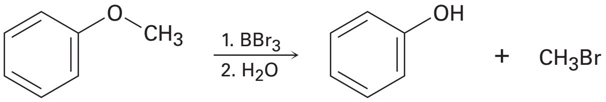
Safrole

18.48 Grignard reagents react with oxetane, a four-membered cyclic ether, to yield primary alcohols, but the reaction is much slower than the corresponding reaction with ethylene oxide. Suggest a reason for the difference in reactivity between oxetane and ethylene oxide.



Oxetane

18.49 Ethers undergo an acid-catalyzed cleavage reaction when treated with the Lewis acid BBr_3 at room temperature. Propose a mechanism for the reaction.

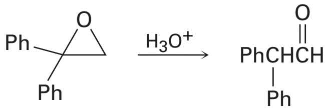


18.50 The *Zeisel method* is an old analytical procedure for determining the number of methoxyl groups in a compound. A weighed amount of the compound is heated with concentrated HI, ether cleavage occurs, and the iodomethane product is distilled off and passed into an alcohol solution of $AgNO_3$, where it reacts to form a precipitate of silver iodide. The AgI is then collected and weighed, and the percentage of methoxyl groups in the sample is thereby determined. For example, 1.06 g of vanillin, the material responsible for the characteristic odor of vanilla, yields 1.60 g of AgI. If vanillin has a molecular weight of 152, how many methoxyl groups does it contain?

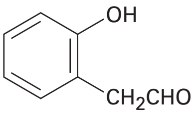
18.51 Disparlure, $C_{19}H_{38}O$, is a sex attractant released by the female gypsy moth, *Lymantria dispar.* The ^1H NMR spectrum of disparlure shows a large absorption in the alkane region, 1 to 2 δ, and a triplet at 2.8 δ. Treatment of disparlure, first with aqueous acid and then with $KMnO_4$, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. ($KMnO_4$ cleaves 1,2-diols to yield carboxylic acids.) Neglecting stereochemistry, propose a structure for disparlure. The actual compound is a chiral molecule with 7*R*,8*S* stereochemistry. Draw disparlure, showing the correct stereochemistry.

18.52 How would you synthesize racemic disparlure (Problem 18.51) from compounds having ten or fewer carbons?

18.53 Treatment of 1,1-diphenyl-1,2-epoxyethane with aqueous acid yields diphenylacetaldehyde as the major product. Propose a mechanism for the reaction.

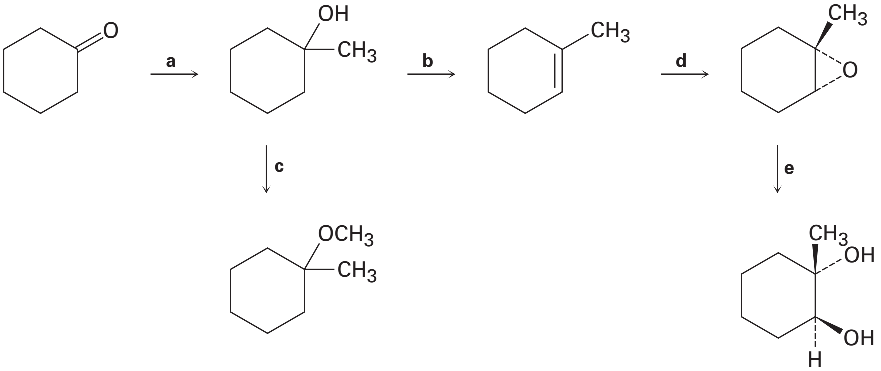


18.54 How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.

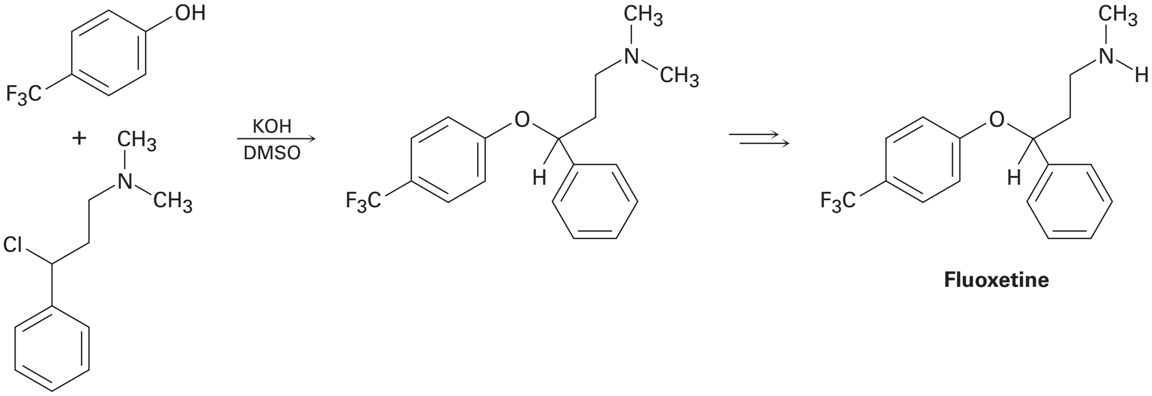


***o*-Hydroxyphenylacetaldehyde**

18.55 Identify the reagents **a–e** in the following scheme:



18.56 Fluoxetine, a heavily prescribed antidepressant marketed under the name Prozac, can be prepared by a route that begins with reaction between a phenol and an alkyl chloride.

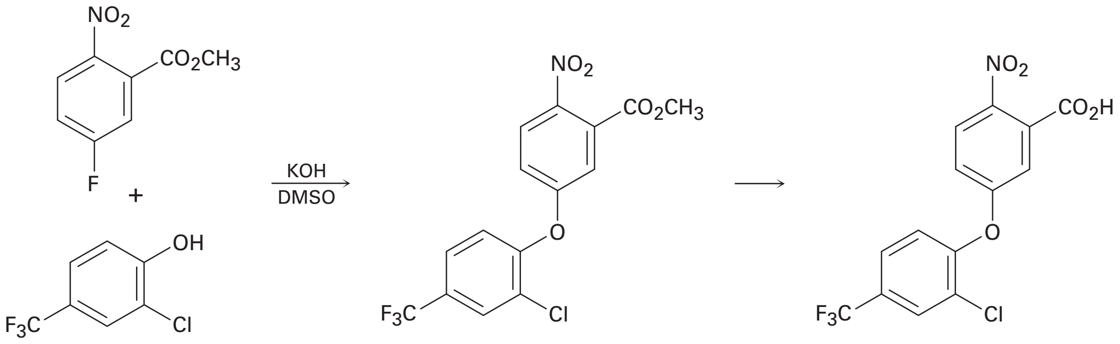


Fluoxetine

(a) The rate of the reaction depends on both phenol and alkyl halide. Is this an S_N1 or an S_N2 reaction? Show the mechanism.

(b) The physiologically active enantiomer of fluoxetine has (*S*) stereochemistry. Based on your answer in part **(a)**, draw the structure of the alkyl chloride you would need, showing the correct stereochemistry.

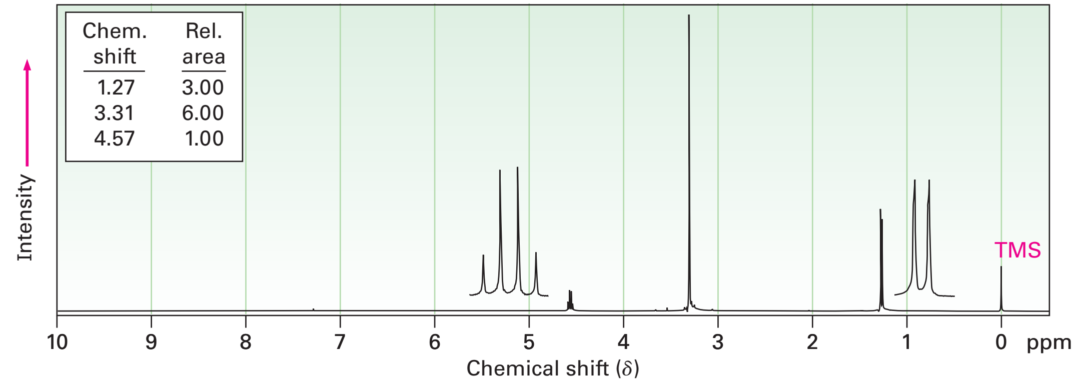
18.57 The herbicide acifluorfen can be prepared by a route that begins with reaction between a phenol and an aryl fluoride. Propose a mechanism.



Acifluorfen

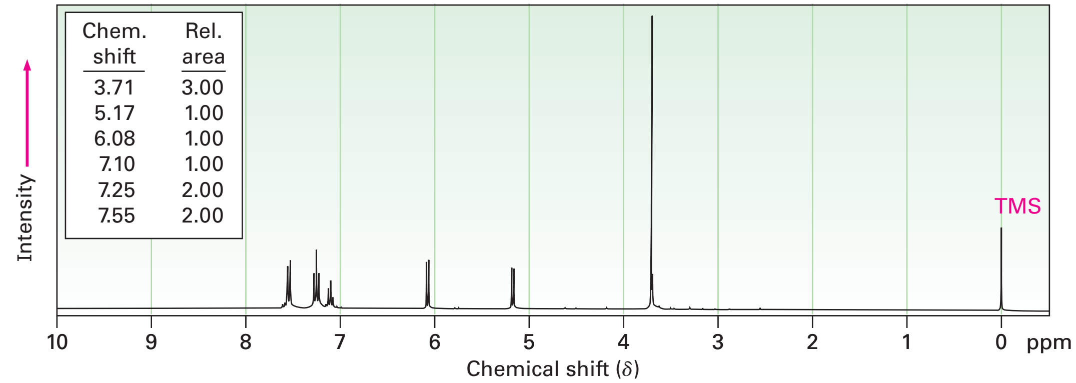
18.58 Propose structures for compounds that have the following ^1H NMR spectra:

(a) $C_4H_{10}O_2$



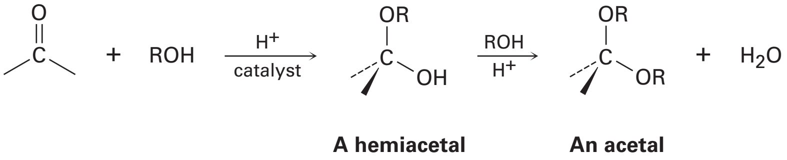
Chem. shift	Rel. area
1.27	3.00
3.31	6.00
4.57	1.00

(b) $C_9H_{10}O$



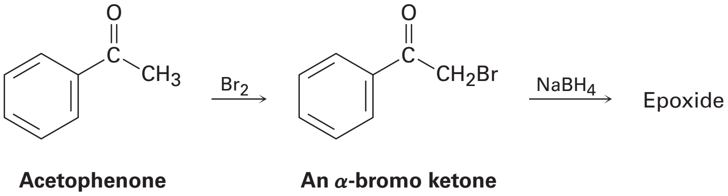
Chem. shift	Rel. area
3.71	3.00
5.17	1.00
6.08	1.00
7.10	1.00
7.25	2.00
7.55	2.00

18.59 Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals,* compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further reaction of a hemiacetal with alcohol then yields an *acetal,* a compound that has two ether-like oxygens bonded to the same carbon.

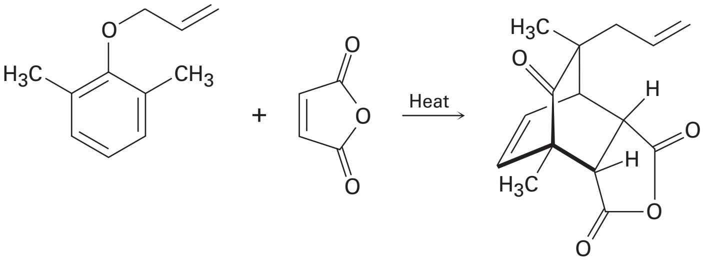


(a) Show the structures of the hemiacetal and acetal you would obtain by reaction of cyclohexanone with ethanol.
(b) Propose a mechanism for the conversion of a hemiacetal into an acetal.

18.60 We saw in Section 17.4 that ketones react with $NaBH_4$ to yield alcohols. We'll also see in Section 22.3 that ketones react with Br_2 to yield α-bromo ketones. Perhaps surprisingly, treatment with $NaBH_4$ of the α-bromo ketone from acetophenone yields an epoxide rather than a bromo alcohol. Show the structure of the epoxide, and explain its formation.



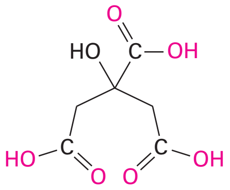
18.61 Propose a mechanism to account for the following transformation. What two kinds of reactions are occurring?



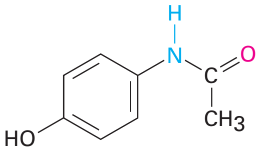
Preview of Carbonyl Chemistry

I Kinds of Carbonyl Compounds
II Nature of the Carbonyl Group
III General Reactions of Carbonyl Compounds
IV Summary

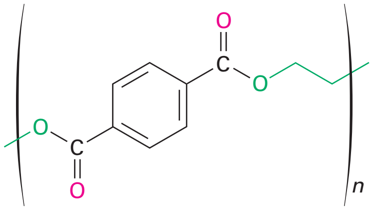
Carbonyl compounds are everywhere. Most biological molecules contain carbonyl groups, as do most pharmaceutical agents and many of the synthetic chemicals that touch our everyday lives. Citric acid, found in lemons and oranges; acetaminophen, the active ingredient in many over-the-counter headache remedies; and Dacron, the polyester material used in clothing, all contain different kinds of carbonyl groups.



Citric acid
(a carboxylic acid)



Acetaminophen
(an amide)



Dacron
(a polyester)

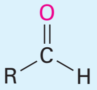
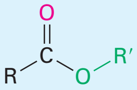
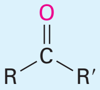
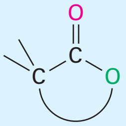
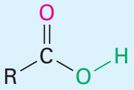
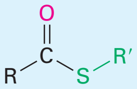
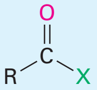
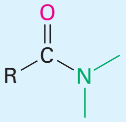
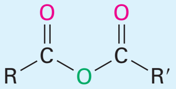
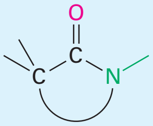
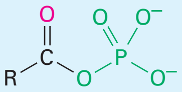
To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. Thus, we'll spend the next five chapters discussing the chemistry of the **carbonyl group**, **C=O** (pronounced car-bo-**neel**). There are many different kinds of carbonyl compounds and many different reactions, but there are only a few fundamental principles that tie the entire field together. The purpose of this brief preview is not to show details of specific reactions but rather to provide a framework for learning carbonyl-group chemistry. Read through this preview now, and return to it on occasion to remind yourself of the larger picture.

I. Kinds of Carbonyl Compounds

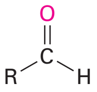
Table 1 shows some of the many different kinds of carbonyl compounds. All contain an **acyl group** (R–C=O) bonded to another substituent. The R part of the acyl group can be practically any organic part-structure, and the other substituent to which the acyl group is bonded might be a carbon, hydrogen, oxygen, halogen, nitrogen, or sulfur.

It's useful to classify carbonyl compounds into two categories based on the kinds of chemistry they undergo. In one category are aldehydes and ketones; in the other are carboxylic acids and their derivatives. The acyl group in an aldehyde or ketone is bonded to an atom (H or C, respectively) that can't stabilize a negative charge and therefore can't act as a leaving group in a nucleophilic substitution reaction. The acyl group in a carboxylic acid or its derivative, however, is bonded to an atom

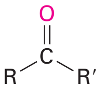
Table 1 Some Types of Carbonyl Compounds

Name	General formula	Name ending	Name	General formula	Name ending
Aldehyde		*-al*	Ester		*-oate*
Ketone		*-one*	Lactone (cyclic ester)		None
Carboxylic acid		*-oic acid*	Thioester		*-thioate*
Acid halide		*-yl or -oyl halide*	Amide		*-amide*
Acid anhydride		*-oic anhydride*	Lactam (cyclic amide)		None
Acyl phosphate		*-yl phosphate*			

(oxygen, halogen, sulfur, nitrogen) that *can* stabilize a negative charge and therefore *can* act as a leaving group in a nucleophilic substitution reaction.

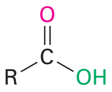


Aldehyde

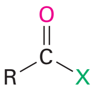


Ketone

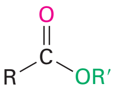
The –R′ and –H in these compounds *can't* act as leaving groups in nucleophilic substitution reactions.



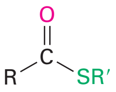
Carboxylic acid



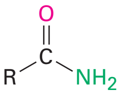
Acid halide



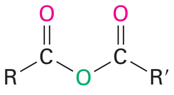
Ester



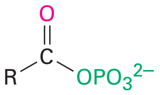
Thioester



Amide



Acid anhydride

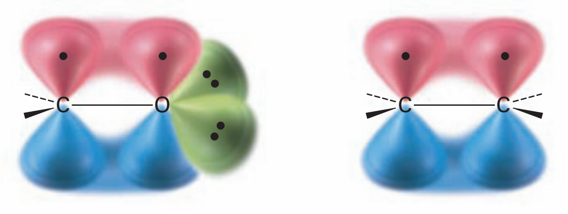


Acyl phosphate

The –OH, –X, –OR′, –SR, –NH$_2$, –OCOR′, and –OPO$_3^{2-}$ in these compounds *can* act as leaving groups in nucleophilic substitution reactions.

II. Nature of the Carbonyl Group

The carbon–oxygen double bond of a carbonyl group is similar in many respects to the carbon–carbon double bond of an alkene. The carbonyl carbon atom is sp^2-hybridized and forms three σ bonds. The fourth valence electron remains in a carbon p orbital and forms a π bond to oxygen by overlap with an oxygen p orbital. The oxygen atom also has two nonbonding pairs of electrons, which occupy its remaining two orbitals.

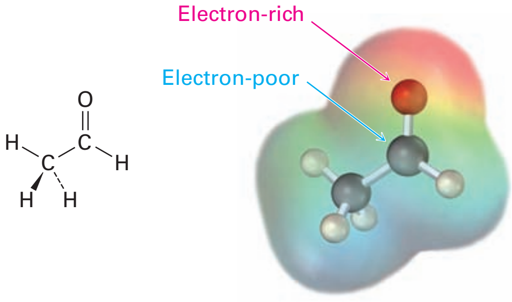


Carbonyl group **Alkene**

Like alkenes, carbonyl compounds are planar about the double bond and have bond angles of approximately 120°. **Figure 1** shows the structure of acetaldehyde and indicates its bond lengths and angles. As you might expect, the carbon–oxygen double bond is both shorter (122 pm versus 143 pm) and stronger [732 kJ/mol (175 kcal/mol) versus 385 kJ/mol (92 kcal/mol)] than a C–O single bond.

Figure 1 Structure of acetaldehyde.

Bond angle	(°)	Bond length	(pm)
H—C—C	118	C=O	122
C—C=O	121	C—C	150
H—C=O	121	OC—H	109



As indicated by the electrostatic potential map in Figure 1, the carbon–oxygen double bond is strongly polarized because of the high electronegativity of oxygen relative to carbon. Thus, the carbonyl carbon atom carries a partial positive charge, is an electrophilic (Lewis acidic) site, and reacts with nucleophiles. Conversely, the carbonyl oxygen atom carries a partial negative charge, is a nucleophilic (Lewis basic) site, and reacts with electrophiles. We'll see in the next five chapters that the majority of carbonyl-group reactions can be rationalized by simple polarity arguments.

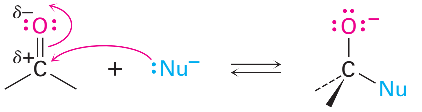
III. General Reactions of Carbonyl Compounds

Both in the laboratory and in living organisms, most reactions of carbonyl compounds take place by one of four general mechanisms: *nucleophilic addition, nucleophilic acyl substitution, alpha substitution,* and *carbonyl condensation.*

These mechanisms have many variations, just as alkene electrophilic addition reactions and S_N2 reactions do, but the variations are much easier to learn when the fundamental features of the mechanisms are made clear. Let's see what the four mechanisms are and what kinds of chemistry carbonyl compounds undergo.

Nucleophilic Addition Reactions of Aldehydes and Ketones (Chapter 19)

The most common reaction of aldehydes and ketones is the **nucleophilic addition reaction**, in which a nucleophile, $:Nu^-$, adds to the electrophilic carbon of the carbonyl group. Since the nucleophile uses an electron pair to form a new bond to carbon, two electrons from the carbon–oxygen double bond must move toward the electronegative oxygen atom to give an alkoxide anion. The carbonyl carbon rehybridizes from *sp*^{2} to *sp*^{3} during the reaction, and the alkoxide ion product therefore has tetrahedral geometry.



A carbonyl compound (*sp*^{2}-hybridized carbon)

A tetrahedral intermediate (*sp*^{3}-hybridized carbon)

Once formed, and depending on the nature of the nucleophile, the tetrahedral alkoxide intermediate can undergo either of two further reactions, as shown in **Figure 2**. Often, the tetrahedral alkoxide intermediate is simply protonated by water or acid to form an alcohol product. Alternatively, the tetrahedral intermediate can be protonated and expel the oxygen to form a new double bond between the carbonyl carbon and the nucleophile. We'll study both processes in detail in Chapter 19.

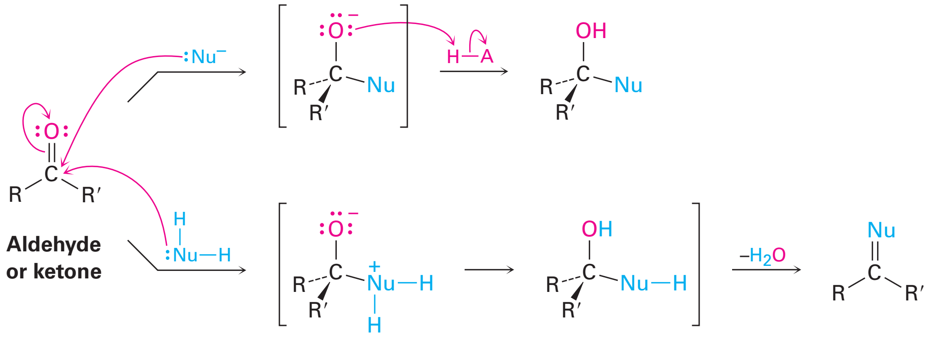
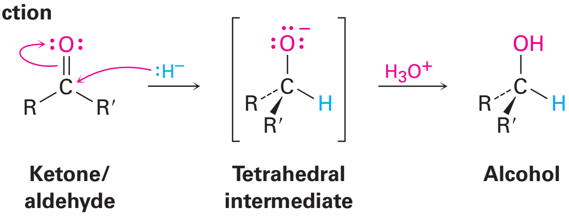


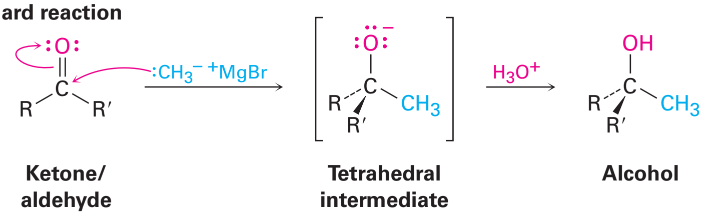
Figure 2 The addition reaction of an aldehyde or a ketone with a nucleophile. Depending on the nucleophile, either an alcohol or a compound with a C=Nu double bond is formed.

Formation of an Alcohol The simplest reaction of a tetrahedral alkoxide intermediate is protonation to yield an alcohol. We've already seen two examples of this kind of process during reduction of aldehydes and ketones with hydride reagents such as $NaBH_4$ and $LiAlH_4$ **(Section 17.4)** and during Grignard reactions **(Section 17.5)**. During a reduction, the nucleophile that adds to the carbonyl group is a hydride ion, H:⁻, while during a Grignard reaction, the nucleophile is a carbanion, $R_3C:^-$.

Reduction



Grignard reaction



Formation of C=Nu The second mode of nucleophilic addition, which often occurs with amine nucleophiles, involves elimination of oxygen and formation of a C=Nu double bond. For example, aldehydes and ketones react with primary amines, RNH_2, to form *imines,* $R_2C{=}NR'$. These reactions proceed through exactly the same kind of tetrahedral intermediate as that formed during hydride reduction and Grignard reaction, but the initially formed alkoxide ion is not isolated. Instead, it is protonated and then loses water to form an imine, as shown in **Figure 3**.

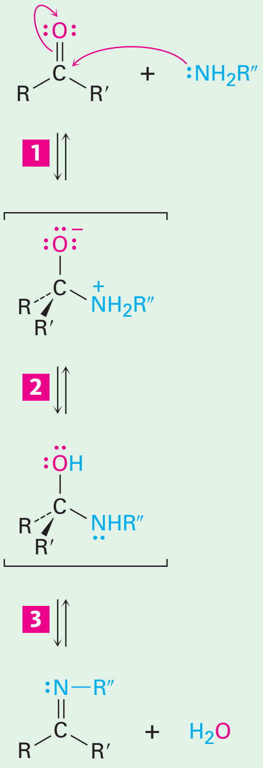
Figure 3 | **MECHANISM**

Formation of an imine, $R_2C{=}NR'$, by reaction of an amine with an aldehyde or a ketone.

1 Addition to the ketone or aldehyde carbonyl group by the neutral amine nucleophile gives a dipolar tetrahedral intermediate.

2 Transfer of a proton from nitrogen to oxygen then yields an amino alcohol intermediate.

3 Dehydration of the amino alcohol intermediate gives neutral imine plus water as final products.



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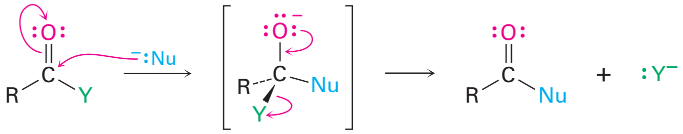
Nucleophilic Acyl Substitution Reactions of Carboxylic Acid Derivatives (Chapter 21)

The second fundamental reaction of carbonyl compounds, **nucleophilic acyl substitution**, is related to the nucleophilic addition reaction just discussed but occurs only with carboxylic acid derivatives rather than with aldehydes and ketones. When the carbonyl group of a carboxylic acid derivative reacts with a nucleophile, addition occurs in the usual way, but the initially formed tetrahedral alkoxide intermediate is not isolated. Because carboxylic acid derivatives have a leaving group bonded to the carbonyl-group carbon, the tetrahedral intermediate can react further by expelling the leaving group and forming a new carbonyl compound:



Carboxylic acid derivative

Tetrahedral intermediate

[Y = –OR (ester), –Cl (acid chloride), $-NH_2$ (amide), or –OCOR (acid anhydride)]

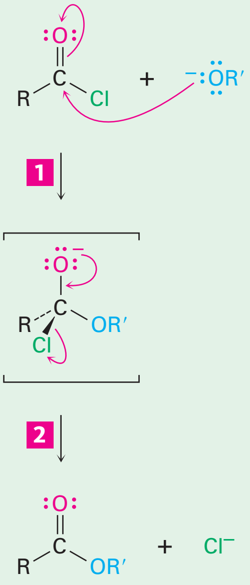
The net effect of nucleophilic acyl substitution is the replacement of the leaving group by the entering nucleophile. We'll see in Chapter 21, for instance, that acid chlorides are rapidly converted into esters by treatment with alkoxide ions **(Figure 4)**.

Figure 4 | **MECHANISM**

The nucleophilic acyl substitution reaction of an acid chloride with an alkoxide ion yields an ester.

1 Nucleophilic addition of alkoxide ion to an acid chloride yields a tetrahedral intermediate.

2 An electron pair from oxygen expels chloride ion and yields the substitution product, an ester.



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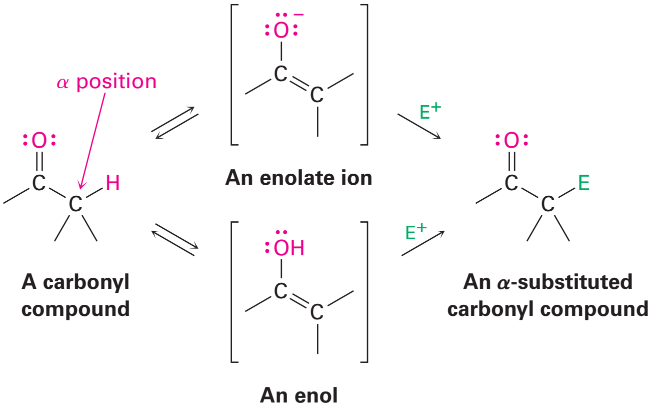
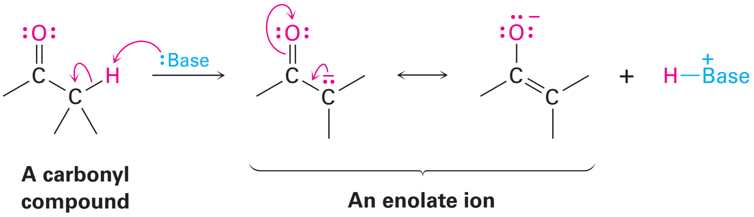
Alpha-Substitution Reactions (Chapter 22)

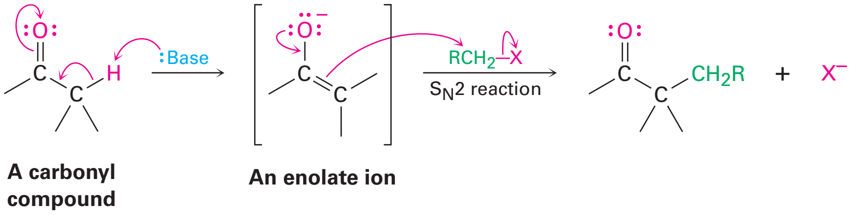
The third major reaction of carbonyl compounds, **alpha substitution**, occurs at the position next to the carbonyl group—the alpha (α) position. This reaction, which takes place with all carbonyl compounds regardless of structure, results in the substitution of an α hydrogen by an electrophile through the formation of an intermediate *enol* or *enolate ion:*



For reasons that we'll explore in Chapter 22, the presence of a carbonyl group renders the hydrogens on the α carbon acidic. Carbonyl compounds therefore react with strong base to yield enolate ions.



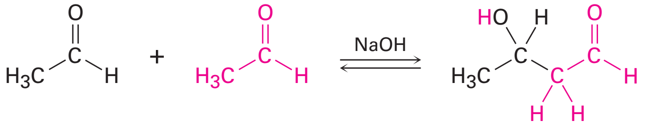
Because they're negatively charged, enolate ions act as nucleophiles and undergo many of the reactions we've already studied. For example, enolates react with primary alkyl halides in the S_N2 reaction. The nucleophilic enolate ion displaces halide ion, and a new C–C bond forms:



The S_N2 alkylation reaction between an enolate ion and an alkyl halide is a powerful method for making C–C bonds, thereby building up larger molecules from smaller precursors. We'll study the alkylation of many kinds of carbonyl compounds in Chapter 22.

Carbonyl Condensation Reactions (Chapter 23)

The fourth and last fundamental reaction of carbonyl groups, **carbonyl condensation**, takes place when two carbonyl compounds react with each other. When acetaldehyde is treated with base, for instance, two molecules combine to yield the hydroxy aldehyde product known as *aldol* (*ald*ehyde + alcohol):



Two acetaldehydes **Aldol**

Although the carbonyl condensation reaction appears different from the three processes already discussed, it's actually quite similar. A carbonyl condensation reaction is simply a combination of a nucleophilic addition step and an α-substitution step. The initially formed enolate ion of one acetaldehyde molecule acts as a nucleophile and adds to the carbonyl group of another acetaldehyde molecule, as shown in **Figure 5**.

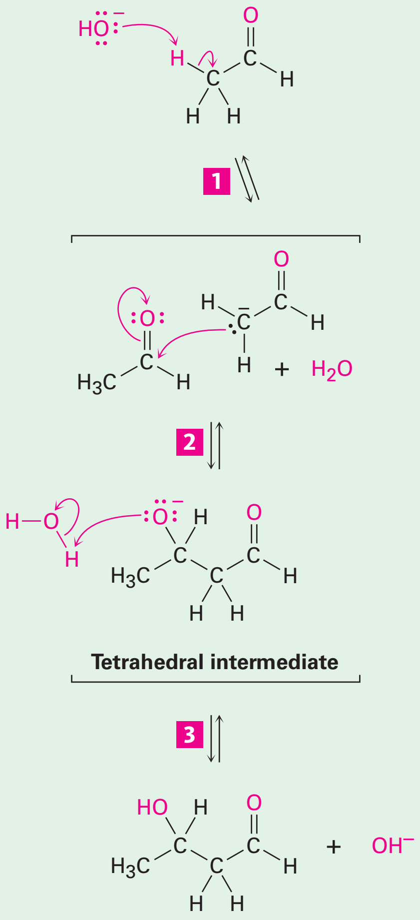
Figure 5 | **MECHANISM**

A carbonyl condensation reaction between two molecules of acetaldehyde yields a hydroxy aldehyde product.

1 Base abstracts an acidic alpha hydrogen from one acetaldehyde molecule, yielding a resonance-stabilized enolate ion.

2 The enolate ion adds as a nucleophile to the carbonyl group of a second acetaldehyde, producing a tetrahedral alkoxide ion.

3 The tetrahedral intermediate is protonated by solvent to yield the neutral aldol product and regenerate the base catalyst.



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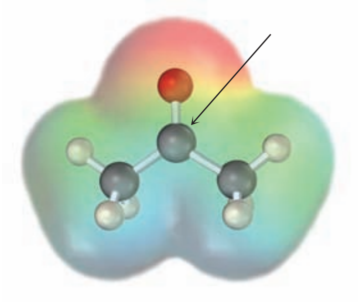
IV. Summary

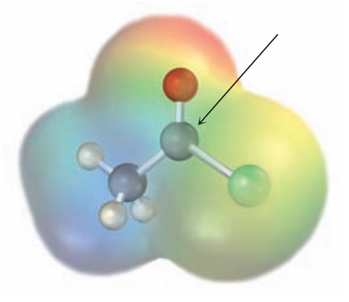
To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. We have not looked at the details of specific carbonyl reactions in this short preview but rather have laid the groundwork for the next five chapters. All the carbonyl-group reactions we'll be studying in Chapters 19 through 23 fall into one of the four fundamental categories discussed in this preview. Knowing where we'll be heading should help you keep matters straight in understanding this most important of all functional groups.

Problems

1. Judging from the following electrostatic potential maps, which kind of carbonyl compound has the more electrophilic carbonyl carbon atom, a ketone or an acid chloride? Which has the more nucleophilic carbonyl oxygen atom? Explain.

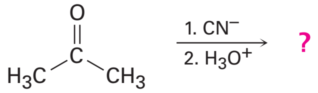


Acetone
(ketone)



Acetyl chloride
(acid chloride)

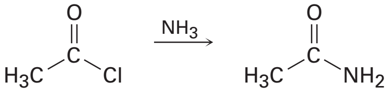
2. Predict the product formed by nucleophilic addition of cyanide ion (CN^-) to the carbonyl group of acetone, followed by protonation to give an alcohol:



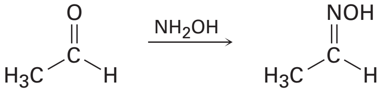
Acetone

3. Identify each of the following reactions as a nucleophilic addition, nucleophilic acyl substitution, an *α* substitution, or a carbonyl condensation:

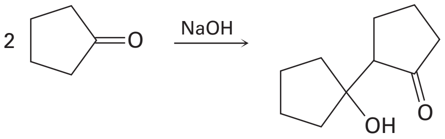
(a)



(b)



(c)



19

Few flowers are more beautiful or more fragrant than roses. Their perfumed odor is due to several simple organic compounds, including the ketone β-damascenone. Image copyright Veronika Trofer, 2010. Used under license from Shutterstock.com

Aldehydes and Ketones: Nucleophilic Addition Reactions

19.1 Naming Aldehydes and Ketones
19.2 Preparing Aldehydes and Ketones
19.3 Oxidation of Aldehydes and Ketones
19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones
19.5 Nucleophilic Addition of H_2O: Hydration
19.6 Nucleophilic Addition of HCN: Cyanohydrin Formation
19.7 Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation
19.8 Nucleophilic Addition of Amines: Imine and Enamine Formation
19.9 Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction
19.10 Nucleophilic Addition of Alcohols: Acetal Formation
19.11 Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction
19.12 Biological Reductions
19.13 Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones
19.14 Spectroscopy of Aldehydes and Ketones
A Deeper Look—Enantioselective Synthesis

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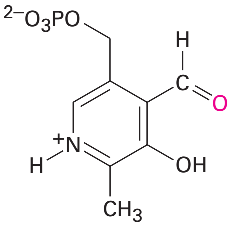
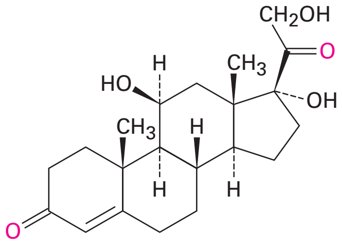
Aldehydes (RCHO) and **ketones (R_2CO)** are among the most widely occurring of all compounds. In nature, many substances required by living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions; the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.

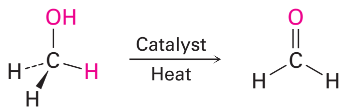


Pyridoxal phosphate (PLP)

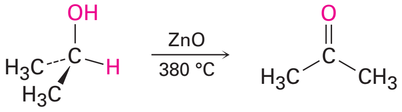


Hydrocortisone

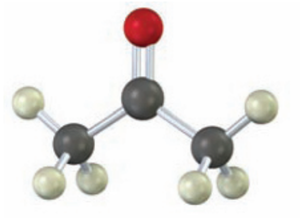
In the chemical industry, simple aldehydes and ketones are produced in large quantities for use as solvents and as starting materials to prepare a host of other compounds. For example, more than 23 million tons per year of formaldehyde, $H_2C{=}O$, is produced worldwide for use in building insulation materials and in the adhesive resins that bind particle board and plywood. Acetone, $(CH_3)_2C{=}O$, is widely used as an industrial solvent; approximately 3.3 million tons per year is produced worldwide. Formaldehyde is synthesized industrially by catalytic oxidation of methanol, and one method of acetone preparation involves oxidation of 2-propanol.



Methanol **Formaldehyde**



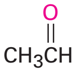
2-Propanol **Acetone**

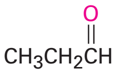


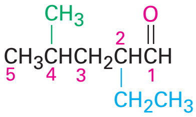
Why This Chapter? Much of organic chemistry is the chemistry of carbonyl compounds. Aldehydes and ketones, in particular, are intermediates in the synthesis of many pharmaceutical agents, in almost all biological pathways, and in numerous industrial processes, so an understanding of their properties and reactions is essential. We'll look in this chapter at some of their most important reactions.

19.1 Naming Aldehydes and Ketones

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the –CHO group, and the –CHO carbon is numbered as carbon 1. Note in the following examples that the longest chain in 2-ethyl-4-methylpentanal is actually a hexane, but this chain does not include the –CHO group and thus is not the parent.

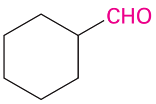

$CH_3CH{=}O$


$CH_3CH_2CH{=}O$

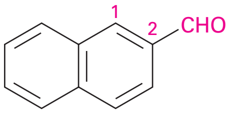

$\overset{5}{C}H_3\overset{4}{C}H(CH_3)\overset{3}{C}H_2\overset{2}{C}H(CH_2CH_3)\overset{1}{C}H{=}O$

Ethanal (acetaldehyde) **Propanal (propionaldehyde)** **2-Ethyl-4-methylpentanal**

For cyclic aldehydes in which the –CHO group is directly attached to a ring, the suffix *-carbaldehyde* is used.



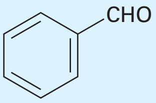
Cyclohexanecarbaldehyde



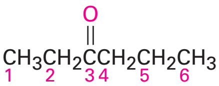
2-Naphthalenecarbaldehyde

A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in Table 19.1.

Table 19.1 Common Names of Some Simple Aldehydes

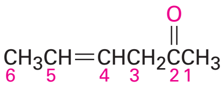
Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$H_2C{=}CHCHO$	Acrolein	Propenal
$CH_3CH{=}CHCHO$	Crotonaldehyde	2-Butenal
	Benzaldehyde	Benzenecarbaldehyde

Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that contains the ketone group, and the numbering begins at the end nearer the carbonyl carbon. As with alkenes **(Section 7.3)** and alcohols **(Section 17.1)**, the locant is placed before the parent name in older rules but before the suffix in newer IUPAC recommendations. For example:



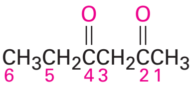
$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

3-Hexanone
(New: Hexan-3-one)



$CH_3CH{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_3$

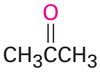
4-Hexen-2-one
(New: Hex-4-en-2-one)



$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$

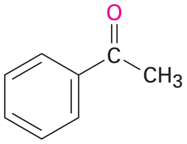
2,4-Hexanedione
(New: Hexane-2,4-dione)

A few ketones are allowed by IUPAC to retain their common names.

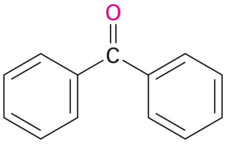


$CH_3\overset{O}{\overset{\|}{C}}CH_3$

Acetone

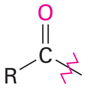


Acetophenone

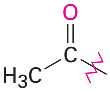


Benzophenone

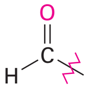
When it's necessary to refer to the R–C=O as a substituent, the name **acyl** (**a**-sil) **group** is used and the name ending *-yl* is attached. Thus, $-COCH_3$ is an *acetyl* group, –CHO is a *formyl* group, –COAr is an *aroyl* group, and $-COC_6H_5$ is a *benzoyl* group.



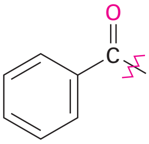
An acyl group



Acetyl

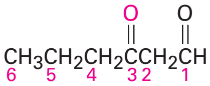


Formyl



Benzoyl

If other functional groups are present and the doubly bonded oxygen is considered a substituent on a parent chain, the prefix *oxo-* is used. For example:



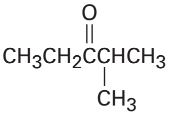
$\underset{6}{CH_3}\underset{5}{CH_2}\underset{4}{CH_2}\underset{3}{\overset{\overset{O}{\|}}{C}}\underset{2}{CH_2}\underset{1}{\overset{\overset{O}{\|}}{C}H}$

3-Oxohexanal

Problem 19.1

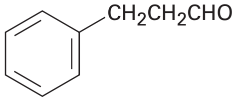
Name the following aldehydes and ketones:

(a)

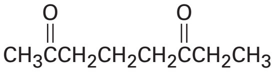


$CH_3CH_2\overset{\overset{O}{\|}}{C}\underset{\underset{CH_3}{|}}{C}HCH_3$

(b)

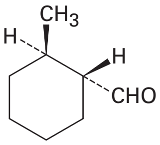


(c)

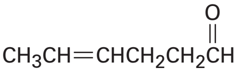


$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3$

(d)

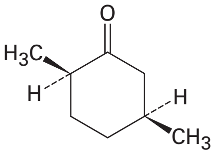


(e)



$CH_3CH{=}CHCH_2CH_2\overset{\overset{O}{\|}}{C}H$

(f)



Problem 19.2

Draw structures corresponding to the following names:

(a) 3-Methylbutanal

(b) 4-Chloro-2-pentanone

(c) Phenylacetaldehyde

(d) *cis*-3-*tert*-Butylcyclohexanecarbaldehyde

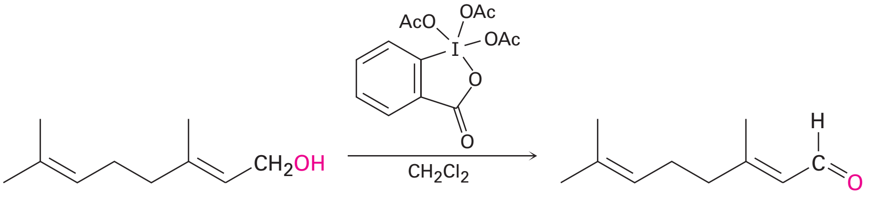
(e) 3-Methyl-3-butenal

(f) 2-(1-Chloroethyl)-5-methylheptanal

19.2 Preparing Aldehydes and Ketones

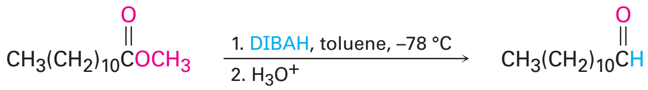
Preparing Aldehydes

One of the best methods of aldehyde synthesis is by oxidation of primary alcohols, as we saw in **Section 17.7**. The reaction is often carried out using the Dess–Martin periodinane reagent in dichloromethane solvent at room temperature:



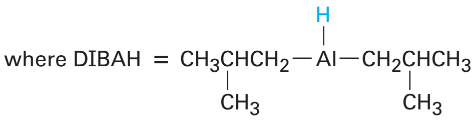
Geraniol **Geranial (84%)**

A second method of aldehyde synthesis is one that we'll mention here just briefly and then return to in **Section 21.6**. Certain carboxylic acid derivatives can be *partially* reduced to yield aldehydes. The partial reduction of an ester by diisobutylaluminum hydride (DIBAH, or DIBAL-H), for instance, is an important laboratory-scale method of aldehyde synthesis, and mechanistically related processes also occur in biological pathways. The reaction is normally carried out at −78 °C (dry-ice temperature) in toluene solution.



$$CH_3(CH_2)_{10}\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \xrightarrow[\text{2. } H_3O^+]{\text{1. DIBAH, toluene, −78 °C}} CH_3(CH_2)_{10}\overset{\overset{\displaystyle O}{\|}}{C}H$$

Methyl dodecanoate **Dodecanal (88%)**



$$\text{where DIBAH} = CH_3\underset{\underset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle H}{|}}{Al}-CH_2\underset{\underset{\displaystyle CH_3}{|}}{C}HCH_3$$

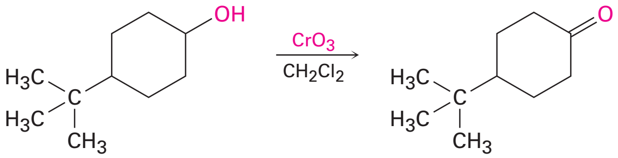
Problem 19.3

How would you prepare pentanal from the following starting materials?

(a) $CH_3CH_2CH_2CH_2CH_2OH$ **(b)** $CH_3CH_2CH_2CH_2CH{=}CH_2$
(c) $CH_3CH_2CH_2CH_2CO_2CH_3$ **(d)** $CH_3CH_2CH_2CH{=}CH_2$

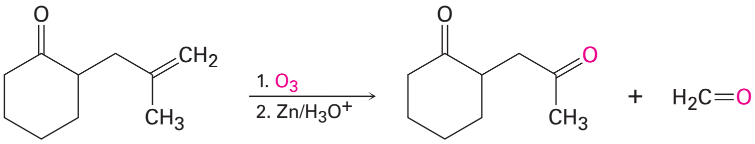
Preparing Ketones

For the most part, methods of ketone synthesis are similar to those for aldehydes. Secondary alcohols are oxidized by a variety of reagents to give ketones **(Section 17.7)**. The choice of oxidant depends on such factors as reaction scale, cost, and acid or base sensitivity of the alcohol. Either the Dess–Martin periodinane or a Cr(VI) regent such as CrO_3 is a common choice.

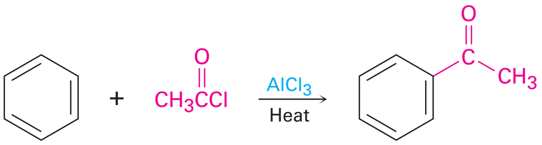


4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (90%)**

Other methods include the ozonolysis of alkenes in which one of the unsaturated carbon atoms is disubstituted **(Section 8.8)** and Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of $AlCl_3$ catalyst **(Section 16.3)**.

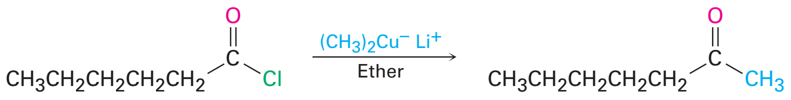


70%



Benzene **Acetyl chloride** **Acetophenone (95%)**

In addition to those methods already discussed, ketones can also be prepared from certain carboxylic acid derivatives, just as aldehydes can. Among the most useful reactions of this sort is that between an acid chloride and a lithium diorganocopper reagent such as we saw in **Section 10.7**. We'll discuss this reaction in more detail in **Section 21.4**.



$$CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}Cl \xrightarrow[\text{Ether}]{(CH_3)_2Cu^- \ Li^+} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$$

Hexanoyl chloride **2-Heptanone (81%)**

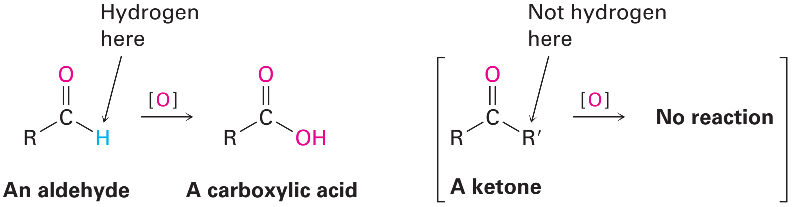
Problem 19.4

How would you carry out the following reactions? More than one step may be required.

(a) 3-Hexyne → 3-Hexanone
(b) Benzene → *m*-Bromoacetophenone
(c) Bromobenzene → Acetophenone
(d) 1-Methylcyclohexene → 2-Methylcyclohexanone

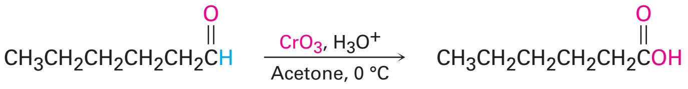
19.3 Oxidation of Aldehydes and Ketones

Aldehydes are easily oxidized to yield carboxylic acids, but ketones are generally inert toward oxidation. The difference is a consequence of structure: aldehydes have a –CHO proton that can be abstracted during oxidation, but ketones do not.



An aldehyde **A carboxylic acid** **A ketone**

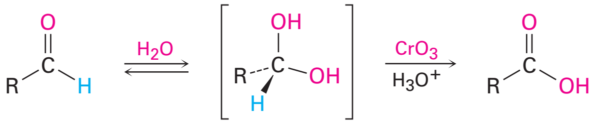
Many oxidizing agents, including $KMnO_4$ and hot HNO_3, convert aldehydes into carboxylic acids, but CrO_3 in aqueous acid is a more common choice. The oxidation occurs rapidly at room temperature and generally results in good yields.



$$CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[\text{Acetone, 0 °C}]{CrO_3,\ H_3O^+} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

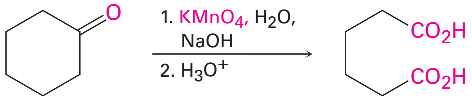
Hexanal **Hexanoic acid (85%)**

Aldehyde oxidations occur through intermediate 1,1-diols, or *hydrates,* which are formed by a reversible nucleophilic addition of water to the carbonyl group. Even though formed to only a small extent at equilibrium, the hydrate reacts like any typical primary or secondary alcohol and is oxidized to a carbonyl compound **(Section 17.7)**.



An aldehyde **A hydrate** **A carboxylic acid**

Ketones are inert to most oxidizing agents but undergo a slow cleavage reaction of the C–C bond next to the carbonyl group when treated with hot alkaline $KMnO_4$. The reaction is not often used and is mentioned here only for completeness.



Cyclohexanone **Hexanedioic acid (79%)**

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

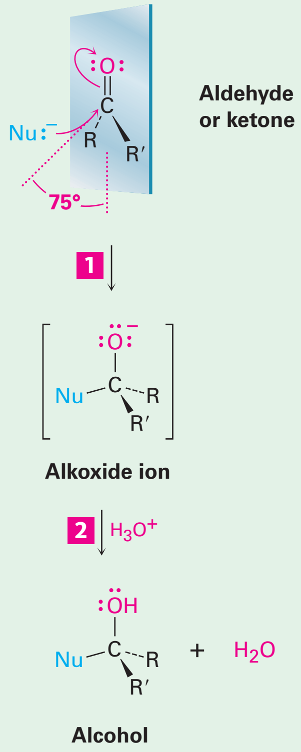
As we saw in the *Preview of Carbonyl Chemistry,* the most general reaction of aldehydes and ketones is the **nucleophilic addition reaction**. As shown in **Figure 19.1**, a nucleophile, :Nu⁻, approaches the carbonyl group from an angle of about 105° opposite the carbonyl oxygen and forms a bond to the electrophilic C=O carbon atom. At the same time, rehybridization of the carbonyl carbon from sp^2 to sp^3 occurs, an electron pair from the C=O bond moves toward the electronegative oxygen atom, and a tetrahedral alkoxide ion intermediate is produced. Protonation of the alkoxide by addition of acid then gives an alcohol.

Figure 19.1 | **MECHANISM**

A nucleophilic addition reaction to an aldehyde or ketone. The nucleophile approaches the carbonyl group from an angle of approximately 75° to the plane of the sp^2 orbitals, the carbonyl carbon rehybridizes from sp^2 to sp^3, and an alkoxide ion is formed. Protonation by addition of acid then gives an alcohol.

1 An electron pair from the nucleophile adds to the electrophilic carbon of the carbonyl group, pushing an electron pair from the C=O bond onto oxygen and giving an alkoxide ion intermediate. The carbonyl carbon rehybridizes from sp^2 to sp^3.

2 Protonation of the alkoxide anion intermediate gives the neutral alcohol addition product.



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The nucleophile can be either negatively charged (**:**Nu$^-$) or neutral (**:**Nu). If it's neutral, however, it usually carries a hydrogen atom that can subsequently be eliminated, **:**Nu–H. For example:

Some negatively charged nucleophiles

- $H\ddot{O}:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $R\ddot{O}:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)

Some neutral nucleophiles

- $H\ddot{O}H$ (water)
- $R\ddot{O}H$ (an alcohol)
- $H_3N:$ (ammonia)
- $R\ddot{N}H_2$ (an amine)

Nucleophilic additions to aldehydes and ketones have two general variations, as shown in **Figure 19.2**. In one variation, the tetrahedral intermediate is protonated by water or acid to give an alcohol as the final product. In the second variation, the carbonyl oxygen atom is protonated and then eliminated as HO$^-$ or H_2O to give a product with a C=Nu double bond.

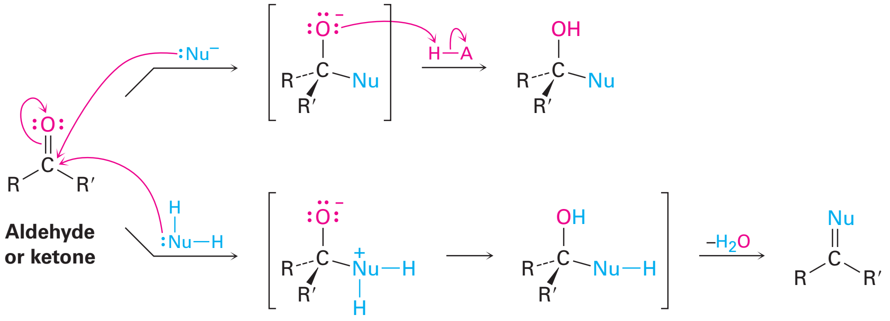


Figure 19.2 Two general reaction pathways following addition of a nucleophile to an aldehyde or ketone. The top pathway leads to an alcohol product; the bottom pathway leads to a product with a C=Nu double bond.

Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons. Sterically, the presence of only one large substituent bonded to the C=O carbon in an aldehyde versus two large substituents in a ketone means that a nucleophile is able to approach an aldehyde more readily. Thus, the transition state leading to the tetrahedral intermediate is less crowded and lower in energy for an aldehyde than for a ketone **(Figure 19.3)**.

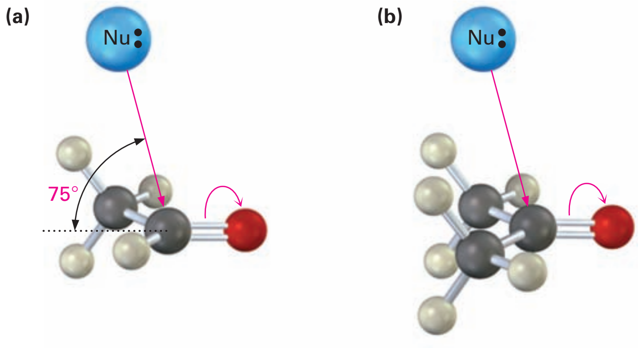
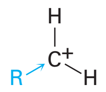
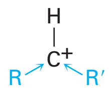


Figure 19.3 **(a)** Nucleophilic addition to an aldehyde is sterically less hindered because only one relatively large substituent is attached to the carbonyl-group carbon. **(b)** A ketone, however, has two large substituents and is more hindered. The approach of the nucleophile is along the C=O bond at an angle of about 75° to the plane of the carbon *sp*^{2} orbitals.

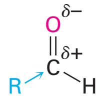
Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde carbonyl groups. To see this polarity difference, recall the stability order of carbocations **(Section 7.9)**. A primary carbocation is higher in energy and thus more reactive than a secondary carbocation because it has only one alkyl group inductively stabilizing the positive charge rather than two. In the same way, an aldehyde has only one alkyl group inductively stabilizing the partial positive charge on the carbonyl carbon rather than two, is a bit more electrophilic, and is therefore more reactive than a ketone.



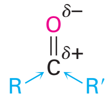
1° carbocation
(less stable, more reactive)



2° carbocation
(more stable, less reactive)

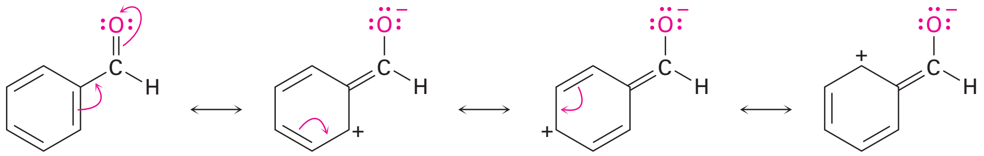


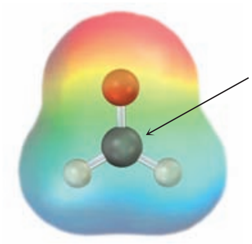
Aldehyde
(less stabilization of δ+, more reactive)



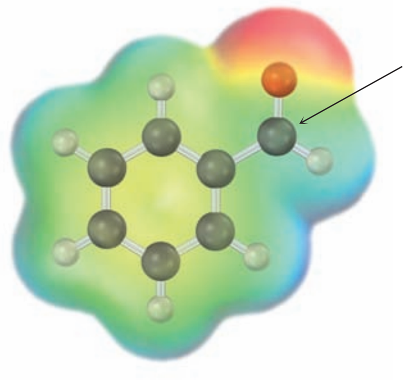
Ketone
(more stabilization of δ+, less reactive)

One further comparison: aromatic aldehydes, such as benzaldehyde, are less reactive in nucleophilic addition reactions than aliphatic aldehydes because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic. Comparing electrostatic potential maps of formaldehyde and benzaldehyde, for example, shows that the carbonyl carbon atom is less positive (less blue) in the aromatic aldehyde.





Formaldehyde



Benzaldehyde

Problem 19.5

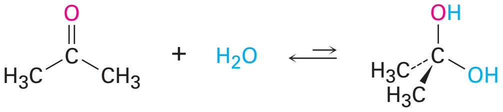
Treatment of an aldehyde or ketone with cyanide ion ($^{-}$**:**C≡N), followed by protonation of the tetrahedral alkoxide ion intermediate, gives a *cyanohydrin*. Show the structure of the cyanohydrin obtained from cyclohexanone.

Problem 19.6

p-Nitrobenzaldehyde is more reactive toward nucleophilic additions than *p*-methoxybenzaldehyde. Explain.

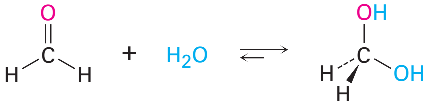
19.5 Nucleophilic Addition of H_2O: Hydration

Aldehydes and ketones react with water to yield 1,1-diols, or *geminal (gem)* diols. The hydration reaction is reversible, and a gem diol can eliminate water to regenerate an aldehyde or ketone.



Acetone (99.9%) **Acetone hydrate (0.1%)**

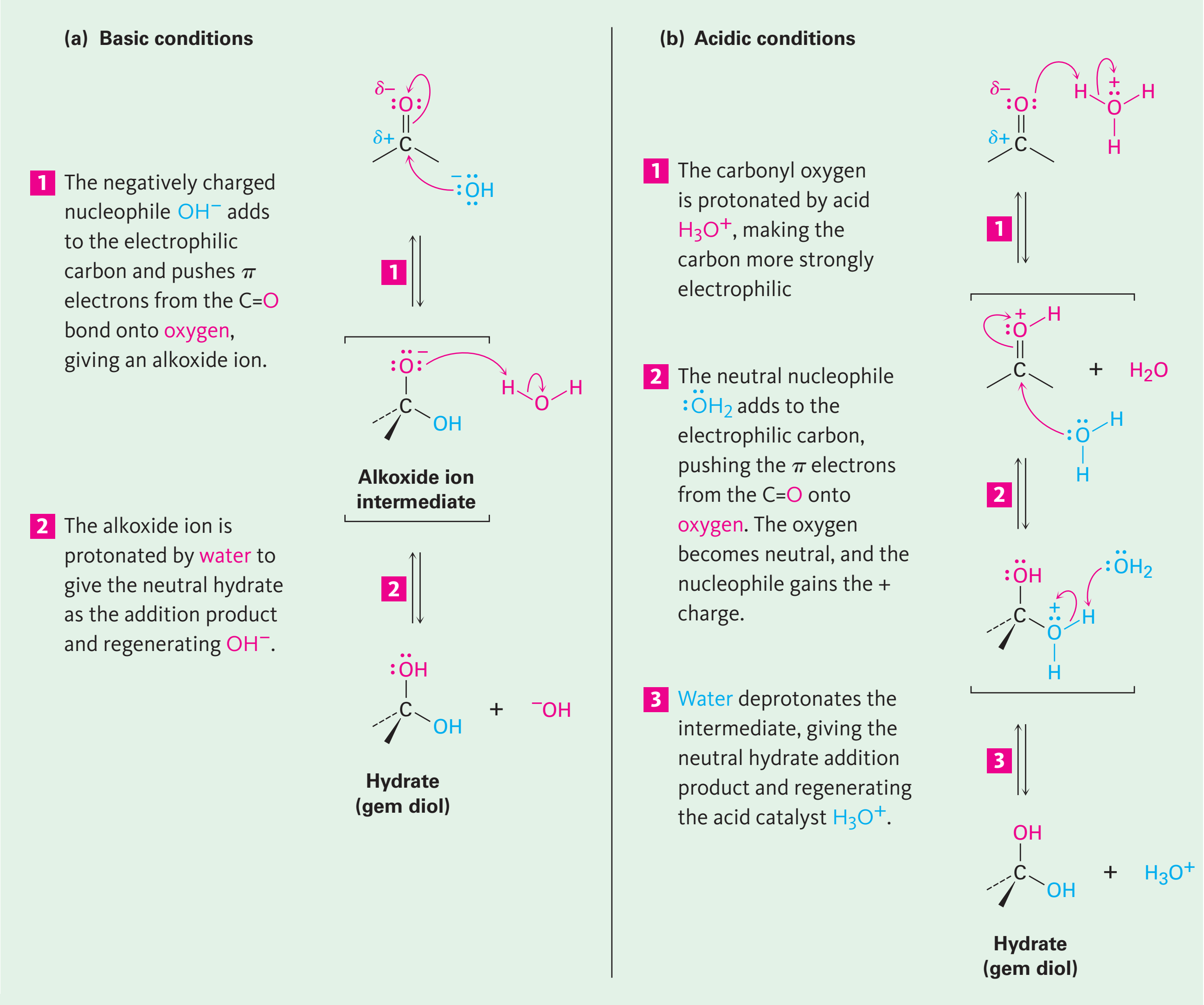
The position of the equilibrium between a gem diol and an aldehyde or ketone depends on the structure of the carbonyl compound. The equilibrium generally favors the carbonyl compound for steric reasons, but the gem diol is favored for a few simple aldehydes. For example, an aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde at equilibrium, whereas an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.



Formaldehyde (0.1%) **Formaldehyde hydrate (99.9%)**

The nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. Under basic conditions **(Figure 19.4a)**, the nucleophile is negatively charged (OH^-) and uses a pair of its electrons to form a bond to the electrophilic carbon atom of the C=O group. At the same time, the C=O carbon atom rehybridizes from *sp*^{2} to *sp*^{3} and two electrons from the C=O π bond are pushed onto the oxygen atom, giving an alkoxide ion. Protonation of the alkoxide ion by water then yields a neutral addition product plus regenerated OH^-.

Under acidic conditions **(Figure 19.4b)**, the carbonyl oxygen atom is first protonated by H_3O^+ to make the carbonyl group more strongly electrophilic. A neutral nucleophile, H_2O, then uses a pair of electrons to bond to the carbon atom of the C=O group, and two electrons from the C=O π bond move onto the oxygen atom. The positive charge on oxygen is thereby neutralized, while the nucleophile gains a positive charge. Finally, deprotonation by water gives the neutral addition product and regenerates the H_3O^+ catalyst.



(a) Basic conditions

1 The negatively charged nucleophile OH^- adds to the electrophilic carbon and pushes π electrons from the C=O bond onto oxygen, giving an alkoxide ion.

2 The alkoxide ion is protonated by water to give the neutral hydrate as the addition product and regenerating OH^-.

(b) Acidic conditions

1 The carbonyl oxygen is protonated by acid H_3O^+, making the carbon more strongly electrophilic

2 The neutral nucleophile $:\ddot{O}H_2$ adds to the electrophilic carbon, pushing the π electrons from the C=O onto oxygen. The oxygen becomes neutral, and the nucleophile gains the + charge.

3 Water deprotonates the intermediate, giving the neutral hydrate addition product and regenerating the acid catalyst H_3O^+.

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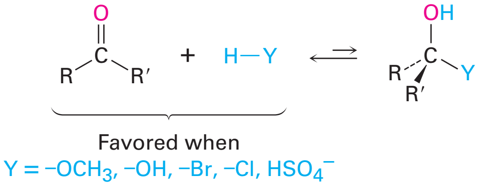
Figure 19.4 | **MECHANISM**

The mechanism of a nucleophilic addition reaction of aldehydes and ketones under both basic and acidic conditions. **(a)** Under basic conditions, a negatively charged nucleophile adds to the carbonyl group to give an alkoxide ion intermediate, which is subsequently protonated. **(b)** Under acidic conditions, protonation of the carbonyl group occurs first, followed by addition of a neutral nucleophile and subsequent deprotonation.

Note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction takes place rapidly because water is converted into hydroxide ion, a much better *nucleophile*. The acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation into a much better *electrophile*.

The hydration reaction just described is typical of what happens when an aldehyde or ketone is treated with a nucleophile of the type H–Y, where the Y atom is electronegative and can stabilize a negative charge (oxygen, halogen, or sulfur, for instance). In such reactions, the nucleophilic addition is reversible, with the equilibrium generally favoring the carbonyl reactant rather than the tetrahedral addition product. In other words, treatment of an aldehyde or ketone with CH_3OH, H_2O, HCl, HBr, or H_2SO_4 does not normally lead to a stable alcohol addition product.



Problem 19.7

When dissolved in water, trichloroacetaldehyde exists primarily as its hydrate, called chloral hydrate. Show the structure of chloral hydrate.

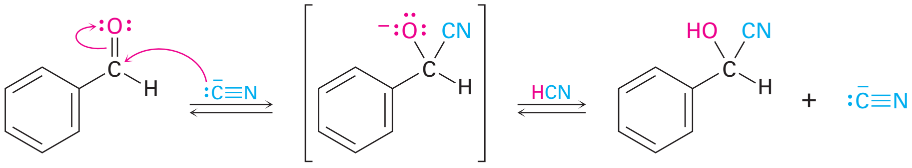
Problem 19.8

The oxygen in water is primarily (99.8%) ^{16}O, but water enriched with the heavy isotope ^{18}O is also available. When an aldehyde or ketone is dissolved in ^{18}O-enriched water, the isotopic label becomes incorporated into the carbonyl group. Explain.

$$R_2C{=}O + H_2\mathbf{O} \rightleftarrows R_2C{=}\mathbf{O} + H_2O \qquad \text{where } \mathbf{O} = {}^{18}O$$

19.6 Nucleophilic Addition of HCN: Cyanohydrin Formation

Aldehydes and unhindered ketones undergo a nucleophilic addition reaction with HCN to yield **cyanohydrins, RCH(OH)C≡N**. Studies carried out in the early 1900s by Arthur Lapworth showed that cyanohydrin formation is reversible and base-catalyzed. Reaction occurs slowly when pure HCN is used but rapidly when a small amount of base is added to generate the nucleophilic cyanide ion, CN^-. Addition of CN^- takes place by a typical nucleophilic addition pathway, yielding a tetrahedral intermediate that is protonated by HCN to give cyanohydrin product plus regenerated CN^-.

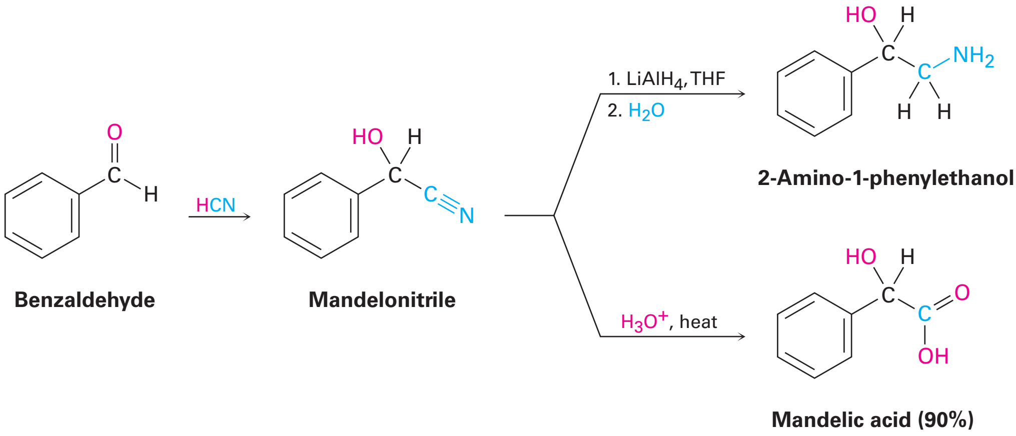


Benzaldehyde **Tetrahedral intermediate** **Mandelonitrile (88%)**

Cyanohydrin formation is somewhat unusual because it is one of the few examples of the addition of a protic acid (H–Y) to a carbonyl group. As noted in the previous section, protic acids such as H_2O, HBr, HCl, and H_2SO_4 don't normally yield carbonyl addition products because the equilibrium constants are unfavorable. With HCN, however, the equilibrium favors the cyanohydrin adduct.

Cyanohydrin formation is useful because of the further chemistry that can be carried out on the product. For example, a nitrile (R–C≡N) can be reduced with

$LiAlH_4$ to yield a primary amine (RCH_2NH_2) and can be hydrolyzed by hot aqueous acid to yield a carboxylic acid. Thus, cyanohydrin formation provides a method for transforming an aldehyde or ketone into a different functional group.



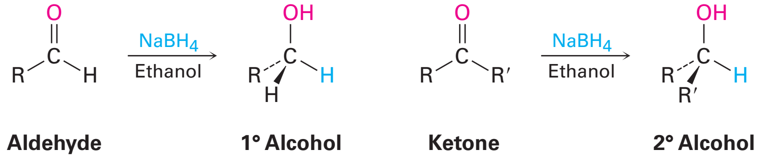
Problem 19.9

Cyclohexanone forms a cyanohydrin in good yield but 2,2,6-trimethylcyclohexanone does not. Explain.

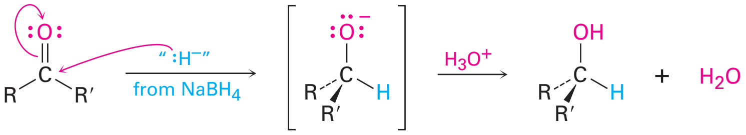
19.7 Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation

Addition of Hydride Reagents: Reduction

We saw in **Section 17.4** that the most common method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of carbonyl compounds. Aldehydes are reduced with sodium borohydride ($NaBH_4$) to give primary alcohols, and ketones are reduced similarly to give secondary alcohols.



Carbonyl reduction occurs by a typical nucleophilic addition mechanism under basic conditions, as shown previously in Figure 19.4a. Although the details of carbonyl-group reductions are complex, $LiAlH_4$ and $NaBH_4$ act as if they were donors of hydride ion nucleophile, **:**H^-, and the initially formed alkoxide ion intermediate is then protonated by addition of aqueous acid. The reaction is effectively irreversible because the reverse process would require expulsion of a very poor leaving group.



Addition of Grignard Reagents, RMgX

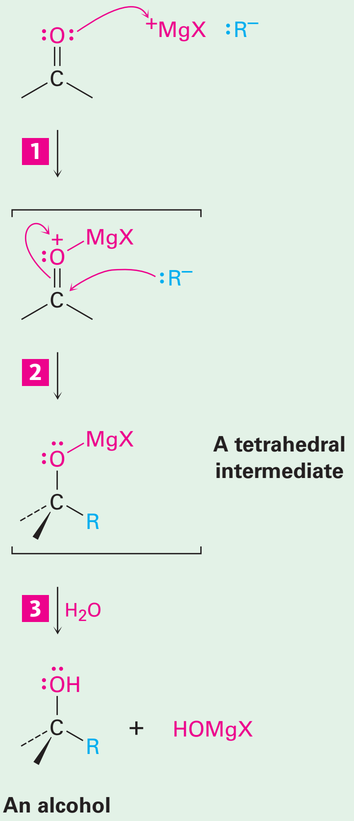
Just as aldehydes and ketones undergo nucleophilic addition with hydride ion to give alcohols, they undergo a similar addition with Grignard reagent nucleophiles, R:⁻ ⁺MgX. Aldehydes give secondary alcohols on reaction with Grignard reagents in ether solution, and ketones give tertiary alcohols.

Aldehyde **2° Alcohol** **Ketone** **3° Alcohol**

As shown in **Figure 19.5**, a Grignard reaction begins with an acid–base complexation of Mg^{2+} to the carbonyl oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better electrophile. Nucleophilic addition of R:⁻ then produces a tetrahedral magnesium alkoxide intermediate, and protonation by addition of water or dilute aqueous acid in a separate step yields the neutral alcohol. Like reduction, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

Figure 19.5 | **MECHANISM**

Mechanism of the Grignard reaction. Complexation of the carbonyl oxygen with the Lewis acid Mg^{2+} and subsequent nucleophilic addition of a carbanion to an aldehyde or ketone is followed by protonation of the alkoxide intermediate to yield an alcohol.



1 The Lewis acid Mg^{2+} first forms an acid–base complex with the basic oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better acceptor.

2 Nucleophilic addition of an alkyl group :R⁻ to the aldehyde or ketone produces a tetrahedral magnesium alkoxide intermediate . . .

3 . . . which undergoes hydrolysis when water is added in a separate step. The final product is a neutral alcohol.

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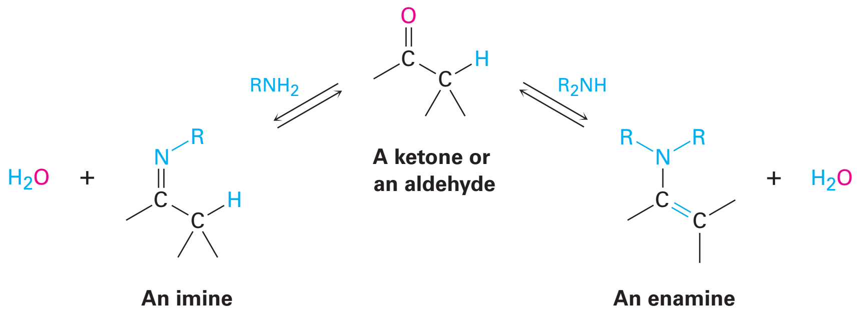
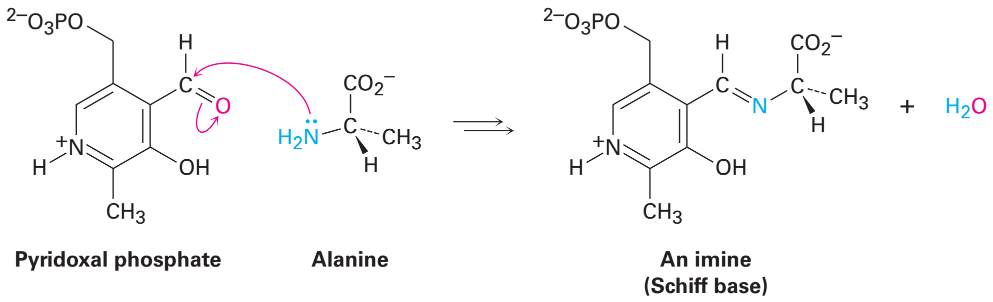
19.8 Nucleophilic Addition of Amines: Imine and Enamine Formation

Primary amines, RNH_2, add to aldehydes and ketones to yield **imines, $R_2C{=}NR$**. Secondary amines, R_2NH, add similarly to yield **enamines, $R_2N{-}CR{=}CR_2$** (*ene* + *amine* = unsaturated amine).



Imines are particularly common as intermediates in many biological pathways, where they are often called **Schiff bases**. The amino acid alanine, for instance, is metabolized in the body by reaction with the aldehyde pyridoxal phosphate (PLP), a derivative of vitamin B_6, to yield a Schiff base that is further degraded.

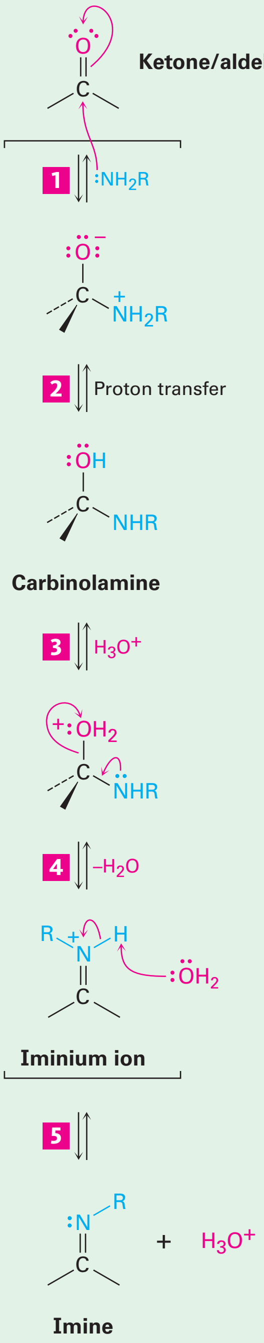


Imine formation and enamine formation appear different because one leads to a product with a C=N bond and the other leads to a product with a C=C bond. Actually, though, the reactions are quite similar. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new C=Nu double bond is formed.

Imines are formed in a reversible, acid-catalyzed process **(Figure 19.6)** that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or *carbinolamine*. Protonation of the carbinolamine oxygen by an acid catalyst then converts the −OH into a better leaving group ($-OH_2^+$), and E1-like loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst.

Figure 19.6 | **MECHANISM**

Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is the initial nucleophilic addition to yield a carbinolamine intermediate, which then loses water to give the imine.



1 Nucleophilic attack on the ketone or aldehyde by the lone-pair electrons of an amine leads to a dipolar tetrahedral intermediate.

2 A proton is then transferred from nitrogen to oxygen, yielding a neutral carbinolamine.

3 Acid catalyst protonates the hydroxyl oxygen.

4 The nitrogen lone-pair electrons expel water, giving an iminium ion.

5 Loss of H^+ from nitrogen then gives the neutral imine product.

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Imine formation with such reagents as hydroxylamine and 2,4-dinitrophenylhydrazine is sometimes useful because the products of these reactions—*oximes* and *2,4-dinitrophenylhydrazones (2,4-DNPs)*, respectively—are often crystalline and easy to handle. Such crystalline derivatives are occasionally prepared as a means of purifying and characterizing liquid ketones or aldehydes.

Oxime

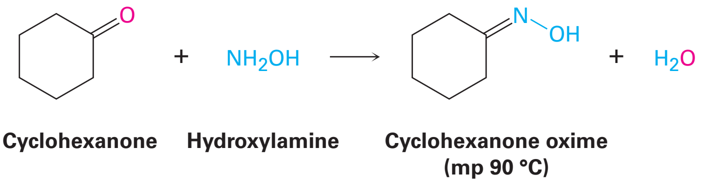


Figure 19.7 | **MECHANISM**

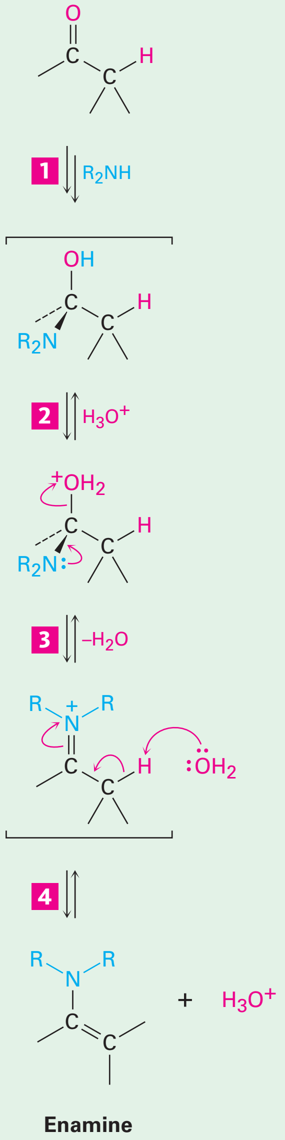
Mechanism of enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH. The iminium ion intermediate formed in step 3 has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.

1 Nucleophilic addition of a secondary amine to the ketone or aldehyde, followed by proton transfer from nitrogen to oxygen, yields an intermediate carbinolamine in the normal way.

2 Protonation of the hydroxyl by acid catalyst converts it into a better leaving group.

3 Elimination of water by the lone-pair electrons on nitrogen then yields an intermediate iminium ion.

4 Loss of a proton from the alpha carbon atom yields the enamine product and regenerates the acid catalyst.



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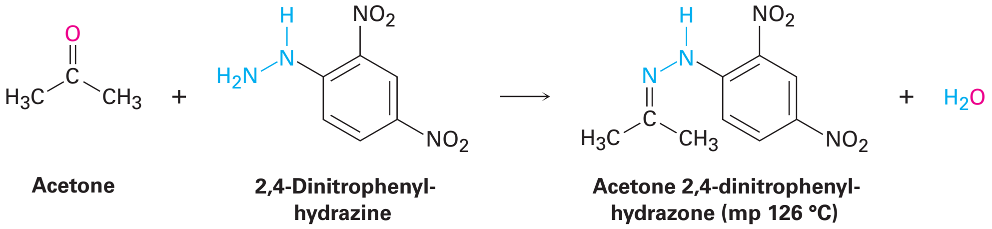
2,4-Dinitrophenylhydrazone



Reaction of an aldehyde or ketone with a secondary amine, R_2NH, rather than a primary amine yields an enamine. As shown in **Figure 19.7**, the process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the α carbon), yielding an enamine.

Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. For example, the profile of pH versus rate shown in **Figure 19.8** for the reaction between acetone and hydroxylamine, NH_2OH, indicates that the maximum reaction rate is obtained at pH 4.5.

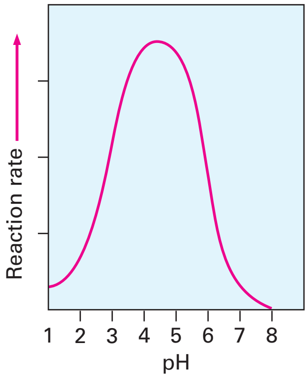


Figure 19.8 Dependence on pH of the rate of reaction between acetone and hydroxylamine: $(CH_3)_2C{=}O + NH_2OH \rightarrow (CH_3)_2C{=}NOH + H_2O$.

We can explain the observed pH dependence of imine formation by looking at the individual steps in the mechanism. As indicated in Figure 19.7, an acid catalyst is required in step 3 to protonate the intermediate carbinolamine, thereby converting the –OH into a better leaving group. Thus, reaction will be slow if not enough acid is present (that is, at high pH). On the other hand, if too much acid is present (low pH), the basic amine nucleophile is completely protonated, so the initial nucleophilic addition step can't occur.

Evidently, a pH of 4.5 represents a compromise between the need for *some* acid to catalyze the rate-limiting dehydration step but *not too much* acid so as to avoid complete protonation of the amine. Each individual nucleophilic addition reaction has its own requirements, and reaction conditions must be optimized to obtain maximum reaction rates.

Worked Example 19.1

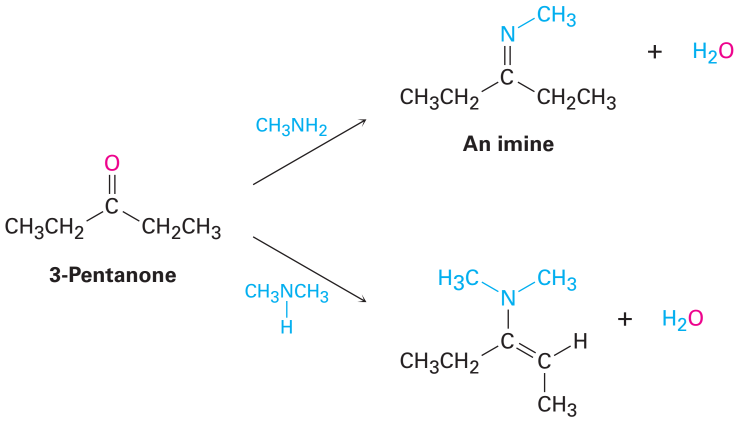
Predicting the Product of Reaction between a Ketone and an Amine

Show the products you would obtain by acid-catalyzed reaction of 3-pentanone with methylamine, CH_3NH_2, and with dimethylamine, $(CH_3)_2NH$.

Strategy

An aldehyde or ketone reacts with a primary amine, RNH_2, to yield an imine, in which the carbonyl oxygen atom has been replaced by the =N–R group of the amine. Reaction of the same aldehyde or ketone with a secondary amine, R_2NH, yields an enamine, in which the oxygen atom has been replaced by the $–NR_2$ group of the amine and the double bond has moved to a position between the former carbonyl carbon and the neighboring carbon.

Solution



An imine

An enamine

Problem 19.10

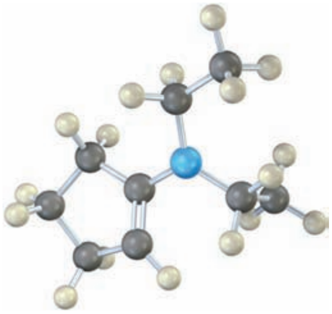
Show the products you would obtain by acid-catalyzed reaction of cyclohexanone with ethylamine, $CH_3CH_2NH_2$, and with diethylamine, $(CH_3CH_2)_2NH$.

Problem 19.11

Imine formation is reversible. Show all the steps involved in the acid-catalyzed reaction of an imine with water (hydrolysis) to yield an aldehyde or ketone plus primary amine.

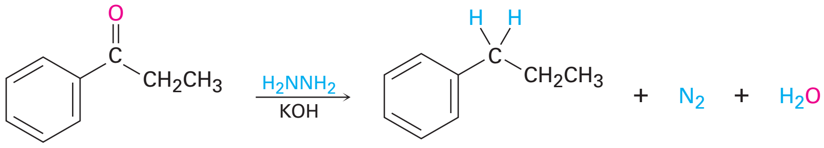
Problem 19.12

Draw the following molecule as a skeletal structure, and show how it can be prepared from a ketone and an amine.



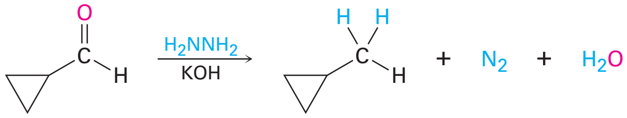
19.9 Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction

A useful variant of the imine-forming reaction just discussed involves the treatment of an aldehyde or ketone with hydrazine, H_2NNH_2, in the presence of KOH. Called the **Wolff–Kishner reaction**, the process is a useful and general method for converting an aldehyde or ketone into an alkane, $R_2C{=}O \rightarrow R_2CH_2$.



Propiophenone

Propylbenzene (82%)



Cyclopropane-carbaldehyde

Methylcyclo-propane (72%)

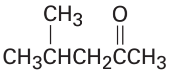
As shown in **Figure 19.9**, the Wolff–Kishner reaction involves formation of a *hydrazone* intermediate, $R_2C{=}NNH_2$, followed by base-catalyzed double-bond migration, loss of N_2 gas to give a carbanion, and protonation to give the alkane product. The double-bond migration takes place when base removes one of the weakly acidic NH protons in step 2 to generate a hydrazone anion, which has an allylic resonance structure that places the double bond between nitrogens and the negative charge on carbon. Reprotonation then occurs on carbon to generate the double-bond rearrangement product. The next step—loss of nitrogen and formation of an alkyl anion—is driven by the large thermodynamic stability of the N_2 molecule.

Note that the Wolff–Kishner reduction accomplishes the same overall transformation as the catalytic hydrogenation of an acylbenzene to yield an alkylbenzene **(Section 16.10)**. The Wolff–Kishner reduction is more general and more useful than catalytic hydrogenation, however, because it works well with both alkyl and aryl ketones.

Problem 19.13

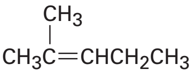
Show how you could prepare the following compounds from 4-methyl-3-penten-2-one, $(CH_3)_2C{=}CHCOCH_3$.

(a)



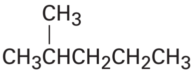
$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}CH_3$

(b)



$CH_3\overset{\overset{CH_3}{|}}{C}{=}CHCH_2CH_3$

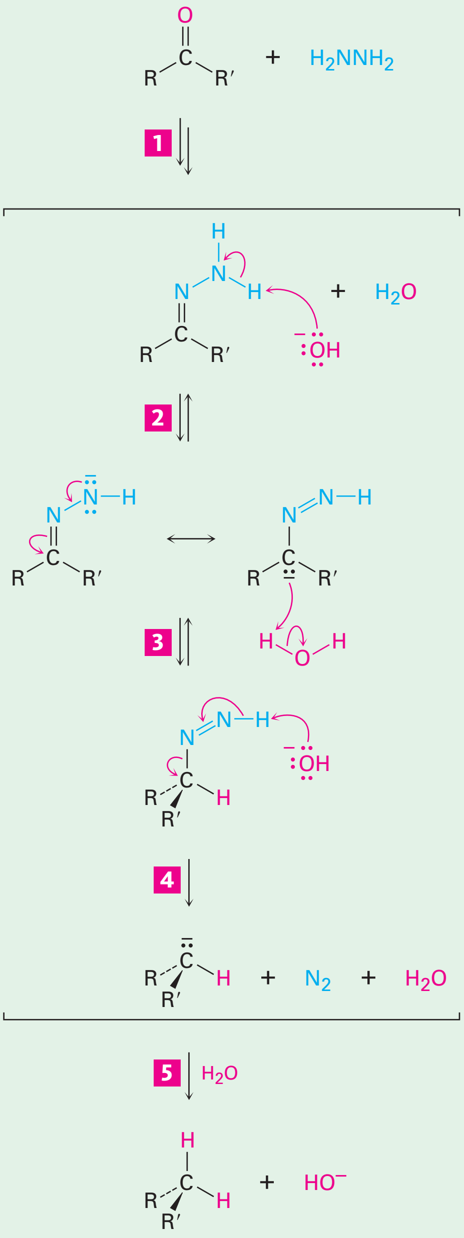
(c)



$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2CH_2CH_3$

Figure 19.9 | **MECHANISM**

Mechanism of the Wolff–Kishner reduction of an aldehyde or ketone to yield an alkane.



1 Reaction of the aldehyde or ketone with hydrazine yields a hydrazone in the normal way.

2 Base abstracts a weakly acidic N–H proton, yielding a hydrazone anion. This anion has a resonance form that places the negative charge on carbon and the double bond between nitrogens.

3 Protonation of the hydrazone anion takes place on carbon to yield a neutral intermediate.

4 Deprotonation of the remaining weakly acidic N–H occurs with simultaneous loss of nitrogen to give a carbanion . . .

5 . . . which is protonated to give the alkane product.

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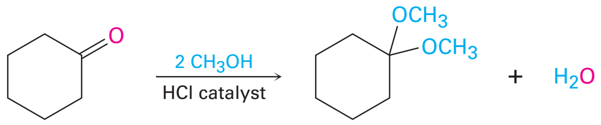
19.10 Nucleophilic Addition of Alcohols: Acetal Formation

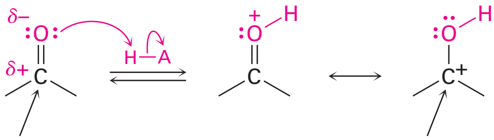
Aldehydes and ketones react reversibly with 2 equivalents of an alcohol in the presence of an acid catalyst to yield **acetals, $R_2C(OR')_2$**, frequently called *ketals* if derived from a ketone. Cyclohexanone, for instance, reacts with methanol in the presence of HCl to give the corresponding dimethyl acetal.



Cyclohexanone

Cyclohexanone dimethyl acetal

Acetal formation is similar to the hydration reaction discussed in **Section 19.5**. Like water, alcohols are weak nucleophiles that add to aldehydes and ketones only slowly under neutral conditions. Under acidic conditions, however, the reactivity of the carbonyl group is increased by protonation, so addition of an alcohol occurs rapidly.



A neutral carbonyl group is moderately electrophilic because of the polarity of the C–O bond.

A protonated carbonyl group is strongly electrophilic because of the positive charge on carbon.

As shown in **Figure 19.10**, nucleophilic addition of an alcohol to the carbonyl group initially yields a hydroxy ether called a **hemiacetal**, analogous to the gem diol formed by addition of water. Hemiacetals are formed reversibly, with the equilibrium normally favoring the carbonyl compound. In the presence of acid, however, a further reaction occurs. Protonation of the −OH group, followed by an E1-like loss of water, leads to an oxonium ion, $R_2C{=}OR^+$, which undergoes a second nucleophilic addition of alcohol to yield the protonated acetal. Loss of a proton completes the reaction.

Because all the steps in acetal formation are reversible, the reaction can be driven either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the conditions. The forward reaction is favored by conditions that remove water from the medium and thus drive the equilibrium to the right. In practice, this is often done by distilling off water as it forms. The reverse reaction is favored by treating the acetal with a large excess of aqueous acid to drive the equilibrium to the left.

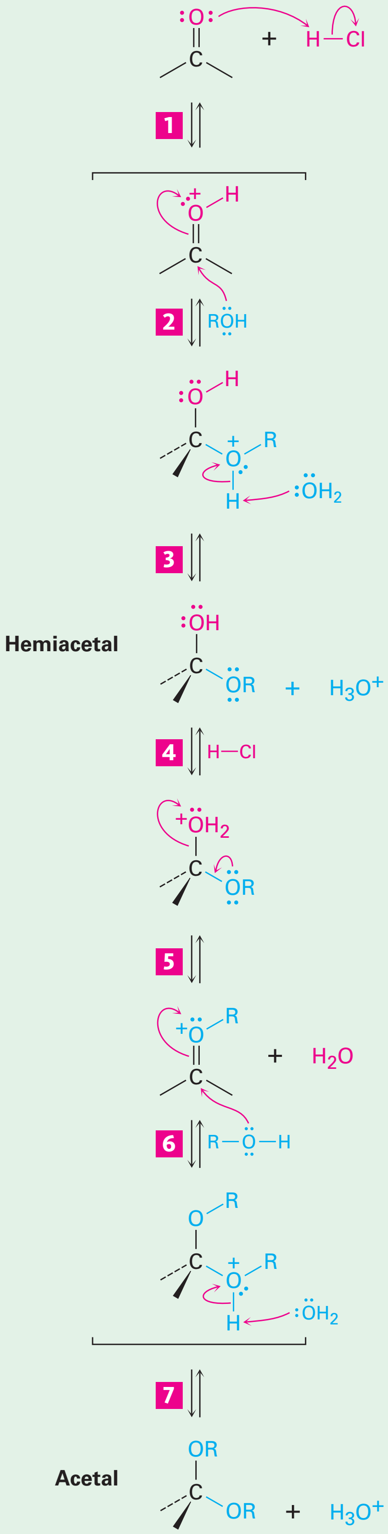
Acetals are useful because they can act as protecting groups for aldehydes and ketones in the same way that trimethylsilyl ethers act as protecting groups for alcohols **(Section 17.8)**. As we saw previously, it sometimes happens that one functional group interferes with intended chemistry elsewhere in a complex molecule. For example, if we wanted to reduce only the ester group of ethyl 4-oxopentanoate, the ketone would interfere. Treatment of the starting keto ester with $LiAlH_4$ would reduce both the keto and the ester groups to give a diol product.

$$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow{?} CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2OH$$

Ethyl 4-oxopentanoate **5-Hydroxy-2-pentanone**

Figure 19.10 | **MECHANISM**

Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.



1 Protonation of the carbonyl oxygen strongly polarizes the carbonyl group and . . .

2 . . . activates the carbonyl group for nucleophilic attack by oxygen lone-pair electrons from the alcohol.

3 Loss of a proton yields a neutral hemiacetal tetrahedral intermediate.

4 Protonation of the hemiacetal hydroxyl converts it into a good leaving group.

5 Dehydration yields an intermediate oxonium ion.

6 Addition of a second equivalent of alcohol gives a protonated acetal.

7 Loss of a proton yields the neutral acetal product.

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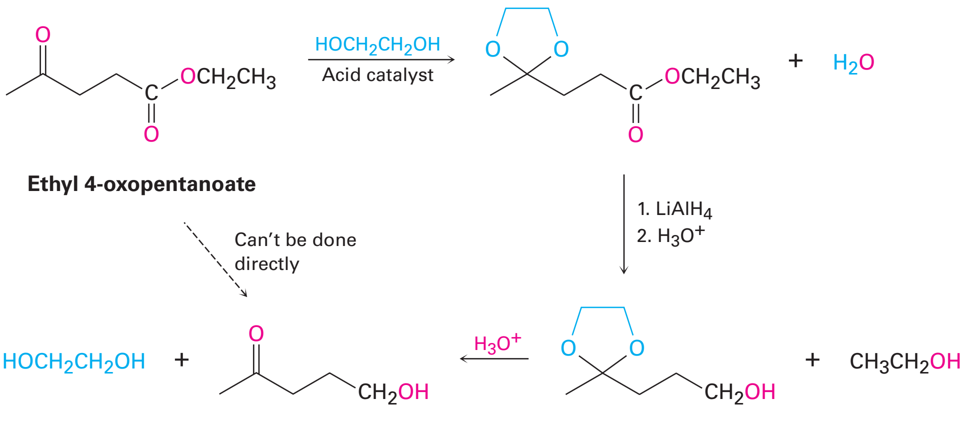
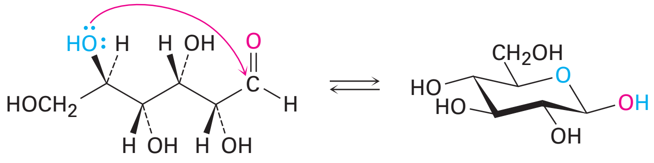
By protecting the keto group as an acetal, however, the problem can be circumvented. Like other ethers, acetals are unreactive to bases, hydride reducing agents, Grignard reagents, and catalytic hydrogenation conditions, but they are cleaved by acid. Thus, we can accomplish the selective reduction of the ester group in ethyl 4-oxopentanoate by first converting the keto group to an acetal, then reducing the ester with $LiAlH_4$, and then removing the acetal by treatment with aqueous acid. (In practice, it's often convenient to use 1 equivalent of a diol such as ethylene glycol as the alcohol and to form a *cyclic* acetal. The mechanism of cyclic acetal formation using 1 equivalent of ethylene glycol is exactly the same as that using 2 equivalents of methanol or other monoalcohol.)



Ethyl 4-oxopentanoate

5-Hydroxy-2-pentanone

Acetal and hemiacetal groups are particularly common in carbohydrate chemistry. Glucose, for instance, is a polyhydroxy aldehyde that undergoes an *internal* nucleophilic addition reaction and exists primarily as a cyclic hemiacetal.



Glucose—open chain

Glucose—cyclic hemiacetal

Predicting the Product of Reaction between a Ketone and an Alcohol

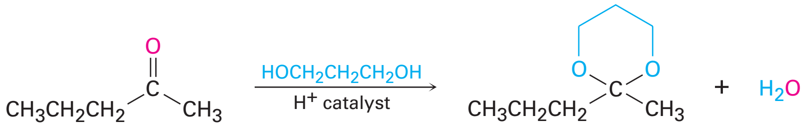
Worked Example 19.2

Show the structure of the acetal you would obtain by acid-catalyzed reaction of 2-pentanone with 1,3-propanediol.

Strategy

Acid-catalyzed reaction of an aldehyde or ketone with 2 equivalents of a monoalcohol or 1 equivalent of a diol yields an acetal, in which the carbonyl oxygen atom is replaced by two —OR groups from the alcohol.

Solution



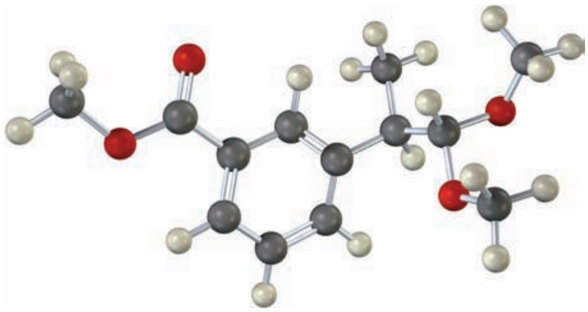
2-Pentanone

Problem 19.14

Show all the steps in the acid-catalyzed formation of a cyclic acetal from ethylene glycol and an aldehyde or ketone.

Problem 19.15

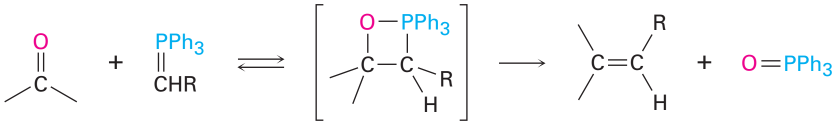
Identify the carbonyl compound and the alcohol that were used to prepare the following acetal:



19.11 Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction

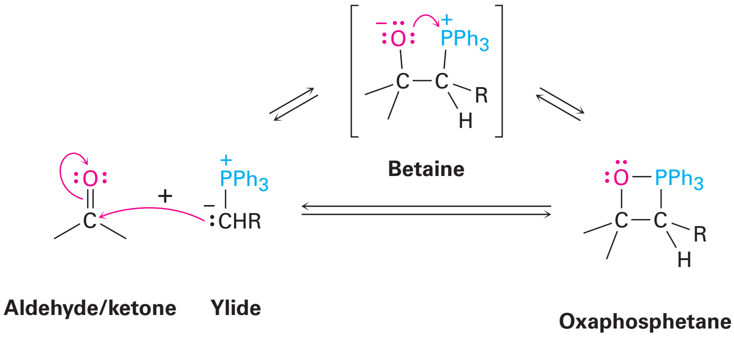
Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition called the **Wittig reaction**. The reaction has no direct biological counterpart but is important both because of its wide use in the laboratory and drug manufacture and because of its mechanistic similarity to reactions of the coenzyme thiamin diphosphate, which we'll see in **Section 29.6**.

In the Wittig reaction, a triphenylphosphorus *ylide,* $R_2\bar{C}-\overset{+}{P}Ph_3$, also called a *phosphorane* and sometimes written in the resonance form $R_2C{=}PPh_3$, adds to an aldehyde or ketone to yield a four-membered cyclic intermediate called an *oxaphosphetane*. The oxaphosphetane is not isolated, but instead spontaneously decomposes to give an alkene plus triphenylphosphine oxide, $O{=}PPh_3$. In effect, the oxygen atom of the aldehyde or ketone and the $R_2C{=}$ bonded to phosphorus exchange places. (An **ylide**—pronounced **ill**-id—is a neutral, dipolar compound with adjacent plus and minus charges.)

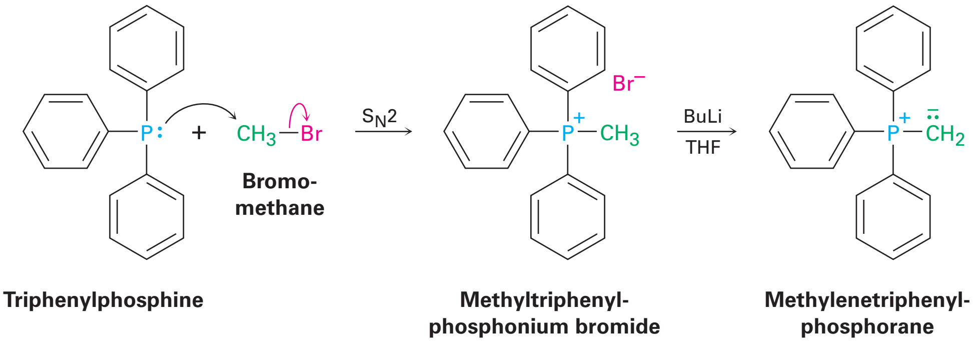


Aldehyde/ketone **Ylide** **Oxaphosphetane** **Alkene** **Triphenylphosphine oxide**

The initial addition step appears to take place by different pathways depending on the structure of the reactants and the exact experimental conditions. One pathway involves a one-step cycloaddition process analogous to the Diels–Alder cycloaddition reaction **(Section 14.4)**. The other pathway involves a nucleophilic addition reaction to give a dipolar intermediate called a *betaine* (**bay**-ta-een), which undergoes ring closure.

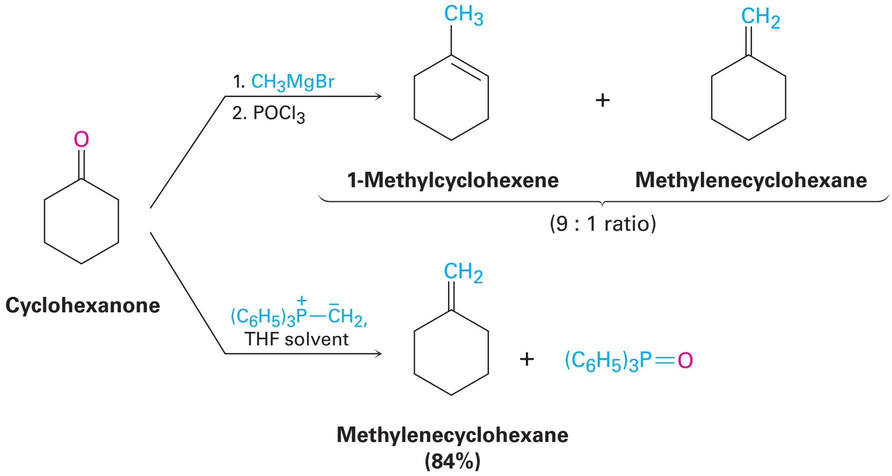


The phosphorus ylides necessary for Wittig reaction are easily prepared by S_N2 reaction of primary (and some secondary) alkyl halides with triphenylphosphine, $(Ph)_3P$, followed by treatment with base. Triphenylphosphine is a good nucleophile in S_N2 reactions, and yields of the resultant alkyltriphenylphosphonium salts are high. Because of the positive charge on phosphorus, the hydrogen on the neighboring carbon is weakly acidic and can be removed by a strong base such as butyllithium (BuLi) to generate the neutral ylide. For example:

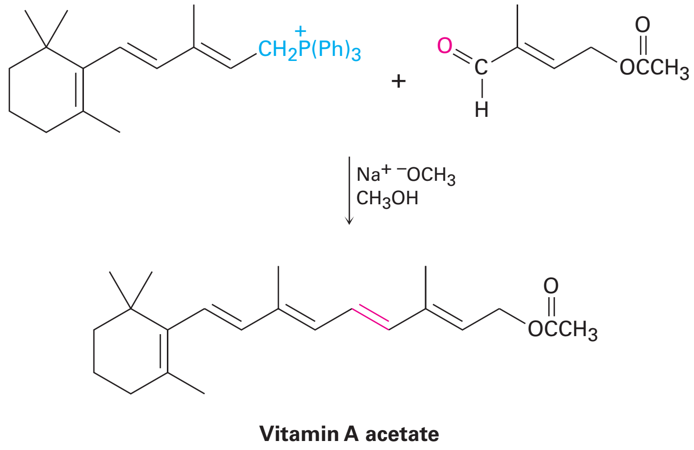


The Wittig reaction is extremely general, and a great many monosubstituted, disubstituted, and trisubstituted alkenes can be prepared from the appropriate combination of phosphorane and aldehyde or ketone. Tetrasubstituted alkenes can't be prepared, however, because of steric hindrance during the reaction.

The real value of the Wittig reaction is that it yields a pure alkene of predictable structure. The C=C bond in the product is always exactly where the C=O group was in the reactant, and no alkene isomers (except E,Z isomers) are formed. For example, Wittig reaction of cyclohexanone with methylenetriphenylphosphorane yields only the single alkene product methylenecyclohexane. By contrast, addition of methylmagnesium bromide to cyclohexanone, followed by dehydration with $POCl_3$, yields a roughly 9:1 mixture of two alkenes.



Wittig reactions are used commercially in the synthesis of numerous pharmaceutical agents. For example, the German chemical company BASF prepares vitamin A by Wittig reaction between a 15-carbon ylide and a 5-carbon aldehyde.



Worked Example 19.3

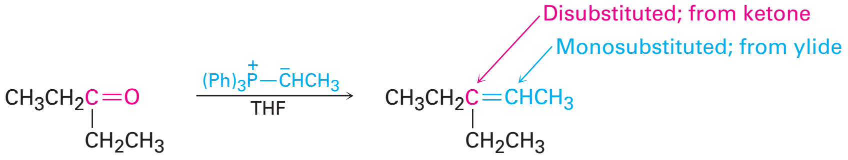
Synthesizing an Alkene Using a Wittig Reaction

What carbonyl compound and what phosphorus ylide might you use to prepare 3-ethyl-2-pentene?

Strategy

An aldehyde or ketone reacts with a phosphorus ylide to yield an alkene in which the oxygen atom of the carbonyl reactant is replaced by the $=CR_2$ of the ylide. Preparation of the phosphorus ylide itself usually involves S_N2 reaction of a primary alkyl halide with triphenylphosphine, so the ylide is typically primary, RCH$=$P(Ph)$_3$. This means that the disubstituted alkene carbon in the product comes from the carbonyl reactant, while the monosubstituted alkene carbon comes from the ylide.

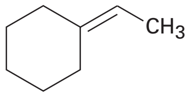
Solution

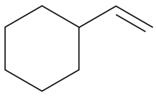


3-Pentanone **3-Ethyl-2-pentene**

Problem 19.16

What carbonyl compound and what phosphorus ylide might you use to prepare each of the following compounds?

(a)


(b)


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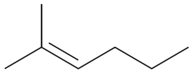

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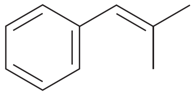
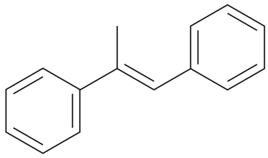
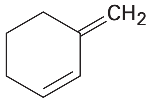
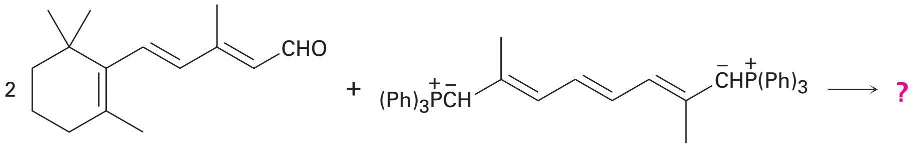


(e)


(f)


Problem 19.17

β-Carotene, a yellow food-coloring agent and dietary source of vitamin A can be prepared by a *double* Wittig reaction between 2 equivalents of *β*-ionylideneacetaldehyde and a *diylide*. Show the structure of the *β*-carotene product.



***β*-Ionylideneacetaldehyde** **A diylide**

19.12 Biological Reductions

As a general rule, nucleophilic addition reactions are characteristic only of aldehydes and ketones, not of carboxylic acid derivatives. The reason for the difference is structural. As discussed previously in the *Preview of Carbonyl Compounds* and shown in **Figure 19.11**, the tetrahedral intermediate produced by addition of a nucleophile to a carboxylic acid derivative can eliminate a leaving group, leading to a net nucleophilic acyl substitution reaction.

The tetrahedral intermediate produced by addition of a nucleophile to an aldehyde or ketone, however, has only alkyl or hydrogen substituents and thus can't usually expel a leaving group. One exception to this rule, however, is the **Cannizzaro reaction**, discovered in 1853.

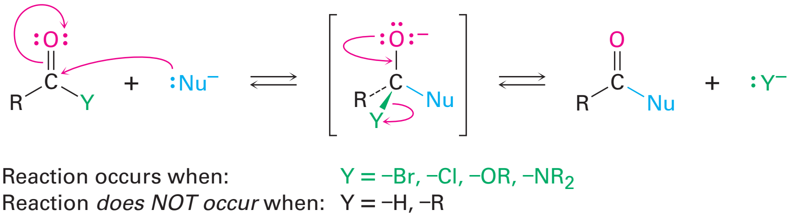
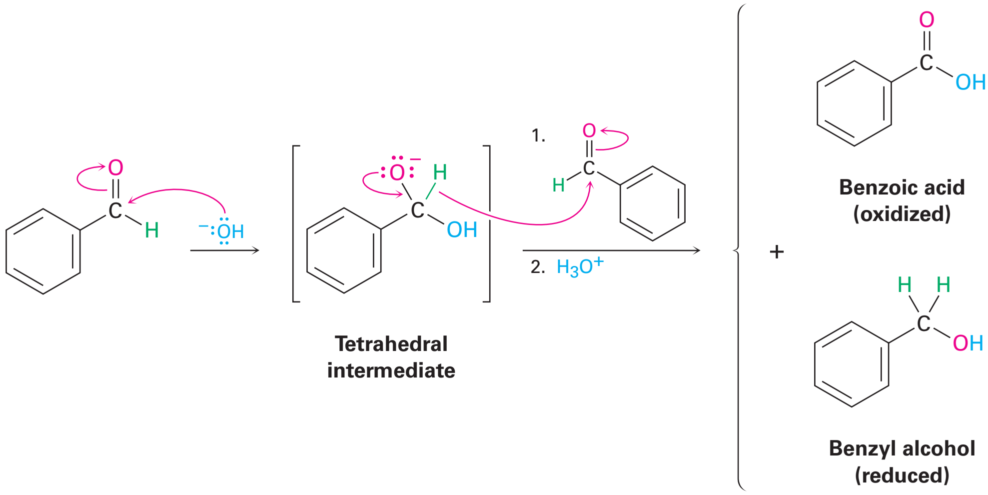


Figure 19.11 Carboxylic acid derivatives have an electronegative substituent Y = —Br, —Cl, —OR, —NR_2 that can be expelled as a leaving group from the tetrahedral intermediate formed by nucleophilic addition. Aldehydes and ketones have no such leaving group and thus do not usually undergo this reaction.

The Cannizzaro reaction takes place by nucleophilic addition of OH^- to an aldehyde to give a tetrahedral intermediate, *which expels hydride ion as a leaving group* and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced. Benzaldehyde, for instance, yields benzyl alcohol plus benzoic acid when heated with aqueous NaOH.



The Cannizzaro reaction is little used today but is interesting mechanistically because it is a simple laboratory analogy for the primary biological pathway by which carbonyl reductions occur in living organisms. In nature, as we saw in **Section 17.4**, one of the most important reducing agents is NADH, reduced nicotinamide adenine dinucleotide. NADH donates H^- to aldehydes and ketones, thereby reducing them, in much the same way that the tetrahedral alkoxide intermediate in a Cannizzaro reaction does. The electron lone pair on a nitrogen atom of NADH expels H^- as leaving group, which adds to a carbonyl group in another molecule **(Figure 19.12)**. As an example, pyruvate is converted during intense muscle activity to (*S*)-lactate, a reaction catalyzed by lactate dehydrogenase.

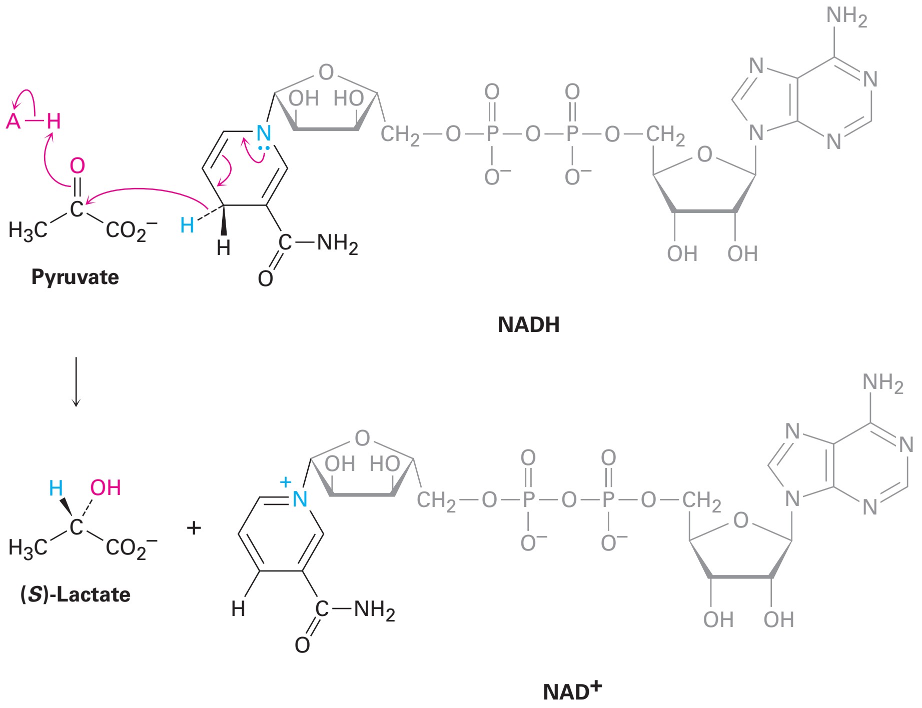
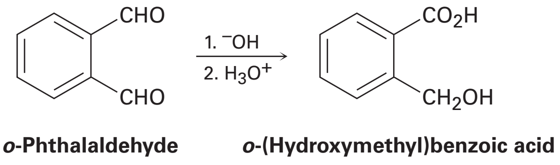


Figure 19.12 Mechanism of biological aldehyde and ketone reductions by the coenzyme NADH. The key step is an expulsion of hydride ion from NADH and donation to the carbonyl group.

Problem 19.18

When *o*-phthalaldehyde is treated with base, *o*-(hydroxymethyl)benzoic acid is formed. Show the mechanism of this reaction.



Problem 19.19

What is the stereochemistry of the pyruvate reduction shown in Figure 19.12? Does NADH lose its *pro-R* or *pro-S* hydrogen? Does addition occur to the *Si* face or *Re* face of pyruvate? (Review **Section 5.11**.)

19.13 Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

All the reactions we've been discussing to this point have involved the addition of a nucleophile directly to the carbonyl group, a so-called **1,2 addition**. Closely related to this direct addition is the **conjugate addition**, or **1,4 addition**, of a nucleophile to the C=C bond of an α,β-unsaturated aldehyde or ketone. (The carbon atom next to a carbonyl group is often called the α carbon, the next carbon is the β carbon, and so on. Thus, an α,β-unsaturated aldehyde or ketone has a double bond conjugated with the carbonyl group.) The initial product of conjugate addition is a resonance-stabilized *enolate ion*, which typically undergoes protonation on the α carbon to give a saturated aldehyde or ketone product **(Figure 19.13)**.

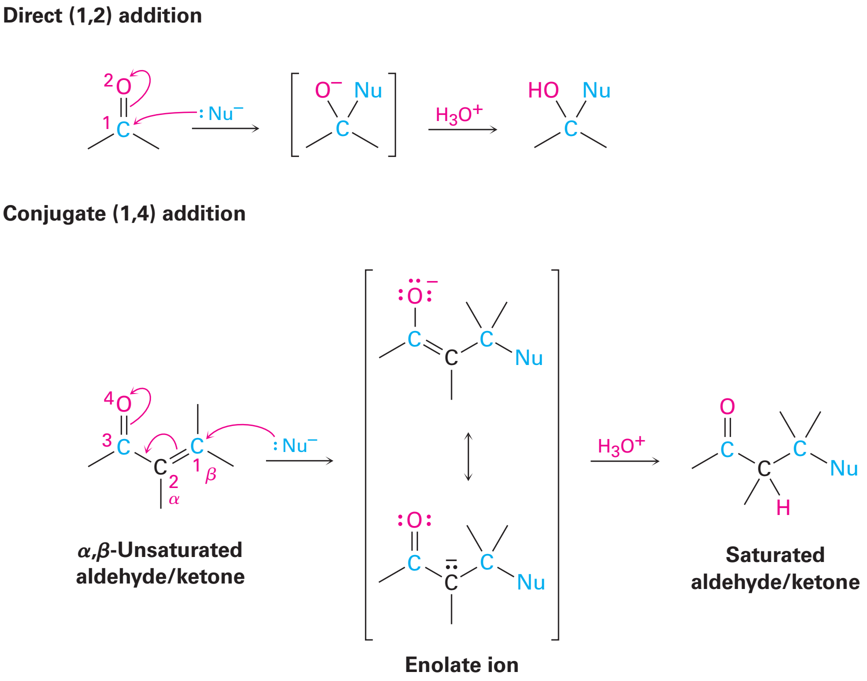
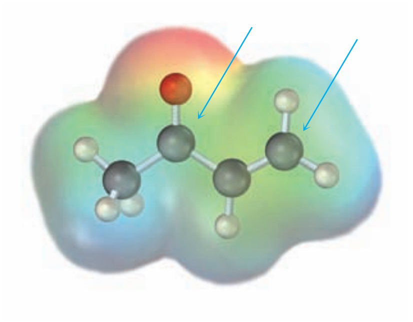
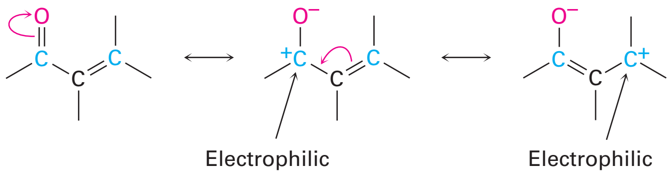


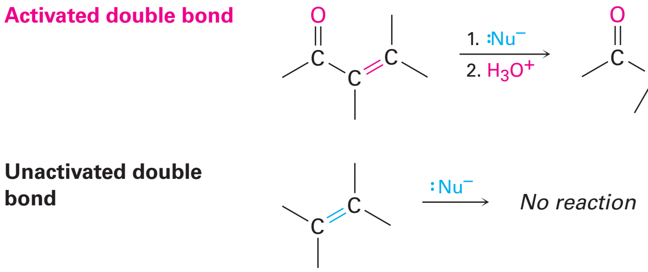
Figure 19.13 A comparison of direct (1,2) and conjugate (1,4) nucleophilic addition reactions. In the conjugate addition, a nucleophile adds to the β carbon of an α,β-unsaturated aldehyde or ketone and protonation occurs on the α carbon.

The conjugate addition of a nucleophile to an α,β-unsaturated aldehyde or ketone is caused by the same electronic factors that are responsible for direct addition. The electronegative oxygen atom of the α,β-unsaturated carbonyl compound withdraws electrons from the β carbon, thereby making it electron-poor and more electrophilic than a typical alkene carbon.



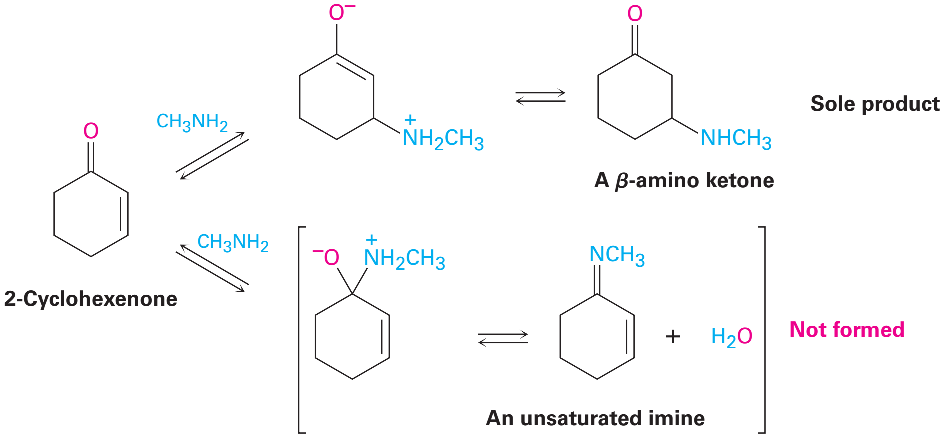


As noted, conjugate addition of a nucleophile to the β carbon of an α,β-unsaturated aldehyde or ketone leads to an enolate ion intermediate, which is protonated on the α carbon to give the saturated product (Figure 19.13). The net effect is addition of the nucleophile to the C=C bond, with the carbonyl group itself unchanged. In fact, of course, the carbonyl group is crucial to the success of the reaction. The C=C bond would not be activated for addition, and no reaction would occur, without the carbonyl group.



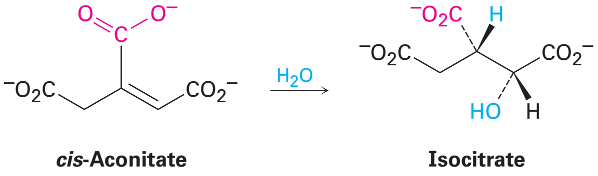
Conjugate Addition of Amines

Both primary and secondary amines add to α,β-unsaturated aldehydes and ketones to yield β-amino aldehydes and ketones rather than the alternative imines. Under typical reaction conditions, both modes of addition occur rapidly. But because the reactions are reversible, they generally proceed with thermodynamic control rather than kinetic control **(Section 14.3)**, so the more stable conjugate addition product is often obtained to the complete exclusion of the less stable direct addition product.



Conjugate Addition of Water

Water can add reversibly to α,β-unsaturated aldehydes and ketones to yield β-hydroxy aldehydes and ketones, although the position of the equilibrium generally favors unsaturated reactant rather than saturated adduct. Related additions to α,β-unsaturated carboxylic acids occur in numerous biological pathways, such as the citric acid cycle of food metabolism in which *cis*-aconitate is converted into isocitrate by conjugate addition of water to a double bond.

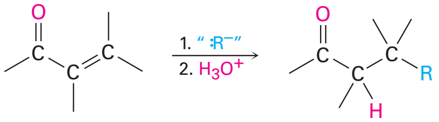


Problem 19.20

Assign *R* or *S* stereochemistry to the two chirality centers in isocitrate, and tell whether OH and H add to the *Si* face or the *Re* face of the double bond.

Conjugate Addition of Alkyl Groups: Organocopper Reactions

The conjugate addition of an alkyl or other organic group to an α,β-unsaturated ketone (but not aldehyde) is one of the more useful 1,4-addition reactions, just as direct addition of a Grignard reagent is one of the more useful 1,2 additions.



α,β-Unsaturated ketone

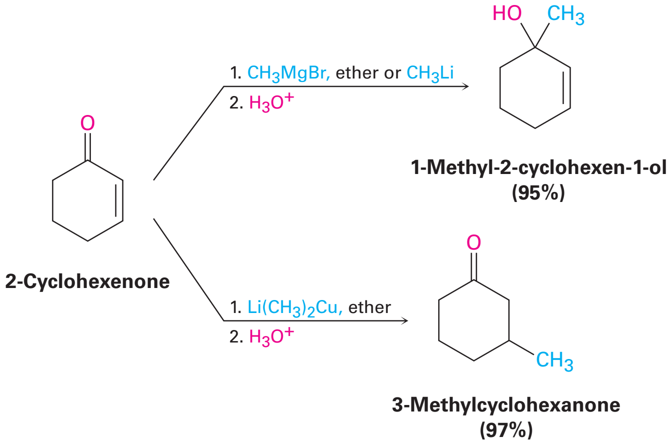
Conjugate addition of an organic group is carried out by treating the α,β-unsaturated ketone with a lithium diorganocopper reagent, R_2CuLi. As we saw in **Section 10.7**, lithium diorganocopper (Gilman) reagents are prepared by reaction between 1 equivalent of copper(I) iodide and 2 equivalents of an organolithium regent, RLi. The organolithium reagent, in turn, is formed by reaction of lithium metal with an organohalide in the same way that a Grignard reagent is prepared by reaction of magnesium metal with an organohalide.

$$RX \xrightarrow[\text{Pentane}]{2\ Li} RLi + Li^+\ X^-$$

$$2\ RLi \xrightarrow[\text{Ether}]{CuI} Li^+(R\overset{-}{Cu}R) + Li^+\ I^-$$

A lithium diorganocopper (Gilman reagent)

Primary, secondary, and even tertiary alkyl groups undergo the conjugate addition reaction, as do aryl and alkenyl groups. Alkynyl groups, however, react poorly in the conjugate addition process. Diorganocopper reagents are unique in their ability to give conjugate addition products. Other organometallic reagents, such as Grignard reagents and organolithiums, normally give direct carbonyl addition on reaction with α,β-unsaturated ketones.

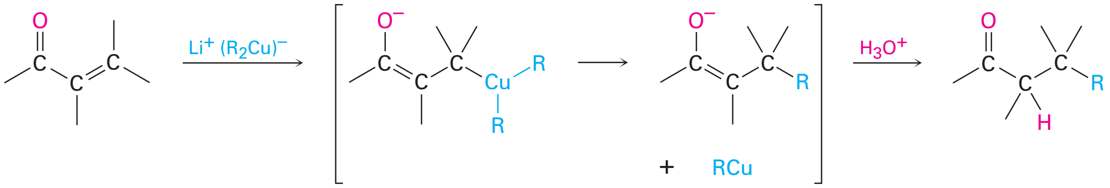


2-Cyclohexenone

1-Methyl-2-cyclohexen-1-ol (95%)

3-Methylcyclohexanone (97%)

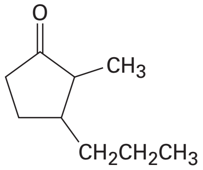
The mechanism of the reaction is thought to involve conjugate nucleophilic addition of the diorganocopper anion, R_2Cu^-, to the unsaturated ketone to give a copper-containing intermediate. Transfer of an R group from copper to carbon, followed by elimination of a neutral organocopper species, RCu, gives the final product.



Synthesis Using a Conjugate Addition Reaction

Worked Example
19.4

How might you use a conjugate addition reaction to prepare 2-methyl-3-propylcyclopentanone?

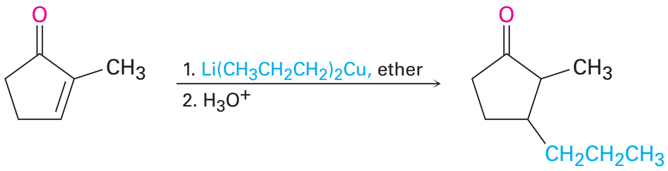


2-Methyl-3-propylcyclopentanone

Strategy

A ketone with a substituent group in its β position might be prepared by a conjugate addition of that group to an α,β-unsaturated ketone. In the present instance, the target molecule has a propyl substituent on the β carbon and might therefore be prepared from 2-methyl-2-cyclopentenone by reaction with lithium dipropylcopper.

Solution



2-Methyl-2-cyclopentenone **2-Methyl-3-propylcyclopentanone**

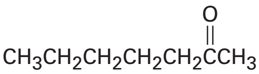
Problem 19.21

Treatment of 2-cyclohexenone with HCN/KCN yields a saturated keto nitrile rather than an unsaturated cyanohydrin. Show the structure of the product, and propose a mechanism for the reaction.

Problem 19.22

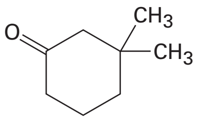
How might conjugate addition reactions of lithium diorganocopper reagents be used to synthesize the following compounds?

(a)

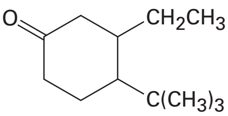


$CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

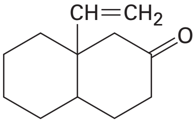
(b)



(c)



(d)



19.14 Spectroscopy of Aldehydes and Ketones

Infrared Spectroscopy

Aldehydes and ketones show a strong C=O bond absorption in the IR region from 1660 to 1770 cm^{-1}, as the spectra of benzaldehyde and cyclohexanone demonstrate **(Figure 19.14)**. In addition, aldehydes show two characteristic C–H absorptions in the range 2720 to 2820 cm^{-1}.

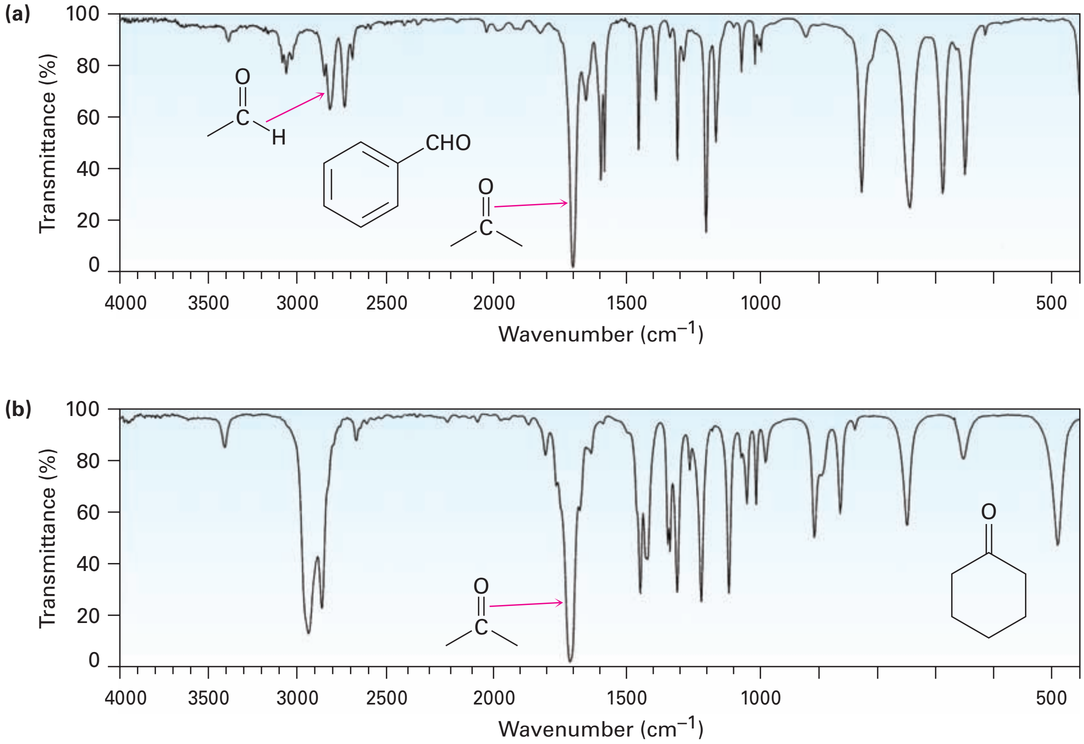


Figure 19.14 Infrared spectra of **(a)** benzaldehyde and **(b)** cyclohexanone.

The exact position of the C=O absorption is diagnostic of the nature of the carbonyl group. As the data in Table 19.2 indicate, saturated aldehydes usually

Table 19.2 Infrared Absorptions of Some Aldehydes and Ketones

Carbonyl type	Example	Absorption (cm^{-1})
Saturated aldehyde	CH_3CHO	1730
Aromatic aldehyde	PhCHO	1705
α,β-Unsaturated aldehyde	$H_2C{=}CHCHO$	1705
Saturated ketone	CH_3COCH_3	1715
Cyclohexanone		1715
Cyclopentanone		1750
Cyclobutanone		1785
Aromatic ketone	$PhCOCH_3$	1690
α,β-Unsaturated ketone	$H_2C{=}CHCOCH_3$	1685

show carbonyl absorptions near 1730 cm^{-1} in the IR spectrum, but conjugation of the aldehyde to an aromatic ring or a double bond lowers the absorption by 25 cm^{-1} to near 1705 cm^{-1}. Saturated aliphatic ketones and cyclohexanones both absorb near 1715 cm^{-1}, and conjugation with a double bond or an aromatic ring again lowers the absorption by 30 cm^{-1} to 1685 to 1690 cm^{-1}. Angle strain in the carbonyl group caused by reducing the ring size of cyclic ketones to four or five raises the absorption position.

The values given in Table 19.2 are remarkably constant from one aldehyde or ketone to another. As a result, IR spectroscopy is a powerful tool for identifying the kind of a carbonyl group in a molecule of unknown structure. An unknown that shows an IR absorption at 1730 cm^{-1} is almost certainly an aldehyde rather than a ketone; an unknown that shows an IR absorption at 1750 cm^{-1} is almost certainly a cyclopentanone, and so on.

Problem 19.23

How might you use IR spectroscopy to determine whether reaction between 2-cyclohexenone and lithium dimethylcopper gives the direct addition product or the conjugate addition product?

Problem 19.24

Where would you expect each of the following compounds to absorb in the IR spectrum?

(a) 4-Penten-2-one
(b) 3-Penten-2-one
(c) 2,2-Dimethylcyclopentanone
(d) *m*-Chlorobenzaldehyde
(e) 3-Cyclohexenone
(f) 2-Hexenal

Nuclear Magnetic Resonance Spectroscopy

Aldehyde protons (RC**H**O) absorb near 10 δ in the ^1H NMR spectrum and are very distinctive because no other absorptions occur in this region. The aldehyde proton shows spin–spin coupling with protons on the neighboring carbon, with coupling constant $J \approx 3$ Hz. Acetaldehyde, for example, shows a quartet at 9.8 δ for the aldehyde proton, indicating that there are three protons neighboring the –CHO group **(Figure 19.15)**.

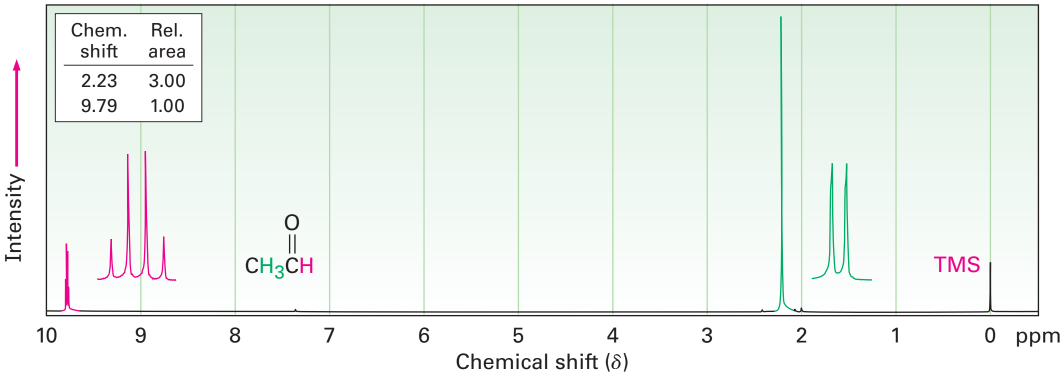
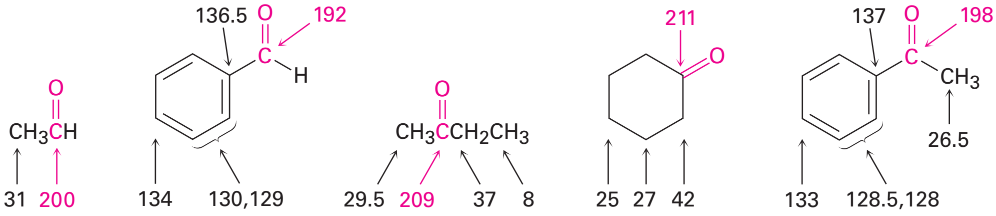


Figure 19.15 ^{1}H NMR spectrum of acetaldehyde. The absorption of the aldehyde proton appears at 9.8 δ and is split into a quartet.

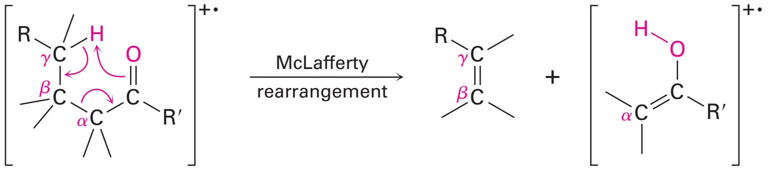
Hydrogens on the carbon next to a carbonyl group are slightly deshielded and normally absorb near 2.0 to 2.3 δ. The acetaldehyde methyl group in Figure 19.15, for instance, absorbs at 2.20 δ. Methyl ketones are particularly distinctive because they always show a sharp three-proton singlet near 2.1 δ.

The carbonyl-group carbon atoms of aldehydes and ketones have characteristic ^{13}C NMR resonances in the range 190 to 215 δ. Since no other kinds of carbons absorb in this range, the presence of an NMR absorption near 200 δ is clear evidence for a carbonyl group. Saturated aldehyde or ketone carbons usually absorb in the region from 200 to 215 δ, while aromatic and α,β-unsaturated carbonyl carbons absorb in the 190 to 200 δ region.

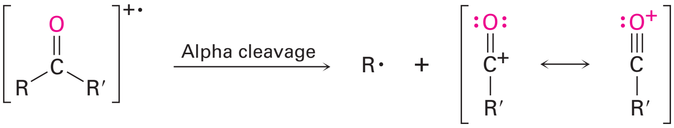


Mass Spectrometry

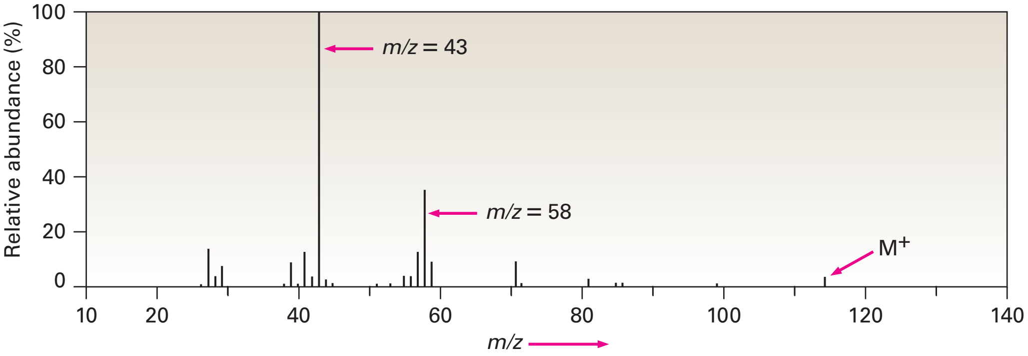
Aliphatic aldehydes and ketones that have hydrogens on their gamma (γ) carbon atoms undergo a characteristic mass spectral cleavage called the *McLafferty rearrangement*. A hydrogen atom is transferred from the γ carbon to the carbonyl oxygen, the bond between the α and β carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition to fragmentation by the McLafferty rearrangement, aldehydes and ketones also undergo cleavage of the bond between the carbonyl group and the α carbon, called an *α cleavage*. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.



Fragment ions from both McLafferty rearrangement and α cleavage are visible in the mass spectrum of 5-methyl-2-hexanone shown in **Figure 19.16**. McLafferty rearrangement with loss of 2-methylpropene yields a fragment with $m/z = 58$. Alpha cleavage occurs primarily at the more substituted side of the carbonyl group, leading to a $[CH_3CO]^+$ fragment with $m/z = 43$.



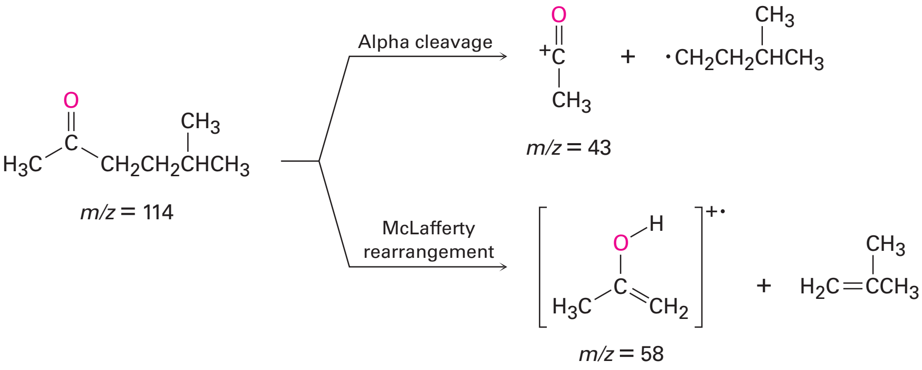


Figure 19.16 Mass spectrum of 5-methyl-2-hexanone. The peak at $m/z = 58$ is due to McLafferty rearrangement. The abundant peak at $m/z = 43$ is due to α cleavage at the more highly substituted side of the carbonyl group. Note that the peak due to the molecular ion is very small.

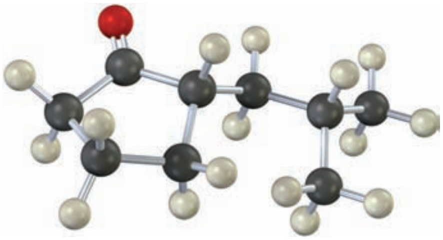
Problem 19.25

How might you use mass spectrometry to distinguish between the following pairs of isomers?

(a) 3-Methyl-2-hexanone and 4-methyl-2-hexanone
(b) 3-Heptanone and 4-heptanone
(c) 2-Methylpentanal and 3-methylpentanal

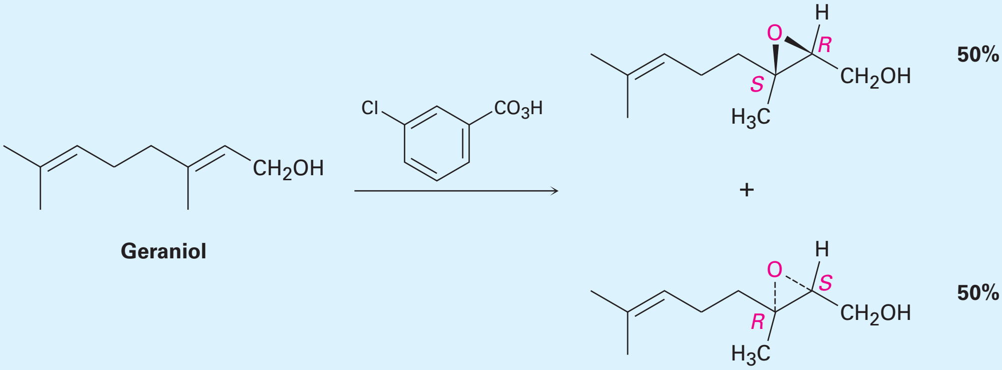
Problem 19.26

Tell the prominent IR absorptions and mass spectral peaks you would expect for the following compound:



Enantioselective Synthesis | A DEEPER LOOK

Whenever a chiral product is formed by reaction between achiral reagents, the product is racemic; that is, both enantiomers of the product are formed in equal amounts. The epoxidation reaction of geraniol with *m*-chloroperoxybenzoic acid, for instance, gives a racemic mixture of (2*R*,3*S*) and (2*S*,3*R*) epoxides.



Unfortunately, it's usually the case that only one enantiomer of a given drug or other important substance has the desired biological properties. The other enantiomer might be inactive or even dangerous. Thus, much work is currently being done on developing *enantioselective* methods of synthesis, which yield only one of two possible enantiomers. So important has enantioselective synthesis become that the 2001 Nobel Prize in Chemistry was awarded to three pioneers in the field: William S. Knowles, K. Barry Sharpless, and Ryoji Noyori.

Several approaches to enantioselective synthesis have been taken, but the most efficient are those that use chiral catalysts to temporarily hold a substrate molecule in an unsymmetrical environment—the same strategy that nature uses when catalyzing reactions with chiral enzymes. While in that unsymmetrical environment, the substrate may be more open to reaction on one side than on another, leading to an excess of one enantiomeric product over another. As an analogy, think about picking up a coffee mug in your right hand to take a drink. The mug by itself is achiral, but as soon as you pick it up by the handle, it becomes chiral. One side of the mug now faces toward you so you can drink from it, but the other side faces away. The two sides are different, with one side much more accessible to you than the other.

(continued)

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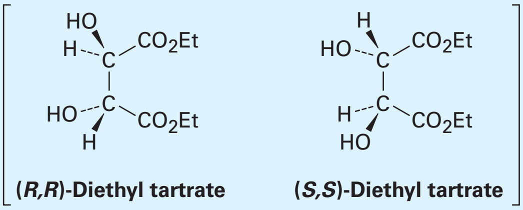
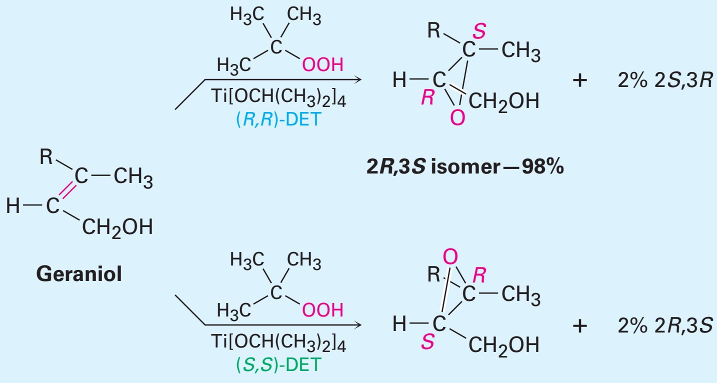
Among the thousands of enantioselective reactions now known, one of the most useful is the so-called Sharpless epoxidation, in which an allylic alcohol, such as geraniol, is treated with *tert*-butyl hydroperoxide, $(CH_3)_3C—OOH$, in the presence of titanium tetraisopropoxide and diethyl tartrate (DET) as a chiral auxiliary reagent. When the (*R*,*R*) tartrate is used, geraniol is converted into its 2*R*,3*S* epoxide with 98% selectivity, whereas use of the (*S*,*S*) tartrate gives the 2*S*,3*R* epoxide enantiomer. We say that the major product in each case is formed with an *enantiomeric excess* of 96%, meaning that 4% of the product is racemic (2% 2*R*,3*S* plus 2% 2*S*,3*R*) and an extra 96% of a single enantiomer is formed. The mechanistic details by which the chiral catalyst works are a bit complex, although it appears that a chiral complex of two tartrate molecules with one titanium is involved.



(*R*,*R*)-Diethyl tartrate **(*S*,*S*)-Diethyl tartrate**



2*S*,3*R* isomer—98%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A substance made from the tartaric acid found at the bottom of this wine vat catalyzes enantioselective reactions.

Summary

Aldehydes and ketones are among the most important of all functional groups, both in the chemical industry and in biological pathways. In this chapter, we've looked at some of their typical reactions. Aldehydes are normally prepared in the laboratory by oxidation of primary alcohols or by partial reduction of esters. Ketones are similarly prepared by oxidation of secondary alcohols.

The **nucleophilic addition reaction** is the most common general reaction type for aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by $NaBH_4$ or $LiAlH_4$ to yield primary and secondary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones also gives alcohols (secondary and tertiary, respectively), and addition of HCN yields **cyanohydrins**. Primary amines add to carbonyl compounds yielding **imines**, or **Schiff bases**, and secondary

Key words

acetal [$R_2C(OR')_2$], 742
acyl group, 724
1,2-addition, 751
1,4-addition, 751
aldehyde (RCHO), 722
Cannizzaro reaction, 750
conjugate addition, 751
cyanohydrin [RCH(OH)C≡N], 733

Key words—cont'd

enamine ($R_2N-CR=CR_2$), 736
hemiacetal, 743
imine ($R_2C=NR$), 736
ketone ($R_2C=O$), 722
nucleophilic addition reaction, 728
Schiff base, 736
Wittig reaction, 746
Wolff–Kishner reaction, 741
ylide, 746

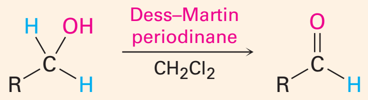
amines yield **enamines**. Reaction of an aldehyde or ketone with hydrazine and base gives an alkane (the **Wolff–Kishner reaction**). Alcohols add to carbonyl groups to yield **acetals**, which are valuable as protecting groups. Phosphorus **ylides** add to aldehydes and ketones in the **Wittig reaction** to give alkenes.

α,β-Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4 addition**. Particularly useful are the conjugate addition of an amine and the conjugate addition of an organic group by reaction with a diorganocopper reagent.

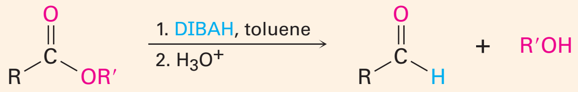
IR spectroscopy is helpful for identifying aldehydes and ketones. Carbonyl groups absorb in the IR range 1660 to 1770 cm^{-1}, with the exact position highly diagnostic of the kind of carbonyl group present in the molecule. ^{13}C NMR spectroscopy is also useful for aldehydes and ketones because their carbonyl carbons show resonances in the 190 to 215 δ range. ^1H NMR is useful for aldehyde –CHO protons, which absorb near 10 δ. Aldehydes and ketones undergo two characteristic kinds of fragmentation in the mass spectrometer: α cleavage and McLafferty rearrangement.

Summary of Reactions

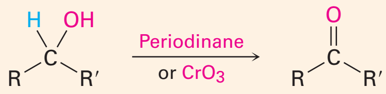
1. Preparation of aldehydes (Section 19.2)
   (a) Oxidation of primary alcohols (Section 17.7)



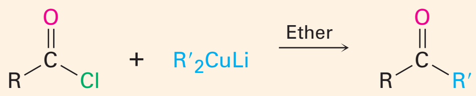
   (b) Partial reduction of esters (Section 19.2)



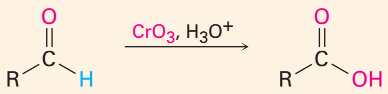
2. Preparation of ketones
   (a) Oxidation of secondary alcohols (Section 17.7)



   (b) Diorganocopper reaction with acid chlorides (Section 19.2)



3. Oxidation of aldehydes (Section 19.3)



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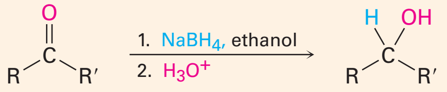
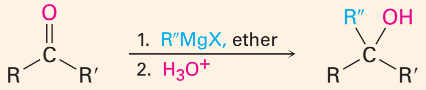
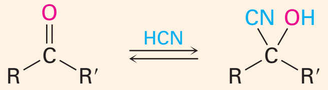
4. Nucleophilic addition reactions of aldehydes and ketones
   (a) Addition of hydride to give alcohols: reduction (Section 19.7)



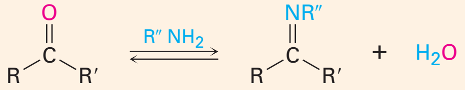
   (b) Addition of Grignard reagents to give alcohols (Section 19.7)



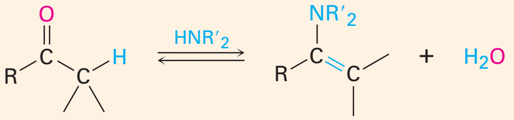
   (c) Addition of HCN to give cyanohydrins (Section 19.6)



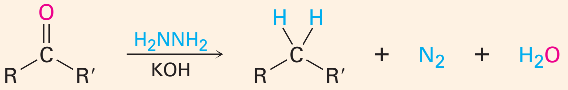
   (d) Addition of primary amines to give imines (Section 19.8)



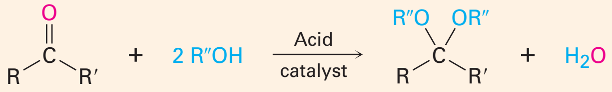
   (e) Addition of secondary amines to give enamines (Section 19.8)



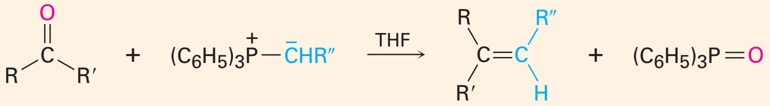
   (f) Wolff–Kishner reaction to give alkanes (Section 19.9)



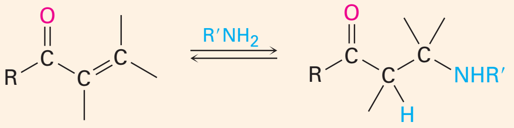
   (g) Addition of alcohols to give acetals (Section 19.10)



   (h) Addition of phosphorus ylides to give alkenes: Wittig reaction (Section 19.11)



5. Conjugate additions to α,β-unsaturated aldehydes and ketones (Section 19.13)
   (a) Conjugate addition of amines



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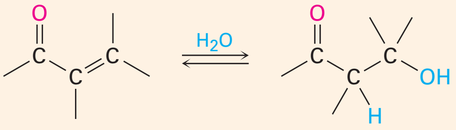
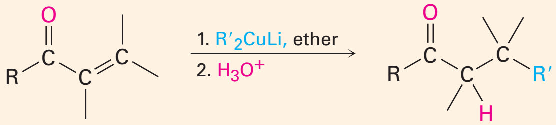
(b) Conjugate addition of water



(c) Conjugate addition of alkyl groups by diorganocopper reaction



Exercises

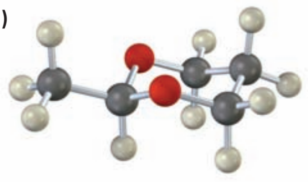
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

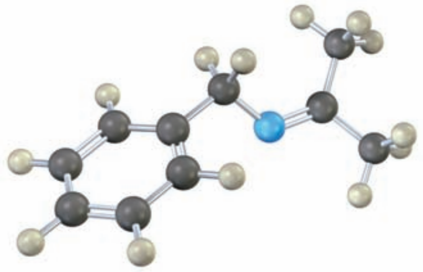
(Problems 19.1–19.26 appear within the chapter.)

19.27 Each of the following substances can be prepared by a nucleophilic addition reaction between an aldehyde or ketone and a nucleophile. Identify the reactants from which each was prepared. If the substance is an acetal, identify the carbonyl compound and the alcohol; if it is an imine, identify the carbonyl compound and the amine; and so forth.

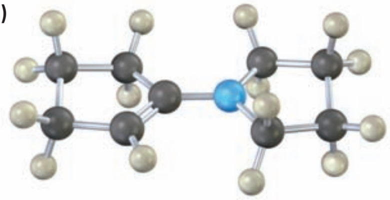
(a)



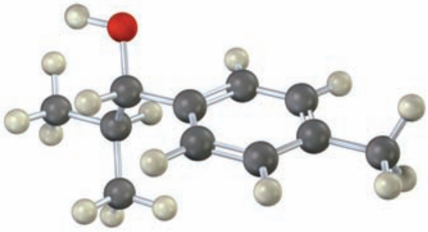
(b)



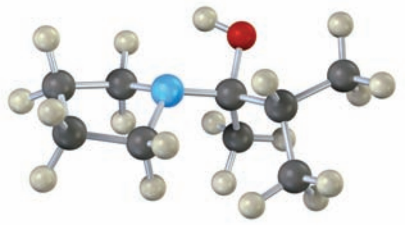
(c)



(d)



19.28 The following molecular model represents a tetrahedral intermediate resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the structure of the final product when the nucleophilic addition reaction is complete.

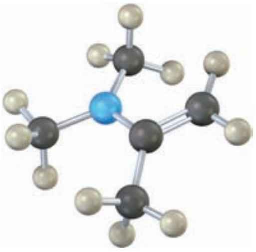


19.29 The enamine prepared from acetone and dimethylamine is shown in its lowest-energy form.

(a) What is the geometry and hybridization of the nitrogen atom?

(b) What orbital on nitrogen holds the lone pair of electrons?

(c) What is the geometric relationship between the *p* orbitals of the double bond and the nitrogen orbital that holds the lone pair? Why do you think this geometry represents the minimum energy?



Additional Problems

Naming Aldehydes and Ketones

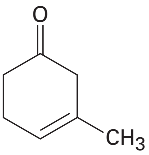
19.30 Draw structures corresponding to the following names:

(a) Bromoacetone
(b) (*S*)-2-Hydroxypropanal
(c) 2-Methyl-3-heptanone
(d) (2*S*,3*R*)-2,3,4-Trihydroxybutanal
(e) 2,2,4,4-Tetramethyl-3-pentanone
(f) 4-Methyl-3-penten-2-one
(g) Butanedial
(h) 3-Phenyl-2-propenal
(i) 6,6-Dimethyl-2,4-cyclohexadienone
(j) *p*-Nitroacetophenone

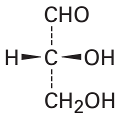
19.31 Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$. Which are chiral?

19.32 Give IUPAC names for the following compounds:

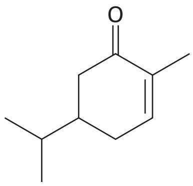
(a)



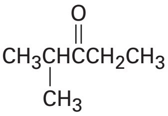
(b)



(c)

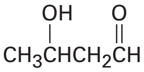


(d)



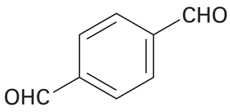
$CH_3\underset{\displaystyle CH_3}{\underset{|}{CH}}\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_3$

(e)



$CH_3\overset{\displaystyle OH}{\overset{|}{C}}HCH_2\overset{\displaystyle O}{\overset{\|}{C}}H$

(f)



19.33 Draw structures of compounds that fit the following descriptions:

(a) An α,β-unsaturated ketone, C_6H_8O
(b) An α-diketone
(c) An aromatic ketone, $C_9H_{10}O$
(d) A diene aldehyde, C_7H_8O

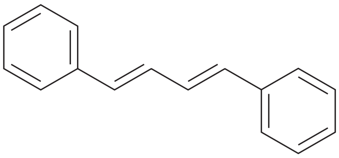
Reactions of Aldehydes and Ketones

19.34 Predict the products of the reaction of (1) phenylacetaldehyde and (2) acetophenone with the following reagents:

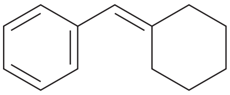
(a) $NaBH_4$, then H_3O^+
(b) Dess–Martin reagent
(c) NH_2OH, HCl catalyst
(d) CH_3MgBr, then H_3O^+
(e) 2 CH_3OH, HCl catalyst
(f) H_2NNH_2, KOH
(g) $(C_6H_5)_3P{=}CH_2$
(h) HCN, KCN

19.35 Show how you might use a Wittig reaction to prepare the following alkenes. Identify the alkyl halide and the carbonyl components.

(a)



(b)



19.36 How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

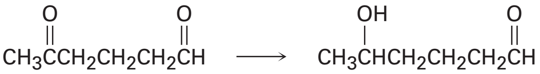
(a) 2-Pentanol
(b) 1-Butanol
(c) 1-Phenylcyclohexanol
(d) Diphenylmethanol

19.37 How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 19.4 that aldehydes are more reactive than ketones toward nucleophilic addition.)

(a)

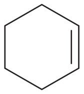
$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}H \longrightarrow CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2OH$

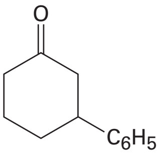
(b)



$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}H \longrightarrow CH_3\overset{\displaystyle OH}{\overset{|}{C}}HCH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}H$

19.38 How would you prepare the following substances from 2-cyclohexenone? More than one step may be needed.

(a)


(b)


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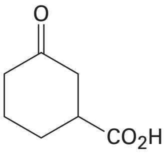

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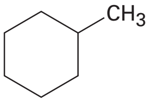
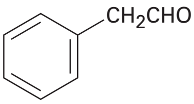


(Two ways)

19.39 How would you synthesize the following substances from benzaldehyde and any other reagents needed?

(a)


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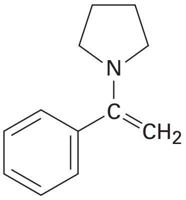

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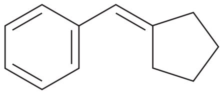
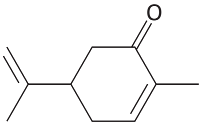


19.40 Carvone is the major constituent of spearmint oil. What products would you expect from reaction of carvone with the following reagents?



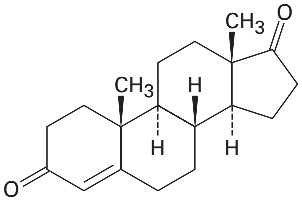
Carvone

(a) $(CH_3)_2Cu^- \ Li^+$, then H_3O^+
(b) $LiAlH_4$, then H_3O^+
(c) CH_3NH_2
(d) C_6H_5MgBr, then H_3O^+
(e) H_2/Pd
(f) CrO_3, H_3O^+
(g) $(C_6H_5)_3\overset{+}{P}\overset{-}{C}HCH_3$
(h) $HOCH_2CH_2OH$, HCl

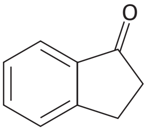
19.41 How would you synthesize the following compounds from cyclohexanone?
(a) 1-Methylcyclohexene
(b) 2-Phenylcyclohexanone
(c) *cis*-1,2-Cyclohexanediol
(d) 1-Cyclohexylcyclohexanol

Spectroscopy

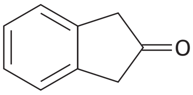
19.42 At what position would you expect to observe IR absorptions for the following molecules?

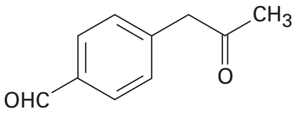
(a)


4-Androstene-3,17-dione

(b)


1-Indanone

(c)


(d)


19.43 Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What possible structures are there for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{-1}, what is its structure?

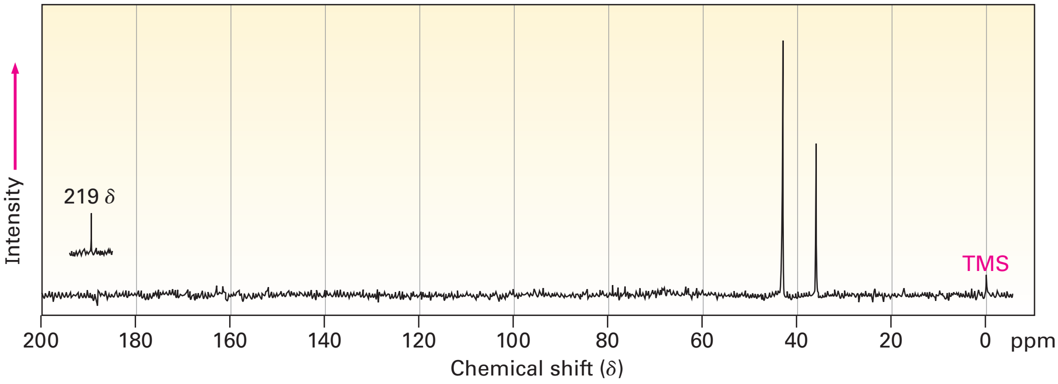
19.44 Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT-NMR.

(a) $C_6H_{12}O$; IR: 1715 cm^{-1}; ^{13}C NMR: 8.0 δ (1°), 18.5 δ (1°), 33.5 δ (2°), 40.6 δ (3°), 214.0 δ (4°)

(b) $C_5H_{10}O$; IR: 1730 cm^{-1}; ^{13}C NMR: 22.6 δ (1°), 23.6 δ (3°), 52.8 δ (2°), 202.4 δ (3°)

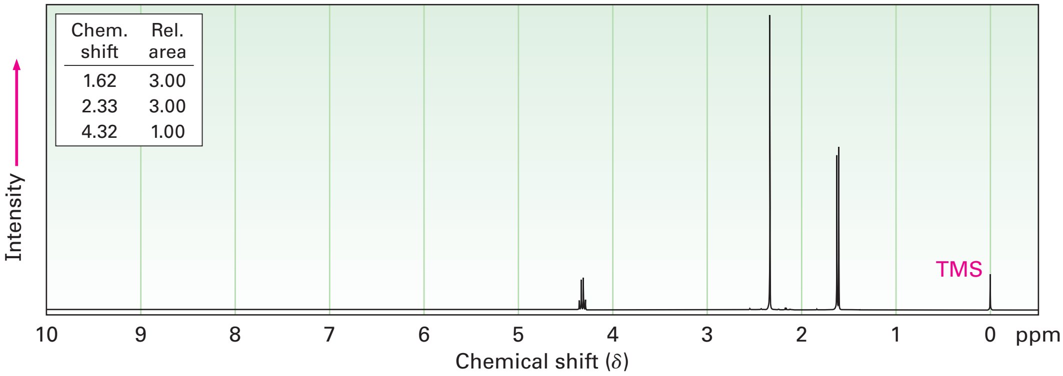
(c) C_6H_8O; IR: 1680 cm^{-1}; ^{13}C NMR: 22.9 δ (2°), 25.8 δ (2°), 38.2 δ (2°), 129.8 δ (3°), 150.6 δ (3°), 198.7 δ (4°)

19.45 Compound **A**, $C_8H_{10}O_2$, has an intense IR absorption at 1750 cm^{-1} and gives the ^{13}C NMR spectrum shown. Propose a structure for **A**.



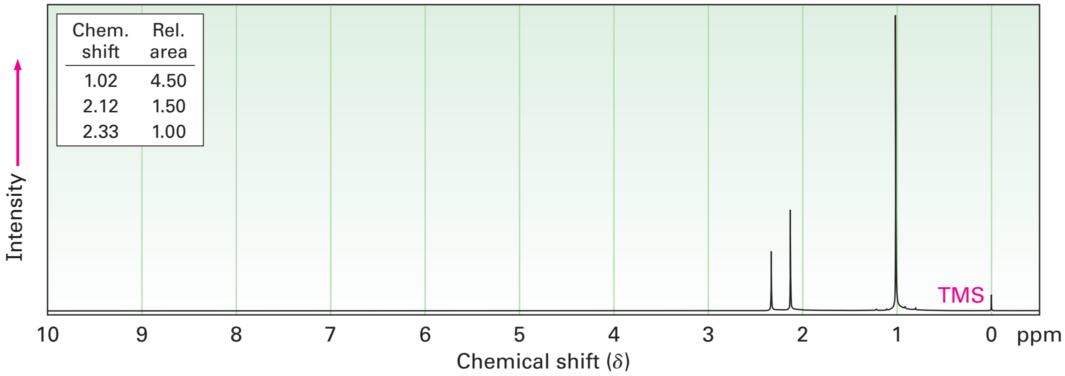
19.46 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

(a) C_4H_7ClO
IR: 1715 cm^{-1}



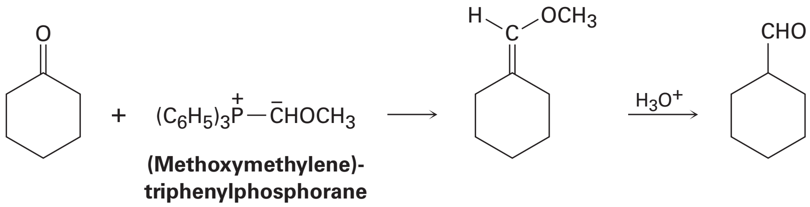
Chem. shift	Rel. area
1.62	3.00
2.33	3.00
4.32	1.00

(b) $C_7H_{14}O$
IR: 1710 cm^{-1}



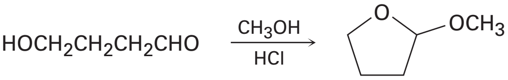
General Problems

19.47 Aldehydes can be prepared by the Wittig reaction using (methoxymethylene)-triphenylphosphorane as the Wittig reagent and then hydrolyzing the product with acid. For example,



(a) How would you prepare the necessary phosphorane?
(b) Propose a mechanism for the hydrolysis step.

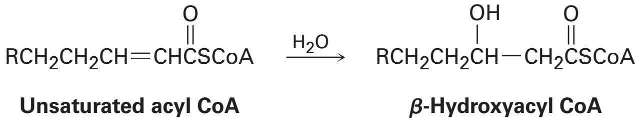
19.48 When 4-hydroxybutanal is treated with methanol in the presence of an acid catalyst, 2-methoxytetrahydrofuran is formed. Explain.



19.49 The S_N2 reaction of (dibromomethyl)benzene, $C_6H_5CHBr_2$, with NaOH yields benzaldehyde rather than (dihydroxymethyl)benzene, $C_6H_5CH(OH)_2$. Explain.

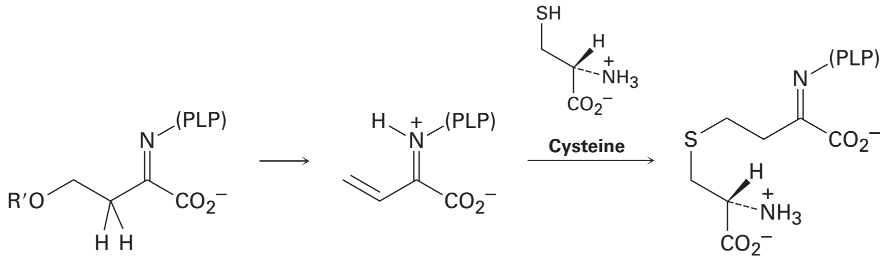
19.50 Reaction of 2-butanone with HCN yields a chiral product. What stereochemistry does the product have? Is it optically active?

19.51 One of the steps in the metabolism of fats is the reaction of an unsaturated acyl CoA with water to give a β-hydroxyacyl CoA. Propose a mechanism.



$$RCH_2CH_2CH{=}CH\overset{O}{\overset{\|}{C}}SCoA \xrightarrow{H_2O} RCH_2CH_2\overset{OH}{\overset{|}{C}H}-CH_2\overset{O}{\overset{\|}{C}}SCoA$$

19.52 The amino acid methionine is biosynthesized by a multistep route that includes reaction of an imine of pyridoxal phosphate (PLP) to give an unsaturated imine, which then reacts with cysteine. What kinds of reactions are occurring in the two steps?

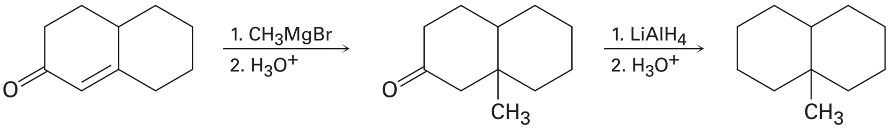


O-Succinylhomoserine–PLP imine

Unsaturated imine

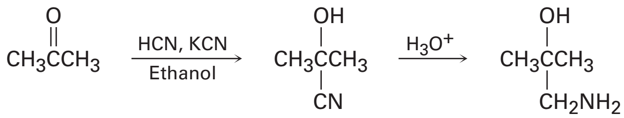
19.53 Each of the following reaction schemes contains one or more flaws. What is wrong in each case? How would you correct each scheme?

(a)



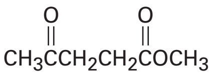
(b) $C_6H_5CH{=}CHCH_2OH \xrightarrow[H_3O^+]{CrO_3} C_6H_5CH{=}CHCHO \xrightarrow{H^+,\ CH_3OH} C_6H_5CH{=}CHCH(OCH_3)_2$

(c)



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{Ethanol}]{\text{HCN, KCN}} CH_3\underset{CN}{\overset{OH}{C}}CH_3 \xrightarrow{H_3O^+} CH_3\underset{CH_2NH_2}{\overset{OH}{C}}CH_3$$

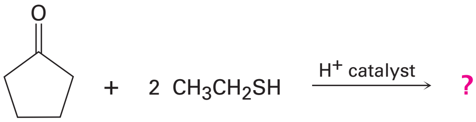
19.54 6-Methyl-5-hepten-2-one is a constituent of lemongrass oil. How could you synthesize this substance from methyl 4-oxopentanoate?



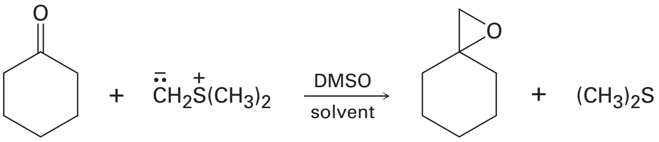
$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$$

Methyl 4-oxopentanoate

19.55 Aldehydes and ketones react with thiols to yield *thioacetals* just as they react with alcohols to yield acetals. Predict the product of the following reaction, and propose a mechanism:

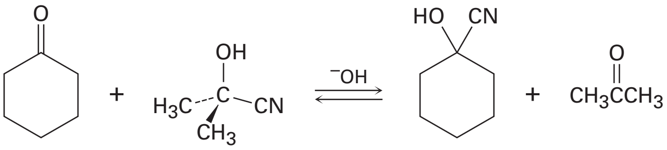


19.56 Ketones react with dimethylsulfonium methylide to yield epoxides. Suggest a mechanism for the reaction.

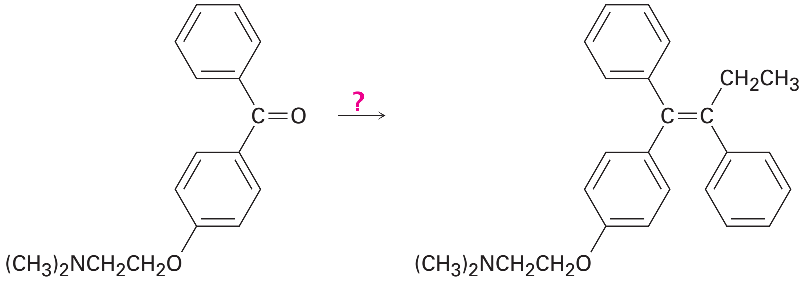


Dimethylsulfonium methylide

19.57 When cyclohexanone is heated in the presence of a large amount of acetone cyanohydrin and a small amount of base, cyclohexanone cyanohydrin and acetone are formed. Propose a mechanism.

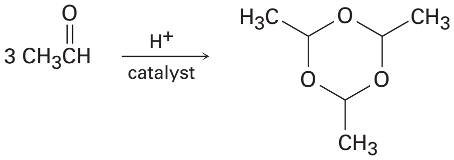


19.58 Tamoxifen is a drug used in the treatment of breast cancer. How would you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?



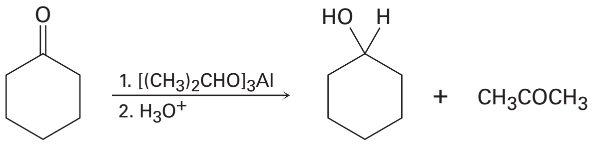
Tamoxifen

19.59 Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism for the reaction.

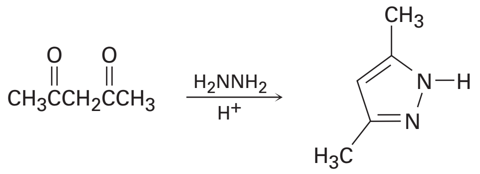


Paraldehyde

19.60 The Meerwein–Ponndorf–Verley reaction involves reduction of a ketone by treatment with an excess of aluminum triisopropoxide, $[(CH_3)_2CHO]_3Al$. The mechanism of the process is closely related to the Cannizzaro reaction in that a hydride ion acts as a leaving group. Propose a mechanism.

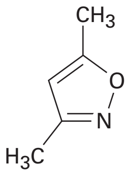


19.61 Propose a mechanism to account for the formation of 3,5-dimethylpyrazole from hydrazine and 2,4-pentanedione. Look carefully to see what has happened to each carbonyl carbon in going from starting material to product.



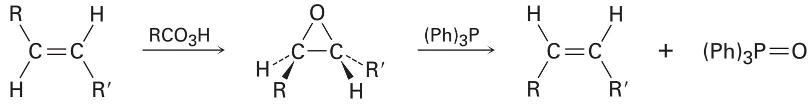
2,4-Pentanedione **3,5-Dimethylpyrazole**

19.62 In light of your answer to Problem 19.61, propose a mechanism for the formation of 3,5-dimethylisoxazole from hydroxylamine and 2,4-pentanedione.

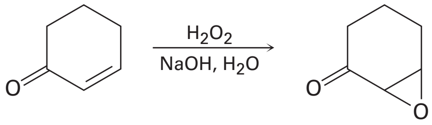


3,5-Dimethylisoxazole

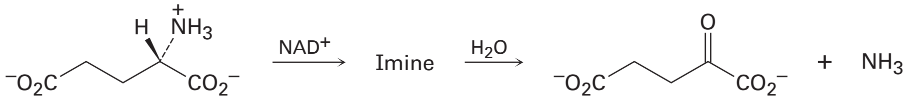
19.63 Trans alkenes are converted into their cis isomers and vice versa on epoxidation followed by treatment of the epoxide with triphenylphosphine. Propose a mechanism for the epoxide → alkene reaction.



19.64 Treatment of an α,β-unsaturated ketone with basic aqueous hydrogen peroxide yields an epoxy ketone. The reaction is specific to unsaturated ketones; isolated alkene double bonds do not react. Propose a mechanism.



19.65 One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) oxidation of the amine by NAD^+ to give an imine and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α-ketoglutarate. Show the structure of the imine intermediate, and propose mechanisms for both steps.



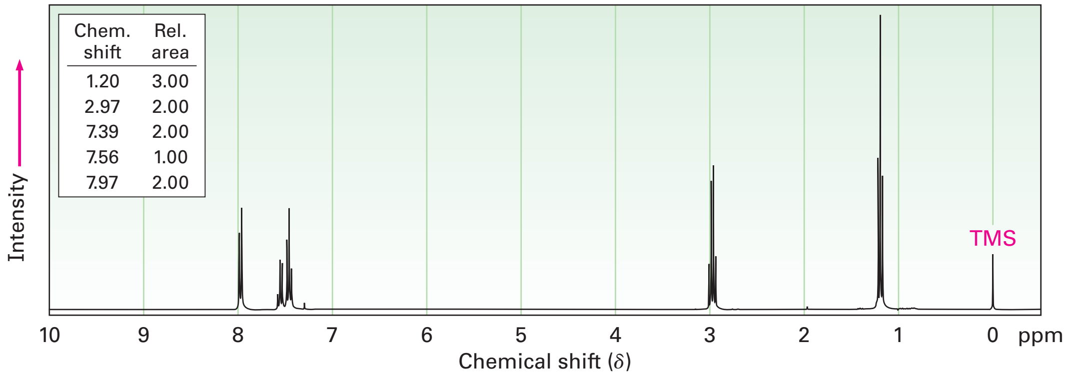
Glutamate

α-Ketoglutarate

19.66 Compound **A**, MW = 86, shows an IR absorption at 1730 cm^{-1} and a very simple ^1H NMR spectrum with peaks at 9.7 δ (1 H, singlet) and 1.2 δ (9 H, singlet). Propose a structure for A.

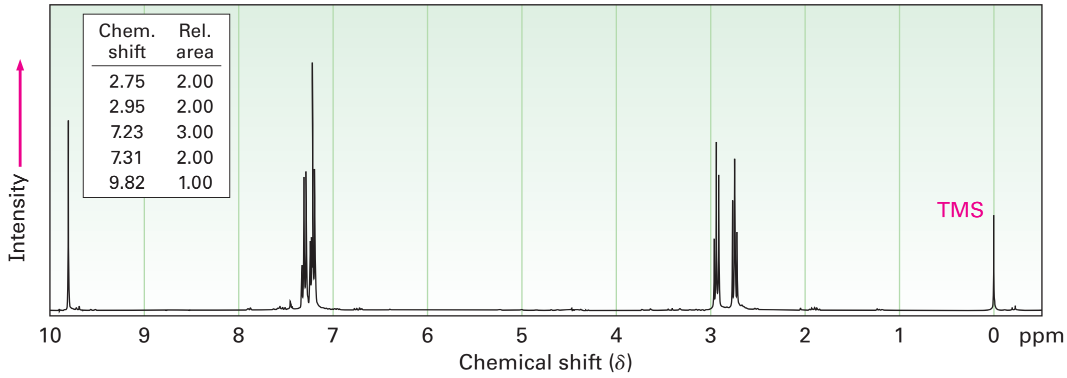
19.67 Compound **B** is isomeric with **A** (Problem 19.66) and shows an IR peak at 1715 cm^{-1}. The ^1H NMR spectrum of **B** has peaks at 2.4 δ (1 H, septet, *J* = 7 Hz), 2.1 δ (3 H, singlet), and 1.2 δ (6 H, doublet, *J* = 7 Hz). What is the structure of **B**?

19.68 The ^1H NMR spectrum shown is that of a compound with formula $C_9H_{10}O$. How many double bonds and/or rings does this compound contain? If the unknown has an IR absorption at 1690 cm^{-1}, what is a likely structure?



Chem. shift	Rel. area
1.20	3.00
2.97	2.00
7.39	2.00
7.56	1.00
7.97	2.00

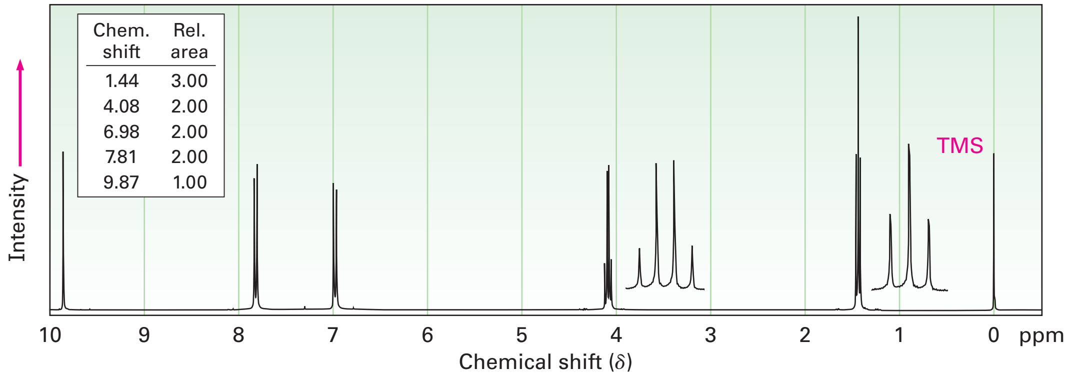
19.69 The ^{1}H NMR spectrum shown is that of a compound isomeric with the one in Problem 19.68. This isomer has an IR absorption at 1730 cm^{-1}. Propose a structure. [*Note:* Aldehyde protons (CHO) often show low coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]



Chem. shift	Rel. area
2.75	2.00
2.95	2.00
7.23	3.00
7.31	2.00
9.82	1.00

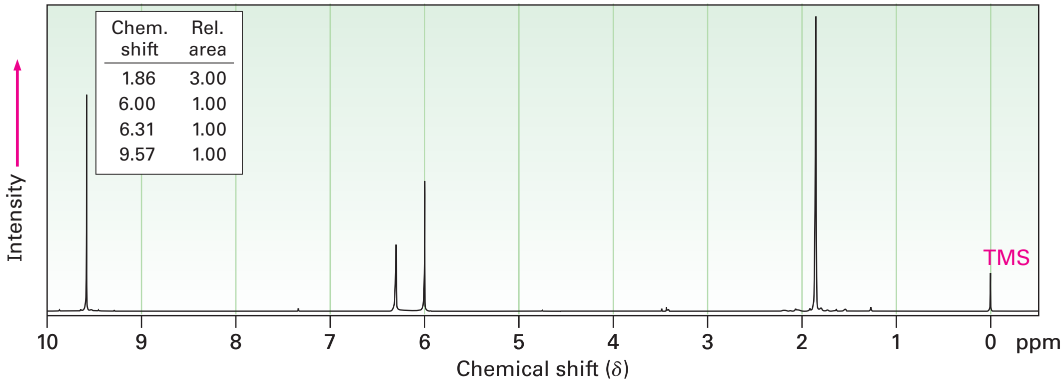
19.70 Propose structures for ketones or aldehydes that have the following ^{1}H NMR spectra:

(a) $C_9H_{10}O_2$
IR: 1695 cm^{-1}



Chem. shift	Rel. area
1.44	3.00
4.08	2.00
6.98	2.00
7.81	2.00
9.87	1.00

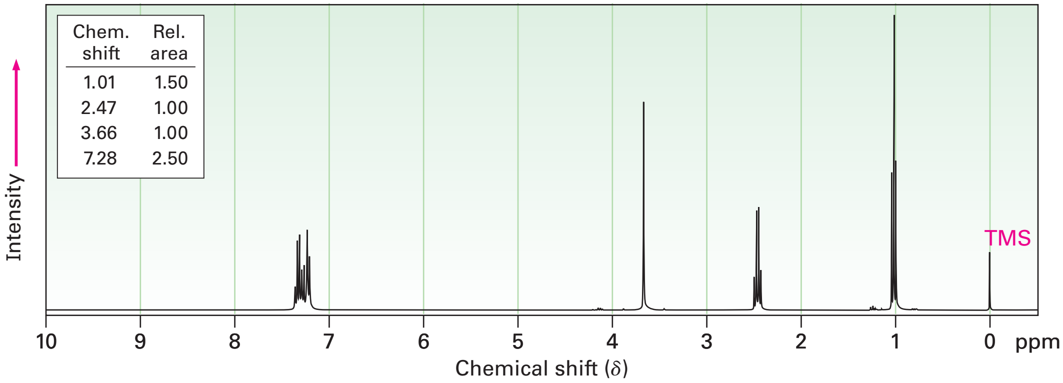
(b) C_4H_6O
IR: 1690 cm^{-1}



Chem. shift	Rel. area
1.86	3.00
6.00	1.00
6.31	1.00
9.57	1.00

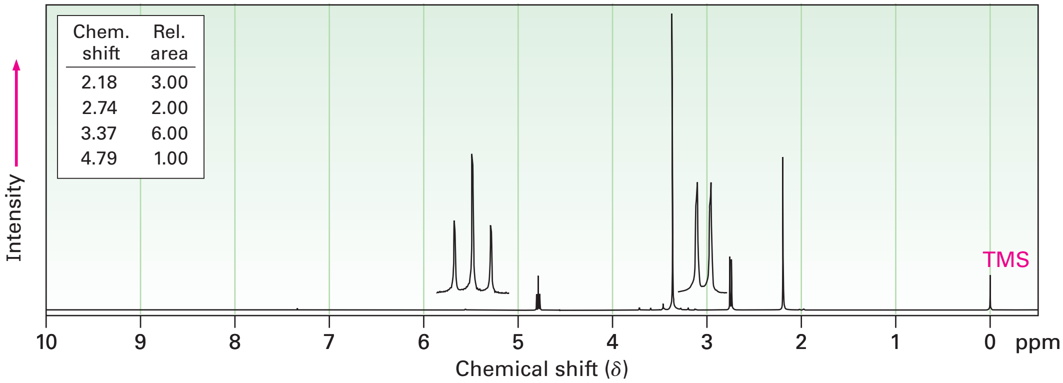
19.71 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra.

(a) $C_{10}H_{12}O$
IR: 1710 cm^{-1}



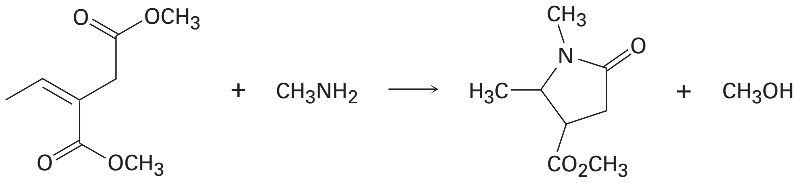
Chem. shift	Rel. area
1.01	1.50
2.47	1.00
3.66	1.00
7.28	2.50

(b) $C_6H_{12}O_3$
IR: 1715 cm^{-1}

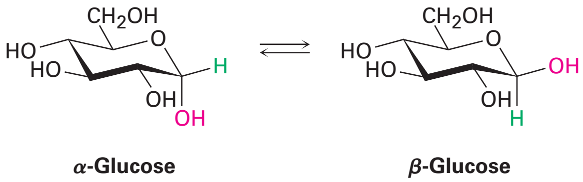


Chem. shift	Rel. area
2.18	3.00
2.74	2.00
3.37	6.00
4.79	1.00

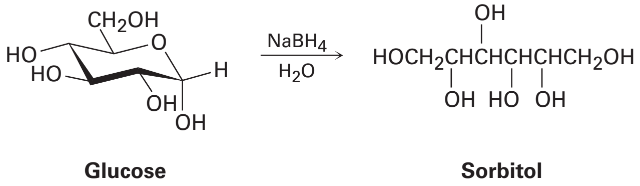
19.72 Primary amines react with esters to yield amides: $RCO_2R' + R''NH_2 \rightarrow RCONHR'' + R'OH$. Propose a mechanism for the following reaction of an α,β-unsaturated ester.



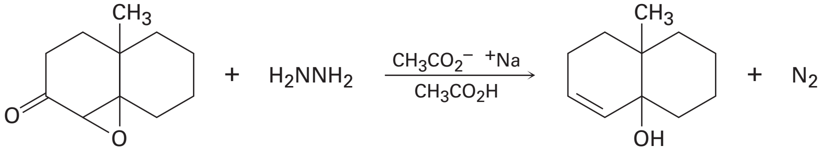
19.73 When crystals of pure α-glucose are dissolved in water, isomerization slowly occurs to produce β-glucose. Propose a mechanism for the isomerization.



19.74 When glucose (Problem 19.73) is treated with $NaBH_4$, reaction occurs to yield *sorbitol,* a polyalcohol commonly used as a food additive. Show how this reduction occurs.



19.75 The Wharton reaction converts an epoxy ketone to an allylic alcohol by reaction with hydrazine. Propose a mechanism. (*Hint:* Review the Wolff–Kishner reaction in Section 19.9.)



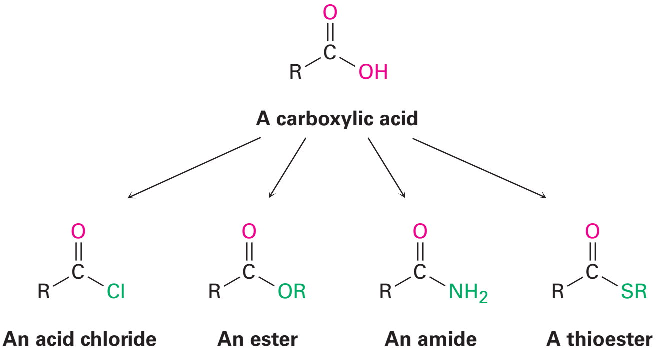
20

The burning sensation produced by touching or eating chili peppers is due to capsaicin, a carboxylic acid derivative called an amide. Image copyright Marie C. Fields, 2010. Used under license from Shutterstock.com

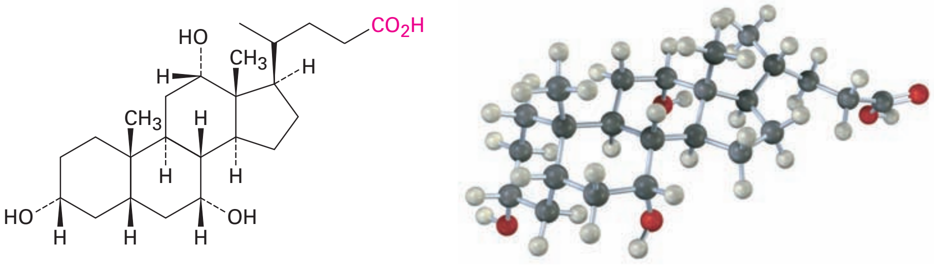
Carboxylic Acids and Nitriles

20.1 Naming Carboxylic Acids and Nitriles
20.2 Structure and Properties of Carboxylic Acids
20.3 Biological Acids and the Henderson–Hasselbalch Equation
20.4 Substituent Effects on Acidity
20.5 Preparing Carboxylic Acids
20.6 Reactions of Carboxylic Acids: An Overview
20.7 Chemistry of Nitriles
20.8 Spectroscopy of Carboxylic Acids and Nitriles
A Deeper Look—Vitamin C

Carboxylic acids, RCO_2H, occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous carboxylic acid derivatives such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways.



A great many carboxylic acids are found in nature: acetic acid, CH_3CO_2H, is the chief organic component of vinegar; butanoic acid, $CH_3CH_2CH_2CO_2H$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $CH_3(CH_2)_4CO_2H$, is responsible for the unmistakable aroma of goats and dirty gym socks (the name comes from the Latin *caper,* meaning "goat"). Other examples are cholic acid, a major component of human bile, and long-chain aliphatic acids such as palmitic acid, $CH_3(CH_2)_{14}CO_2H$, a biological precursor of fats and vegetable oils.



Cholic acid

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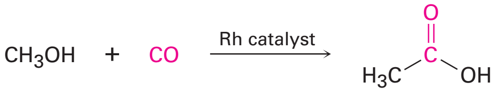
Approximately 5 million metric tons of acetic acid is produced worldwide each year for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



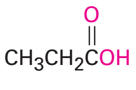
$$CH_3OH + CO \xrightarrow{\text{Rh catalyst}} H_3C{-}\overset{O}{\overset{\|}{C}}{-}OH$$

Why This Chapter? Carboxylic acids are present in many industrial processes and most biological pathways and are the starting materials from which other acyl derivatives are made. Thus, an understanding of their properties and reactions is fundamental to understanding organic chemistry. We'll look both at acids and at their close relatives, nitriles ($RC{\equiv}N$), in this chapter and at carboxylic acid derivatives in the next chapter.

20.1 Naming Carboxylic Acids and Nitriles

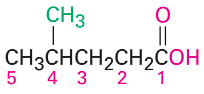
Carboxylic Acids, RCO_2H

Simple carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. The $-CO_2H$ carbon atom is numbered C1.



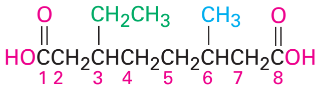
$$CH_3CH_2\overset{O}{\overset{\|}{C}}OH$$

Propanoic acid



$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

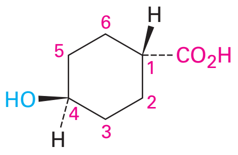
4-Methylpentanoic acid



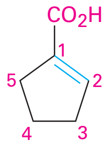
$$HO\overset{O}{\overset{\|}{C}}CH_2\overset{CH_2CH_3}{\overset{|}{C}}HCH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}OH$$

3-Ethyl-6-methyloctanedioic acid

Compounds that have a $-CO_2H$ group bonded to a ring are named using the suffix *-carboxylic acid*. The CO_2H carbon is attached to C1 in this system and is not itself numbered. As a substituent, the CO_2H group is called a **carboxyl group**.



***trans*-4-Hydroxycyclohexanecarboxylic acid**



1-Cyclopentenecarboxylic acid

Because many carboxylic acids were among the first organic compounds to be isolated and purified, a large number of common names exist (Table 20.1). Biological chemists, in particular, make frequent use of these names, so you may find yourself referring back to this list on occasion. We'll use systematic names in this book, with a few exceptions such as formic (methanoic) acid and acetic (ethanoic) acid, whose names are accepted by IUPAC and are so well known that it makes little sense to refer to them any other way.

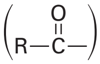
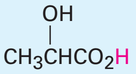
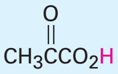
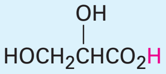
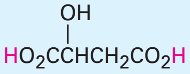
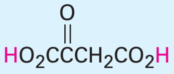
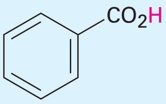
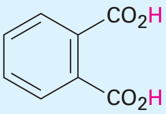
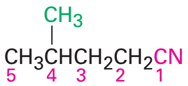
Also listed in Table 20.1 are the names of acyl groups  $\left(R-\overset{\overset{O}{\|}}{C}-\right)$ derived from the parent acids. Except for the eight entries at the top of Table 20.1, whose names have a -*yl* ending, all other acyl groups are named using an -*oyl* ending.

Table 20.1 **Common Names of Some Carboxylic Acids and Acyl Groups**

Structure	Name	Acyl group
HCO_2H	Formic	Formyl
CH_3CO_2H	Acetic	Acetyl
$CH_3CH_2CO_2H$	Propionic	Propionyl
$CH_3CH_2CH_2CO_2H$	Butyric	Butyryl
HO_2CCO_2H	Oxalic	Oxalyl
$HO_2CCH_2CO_2H$	Malonic	Malonyl
$HO_2CCH_2CH_2CO_2H$	Succinic	Succinyl
$HO_2CCH_2CH_2CH_2CO_2H$	Glutaric	Glutaryl
$HO_2CCH_2CH_2CH_2CH_2CO_2H$	Adipic	Adipoyl
$H_2C{=}CHCO_2H$	Acrylic	Acryloyl
$HO_2CCH{=}CHCO_2H$	Maleic (cis)	Maleoyl
	Fumaric (trans)	Fumaroyl
$HOCH_2CO_2H$	Glycolic	Glycoloyl
 $CH_3\overset{\overset{OH}{\vert}}{C}HCO_2H$	Lactic	Lactoyl
 $CH_3\overset{\overset{O}{\|}}{C}CO_2H$	Pyruvic	Pyruvoyl
 $HOCH_2\overset{\overset{OH}{\vert}}{C}HCO_2H$	Glyceric	Gylceroyl
 $HO_2C\overset{\overset{OH}{\vert}}{C}HCH_2CO_2H$	Malic	Maloyl
 $HO_2C\overset{\overset{O}{\|}}{C}CH_2CO_2H$	Oxaloacetic	Oxaloacetyl
	Benzoic	Benzoyl
	Phthalic	Phthaloyl

Nitriles, RC≡N

Compounds containing the $-C{\equiv}N$ functional group are called **nitriles** and undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.

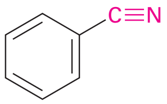

$CH_3\overset{CH_3}{C}HCH_2CH_2CN$

4-Methylpentanenitrile

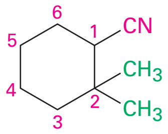
Nitriles can also be named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile,* or by replacing the *-carboxylic acid* ending with *-carbonitrile.* The nitrile carbon atom is attached to C1 but is not itself numbered.

$CH_3C{\equiv}N$

Acetonitrile
(from acetic acid)

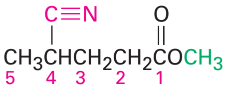


Benzonitrile
(from benzoic acid)



2,2-Dimethylcyclohexanecarbonitrile
(from 2,2-dimethylcyclohexane-carboxylic acid)

If another carboxylic acid derivative is present in the same molecule, the prefix *cyano-* is used for the $C{\equiv}N$ group.

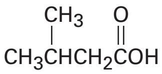

$CH_3\overset{C\equiv N}{C}HCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$

Methyl 4-cyanopentanoate

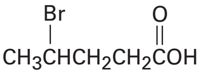
Problem 20.1

Give IUPAC names for the following compounds:

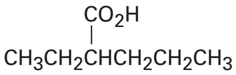
(a)


$CH_3\overset{CH_3}{C}HCH_2\overset{O}{\overset{\|}{C}}OH$

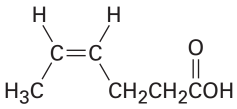
(b)


$CH_3\overset{Br}{C}HCH_2CH_2\overset{O}{\overset{\|}{C}}OH$

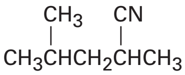
(c)


$CH_3CH_2\overset{CO_2H}{C}HCH_2CH_2CH_3$

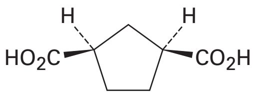
(d)



(e)


$CH_3\overset{CH_3}{C}HCH_2\overset{CN}{C}HCH_3$

(f)



Problem 20.2

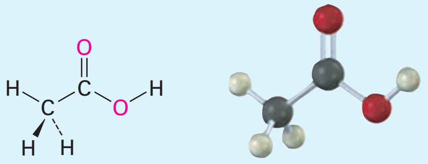
Draw structures corresponding to the following IUPAC names:

(a) 2,3-Dimethylhexanoic acid
(b) 4-Methylpentanoic acid
(c) *trans*-1,2-Cyclobutanedicarboxylic acid
(d) *o*-Hydroxybenzoic acid
(e) (9*Z*,12*Z*)-9,12-Octadecadienoic acid
(f) 2-Pentenenitrile

20.2 Structure and Properties of Carboxylic Acids

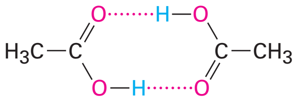
Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is *sp*^{2}-hybridized, and carboxylic acid groups are therefore planar with C–C=O and O=C–O bond angles of approximately 120° (Table 20.2).

Table 20.2 Physical Parameters for Acetic Acid

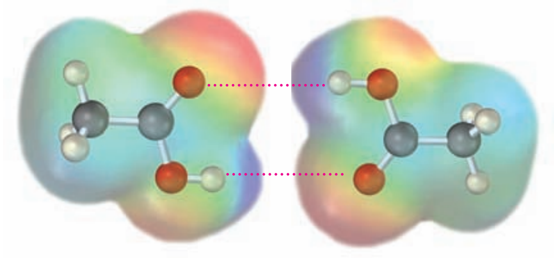


Bond angle	(degrees)	Bond length	(pm)
C–C=O	119	C–C	152
C–C–OH	119	C=O	125
O=C–OH	122	C–OH	131

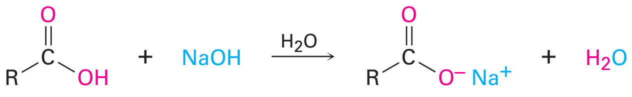
Like alcohols, carboxylic acids are strongly associated because of hydrogen-bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.



Acetic acid dimer



The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. They therefore react with bases such as NaOH and $NaHCO_3$ to give metal carboxylate salts, RCO_2^- M^+. Carboxylic acids with more than six carbons are only slightly soluble in water, but the alkali metal salts of carboxylic acids are often highly water-soluble. In fact, it's often possible to purify an acid by extracting its salt into aqueous base, then reacidifying and extracting the pure acid back into an organic solvent.

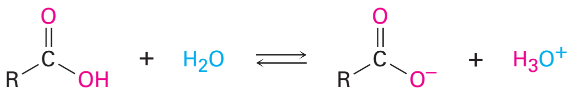


$$RCOOH + NaOH \xrightarrow{H_2O} RCOO^- Na^+ + H_2O$$

A carboxylic acid (water-insoluble)

A carboxylic acid salt (water-soluble)

Like other Brønsted–Lowry acids discussed in **Section 2.7**, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ and the corresponding carboxylate anions, RCO_2^-. The extent of dissociation is given by an acidity constant, K_a.



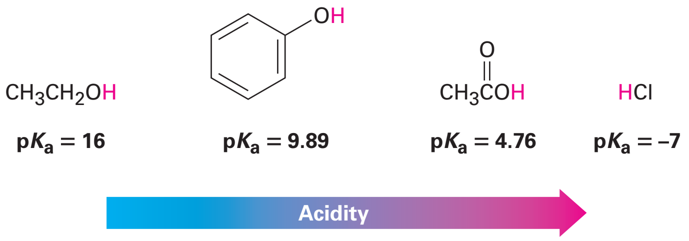
$$K_a = \frac{[RCO_2^-][H_3O^+]}{[RCO_2H]} \quad \text{and} \quad pK_a = -\log K_a$$

A list of K_a values for various carboxylic acids is given in Table 20.3. For most, K_a is approximately 10^{-4} to 10^{-5}. Acetic acid, for instance, has $K_a = 1.75 \times 10^{-5}$ at 25 °C, which corresponds to a pK_a of 4.76. In practical terms, a K_a value near 10^{-5} means that only about 0.1% of the molecules in a 0.1 M solution are dissociated, as opposed to the 100% dissociation found with strong mineral acids like HCl.

Table 20.3 Acidity of Some Carboxylic Acids

Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	Stronger acid
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C{=}CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	
CH_3CH_2OH (ethanol)	(1.00×10^{-16})	(16.00)	Weaker acid

Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16}, making ethanol a weaker acid than acetic acid by a factor of 10^{11}.



Why are carboxylic acids so much more acidic than alcohols, even though both contain –OH groups? An alcohol dissociates to give an alkoxide ion, in which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge is delocalized over two equivalent oxygen atoms **(Figure 20.1)**. In resonance terms **(Section 2.4)**, a carboxylate ion is a stabilized resonance hybrid of two equivalent structures. Since a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and more favored in the dissociation equilibrium.

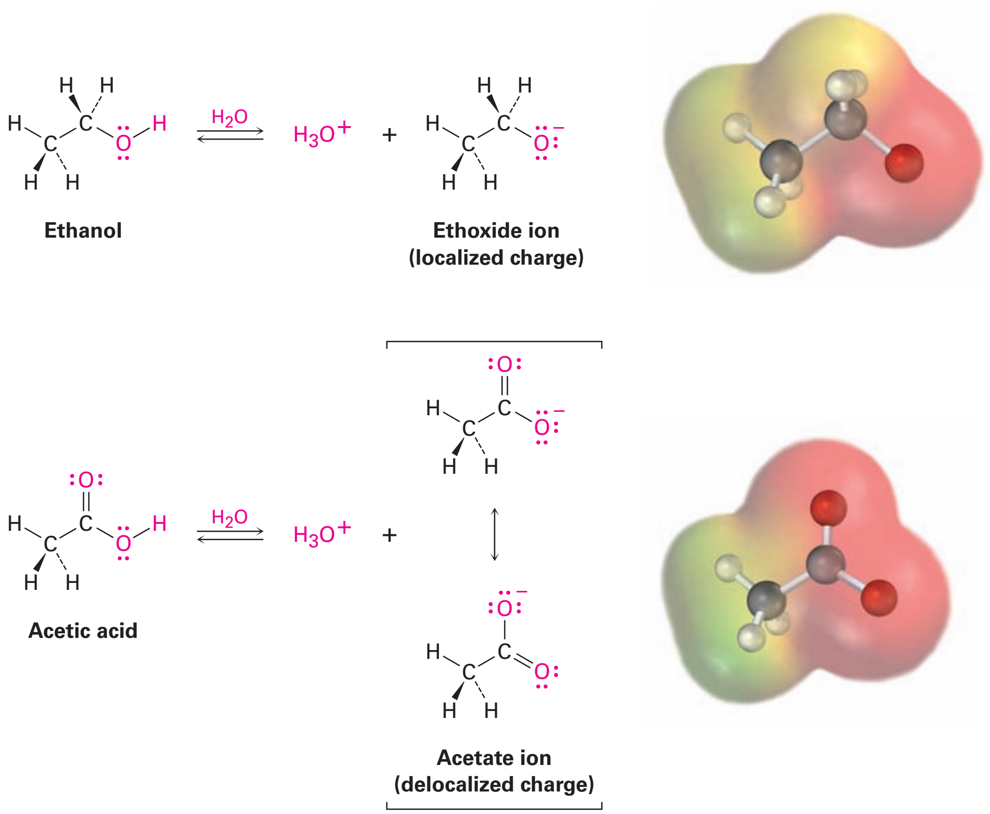
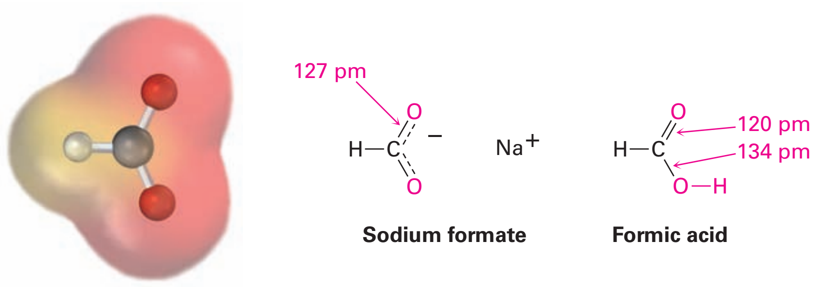


Figure 20.1 An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable.

Experimental evidence for the equivalence of the two carboxylate oxygens comes from X-ray crystallographic studies on sodium formate. Both carbon–oxygen bonds are 127 pm in length, midway between the C=O double bond (120 pm) and C–O single bond (134 pm) of formic acid. An electrostatic potential map of the formate ion also shows how the negative charge (red) is spread equally over both oxygens.



Problem 20.3

Assume you have a mixture of naphthalene and benzoic acid that you want to separate. How might you take advantage of the acidity of one component in the mixture to effect a separation?

Problem 20.4

The K_a for dichloroacetic acid is 3.32×10^{-2}. Approximately what percentage of the acid is dissociated in a 0.10 M aqueous solution?

20.3 Biological Acids and the Henderson–Hasselbalch Equation

In acidic solution, at low pH, a carboxylic acid is completely undissociated and exists entirely as RCO_2H. In basic solution, at high pH, a carboxylic acid is completely dissociated and exists entirely as $RCO_2{}^-$. Inside living cells, however, the pH is neither acidic nor basic but is instead buffered to nearly neutral pH—in humans, to pH = 7.3, a value often referred to as *physiological pH*. In what form, then, do carboxylic acids exist inside cells? The question is an important one for understanding the acid catalysts so often found in biological reactions.

If the pK_a value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using the **Henderson–Hasselbalch equation**.

For any acid HA, we have

$$\begin{aligned} pK_a &= -\log \frac{[H_3O^+][A^-]}{[HA]} = -\log [H_3O^+] - \log \frac{[A^-]}{[HA]} \\ &= pH - \log \frac{[A^-]}{[HA]} \end{aligned}$$

which can be rearranged to give

$$pH = pK_a + \log \frac{[A^-]}{[HA]} \qquad \textbf{Henderson–Hasselbalch equation}$$

$$\text{so} \qquad \log \frac{[A^-]}{[HA]} = pH - pK_a$$

This equation says that the logarithm of the concentration of dissociated acid $[A^-]$ divided by the concentration of undissociated acid [HA] is equal to the pH of the solution minus the pK_a of the acid. Thus, if we know both the pH of the solution and the pK_a of the acid, we can calculate the ratio of $[A^-]$ to [HA]. Furthermore, when pH = pK_a, the two forms HA and A^- are present in equal amounts because log 1 = 0.

As an example of how to use the Henderson–Hasselbalch equation, let's find out what species are present in a 0.0010 M solution of acetic acid at pH = 7.3.

According to Table 20.3, the pK_a of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\log \frac{[A^-]}{[HA]} = pH - pK_a = 7.3 - 4.76 = 2.54$$

$$\frac{[A^-]}{[HA]} = \text{antilog}\,(2.54) = 3.5 \times 10^2 \quad \text{so} \quad [A^-] = (3.5 \times 10^2)\,[HA]$$

In addition, we know that

$$[A^-] + [HA] = 0.0010\ M$$

Solving the two simultaneous equations gives $[A^-] = 0.0010$ M and $[HA] = 3 \times 10^{-6}$ M. In other words, at a physiological pH of 7.3, essentially 100% of acetic acid molecules in a 0.0010 M solution are dissociated to the acetate ion.

What is true for acetic acid is also true for other carboxylic acids: at the physiological pH that exists inside cells, carboxylic acids are almost entirely dissociated. To reflect this fact, we always refer to cellular carboxylic acids by the name of their anion—acetate, lactate, citrate, and so forth, rather than acetic acid, lactic acid, and citric acid.

Problem 20.5

Calculate the percentages of dissociated and undissociated forms present in the following solutions:

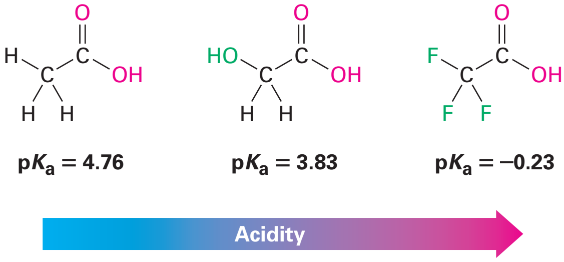
(a) 0.0010 M glycolic acid ($HOCH_2CO_2H$; pK_a = 3.83) at pH = 4.50

(b) 0.0020 M propanoic acid (pK_a = 4.87) at pH = 5.30

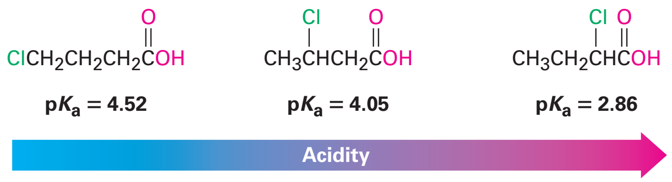
20.4 Substituent Effects on Acidity

The listing of pK_a values shown previously in Table 20.3 indicates that there are substantial differences in acidity from one carboxylic acid to another. For example, trifluoroacetic acid ($K_a = 0.59$) is 33,000 times as strong as acetic acid ($K_a = 1.75 \times 10^{-5}$). How can we account for such differences?

Because the dissociation of a carboxylic acid is an equilibrium process, any factor that stabilizes the carboxylate anion relative to undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. For instance, three electron-withdrawing fluorine atoms delocalize the negative charge in the trifluoroacetate anion, thereby stabilizing the ion and increasing the acidity of CF_3CO_2H. In the same way, glycolic acid ($HOCH_2CO_2H$; pK_a = 3.83) is stronger than acetic acid because of the electron-withdrawing effect of the electronegative oxygen atom.



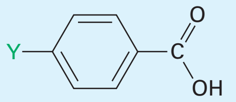
Because inductive effects operate through σ bonds and are dependent on distance, the effect of halogen substitution decreases as the substituent moves farther from the carboxyl. Thus, 2-chlorobutanoic acid has $pK_a = 2.86$, 3-chlorobutanoic acid has $pK_a = 4.05$, and 4-chlorobutanoic acid has $pK_a = 4.52$, similar to that of butanoic acid itself.



$ClCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$ $CH_3\overset{Cl}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}OH$ $CH_3CH_2\overset{Cl}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}OH$

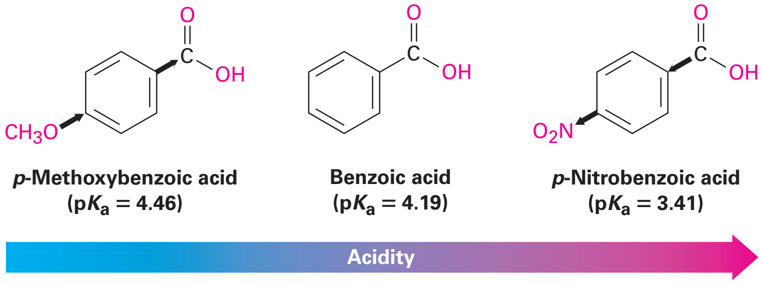
Substituent effects on acidity are also found in substituted benzoic acids. We said during the discussion of electrophilic aromatic substitution in **Section 16.5** that substituents on the aromatic ring strongly affect reactivity. Aromatic rings with electron-donating groups are activated toward further electrophilic substitution, and aromatic rings with electron-withdrawing groups are deactivated. Exactly the same effects are noticed on the acidity of substituted benzoic acids (Table 20.4).

Table 20.4 Substituent Effects on Acidity of *p*-Substituted Benzoic Acids



	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid	$-NO_2$	39	3.41	Deactivating groups
	$-CN$	28	3.55	
	$-CHO$	18	3.75	
	$-Br$	11	3.96	
	$-Cl$	10	4.0	
	$-H$	6.46	4.19	
	$-CH_3$	4.3	4.34	Activating groups
	$-OCH_3$	3.5	4.46	
Weaker acid	$-OH$	3.3	4.48	

As Table 20.4 shows, an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion and an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion.

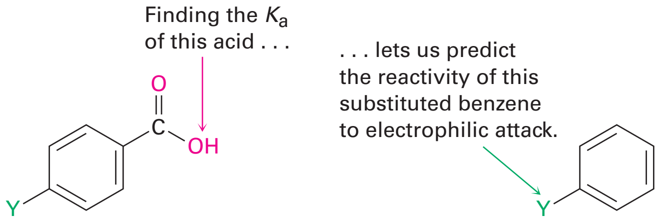


***p*-Methoxybenzoic acid**
(pK_a = 4.46)

Benzoic acid
(pK_a = 4.19)

***p*-Nitrobenzoic acid**
(pK_a = 3.41)

Because it's much easier to measure the acidity of a substituted benzoic acid than it is to determine the relative reactivity of an aromatic ring toward electrophilic substitution, the correlation between the two effects is useful for predicting reactivity. If we want to know the effect of a certain substituent on electrophilic reactivity, we can simply find the acidity of the corresponding benzoic acid. Worked Example 20.1 gives an illustration.


Finding the K_a of this acid . . .

. . . lets us predict the reactivity of this substituted benzene to electrophilic attack.

Worked Example 20.1 Predicting the Effect of a Substituent on the Reactivity of an Aromatic Ring toward Electrophilic Substitution

The pK_a of *p*-(trifluoromethyl)benzoic acid is 3.6. Is the trifluoromethyl substituent an activating or deactivating group in electrophilic aromatic substitution?

Strategy

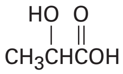
Decide whether *p*-(trifluoromethyl)benzoic acid is stronger or weaker than benzoic acid. A substituent that strengthens the acid is a deactivating group because it withdraws electrons, and a substituent that weakens the acid is an activating group because it donates electrons.

Solution

A pK_a of 3.6 means that *p*-(trifluoromethyl)benzoic acid is stronger than benzoic acid, whose pK_a is 4.19. Thus, the trifluoromethyl substituent favors dissociation by helping stabilize the negative charge. Trifluoromethyl must therefore be an electron-withdrawing, deactivating group.

Problem 20.6

Which would you expect to be a stronger acid, the lactic acid found in tired muscles or acetic acid? Explain.


$CH_3\overset{HO}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}OH$

Lactic acid

Problem 20.7

Dicarboxylic acids have two dissociation constants, one for the initial dissociation into a monoanion and one for the second dissociation into a dianion. For oxalic acid, $HO_2C—CO_2H$, the first ionization constant is $pK_{a1} = 1.2$ and the second ionization constant is $pK_{a2} = 4.2$. Why is the second carboxyl group so much less acidic than the first?

Problem 20.8

The pK_a of *p*-cyclopropylbenzoic acid is 4.45. Is cyclopropylbenzene likely to be more reactive or less reactive than benzene toward electrophilic bromination? Explain.

Problem 20.9

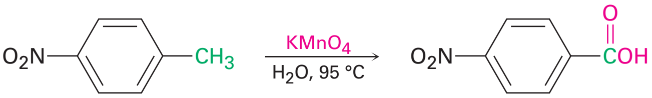
Rank the following compounds in order of increasing acidity. Don't look at a table of pK_a data to help with your answer.

(a) Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid
(b) *p*-Nitrobenzoic acid, acetic acid, benzoic acid

20.5 Preparing Carboxylic Acids

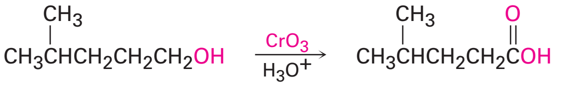
Let's review briefly some of the methods for preparing carboxylic acids that we've seen in previous chapters.

- Oxidation of a substituted alkylbenzene with $KMnO_4$ or $Na_2Cr_2O_7$ gives a substituted benzoic acid **(Section 16.9)**. Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



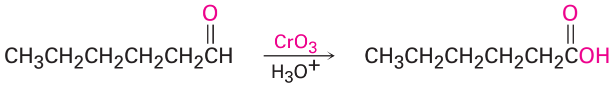
***p*-Nitrotoluene** ***p*-Nitrobenzoic acid (88%)**

- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid **(Sections 17.7 and 19.3)**. Primary alcohols are often oxidized with CrO_3 in aqueous acid, and aldehydes are similarly oxidized.



$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_2CH_2OH \xrightarrow[H_3O^+]{CrO_3} CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OH$$

4-Methyl-1-pentanol **4-Methylpentanoic acid**

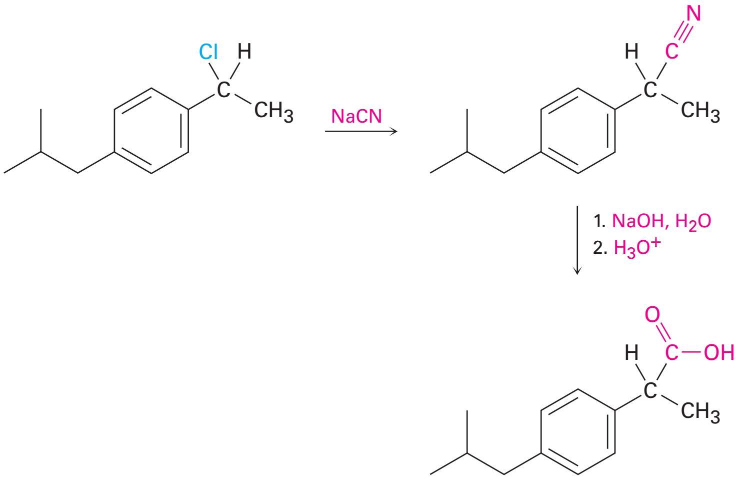


$$CH_3CH_2CH_2CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}H \xrightarrow[H_3O^+]{CrO_3} CH_3CH_2CH_2CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OH$$

Hexanal **Hexanoic acid**

Hydrolysis of Nitriles

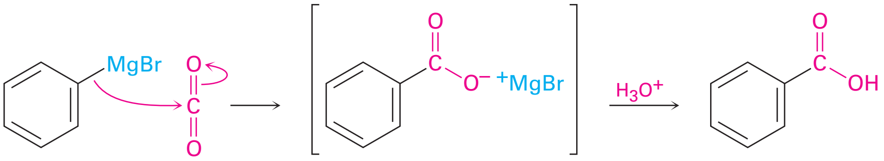
Carboxylic acids can be prepared from nitriles on heating with aqueous acid or base by a mechanism that we'll see in **Section 20.7**. Since nitriles themselves are usually made by S_N2 reaction of a primary or secondary alkyl halide with CN^-, the two-step sequence of cyanide displacement followed by nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($RBr \rightarrow RC{\equiv}N \rightarrow RCO_2H$). Note that the product acid has one more carbon than the starting alkyl halide. An example occurs in one commercial route for the synthesis of the nonsteroidal anti-inflammatory drug ibuprofen. (See Chapter 15 *A Deeper Look*.)



Ibuprofen

Carboxylation of Grignard Reagents

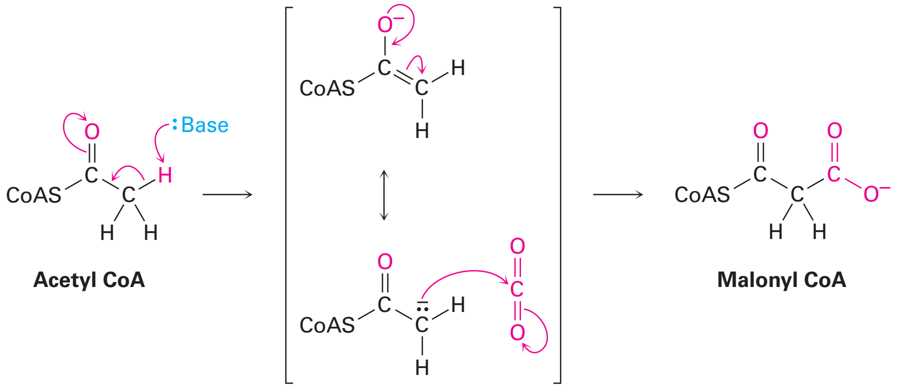
Another method for preparing carboxylic acids is by reaction of a Grignard reagent with CO_2 to yield a metal carboxylate, followed by protonation to give the carboxylic acid. This **carboxylation** reaction is usually carried out by bubbling a stream of dry CO_2 gas through a solution of the Grignard reagent. The organomagnesium halide adds to a C=O bond of carbon dioxide in a typical nucleophilic carbonyl addition reaction, and protonation of the carboxylate by addition of aqueous HCl in a separate step then gives the free carboxylic acid. For example



Phenylmagnesium bromide

Benzoic acid

As noted previously, there are no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated. One of the initial steps in fatty-acid biosynthesis, for instance, involves formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.



Devising a Synthesis Route for a Carboxylic Acid

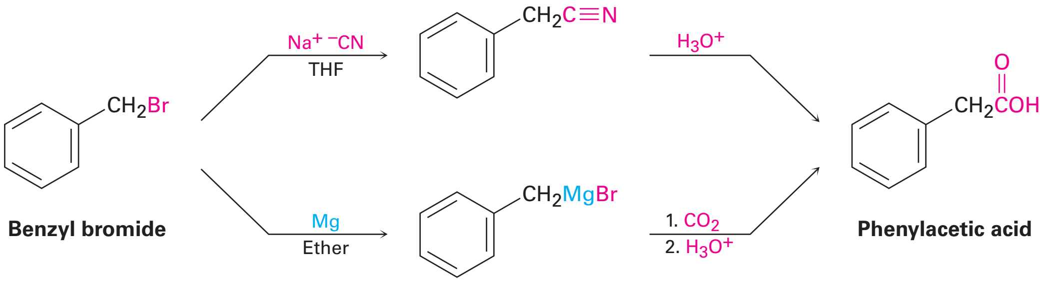
Worked Example 20.2

How would you prepare phenylacetic acid ($PhCH_2CO_2H$) from benzyl bromide ($PhCH_2Br$)?

Strategy

We've seen two methods for preparing carboxylic acids from alkyl halides: (1) cyanide ion displacement followed by hydrolysis and (2) formation of a Grignard reagent followed by carboxylation. The first method involves an S_N2 reaction and is therefore limited to use with primary and some secondary alkyl halides. The second method involves formation of a Grignard reagent and is therefore limited to use with organic halides that have no acidic hydrogens or reactive functional groups elsewhere in the molecule. In the present instance, either method would work well.

Solution



Problem 20.10

How would you prepare the following carboxylic acids?

(a) $(CH_3)_3CCO_2H$ from $(CH_3)_3CCl$

(b) $CH_3CH_2CH_2CO_2H$ from $CH_3CH_2CH_2Br$

20.6 Reactions of Carboxylic Acids: An Overview

We commented earlier in this chapter that carboxylic acids are similar in some respects to both alcohols and ketones. Like alcohols, carboxylic acids can be deprotonated to give anions, which are good nucleophiles in S_N2 reactions. Like ketones, carboxylic acids undergo addition of nucleophiles to the carbonyl group. In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones. **Figure 20.2** shows some of the general reactions of carboxylic acids.

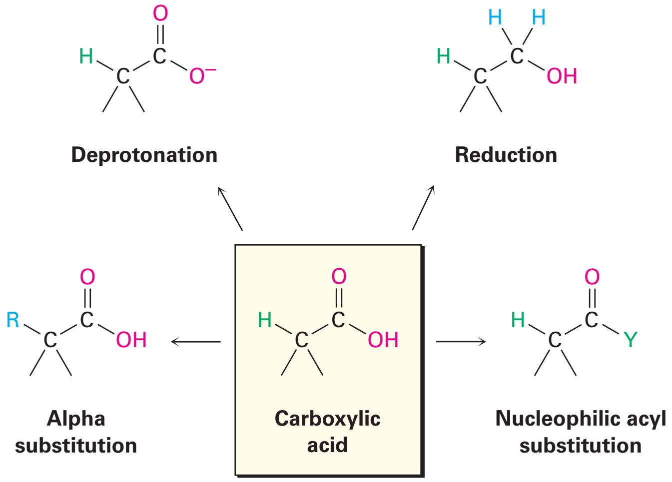
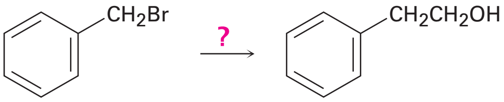


Figure 20.2 Some general reactions of carboxylic acids.

Reactions of carboxylic acids can be grouped into the four categories indicated in Figure 20.2. Of the four, we've already discussed the acidic behavior of carboxylic acids in **Sections 20.2 through 20.4**, and we mentioned reduction by treatment of the acid with $LiAlH_4$ in **Section 17.4**. The remaining two categories are examples of fundamental carbonyl-group reaction mechanisms—nucleophilic acyl substitution and α substitution—that will be discussed in detail in Chapters 21 and 22.

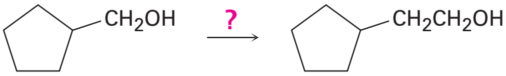
Problem 20.11

How might you prepare 2-phenylethanol from benzyl bromide? More than one step is needed.



Problem 20.12

How might you carry out the following transformation? More than one step is needed.

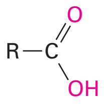


20.7 Chemistry of Nitriles

Nitriles are analogous to carboxylic acids in that both have a carbon atom with three bonds to an electronegative atom and both contain a π bond. Thus, some reactions of nitriles and carboxylic acids are similar. Both kinds of compounds are electrophiles, for instance, and both undergo nucleophilic addition reactions.

$R{-}C{\equiv}N$

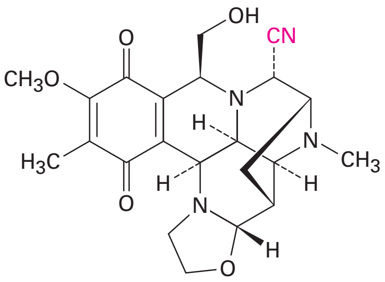
A nitrile—three bonds to nitrogen



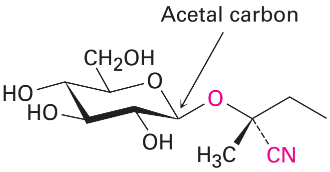
$R{-}C({=}O){-}OH$

An acid—three bonds to two oxygens

Nitriles occur infrequently in living organisms, although several hundred examples are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and found to have both antimicrobial and antitumor activity. In addition, more than 1000 compounds called *cyanogenic glycosides* are known. Derived primarily from plants, cyanogenic glycosides contain a sugar with an acetal carbon, one oxygen of which is bonded to a nitrile-bearing carbon (sugar–O–C–CN). On hydrolysis with aqueous acid, the acetal is cleaved **(Section 19.10)**, generating a cyanohydrin (HO–C–CN), which releases hydrogen cyanide. It's thought that the primary function of cyanogenic glycosides is to protect the plant by poisoning any animal foolish enough to eat it. Lotaustralin from the cassava plant is an example.



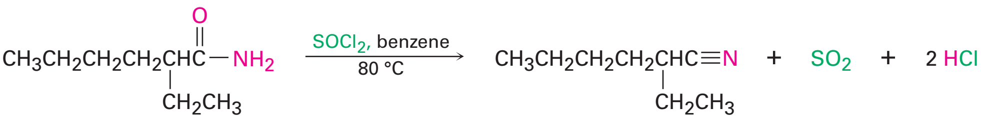
Cyanocycline A



Lotaustralin (a cyanogenic glycoside)

Preparation of Nitriles

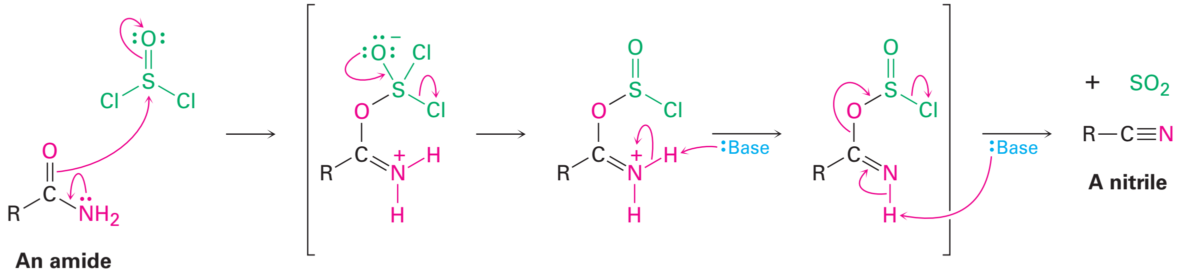
The simplest method of nitrile preparation is the S_N2 reaction of CN^- with a primary or secondary alkyl halide, as discussed in **Section 20.5**. Another method for preparing nitriles is by dehydration of a primary amide, $RCONH_2$. Thionyl chloride is often used for the reaction, although other dehydrating agents such as $POCl_3$ also work.



$$CH_3CH_2CH_2CH_2CH(CH_2CH_3)C({=}O){-}NH_2 \xrightarrow[80\ ^\circ C]{SOCl_2,\ benzene} CH_3CH_2CH_2CH_2CH(CH_2CH_3)C{\equiv}N + SO_2 + 2\ HCl$$

2-Ethylhexanamide **2-Ethylhexanenitrile (94%)**

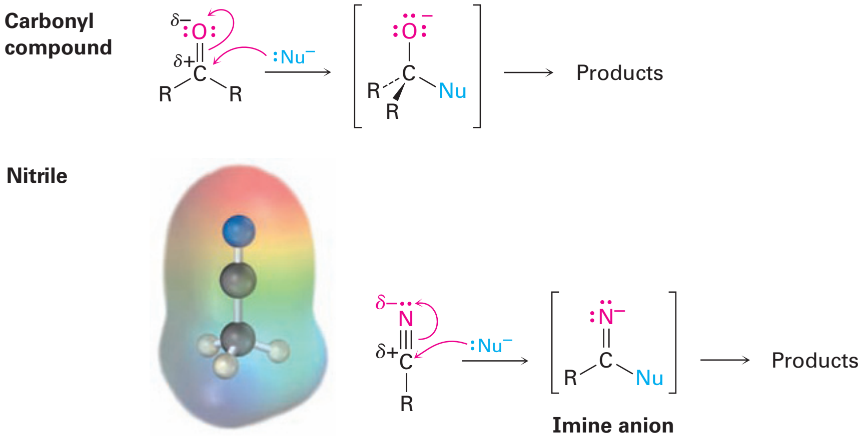
The dehydration occurs by initial reaction of $SOCl_2$ on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.



Both methods of nitrile synthesis—S_N2 displacement by CN^- on an alkyl halide and amide dehydration—are useful, but the synthesis from amides is more general because it is not limited by steric hindrance.

Reactions of Nitriles

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2-hybridized imine anions in a reaction analogous to the formation of an sp^3-hybridized alkoxide ion by nucleophilic addition to a carbonyl group.



Some general reactions of nitriles are shown in **Figure 20.3**.

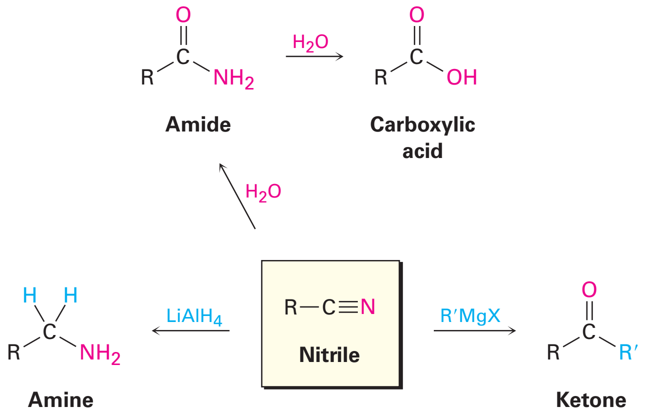
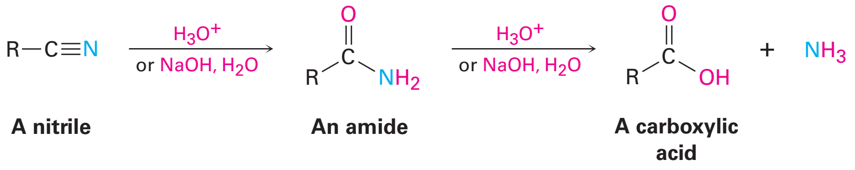


Figure 20.3 Some reactions of nitriles.

Hydrolysis: Conversion of Nitriles into Carboxylic Acids Among the most useful reactions of nitriles is their hydrolysis to yield first an amide and then a carboxylic acid plus ammonia or an amine. The reaction occurs in either basic or acidic aqueous solution:



As shown in **Figure 20.4**, base-catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion in a process similar to nucleophilic addition to a polar C=O bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes **(Section 9.4)** to an amide in a step similar to the tautomerization of an enol to a ketone. Further hydrolysis gives a carboxylate ion.

1 Nucleophilic addition of hydroxide ion to the CN triple bond gives an imine anion addition product.

2 Protonation of the imine anion by water yields a hydroxyimine and regenerates the base catalyst.

3 Tautomerization of the hydroxyimine yields an amide in a reaction analgous to the tautomerization of an enol to give a ketone.

4 Further hydrolysis of the amide gives the anion of a carboxylic acid by a mechanism we'll discuss in Section 21.7.

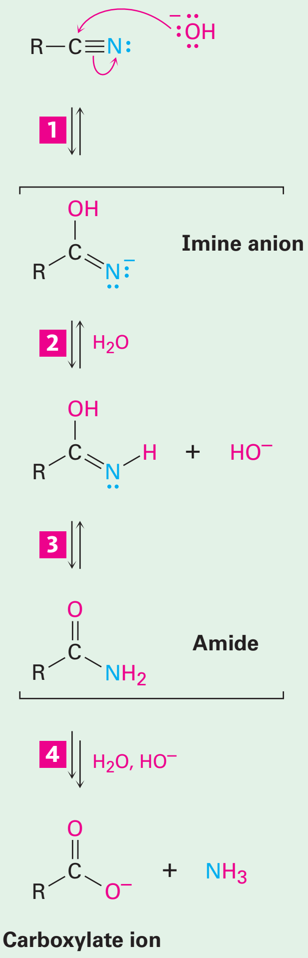
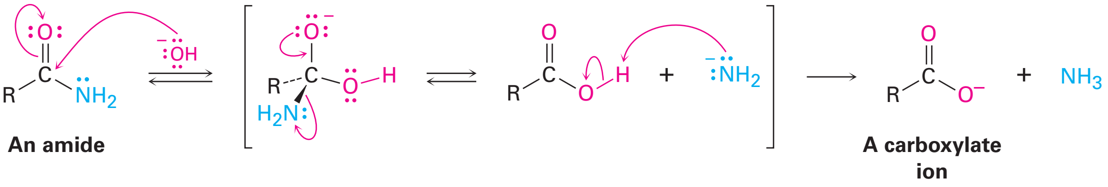


Figure 20.4 | **MECHANISM**

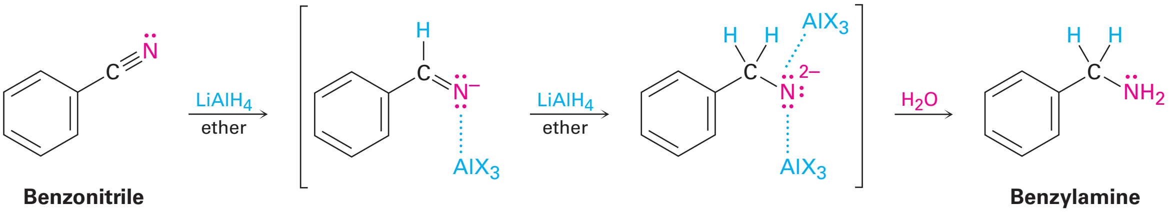
Mechanism of the basic hydrolysis of a nitrile to yield an amide, which is subsequently hydrolyzed further to a carboxylic acid anion.

© John McMurry

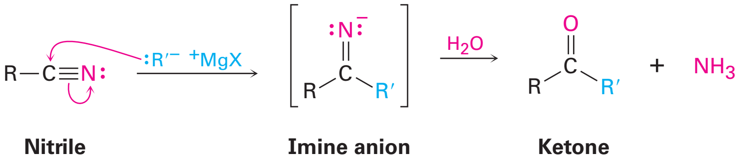
The further hydrolysis of the amide intermediate takes place by a nucleophilic addition of hydroxide ion to the amide carbonyl group, which yields a tetrahedral alkoxide ion. Expulsion of amide ion, NH_2^-, as leaving group gives the carboxylate ion, thereby driving the reaction toward products. Subsequent acidification in a separate step yields the carboxylic acid. We'll look at this process in more detail in **Section 21.7**.



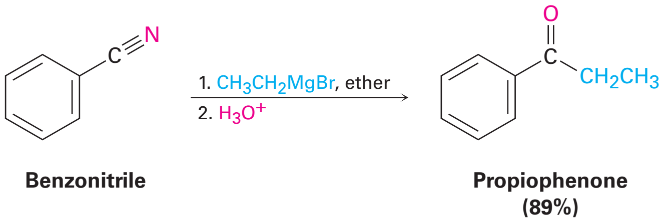
Reduction: Conversion of Nitriles into Amines Reduction of a nitrile with $LiAlH_4$ gives a primary amine, RNH_2. The reaction occurs by nucleophilic addition of hydride ion to the polar C≡N bond, yielding an imine anion, which still contains a C=N bond and therefore undergoes a second nucleophilic addition of hydride to give a *dianion*. Both monoanion and dianion intermediates are undoubtedly stabilized by Lewis acid–base complexation to an aluminum species, facilitating the second addition that would otherwise be difficult. Protonation of the dianion by addition of water in a subsequent step gives the amine.



Reaction of Nitriles with Grignard Reagents Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone. The mechanism of the hydrolysis is the exact reverse of imine formation (see Figure 19.6 on page 737).



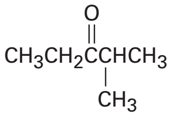
The reaction is similar to the reduction of a nitrile to an amine, except that only one nucleophilic addition occurs rather than two and the attacking nucleophile is a carbanion (R:⁻) rather than a hydride ion. For example:



Synthesizing a Ketone from a Nitrile

Worked Example 20.3

How would you prepare 2-methyl-3-pentanone from a nitrile?



$CH_3CH_2\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}HCH_3$

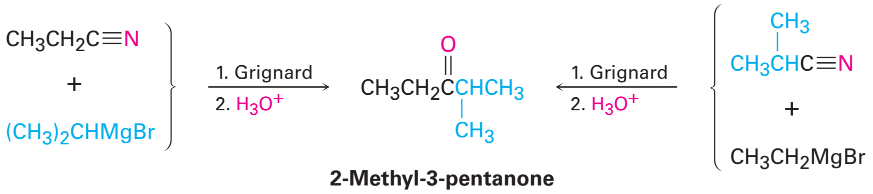
2-Methyl-3-pentanone

Strategy

A ketone results from the reaction between a Grignard reagent and a nitrile, with the C≡N carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent, and the other will come from the nitrile.

Solution

There are two possibilities.

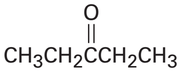


2-Methyl-3-pentanone

Problem 20.13

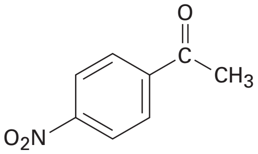
How would you prepare the following carbonyl compounds from a nitrile?

(a)



$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$

(b)



Problem 20.14

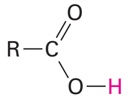
How would you prepare 1-phenyl-2-butanone, $C_6H_5CH_2COCH_2CH_3$, from benzyl bromide, $C_6H_5CH_2Br$? More than one step is required.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

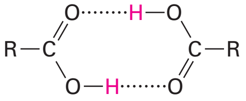
Infrared Spectroscopy

Carboxylic acids have two characteristic IR absorptions that make the $-CO_2H$ group easily identifiable. The O–H bond of the carboxyl group gives rise to a very broad absorption over the range 2500 to 3300 cm^{-1}, and the C=O bond shows an absorption between 1710 and 1760 cm^{-1}. The exact position of C=O absorption depends both on the structure of the molecule and on whether the acid is free (monomeric) or hydrogen-bonded (dimeric). Free carboxyl groups absorb at 1760 cm^{-1}, but the more commonly encountered dimeric carboxyl groups absorb in a broad band centered around 1710 cm^{-1}.

Free carboxyl
(uncommon),
1760 cm^{-1}



Associated carboxyl
(usual case),
1710 cm^{-1}



Both the broad O–H absorption and the C=O absorption at 1710 cm^{-1} (dimeric) are identified in the IR spectrum of butanoic acid shown in **Figure 20.5**.

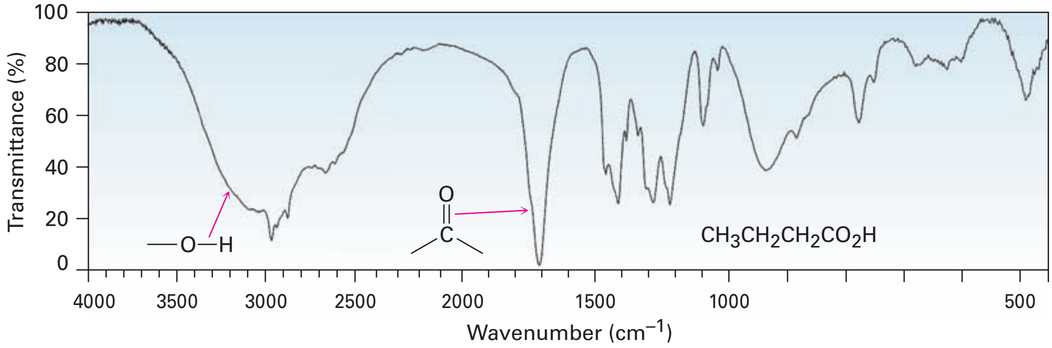


Figure 20.5 IR spectrum of butanoic acid, $CH_3CH_2CH_2CO_2H$.

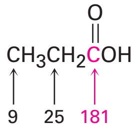
Nitriles show an intense and easily recognizable C≡N bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules. Few other functional groups absorb in this region, so IR spectroscopy is highly diagnostic for nitriles.

Problem 20.15

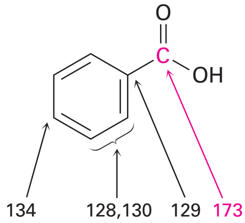
Cyclopentanecarboxylic acid and 4-hydroxycyclohexanone have the same formula ($C_6H_{10}O_2$), and both contain an —OH and a C=O group. How could you distinguish between them by IR spectroscopy?

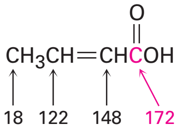
Nuclear Magnetic Resonance Spectroscopy

Carboxyl carbon atoms absorb in the range 165 to 185 δ in the ^{13}C NMR spectrum, with aromatic and α,β-unsaturated acids near the upfield end of the range (~165 δ) and saturated aliphatic acids near the downfield end (~185 δ). Nitrile carbons absorb in the range 115 to 130 δ.

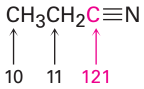


$CH_3CH_2\overset{O}{\overset{\|}{C}}OH$





$CH_3CH{=}CH\overset{O}{\overset{\|}{C}}OH$



In the ^{1}H NMR spectrum, the acidic $-CO_2H$ proton normally absorbs as a singlet near 12 δ. As with alcohols **(Section 17.11)**, the $-CO_2H$ proton can be replaced by deuterium when D_2O is added to the sample tube, causing the absorption to disappear from the NMR spectrum. **Figure 20.6** shows the ^{1}H NMR spectrum of phenylacetic acid. Note that the carboxyl proton absorption occurs at 12.0 δ.

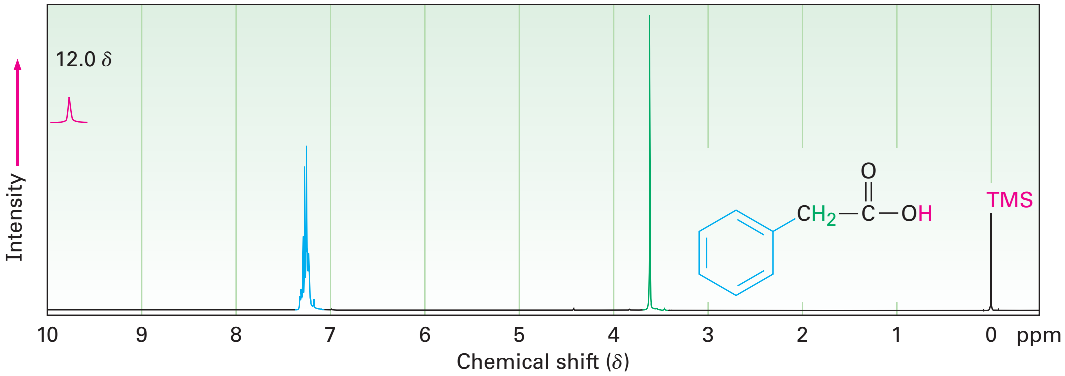


Figure 20.6 Proton NMR spectrum of phenylacetic acid, $C_6H_5CH_2CO_2H$.

Problem 20.16

How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by ^{1}H and ^{13}C NMR spectroscopy? (See Problem 20.15.)

A DEEPER LOOK Vitamin C

The word *vitamin,* despite its common usage, is actually an imprecise term. Generally speaking, a vitamin is an organic substance that a given organism requires in small amounts to live and grow but is unable to synthesize and must obtain in its diet. Thus, to be considered a vitamin, only a *small* amount of the substance is needed—anywhere from a few micrograms to 100 mg or so per day. Dietary substances needed in larger amounts, such as some amino acids and unsaturated fats, are not considered vitamins.

Furthermore, different organisms need different vitamins. More than 4000 species of mammals can synthesize ascorbic acid in their bodies, for instance, but humans are not among them. Ascorbic acid is therefore a human vitamin—what we all know as vitamin C—and must be obtained in our diet. Small amounts of more than a dozen other substances are similarly required by humans: retinol (vitamin A), thiamine (vitamin B_1), and tocopherol (vitamin E), for instance.

Vitamin C is surely the best known of all human vitamins. It was the first to be discovered (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 110,000 metric tons of vitamin C is synthesized worldwide each year, more than the total amount of all other vitamins

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In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency.

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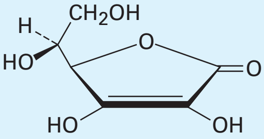
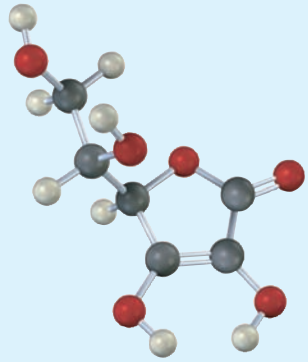
combined. In addition to its use as a vitamin supplement, vitamin C is used as a food preservative, a “flour improver” in bakeries, and an animal food additive.



Vitamin C
(ascorbic acid)



Vitamin C is perhaps most well known for its antiscorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high. The Portuguese explorer Vasco da Gama lost more than half his crew to scurvy during his 2-year voyage around the Cape of Good Hope in 1497–1499.

In more recent times, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in acquired immunodeficiency syndrome (AIDS), and inhibit the development of gastric and cervical cancers. None of these claims have been backed by medical evidence, however. In the largest study yet done of the effect of vitamin C on the common cold, a meta-analysis of more than 100 separate trials covering 40,000 people found no difference in the incidence of colds between those who took supplemental vitamin C regularly and those who did not. When taken *during* a cold, however, vitamin C does appear to decrease the cold’s duration by perhaps a day.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry, beginning with glucose and following the five-step route shown in **Figure 20.7**. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which

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Summary

Key words

carboxyl group, 779
carboxylation, 790
carboxylic acid (RCO_2H), 778
Henderson–Hasselbalch equation, 785
nitrile ($RC{\equiv}N$), 781

Carboxylic acids are among the most useful building blocks for synthesizing other molecules, both in nature and in the chemical laboratory. Thus, an understanding of their properties and reactions is fundamental to understanding biological chemistry. In this chapter, we’ve looked both at acids and at their close relatives, **nitriles** ($RC{\equiv}N$).

Carboxylic acids are named systematically by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. Like aldehydes and ketones, the carbonyl carbon atom is sp^2-hybridized; like alcohols, carboxylic acids are associated through hydrogen-bonding and therefore have high boiling points.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids such as HCl, carboxylic acids dissociate much more readily than alcohols because the resultant carboxylate ions are stabilized by resonance between two equivalent forms.

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is then oxidized by the microorganism *Acetobacter suboxydans*. No chemical reagent is known that is selective enough to oxidize only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used. Treatment with acetone and an acid catalyst then converts four of the other hydroxyl groups into acetal linkages, and the remaining hydroxyl group is chemically oxidized to a carboxylic acid by reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetal groups and causes an internal ester-forming reaction to take place to give ascorbic acid. Each of the five steps takes place in better than 90% yield.

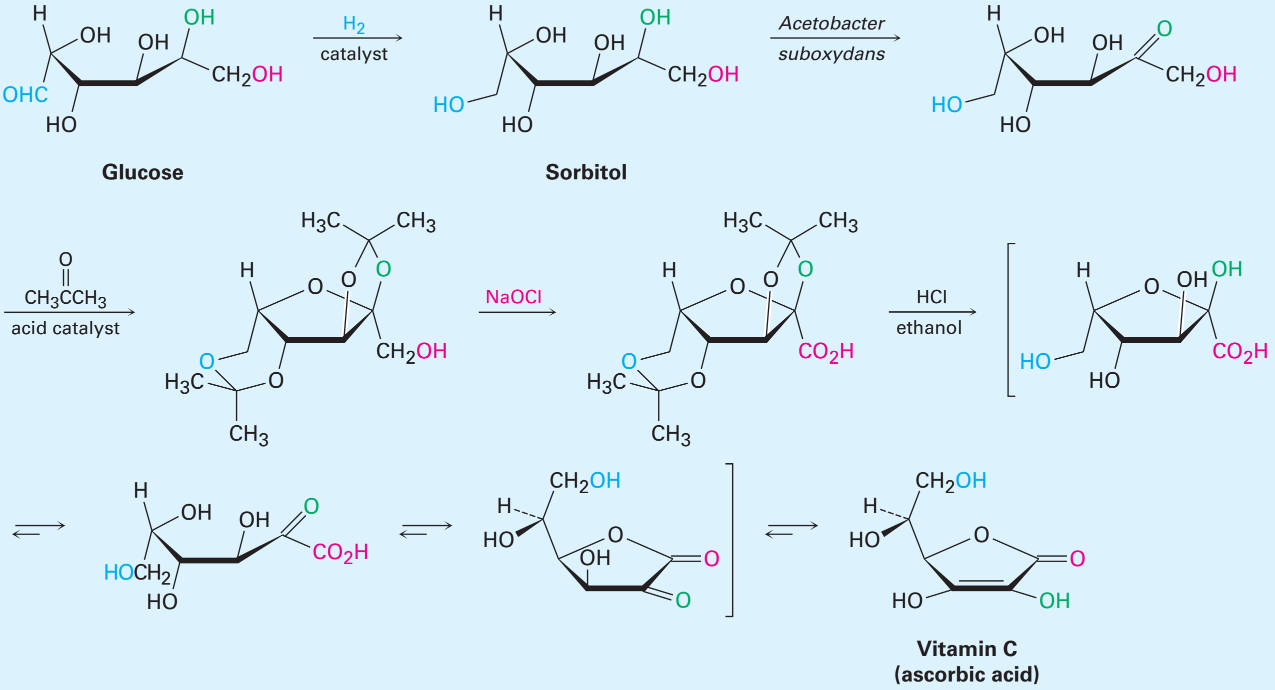


Figure 20.7 The industrial synthesis of ascorbic acid from glucose.

Most carboxylic acids have pK_a values near 5, but the exact pK_a of a given acid depends on structure. Carboxylic acids substituted by electron-withdrawing groups are more acidic (have a lower pK_a) because their carboxylate ions are stabilized. Carboxylic acids substituted by electron-donating groups are less acidic (have a higher pK_a) because their carboxylate ions are destabilized. The extent of dissociation of a carboxylic acid in a buffered solution of a given pH can be calculated with the **Henderson–Hasselbalch equation**. Inside living cells, where the physiological pH = 7.3, carboxylic acids are entirely dissociated and exist as their carboxylate anions.

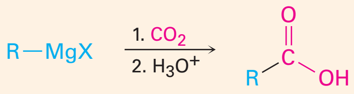
Methods of synthesis for carboxylic acids include (1) oxidation of alkylbenzenes, (2) oxidation of primary alcohols or aldehydes, (3) reaction of Grignard reagents with CO_2 **(carboxylation)**, and (4) hydrolysis of nitriles. General reactions of carboxylic acids include (1) loss of the acidic proton, (2) nucleophilic acyl substitution at the carbonyl group, (3) substitution on the α carbon, and (4) reduction.

Nitriles are similar in some respects to carboxylic acids and are prepared either by S_N2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar $C{\equiv}N$ bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with Grignard reagents to yield ketones.

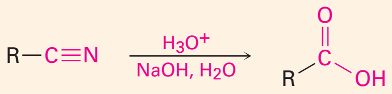
Carboxylic acids and nitriles are easily distinguished spectroscopically. Acids show a characteristic IR absorption at 2500 to 3300 cm^{-1} due to the O–H bond and another at 1710 to 1760 cm^{-1} due to the $C{=}O$ bond; nitriles have an absorption at 2250 cm^{-1}. Acids also show ^{13}C NMR absorptions at 165 to 185 δ and ^{1}H NMR absorptions near 12 δ. Nitriles have a ^{13}C NMR absorption in the range 115 to 130 δ.

Summary of Reactions

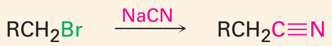
1. Preparation of carboxylic acids (Section 20.5)
   (a) Carboxylation of Grignard reagents



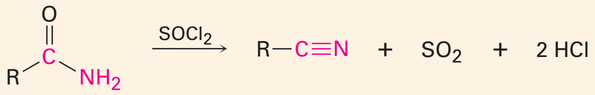
   (b) Hydrolysis of nitriles



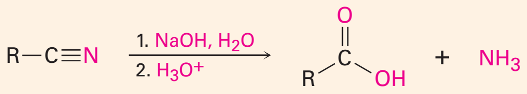
2. Preparation of nitriles (Section 20.7)
   (a) S_N2 reaction of alkyl halides



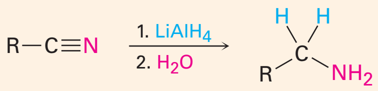
   (b) Dehydration of amides



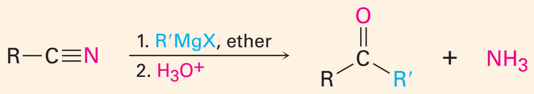
3. Reactions of nitriles (Section 20.7)
   (a) Hydrolysis to yield carboxylic acids



   (b) Reduction to yield primary amines



(c) Reaction with Grignard reagents to yield ketones



$$R{-}C{\equiv}N \xrightarrow[\text{2. } H_3O^+]{\text{1. } R'MgX\text{, ether}} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R' \;+\; NH_3$$

Exercises

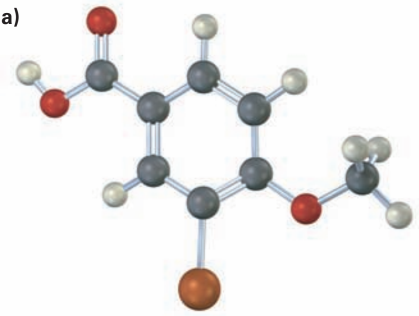
Visualizing Chemistry

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

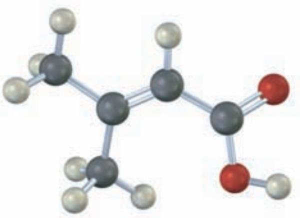
(Problems 20.1–20.16 appear within the chapter.)

20.17 Give IUPAC names for the following carboxylic acids (reddish brown = Br):

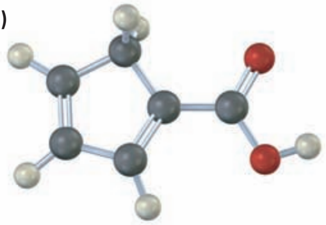
(a)



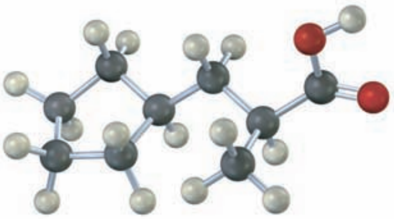
(b)



(c)

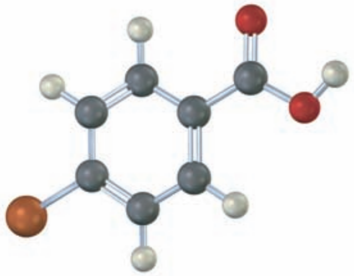


(d)

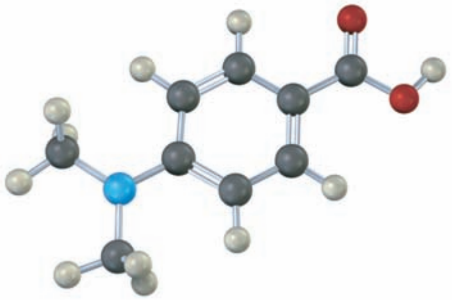


20.18 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Reddish brown = Br.)

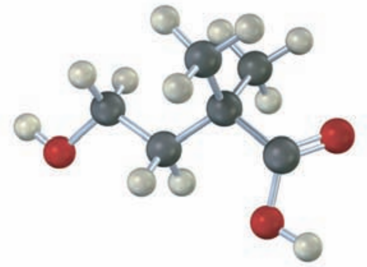
(a)



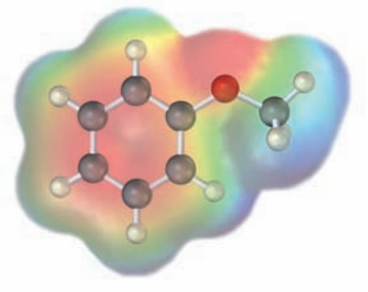
(b)



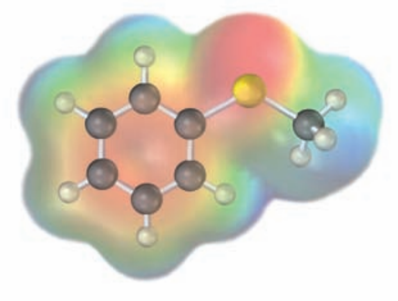
20.19 The following carboxylic acid can't be prepared from an alkyl halide by either the nitrile hydrolysis route or the Grignard carboxylation route. Explain.



20.20 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.



Anisole ($C_6H_5OCH_3$)



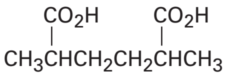
Thioanisole ($C_6H_5SCH_3$)

Additional Problems

Naming Carboxylic Acids and Nitriles

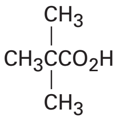
20.21 Give IUPAC names for the following compounds:

(a)



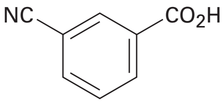
$CH_3\overset{CO_2H}{\overset{|}{C}}HCH_2CH_2\overset{CO_2H}{\overset{|}{C}}HCH_3$

(b)

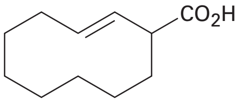


$CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CO_2H$

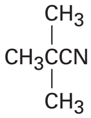
(c)



(d)

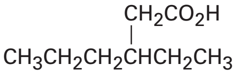


(e)



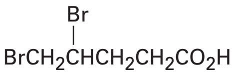
$CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CN$

(f)



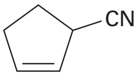
$CH_3CH_2CH_2\overset{CH_2CO_2H}{\overset{|}{C}}HCH_2CH_3$

(g)



$BrCH_2\overset{Br}{\overset{|}{C}}HCH_2CH_2CO_2H$

(h)



20.22 Draw structures corresponding to the following IUPAC names:

(a) *cis*-1,2-Cyclohexanedicarboxylic acid **(b)** Heptanedioic acid
(c) 2-Hexen-4-ynoic acid **(d)** 4-Ethyl-2-propyloctanoic acid
(e) 3-Chlorophthalic acid **(f)** Triphenylacetic acid
(g) 2-Cyclobutenecarbonitrile **(h)** *m*-Benzoylbenzonitrile

20.23 Draw and name the following:

(a) The eight carboxylic acids with the formula $C_6H_{12}O_2$
(b) Three nitriles with the formula C_5H_7N

20.24 Pregabalin, marketed as Lyrica, is an anticonvulsant drug that is also effective in treating chronic pain. The IUPAC name of pregabalin is (*S*)-3-(aminomethyl)-5-methylhexanoic acid. (An aminomethyl group is $-CH_2NH_2$.) Draw the structure of pregabalin.

20.25 Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentanedioic acid. Draw the structure.

Acidity of Carboxylic Acids

20.26 Order the compounds in each of the following sets with respect to increasing acidity:

(a) Acetic acid, oxalic acid, formic acid
(b) *p*-Bromobenzoic acid, *p*-nitrobenzoic acid, 2,4-dinitrobenzoic acid
(c) Fluoroacetic acid, 3-fluoropropanoic acid, iodoacetic acid

20.27 Arrange the compounds in each of the following sets in order of increasing basicity:

(a) Magnesium acetate, magnesium hydroxide, methylmagnesium bromide
(b) Sodium benzoate, sodium *p*-nitrobenzoate, sodium acetylide
(c) Lithium hydroxide, lithium ethoxide, lithium formate

20.28 Calculate pK_a's for the following acids:

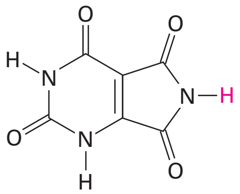
(a) Lactic acid, $K_a = 8.4 \times 10^{-4}$ **(b)** Acrylic acid, $K_a = 5.6 \times 10^{-6}$

20.29 Calculate K_a's for the following acids:

(a) Citric acid, pK_a = 3.14 **(b)** Tartaric acid, pK_a = 2.98

20.30 Thioglycolic acid, $HSCH_2CO_2H$, a substance used in depilatory agents (hair removers) has pK_a = 3.42. What is the percent dissociation of thioglycolic acid in a buffer solution at pH = 3.0?

20.31 In humans, the final product of purine degradation from DNA is uric acid, pK_a = 5.61, which is excreted in the urine. What is the percent dissociation of uric acid in urine at a typical pH = 6.0? Why do you think uric acid is acidic even though it does not have a CO_2H group?



Uric acid

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20.32 Some pK_a data for simple dibasic acids are shown. How can you account for the fact that the difference between the first and second ionization constants decreases with increasing distance between the carboxyl groups?

Name	Structure	pK_1	pK_2
Oxalic	HO_2CCO_2H	1.2	4.2
Succinic	$HO_2CCH_2CH_2CO_2H$	4.2	5.6
Adipic	$HO_2C(CH_2)_4CO_2H$	4.4	5.4

Reactions of Carboxylic Acids and Nitriles

20.33 How could you convert butanoic acid into the following compounds? Write each step showing the reagents needed.
(a) 1-Butanol **(b)** 1-Bromobutane **(c)** Pentanoic acid
(d) 1-Butene **(e)** Octane

20.34 How could you convert each of the following compounds into butanoic acid? Write each step showing all reagents.
(a) 1-Butanol **(b)** 1-Bromobutane **(c)** 1-Butene
(d) 1-Bromopropane **(e)** 4-Octene

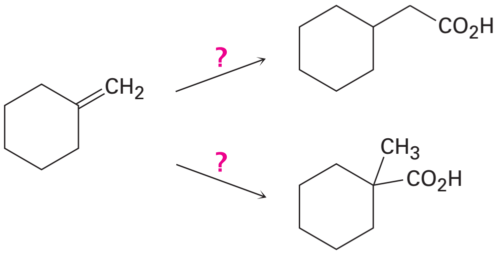
20.35 How could you convert butanenitrile into the following compounds? Write each step showing the reagents needed.
(a) 1-Butanol **(b)** Butylamine **(c)** 2-Methyl-3-hexanone

20.36 How would you prepare the following compounds from benzene? More than one step is required in each case.
(a) *m*-Chlorobenzoic acid **(b)** *p*-Bromobenzoic acid
(c) Phenylacetic acid, $C_6H_5CH_2CO_2H$

20.37 Predict the product of the reaction of *p*-methylbenzoic acid with each of the following:
(a) $LiAlH_4$, then H_3O^+ **(b)** *N*-Bromosuccinimide in CCl_4
(c) CH_3MgBr in ether, then H_3O^+ **(d)** $KMnO_4$, H_3O^+

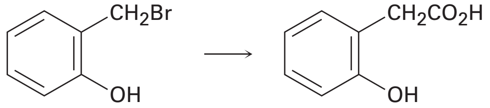
20.38 Using $^{13}CO_2$ as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?
(a) $CH_3CH_2{}^{13}CO_2H$ **(b)** $CH_3{}^{13}CH_2CO_2H$

20.39 How would you carry out the following transformations?



20.40 Which method—Grignard carboxylation or nitrile hydrolysis—would you use for each of the following reactions? Explain.

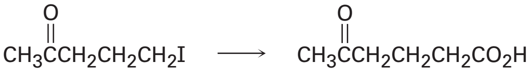
(a)



(b)

$CH_3CH_2\overset{\displaystyle Br}{\overset{|}{C}}HCH_3 \longrightarrow CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCO_2H$

(c)



$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2I \longrightarrow CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2CO_2H$

(d) $HOCH_2CH_2CH_2Br \longrightarrow HOCH_2CH_2CH_2CO_2H$

20.41 1,6-Hexanediamine, a starting material needed for making nylon, can be made from 1,3-butadiene. How would you accomplish the synthesis?

$$H_2C{=}CHCH{=}CH_2 \xrightarrow{?} H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$$

20.42 3-Methyl-2-hexenoic acid (mixture of *E* and *Z* isomers) has been identified as the substance responsible for the odor of human sweat. Synthesize the compound from starting materials having five or fewer carbons.

Spectroscopy

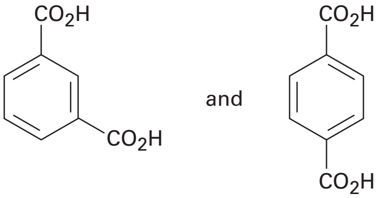
20.43 Propose a structure for a compound $C_6H_{12}O_2$ that dissolves in dilute NaOH and shows the following ^1H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).

20.44 What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.

$CH_3(CH_2)_3CO_2H$	$(CH_3)_2CHCH_2CO_2H$	$(CH_3)_3CCO_2H$
Pentanoic acid	**3-Methylbutanoic acid**	**2,2-Dimethylpropanoic acid**

20.45 How would you use NMR (either ^{13}C or ^1H) to distinguish between the following pairs of isomers?

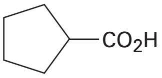
(a)



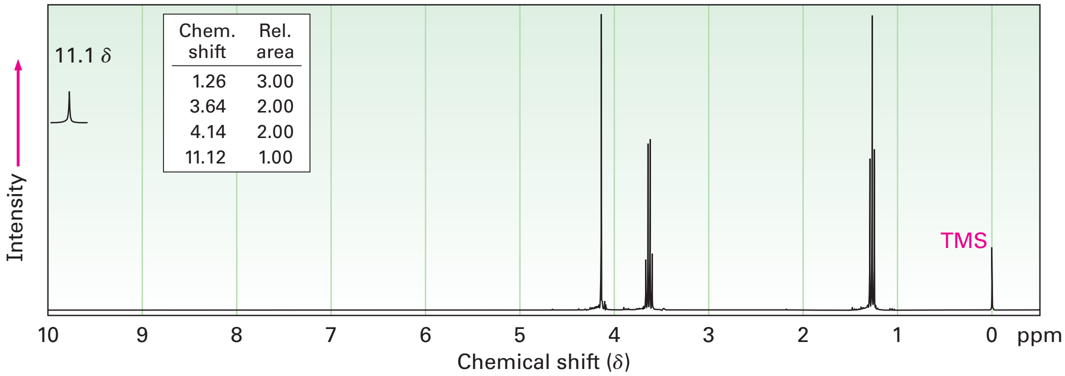
(b) $HO_2CCH_2CH_2CO_2H$ and $CH_3CH(CO_2H)_2$

(c) $CH_3CH_2CH_2CO_2H$ and $HOCH_2CH_2CH_2CHO$

(d) $(CH_3)_2C{=}CHCH_2CO_2H$ and



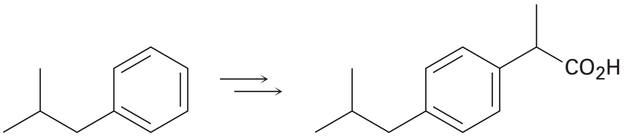
20.46 Compound **A**, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for **A**.



General Problems

20.47 A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN, followed by hydrolysis of the product. After the reaction sequence was carried out, however, none of the desired product could be found. What do you suppose went wrong?

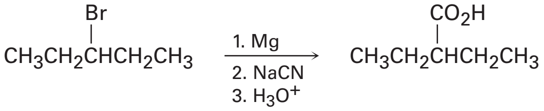
20.48 Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.



Isobutylbenzene **Ibuprofen**

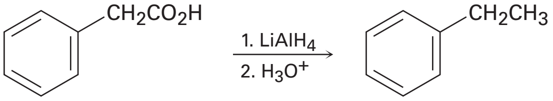
20.49 The following synthetic schemes all have at least one flaw in them. What is wrong with each?

(a)

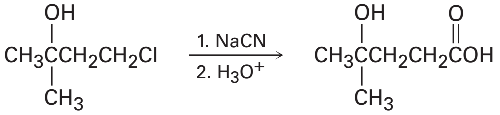


$$\text{CH}_3\text{CH}_2\overset{\text{Br}}{\text{C}}\text{HCH}_2\text{CH}_3 \xrightarrow[\substack{\text{2. NaCN} \\ \text{3. H}_3\text{O}^+}]{\text{1. Mg}} \text{CH}_3\text{CH}_2\overset{\text{CO}_2\text{H}}{\text{C}}\text{HCH}_2\text{CH}_3$$

(b)



(c)

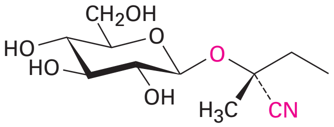


$$\text{CH}_3\underset{\text{CH}_3}{\overset{\text{OH}}{\text{C}}}\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. NaCN}} \text{CH}_3\underset{\text{CH}_3}{\overset{\text{OH}}{\text{C}}}\text{CH}_2\text{CH}_2\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OH}$$

20.50 Naturally occurring compounds called *cyanogenic glycosides,* such as lotaustralin, release hydrogen cyanide, HCN, when treated with aqueous acid. The reaction occurs by hydrolysis of the acetal linkage to form a cyanohydrin, which then expels HCN and gives a carbonyl compound.

(a) Show the mechanism of the acetal hydrolysis and the structure of the cyanohydrin that results.

(b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.

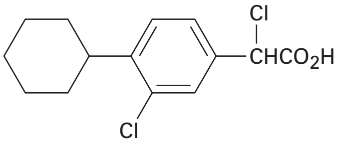


Lotaustralin

20.51 Acid-catalyzed hydrolysis of a nitrile to give a carboxylic acid occurs by initial protonation of the nitrogen atom, followed by nucleophilic addition of water. Review the mechanism of base-catalyzed nitrile hydrolysis in Section 20.7, and then write all the steps involved in the acid-catalyzed reaction, using curved arrows to represent electron flow in each step.

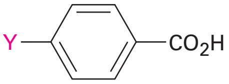
20.52 *p*-Aminobenzoic acid (PABA) is widely used as a sunscreen agent. Propose a synthesis of PABA starting from toluene.

20.53 Propose a synthesis of the anti-inflammatory drug Fenclorac from phenylcyclohexane.



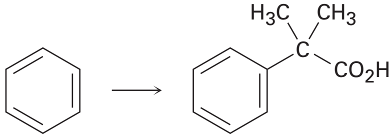
Fenclorac

20.54 The pK_a's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) follow. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has pK_a = 4.19, which of the substituents are activators and which are deactivators?

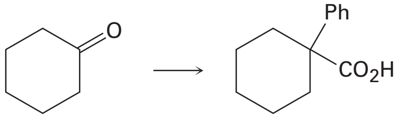
Substituent Y	**pK_a of Y——CO_2H**
—$Si(CH_3)_3$	4.27
—CH=CHC≡N	4.03
—$HgCH_3$	4.10
—OSO_2CH_3	3.84
—PCl_2	3.59

20.55 How would you carry out the following transformations? More than one step is needed in each case.

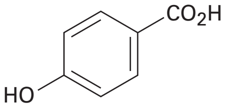
(a)



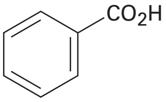
(b)



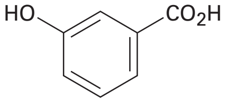
20.56 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.



pK_a = 4.48

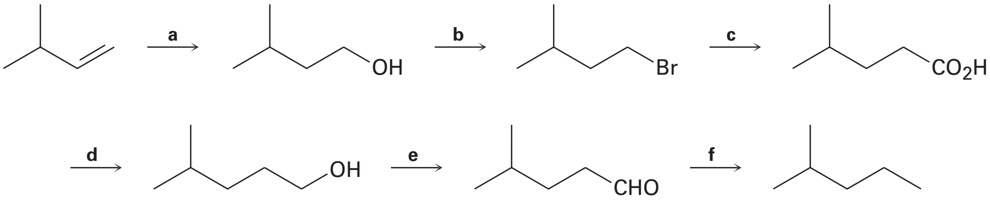


pK_a = 4.19

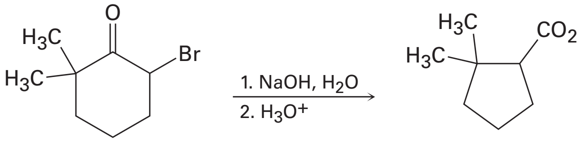


pK_a = 4.07

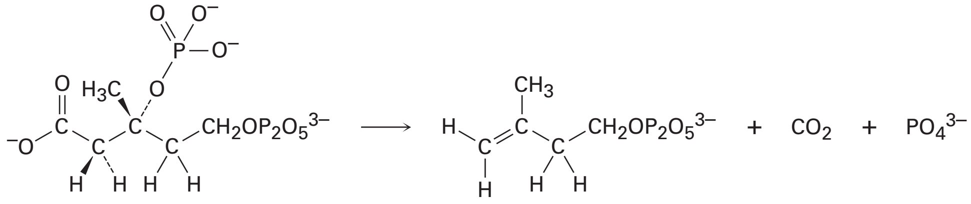
20.57 Identify the missing reagents **a–f** in the following scheme:



20.58 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentanecarboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the *Favorskii reaction*. Propose a mechanism.



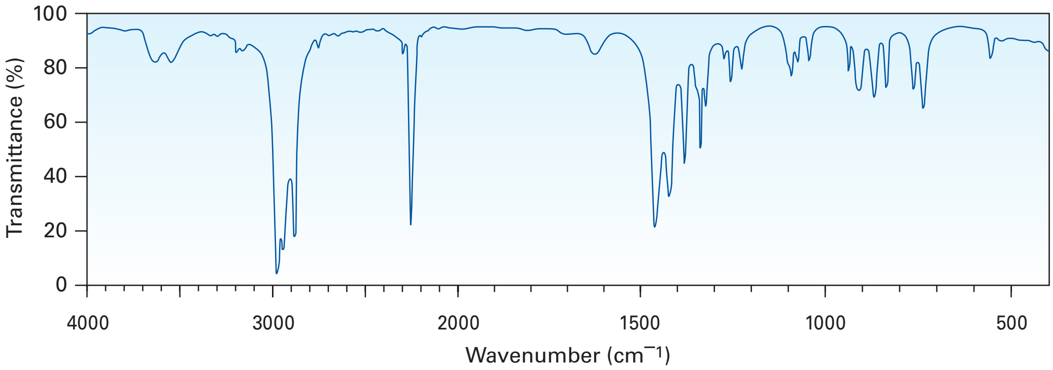
20.59 Naturally occurring compounds called *terpenoids,* which we'll discuss in Section 27.5, are biosynthesized by a pathway that involves loss of CO_2 from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.

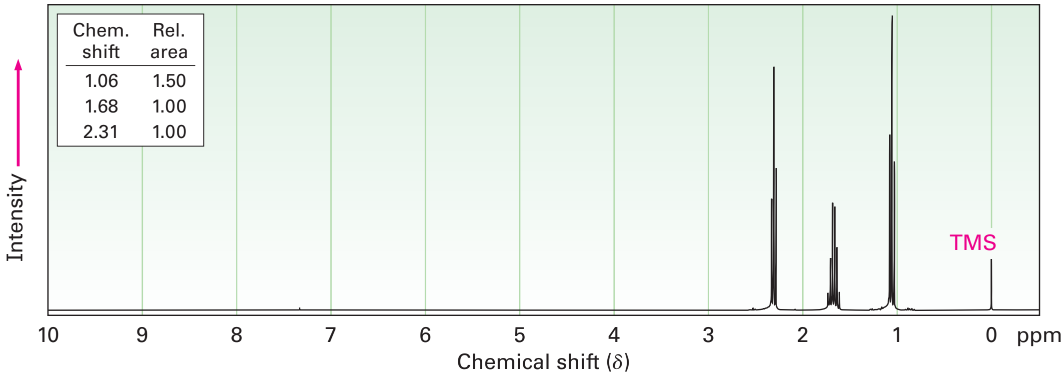


3-Phosphomevalonate 5-diphosphate

Isopentenyl diphosphate

20.60 Propose a structure for a compound, C_4H_7N, that has the following IR and ^1H NMR spectra:

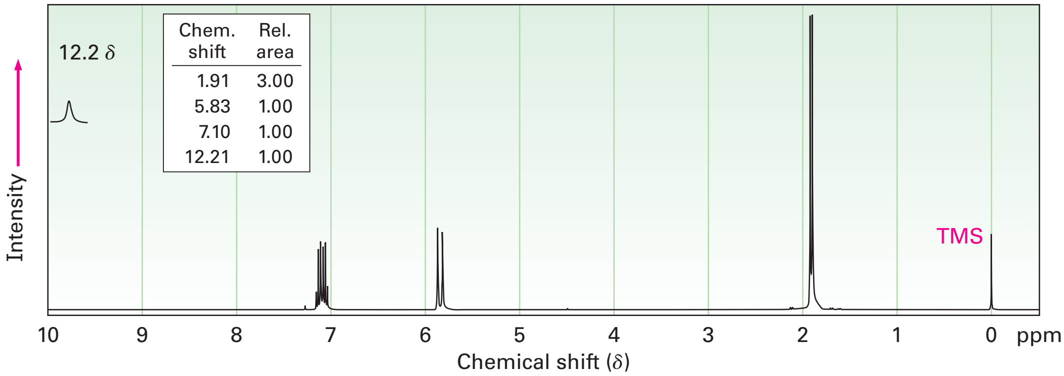




Chem. shift	Rel. area
1.06	1.50
1.68	1.00
2.31	1.00

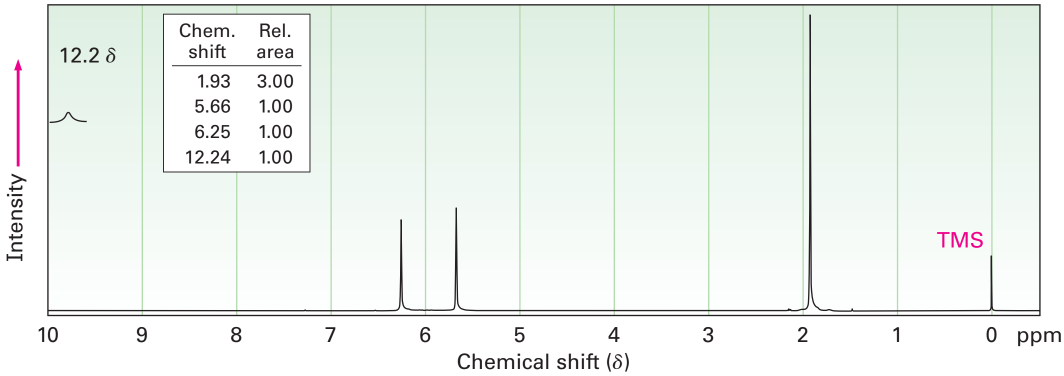
20.61 The two ^1H NMR spectra shown here belong to crotonic acid (*trans*-$CH_3CH{=}CHCO_2H$) and methacrylic acid [$H_2C{=}C(CH_3)CO_2H$]. Which spectrum corresponds to which acid? Explain.

(a)



Chem. shift	Rel. area
1.91	3.00
5.83	1.00
7.10	1.00
12.21	1.00

(b)



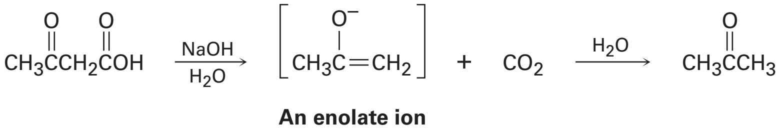
Chem. shift	Rel. area
1.93	3.00
5.66	1.00
6.25	1.00
12.24	1.00

20.62 Propose structures for carboxylic acids that show the following peaks in their ^{13}C NMR spectra. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT-NMR.

(a) $C_7H_{12}O_2$: 25.5 δ (2°), 25.9 δ (2°), 29.0 δ (2°), 43.1 δ (3°), 183.0 δ (4°)

(b) $C_8H_8O_2$: 21.4 δ (1°), 128.3 δ (4°), 129.0 δ (3°), 129.7 δ (3°), 143.1 δ (4°), 168.2 δ (4°)

20.63 Carboxylic acids having a second carbonyl group two atoms away lose CO_2 *(decarboxylate)* through an intermediate enolate ion when treated with base. Write the mechanism of this decarboxylation reaction using curved arrows to show the electron flow in each step.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow[H_2O]{NaOH} \left[CH_3\overset{O^-}{\overset{|}{C}}{=}CH_2 \right] + CO_2 \xrightarrow{H_2O} CH_3\overset{O}{\overset{\|}{C}}CH_3}$$

20.64 In the Ritter reaction, an alkene reacts with a nitrile in the presence of strong aqueous sulfuric acid to yield an amide. Propose a mechanism.