

16

Chemistry of Benzene: Electrophilic Aromatic Substitution

Organic KNOWLEDGE TOOLS

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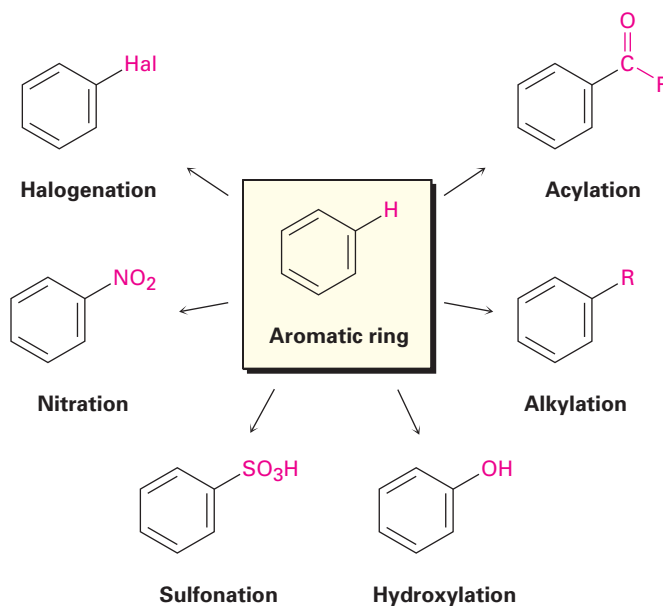


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In the preceding chapter, we looked at *aromaticity*—the stability associated with benzene and related compounds that contain a cyclic conjugated system of $4n + 2 \pi$ electrons. In this chapter, we'll look at some of the unique reactions that aromatic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

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**. That is, an electrophile 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 ($-\text{Cl}$, $-\text{Br}$, I), a nitro group ($-\text{NO}_2$), a sulfonic acid group ($-\text{SO}_3\text{H}$), a hydroxyl group ($-\text{OH}$), an alkyl group ($-\text{R}$), or an acyl group ($-\text{COR}$). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.



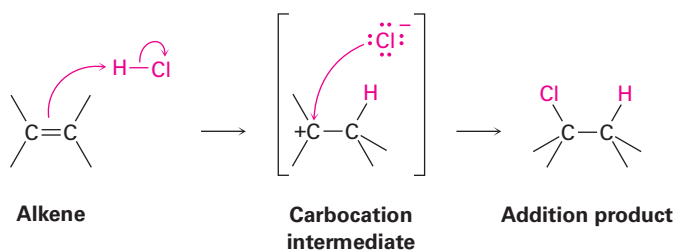
WHY THIS CHAPTER?

This chapter generally 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

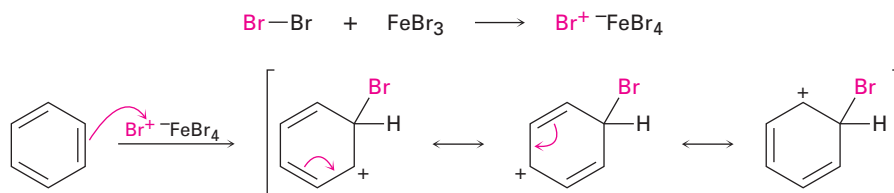
ThomsonNOW Click *Organic Process* to view an animation of the bromination of aromatic rings.

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall what we said in Chapter 6 about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the p orbitals 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.



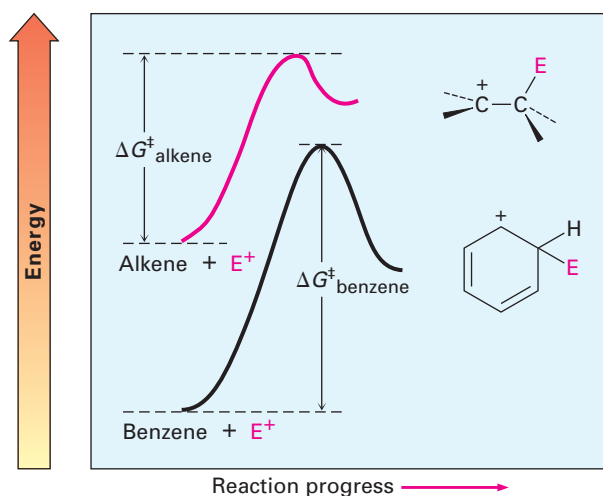
ThomsonNOW Click *Organic Interactive* to practice your problem-solving skills on the mechanism of electrophilic aromatic substitution.

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 $\text{FeBr}_4^- \text{Br}^+$ 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.



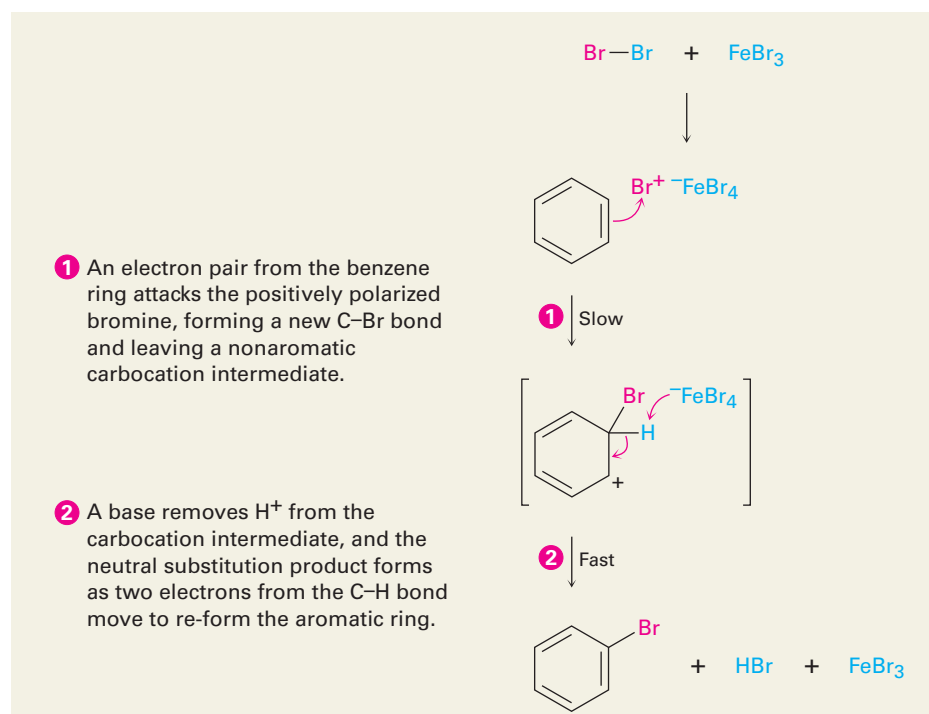
Although more stable than a typical alkyl carbocation because of resonance, the intermediate in electrophilic aromatic substitution is nevertheless much less stable than the starting benzene ring itself, with its 150 kJ/mol (36 kcal/mol) of aromatic stability. Thus, the reaction of an electrophile with 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 ΔG^\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: $\Delta G^\ddagger_{\text{alkene}} < \Delta G^\ddagger_{\text{benzene}}$.



A second 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.

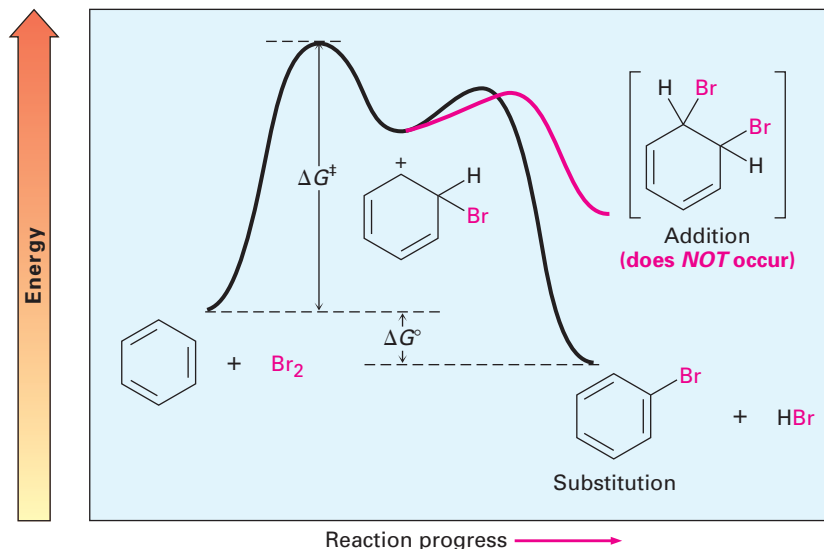
Figure 16.2 MECHANISM: The mechanism of the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.



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. The overall process is exergonic.



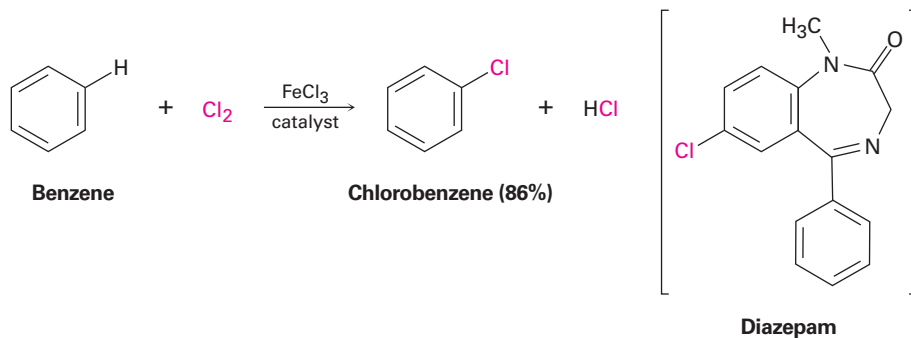
Problem 16.1 Monobromination of toluene gives a mixture of three bromotoluene products. Draw and name them.

16.2 Other Aromatic Substitutions

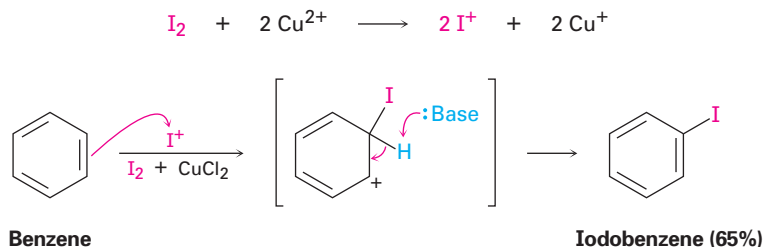
There are many other kinds of electrophilic aromatic substitutions besides bromination, and all are thought to occur by the same general mechanism. Let's look at some of these other reactions briefly.

Aromatic Chlorination and Iodination

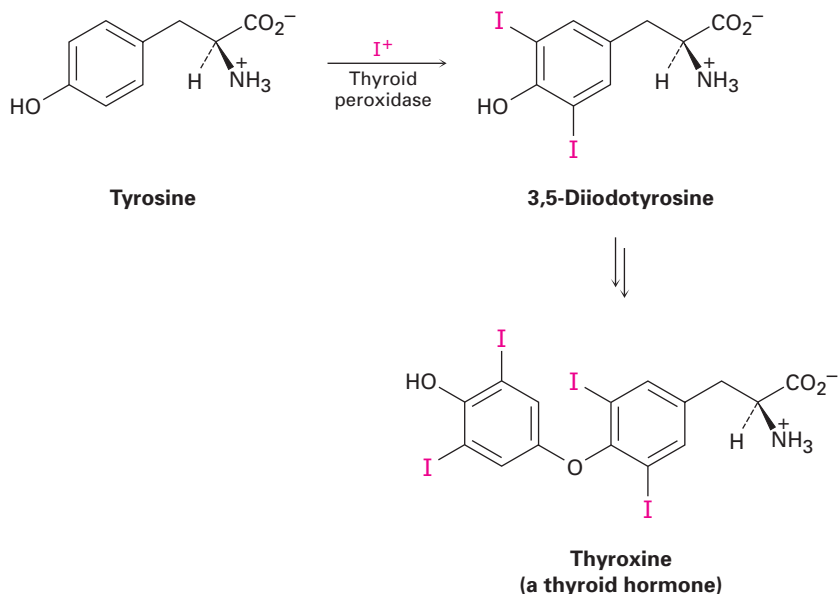
Chlorine and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of monofluoroaromatic products are obtained by direct fluorination. Aromatic rings react with Cl_2 in the presence of FeCl_3 catalyst to yield chlorobenzenes, 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 antianxiety agent diazepam, marketed as Valium.



Iodine itself is unreactive toward aromatic rings, and 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.



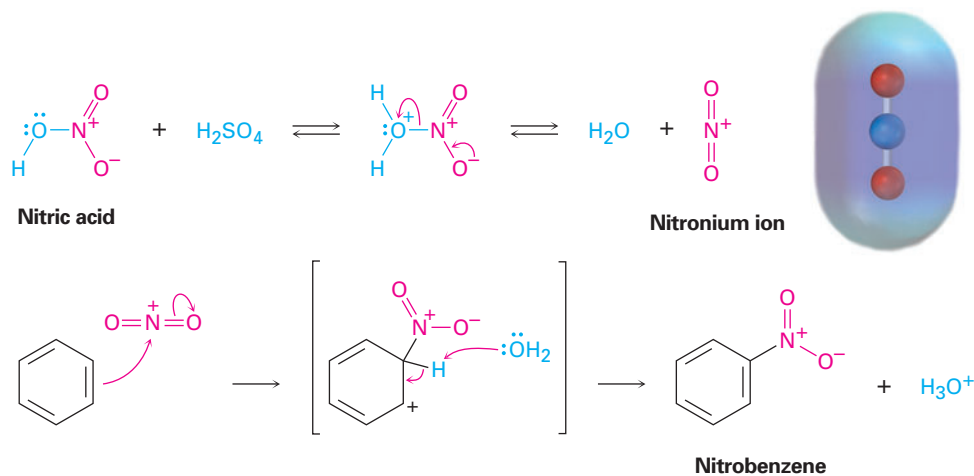
Electrophilic aromatic halogenations occur in the biosynthesis of numerous naturally occurring molecules, particularly those produced by marine organisms. In humans, the best-known example occurs in the thyroid gland during the biosynthesis of thyroxine, a thyroid hormone involved in regulating growth 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 .



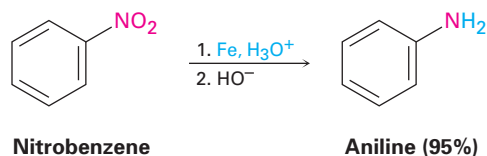
Aromatic Nitration

Aromatic rings can be nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2^+ , which is generated 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 (blue).



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.

Like nitration, 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.

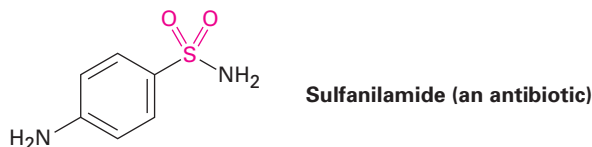
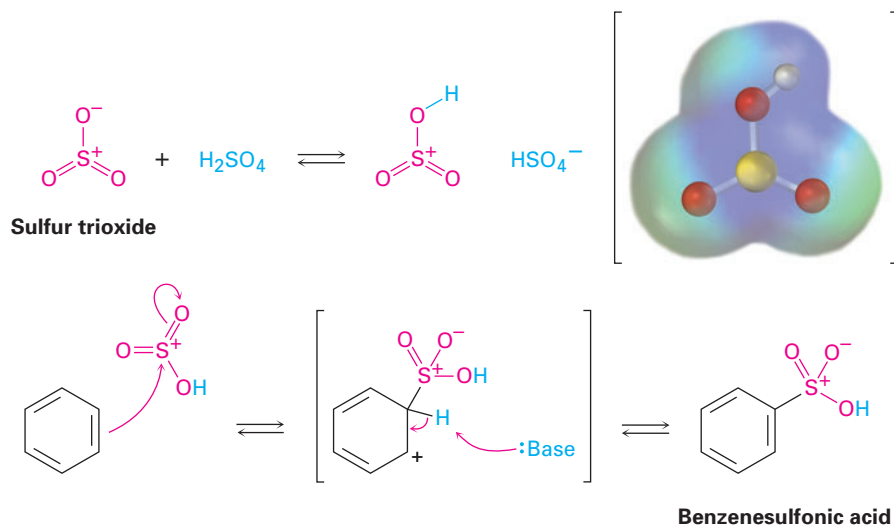
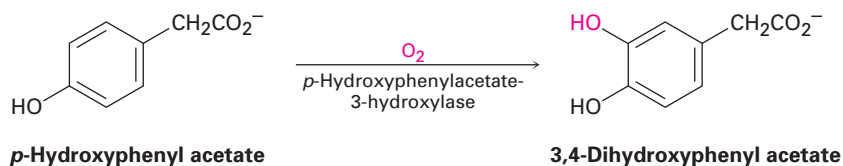


Figure 16.5 The mechanism of electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile HOSO_2^+ shows that sulfur and hydrogen are the most positive atoms (blue).



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*-hydroxyphenyl acetate to give 3,4-dihydroxyphenyl acetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated FADH_2 .



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 exactly what happens, with the electrophilic oxygen arising by protonation of FAD hydroperoxide, RO-OH (Figure 16.6); that is, $\text{RO-OH} + \text{H}^+ \rightarrow \text{ROH} + \text{OH}^+$. The FAD hydroperoxide is itself formed by reaction of FADH_2 with O_2 .

Problem 16.2 How many products might be formed on chlorination of *o*-xylene (*o*-dimethylbenzene), *m*-xylene, and *p*-xylene?

Problem 16.3 When benzene is treated with D_2SO_4 , deuterium slowly replaces all six hydrogens in the aromatic ring. Explain.

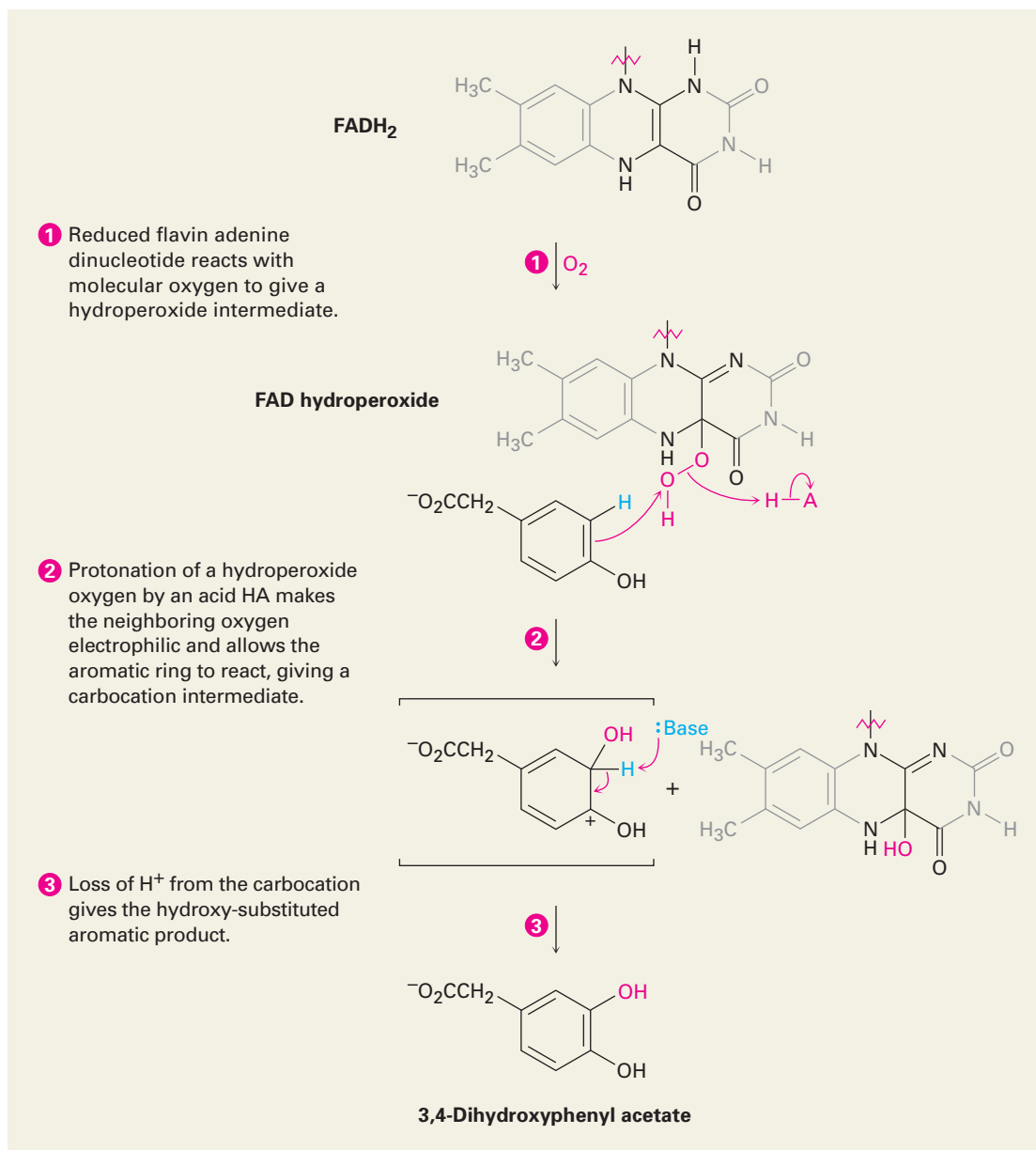


Figure 16.6 MECHANISM: Mechanism of the electrophilic hydroxylation of *p*-hydroxyphenyl acetate, by reaction with FAD hydroperoxide. The hydroxylating species is an “OH⁺ equivalent” that arises by protonation of FAD hydroperoxide, RO–OH + H⁺ → ROH + OH⁺.

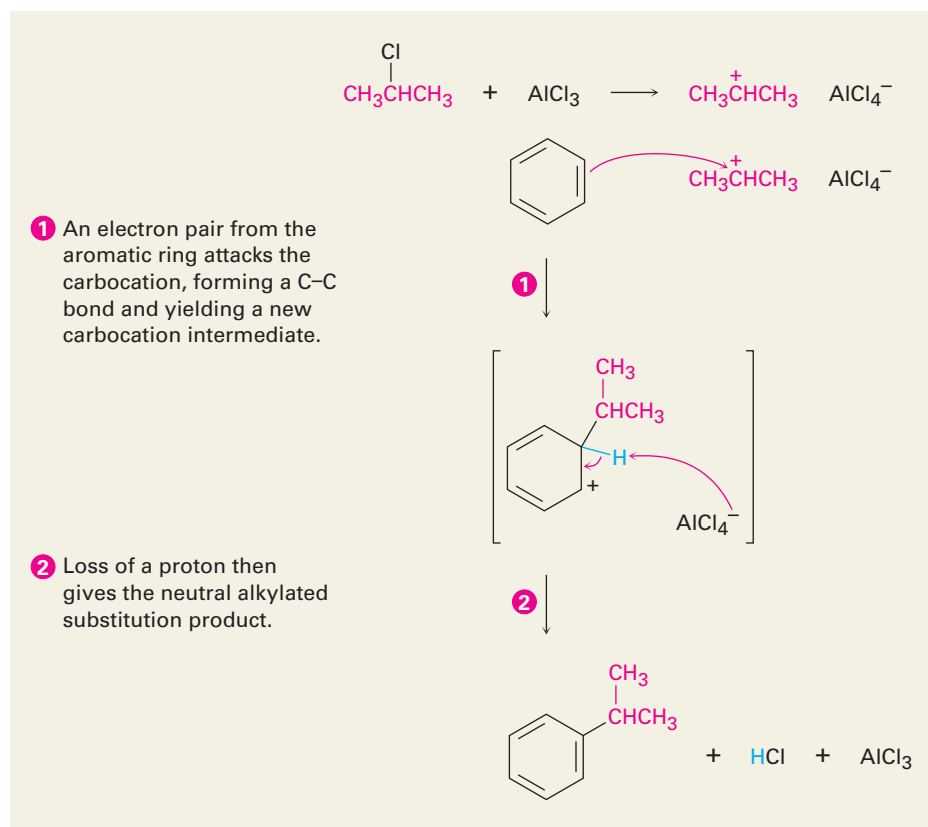
16.3 Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction

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).

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.



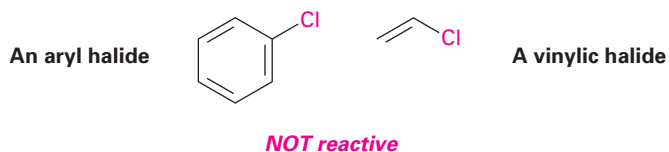
Charles Friedel

Charles Friedel (1832–1899) was born in Strasbourg, France, and studied at the Sorbonne in Paris. Trained as both a mineralogist and a chemist, he was among the first to attempt to manufacture synthetic diamonds. He was professor of mineralogy at the School of Mines before becoming professor of chemistry at the Sorbonne (1884–1899).

James Mason Crafts

James Mason Crafts (1839–1917) was born in Boston, Massachusetts, and graduated from Harvard in 1858. Although he did not receive a Ph.D., he studied with eminent chemists in Europe for several years and was appointed in 1868 as the first professor of chemistry at the newly founded Cornell University in Ithaca, New York. Ithaca winters proved too severe, however, and he soon moved to the Massachusetts Institute of Technology, where he served as president from 1897 to 1900.

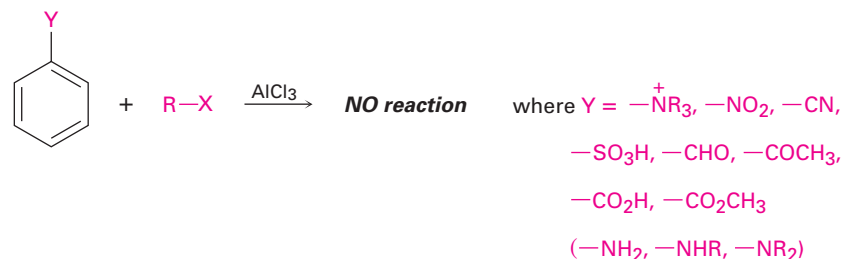
Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only *alkyl* halides can be used. Aromatic (*aryl*) halides and vinylic halides do not react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.



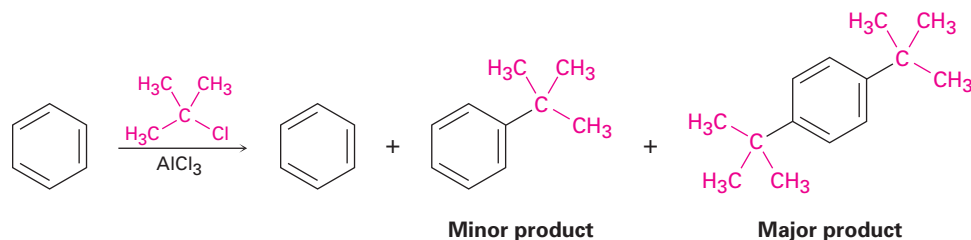
Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group

such as carbonyl (C=O) or by an amino group ($-\text{NH}_2$, NHR , $-\text{NR}_2$). 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.

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 an amino group.

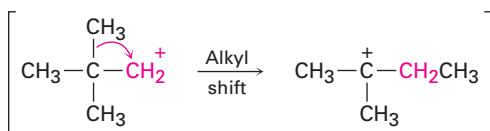
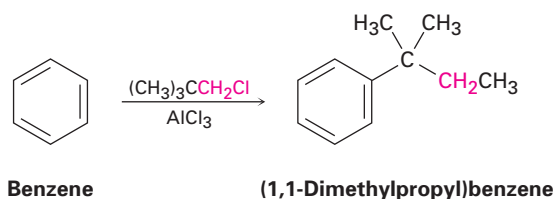
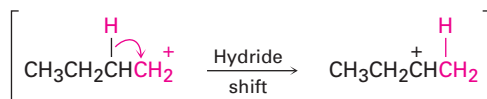
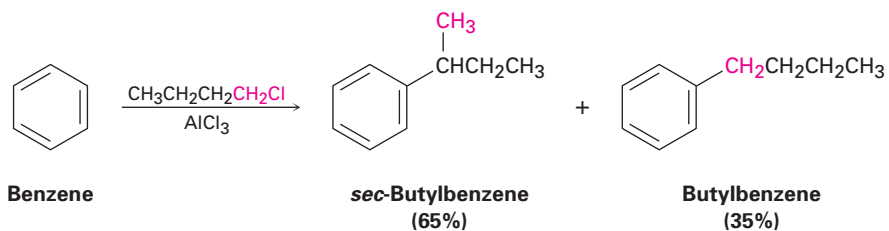


A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation*. 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.

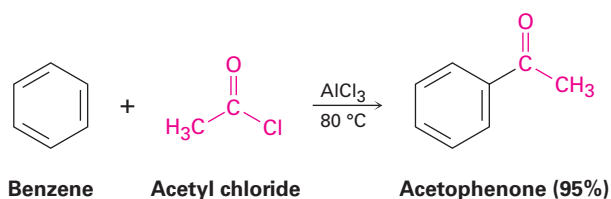


Yet a final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2:1 ratio 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 6.11) 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** ($-\text{COR}$; 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.

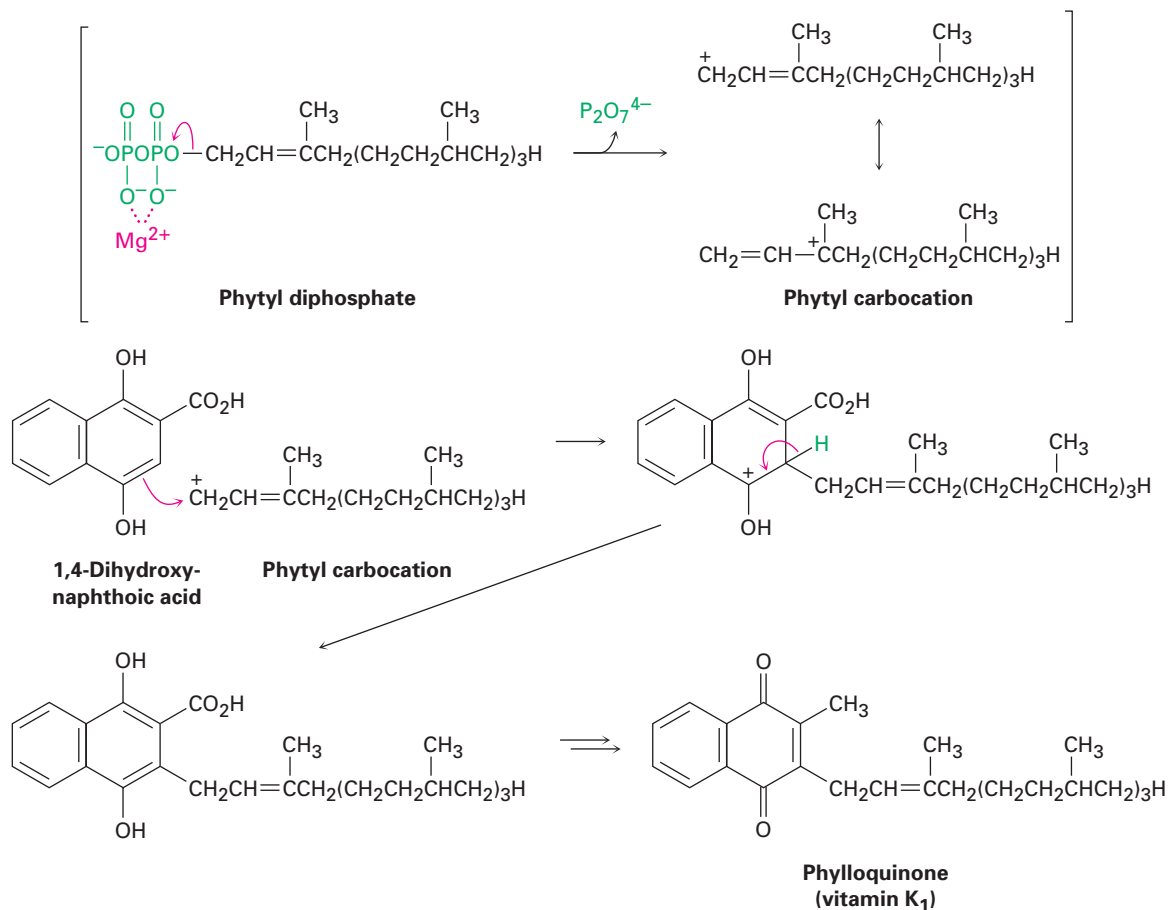


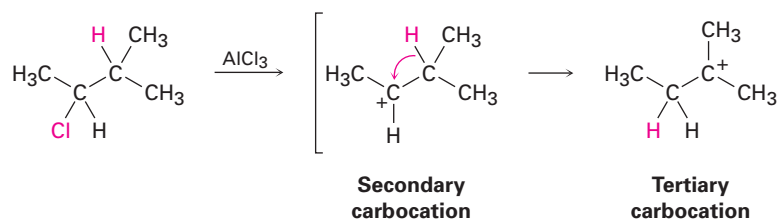
Figure 16.10 Biosynthesis of phylloquinone (vitamin K₁) from 1,4-dihydroxynaphthoic acid. The key step that joins the 20-carbon phytol side chain to the aromatic ring is a Friedel–Crafts-like electrophilic substitution reaction.

WORKED EXAMPLE 16.1

Predicting the Product of a Carbocation Rearrangement

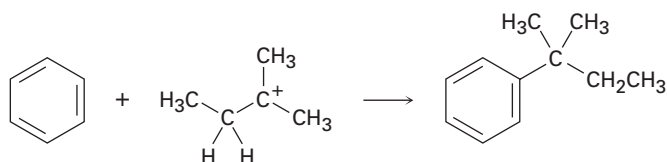
The Friedel–Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of AlCl_3 occurs with a carbocation rearrangement. What is the structure of the product?

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

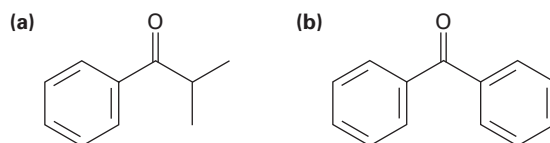


Problem 16.4 Which of the following alkyl halides would you expect to undergo Friedel–Crafts reaction *without* rearrangement? Explain.

- (a) $\text{CH}_3\text{CH}_2\text{Cl}$ (b) $\text{CH}_3\text{CH}_2\text{CH}(\text{Cl})\text{CH}_3$ (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$
 (d) $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$ (e) Chlorocyclohexane

Problem 16.5 What is the major monosubstitution product from the Friedel–Crafts reaction of benzene with 1-chloro-2-methylpropane in the presence of AlCl_3 ?

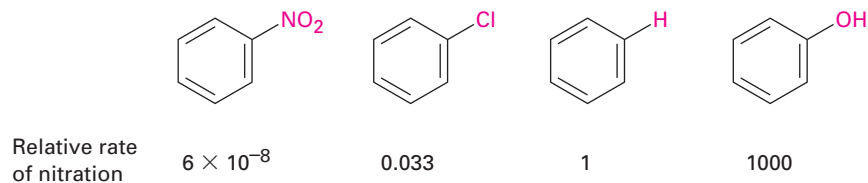
Problem 16.6 Identify the carboxylic acid chloride that might be used in a Friedel–Crafts acylation reaction to prepare each of the following acylbenzenes:



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.

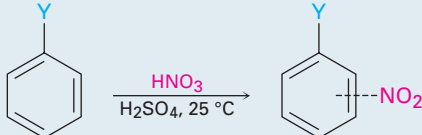
■ **Substituents affect the reactivity of the aromatic ring.** Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an $-\text{OH}$ substituent makes the ring 1000 times more reactive than benzene, while an $-\text{NO}_2$ 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. Table 16.1 lists

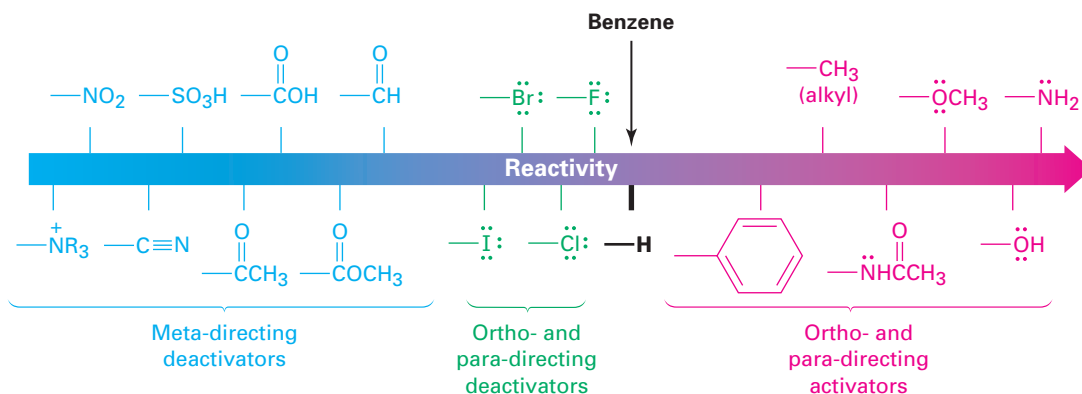
experimental results for the nitration of some substituted benzenes and shows that some groups direct substitution primarily to the ortho and para positions, while other groups direct substitution primarily to the meta position.

Table 16.1 Orientation of Nitration in Substituted Benzenes



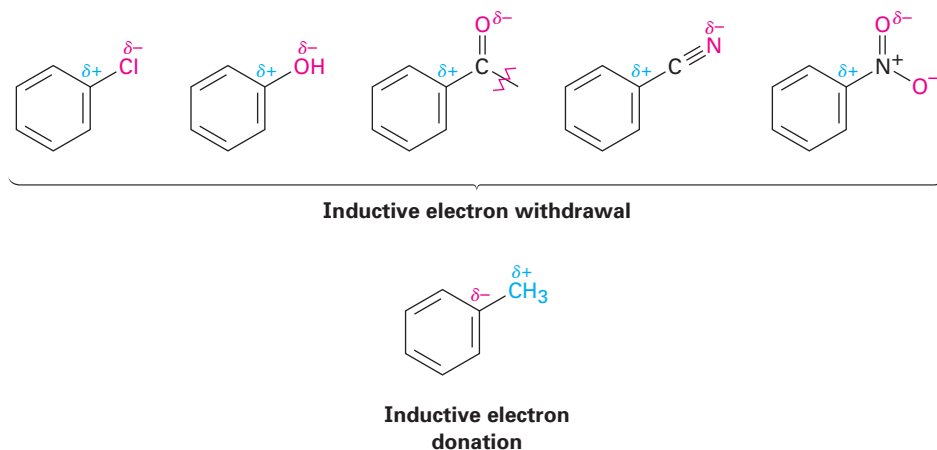
	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				Ortho- and para-directing deactivators			
$-\overset{+}{\text{N}}(\text{CH}_3)_3$	2	87	11	$-\text{F}$	13	1	86
$-\text{NO}_2$	7	91	2	$-\text{Cl}$	35	1	64
$-\text{CO}_2\text{H}$	22	76	2	$-\text{Br}$	43	1	56
$-\text{CN}$	17	81	2	$-\text{I}$	45	1	54
$-\text{CO}_2\text{CH}_3$	28	66	6	Ortho- and para-directing activators			
$-\text{COCH}_3$	26	72	2	$-\text{CH}_3$	63	3	34
$-\text{CHO}$	19	72	9	$-\text{OH}$	50	0	50
				$-\text{NHCOCH}_3$	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 effects of the groups correlate with their reactivities. All meta-directing groups are deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

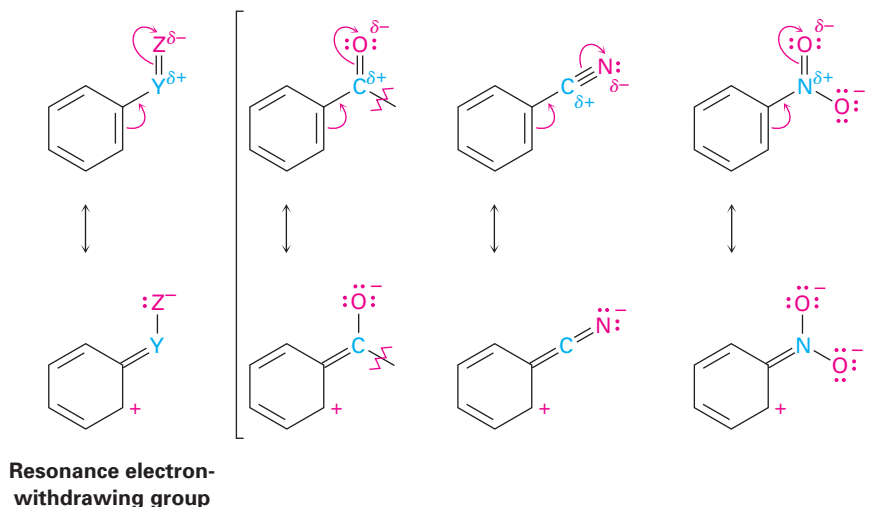


Active Figure 16.11 Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.

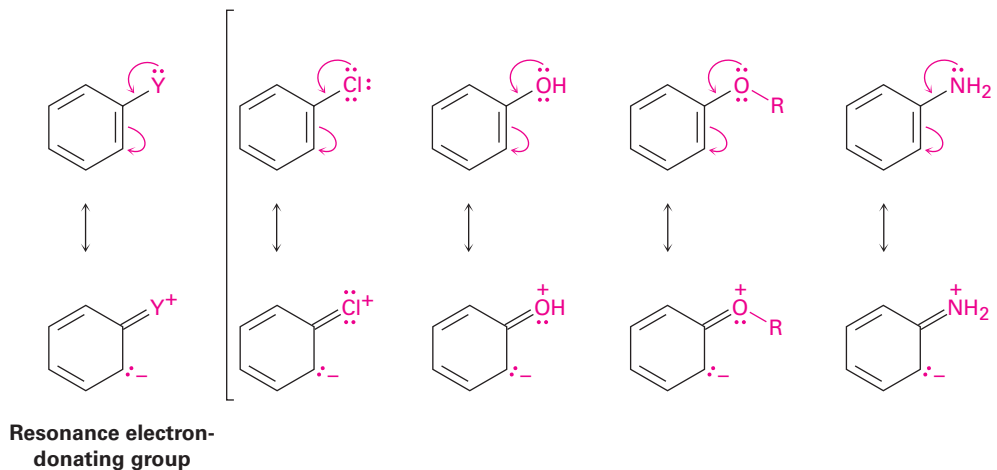
Reactivity and orientation in electrophilic aromatic substitutions are controlled by an interplay of inductive effects and resonance effects. As we saw in Sections 2.1 and 6.9, an **inductive effect** is the withdrawal or donation of electrons through a σ bond due to electronegativity. Halogens, hydroxyl 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 6.6) and carbocations (Section 6.9).



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. Pi electrons flow from the rings to the substituents, 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.



Conversely, halogen, hydroxyl, alkoxy (–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.



ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from electrophilic aromatic substitutions on substituted arenes.

One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxy, 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 same $-X$, $-O$, or $-N$ atoms. When the two effects act in opposite directions, the stronger of the two dominates.

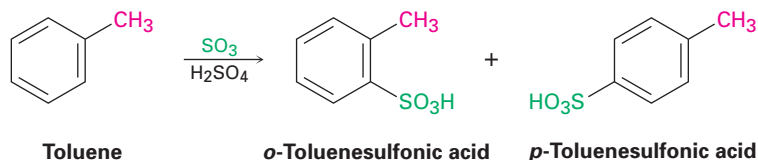
WORKED EXAMPLE 16.2

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



Problem 16.7 Write resonance structures for nitrobenzene to show the electron-withdrawing resonance effect of the nitro group.

Problem 16.8 Write resonance structures for chlorobenzene to show the electron-donating resonance effect of the chloro group.

- 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. Hydroxyl, alkoxy, and amino groups are activating because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Alkyl groups are activating because of their electron-donating inductive effect.

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. Carbonyl, cyano, and nitro groups are deactivating because of both electron-withdrawing resonance and inductive effects. Halogens are deactivating because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect.

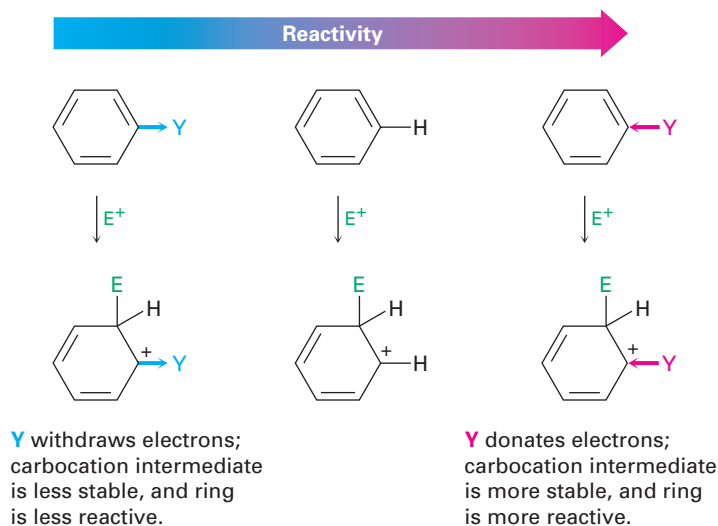
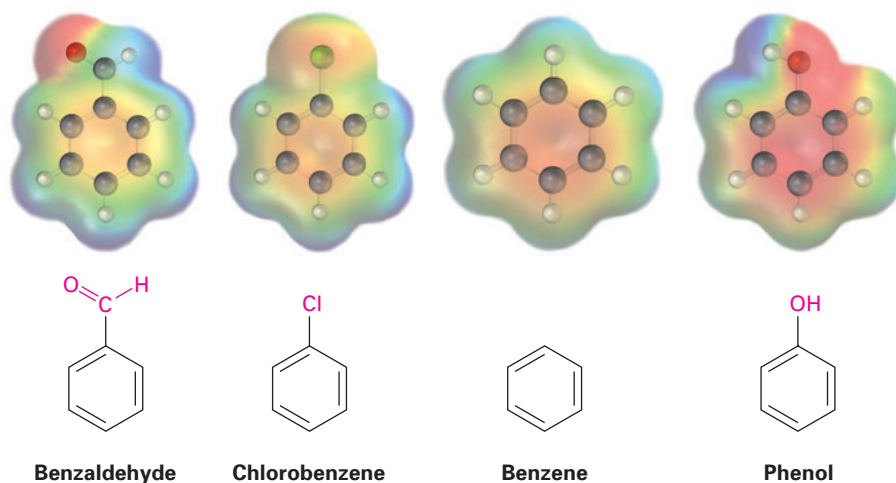


Figure 16.12 compares electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. The ring is more positive (yellow-green) when an electron-withdrawing group such as $-\text{CHO}$ or $-\text{Cl}$ is present and more negative (red) when an electron-donating group such as $-\text{OH}$ is present.

Figure 16.12 Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group ($-\text{CHO}$ or $-\text{Cl}$) makes the ring more electron-poor (yellow-green), while an electron-donating group ($-\text{OH}$) makes the ring more electron-rich (red).

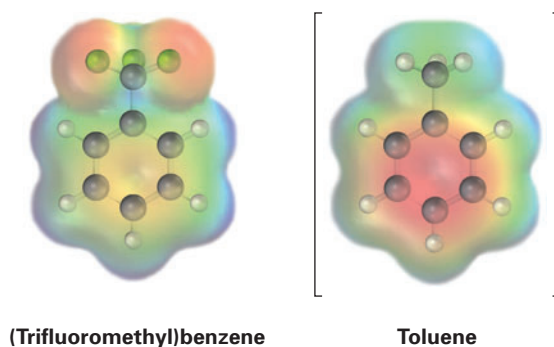


Problem 16.10 Rank the compounds in each group in order of their reactivity to electrophilic substitution:

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

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

Problem 16.12 An electrostatic potential map of (trifluoromethyl)benzene, $\text{C}_6\text{H}_5\text{CF}_3$, is shown. Would you expect (trifluoromethyl)benzene to be more reactive or less reactive than toluene toward electrophilic substitution? Explain.



Ortho- and Para-Directing Activators: Alkyl Groups

Inductive and resonance effects account for the directing effects of substituents as well as for their activating or deactivating effects. 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.

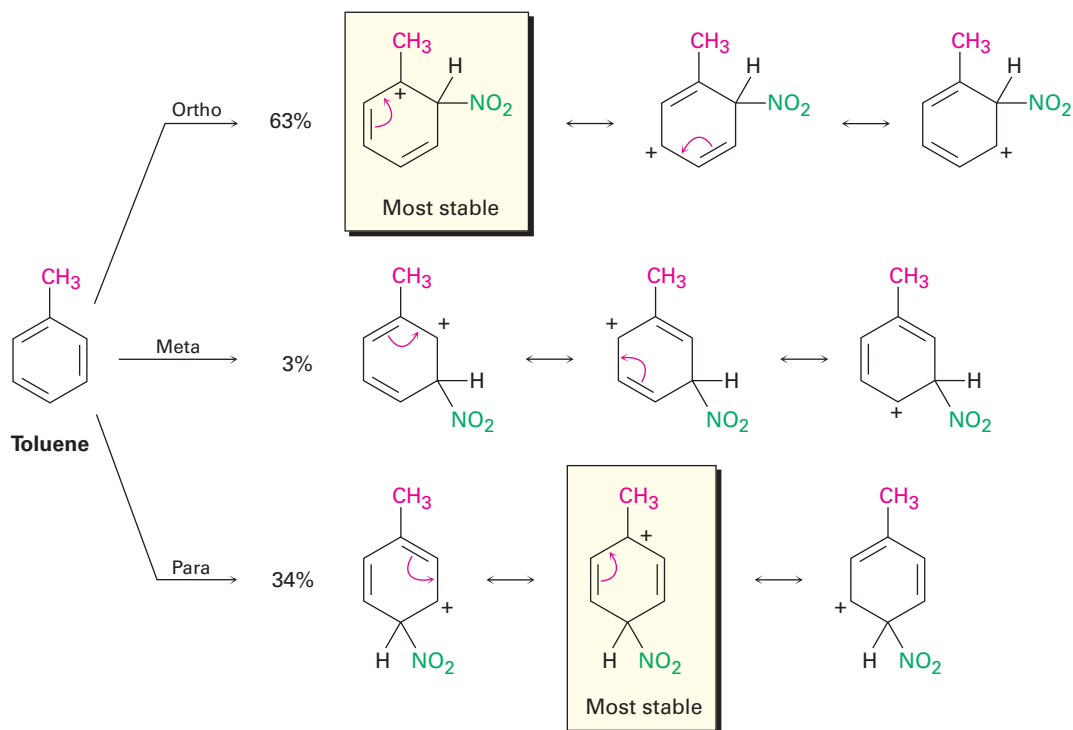


Figure 16.13 Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in Figure 16.13. All three intermediates are resonance-stabilized, but *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 best 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 NH₂

Hydroxyl, alkoxy, and amino groups are also ortho–para activators, but for a different reason than for alkyl groups. As described in the previous section, hydroxyl, alkoxy, and amino groups have a strong, electron-donating resonance effect that outweighs a weaker electron-withdrawing inductive effect. When phenol is nitrated, for instance, only ortho and para reaction is observed. As shown in Figure 16.14, all three possible carbocation intermediates are stabilized by resonance, but the intermediates from ortho and para reaction are stabilized most. Only the ortho and para intermediates have resonance forms in which the positive charge is stabilized by donation of an electron pair from oxygen. The intermediate from meta reaction has no such stabilization.

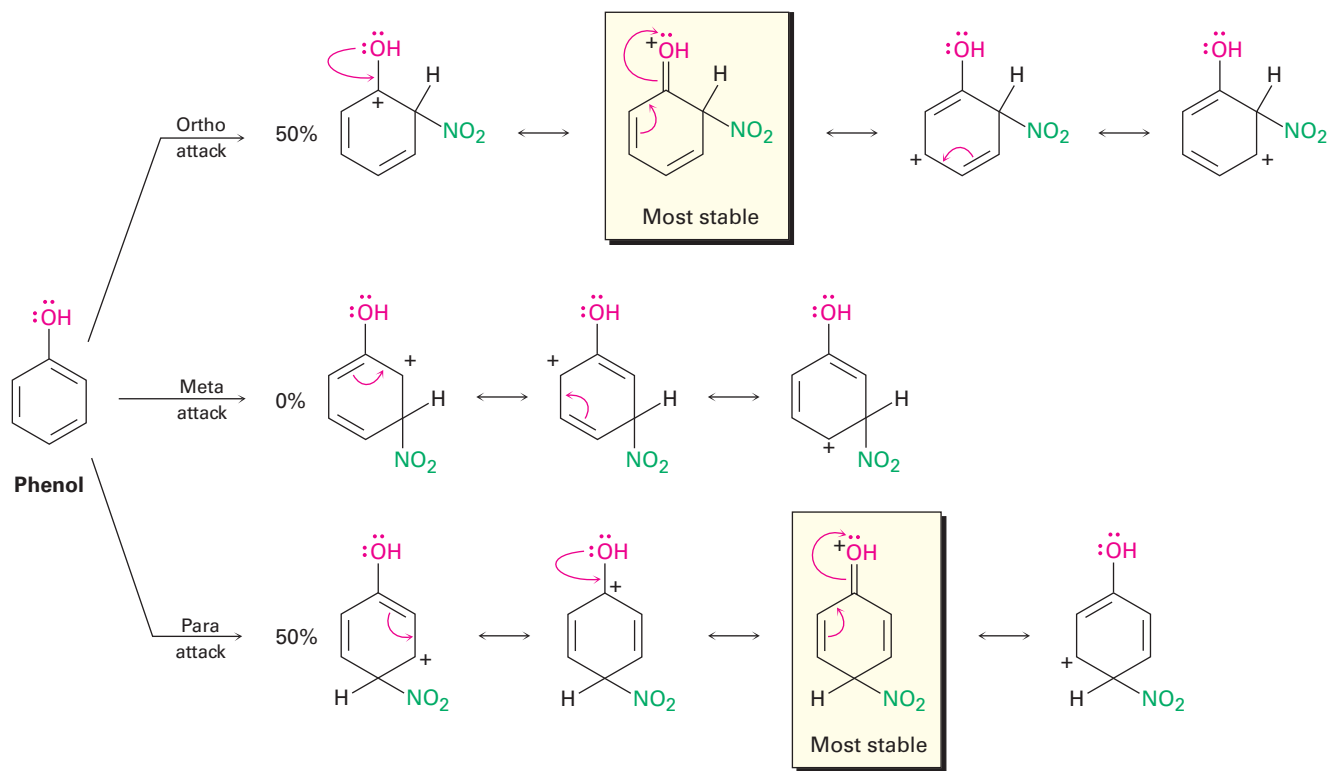
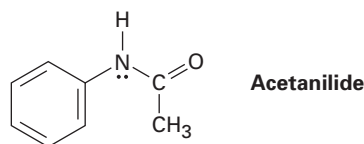


Figure 16.14 Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because of resonance donation of electrons from oxygen.

Problem 16.13 Acetanilide is less reactive than aniline toward electrophilic substitution. Explain.



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 felt only at the ortho and para positions (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.

Note again that halogens, hydroxyl, alkoxy, and amino groups *withdraw* electrons inductively and *donate* electrons by resonance. Halogens have a

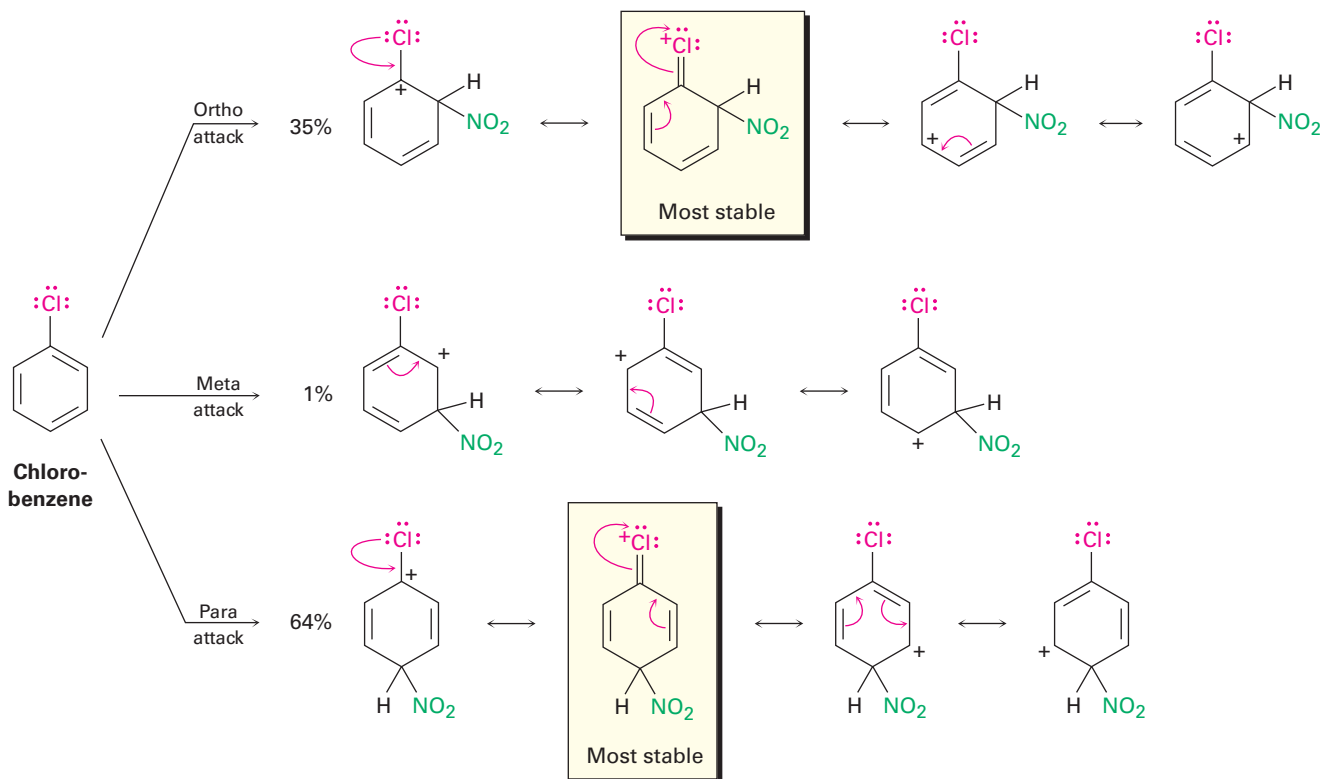


Figure 16.15 Carbocation intermediates in the nitration of chlorobenzene. The ortho and para intermediates are more stable than the meta intermediate because of electron donation of the halogen lone-pair electrons.

stronger electron-withdrawing inductive effect but a weaker electron-donating resonance effect and are thus deactivators. Hydroxyl, alkoxy, 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

Meta-directing deactivators, such as $-\text{CHO}$, act through a combination of electron-withdrawing inductive and resonance effects that reinforce each other and are felt most strongly at the ortho and para positions. As a result, the ortho and para intermediates are less stable so reaction with an electrophile occurs at the meta position (Figure 16.16).

Problem 16.14 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?

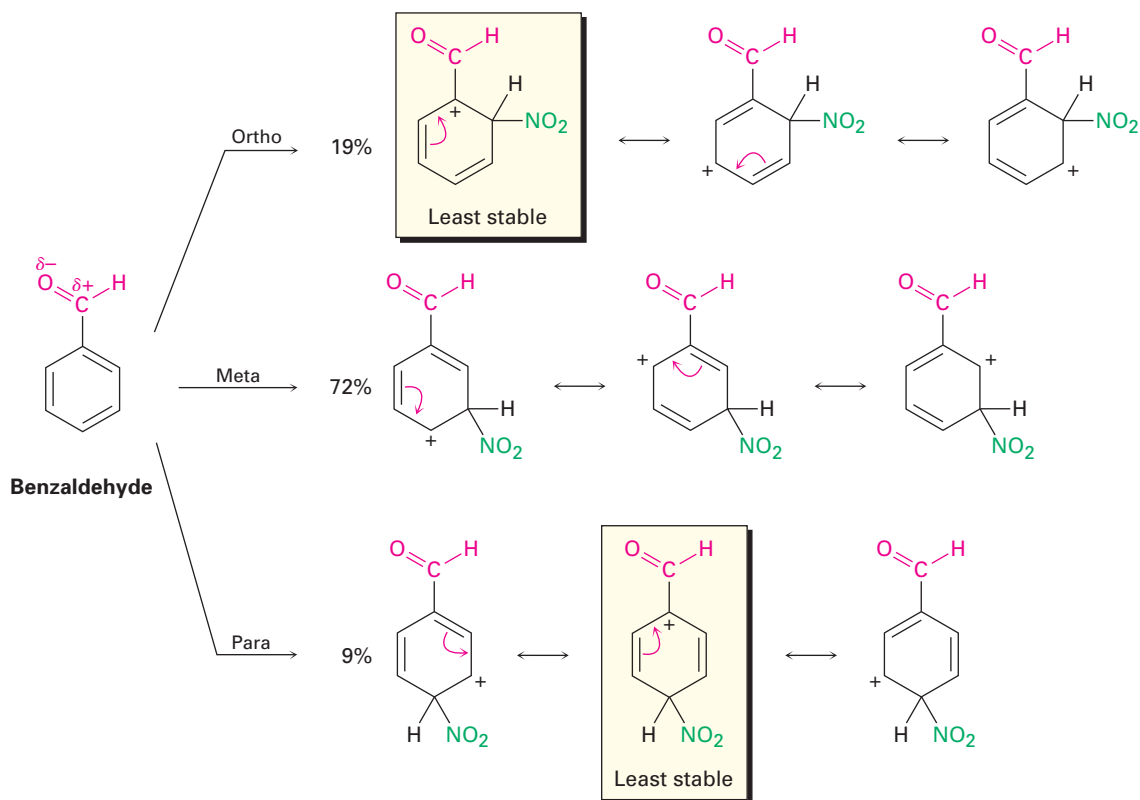


Figure 16.16 Carbocation intermediates in the chlorination of benzaldehyde. The ortho and para intermediates are less stable than the meta intermediate.

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

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.

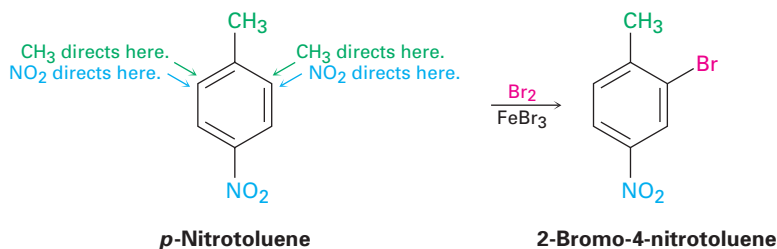
Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

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 ₂ R -COR, -CO ₂ H	Deactivating	Meta	Strong withdrawing	Strong withdrawing

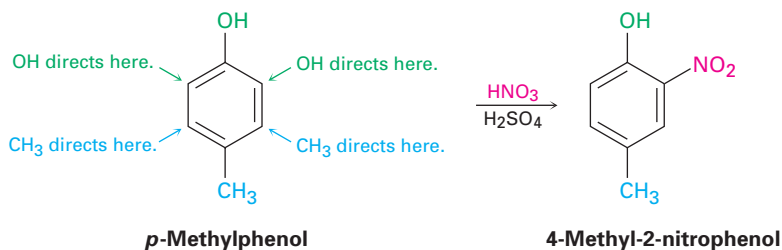
16.6 Trisubstituted Benzenes: Additivity of Effects

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 now 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.

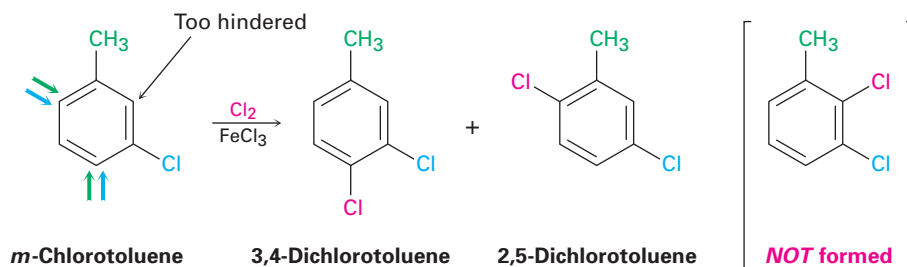
1. If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic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



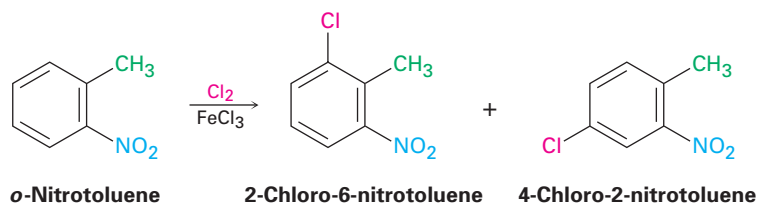
2. If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products often result. For example, bromination of *p*-methylphenol yields primarily 2-bromo-4-methylphenol because $-\text{OH}$ is a more powerful activator than $-\text{CH}_3$.



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, usually by substitution of an ortho-disubstituted compound.



But:



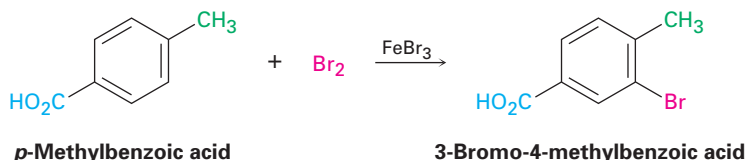
WORKED EXAMPLE 16.3

Predicting the Product of Substitution on a Disubstituted Benzene

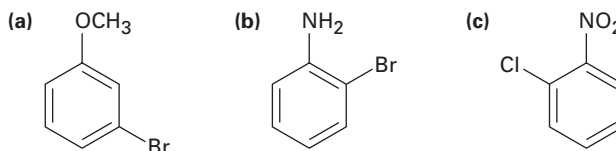
What product would you expect from bromination of *p*-methylbenzoic acid?

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 ($-\text{CO}_2\text{H}$) 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.

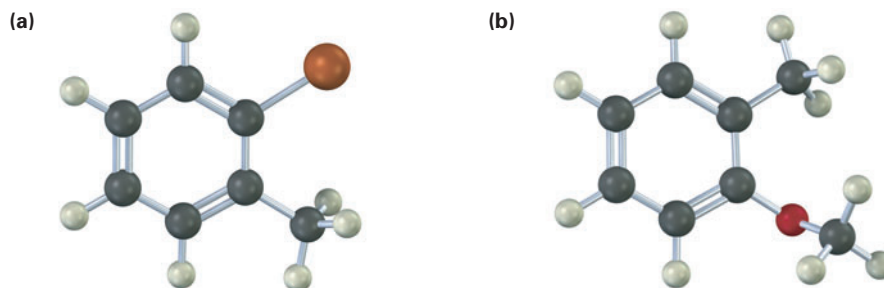
Solution



Problem 16.15 At what position would you expect electrophilic substitution to occur in each of the following substances?



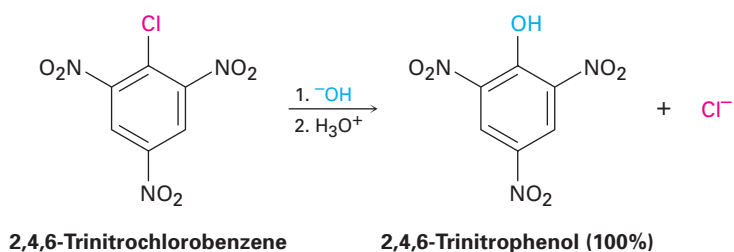
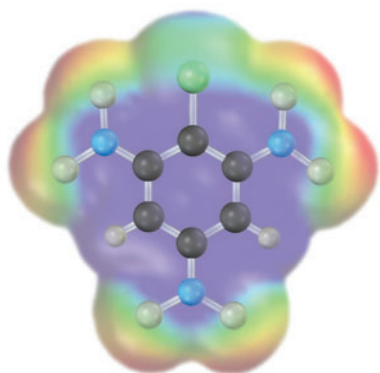
Problem 16.16 Show the major product(s) from reaction of the following substances with (i) $\text{CH}_3\text{CH}_2\text{Cl}$, AlCl_3 and (ii) HNO_3 , H_2SO_4 .



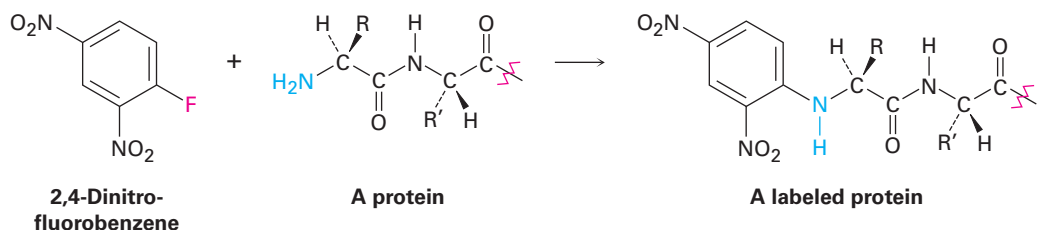
16.7 Nucleophilic Aromatic Substitution

ThomsonNOW™ Click *Organic Process* to view an animation showing a nucleophilic aromatic substitution reaction.

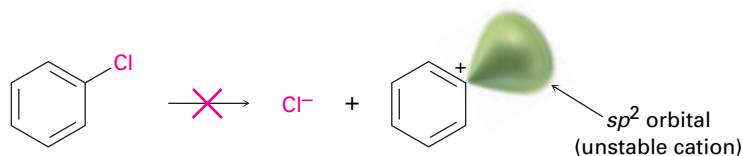
As we've seen, aromatic substitution reactions usually occur by an *electrophilic* mechanism. Aryl halides that have electron-withdrawing substituents, however, can also undergo **nucleophilic aromatic substitution**. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature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



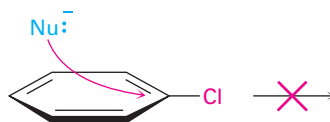
Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent*, to attach a "label" to the terminal NH_2 group of the amino acid at one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



How does this reaction take place? Although it appears superficially similar to the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ nucleophilic substitution reactions of alkyl halides discussed in Chapter 11, it must be different because aryl halides are inert to both $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ conditions. $\text{S}_{\text{N}}1$ 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. $\text{S}_{\text{N}}2$ 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.



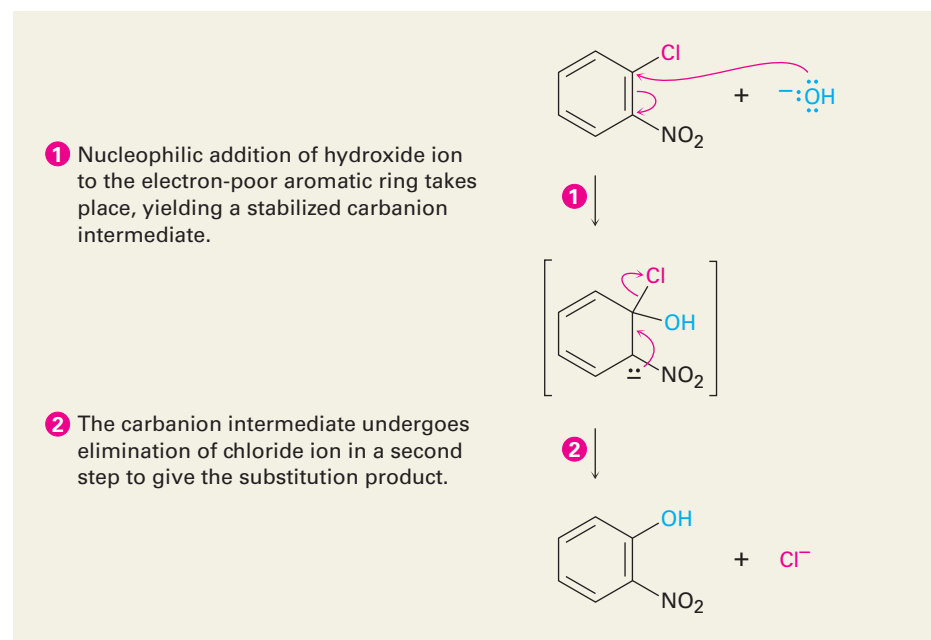
Backside displacement is sterically blocked; therefore, no S_N2 reaction.

Jacob Meisenheimer

Jacob Meisenheimer (1876–1934) was born in Greisheim, Germany, and received his Ph.D. at Munich. He was professor of chemistry at the universities of Berlin and Tübingen.

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*. Halide ion is then eliminated in the second step.

Figure 16.17 MECHANISM: Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance-stabilized carbanion intermediate.



Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group. The more such substituents there are, the faster the reaction. As shown in Figure 16.18, only ortho and para electron-withdrawing substituents stabilize the anion intermediate through resonance; 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^- .

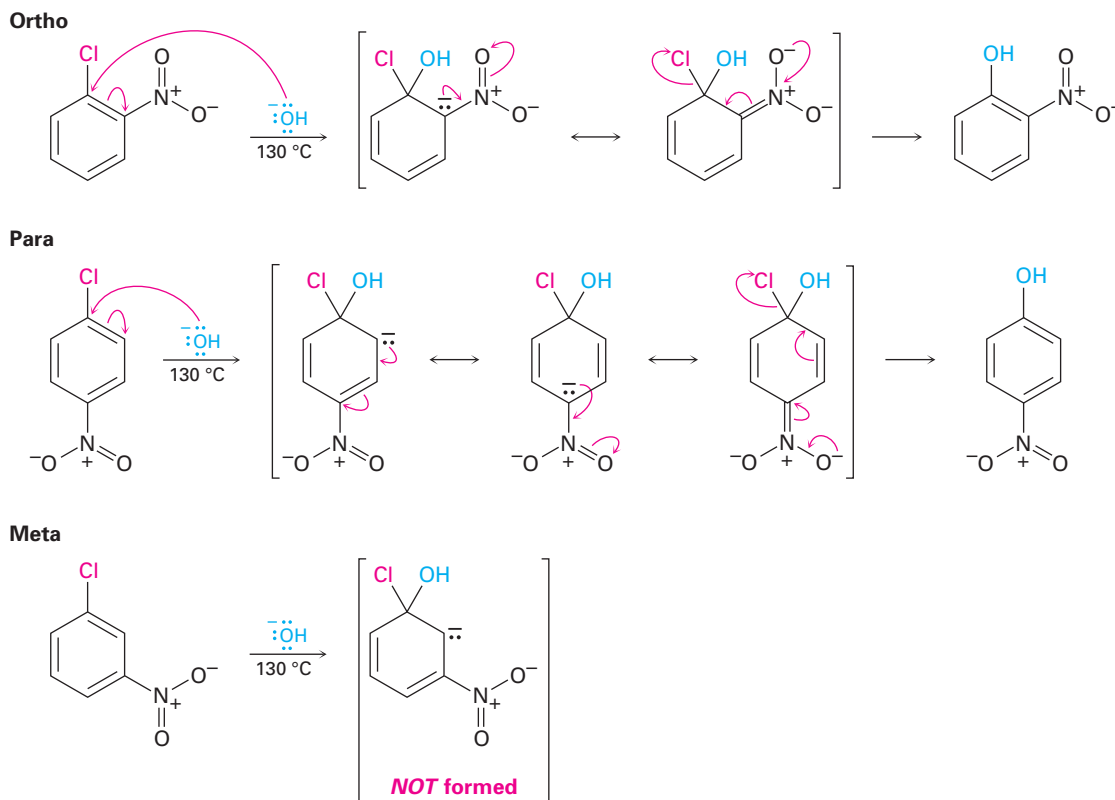
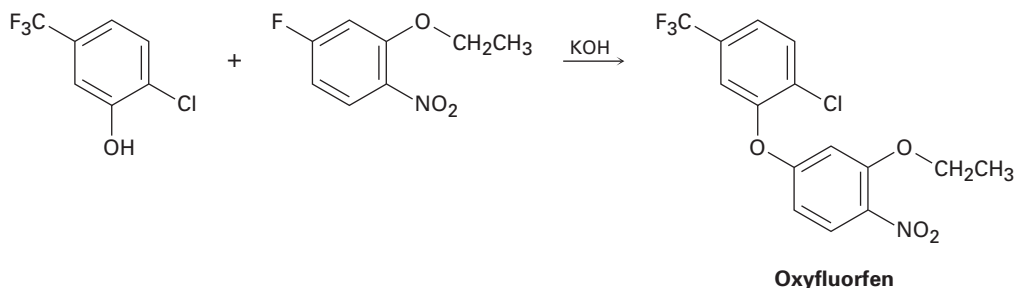


Figure 16.18 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

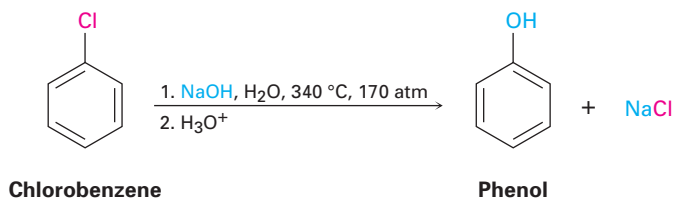
Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize the carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize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

Problem 16.17 | The herbicide oxyfluorfen can be prepared by reaction between a phenol and an aryl fluoride. Propose a mechanism.

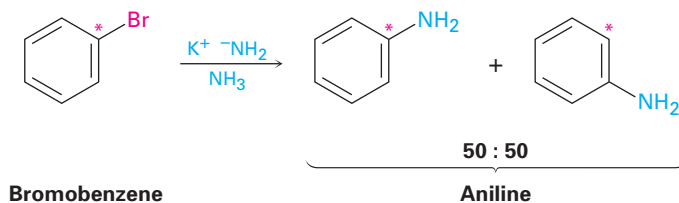


16.8 Benzyne

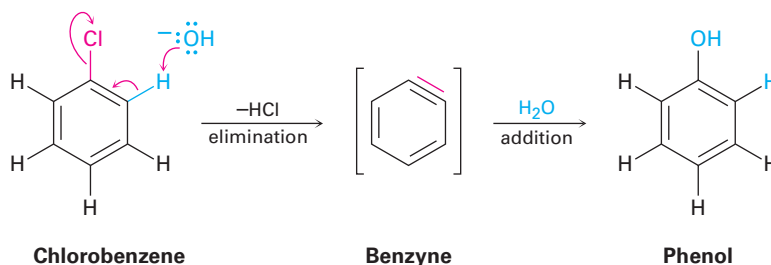
Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. Chemists at the Dow Chemical Company discovered in 1928 that phenol could be prepared on a large industrial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

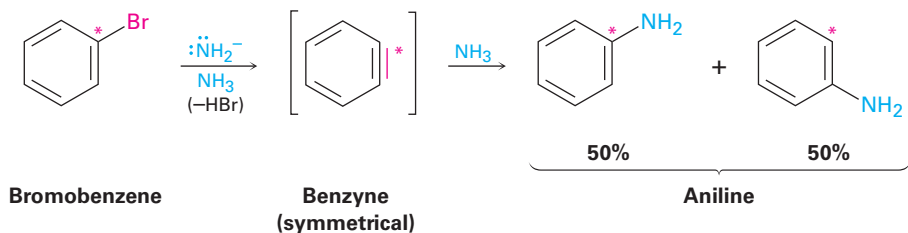


A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH₂) in liquid NH₃ solvent, for instance, gives aniline. Curiously, though, when bromobenzene labeled with radioactive ¹⁴C at the C1 position is used, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.



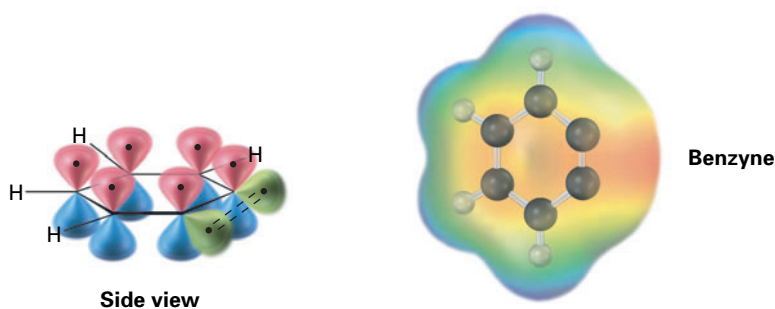
Further mechanistic evidence comes from trapping experiments. When bromobenzene is treated with KNH₂ in the presence of a diene such as furan, a Diels–Alder reaction (Section 14.5) occurs, implying that the symmetrical intermediate is a **benzyne**, formed by elimination of HBr from bromobenzene. Benzyne 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.

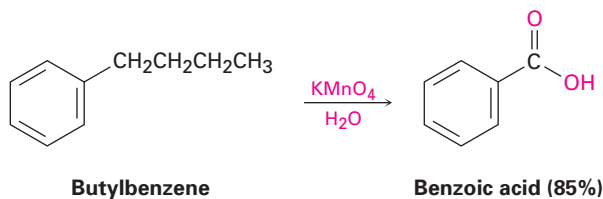


Problem 16.18 Treatment of *p*-bromotoluene with NaOH at 300 °C yields a mixture of *two* products, but treatment of *m*-bromotoluene with NaOH yields a mixture of *three* products. Explain.

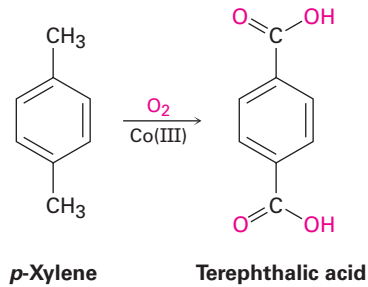
16.9 Oxidation of Aromatic Compounds

Oxidation of Alkylbenzene Side Chains

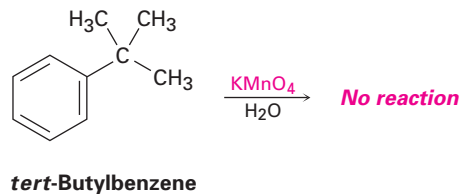
Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as KMnO_4 and $\text{Na}_2\text{Cr}_2\text{O}_7$, reagents that will cleave alkene carbon-carbon bonds (Section 7.9). It turns out, however, that the presence of the aromatic ring has a dramatic effect on alkyl side chains. Alkyl side chains react rapidly with oxidizing agents and are converted into carboxyl groups, $-\text{CO}_2\text{H}$. The net effect is conversion of an alkylbenzene into a benzoic acid, $\text{Ar}-\text{R} \rightarrow \text{Ar}-\text{CO}_2\text{H}$. As an example, butylbenzene is oxidized by aqueous KMnO_4 in high yield to give benzoic acid.



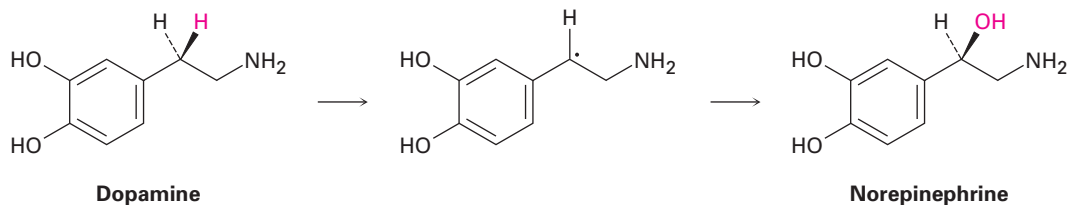
A similar oxidation is employed industrially for the preparation of the terephthalic acid used in the production of polyester fibers. Approximately 5 million tons per year of *p*-xylene are oxidized, using air as the oxidant and Co(III) salts as catalyst.



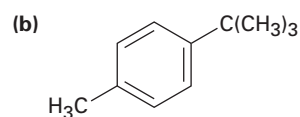
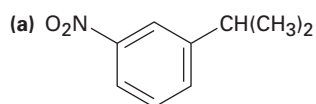
The mechanism of side-chain oxidation is complex and involves reaction of C–H bonds at the position next to the aromatic ring to form intermediate benzylic radicals. *tert*-Butylbenzene has no benzylic hydrogens, however, and is therefore inert.



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.

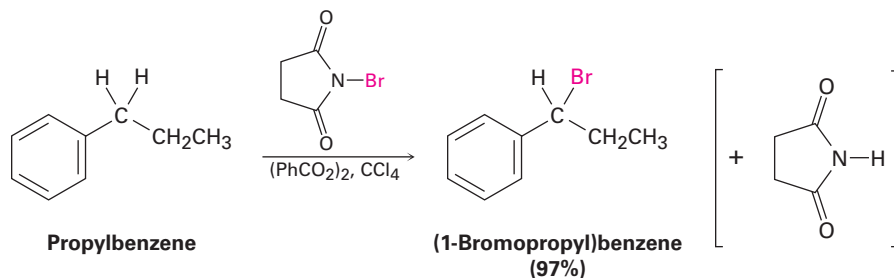


Problem 16.19 What aromatic products would you obtain from the KMnO_4 oxidation of the following substances?

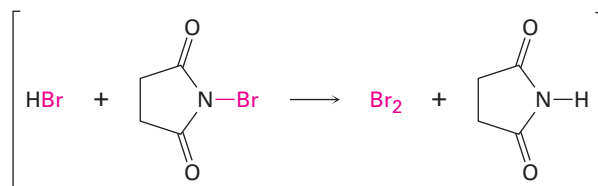
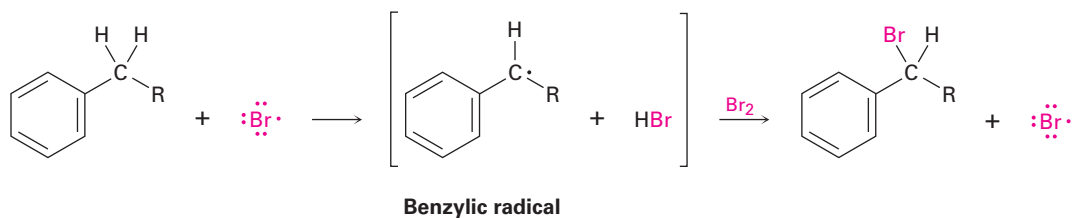


Bromination of Alkylbenzene Side Chains

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, $(\text{PhCO}_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position and does not give a mixture of products.



The mechanism of benzylic bromination is similar to that discussed in Section 10.4 for allylic bromination of alkenes. Abstraction of a benzylic hydrogen atom generates an intermediate benzylic radical, which reacts with Br_2 to yield product and a $\text{Br}\cdot$ radical that cycles back into the reaction to carry on the chain. The Br_2 necessary for reaction with the benzylic radical is produced 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 benzylic radical is stabilized by overlap of its *p* orbital with the ring π electron system.

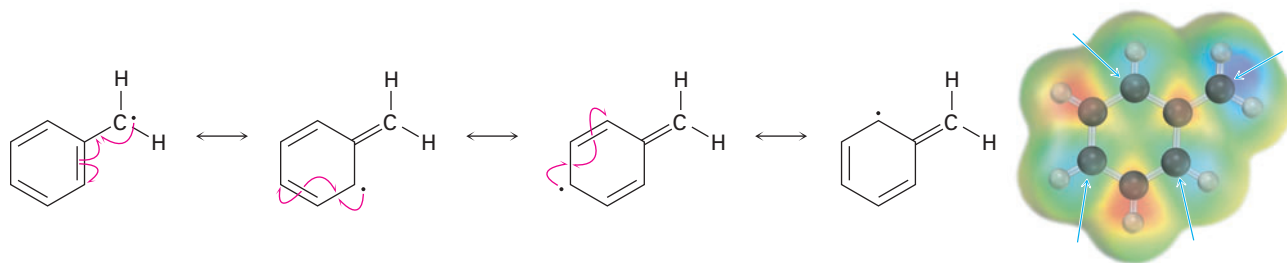
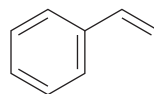


Figure 16.20 A resonance-stabilized benzylic radical. The spin-density surface shows that the unpaired electron (blue) is shared by the ortho and para carbons of the ring.

Problem 16.20 Refer to Table 5.3 on page 156 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 16.21 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?

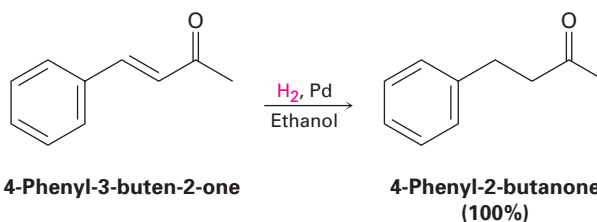


Styrene

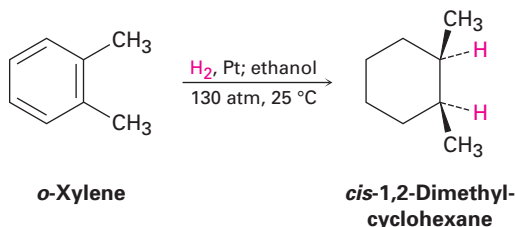
16.10 Reduction of Aromatic Compounds

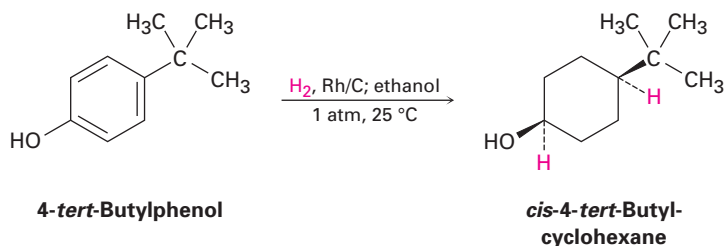
Catalytic Hydrogenation of Aromatic Rings

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 at room temperature and atmospheric pressure using a palladium catalyst. Neither the benzene ring nor the ketone carbonyl group is affected.



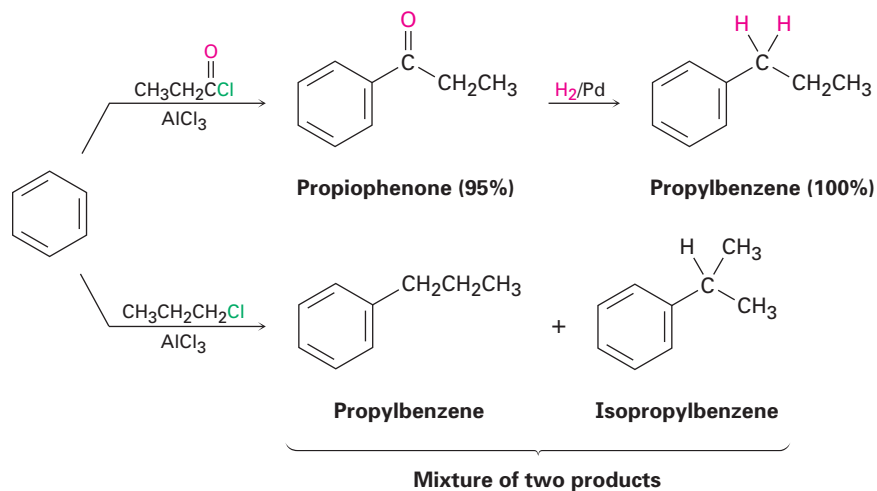
To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at several hundred atmospheres pressure or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For example, *o*-xylene yields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



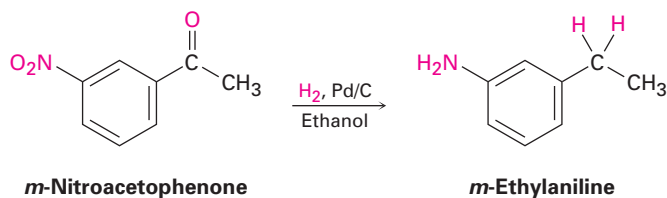


Reduction of Aryl Alkyl Ketones

Just as an aromatic ring activates a neighboring (benzylic) hydrogen toward oxidation, it also activates a neighboring 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).



Note that the conversion of a carbonyl group into a methylene group (C=O → CH₂) 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 all ketone carbonyl groups to yield alkanes in Section 19.9.



Problem 16.22 How would you prepare diphenylmethane, $(\text{Ph})_2\text{CH}_2$, from benzene and an acid chloride?

16.11 Synthesis of Trisubstituted 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 valuable 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 an excellent way to gain confidence using the many reactions learned in the past few chapters.

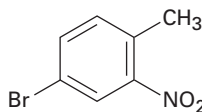
During our previous discussion of strategies for working synthesis problems in Section 8.9, we said that it's usually best to work a problem backward, or *retrosynthetically*. Look at the target molecule and ask yourself, "What is an immediate precursor of this compound?" Choose a likely answer and continue working backward, one step at a time, until you arrive at a simple starting material. Let's try some examples.

WORKED EXAMPLE 16.4

Synthesizing a Polysubstituted Benzene

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.

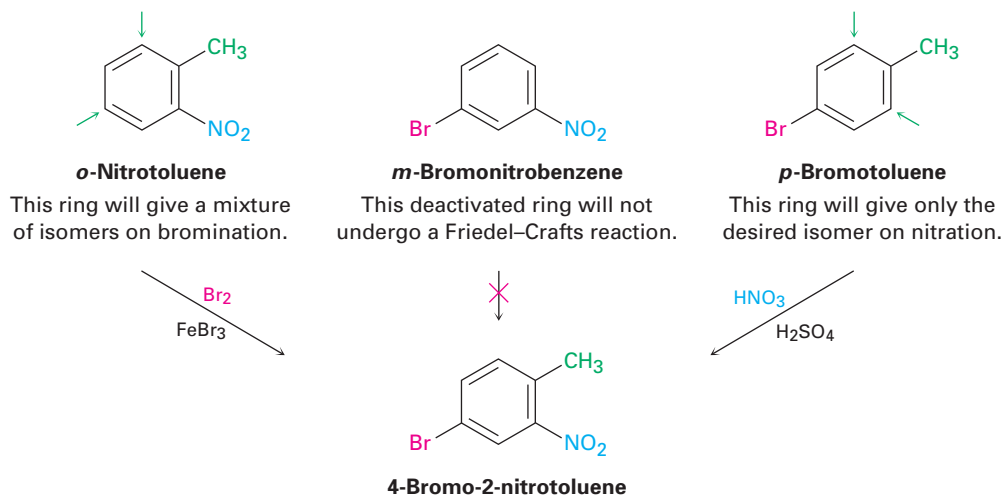


4-Bromo-2-nitrotoluene

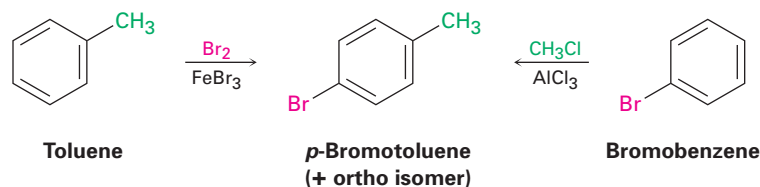
The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $\text{Br}_2/\text{FeBr}_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $\text{CH}_3\text{Cl}/\text{AlCl}_3$, and a nitro group can be introduced by nitration with $\text{HNO}_3/\text{H}_2\text{SO}_4$.

Solution "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.

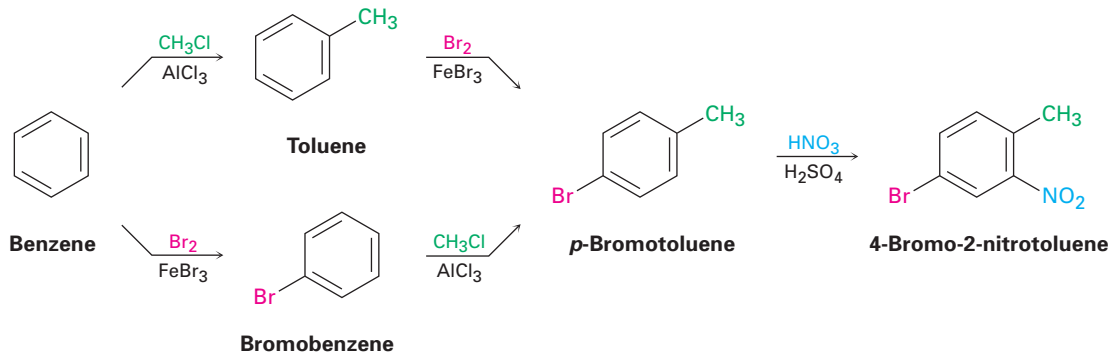


Next ask yourself, “What is an immediate precursor of *p*-bromotoluene?” Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts 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.

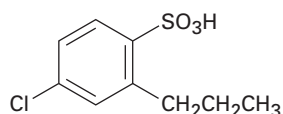


WORKED EXAMPLE 16.5

Synthesizing a Polysubstituted Benzene

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

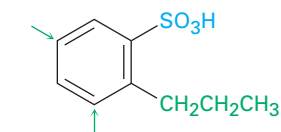
Strategy Draw the target molecule, identify its substituents, and recall how each of the three can be introduced. Then plan retrosynthetically.



4-Chloro-2-propylbenzenesulfonic acid

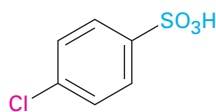
The three substituents on the ring are a chlorine, a propyl group, and a sulfonic acid group. A chlorine can be introduced by chlorination with $\text{Cl}_2/\text{FeCl}_3$, a propyl group can be introduced by Friedel–Crafts acylation with $\text{CH}_3\text{CH}_2\text{COCl}/\text{AlCl}_3$ followed by reduction with H_2/Pd , and a sulfonic acid group can be introduced by sulfonation with $\text{SO}_3/\text{H}_2\text{SO}_4$.

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.



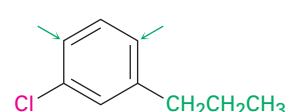
***o*-Propylbenzenesulfonic acid**

This ring will give the wrong isomer on chlorination.



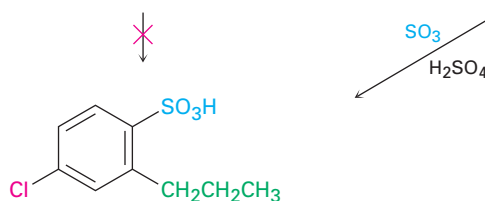
***p*-Chlorobenzenesulfonic acid**

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



***m*-Chloropropylbenzene**

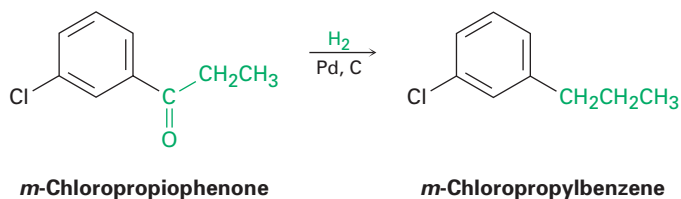
This ring will give the desired product on sulfonation.



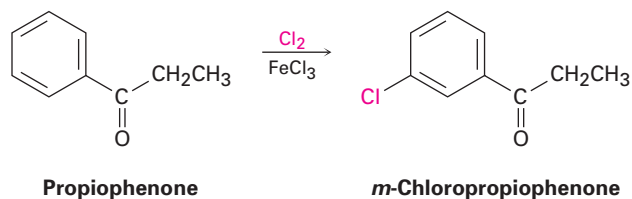
4-Chloro-2-propylbenzenesulfonic acid

“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

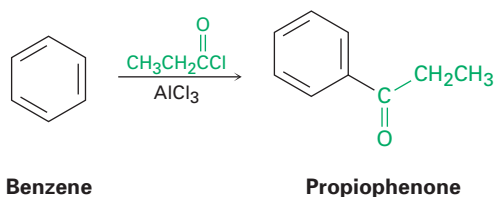
m-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced.



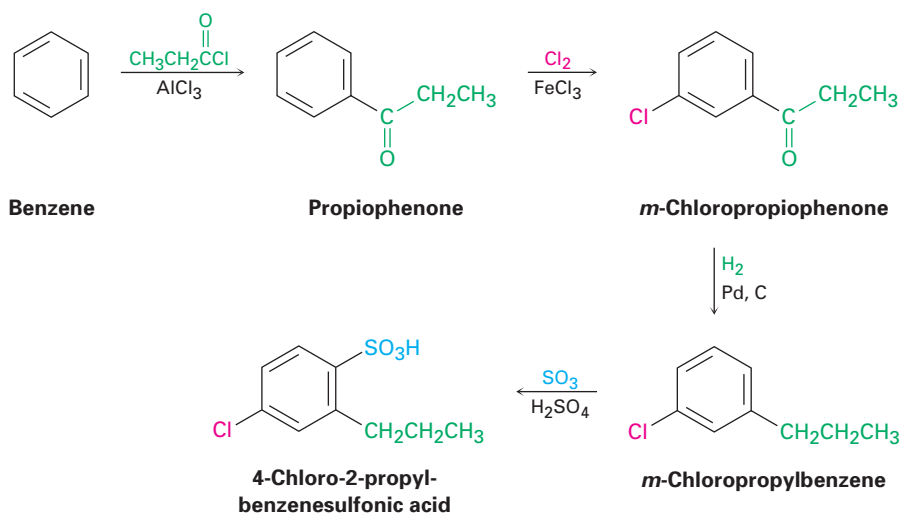
“What is an immediate precursor of *m*-chloropropiophenone?” Propiophenone, which could be chlorinated in the meta position.



“What is an immediate precursor of propiophenone?” Benzene, which could undergo Friedel–Crafts acylation with propanoyl chloride and AlCl₃.



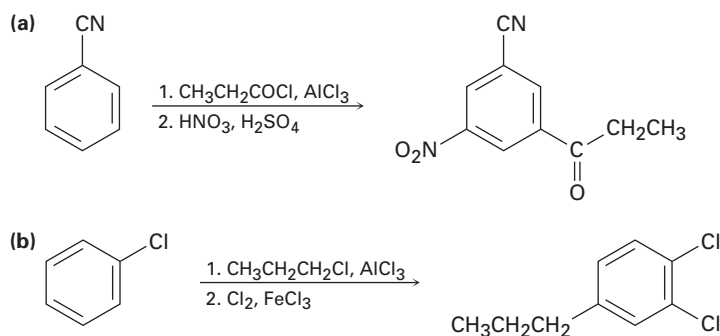
The final synthesis is a four-step route from benzene:



Planning organic syntheses 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 is not always easy, but there is no surer way to learn organic chemistry.

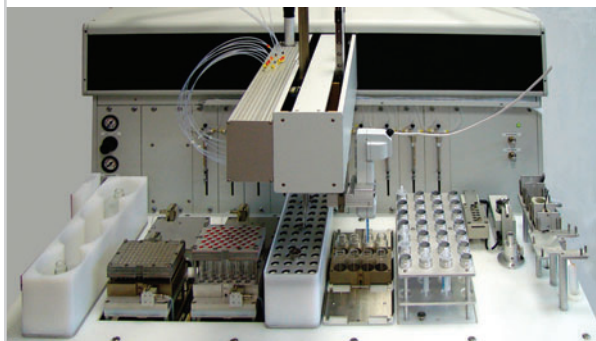
- Problem 16.23** Propose syntheses of the following substances from benzene:
- (a) *m*-Chloronitrobenzene (b) *m*-Chloroethylbenzene
 (c) 4-Chloro-1-nitro-2-propylbenzene (d) 3-Bromo-2-methylbenzenesulfonic acid

- Problem 16.24** 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?



Focus On . . .

Combinatorial Chemistry



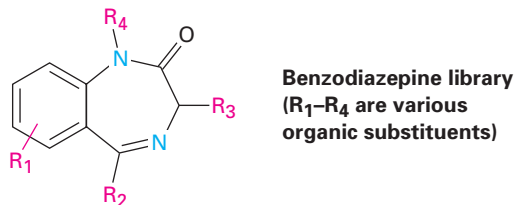
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Organic chemistry by robot means no spilled flasks!

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.

(continued)

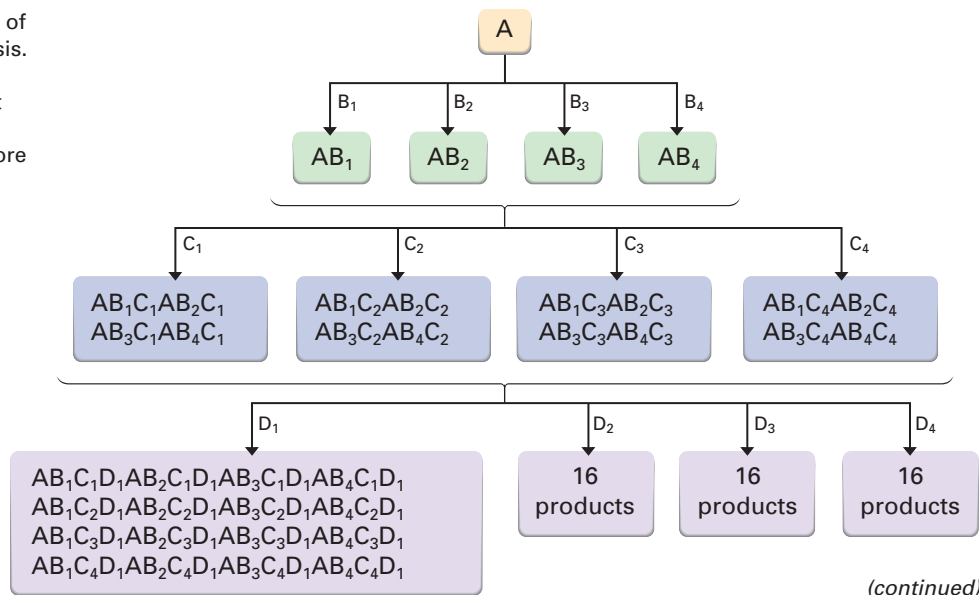
To speed the process of drug discovery, *combinatorial chemistry* has been developed to prepare what are called *combinatorial libraries*, in which anywhere from a few dozen to several hundred thousand substances are prepared simultaneously. Among the early successes of combinatorial chemistry is the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



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 $4 \rightarrow 16 \rightarrow 64 \rightarrow 256$. After 10 steps, more than 1 million compounds have been prepared (Figure 16.21).

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 1 million compounds result after 10 steps.

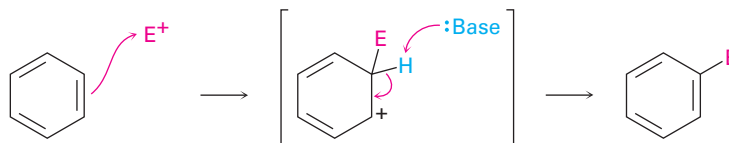


Of course, with so many different final products mixed together, the problem is to identify them. What structure is linked to what bead? Several approaches to this problem have been developed, all of which involve the attachment of encoding labels to each polymer bead to keep track of the chemistry each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

SUMMARY AND KEY WORDS

acyl group, 557
acylation, 557
alkylation, 554
benzyne, 575
electrophilic aromatic substitution, 547
Friedel–Crafts reaction, 554
inductive effect, 562
nucleophilic aromatic substitution, 572
resonance effect, 562

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.

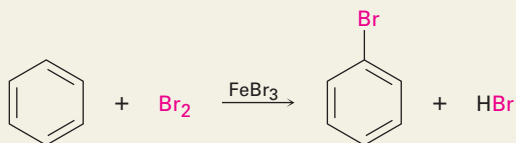
Halobenzenes undergo **nucleophilic aromatic substitution** through either of two mechanisms. If the halobenzene has a strongly electron-withdrawing substituent in the ortho or para position, substitution occurs by addition of a nucleophile to the ring, followed by elimination of halide from the intermediate 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 $KMnO_4$. Although aromatic rings are less reactive than isolated alkene double bonds, they can be reduced to cyclohexanes by hydrogenation over a platinum or rhodium catalyst. In addition, aryl alkyl ketones are reduced to alkylbenzenes by hydrogenation over a platinum catalyst.

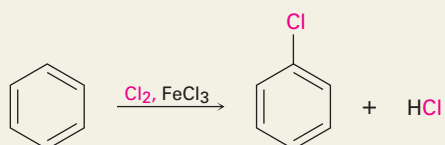
SUMMARY OF REACTIONS

1. Electrophilic aromatic substitution

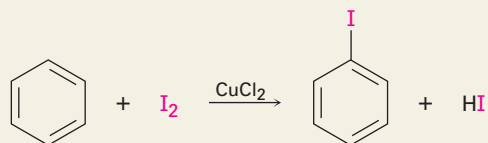
(a) Bromination (Section 16.1)



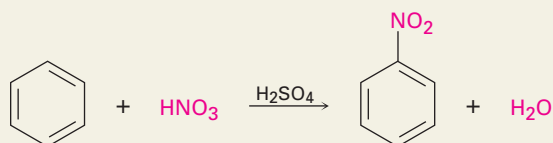
(b) Chlorination (Section 16.2)



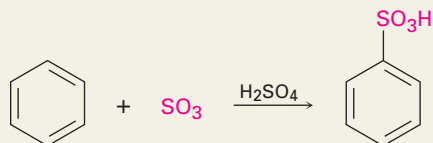
(c) Iodination (Section 16.2)



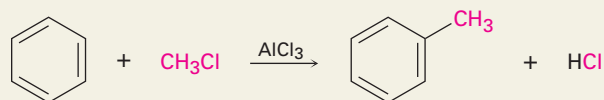
(d) Nitration (Section 16.2)



(e) Sulfonation (Section 16.2)

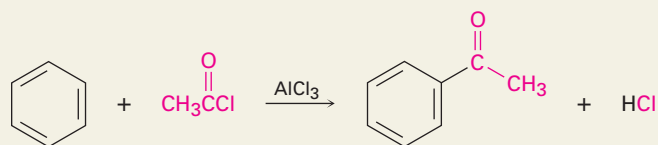


(f) Friedel–Crafts alkylation (Section 16.3)

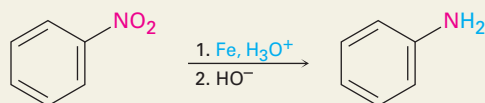


Aromatic ring. Must be at least as reactive as a halobenzene.
 Alkyl halide. Primary alkyl halides undergo carbocation rearrangement.

(g) Friedel–Crafts acylation (Section 16.3)

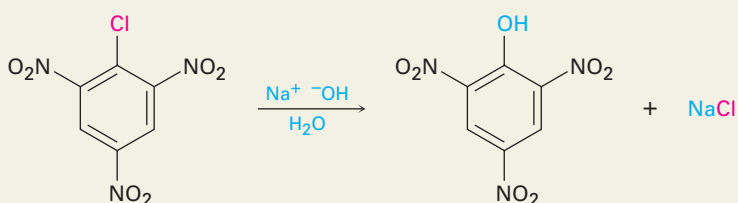


2. Reduction of aromatic nitro groups (Section 16.2)

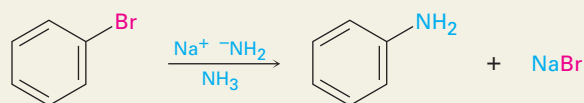


3. Nucleophilic aromatic substitution

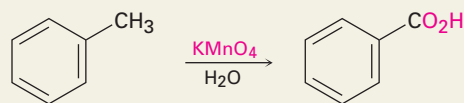
(a) By addition to activated aryl halides (Section 16.7)



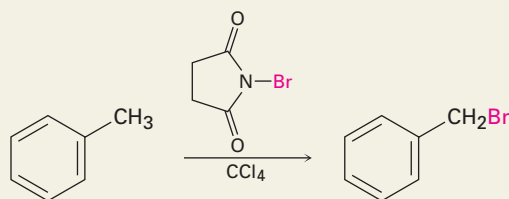
(b) By formation of benzyne intermediate from unactivated aryl halide (Section 16.8)



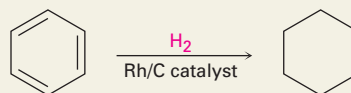
4. Oxidation of alkylbenzene side chain (Section 16.9)



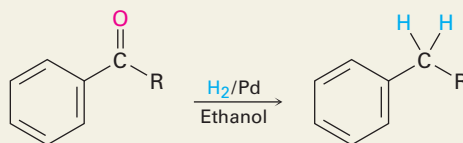
5. Benzylic bromination of alkylbenzene side chain (Section 16.9)



6. Catalytic hydrogenation of aromatic ring (Section 16.10)



7. Reduction of aryl alkyl ketones (Section 16.10)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.



Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

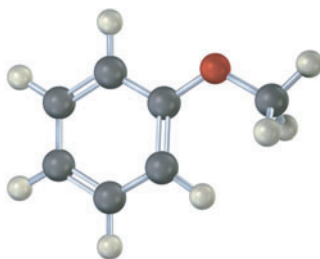
▲ denotes problems linked to Key Ideas of this chapter and testable in ThomsonNOW.

VISUALIZING CHEMISTRY

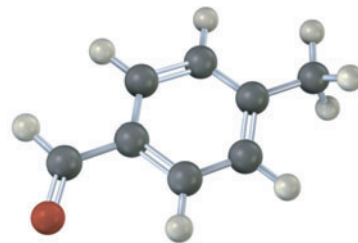
(Problems 16.1–16.24 appear within the chapter.)

16.25 ■ Draw the product from reaction of each of the following substances with (i) Br_2 , FeBr_3 and (ii) CH_3COCl , AlCl_3 .

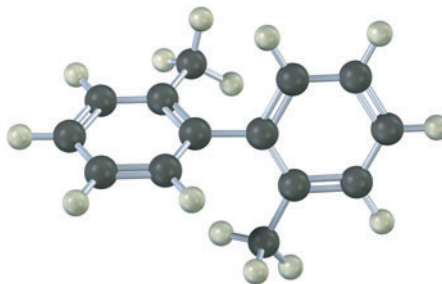
(a)



(b)

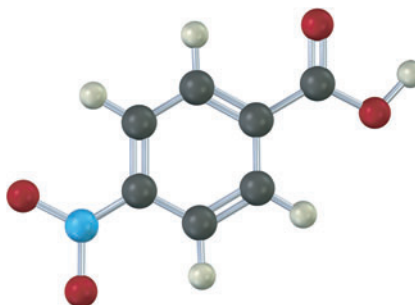


16.26 The following molecular model of a dimethyl-substituted biphenyl represents the lowest-energy conformation of the molecule. Why are the two benzene rings tilted at a 63° angle to each other rather than being in the same plane so that their p orbitals can overlap? Why doesn't complete rotation around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

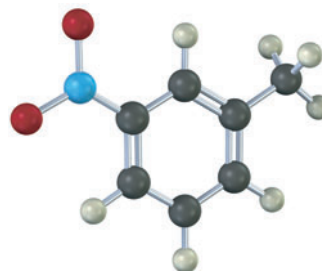


■ Assignable in OWL ▲ Key Idea Problems

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

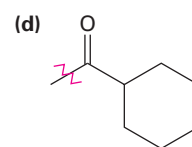
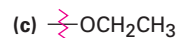


- 16.28 The following compound can't be synthesized using the methods discussed in this chapter. Why not?



ADDITIONAL PROBLEMS

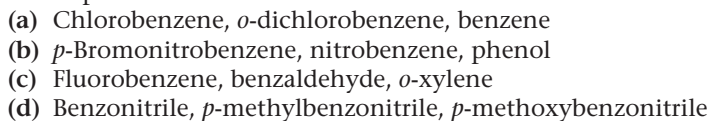
- 16.29 ■ Identify each of the following groups as an activator or deactivator and as an *o,p*-director or *m*-director:



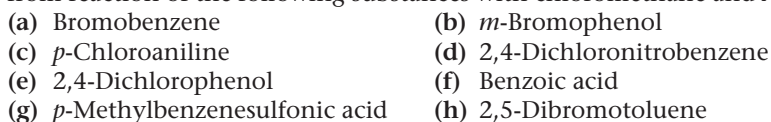
- 16.30 ■ Predict the major product(s) of nitration of the following substances. Which react faster than benzene, and which slower?



- 16.31 ■ ▲ Rank the compounds in each group according to their reactivity toward electrophilic substitution.



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



16.33 ■ 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

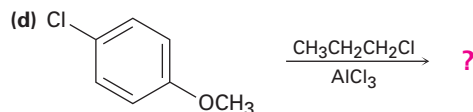
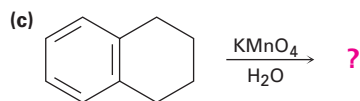
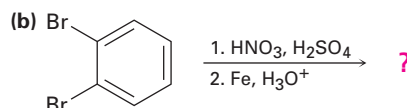
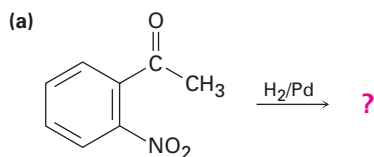
16.34 Predict the major product(s) you would obtain from sulfonation of the following compounds:

- (a) Fluorobenzene (b) *m*-Bromophenol
(c) *m*-Dichlorobenzene (d) 2,4-Dibromophenol

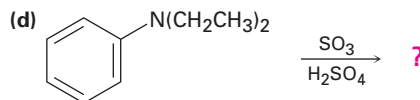
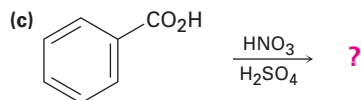
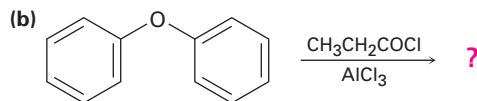
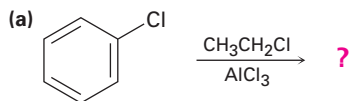
16.35 Rank the following aromatic compounds in the expected order of their reactivity toward Friedel–Crafts alkylation. Which compounds are unreactive?

- (a) Bromobenzene (b) Toluene (c) Phenol
(d) Aniline (e) Nitrobenzene (f) *p*-Bromotoluene

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



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



16.38 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.

16.39 ■ The sulfonation of an aromatic ring with SO₃ and H₂SO₄ is reversible. That is, heating benzenesulfonic acid with H₂SO₄ yields benzene. Show the mechanism of the desulfonation reaction. What is the electrophile?

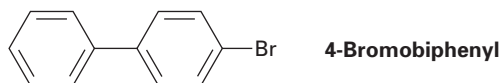
16.40 ■ The carbocation electrophile in a Friedel–Crafts reaction can be generated in ways other than by reaction of an alkyl chloride with AlCl₃. For example, reaction of benzene with 2-methylpropene in the presence of H₃PO₄ yields *tert*-butylbenzene. Propose a mechanism for this reaction.

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

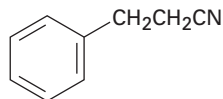
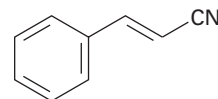
- 16.42** The nitroso group, $-N=O$, is one of the few nonhalogens that is an ortho- and para-directing deactivator. Explain by drawing resonance structures of the carbocation intermediates in ortho, meta, and para electrophilic reaction on nitrosobenzene, $C_6H_5N=O$.
- 16.43** Using resonance structures of the intermediates, explain why bromination of biphenyl occurs at ortho and para positions rather than at meta.



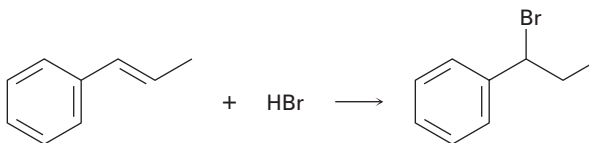
- 16.44** ■ ▲ At what position and on what ring do you expect nitration of 4-bromobiphenyl to occur? Explain, using resonance structures of the potential intermediates.



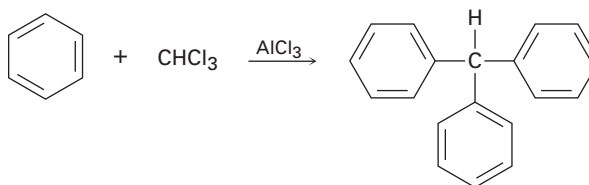
- 16.45** ▲ Electrophilic substitution on 3-phenylpropanenitrile occurs at the ortho and para positions, but reaction with 3-phenylpropenenitrile occurs at the meta position. Explain, using resonance structures of the intermediates.

**3-Phenylpropanenitrile****3-Phenylpropenenitrile**

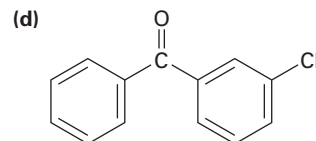
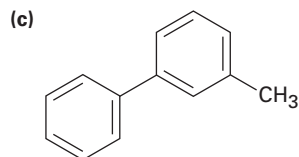
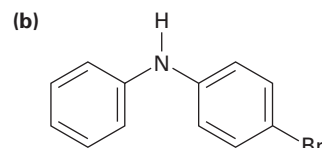
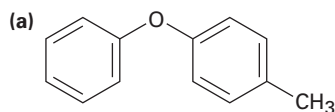
- 16.46** Addition of HBr to 1-phenylpropene yields only (1-bromopropyl)benzene. Propose a mechanism for the reaction, and explain why none of the other regioisomer is produced.



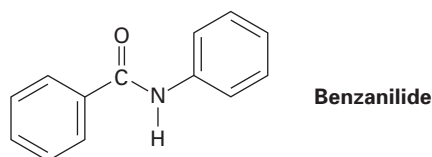
- 16.47** Triphenylmethane can be prepared by reaction of benzene and chloroform in the presence of $AlCl_3$. Propose a mechanism for the reaction.



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



16.49 ■ At what position, and on what ring, would you expect bromination of benzanilide to occur? Explain by drawing resonance structures of the intermediates.



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

16.51 ■ 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

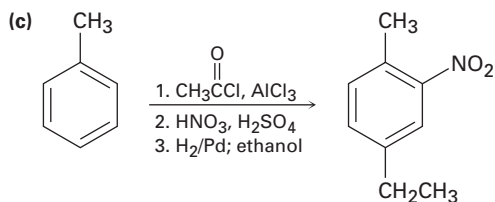
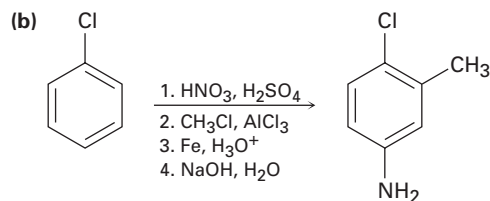
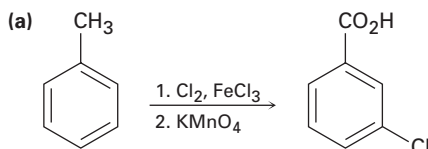
16.52 ■ Starting with benzene as your only source of aromatic compounds, how would you synthesize the following substances? Assume that you can separate ortho and para isomers if necessary.

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

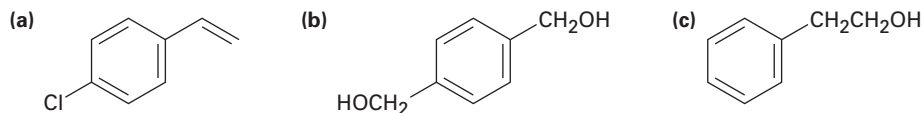
16.53 ■ Starting with either benzene or toluene, how would you synthesize the following substances? Assume that ortho and para isomers can be separated.

- (a) 2-Bromo-4-nitrotoluene (b) 1,3,5-Trinitrobenzene
(c) 2,4,6-Tribromoaniline

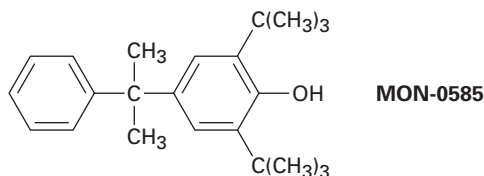
16.54 As written, the following syntheses have flaws. What is wrong with each?



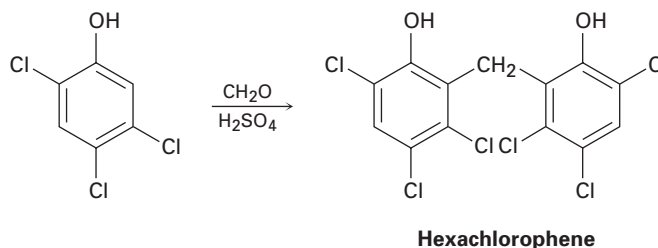
16.55 ■ How would you synthesize the following substances starting from benzene?



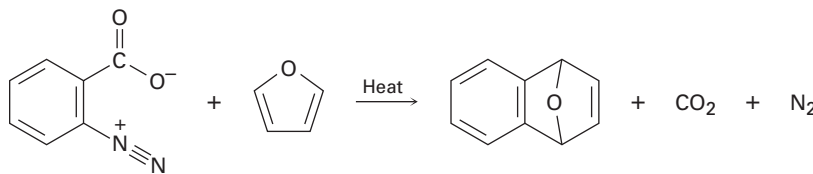
16.56 The compound MON-0585 is a nontoxic, biodegradable larvicide that is highly selective against mosquito larvae. Synthesize MON-0585 using either benzene or phenol as a source of the aromatic rings.



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.



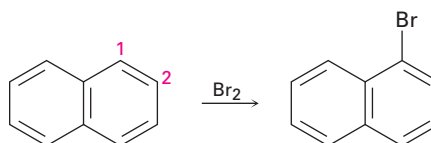
16.58 ■ Benzenediazonium carboxylate decomposes when heated to yield N_2 , CO_2 , and a reactive substance that can't be isolated. When benzenediazonium carboxylate is heated in the presence of furan, the following reaction is observed:



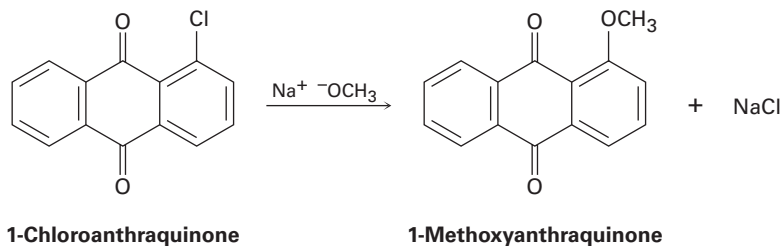
What intermediate is involved in this reaction? Propose a mechanism for its formation.

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.

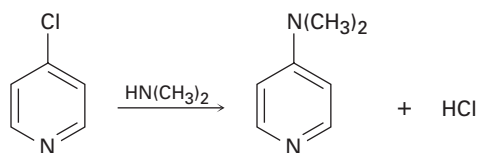
16.60 Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic substitution at C1 rather than C2.



- 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.

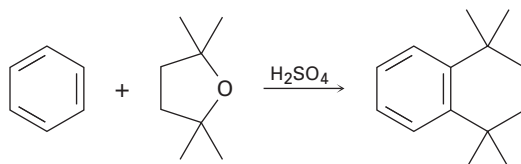


- 16.62** ■ 4-Chloropyridine undergoes reaction with dimethylamine to yield 4-dimethylaminopyridine. Propose a mechanism for the reaction.

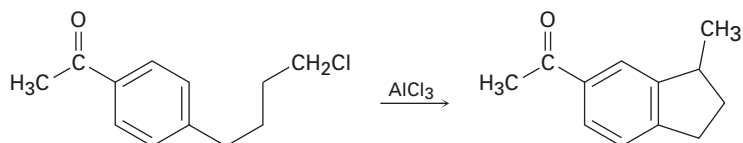


- 16.63** ■ *p*-Bromotoluene reacts with potassium amide to give a mixture of *m*- and *p*-methylaniline. Explain.

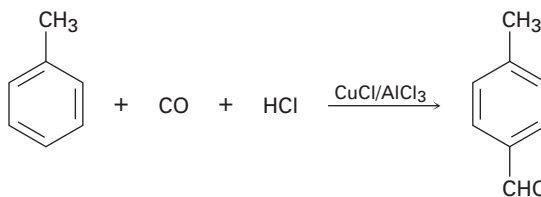
- 16.64** ■ Propose a mechanism to account for the reaction of benzene with 2,2,5,5-tetramethyltetrahydrofuran.



- 16.65** Propose a mechanism to account for the following reaction:

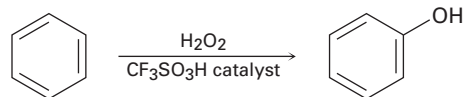


- 16.66** ■ In the *Gatterman-Koch reaction*, a formyl group ($-\text{CHO}$) is introduced directly onto a benzene ring. For example, reaction of toluene with CO and HCl in the presence of mixed $\text{CuCl}/\text{AlCl}_3$ gives *p*-methylbenzaldehyde. Propose a mechanism.

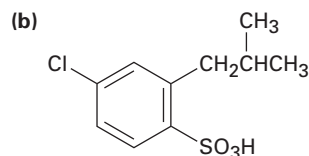
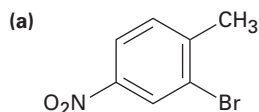


16.67 ■ Treatment of *p*-*tert*-butylphenol with a strong acid such as H_2SO_4 yields phenol and 2-methylpropene. Propose a mechanism.

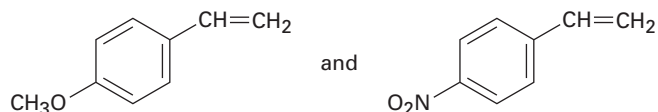
16.68 ■ Benzene and alkyl-substituted benzenes can be hydroxylated by reaction with H_2O_2 in the presence of an acidic catalyst. What is the structure of the reactive electrophile? Propose a mechanism for the reaction.



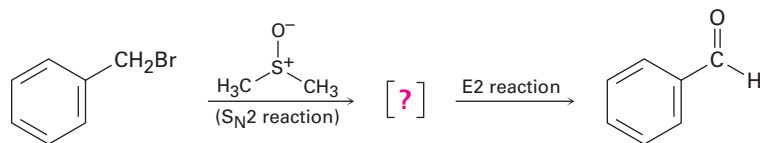
16.69 How would you synthesize the following compounds from benzene? Assume that ortho and para isomers can be separated.



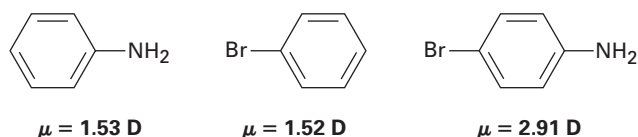
16.70 You know the mechanism of HBr addition to alkenes, and you know the effects of various substituent groups on aromatic substitution. Use this knowledge to predict which of the following two alkenes reacts faster with HBr. Explain your answer by drawing resonance structures of the carbocation intermediates.



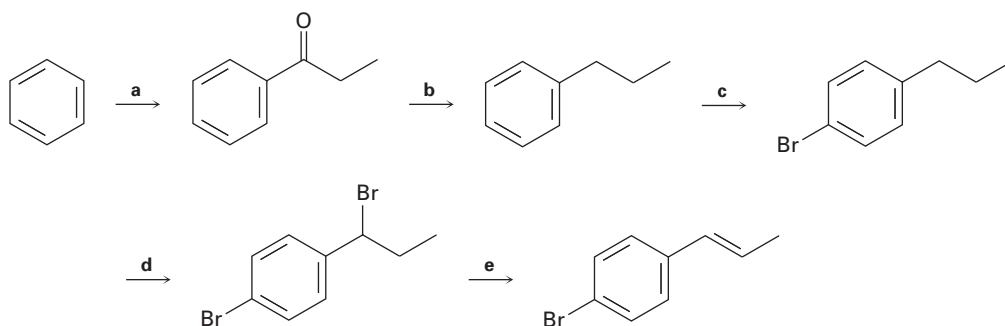
16.71 Benzyl bromide is converted into benzaldehyde by heating in dimethyl sulfoxide. Propose a structure for the intermediate, and show the mechanisms of the two steps in the reaction.



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



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



16.74 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.

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

17

Alcohols and Phenols

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at www.thomsonedu.com for online self-study and interactive tutorials based on your level of understanding.

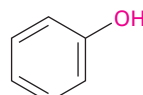


Online homework for this chapter may be assigned in Organic OWL.

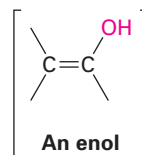
Alcohols and phenols can be thought of as organic derivatives of water in which one of the water hydrogens is replaced by an organic group: H–O–H versus R–O–H and Ar–O–H. In practice, the group name *alcohol* is restricted to compounds that have their –OH group bonded to a saturated, sp^3 -hybridized 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

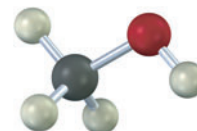
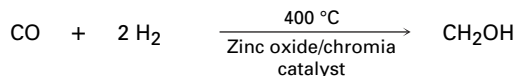


A phenol



An enol

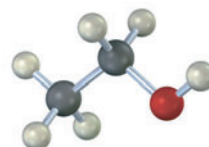
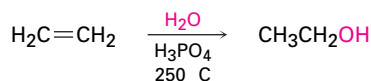
Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 1.3 billion gallons of methanol is manufactured each year in the United States 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 ($\text{CH}_3\text{CO}_2\text{H}$).



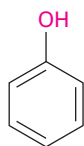
Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Today, approximately 4 billion gallons of ethanol is produced

annually in the United States by fermentation of corn, barley, and sorghum, and production is expected to double by 2012. Essentially the entire amount is used to make E85 automobile fuel, a blend of 85% ethanol and 15% gasoline.

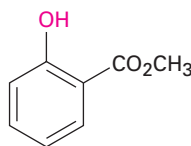
Ethanol for nonbeverage use is obtained by acid-catalyzed hydration of ethylene. Approximately 110 million gallons of ethanol a year is produced in the United States for use as a solvent or as a chemical intermediate in other industrial reactions.



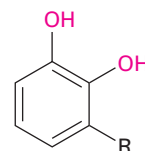
Phenols occur widely throughout nature and also serve as intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar; methyl salicylate is a flavoring agent found in oil of wintergreen; and the urushiols are 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 C₁₅ alkyl
and alkenyl chains)

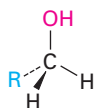
WHY THIS CHAPTER?

Up to this point, we've focused on developing some general ideas of organic reactivity, on looking at the chemistry of hydrocarbons, and 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 biological chemistry. We'll look at alcohols in this chapter and then move on to carbonyl compounds in Chapters 19 through 23.

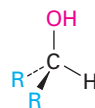
17.1 Naming Alcohols and Phenols

ThomsonNOW Click *Organic Interactive* to use a web-based palette to draw structures of alcohols based on their IUPAC names.

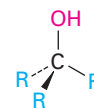
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



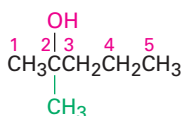
A secondary (2°) alcohol



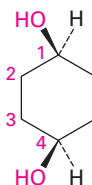
A tertiary (3°) alcohol

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

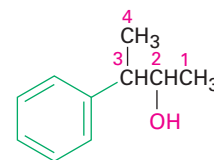
- Rule 1** Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.
- Rule 2** Number 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 6.3), newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.



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

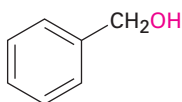


***cis*-1,4-Cyclohexanediol**
(New: ***cis*-Cyclohexane-1,4-diol**)



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

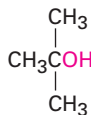
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



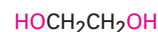
Benzyl alcohol
(phenylmethanol)



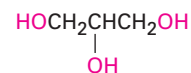
Allyl alcohol
(2-propen-1-ol)



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

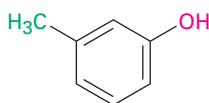


Ethylene glycol
(1,2-ethanediol)

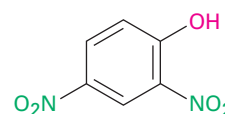


Glycerol
(1,2,3-propanetriol)

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*.

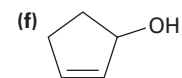
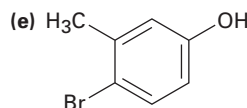
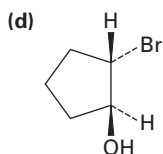
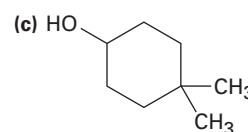
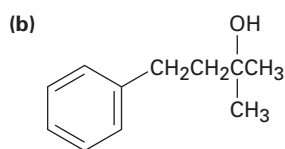
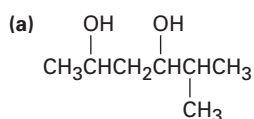


***m*-Methylphenol**
(*m*-Cresol)



2,4-Dinitrophenol

Problem 17.1 Give IUPAC names for the following compounds:



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

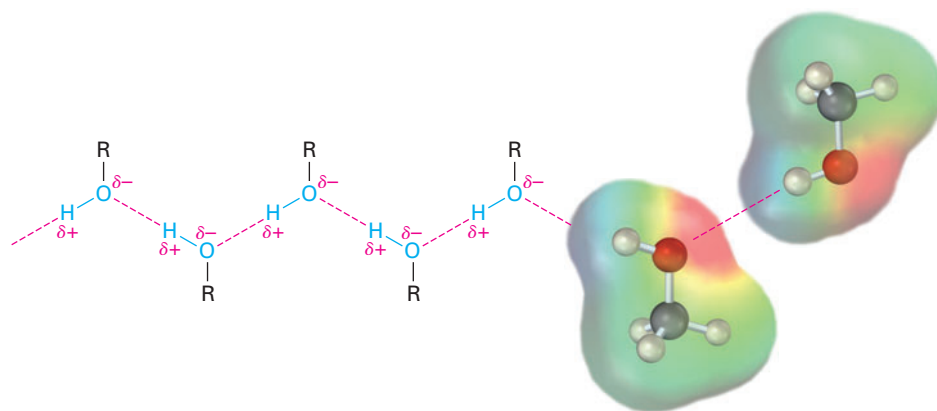
(f) *o*-(2-Hydroxyethyl)phenol

17.2 Properties of Alcohols and Phenols

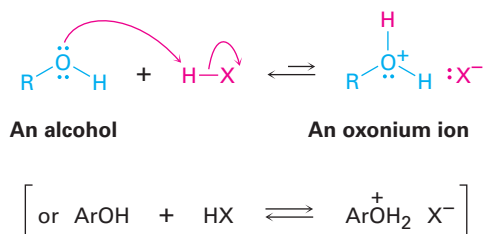
Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The R–O–H bond angle has an approximately tetrahedral value (109° in methanol, for example), and the oxygen atom is sp^3 -hybridized.

Also like water, alcohols and phenols have higher boiling points than might be expected because of hydrogen-bonding (Section 2.13). 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.

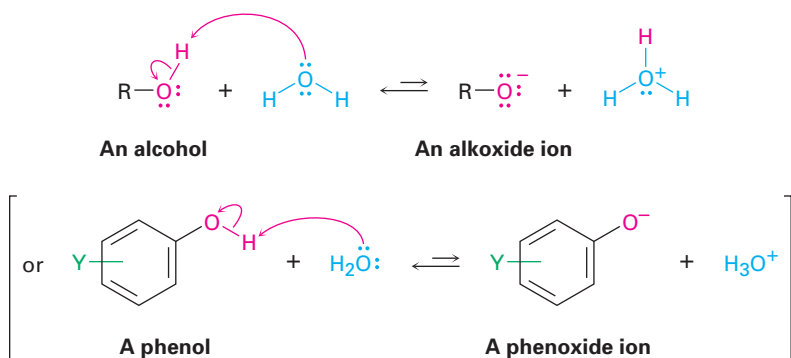
Figure 17.1 Hydrogen-bonding in alcohols and phenols. A weak attraction between a positively polarized OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the positively polarized O–H hydrogen (blue) and the negatively polarized oxygen (red).



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^+ .



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^- .



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

$$K_a = \frac{[\text{A}^-] [\text{H}_3\text{O}^+]}{[\text{HA}]} \quad \text{p}K_a = -\log K_a$$

Compounds with a smaller K_a and larger $\text{p}K_a$ are less acidic, whereas compounds with a larger K_a and smaller $\text{p}K_a$ 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 substituent groups can have a significant effect. *tert*-Butyl alcohol is a weaker acid, for instance, and 2,2,2-trifluoroethanol is stronger. 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 that results from 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

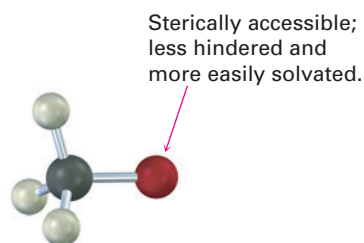
Table 17.1 Acidity Constants of Some Alcohols and Phenols

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

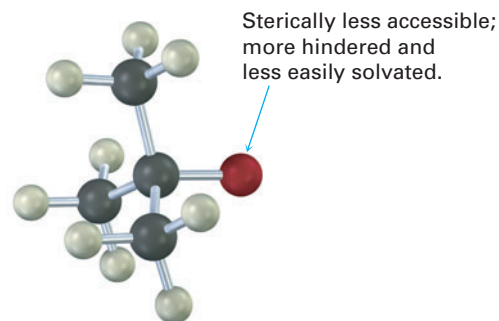
Weaker acid

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.



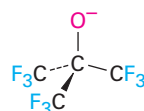
Methoxide ion, CH_3O^-
($pK_a = 15.54$)



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

Inductive effects (Section 16.4) are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for example, 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 .

 $pK_a = 5.4$

versus

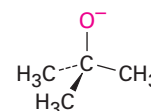
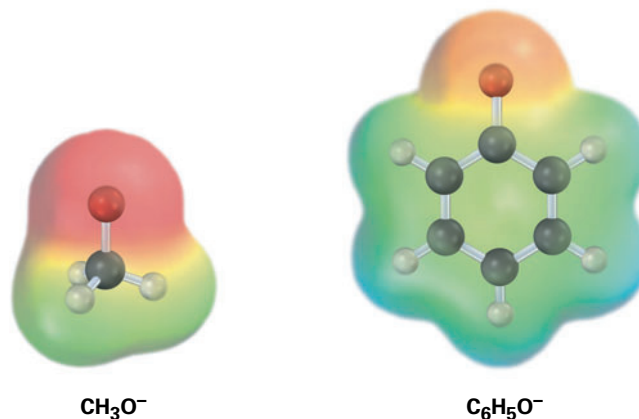
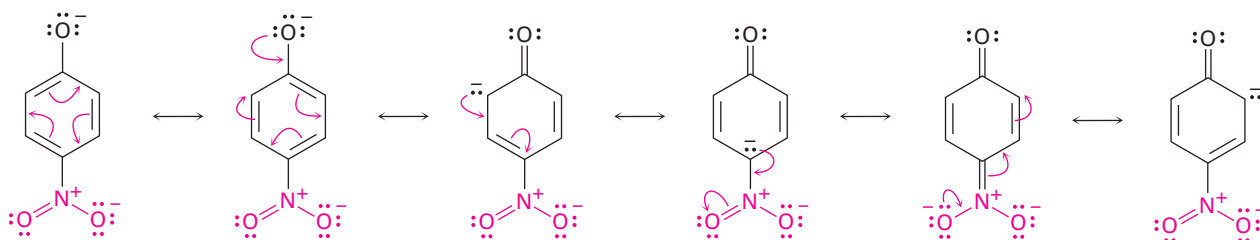
 $pK_a = 18.0$

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 16.4). 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.



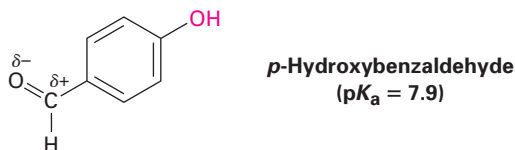
WORKED EXAMPLE 17.1

Predicting the Relative Acidity of a Substituted Phenol

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 16.4 that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde is more acidic ($\text{p}K_{\text{a}} = 7.9$) than phenol ($\text{p}K_{\text{a}} = 9.89$).

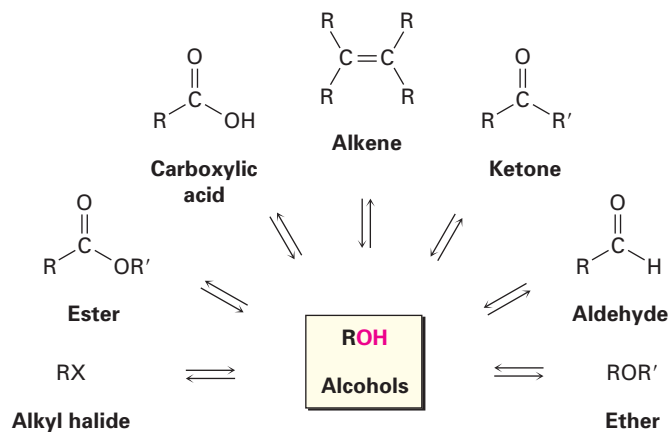


- Problem 17.3** The following data for isomeric four-carbon alcohols show that there is a decrease in boiling point with increasing substitution of the OH-bearing carbon. How might you account for this trend?
 1-Butanol, bp 117.5 °C
 2-Butanol, bp 99.5 °C
 2-Methyl-2-propanol, bp 82.2 °C
- Problem 17.4** Rank the following substances in order of increasing acidity:
 (a) $(\text{CH}_3)_2\text{CHOH}$, $\text{HC}\equiv\text{CH}$, $(\text{CF}_3)_2\text{CHOH}$, 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).

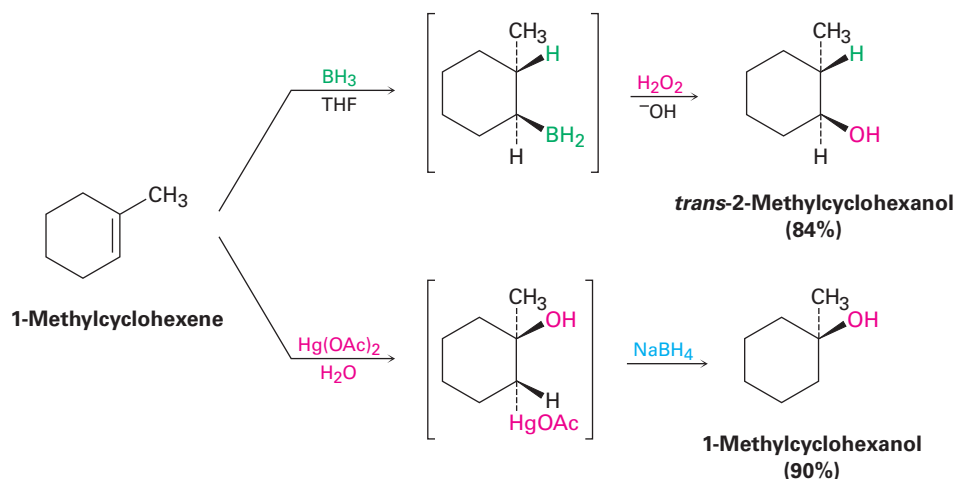
Figure 17.3 The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.



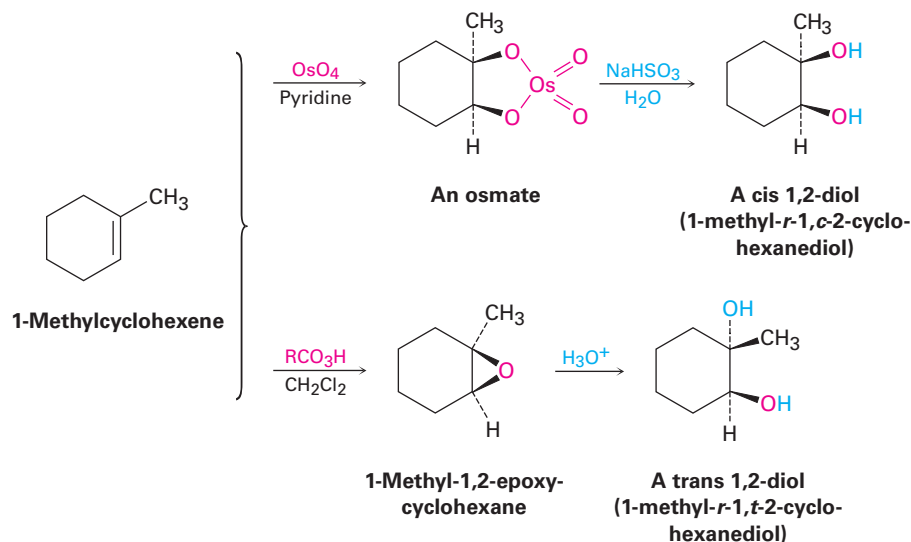
We've already seen several methods of alcohol synthesis:

- 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 7.5), whereas

oxymercuration/reduction yields the product of Markovnikov hydration (Section 7.4).

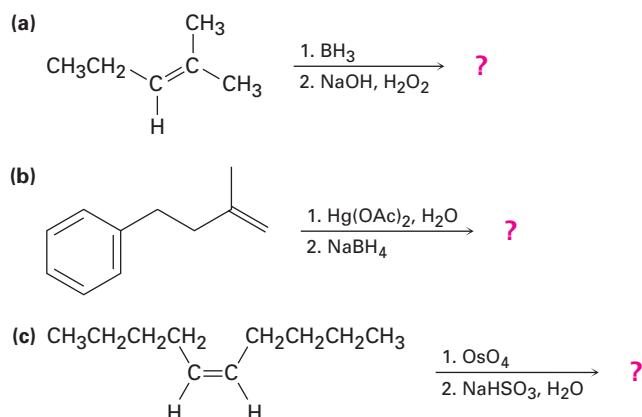


- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with NaHSO_3 or by acid-catalyzed hydrolysis of an epoxide (Section 7.8). The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.



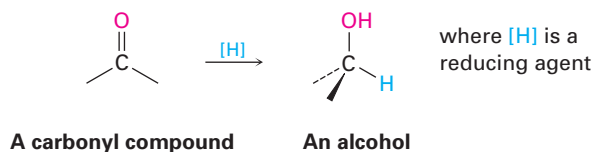
As noted at the end of Section 7.8, the prefixes *cis*- and *trans*- would be ambiguous when naming the diols derived from 1-methylcyclohexene because the ring has three substituents. Instead, a reference substituent *r* is chosen and other substituents are either *cis* (*c*) or *trans* (*t*) to that reference. For the two 1-methyl-1,2-cyclohexanediol isomers, the $-\text{OH}$ group at C1 is the reference (*r*-1), and the $-\text{OH}$ at C2 is either *cis* (*c*-2) or *trans* (*t*-2) to that reference. Thus, the diol isomer derived by *cis* hydroxylation is named 1-methyl-*r*-1,*c*-2-cyclohexanediol, and the isomer derived by *trans* hydroxylation is named 1-methyl-*r*-1,*t*-2-cyclohexanediol.

Problem 17.6 Predict the products of the following reactions:



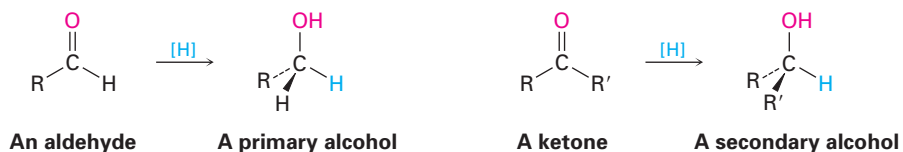
17.4 Alcohols from Reduction of Carbonyl Compounds

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 7.7), 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.



Reduction of Aldehydes and Ketones

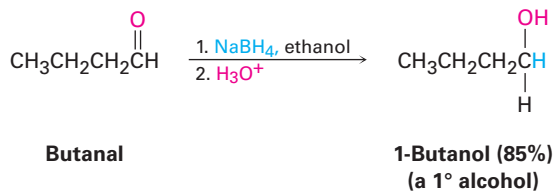
Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.



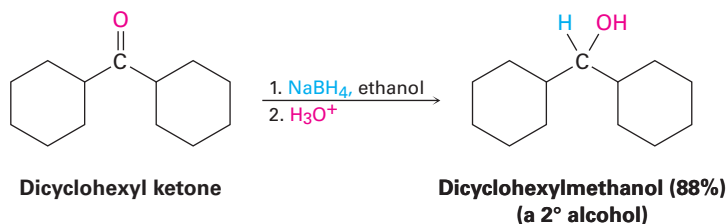
Literally dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, NaBH₄, is usually chosen because of its safety and ease of handling. Sodium borohydride

is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution to give high yields of products.

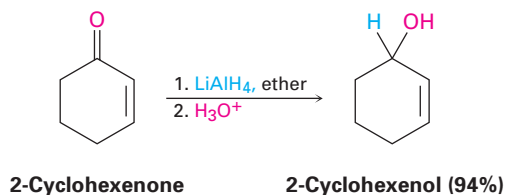
Aldehyde reduction



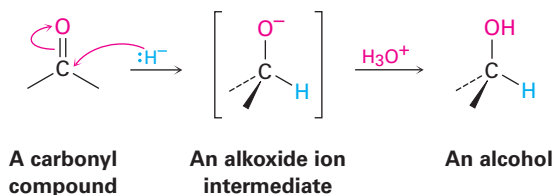
Ketone reduction



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 .



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 ($:\text{H}^-$) 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.



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, 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.

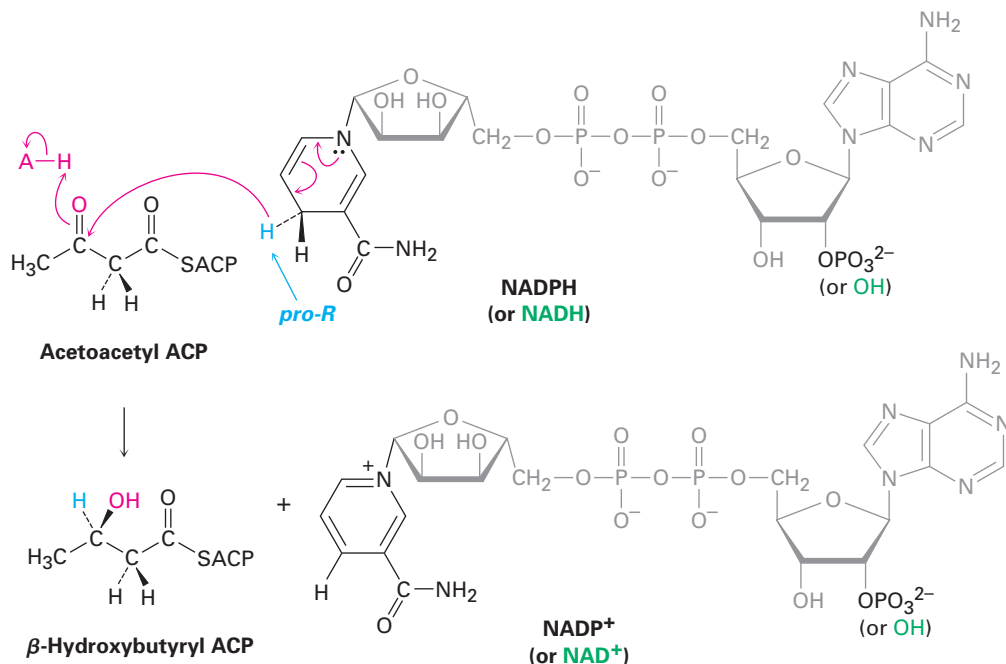
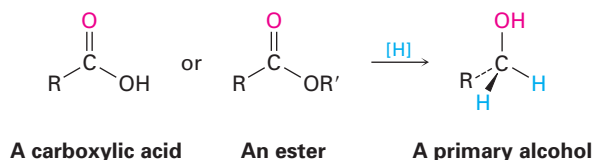


Figure 17.4 The biological reduction of a ketone (acetoacetyl ACP) to an alcohol (β -hydroxybutyryl ACP) by NADPH.

Reduction of Carboxylic Acids and Esters

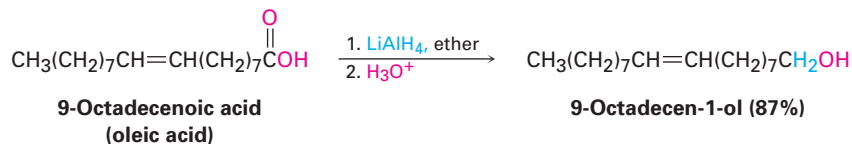
Carboxylic acids and esters are reduced to give primary alcohols.



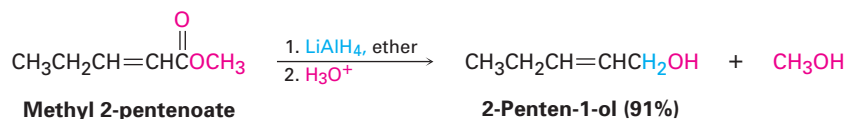
These reactions aren’t as rapid as the reductions of aldehydes and ketones. NaBH_4 reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent LiAlH_4 . All carbonyl groups, including 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



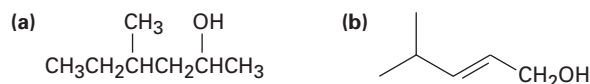
Ester reduction



WORKED EXAMPLE 17.2

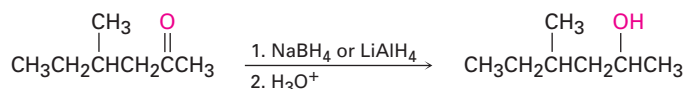
Predicting the Structure of a Reactant, Given the Product

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

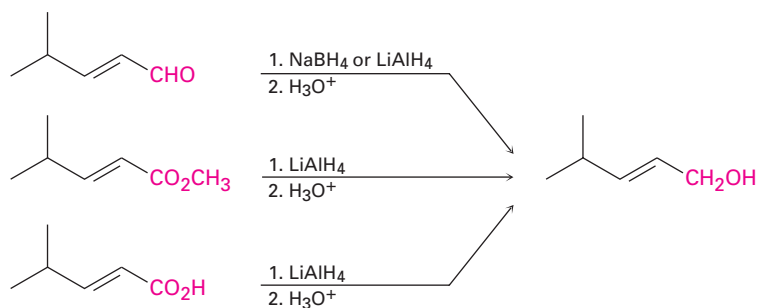


Strategy Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

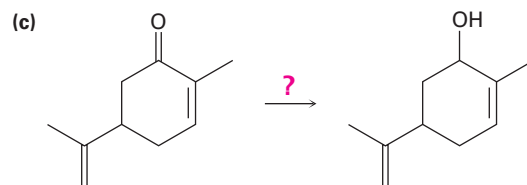
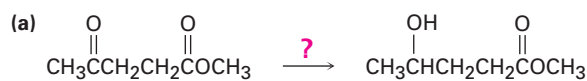
Solution (a) The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either NaBH_4 or LiAlH_4 can be used.



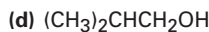
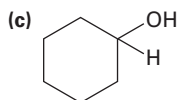
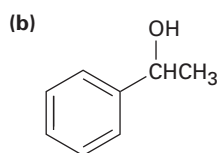
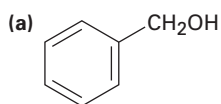
(b) The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. LiAlH_4 is needed for the ester and carboxylic acid reductions.



Problem 17.7 What reagent would you use to accomplish each of the following reactions?



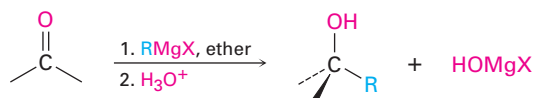
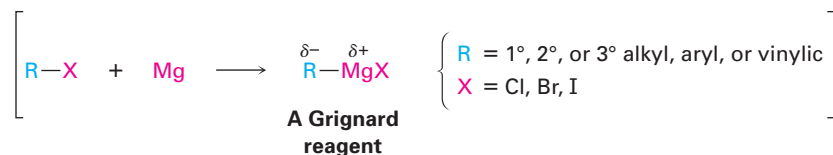
Problem 17.8 What carbonyl compounds give the following alcohols on reduction with LiAlH_4 ? Show all possibilities.



17.5 Alcohols from Reaction of Carbonyl Compounds with Grignard Reagents

ThomsonNOW Click *Organic Interactive* to find supplemental problems and stepwise solutions to the design of Grignard syntheses.

We saw in Section 10.7 that alkyl, aryl, and vinylic halides react with magnesium in ether or tetrahydrofuran to generate Grignard reagents, RMgX , which act as carbon-based nucleophiles. These Grignard reagents react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do.

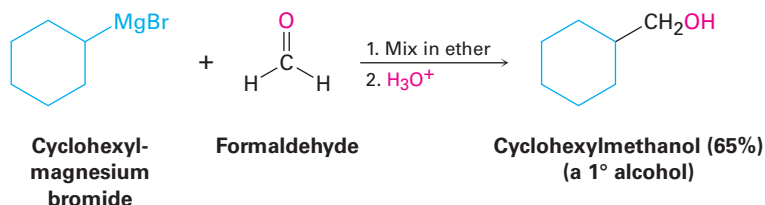


The reaction of Grignard reagents with carbonyl compounds has no direct biological counterpart, because organomagnesium compounds are too

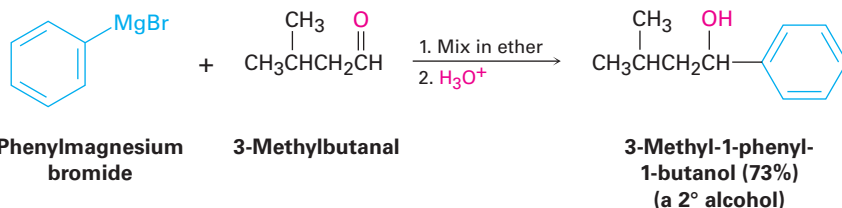
strongly basic to exist in an aqueous medium. The reaction *does* have an indirect biological counterpart, however, for we'll see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon-carbon bonds.

As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $\text{H}_2\text{C}=\text{O}$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

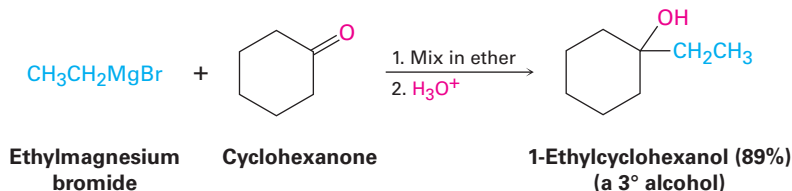
Formaldehyde reaction



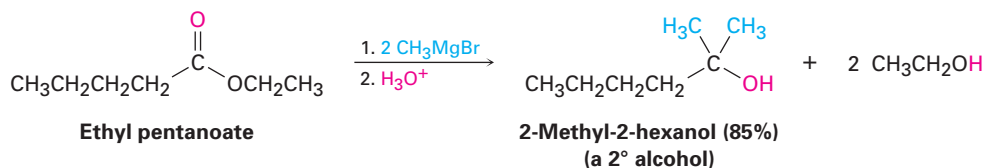
Aldehyde reaction



Ketone reaction

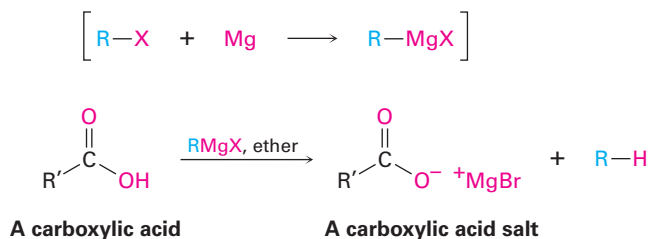


Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as LiAlH_4 reduction of an ester adds two hydrogens.

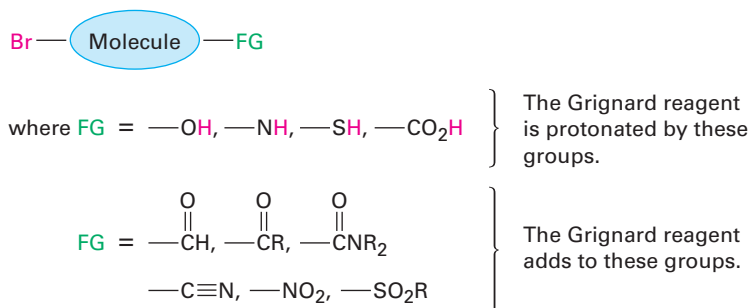


Carboxylic acids don't give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to

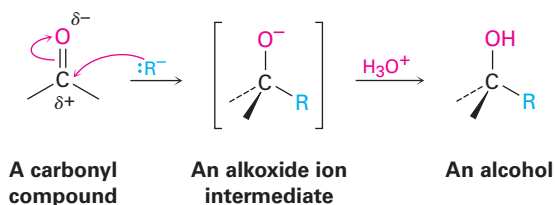
yield a hydrocarbon and the magnesium salt of the acid. We saw this reaction in Section 10.7 as a means of reducing an alkyl halide to an alkane.



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 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_2H , ROH , or RNH_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):



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 carbon anions, or *carbanions* ($:\text{R}^-$), and that the addition of a Grignard reagent 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.

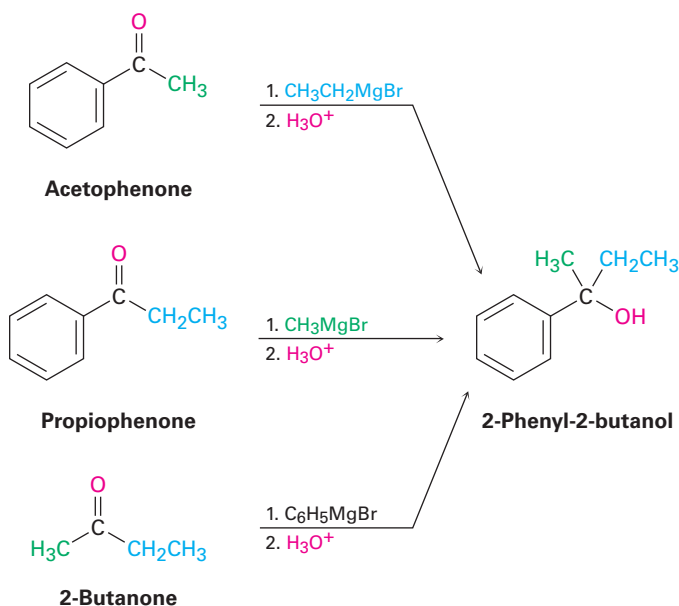


WORKED EXAMPLE 17.3**Using a Grignard Reaction to Synthesize an Alcohol**

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.

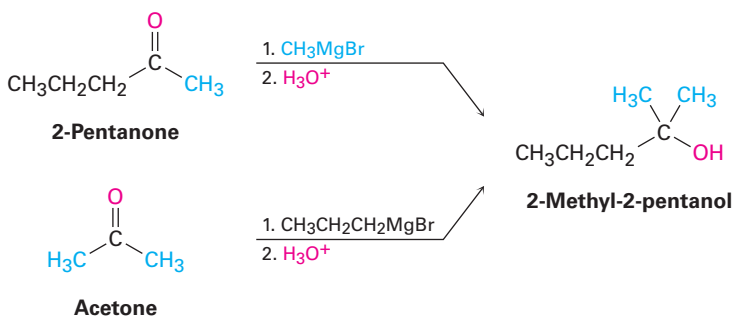
Solution 2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group ($-\text{C}_6\text{H}_5$) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.

**WORKED EXAMPLE 17.4****Using a Grignard Reaction to Synthesize an Alcohol**

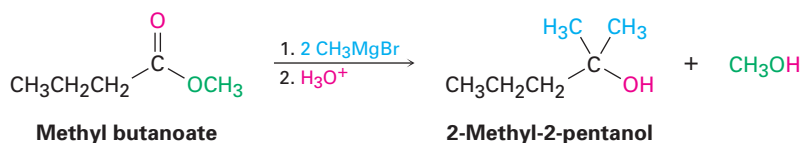
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?

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.



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



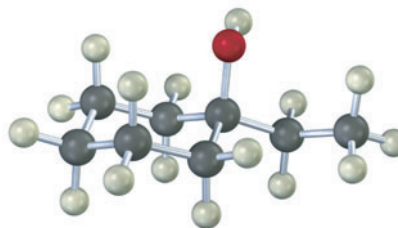
Problem 17.9 Show the products obtained from addition of methylmagnesium bromide to the following compounds:

- (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-Methylcyclohexanol (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

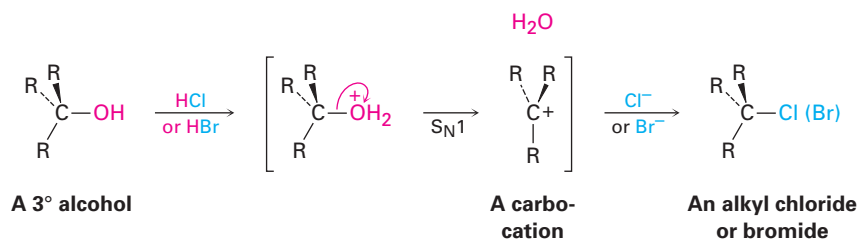
ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of reactions involving alcohols.

We've already seen several reactions of alcohols—their conversion into alkyl halides and tosylates in Section 10.6 and their dehydration to give alkenes in Section 7.1—although without mechanistic details. Let's now look at those details.

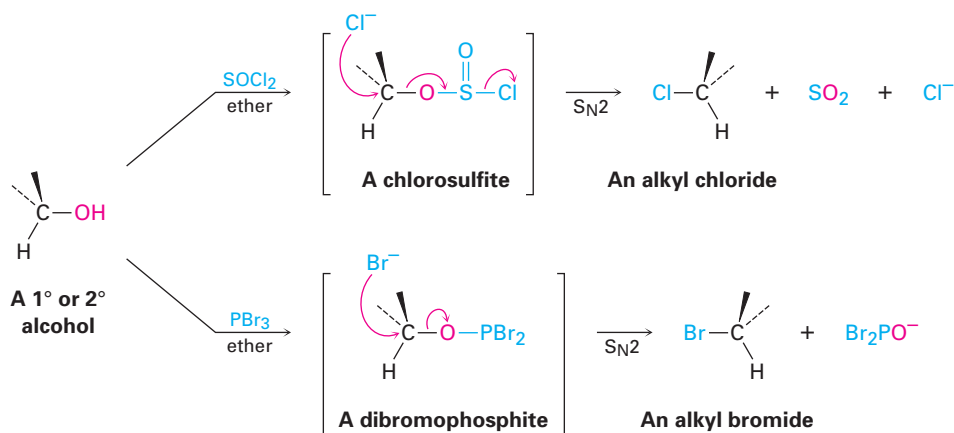
Conversion of Alcohols into Alkyl Halides

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 SOCl₂ or PBr₃ 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.

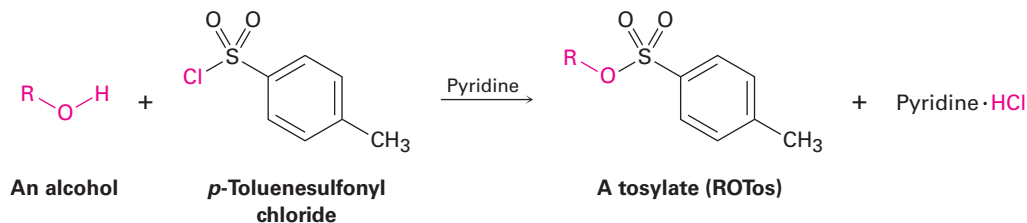


The reactions of primary and secondary alcohols with SOCl₂ and PBr₃ take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with SOCl₂ or PBr₃ converts the -OH into a much better leaving group, either a chlorosulfite (-OSOCl) or a dibromophosphite (-OPBr₂), that is readily expelled by backside nucleophilic substitution.

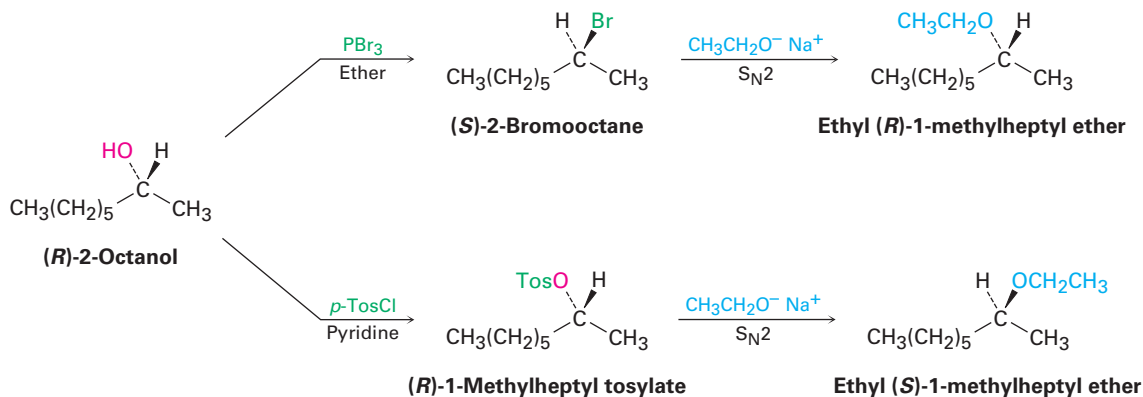


Conversion of Alcohols into Tosylates

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.



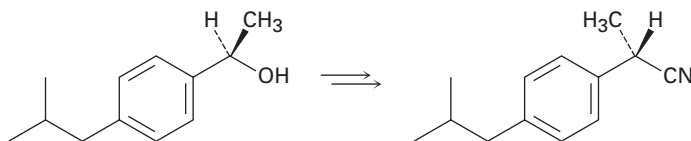
One of the most important reasons for using tosylates in S_N2 reactions is stereochemical. The S_N2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry 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.



Active 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. *Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.*

Problem 17.12

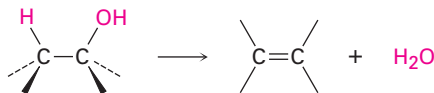
How would you carry out the following transformation, a step used in the commercial synthesis of (*S*)-ibuprofen?



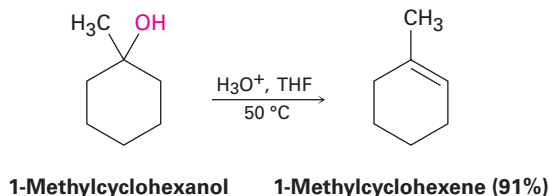
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. The C–O bond and a neighboring C–H are broken, and an alkene π bond is formed.

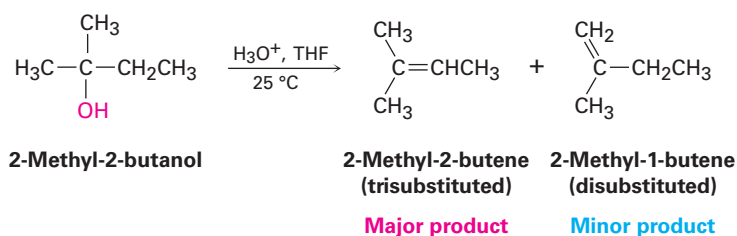
A dehydration reaction



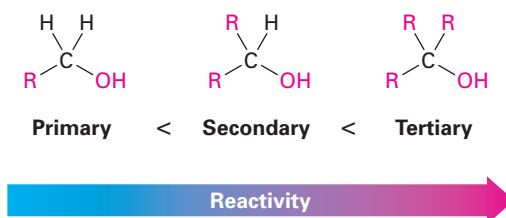
Because of the usefulness of the reaction, a number of ways have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in Section 7.1. For example, treatment of 1-methylcyclohexanol with warm aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



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).



The reaction is an E1 process and occurs through the three-step mechanism shown in Figure 17.6). As usual for E1 reactions (Section 11.10), only tertiary alcohols are readily dehydrated with acid. Secondary alcohols can be made to react, but the conditions are severe (75% H₂SO₄, 100 °C) and sensitive molecules don't survive. Primary alcohols are even less reactive than secondary ones, and very harsh conditions are necessary to cause dehydration (95% H₂SO₄, 150 °C). Thus, the reactivity order for acid-catalyzed dehydrations is



To circumvent the need for strong acid and allow the dehydration of secondary alcohols, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride (POCl₃) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.

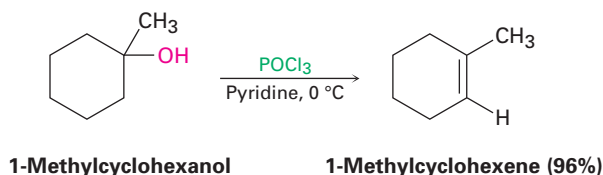
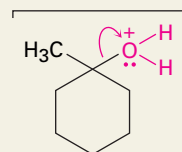
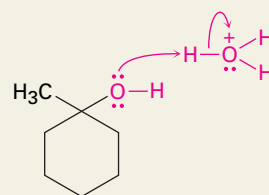


Figure 17.6 MECHANISM:

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

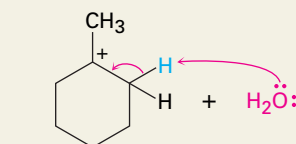
ThomsonNOW Click *Organic Process* to view animations showing the E1 acid-catalyzed dehydration of an alcohol.

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



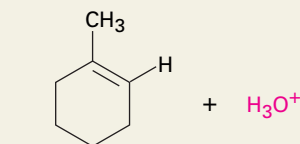
Protonated alcohol

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



Carbocation

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



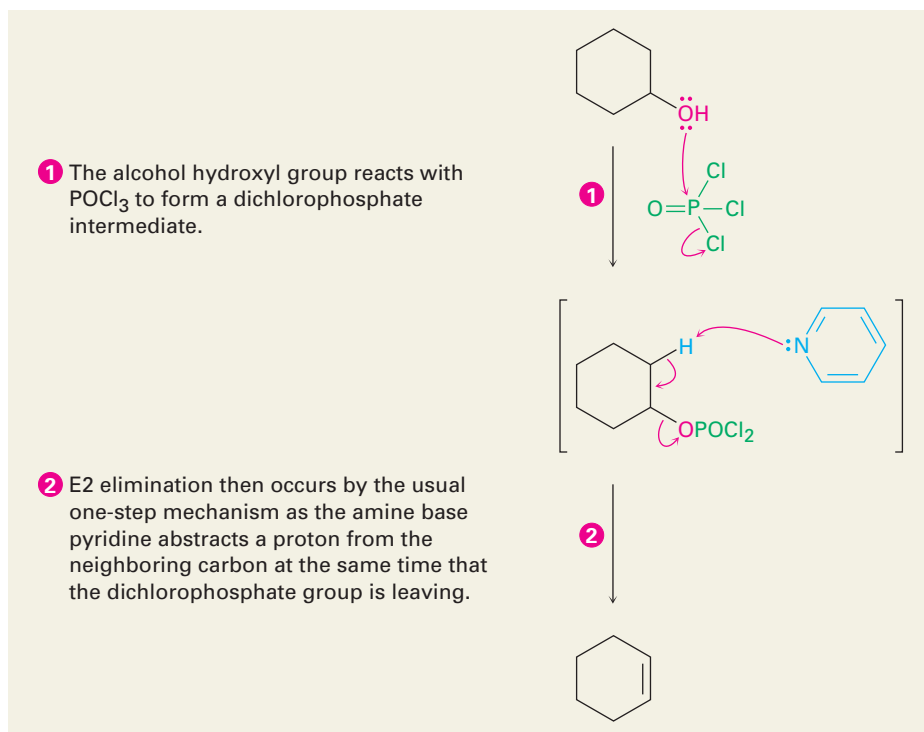
© John McMurry

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, direct E2 elimination of water from an alcohol does not occur. On reaction with POCl_3 , however, the $-\text{OH}$ group is converted into a dichlorophosphate ($-\text{OPOCl}_2$), 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.

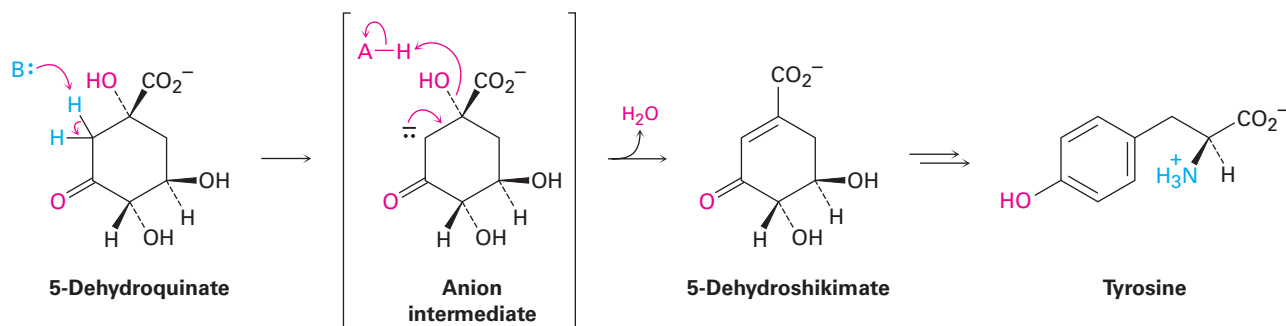
As noted previously in Section 11.10, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the $-\text{OH}$ group is two carbons away from a carbonyl group. An example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate

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.

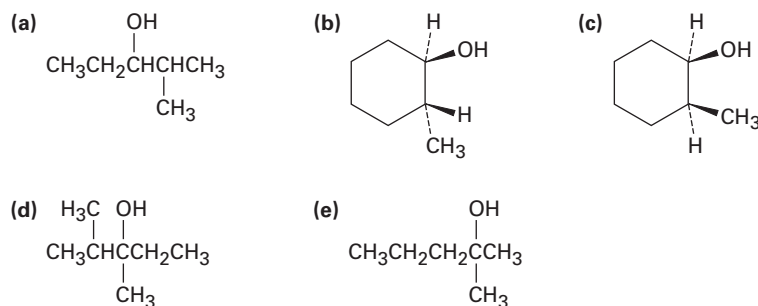
ThomsonNOW Click *Organic Process* to view animations showing the E2 dehydration of an alcohol with POCl_3 .



then expels the $-\text{OH}$ group with simultaneous protonation by an acid (HA) to form water.

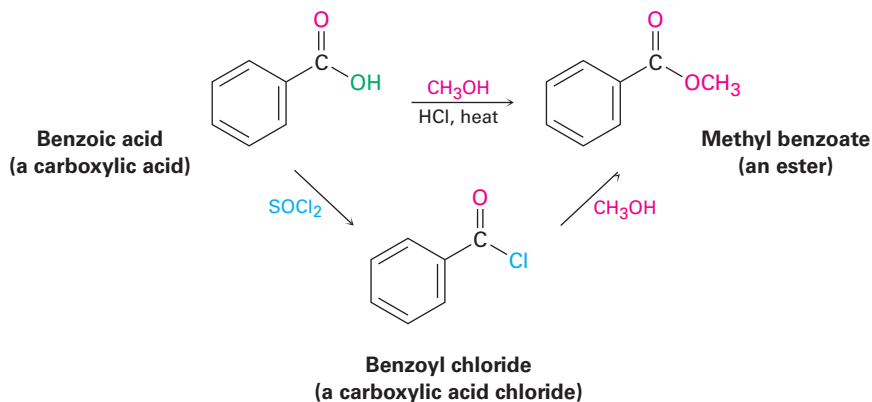


Problem 17.13 What product(s) would you expect from dehydration of the following alcohols with POCl_3 in pyridine? Indicate the major product in each case.

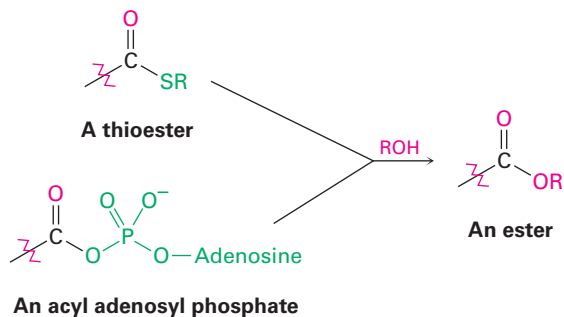


Conversion of Alcohols into Esters

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. We'll look in detail at the mechanisms of these reactions in Chapter 21.

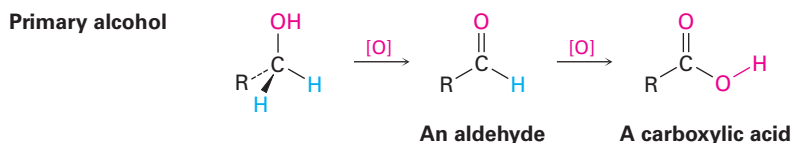


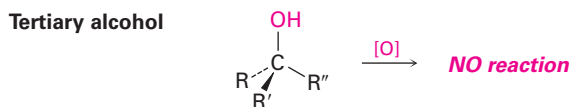
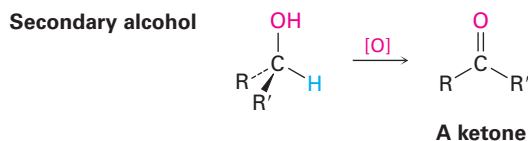
In living organisms, a similar process occurs, although a thioester or acyl adenosyl phosphate is the substrate rather than a carboxylic acid chloride.



17.7 Oxidation of Alcohols

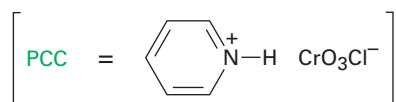
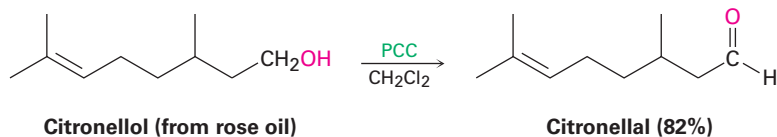
Perhaps the most valuable reaction of alcohols is their oxidation to yield carbonyl compounds—the opposite of the reduction of carbonyl compounds to yield alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don't normally react with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



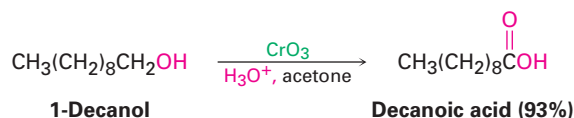


The oxidation of a primary or secondary alcohol can be accomplished by any of a large number of reagents, including KMnO_4 , CrO_3 , and $\text{Na}_2\text{Cr}_2\text{O}_7$. Which reagent is used in a specific case depends on such factors as cost, convenience, reaction yield, and alcohol sensitivity. For example, the large-scale oxidation of a simple, inexpensive alcohol such as cyclohexanol might best be done with a cheap oxidant such as $\text{Na}_2\text{Cr}_2\text{O}_7$. 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.

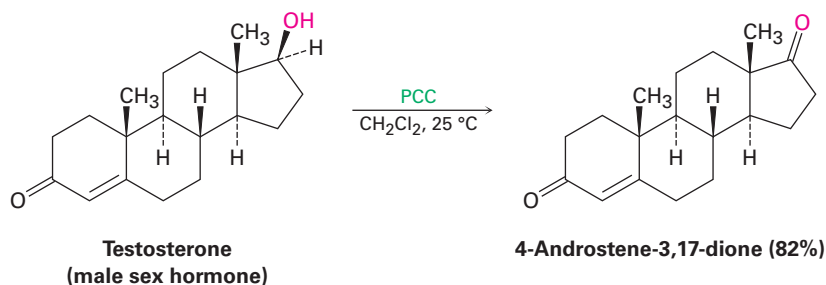
Primary alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagents chosen and the conditions used. One of the best methods for preparing an aldehyde from a primary alcohol on a small laboratory scale, as opposed to a large industrial scale, is to use pyridinium chlorochromate (PCC, $\text{C}_5\text{H}_6\text{N}^+\text{CrO}_3\text{Cl}^-$) in dichloromethane solvent.



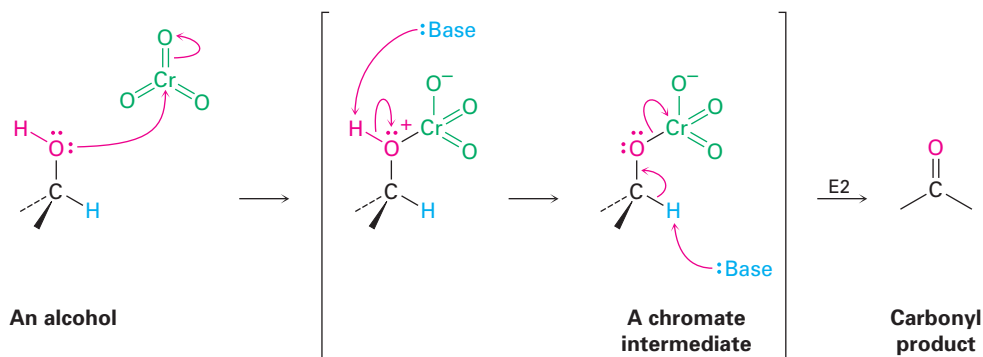
Most other oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can't usually be isolated because it is further oxidized too rapidly.



Secondary alcohols are oxidized easily and in high yield to give ketones. For large-scale oxidations, an inexpensive reagent such as $\text{Na}_2\text{Cr}_2\text{O}_7$ in aqueous acetic acid might be used. For a more sensitive or costly alcohol, however, pyridinium chlorochromate is often used because the reaction is milder and occurs at lower temperatures.

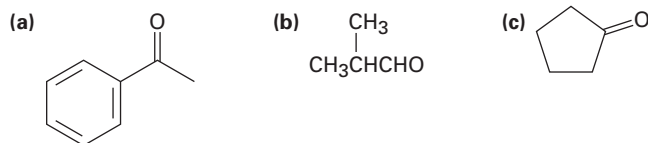


All these oxidations occur by a pathway that is closely related to the E2 reaction (Section 11.8). The first step involves reaction between the alcohol and a Cr(VI) reagent to form a *chromate* intermediate, followed by expulsion of chromium as the leaving group to yield the carbonyl product. Although 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 metal as the leaving group.



Biological alcohol oxidations are the exact 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.

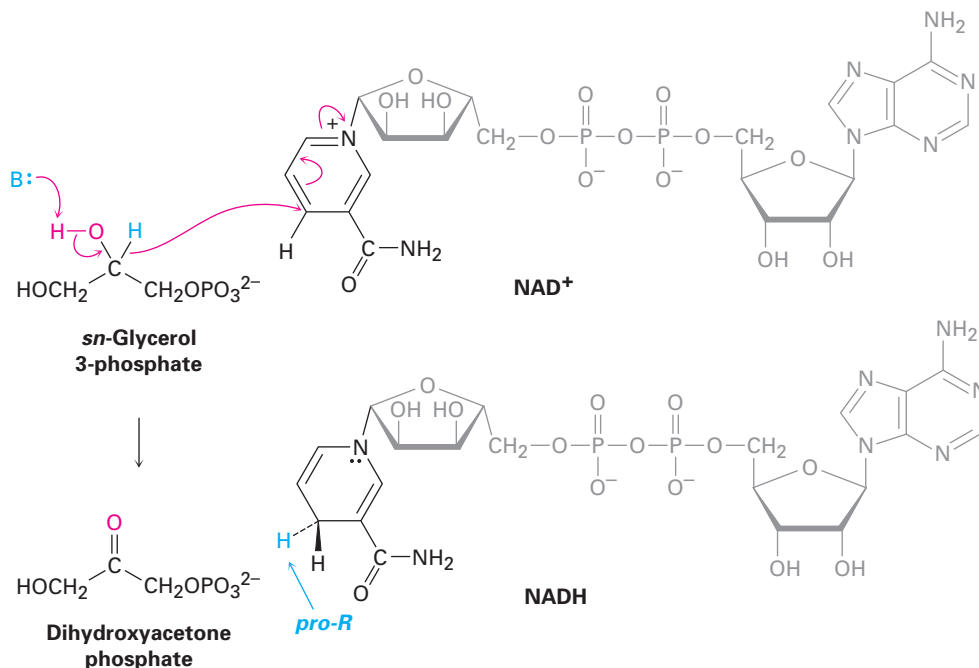
Problem 17.14 What alcohols would give the following products on oxidation?



Problem 17.15 What products would you expect from oxidation of the following compounds with CrO₃ in aqueous acid? With pyridinium chlorochromate?

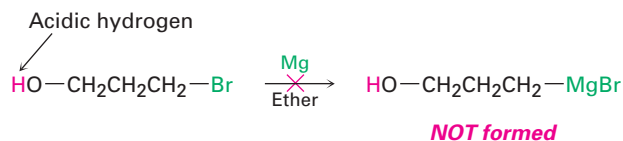
- (a) 1-Hexanol (b) 2-Hexanol (c) Hexanal

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.



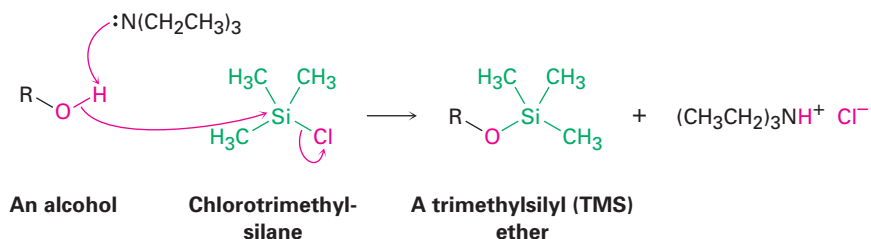
17.8 Protection of Alcohols

It often happens, particularly during the synthesis of complex molecules, that one functional group in a molecule interferes with an intended reaction on a second functional group elsewhere in the same molecule. For example, we saw earlier in this chapter 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.

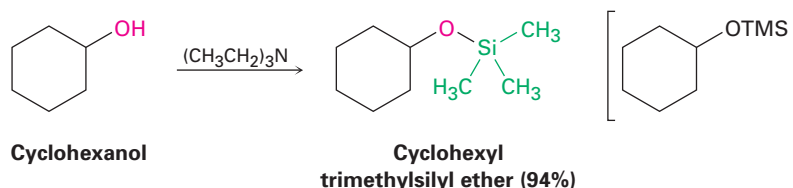


When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (1) introducing a **protecting group** to block the interfering function, (2) carrying out the desired reaction, and (3) removing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

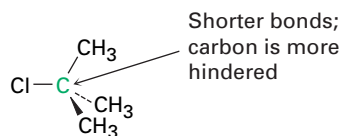
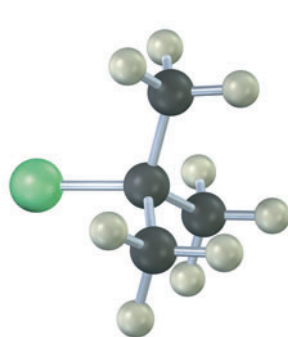
One of the more common methods of alcohol protection is by reaction with a chlorotrialkylsilane, Cl–SiR₃, to yield a trialkylsilyl ether, R'–O–SiR₃. Chlorotrimethylsilane is often used, and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.



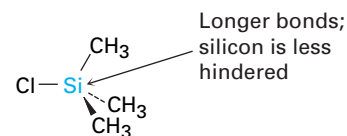
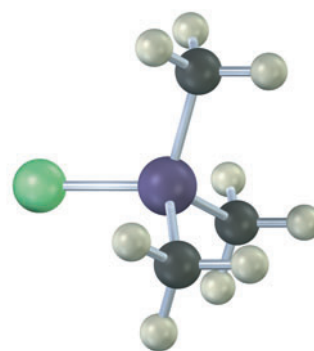
For example:



The ether-forming step is an S_N2 -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.



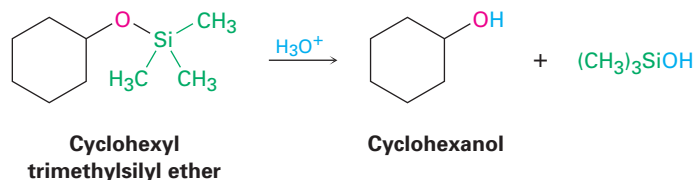
C–C bond length: 154 pm



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

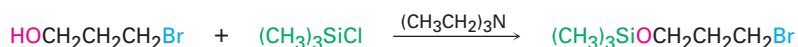
oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol.



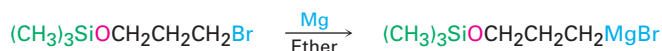
To now solve the problem posed at the beginning of this section, it's possible to use a halo alcohol in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromo-1-propanol to acetaldehyde by the route shown in Figure 17.9.

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

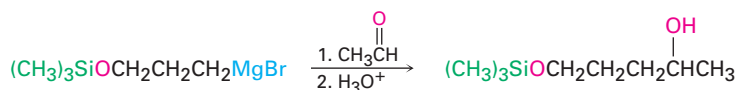
Step 1 Protect alcohol:



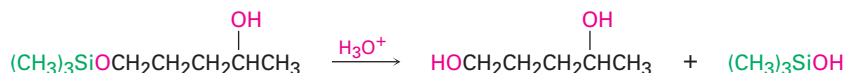
Step 2a Form Grignard reagent:



Step 2b Do Grignard reaction:



Step 3 Remove protecting group:



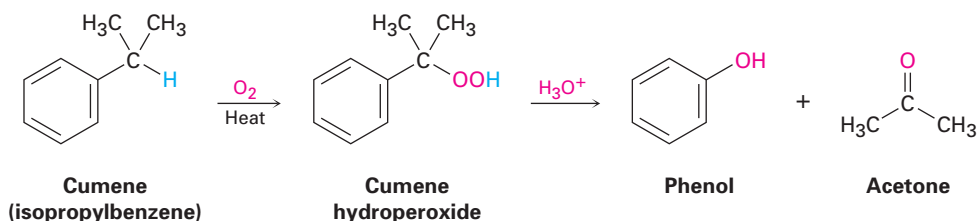
Problem 17.16 TMS ethers can be removed by treatment with fluoride ion as well as by acid-catalyzed hydrolysis. Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF. Fluorotrimethylsilane is a product.

17.9 Phenols and Their Uses

Historically, the outbreak of the first World War 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, more than 2 million tons of phenol is manufactured each year in the United States for use in such products as Bakelite resin and adhesives for binding plywood.

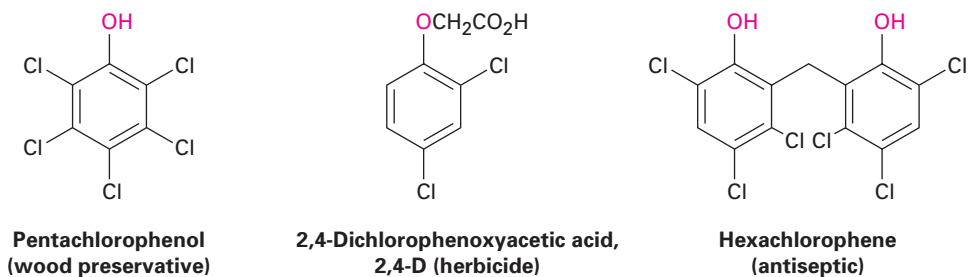
Phenol was manufactured for many years by the Dow process, in which chlorobenzene reacts with NaOH at high temperature and pressure (Section 16.8). Now, however, an alternative synthesis from isopropylbenzene, commonly called

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.

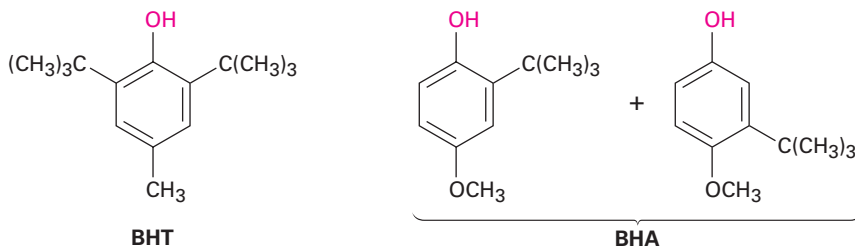


The reaction occurs by protonation of oxygen, followed by rearrangement of the phenyl group from carbon to oxygen with simultaneous loss of water. Readdition of water then yields an intermediate called a *hemiacetal*—a compound that contains one $-\text{OR}$ group and one $-\text{OH}$ group bonded to the same carbon atom—which breaks down to phenol and acetone (Figure 17.10).

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.



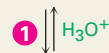
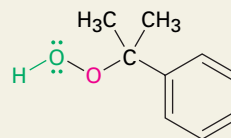
The food preservative BHT is prepared by Friedel–Crafts alkylation of *p*-methylphenol (*p*-cresol) with 2-methylpropene in the presence of acid; BHA is prepared similarly by alkylation of *p*-methoxyphenol.



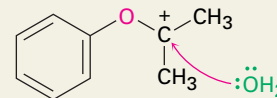
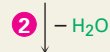
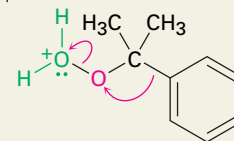
Problem 17.17 Show the mechanism of the reaction of *p*-methylphenol with 2-methylpropene and H_3PO_4 catalyst to yield the food additive BHT.

Figure 17.10 MECHANISM:
Mechanism of the formation of phenol by acid-catalyzed rearrangement of cumene hydroperoxide.

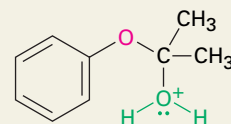
- 1 Protonation of the hydroperoxy group on the terminal oxygen atom gives an oxonium ion . . .



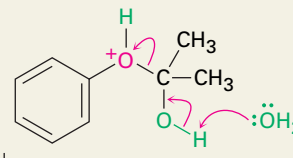
- 2 . . . which undergoes rearrangement by migration of the phenyl ring from carbon to oxygen, expelling water as the leaving group and giving a carbocation.



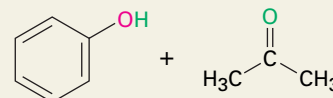
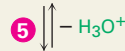
- 3 Nucleophilic addition of water to the carbocation yields another oxonium ion . . .



- 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.

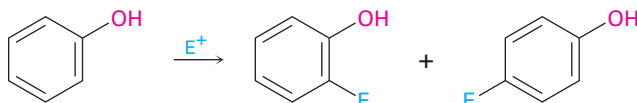


17.10 Reactions of Phenols

ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of reactions involving phenols.

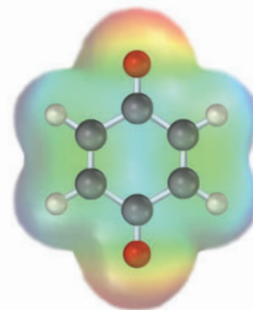
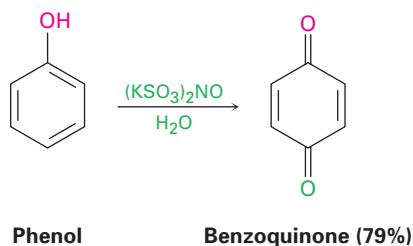
Electrophilic Aromatic Substitution Reactions

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.

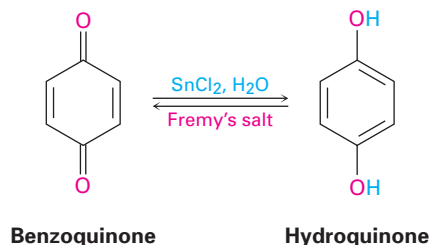


Oxidation of Phenols: Quinones

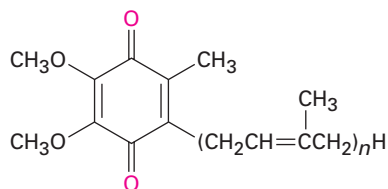
Phenols don't undergo oxidation in the same way that alcohols do because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, reaction of a phenol with a strong oxidizing agent yields a 2,5-cyclohexadiene-1,4-dione, or **quinone**. Older procedures employed $\text{Na}_2\text{Cr}_2\text{O}_7$ as oxidant, but Fremy's salt [potassium nitrosodisulfonate, $(\text{KSO}_3)_2\text{NO}$] is now preferred. The reaction takes place under mild conditions through a radical mechanism.



Quinones are an interesting and 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 Fremy's salt.



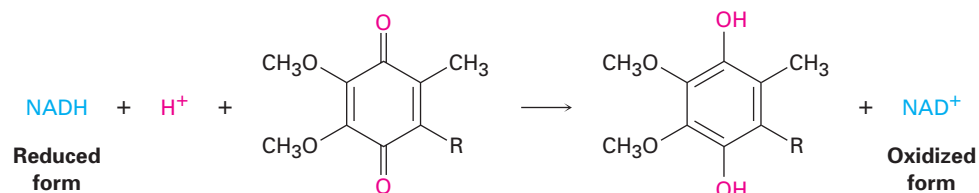
The redox properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q*, are components of the cells of all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



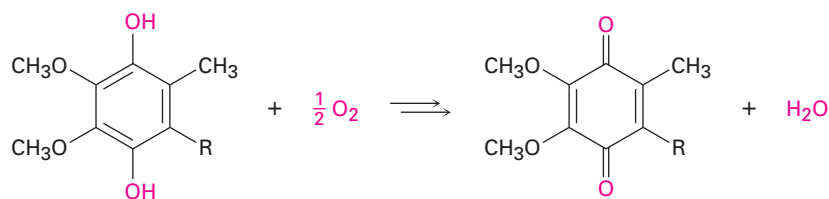
Ubiquinones ($n = 1-10$)

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.

Step 1



Step 2



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).

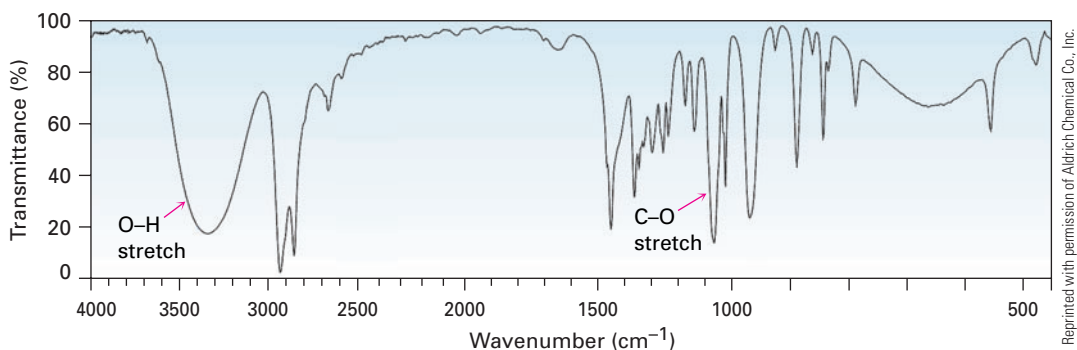


Figure 17.11 Infrared spectrum of cyclohexanol. Characteristic O–H and C–O stretching absorptions are indicated.

Phenols also show a characteristic broad IR absorption at 3500 cm^{-1} due to the $-\text{OH}$ 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.

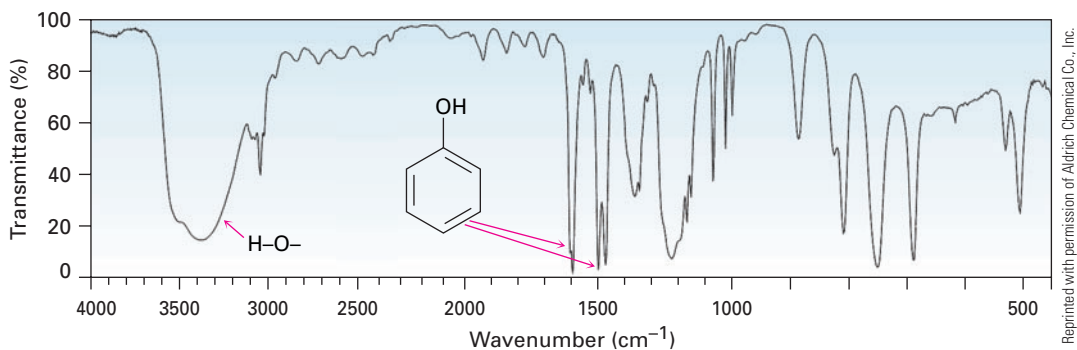
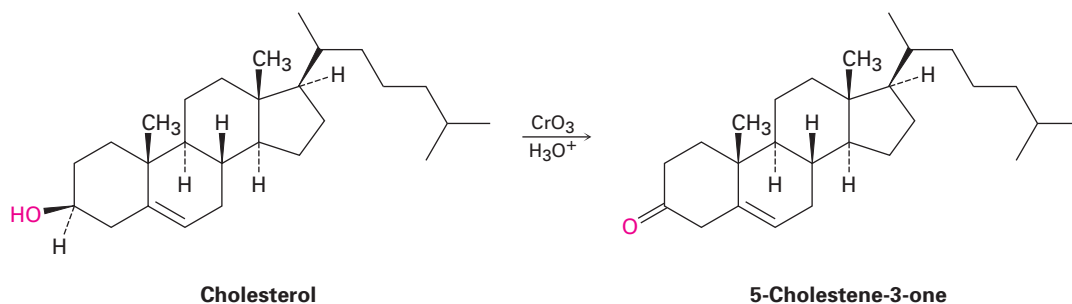


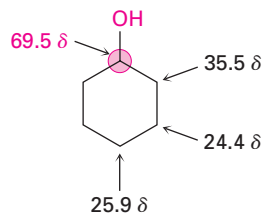
Figure 17.12 Infrared spectrum of phenol.

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?



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 ^1H 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 $\text{-CH}_2\text{-}$ protons in 1-propanol is split into a triplet by coupling with the neighboring $\text{-CH}_2\text{-}$ protons (Figure 17.13).

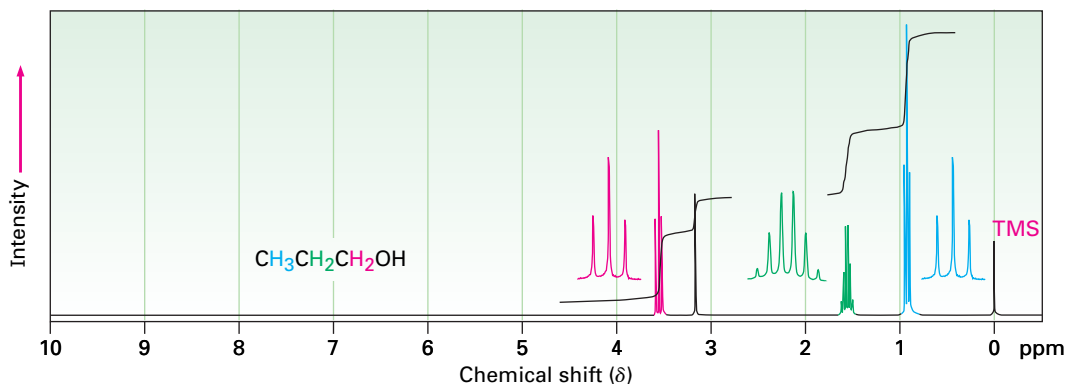


Figure 17.13 ^1H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ .

Phenols, like all aromatic compounds, show ^1H NMR absorptions near 7 to 8 δ , the expected position for aromatic-ring protons (Section 15.8). In addition, phenol O-H protons absorb at 3 to 8 δ . In neither case are these

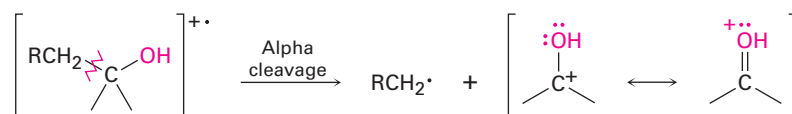
absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

Problem 17.19 When the ^1H 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?

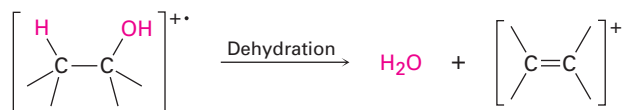
- (a) 2-Methyl-2-propanol (b) Cyclohexanol (c) Ethanol
(d) 2-Propanol (e) Cholesterol (f) 1-Methylcyclohexanol

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.

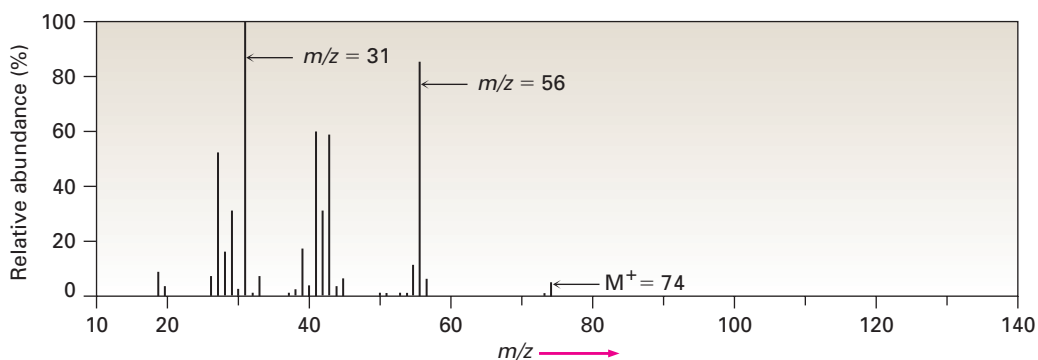
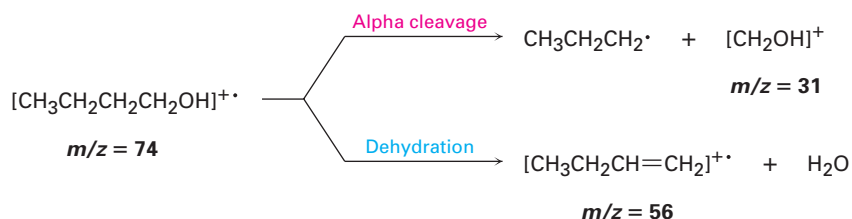


Figure 17.14 Mass spectrum of 1-butanol ($M^+ = 74$). Dehydration gives a peak at $m/z = 56$, and fragmentation by alpha cleavage gives a peak at $m/z = 31$.



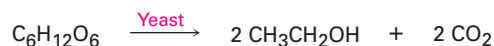
Focus On . . .

Ethanol: Chemical, Drug, and Poison



The Harger Drunkometer was 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 E85 automobile fuel.



A carbohydrate

Ethanol is classified for medical purposes 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 *Focus On*).

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 ($\text{CH}_3\text{CO}_2\text{H}$). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration

(continued)

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 last 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 AND KEY WORDS

alcohol (ROH), 599
 alkoxide ion (RO^-), 603
 hydroquinone, 631
 phenol (ArOH), 599
 phenoxide ion (ArO^-), 603
 protecting group, 626
 quinone, 631

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, ketones, esters, and carboxylic acids are reduced by reaction with $LiAlH_4$. Aldehydes, esters, and carboxylic acids yield primary alcohols (RCH_2OH) on reduction; ketones 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 reaction 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. Pyridinium chlorochromate (PCC) in dichloromethane is often used for oxidizing primary alcohols to aldehydes and secondary alcohols to ketones. A solution of CrO_3 in aqueous acid is frequently used for oxidizing primary alcohols to carboxylic acids and secondary alcohols to ketones.

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

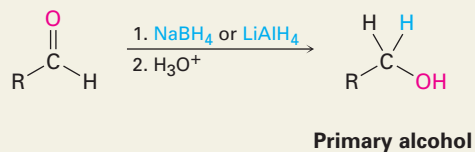
can be oxidized to **quinones** by reaction with Fremy's salt (potassium nitrosodisulfonate), and quinones can be reduced to **hydroquinones** by reaction with NaBH_4 .

SUMMARY OF REACTIONS

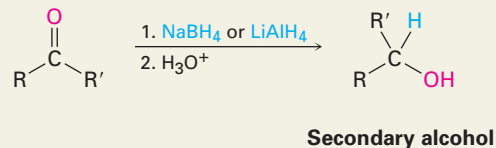
1. Synthesis of alcohols

(a) Reduction of carbonyl compounds (Section 17.4)

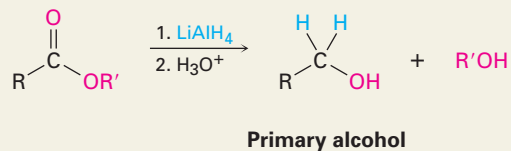
(1) Aldehydes



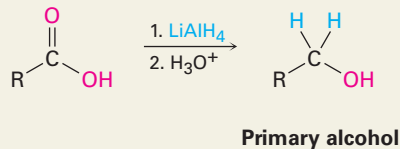
(2) Ketones



(3) Esters

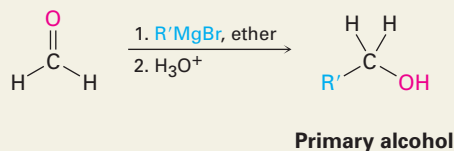


(4) Carboxylic acids

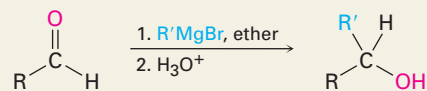


(b) Grignard addition to carbonyl compounds (Section 17.5)

(1) Formaldehyde

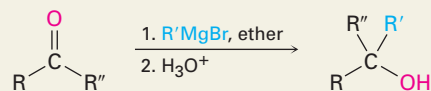


(2) Aldehydes



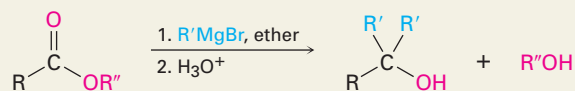
Secondary alcohol

(3) Ketones



Tertiary alcohol

(4) Esters

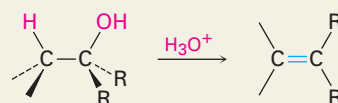


Tertiary alcohol

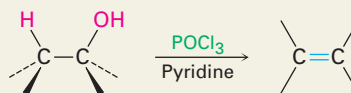
2. Reactions of alcohols

(a) Dehydration (Section 17.6)

(1) Tertiary alcohols

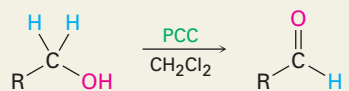


(2) Secondary and tertiary alcohols

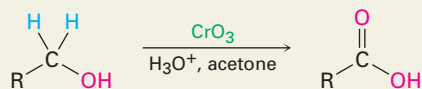


(b) Oxidation (Section 17.7)

(1) Primary alcohols

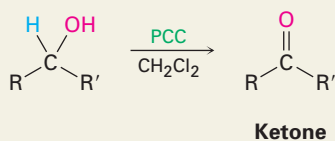


Aldehyde

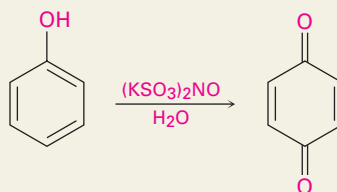


Carboxylic acid

(2) Secondary alcohols



3. Oxidation of phenols to quinones (Section 17.10)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.



Online homework for this chapter may be assigned in Organic OWL.

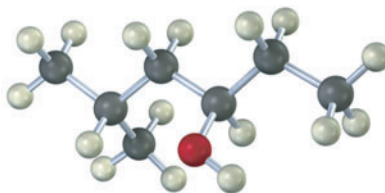
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

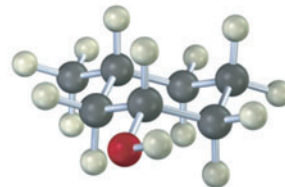
(Problems 17.1–17.19 appear within the chapter.)

17.20 ■ Give IUPAC names for the following compounds:

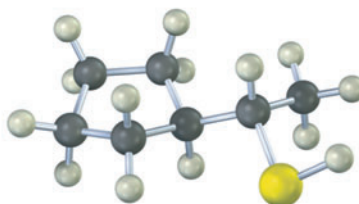
(a)



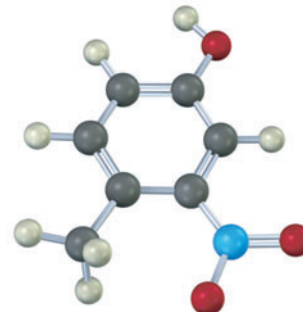
(b)



(c)

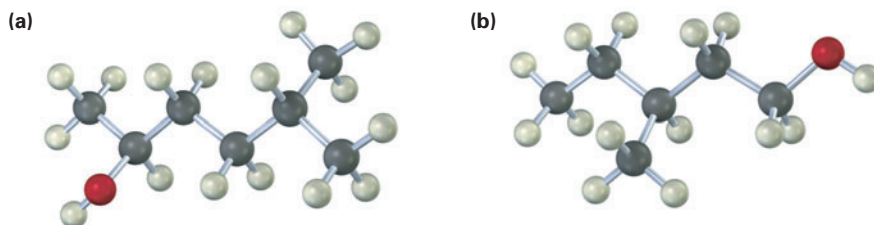


(d)



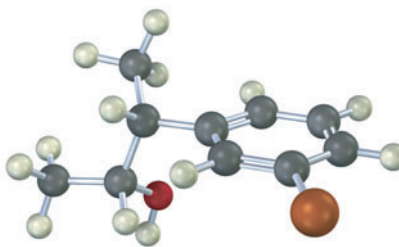
■ Assignable in OWL

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 (i) Na metal, (ii) SOCl_2 , and (iii) pyridinium chlorochromate.



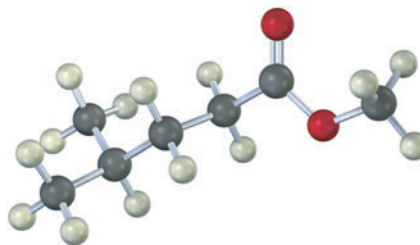
17.22 ■ Predict the product from reaction of the following substance (reddish brown = Br) with:

- (a) PBr_3 (b) Aqueous H_2SO_4 (c) SOCl_2
 (d) PCC (e) $\text{Br}_2, \text{FeBr}_3$

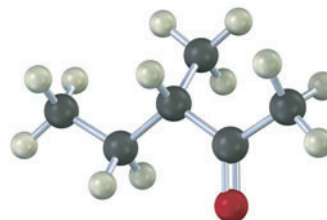


17.23 ■ Predict the product from reaction of the following substance with:

- (a) NaBH_4 ; then H_3O^+ (b) LiAlH_4 ; then H_3O^+
 (c) $\text{CH}_3\text{CH}_2\text{MgBr}$; then H_3O^+



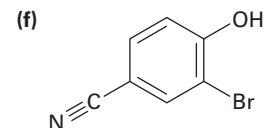
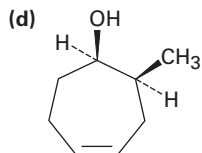
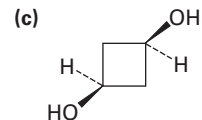
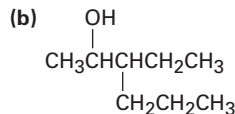
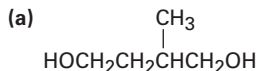
17.24 Name and assign *R* or *S* stereochemistry to the product(s) you would obtain by reaction of the following substance with ethylmagnesium bromide. Is the product chiral? Is it optically active? Explain.



■ Assignable in OWL

ADDITIONAL PROBLEMS

17.25 ■ Give IUPAC names for the following compounds:

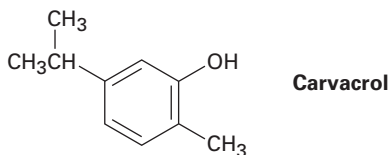


17.26 Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$.

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?



17.30 ■ 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) PCC

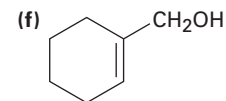
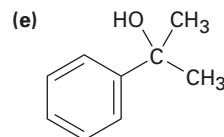
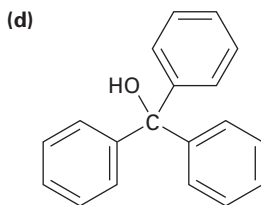
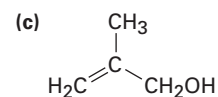
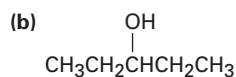
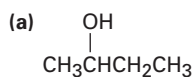
17.31 ■ How would you prepare the following compounds from 2-phenylethanol? More than one step may be required.

(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

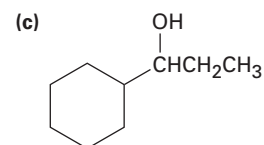
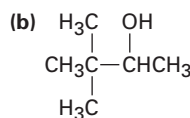
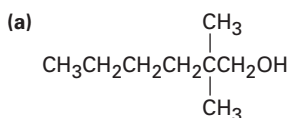
17.32 ■ How would you prepare the following compounds from 1-phenylethanol? More than one step may be required.

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

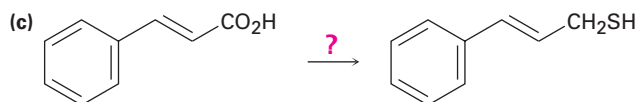
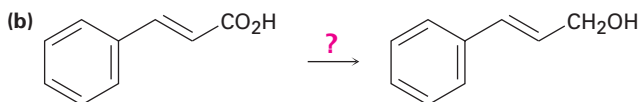
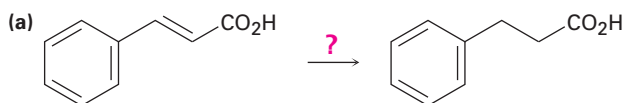
17.33 ■ What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols?



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



17.35 ■ How would you carry out the following transformations?



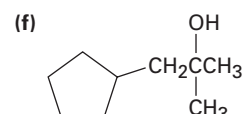
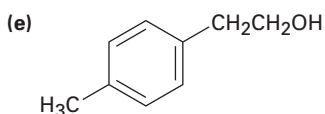
17.36 ■ What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

(a) 2-Methyl-2-propanol

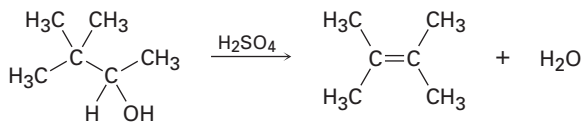
(b) 1-Ethylcyclohexanol

(c) 3-Phenyl-3-pentanol

(d) 2-Phenyl-2-pentanol



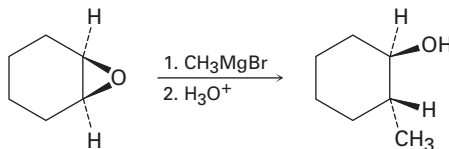
- 17.37** ■ Evidence for the intermediate carbocations in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethyl-2-butene from 3,3-dimethyl-2-butanol.



- 17.38** ■ 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.



- 17.39** Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.

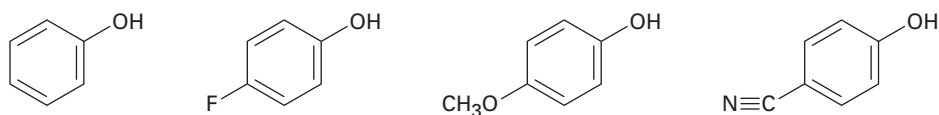


- 17.40** ■ How would you prepare the following substances from cyclopentanol? More than one step may be required.
 (a) Cyclopentanone (b) Cyclopentene
 (c) 1-Methylcyclopentanol (d) *trans*-2-Methylcyclopentanol
- 17.41** ■ What products would you expect to obtain from reaction of 1-methylcyclohexanol with the following reagents?
 (a) HBr (b) NaH (c) H₂SO₄ (d) Na₂Cr₂O₇
- 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.

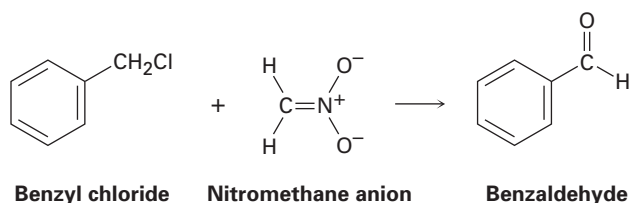


17.43 Benzoquinone is an excellent dienophile in the Diels–Alder reaction. What product would you expect from reaction of benzoquinone with 1 equivalent of 1,3-butadiene? From reaction with 2 equivalents of 1,3-butadiene?

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

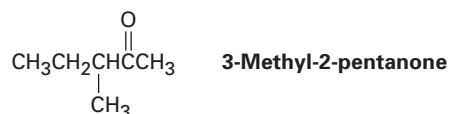


17.45 Benzyl chloride can be converted into benzaldehyde by treatment with nitromethane and base. The reaction involves initial conversion of nitromethane into its anion, followed by S_N2 reaction of the anion with benzyl chloride and subsequent E2 reaction. Write the mechanism in detail, using curved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

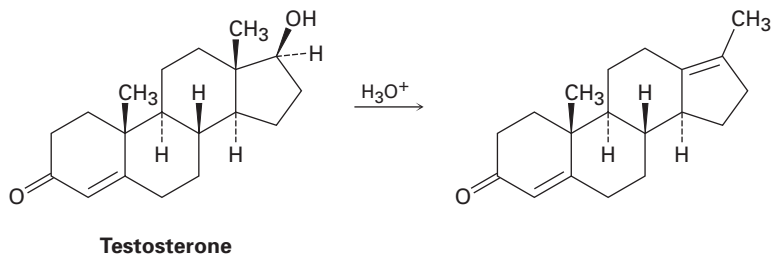


17.46 Reduction of 2-butanone with NaBH_4 yields 2-butanol. Is the product chiral? Is it optically active? Explain.

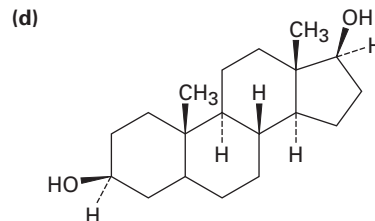
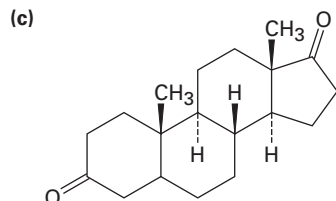
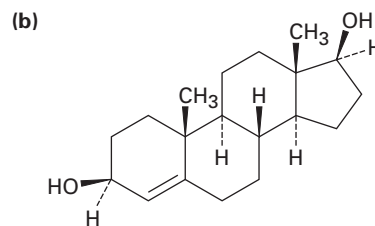
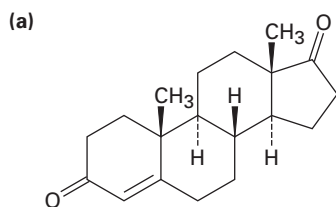
17.47 Reaction of (*S*)-3-methyl-2-pentanone with methylmagnesium bromide followed by acidification yields 2,3-dimethyl-2-pentanol. What is the stereochemistry of the product? Is the product optically active?



17.48 ■ 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.



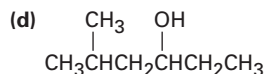
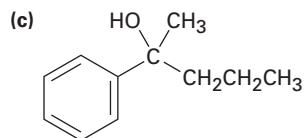
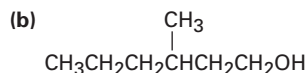
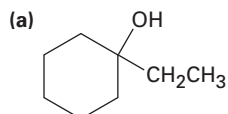
17.49 Starting from testosterone (Problem 17.48), how would you prepare the following substances?



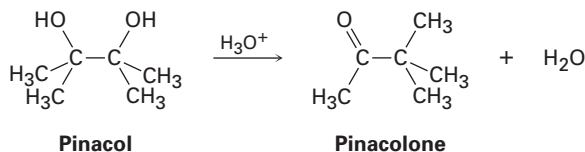
17.50 Compound A, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at $25^\circ C$ to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, B, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Write the reactions involved, and identify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

17.51 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!)

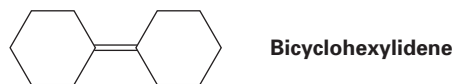
17.52 How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?



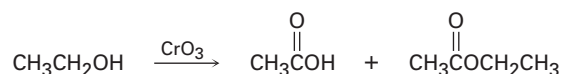
17.53 ■ 2,3-Dimethyl-2,3-butanediol has the common name *pinacol*. On heating with aqueous acid, pinacol rearranges to *pinacolone*, 3,3-dimethyl-2-butanone. Suggest a mechanism for this reaction.



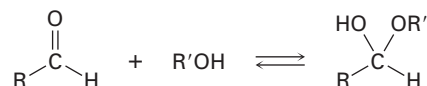
- 17.54** As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.
- 17.55** Propose a synthesis of bicyclohexylidene, starting from cyclohexanone as the only source of carbon.



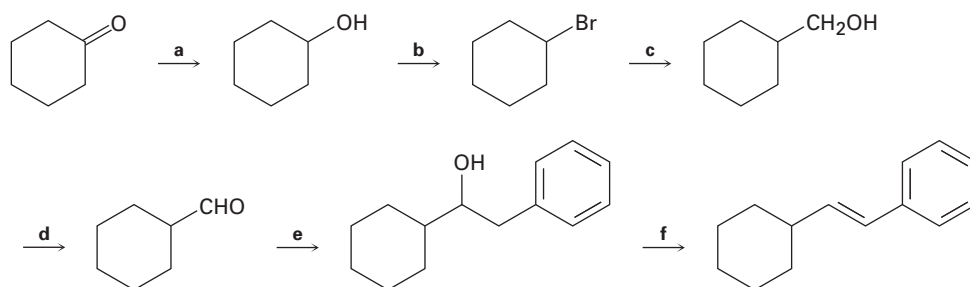
- 17.56** A problem often encountered in the oxidation of primary alcohols to acids is that esters are sometimes produced as by-products. For example, oxidation of ethanol yields acetic acid and ethyl acetate:



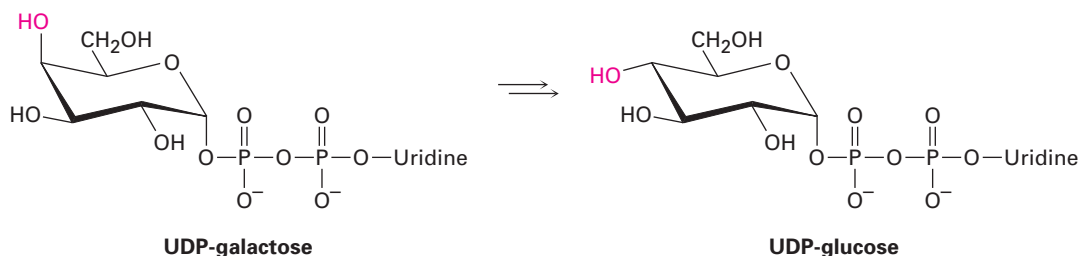
Propose a mechanism to account for the formation of ethyl acetate. Take into account the reversible reaction between aldehydes and alcohols:



- 17.57** Identify the reagents a–f in the following scheme:



- 17.58** 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.

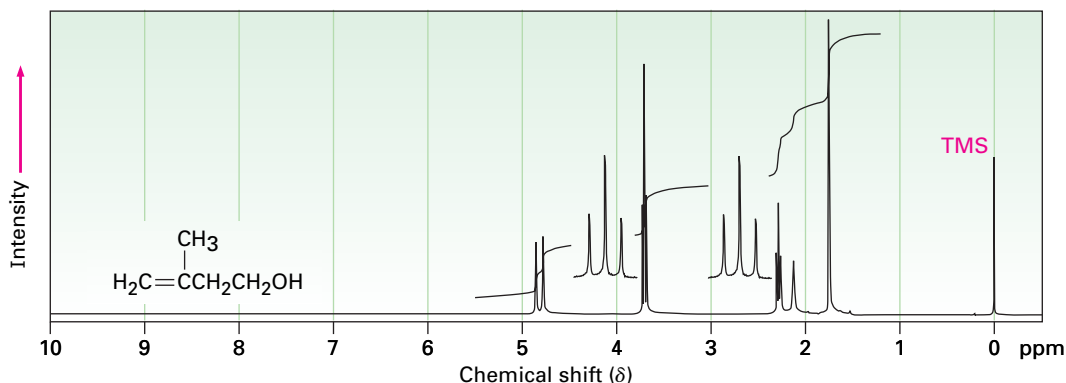


17.59 ■ Propose a structure consistent with the following spectral data for a compound $C_8H_{18}O_2$:

IR: 3350 cm^{-1}

$^1\text{H NMR}$: $1.24\ \delta$ (12 H, singlet); $1.56\ \delta$ (4 H, singlet); $1.95\ \delta$ (2 H, singlet)

17.60 The $^1\text{H NMR}$ 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.



17.61 ■ 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}

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

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

17.62 ■ A compound of unknown structure gave the following spectroscopic data:

Mass spectrum: $M^+ = 88.1$

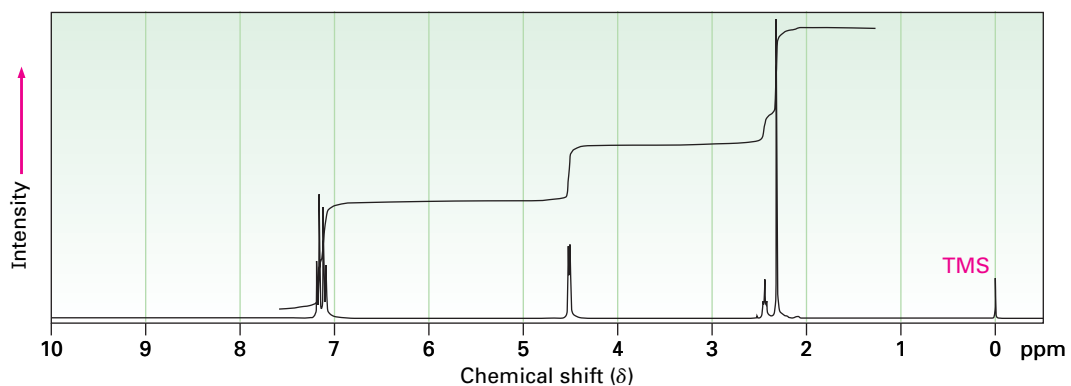
IR: 3600 cm^{-1}

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

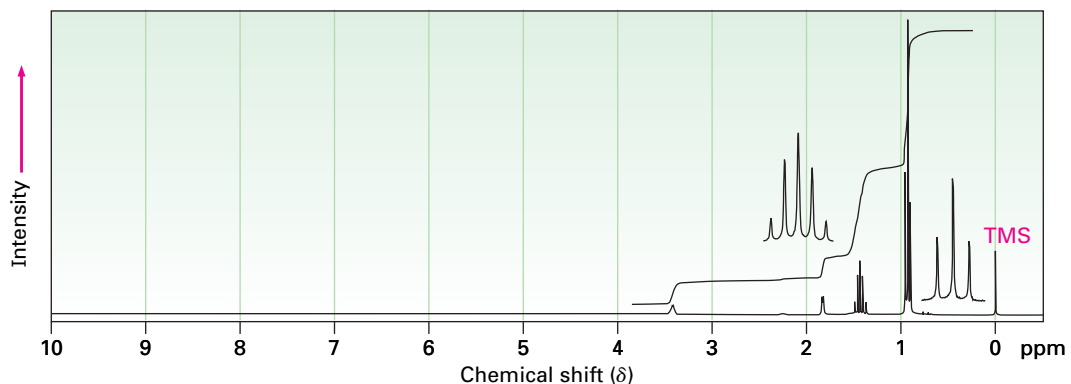
$^{13}\text{C NMR}$: $74, 35, 27, 25\ \delta$

- Assuming that the compound contains C and H but may or may not contain O, give three possible molecular formulas.
- How many protons (H) does the compound contain?
- What functional group(s) does the compound contain?
- How many carbons does the compound contain?
- What is the molecular formula of the compound?
- What is the structure of the compound?
- Assign the peaks in the $^1\text{H NMR}$ spectrum of the molecule to specific protons.

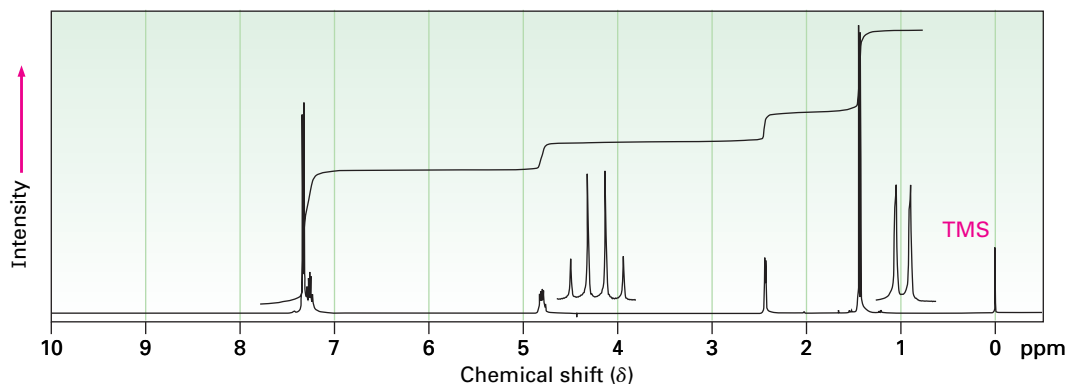
17.63 ■ The following ^1H NMR spectrum is that of an alcohol, $\text{C}_8\text{H}_{10}\text{O}$. Propose a structure.



17.64 ■ Propose structures for alcohols that have the following ^1H NMR spectra:
(a) $\text{C}_5\text{H}_{12}\text{O}$



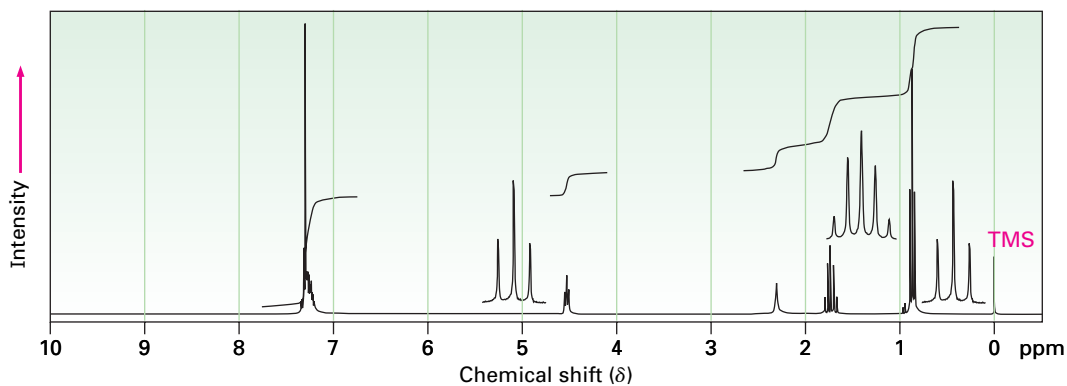
(b) $\text{C}_8\text{H}_{10}\text{O}$



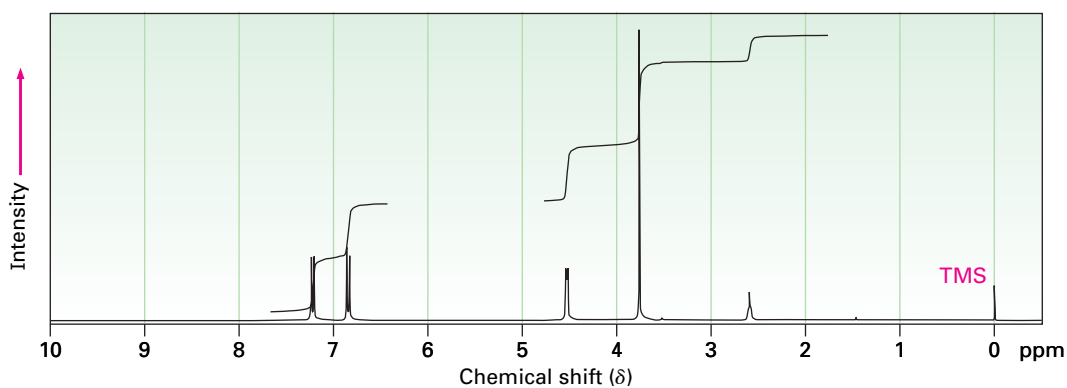
■ Assignable in OWL

17.65 ■ Propose structures for alcohols that have the following ^1H NMR spectra:

(a) $\text{C}_9\text{H}_{12}\text{O}$

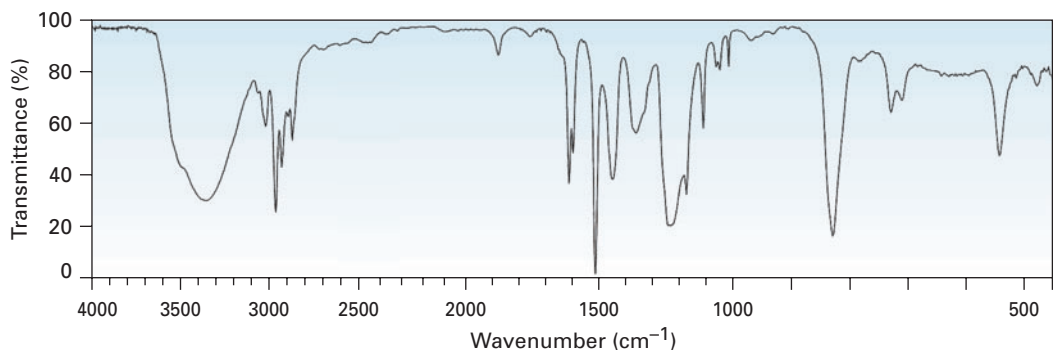


(b) $\text{C}_8\text{H}_{10}\text{O}_2$

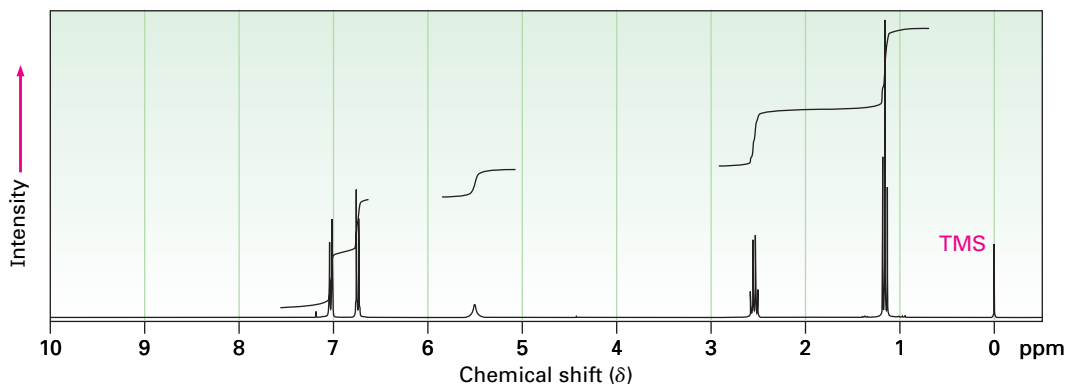


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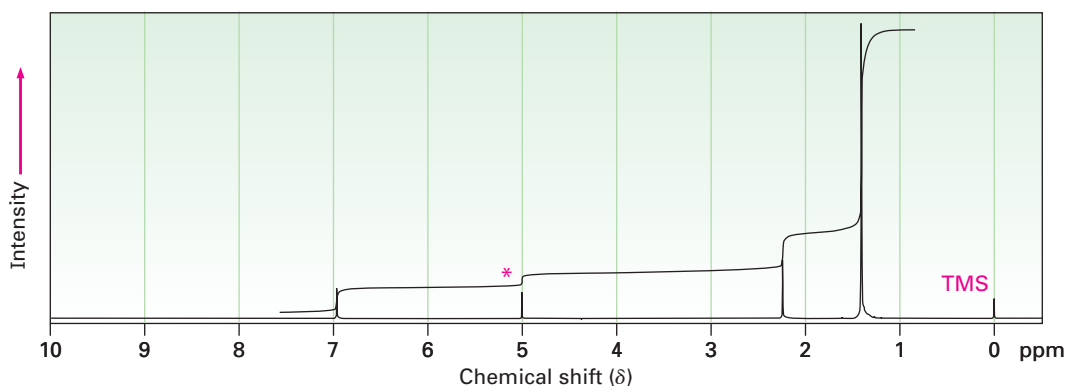
17.66 ■ Compound A, $\text{C}_8\text{H}_{10}\text{O}$, has the IR and ^1H NMR spectra shown. Propose a structure consistent with the observed spectra, and assign each peak in the NMR spectrum. Note that the absorption at $5.5\ \delta$ disappears when D_2O is added.



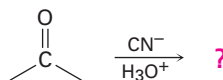
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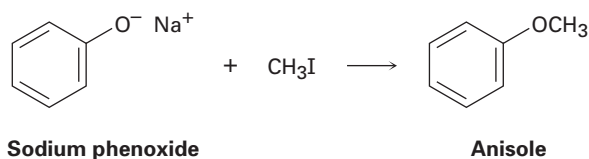
- 17.67** ■ Propose a structure for a compound $C_{15}H_{24}O$ that has the following 1H NMR spectrum. The peak marked by an asterisk disappears when D_2O is added to the sample.



- 17.68** 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?



- 17.69** 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.



18

Ethers and Epoxides; Thiols and Sulfides

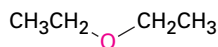
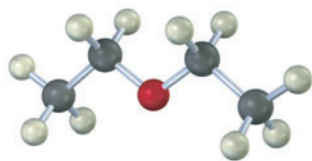
Organic KNOWLEDGE TOOLS

ThomsonNOW Throughout this chapter, sign in at www.thomsonedu.com for online self-study and interactive tutorials based on your level of understanding.

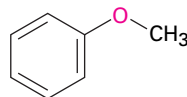
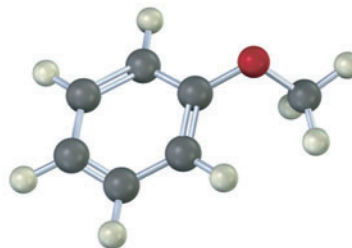


Online homework for this chapter may be assigned in Organic OWL.

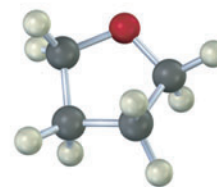
Ethers (R–O–R'), like the alcohols we saw in the preceding chapter, are also organic derivatives of water but have two organic groups bonded to the same oxygen atom rather than one. The organic groups might be alkyl, aryl, or vinylic, and the oxygen atom might be in an open chain or a ring. Perhaps the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

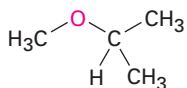
Thiols (R–S–H) and **sulfides (R–S–R')** are sulfur analogs of alcohols and ethers, respectively. Both functional groups are found in various biomolecules, although not as commonly as their oxygen-containing relatives.

WHY THIS CHAPTER?

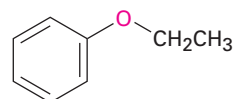
This chapter finishes the coverage of functional groups with C–O and C–S single bonds that was begun in Chapter 17. We'll focus primarily on ethers and take only a brief look at thiols and sulfides before going on to an extensive coverage of compounds with C=O bonds in Chapters 19 through 23.

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*.

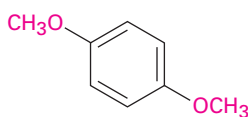


Isopropyl methyl ether

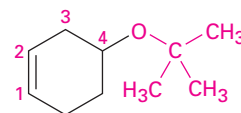


Ethyl phenyl ether

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



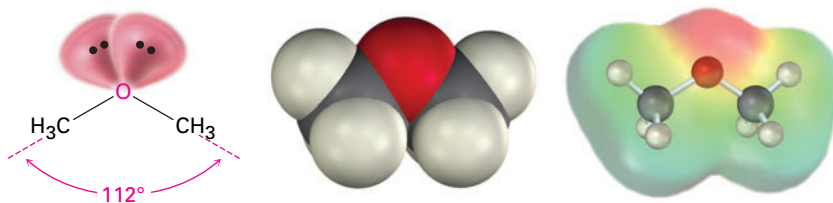
p-Dimethoxybenzene



4-*tert*-Butoxy-1-cyclohexene

ThomsonNOW Click *Organic Interactive* to use a web-based palette to draw ether structures based on their IUPAC names.



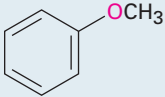
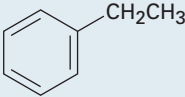
Like alcohols, ethers have nearly the same geometry as water. The R–O–R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is sp^3 -hybridized.



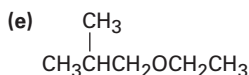
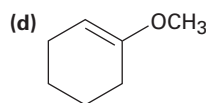
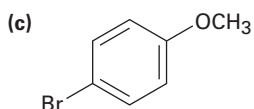
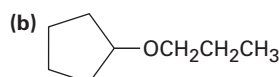
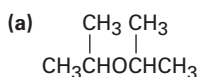
The electronegative oxygen atom gives ethers a slight dipole moment, and the boiling points of ethers are often slightly higher than the boiling points of comparable alkanes. Table 18.1 compares the boiling points of some common ethers and the corresponding hydrocarbons.

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.

Table 18.1 Comparison of Boiling Points of Ethers and Hydrocarbons

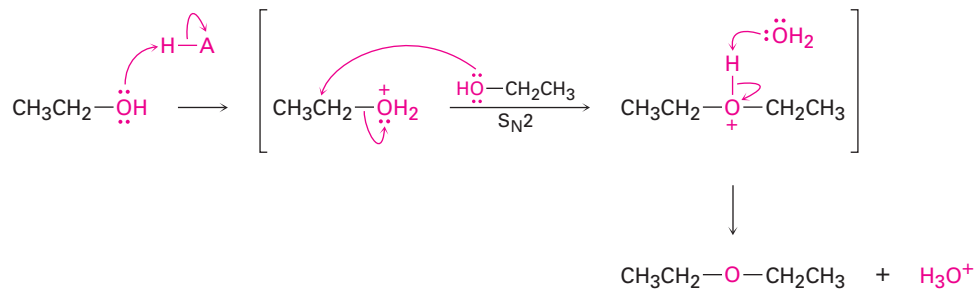
Ether	Boiling point °C	Hydrocarbon	Boiling point °C
CH_3OCH_3	-25	$\text{CH}_3\text{CH}_2\text{CH}_3$	-45
$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	34.6	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	36
	65		49
	158		136

Problem 18.1 Name the following ethers:



18.2 Synthesis of Ethers

Diethyl ether and other simple symmetrical ethers are prepared industrially by the sulfuric acid-catalyzed dehydration of alcohols. The reaction occurs by $\text{S}_{\text{N}}2$ 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).

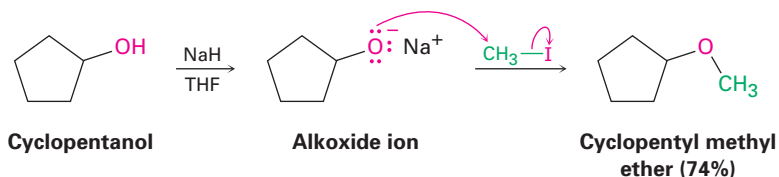


Alexander W. Williamson

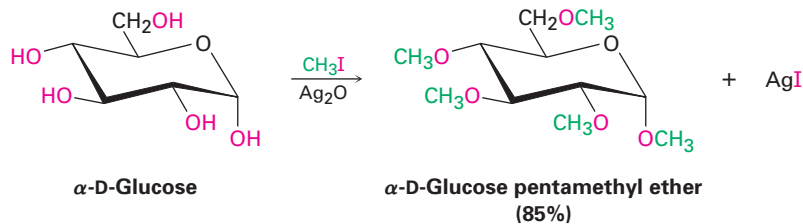
Alexander W. Williamson (1824–1904) was born in London, England, and received his Ph.D. at the University of Giessen in 1846. His ability to work in the laboratory was hampered by a childhood injury that caused the loss of an arm. From 1849 until 1887, he was professor of chemistry at University College, London.

The Williamson Ether Synthesis

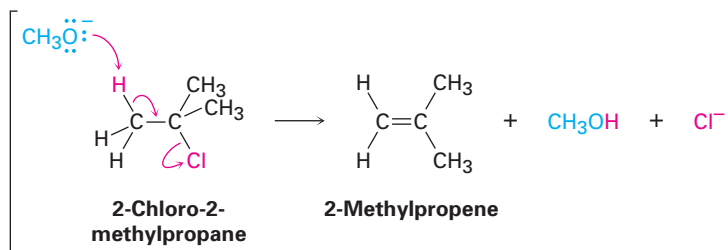
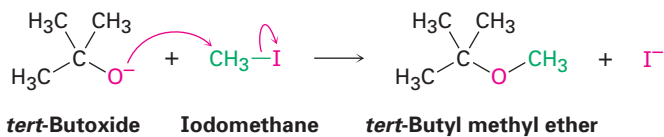
The most generally useful method of preparing ethers is by the *Williamson ether synthesis*, in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an S_N2 reaction. As we saw earlier in Section 17.2, the alkoxide ion is normally prepared by reaction of an alcohol with a strong base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



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.



Because the Williamson synthesis is an S_N2 reaction, it is subject to all the usual constraints, as discussed in Section 11.2. 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.

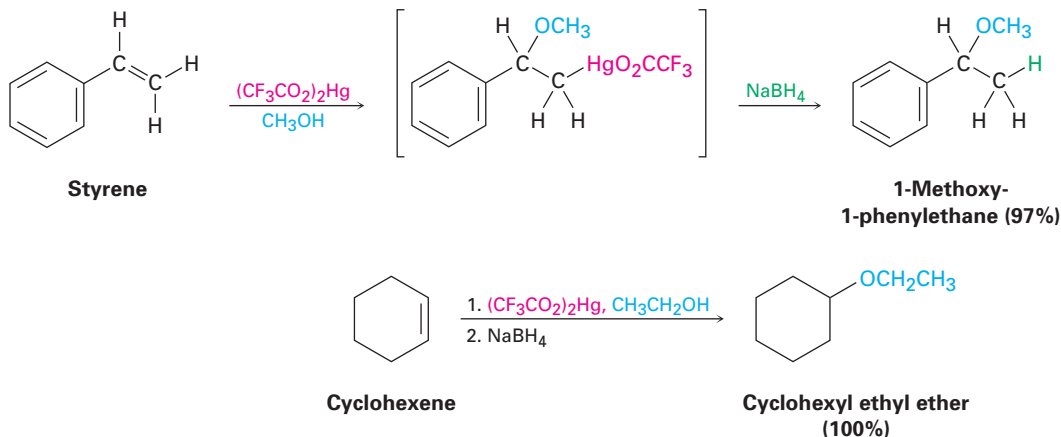


Problem 18.2 Why do you suppose only symmetrical ethers are prepared by the sulfuric acid-catalyzed dehydration procedure? What product(s) would you expect if ethanol and 1-propanol were allowed to react together? In what ratio would the products be formed if the two alcohols were of equal reactivity?

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 7.4 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, $(\text{CF}_3\text{CO}_2)_2\text{Hg}$. Demercuration by reaction with NaBH_4 then yields an ether. The net result is Markovnikov addition of the alcohol to the alkene.



ThomsonNOW™ Click *Organic Interactive* to practice your problem-solving skills designing syntheses of ethers.

The mechanism of the alkoxymercuration reaction is similar to that described in Section 7.4 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.

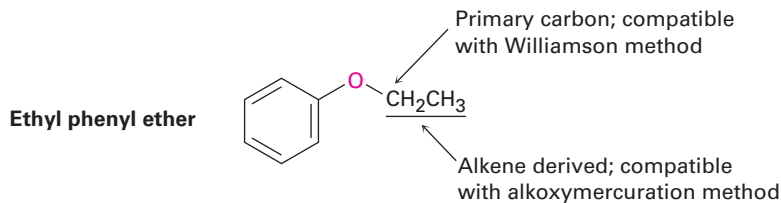
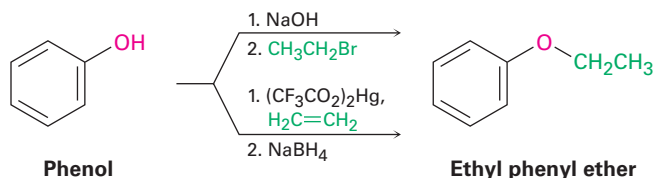
WORKED EXAMPLE 18.1

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 $\text{S}_{\text{N}}2$ reaction and requires that one of the two groups attached to oxygen be either

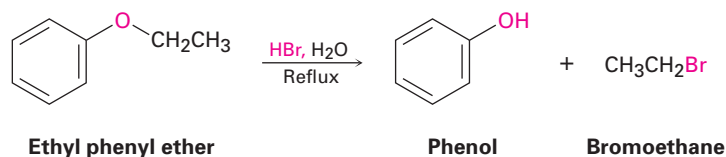
secondary or (preferably) primary. The alkoxymercuration reaction requires that one of the two groups come from an alkene precursor. Ethyl phenyl ether could be made by either method.

**Solution**

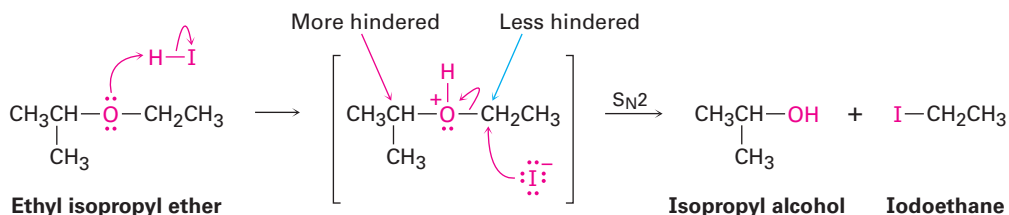
- Problem 18.4** Review the mechanism of oxymercuration shown in Figure 7.4 (p. 225), and then write the mechanism of the alkoxymercuration reaction of 1-methylcyclopentene with ethanol. Use curved arrows to show the electron flow in each step.
- Problem 18.5** How would you prepare the following ethers? 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

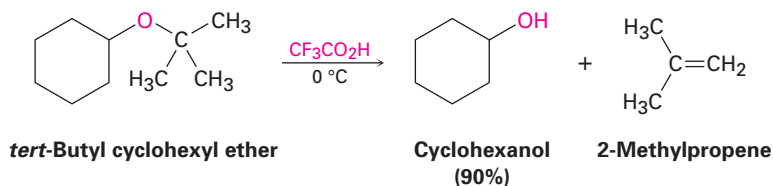
Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents. Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one reaction of general use—they are cleaved by strong acids.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



Acidic ether cleavages are typical nucleophilic substitution reactions, either S_N1 or S_N2 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.



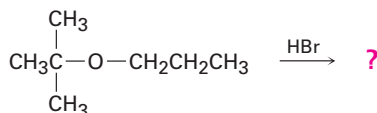
Ethers with a tertiary, benzylic, or allylic group cleave by an S_N1 or $E1$ mechanism because these substrates can produce stable intermediate carbocations. These reactions are often fast and take place at moderate temperatures. *tert*-Butyl ethers, for example, react by an $E1$ mechanism on treatment 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.



WORKED EXAMPLE 18.2

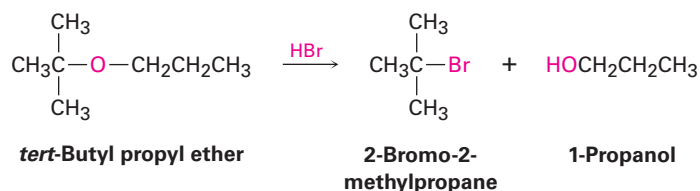
Predicting the Product of an Ether Cleavage Reaction

Predict the products of the following reaction:

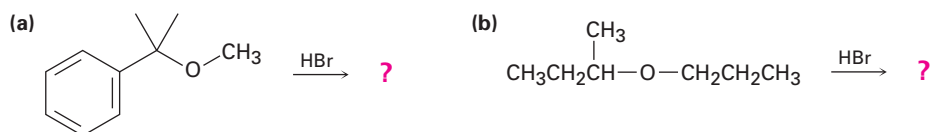


Strategy Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl groups usually undergoes cleavage by S_N2 attack of a nucleophile 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.

Solution



Problem 18.7 Predict the products of the following reactions:



Problem 18.8 Write the mechanism of the acid-catalyzed cleavage of *tert*-butyl cyclohexyl ether to yield cyclohexanol and 2-methylpropene.

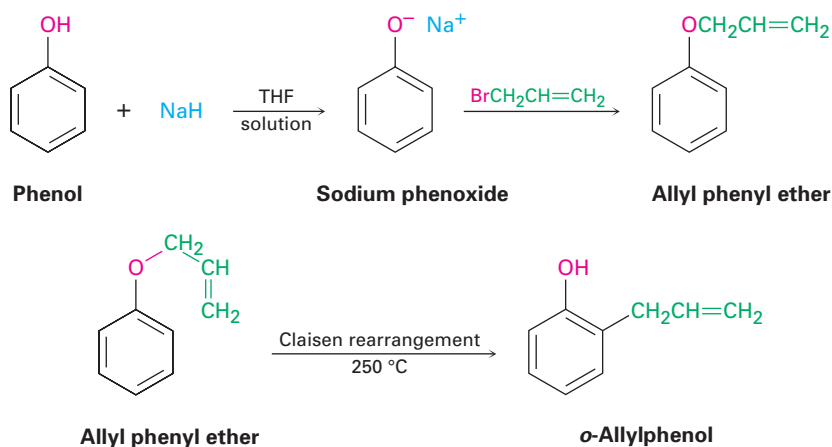
Problem 18.9 Why are HI and HBr more effective than HCl in cleaving ethers? (See Section 11.3.)

18.4 Reactions of Ethers: Claisen Rearrangement

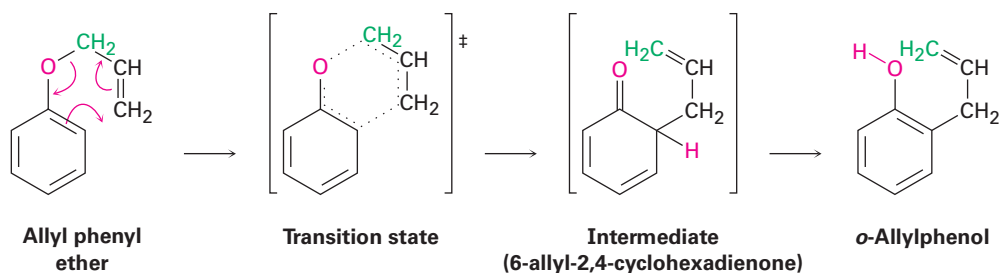
Ludwig Claisen

Ludwig Claisen (1851–1930) was born in Cologne, Germany, and received his Ph.D. at the University of Bonn, studying under August Kekulé. He never married, but devoted himself throughout his life to organic chemistry. Among his positions, he was professor at the University of Bonn, Owens College (Manchester), and the universities of Munich, Aachen, Kiel, and Berlin.

Unlike the acid-catalyzed ether cleavage reaction discussed in the previous section, which is general to all ethers, the **Claisen rearrangement** is specific to allyl aryl ethers, $\text{Ar}-\text{O}-\text{CH}_2\text{CH}=\text{CH}_2$. 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 to 250 °C then effects Claisen rearrangement, leading to an *o*-allylphenol. The net result is alkylation of the phenol in an ortho position.



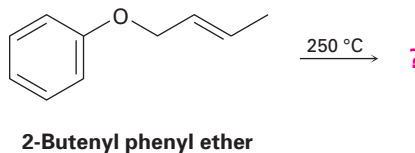
Like the Diels–Alder reaction discussed in Sections 14.4 and 14.5, the Claisen rearrangement reaction takes place through a pericyclic mechanism in which a concerted reorganization of bonding electrons occurs through a six-membered, cyclic transition state. The 6-allyl-2,4-cyclohexadienone intermediate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



Active Figure 18.1 The mechanism of the Claisen rearrangement. The C–O bond-breaking and C–C bond-making occur simultaneously. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.

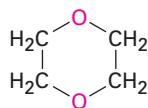
Evidence for this mechanism comes from the observation that the rearrangement takes place with an inversion of the allyl group. That is, allyl phenyl ether containing a ^{14}C label on the allyl ether carbon atom yields *o*-allylphenol in which the label is on the terminal vinylic carbon (green in Figure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

Problem 18.10 What product would you expect from Claisen rearrangement of 2-butenyl phenyl ether?

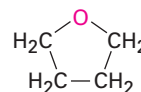


18.5 Cyclic Ethers: Epoxides

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

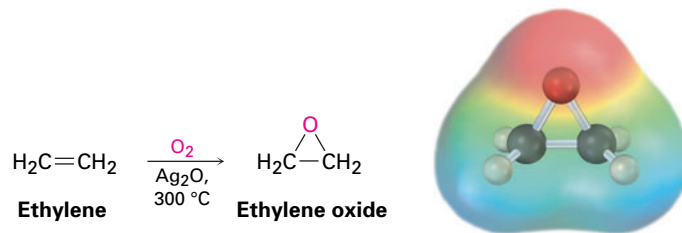


Tetrahydrofuran

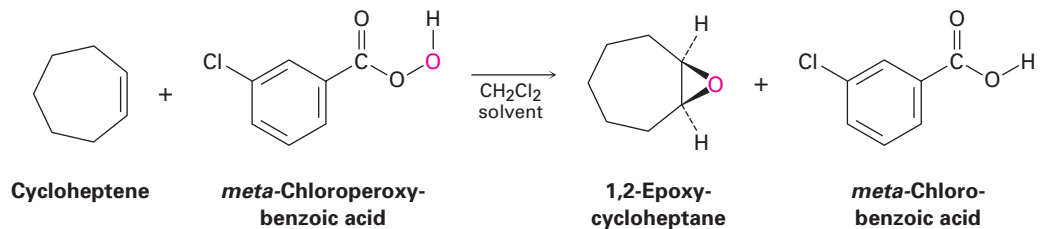
The one group of cyclic ethers that behaves differently from open-chain ethers contains the three-membered-ring compounds called *epoxides*, or *oxiranes*,

which we saw in Section 7.8. The strain of the three-membered ring gives epoxides unique chemical reactivity.

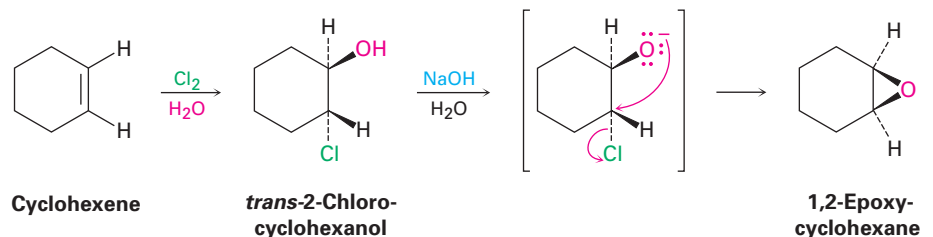
Ethylene oxide, the simplest epoxide, is an intermediate in the manufacture of both ethylene glycol, used for automobile antifreeze, and polyester polymers. More than 4 million tons of ethylene oxide is produced each year in the United States by air oxidation of ethylene over a silver oxide catalyst 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.



In the laboratory, as we saw in Section 7.8, epoxides are prepared by treatment of an alkene with a peroxyacid (RCO_3H), typically *m*-chloroperoxybenzoic acid.



Another method for the synthesis of epoxides is through the use of halohydrins, prepared by electrophilic addition of $\text{HO}-\text{X}$ to alkenes (Section 7.3). When halohydrins are 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.

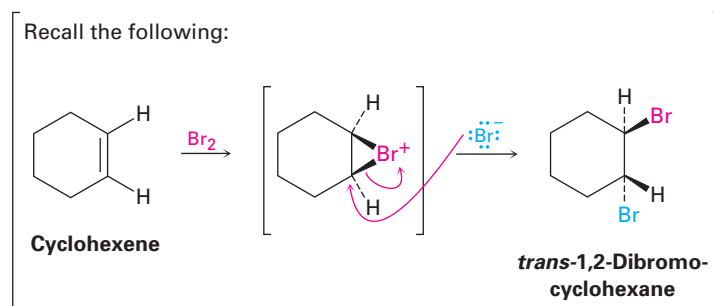
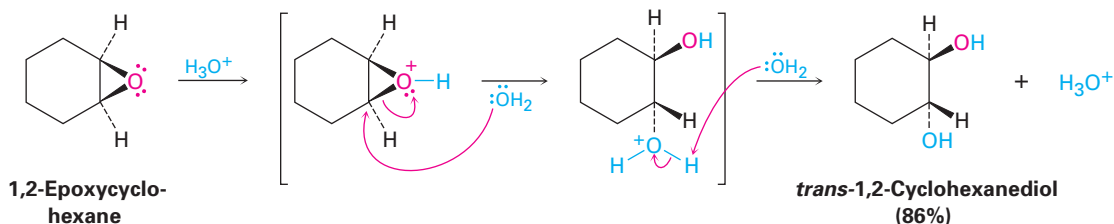


Problem 18.11 | Reaction of *cis*-2-butene with *m*-chloroperoxybenzoic acid yields an epoxide different from that obtained by reaction of the *trans* isomer. Explain.

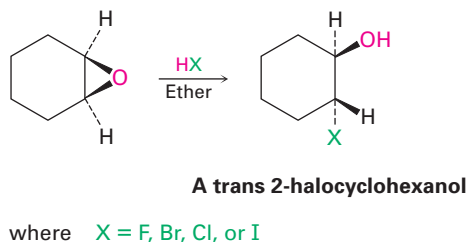
18.6 Reactions of Epoxides: Ring-Opening

Acid-Catalyzed Epoxide Opening

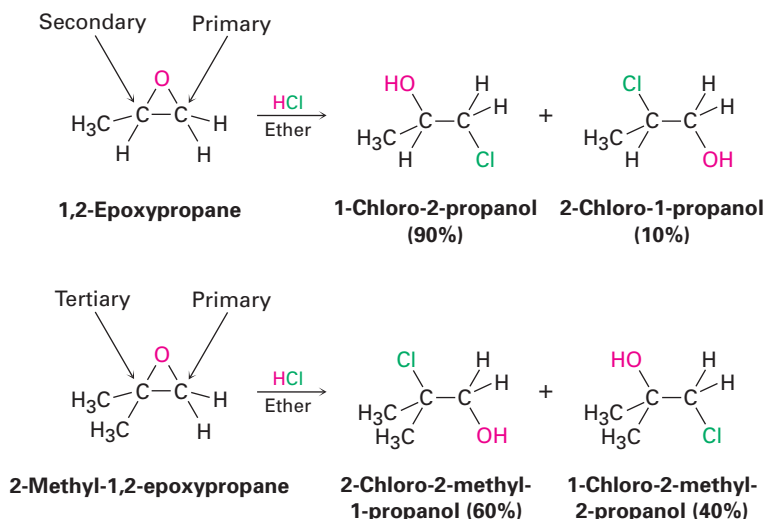
Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain. As we saw in Section 7.8, dilute aqueous acid at room temperature is sufficient to cause the hydrolysis of epoxides to 1,2-diols, also called *vicinal glycols*. (The word *vicinal* 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.



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.



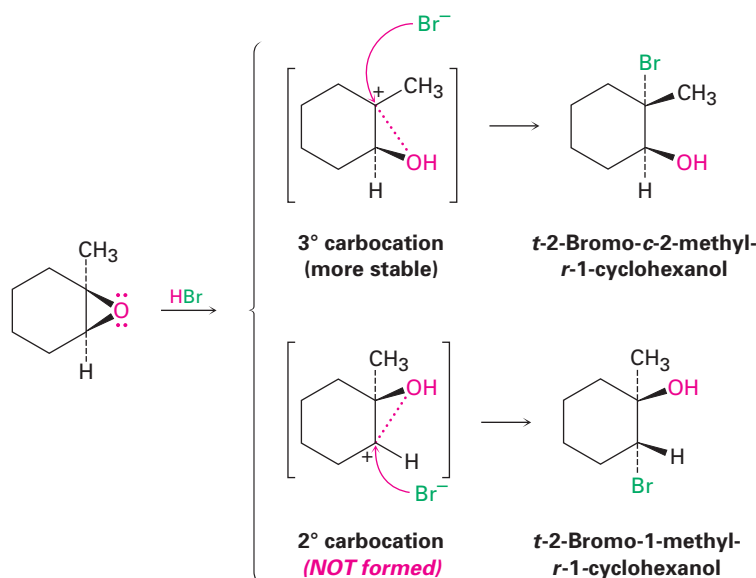
The regiochemistry of acid-catalyzed ring-opening depends on the epoxide's structure, and a mixture of products is often formed. When both epoxide carbon atoms are either primary or secondary, attack of the nucleophile occurs primarily at the *less* highly substituted site—an S_N2 -like result. When 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.



The mechanisms of these acid-catalyzed epoxide openings are more complex than they at first appear. They seem to be neither purely $\text{S}_{\text{N}}1$ nor $\text{S}_{\text{N}}2$ 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 $-\text{Br}$ and $-\text{OH}$ groups are trans, an $\text{S}_{\text{N}}2$ -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 $\text{S}_{\text{N}}1$ -like result in which the more stable, tertiary carbocation is involved.

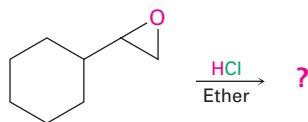
Evidently, the transition state for acid-catalyzed epoxide opening has an $\text{S}_{\text{N}}2$ -like geometry but also has a large amount of $\text{S}_{\text{N}}1$ -like carbocationic character. Since the positive charge in the protonated epoxide is shared by the more highly substituted carbon atom, backside attack of Br^- occurs at the more highly substituted site.

Active Figure 18.2 Acid-induced ring-opening of 1,2-epoxy-1-methylcyclohexane with HBr. There is a high degree of $\text{S}_{\text{N}}1$ -like carbocation character in the transition state, which leads to backside attack of the nucleophile at the tertiary center and to formation of the isomer of 2-bromo-2-methylcyclohexanol that has $-\text{Br}$ and $-\text{OH}$ groups trans. (Naming of trisubstituted cyclohexanes was explained in Section 7.8.) *Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.*

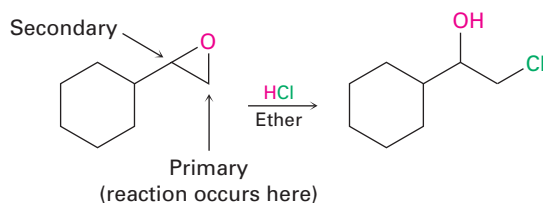


WORKED EXAMPLE 18.3**Predicting the Product of Epoxide Ring-Opening**

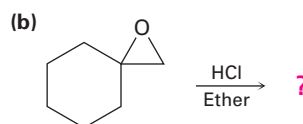
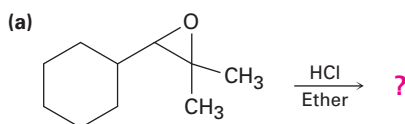
Predict the major product of the following reaction:



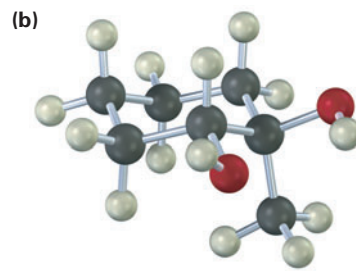
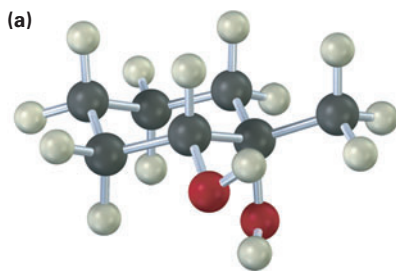
Strategy Identify the substitution pattern of the two epoxide carbon atoms—in this case, one carbon is secondary and one is primary. Then recall the guidelines for epoxide cleavages. An epoxide with only primary and secondary carbons usually undergoes cleavage by S_N2 -like attack of a nucleophile on 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:

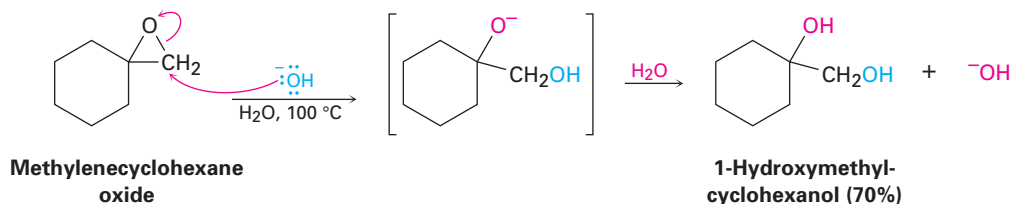


Problem 18.13 How would you prepare the following diols?

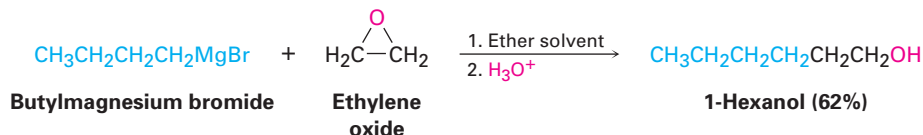


Base-Catalyzed Epoxide Opening

Unlike other ethers, epoxide rings can be cleaved by base 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.

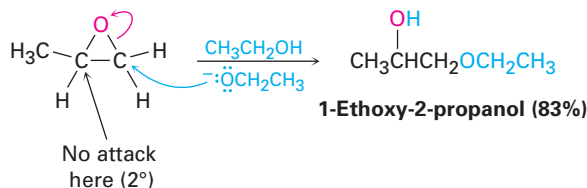


A similar nucleophilic ring-opening occurs when epoxides are treated with Grignard reagents. Ethylene oxide is frequently used, thereby allowing the conversion of a Grignard reagent into a primary alcohol having two more carbons than the starting alkyl halide. 1-Bromobutane, for example, is converted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

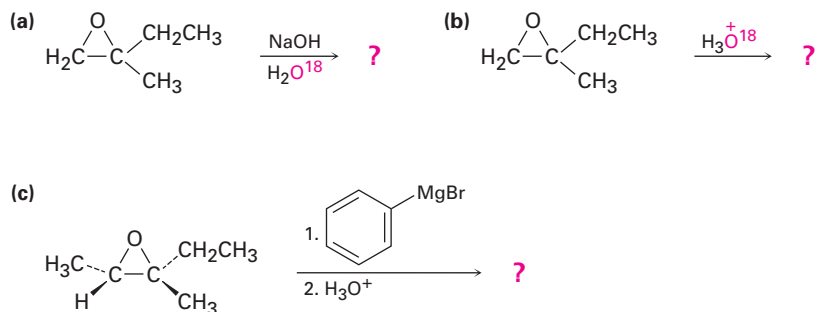


ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of reactions involving ethers and epoxides.

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.



Problem 18.14 Predict the major product of the following reactions:



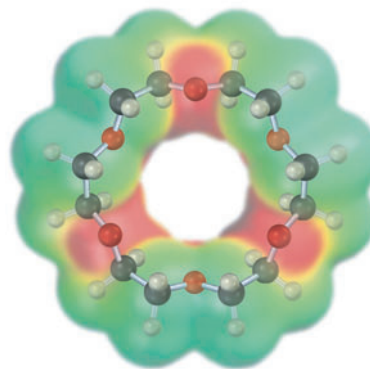
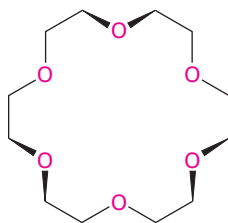
18.7 Crown Ethers

Charles John Pedersen

Charles John Pedersen

(1904–1989) was born in Pusan, Korea, to a Korean mother and Norwegian father. A U.S. citizen, he moved to the United States in the early 1920s and received an M.Sc. at the Massachusetts Institute of Technology in 1927. He spent his entire scientific career at the DuPont Company (1927–1969) and received the 1987 Nobel Prize in chemistry. He is among a very small handful of Nobel Prize-winning scientists who never received a formal doctorate.

Crown ethers, discovered in the early 1960s by Charles Pedersen at the DuPont Company, are a relatively recent addition to the ether family. Crown ethers 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.



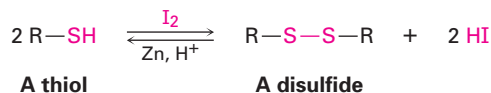
18-Crown-6 ether

The importance of crown ethers derives from their extraordinary ability to solvate metal cations by sequestering the metal in the center of the polyether cavity. For example, 18-crown-6 complexes strongly with potassium ion. Complexes between crown ethers and ionic salts are soluble in nonpolar organic solvents, thus allowing many reactions to be carried out under aprotic conditions that would otherwise have to be carried out in aqueous solution. 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.

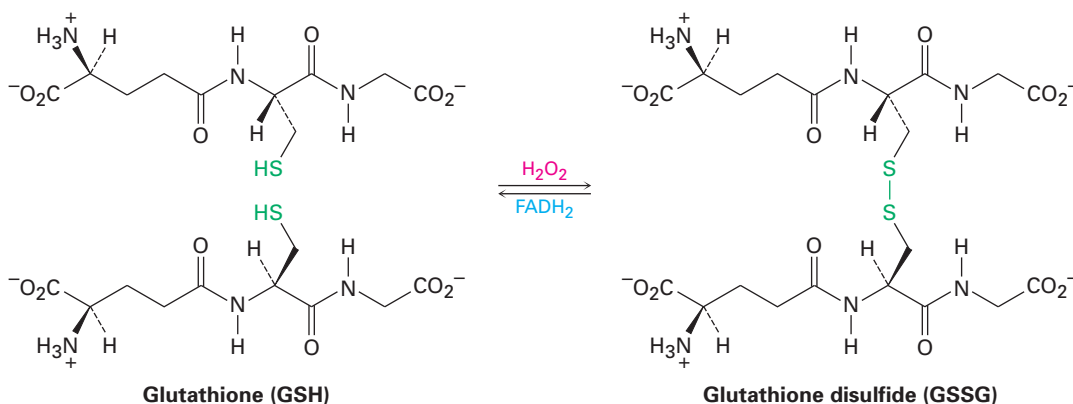
Many other inorganic salts, including KF , KCN , and NaN_3 , also dissolve in organic solvents with the help of crown ethers. The effect of using a crown ether to dissolve a salt in a hydrocarbon or ether solvent is similar to the effect of dissolving the salt in a polar aprotic solvent such as DMSO, DMF, or HMPA (Section 11.3). In both cases, the metal cation is strongly solvated, leaving the anion bare. Thus, the $\text{S}_{\text{N}}2$ 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.

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.

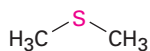


This thiol–disulfide interconversion is a key part of numerous biological processes. We'll see in Chapter 26, for instance, that disulfide formation is involved in defining the structure and three-dimensional conformations of proteins, where disulfide “bridges” often form cross-links between cysteine 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 flavin adenine dinucleotide (reduced), abbreviated FADH_2 .

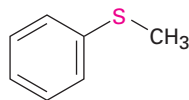


Sulfides

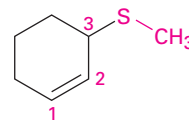
Sulfides are the sulfur analogs of ethers just as thiols are the sulfur analogs of alcohols. Sulfides are named by following the same rules used for ethers, with *sulfide* used in place of *ether* for simple compounds and *alkylthio* used in place of *alkoxy* for more complex substances.



Dimethyl sulfide



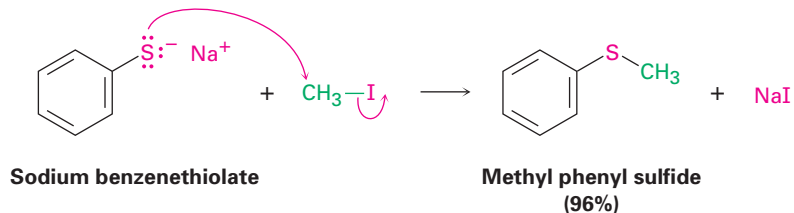
Methyl phenyl sulfide



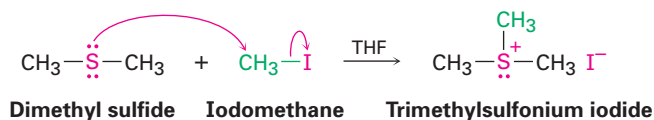
3-(Methylthio)cyclohexene

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 $\text{S}_\text{N}2$ mechanism, analogous to the Williamson synthesis of ethers (Section 18.2). Thiolate anions are among

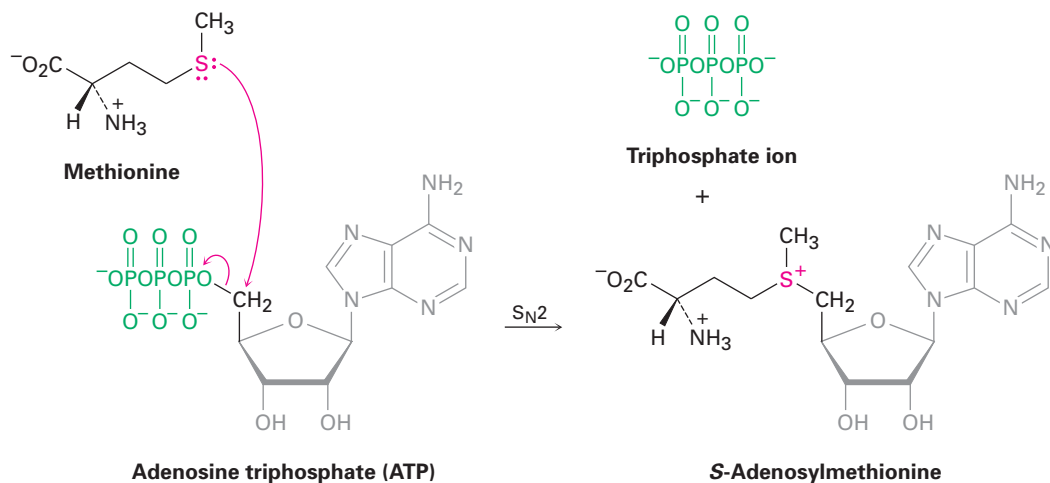
the best nucleophiles known, and product yields are usually high in these S_N2 reactions.



Perhaps surprisingly in light of their close structural similarity, disulfides 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 ($3p$ electrons versus $2p$ electrons), sulfur compounds are more nucleophilic than their oxygen analogs. Unlike dialkyl ethers, dialkyl sulfides are good nucleophiles that react rapidly with primary alkyl halides by an S_N2 mechanism to give **sulfonium ions** (R_3S^+).



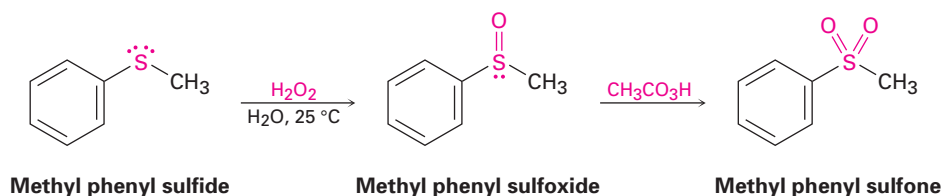
The most common example of this process in living organisms is the reaction of the amino acid methionine with adenosine triphosphate (ATP; Section 5.8) to give *S*-adenosylmethionine. The reaction is somewhat unusual in that the biological leaving group in this S_N2 process is the *triphosphate* ion rather than the more frequently seen *diphosphate* ion (Section 11.6).



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) in which *S*-adenosylmethionine transferred a methyl group to norepinephrine to give adrenaline.

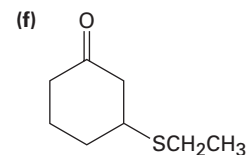
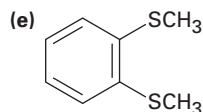
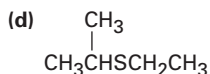
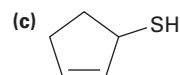
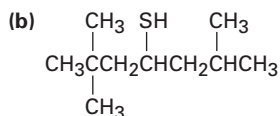
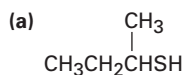
Another difference between sulfides and ethers is that sulfides are easily oxidized. Treatment of a sulfide with hydrogen peroxide, H_2O_2 , at room temperature yields the corresponding **sulfoxide** (R_2SO), and further oxidation of the sulfoxide with a peroxyacid yields a **sulfone** (R_2SO_2).



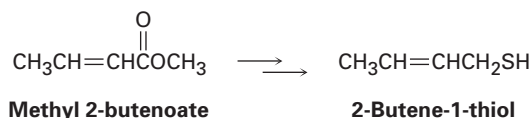
Dimethyl sulfoxide (DMSO) is a particularly well-known sulfoxide that is often used as a polar aprotic solvent. It must be handled with care, however, because it has a remarkable ability to penetrate the skin, carrying along whatever is dissolved in it.



Problem 18.16 Name the following compounds:



Problem 18.17 2-Butene-1-thiol is one component of skunk spray. How would you synthesize this substance from methyl 2-butenate? From 1,3-butadiene?



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.

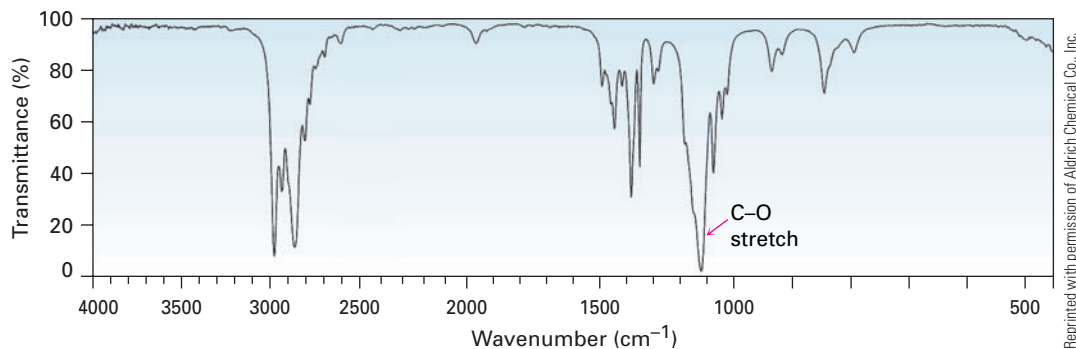


Figure 18.3 The infrared spectrum of diethyl ether, $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$.

Nuclear Magnetic Resonance Spectroscopy

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

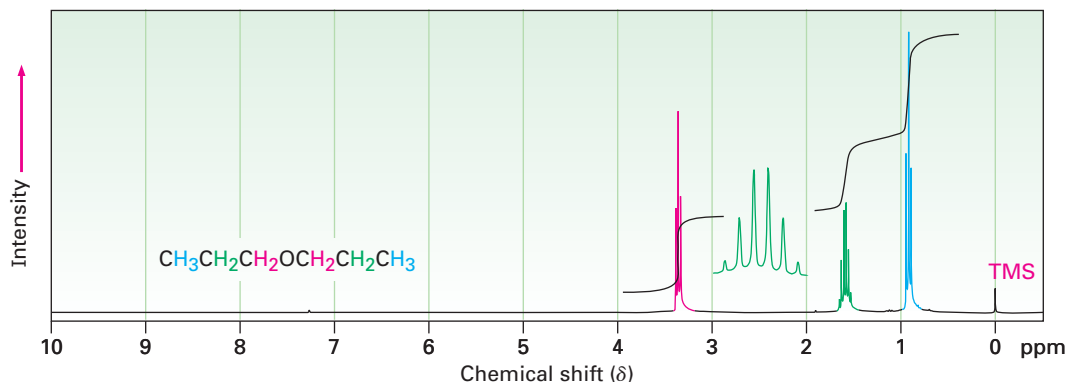


Figure 18.4 The ^1H NMR spectrum of dipropyl ether. Protons on carbon next to oxygen are shifted downfield to $3.4\ \delta$.

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

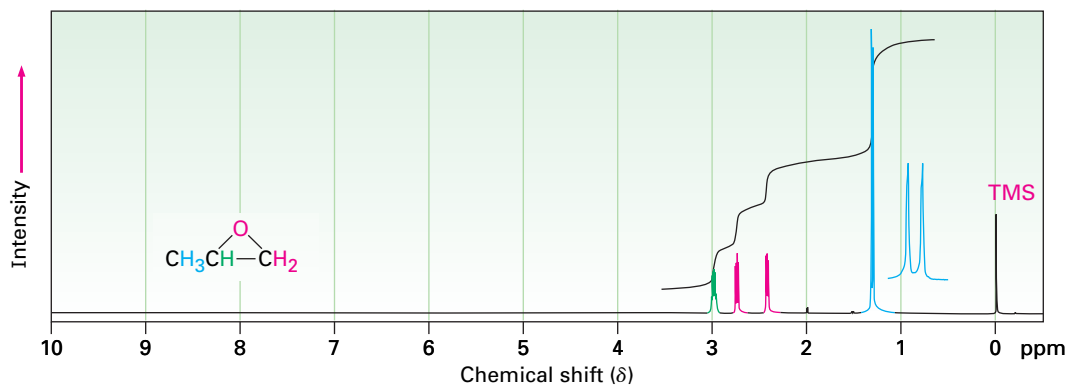
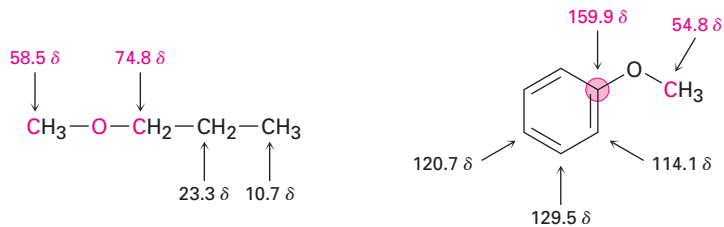
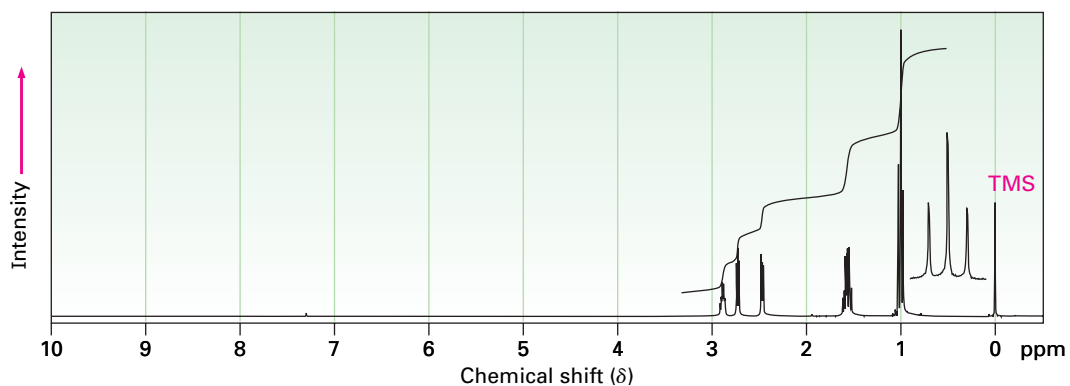


Figure 18.5 The ^1H NMR spectrum of 1,2-epoxypropane.

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 ^1H NMR spectrum shown is that of an ether with the formula $\text{C}_4\text{H}_8\text{O}$. Propose a structure.



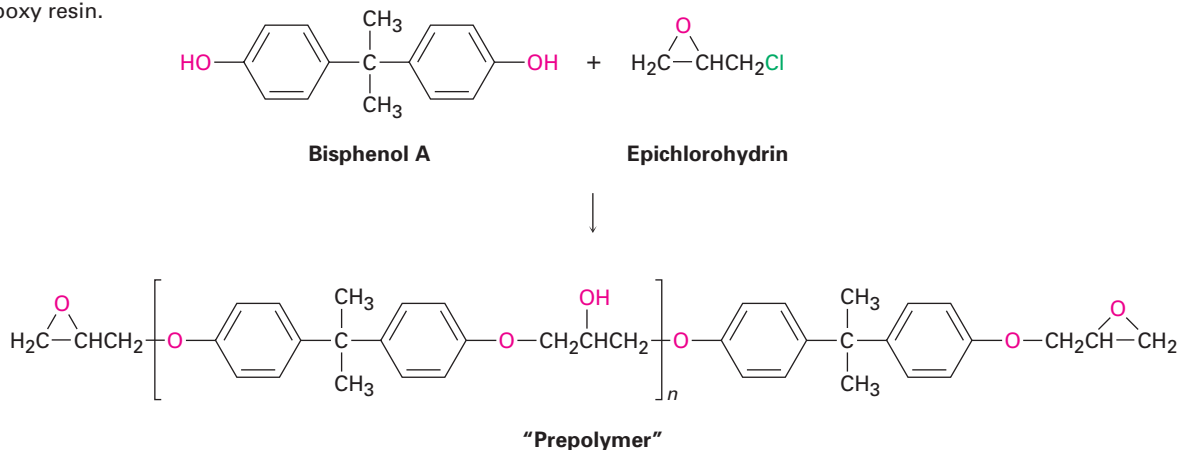
Focus On . . .

Epoxy Resins and Adhesives



© Karl Weatherly/Getty Images

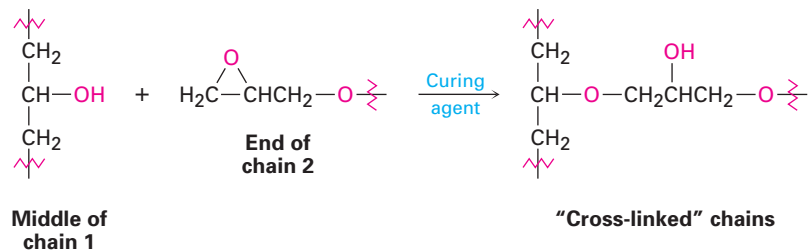
Kayaks are often made of a high-strength polymer coated with epoxy resin.



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 epoxide

(continued)

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.



SUMMARY AND KEY WORDS

alkoxymercuration, 656
 Claisen rearrangement, 659
 crown ether, 666
 disulfide (RSSR'), 668
 ether (ROR'), 652
 mercapto group (-SH), 667
 sulfide (RSR'), 652
 sulfone (R_2SO_2), 670
 sulfonium ion (R_3S^+), 669
 sulfoxide (R_2SO), 670
 thiol (RSH), 652
 thiolate ion (RS^-), 668

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 $\text{S}_{\text{N}}2$ 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 $\text{S}_{\text{N}}2$ mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen, but by an $\text{S}_{\text{N}}1$ or $\text{E}1$ mechanism if one of the alkyl groups bonded to oxygen is tertiary. Aryl allyl ethers undergo **Claisen rearrangement** to give *o*-allylphenols.

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-induced 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 $\text{S}_{\text{N}}2$ reaction of a nucleophile at the less hindered epoxide carbon.

Thiols, the sulfur analogs of alcohols, are usually prepared by $\text{S}_{\text{N}}2$ 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 $\text{S}_{\text{N}}2$ reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are much more nucleophilic than ethers and can be oxidized to **sulfoxides** and to **sulfones**. Sulfides can also be alkylated by reaction with a primary alkyl halide to yield **sulfonium ions**.

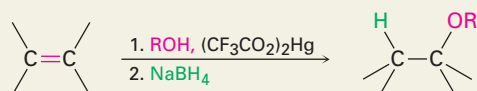
SUMMARY OF REACTIONS

1. Synthesis of ethers (Section 18.2)

(a) Williamson ether synthesis

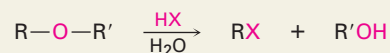


(b) Alkoxymercuration/demercuration

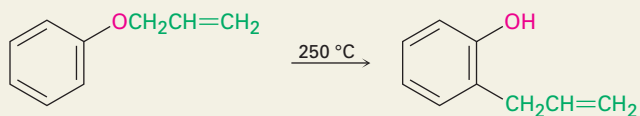


2. Reactions of ethers

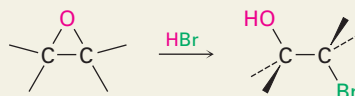
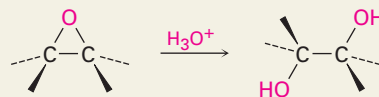
(a) Cleavage by HBr or HI (Section 18.3)



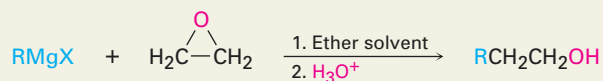
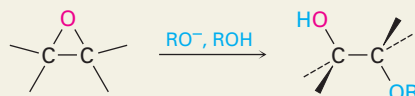
(b) Claisen rearrangement (Section 18.4)



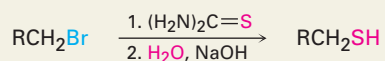
(c) Acid-catalyzed epoxide opening (Section 18.6)



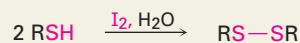
(d) Base-catalyzed epoxide opening (Section 18.6)



3. Synthesis of thiols (Section 18.8)



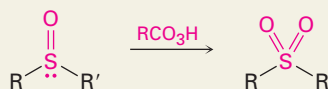
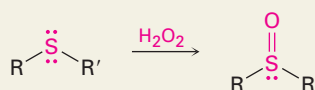
4. Oxidation of thiols to disulfides (Section 18.8)



5. Synthesis of sulfides (Section 18.8)



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



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.



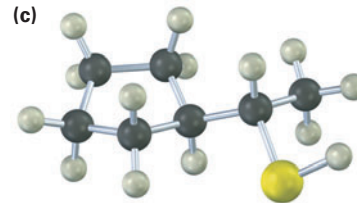
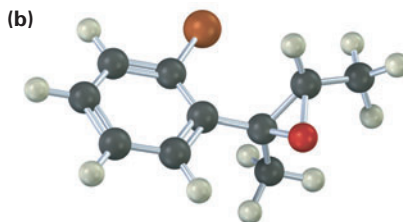
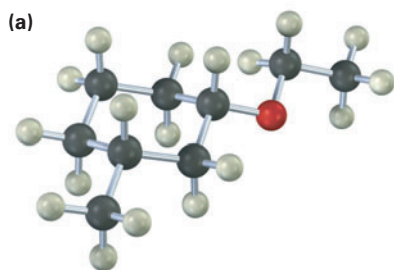
Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

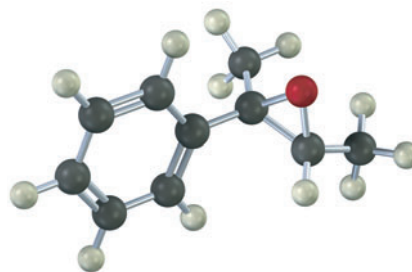
(Problems 18.1–18.18 appear within the chapter)

18.19 ■ Give IUPAC names for the following compounds (reddish brown = Br):

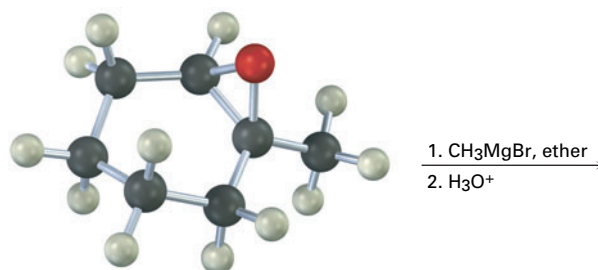


■ Assignable in OWL

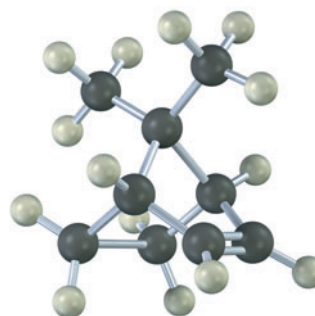
- 18.20 ■ Show the product, including stereochemistry, that would result from reaction of the following epoxide with HBr:



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



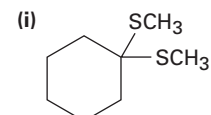
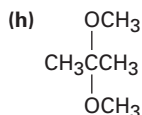
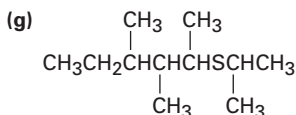
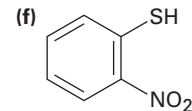
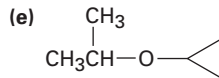
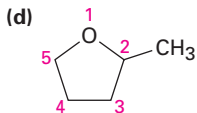
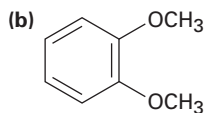
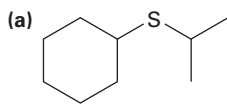
- 18.22 Treatment of the following alkene with a peroxyacid yields an epoxide different from that obtained by reaction with aqueous Br_2 followed by base treatment. Propose structures for the two epoxides, and explain the result.



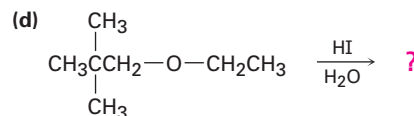
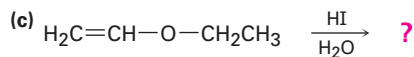
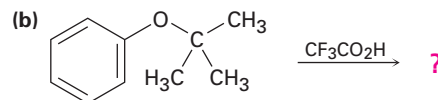
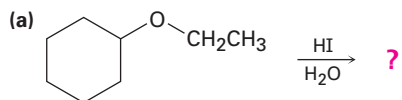
ADDITIONAL PROBLEMS

- 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)

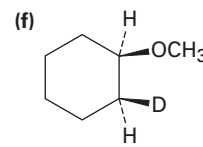
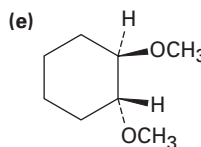
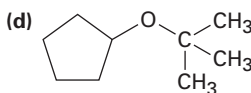
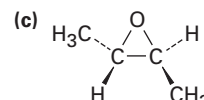
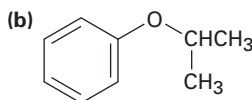
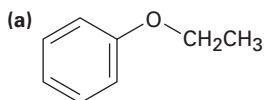
18.24 ■ Give IUPAC names for the following structures:



18.25 ■ Predict the products of the following ether cleavage reactions:



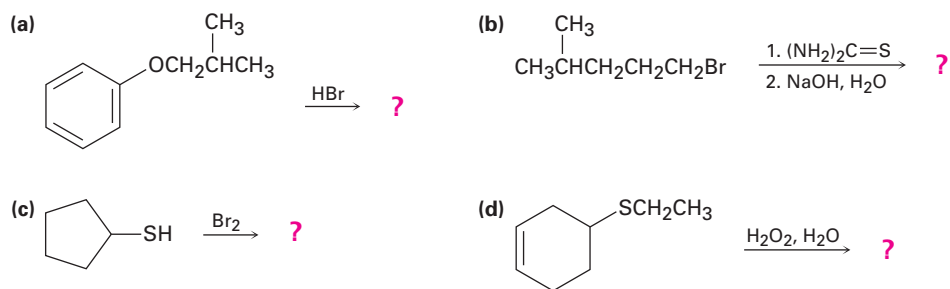
18.26 ■ How would you prepare the following ethers?



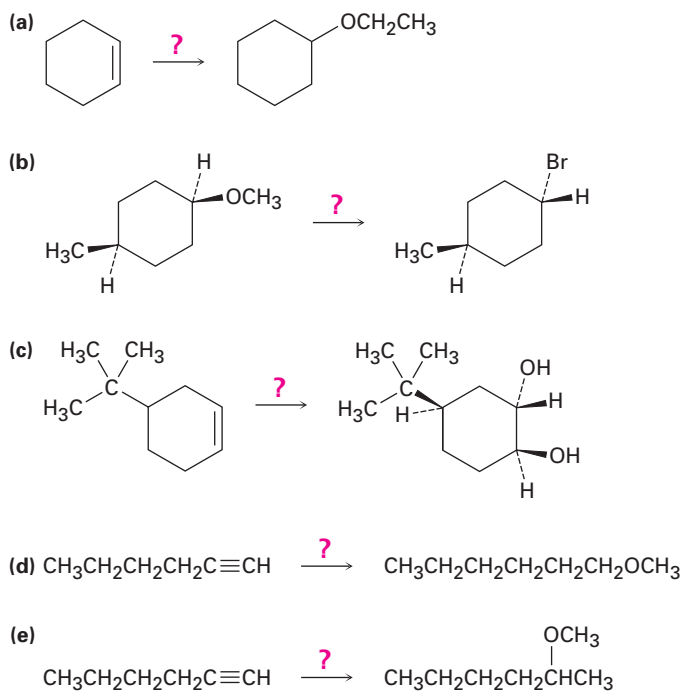
18.27 ■ How would you prepare the following compounds from 1-phenylethanol?

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

18.28 ■ Predict the products of the following reactions:



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



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

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

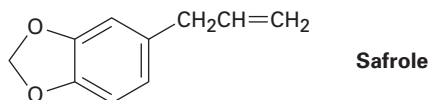
18.32 ■ When 2-methyl-2,5-pentandiol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?



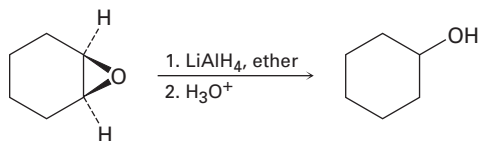
- 18.33** ■ Write the mechanism of the hydrolysis of *cis*-5,6-epoxydecane by reaction with aqueous acid. What is the stereochemistry of the product, assuming normal backside S_N2 attack?
- 18.34** What is the stereochemistry of the product from acid-catalyzed hydrolysis of *trans*-5,6-epoxydecane? How does the product differ from that formed in Problem 18.33?
- 18.35** 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.
- 18.36** ■ *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.
- 18.37** *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.



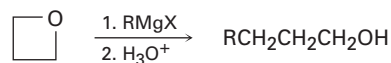
- 18.38** Safrole, a substance isolated from oil of sassafras, is used as a perfumery agent. Propose a synthesis of safrole from catechol (1,2-benzenediol).



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

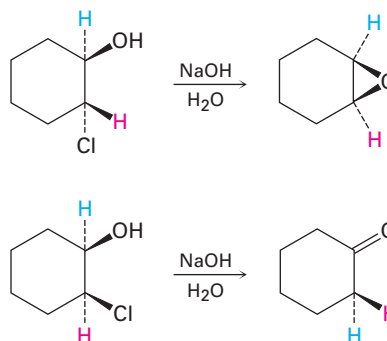


- 18.40** Show the structure and stereochemistry of the alcohol that would result if 1,2-epoxycyclohexane (Problem 18.39) were reduced with lithium aluminum deuteride, LiAlD_4 .
- 18.41** Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a *trans*-dial 1,2-diol. What product would you expect 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.)
- 18.42** 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.

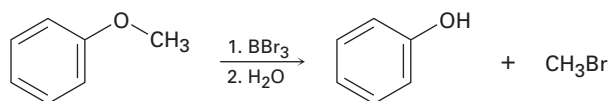


Oxetane

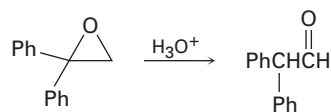
- 18.43** Treatment of *trans*-2-chlorocyclohexanol with NaOH yields 1,2-epoxycyclohexane, but reaction of the *cis* isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions, and explain why the different results are obtained.



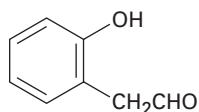
- 18.44** Ethers undergo an acid-catalyzed cleavage reaction when treated with the Lewis acid BBr₃ at room temperature. Propose a mechanism for the reaction.



- 18.45** The *Zeisel method* is an 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 AgNO₃, 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?
- 18.46** Disparlure, C₁₉H₃₈O, 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 KMnO₄, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. (KMnO₄ 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.
- 18.47** How would you synthesize racemic disparlure (Problem 18.46) from compounds having ten or fewer carbons?
- 18.48** ■ Treatment of 1,1-diphenyl-1,2-epoxyethane with aqueous acid yields diphenylacetaldehyde as the major product. Propose a mechanism for the reaction.

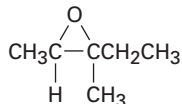


18.49 How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.



***o*-Hydroxyphenylacetaldehyde**

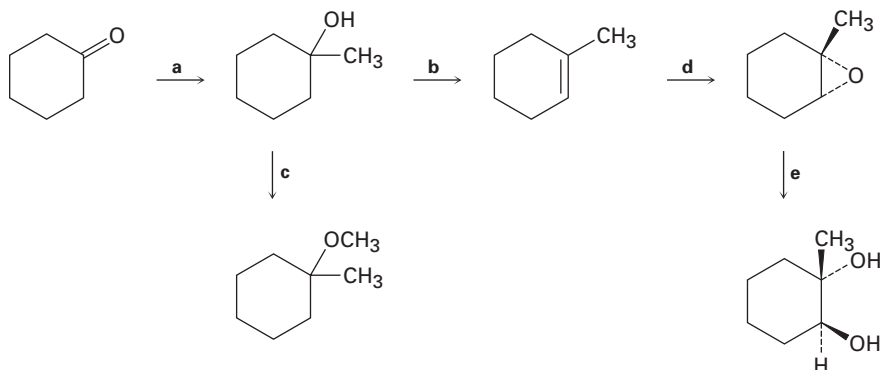
18.50 ■ Imagine that you have treated (2*R*,3*R*)-2,3-epoxy-3-methylpentane with aqueous acid to carry out a ring-opening reaction.



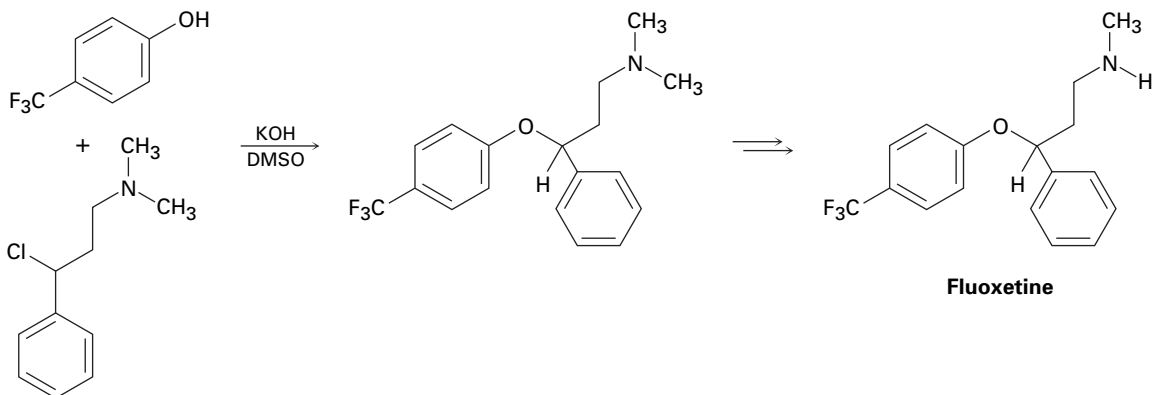
2,3-Epoxy-3-methylpentane
(no stereochemistry implied)

- Draw the epoxide, showing stereochemistry.
- Draw and name the product, showing stereochemistry.
- Is the product chiral? Explain.
- Is the product optically active? Explain.

18.51 Identify the reagents a–e in the following scheme:



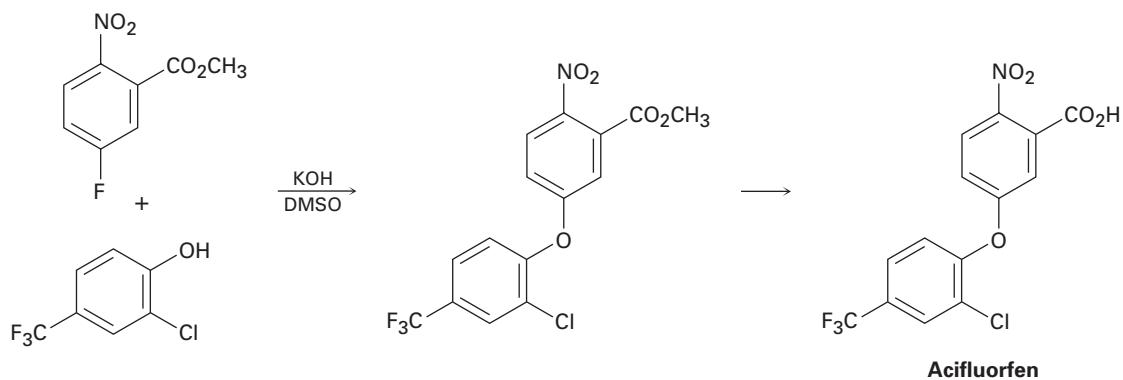
18.52 Fluoxetine, a heavily prescribed antidepressant marketed under the name Prozac, can be prepared by a route that begins with reaction between a phenol and an alkyl chloride.



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.

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

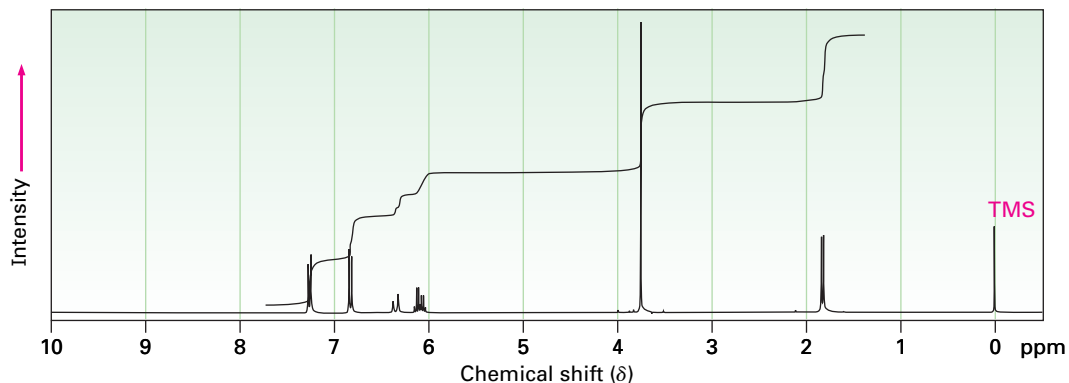


18.54 ■ The red fox (*Vulpes vulpes*) uses a chemical communication system based on scent marks in urine. Recent work has shown one component of fox urine to be a sulfide. Mass spectral analysis of the pure scent-mark component shows $M^+ = 116$. IR spectroscopy shows an intense band at 890 cm^{-1} , and $^1\text{H NMR}$ spectroscopy reveals the following peaks:

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

Propose a structure consistent with these data. [Note: $(\text{CH}_3)_2\text{S}$ absorbs at 2.1 δ .]

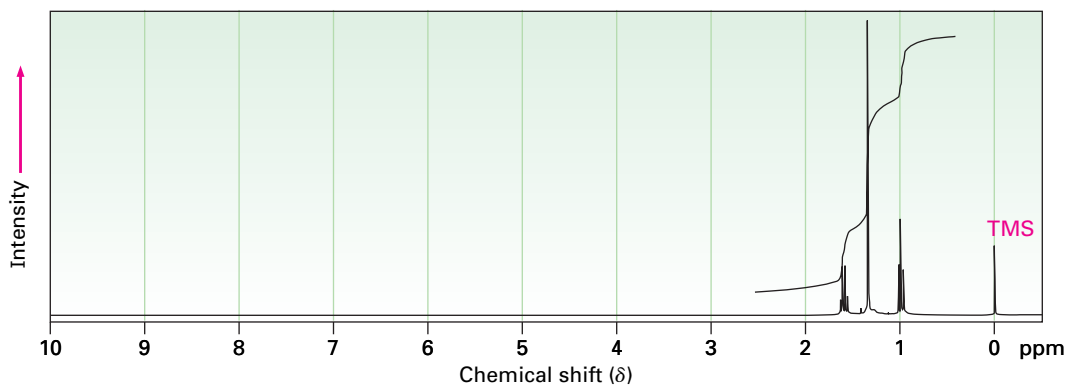
18.55 ■ Anethole, $\text{C}_{10}\text{H}_{12}\text{O}$, a major constituent of the oil of anise, has the $^1\text{H NMR}$ spectrum shown. On oxidation with $\text{Na}_2\text{Cr}_2\text{O}_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.



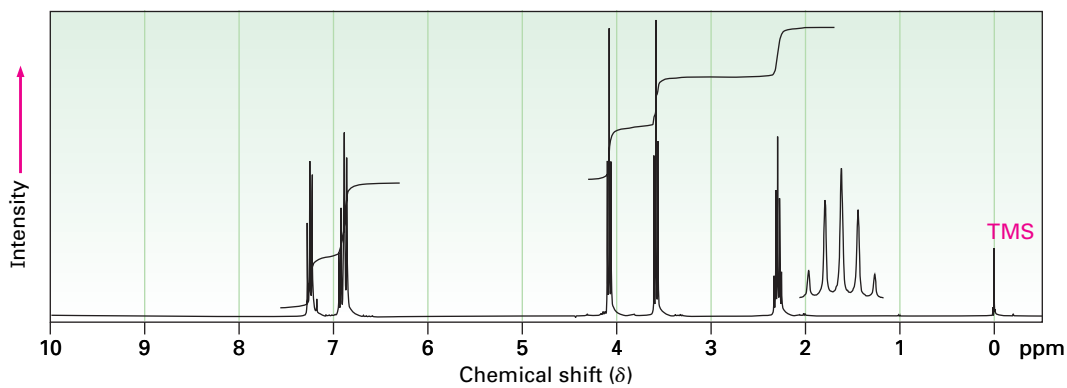
18.56 How would you synthesize anethole (Problem 18.55) from phenol?

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

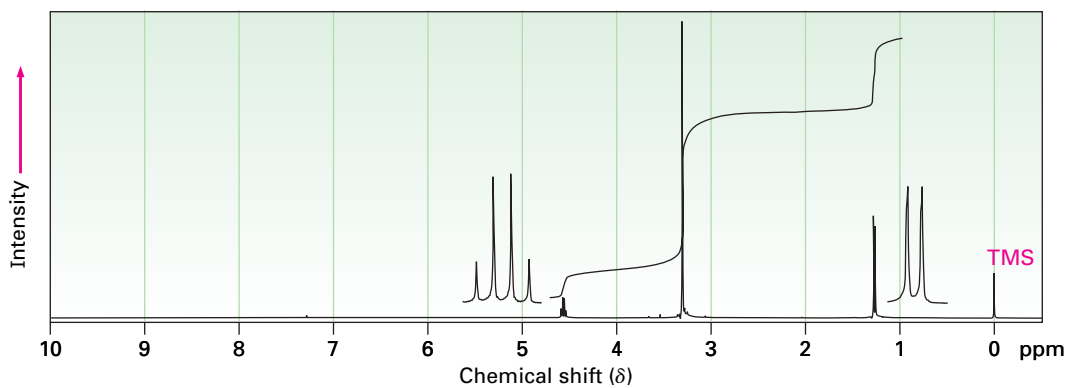
(a) $\text{C}_5\text{H}_{12}\text{S}$



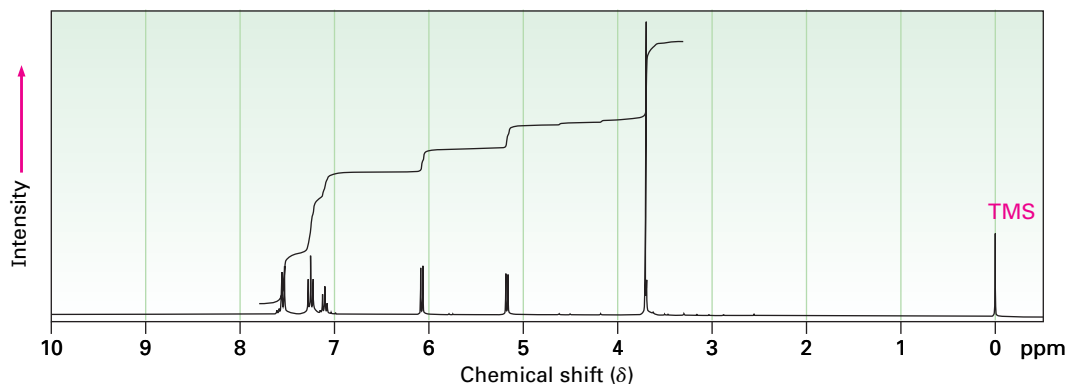
(b) $\text{C}_9\text{H}_{11}\text{BrO}$



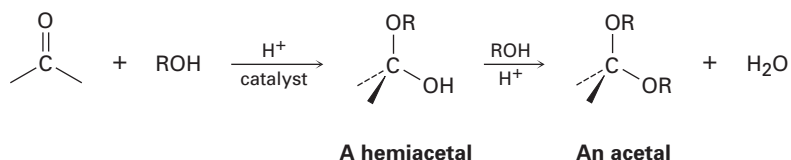
(c) $\text{C}_4\text{H}_{10}\text{O}_2$



■ Assignable in OWL

(d) $C_9H_{10}O$ 

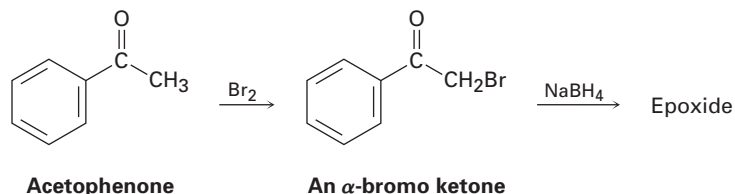
18.58 Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals*, compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further reaction of a hemiacetal with alcohol then yields an *acetal*, a compound that has two ether-like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

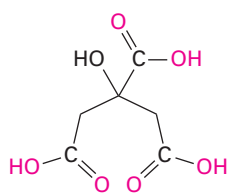
18.59 We saw in Section 17.4 that ketones react with NaBH_4 to yield alcohols. We'll also see in Section 22.3 that ketones react with Br_2 to yield α -bromo ketones. Perhaps surprisingly, treatment with NaBH_4 of the α -bromo ketone from acetophenone yields an epoxide rather than a bromo alcohol. Show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



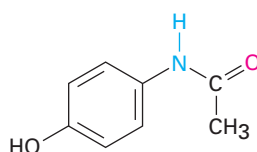


A Preview of Carbonyl Compounds

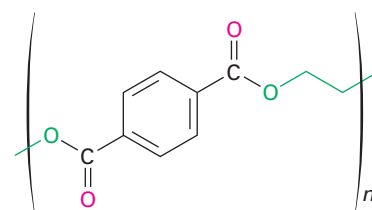
Carbonyl compounds are everywhere. Most biological molecules contain carbonyl groups, as do most pharmaceutical agents and many of the synthetic chemicals that touch our everyday lives. Citric acid, found in lemons and oranges; acetaminophen, the active ingredient in many over-the-counter headache remedies;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

In the next five chapters, we'll discuss the chemistry of the **carbonyl group**, $C=O$ (pronounced car-bo-neel). Although there are many different kinds of carbonyl compounds and many different reactions, 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

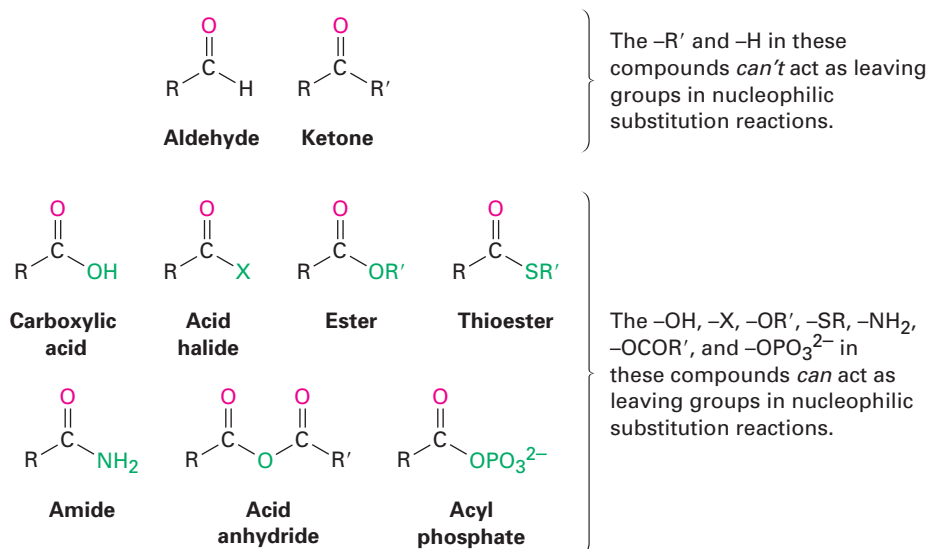
Table 1 shows some of the many different kinds of carbonyl compounds. All contain an **acyl group** ($R-C=O$) bonded to another substituent. The R part of the acyl group can be practically any organic part-structure, and the other substituent to which the acyl group is bonded can be a carbon, hydrogen,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

Table 1 | Some Types of Carbonyl Compounds

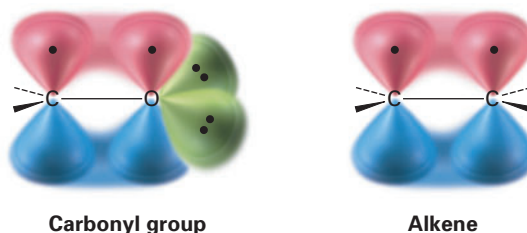
Name	General formula	Name ending	Name	General formula	Name ending
Aldehyde		-al	Ester		-oate
Ketone		-one	Lactone (cyclic ester)		None
Carboxylic acid		-oic acid	Thioester		-thioate
Acid halide		-yl or -oyl halide	Amide		-amide
Acid anhydride		-oic anhydride	Lactam (cyclic amide)		None
Acyl phosphate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

negative charge and therefore *can* act as a leaving group in a nucleophilic substitution reaction.



II. Nature of the Carbonyl Group

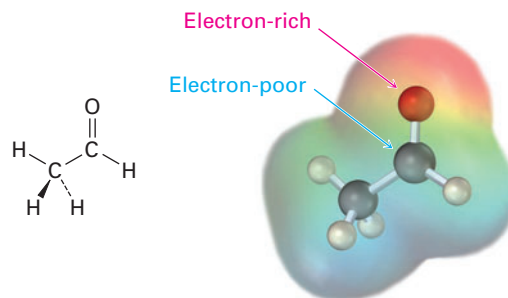
The carbon–oxygen double bond of a carbonyl group is similar in many respects to the carbon–carbon double bond of an alkene. The carbonyl carbon atom is sp^2 -hybridized and forms three σ bonds. The fourth valence electron remains in a carbon p orbital and forms a π bond to oxygen by overlap with an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



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	($^\circ$)	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.

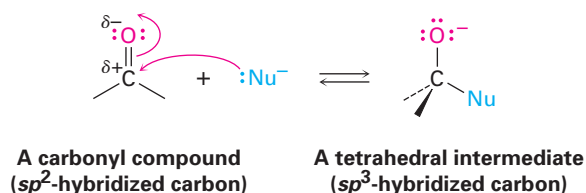
III. General Reactions of Carbonyl Compounds

Both in the laboratory and in living organisms, the 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.

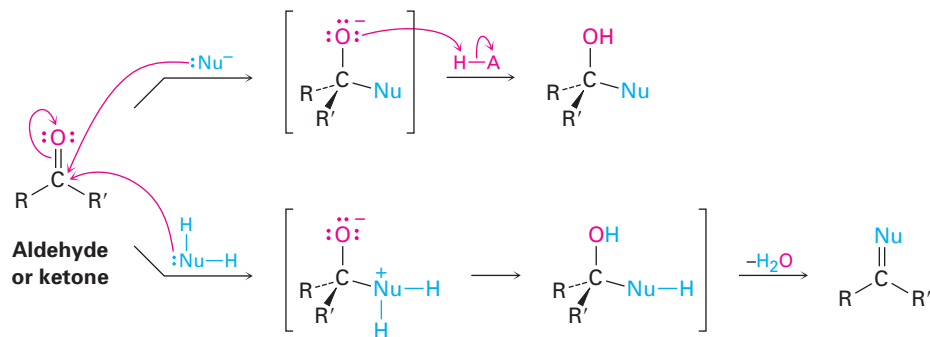
Nucleophilic Addition Reactions of Aldehydes and Ketones (Chapter 19)

The most common reaction of aldehydes and ketones is the **nucleophilic addition reaction**, in which a nucleophile, $:\text{Nu}^-$, 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.



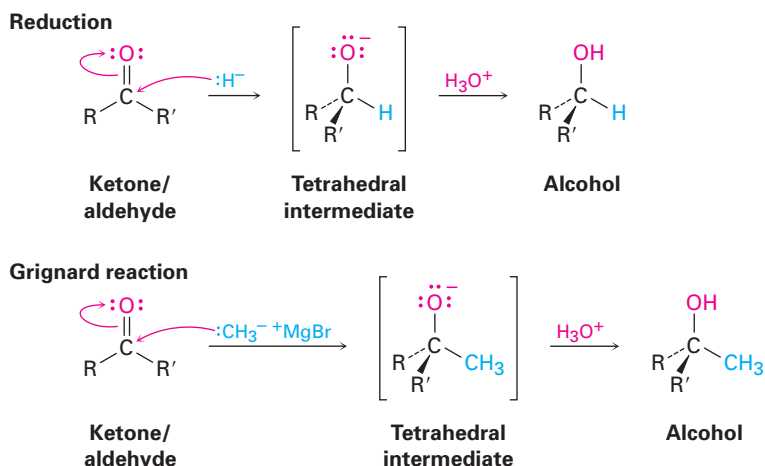
Once formed, and depending on the nature of the nucleophile, the tetrahedral alkoxide intermediate can undergo either of two further reactions, as shown in Figure 2. Often, the tetrahedral alkoxide intermediate is simply protonated by water or acid to form an alcohol product. Alternatively, the tetrahedral 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 $\text{C}=\text{Nu}$ bond is formed.



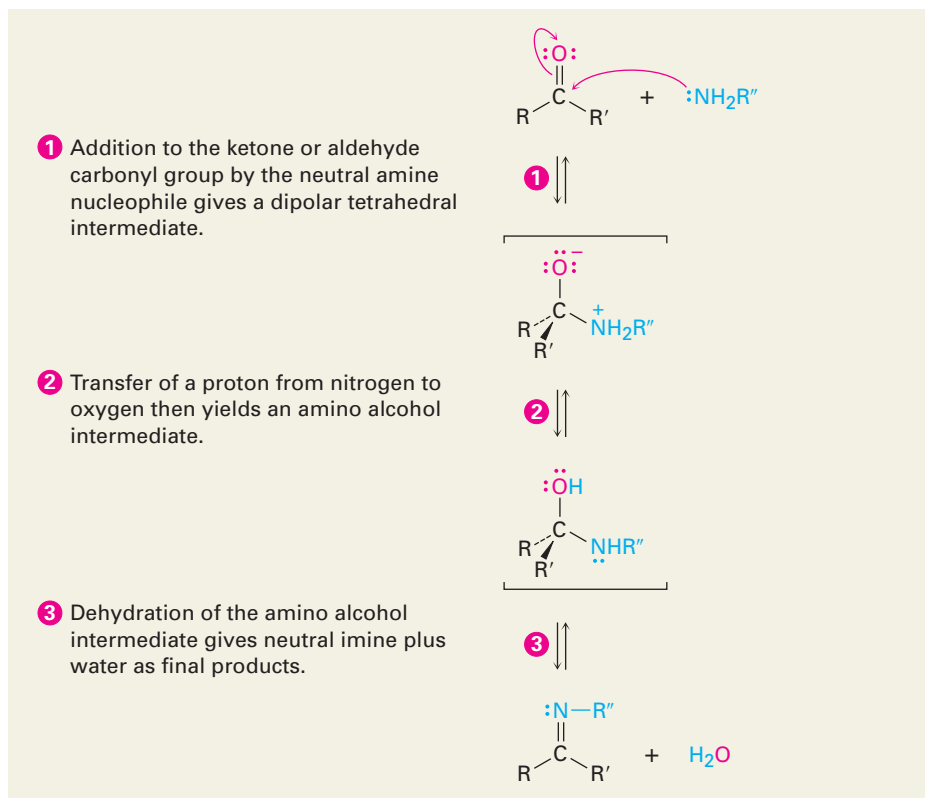
Formation of an Alcohol The simplest reaction of a tetrahedral alkoxide intermediate is protonation to yield an alcohol. We've already seen two examples of this kind of process during reduction of aldehydes and ketones with hydride reagents such as NaBH_4 and LiAlH_4 (Section 17.4) and during Grignard 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^- .



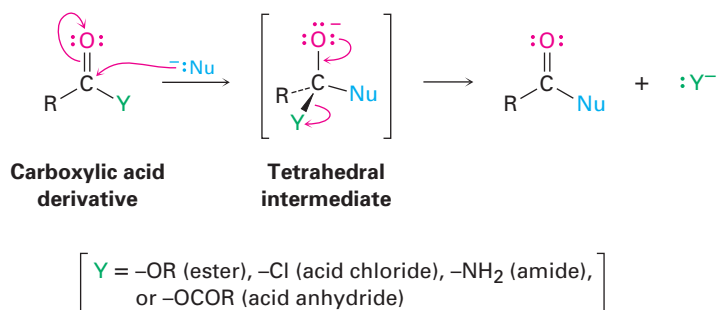
Formation of C=Nu The second mode of nucleophilic addition, which often occurs with amine nucleophiles, involves elimination of oxygen and formation of a $\text{C}=\text{Nu}$ bond. For example, aldehydes and ketones react with primary amines, RNH_2 , to form *imines*, $\text{R}_2\text{C}=\text{NR}'$. 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, $\text{R}_2\text{C}=\text{NR}'$, by reaction of an amine with an aldehyde or a ketone.



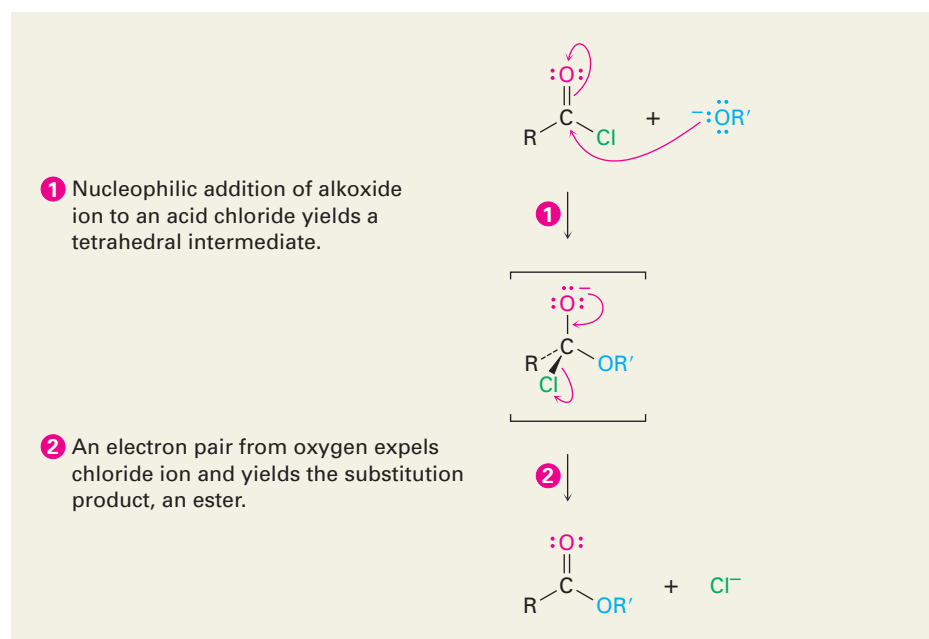
Nucleophilic Acyl Substitution Reactions of Carboxylic Acid Derivatives (Chapter 21)

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:



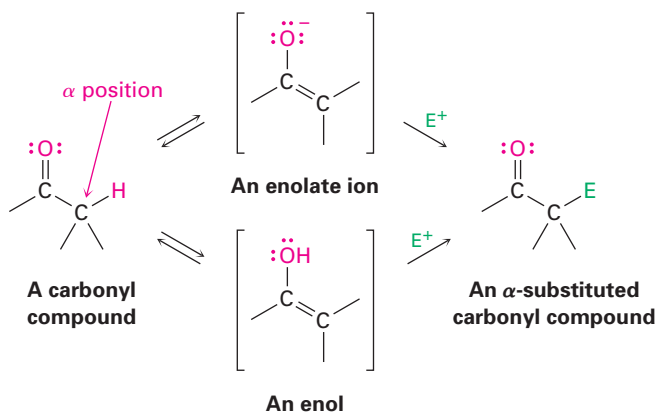
The net effect of nucleophilic acyl substitution is the replacement of the leaving group by the entering nucleophile. We'll see in Chapter 21, for instance, that acid chlorides are rapidly converted into esters by treatment with alkoxide ions (Figure 4).

Figure 4 MECHANISM: The nucleophilic acyl substitution reaction of an acid chloride with an alkoxide ion yields an ester.

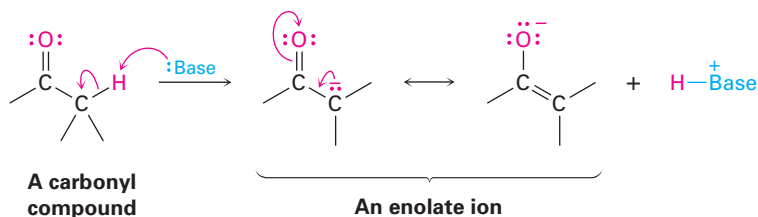


Alpha-Substitution Reactions (Chapter 22)

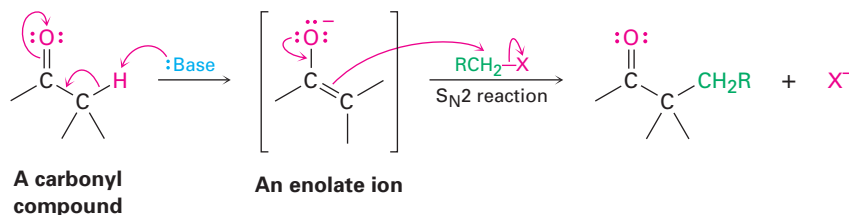
The third major reaction of carbonyl compounds, **alpha substitution**, occurs at the position *next to* the carbonyl group—the alpha (α) position. This reaction, which takes place with all carbonyl compounds regardless of structure, results in the substitution of an α hydrogen by an electrophile through 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.



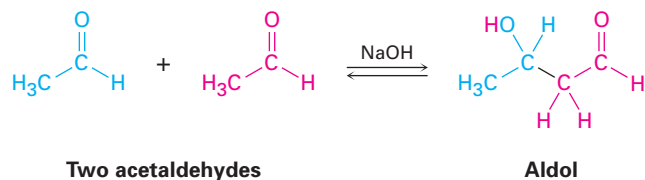
Because they're negatively charged, enolate ions act as nucleophiles and undergo many of the reactions we've already studied. For example, enolates react with primary alkyl halides in the S_N2 reaction. The nucleophilic enolate ion displaces halide ion, and a new C–C bond forms:



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)

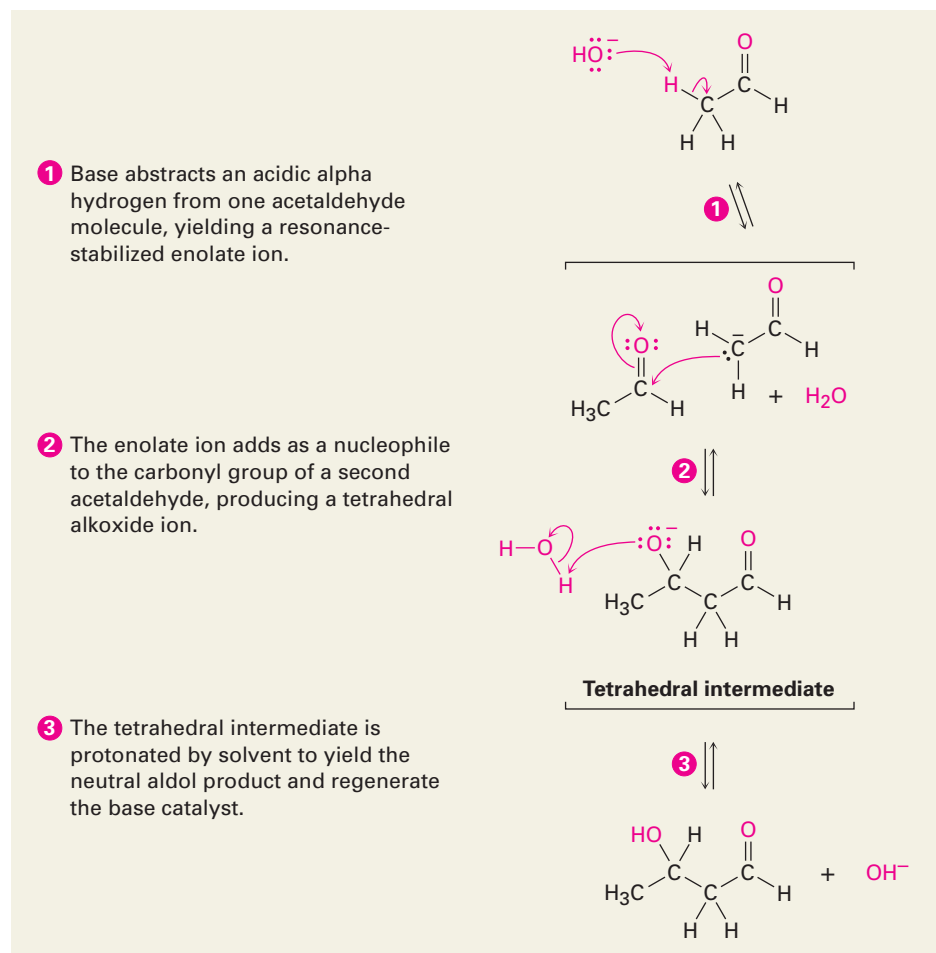
The fourth and last fundamental reaction of carbonyl groups, **carbonyl condensation**, takes place when two carbonyl compounds react with each other. When acetaldehyde is treated with base, for instance, two molecules combine to yield the hydroxy aldehyde product known as *aldol* (aldehyde + alcohol):



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.

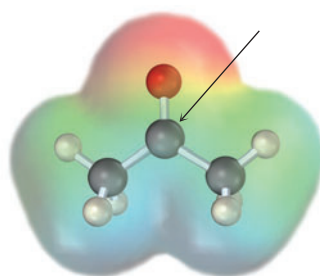


IV. Summary

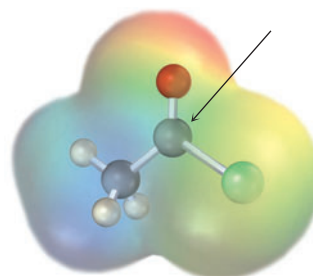
The purpose of this short preview is not to show details of specific reactions but rather to lay the groundwork for the next five chapters. All the carbonyl-group reactions we'll be studying in Chapters 19 through 23 fall into one of the four fundamental categories discussed in this preview. Knowing where we'll be heading should help you to 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.

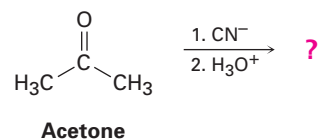


Acetone
(ketone)

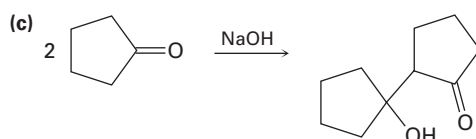
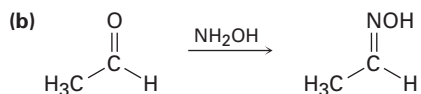
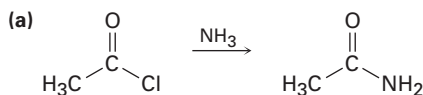


Acetyl chloride
(acid chloride)

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:



3. Identify each of the following reactions as a nucleophilic addition, nucleophilic acyl substitution, an α substitution, or a carbonyl condensation:



19

Aldehydes and Ketones: Nucleophilic Addition Reactions

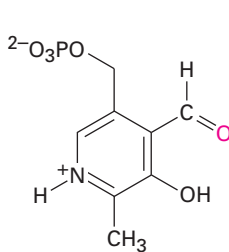
Organic KNOWLEDGE TOOLS

ThomsonNOW Throughout this chapter, sign in at www.thomsonedu.com for online self-study and interactive tutorials based on your level of understanding.

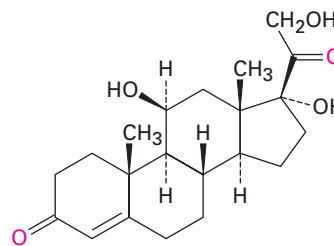


Online homework for this chapter may be assigned in Organic OWL.

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.

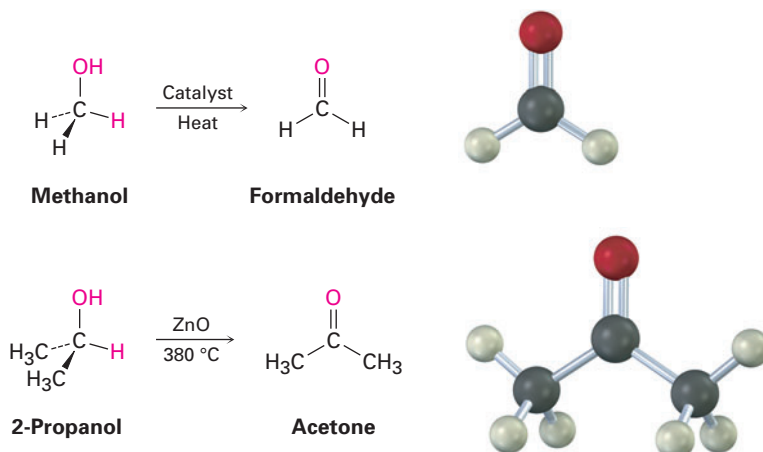


Pyridoxal
phosphate (PLP)



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 1.9 million tons per year of formaldehyde, $\text{H}_2\text{C}=\text{O}$, is produced in the United States for use in building insulation materials and in the adhesive resins that bind particle board and plywood. Acetone, $(\text{CH}_3)_2\text{C}=\text{O}$, is widely used as an industrial solvent; approximately 1.2 million tons per year is produced in the United States. Formaldehyde is synthesized industrially by catalytic oxidation of methanol, and one method of acetone preparation involves oxidation of 2-propanol.



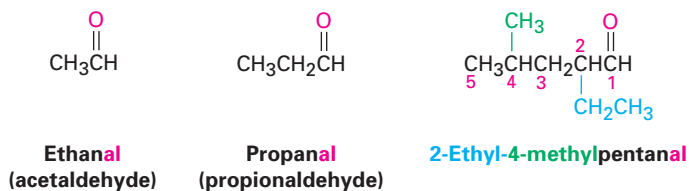
WHY THIS CHAPTER?

Much of organic chemistry is simply 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

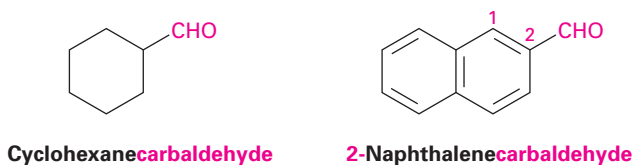
ThomsonNOW Click *Organic Interactive* to use a web-based palette to draw structures of aldehydes and ketones based on their IUPAC names.

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the $-\text{CHO}$ group, and the $-\text{CHO}$ carbon is numbered as carbon 1. For example:



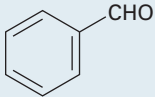
Note that the longest chain in 2-ethyl-4-methylpentanal is a hexane, but this chain does not include the $-\text{CHO}$ group and thus is not considered the parent.

For cyclic aldehydes in which the $-\text{CHO}$ group is directly attached to a ring, the suffix *-carbaldehyde* is used.

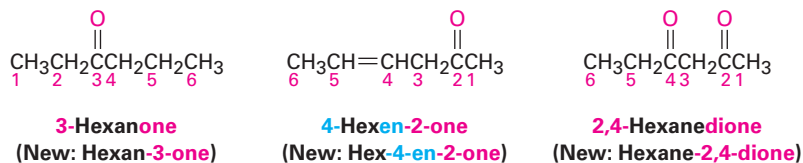


A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in Table 19.1.

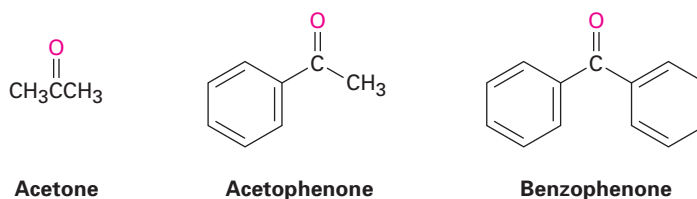
Table 19.1 Common Names of Some Simple Aldehydes

Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH ₃ CHO	Acetaldehyde	Ethanal
H ₂ C=CHCHO	Acrolein	Propenal
CH ₃ CH=CHCHO	Crotonaldehyde	2-Butenal
	Benzaldehyde	Benzenecarbaldehyde

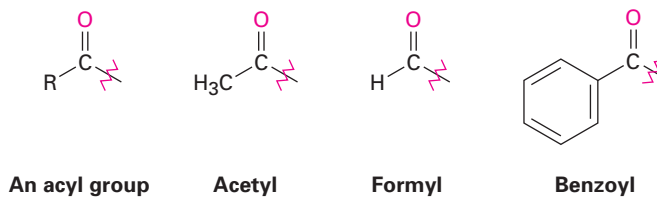
Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that contains the ketone group, and the numbering begins at the end nearer the carbonyl carbon. As with alkenes (Section 6.3) and alcohols (Section 17.1), the locant is placed before the parent name in older rules but before the suffix in newer IUPAC recommendations. For example:



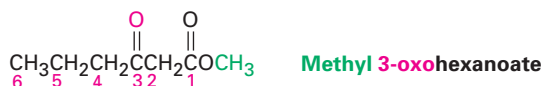
A few ketones are allowed by IUPAC to retain their common names.



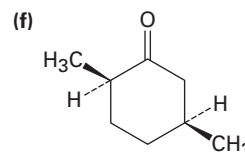
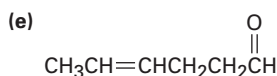
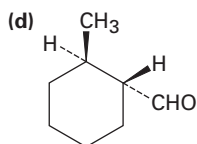
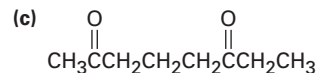
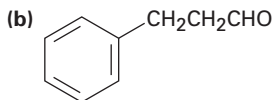
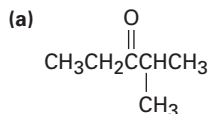
When it's necessary to refer to the R-C=O as a substituent, the name **acyl (a-sil) group** is used and the name ending *-yl* is attached. Thus, CH₃CO is an *acetyl* group, CHO is a *formyl* group, and C₆H₅CO is a *benzoyl* group.



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:



Problem 19.1 Name the following aldehydes and ketones according to IUPAC rules:



Problem 19.2 Draw structures corresponding to the following names:

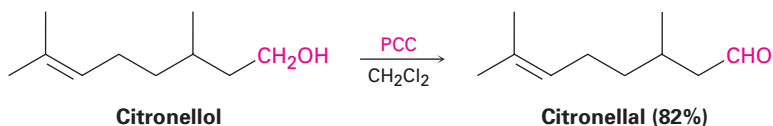
- (a) 3-Methylbutanal (b) 4-Chloro-2-pentanone
 (c) Phenylacetaldehyde (d) *cis*-3-*tert*-Butylcyclohexanecarbaldehyde
 (e) 3-Methyl-3-butenal (f) 2-(1-Chloroethyl)-5-methylheptanal

19.2 Preparation of Aldehydes and Ketones

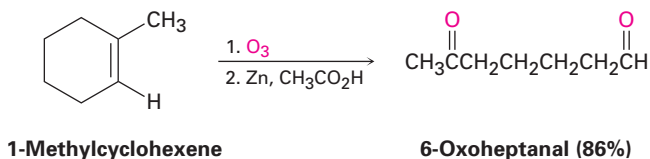
Preparing Aldehydes

We've already discussed two methods of aldehyde synthesis: oxidation of primary alcohols and oxidative cleavage of alkenes.

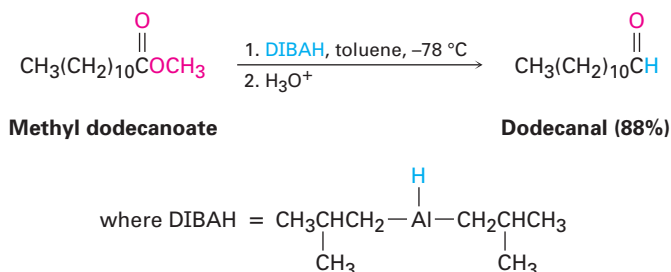
- Primary alcohols can be oxidized to give aldehydes (Section 17.7). The reaction is often carried out using pyridinium chlorochromate (PCC) in dichloromethane solvent at room temperature.



- Alkenes with at least one vinylic hydrogen undergo oxidative cleavage when treated with ozone, yielding aldehydes (Section 7.9). If the ozonolysis reaction is carried out on a cyclic alkene, a dicarbonyl compound results.



A third 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), 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 $-78\text{ }^{\circ}\text{C}$ (dry-ice temperature) in toluene solution.

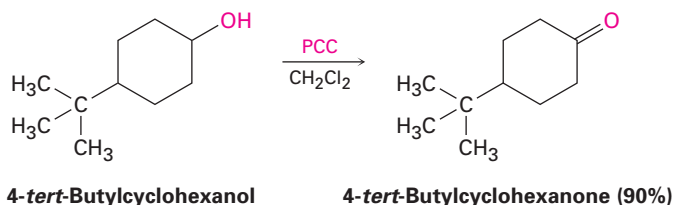


- Problem 19.3** How would you prepare pentanal from the following starting materials?
 (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$
 (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$

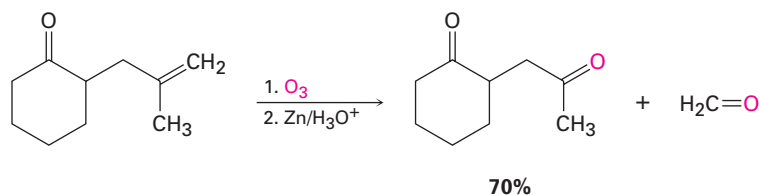
Preparing Ketones

For the most part, methods of ketone synthesis are similar to those for aldehydes.

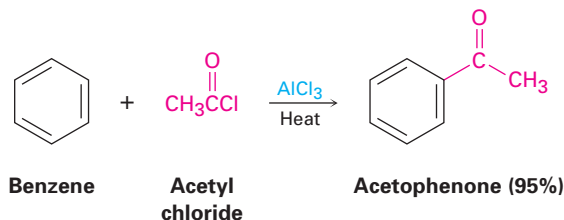
- Secondary alcohols are oxidized by a variety of reagents to give ketones (Section 17.8). The choice of oxidant depends on such factors as reaction scale, cost, and acid or base sensitivity of the alcohol.



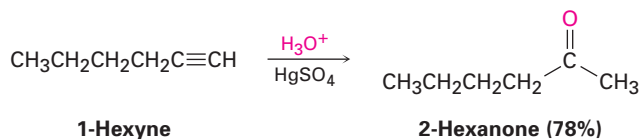
- Ozonolysis of alkenes yields ketones if one of the unsaturated carbon atoms is disubstituted (Section 7.9).



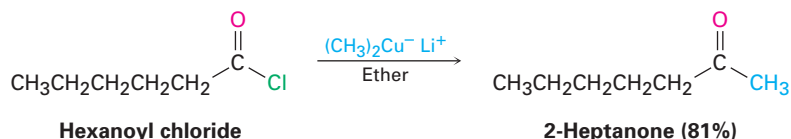
- Aryl ketones are prepared by Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of AlCl_3 catalyst (Section 16.3).



- Methyl ketones are prepared by hydration of terminal alkynes in the presence of Hg^{2+} catalyst (Section 8.4).



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 type is that between an acid chloride and a Gilman diorganocopper reagent such as we saw in Section 10.8. We'll discuss this subject in more detail in Section 21.4.

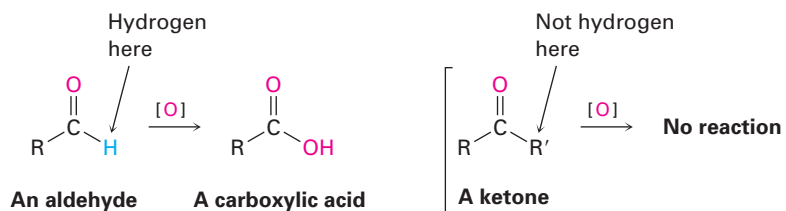


- Problem 19.4** How would you carry out the following reactions? More than one step may be required.
- 3-Hexyne \rightarrow 3-Hexanone
 - Benzene \rightarrow *m*-Bromoacetophenone
 - Bromobenzene \rightarrow Acetophenone
 - 1-Methylcyclohexene \rightarrow 2-Methylcyclohexanone

19.3 Oxidation of Aldehydes and Ketones

ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of oxidation reactions involving aldehydes and ketones.

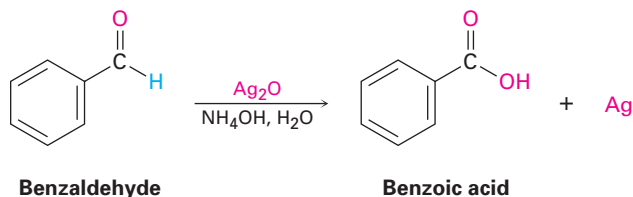
Aldehydes are easily oxidized to yield carboxylic acids, but ketones are generally inert toward oxidation. The difference is a consequence of structure: aldehydes have a $-\text{CHO}$ proton that can be abstracted during oxidation, but ketones do not.



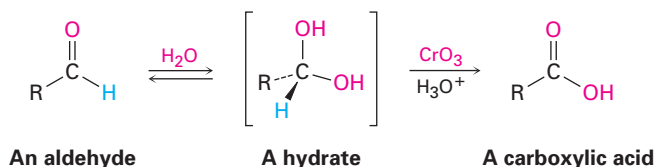
Many oxidizing agents, including KMnO_4 and hot HNO_3 , convert aldehydes into carboxylic acids, but CrO_3 in aqueous acid is a more common choice. The oxidation occurs rapidly at room temperature and generally results in good yields.



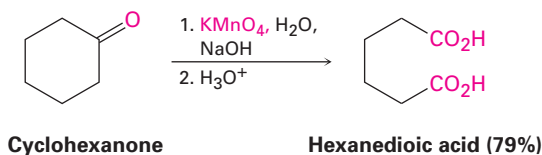
One drawback to this CrO_3 oxidation is that it takes place under acidic conditions, and sensitive molecules sometimes undergo side reactions. In such cases, the laboratory oxidation of an aldehyde can be carried out using a solution of silver oxide, Ag_2O , in aqueous ammonia, the so-called Tollens' reagent. Aldehydes are oxidized by Tollens' reagent in high yield without harming carbon-carbon double bonds or other acid-sensitive functional groups in a molecule.



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).



Ketones are inert to most oxidizing agents but undergo a slow cleavage reaction when treated with hot alkaline KMnO_4 . The C-C bond next to the carbonyl group is broken, and carboxylic acids are produced. The reaction is useful primarily for symmetrical ketones such as cyclohexanone because product mixtures are formed from unsymmetrical ketones.



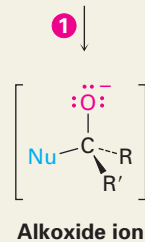
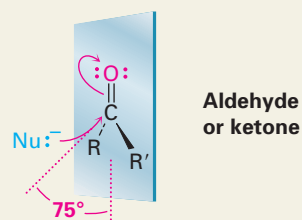
19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

As we saw in *A Preview of Carbonyl Compounds*, the most general reaction of aldehydes and ketones is the **nucleophilic addition reaction**. A nucleophile, :Nu^- , approaches along the $\text{C}=\text{O}$ bond from an angle of about 75° to the plane of the carbonyl group and adds to the electrophilic $\text{C}=\text{O}$ carbon atom. At the same time, rehybridization of the carbonyl carbon from sp^2 to sp^3 occurs, an electron pair from the $\text{C}=\text{O}$ bond moves toward the electronegative oxygen atom, and a tetrahedral alkoxide ion intermediate is produced (Figure 19.1).

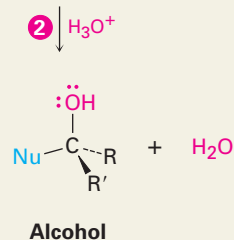
Figure 19.1 MECHANISM:

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.

- 1 An electron pair from the nucleophile adds to the electrophilic carbon of the carbonyl group, pushing an electron pair from the $\text{C}=\text{O}$ 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.



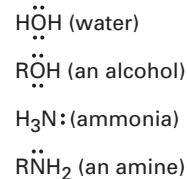
© John McMurry

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

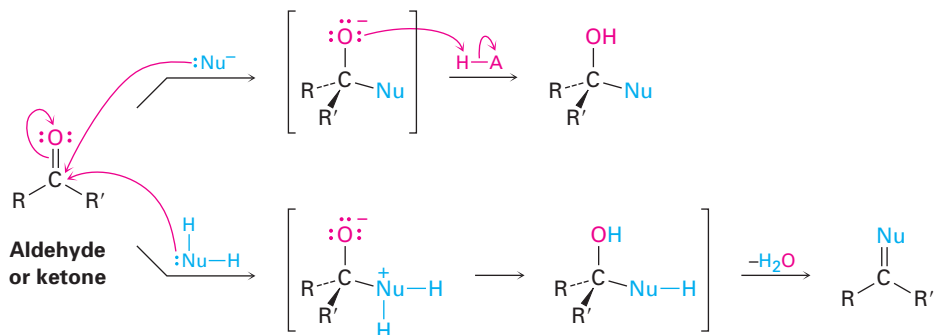
- HO^- (hydroxide ion)
- H^- (hydride ion)
- R_3C^- (a carbanion)
- RO^- (an alkoxide ion)
- $\text{N}\equiv\text{C}^-$ (cyanide ion)

Some neutral nucleophiles



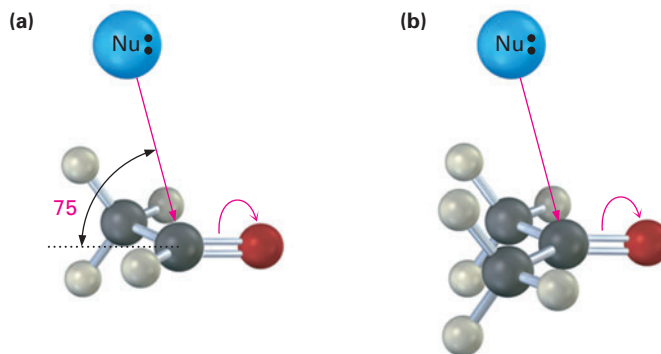
Nucleophilic additions to aldehydes and ketones have two general variations, as shown in Figure 19.2. In one variation, the tetrahedral intermediate is protonated by water or acid to give an alcohol as the final product; in the second variation, the carbonyl oxygen atom is protonated and then eliminated as HO^- or H_2O to give a product with a $\text{C}=\text{Nu}$ bond.

Active 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 $\text{C}=\text{Nu}$ bond. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.



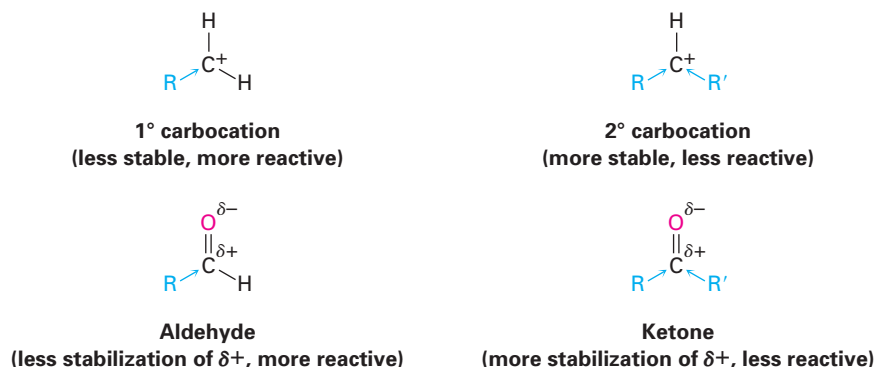
Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons. Sterically, the presence of only one large substituent bonded to the $\text{C}=\text{O}$ carbon in an aldehyde versus two large substituents in a ketone means that a nucleophile 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.

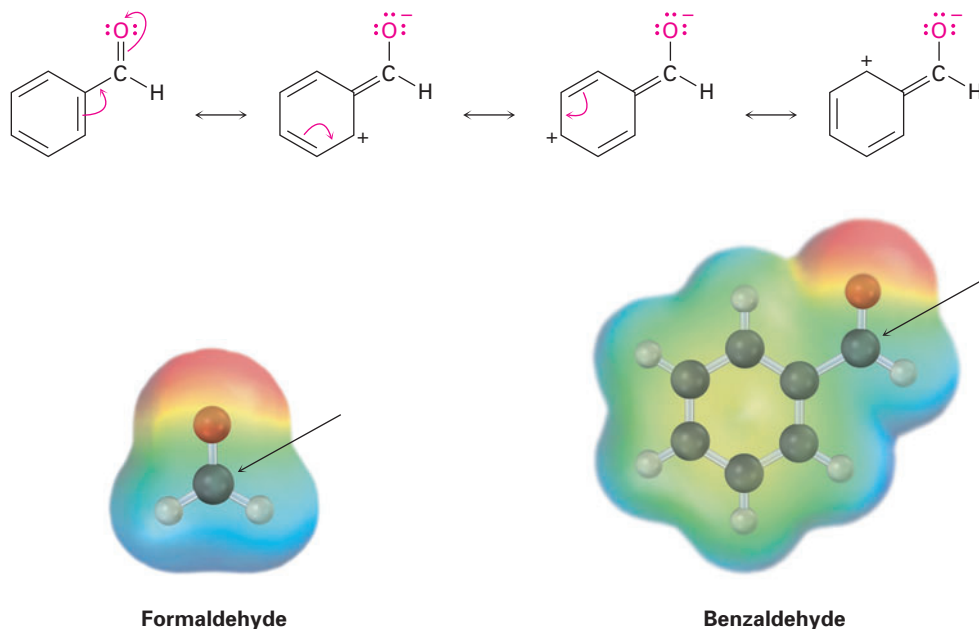


Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde carbonyl groups. To see this polarity difference, recall the stability order of carbocations (Section 6.9). A primary carbocation is higher in energy and thus more reactive than a secondary carbocation 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.



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.

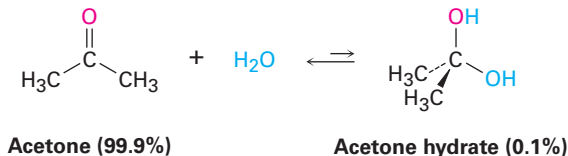


Problem 19.5 Treatment of an aldehyde or ketone with cyanide ion ($^-:\text{C}\equiv\text{N}$), followed by protonation of the tetrahedral alkoxide ion intermediate, gives a *cyanohydrin*. Show the structure of the cyanohydrin obtained from cyclohexanone.

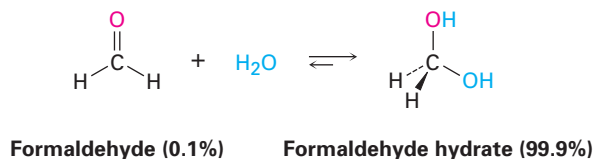
Problem 19.6 *p*-Nitrobenzaldehyde is more reactive toward nucleophilic additions than *p*-methoxybenzaldehyde. Explain.

19.5 Nucleophilic Addition of H₂O: 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.



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, whereas an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.

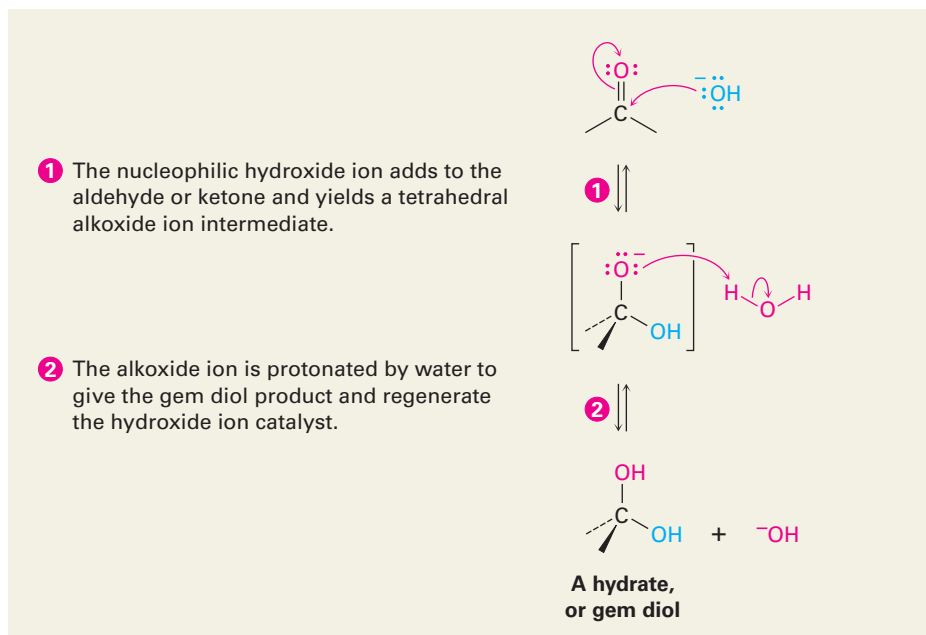


The nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. The base-catalyzed hydration reaction takes place as shown in Figure 19.4. The nucleophile is the

Figure 19.4 MECHANISM:

The mechanism of base-catalyzed hydration of an aldehyde or ketone. Hydroxide ion is a more reactive nucleophile than neutral water.

ThomsonNOW Click *Organic Process* to view an animation of the base-catalyzed hydration of a carbonyl.



hydroxide ion, which is much more reactive than neutral water because of its negative charge.

The acid-catalyzed hydration reaction begins with protonation of the carbonyl oxygen atom, which places a positive charge on oxygen and makes the carbonyl group more electrophilic. Subsequent nucleophilic addition of water to the protonated aldehyde or ketone then yields a protonated gem diol, which loses H^+ to give the neutral product (Figure 19.5).

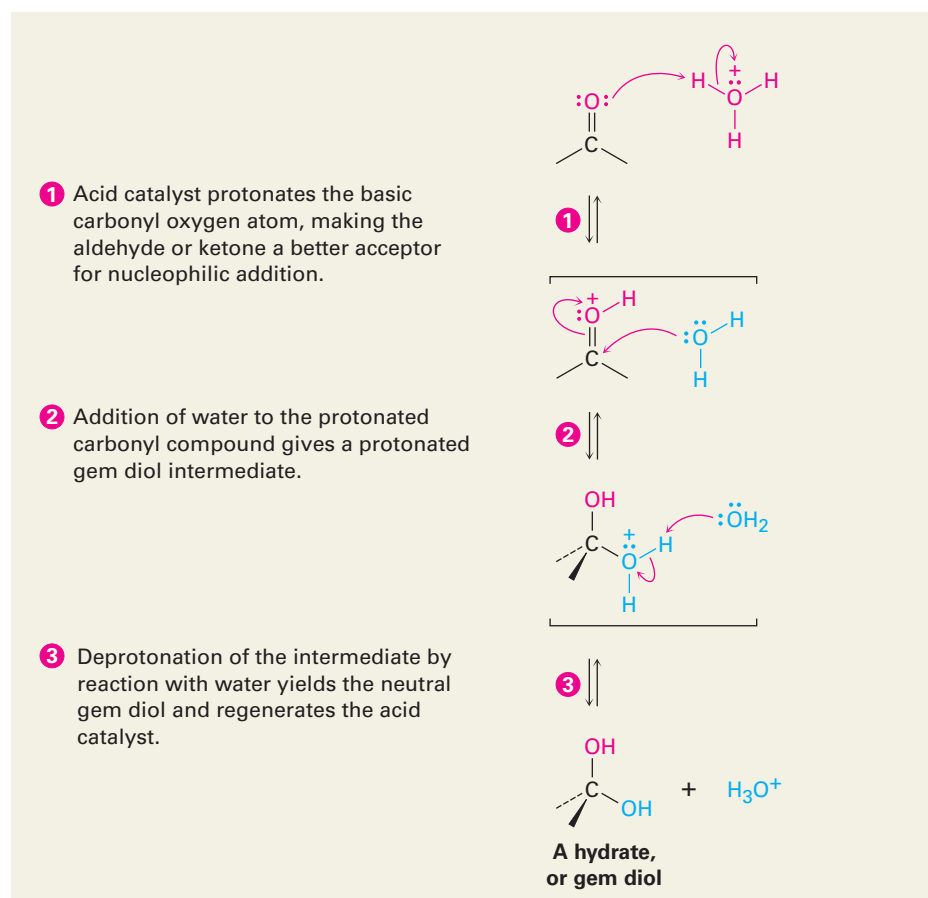
Note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction takes place rapidly because water is converted into hydroxide ion, a much better *nucleophile*. The acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation 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

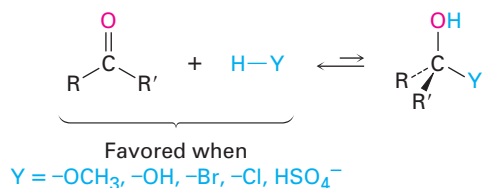
Figure 19.5 MECHANISM:

The mechanism of acid-catalyzed hydration of an aldehyde or ketone. Acid protonates the carbonyl group, making it more electrophilic and more reactive.

ThomsonNOW Click *Organic Process* to view an animation of the acid-catalyzed hydration of a carbonyl.

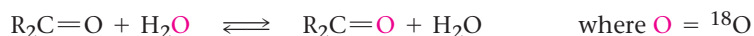


ketone with CH_3OH , H_2O , HCl , HBr , or H_2SO_4 does not normally lead to a stable alcohol addition product.



Problem 19.7 When dissolved in water, trichloroacetaldehyde (chloral, CCl_3CHO) exists primarily as chloral hydrate, $\text{CCl}_3\text{CH}(\text{OH})_2$, better known as “knockout drops.” 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.

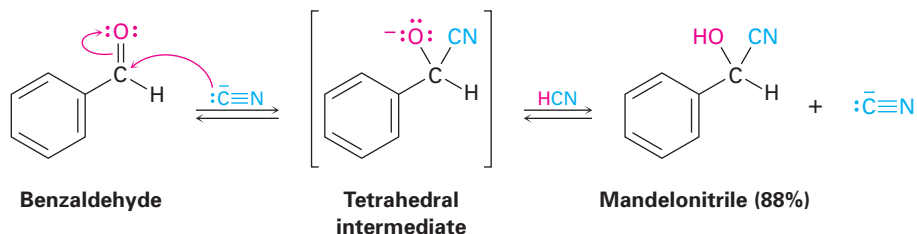


19.6 Nucleophilic Addition of HCN: Cyanohydrin Formation

Arthur Lapworth

Arthur Lapworth (1872–1941) was born in Galashiels, Scotland, and received a D.Sc. at the City and Guilds Institute, London. He was professor of chemistry at the University of Manchester from 1909 until his retirement in 1937.

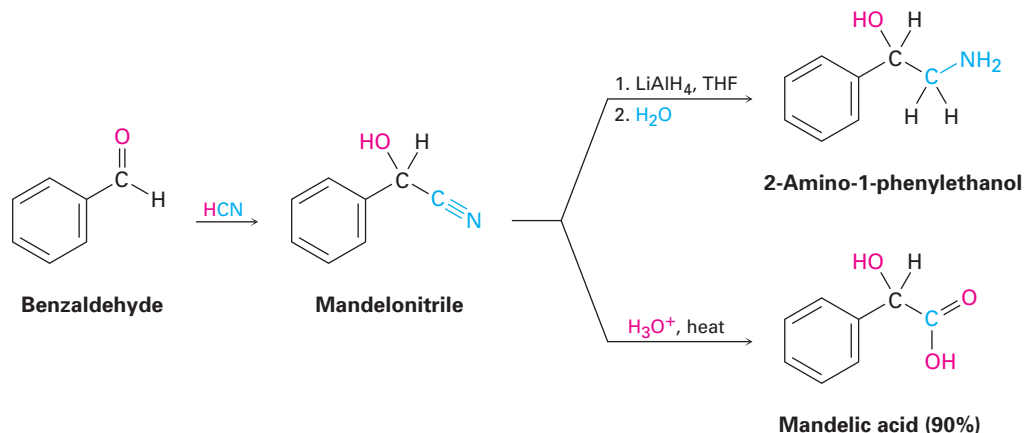
Aldehydes and unhindered ketones undergo a nucleophilic addition reaction with HCN to yield **cyanohydrins**, $\text{RCH}(\text{OH})\text{C}\equiv\text{N}$. Studies carried out in the early 1900s by Arthur Lapworth showed that cyanohydrin formation is reversible and base-catalyzed. Reaction occurs slowly when pure HCN is used but rapidly when a small amount of base is added to generate the nucleophilic cyanide ion, CN^- . Alternatively, a small amount of KCN can be added to HCN to catalyze the reaction. 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^- .



Cyanohydrin formation is somewhat unusual because it is one of the few examples of the addition of a protic acid ($\text{H}-\text{Y}$) 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 ($\text{R}-\text{C}\equiv\text{N}$) can be reduced with LiAlH_4 to yield a primary amine (RCH_2NH_2) and can be hydrolyzed by hot

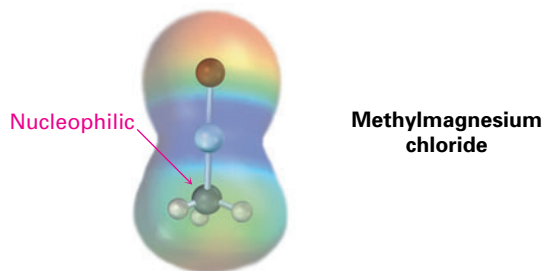
aqueous acid to yield a carboxylic acid. Thus, cyanohydrin formation provides a method for transforming an aldehyde or ketone into a different functional group.



Problem 19.9 | Cyclohexanone forms a cyanohydrin in good yield but 2,2,6-trimethylcyclohexanone does not. Explain.

19.7 Nucleophilic Addition of Grignard and Hydride Reagents: Alcohol Formation

We saw in Section 17.5 that treatment of an aldehyde or ketone with a Grignard reagent, RMgX , yields an alcohol by nucleophilic addition of a carbon anion, or **carbanion**. A carbon–magnesium bond is strongly polarized, so a Grignard reagent reacts for all practical purposes as $\text{R}^- + \text{MgX}$.

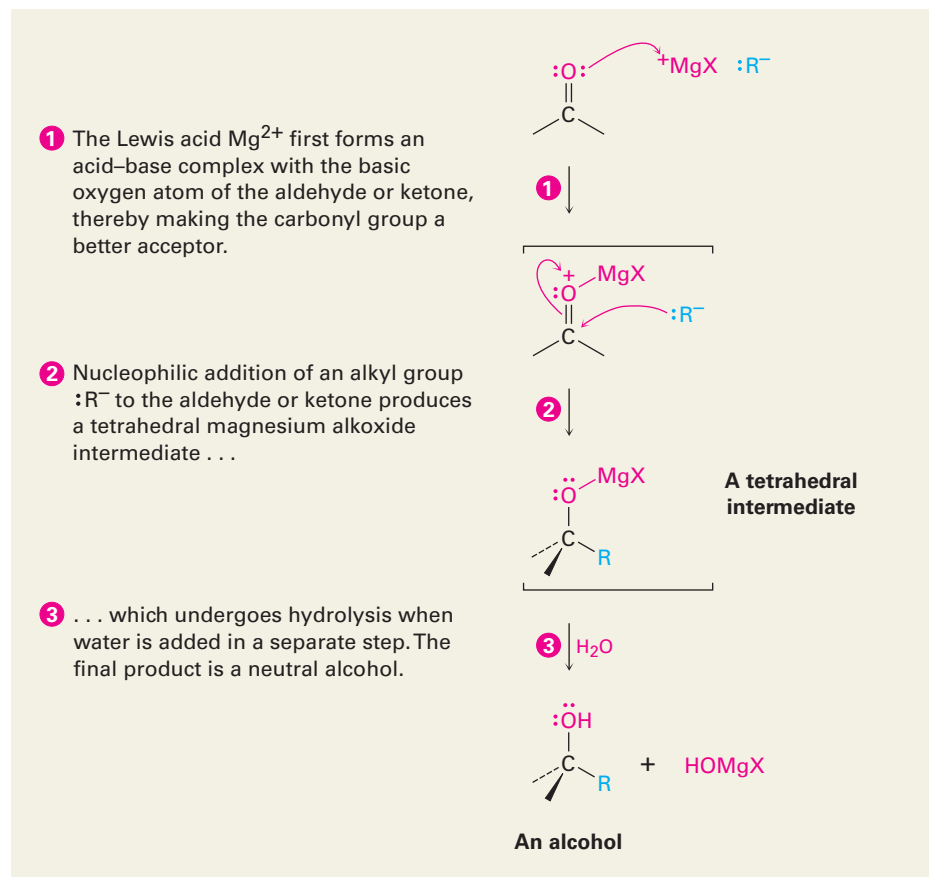


A Grignard reaction begins with an acid–base complexation of Mg^{2+} to the carbonyl oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better electrophile. Nucleophilic addition of R^- then produces a tetrahedral magnesium alkoxide intermediate, and protonation by addition of water

or dilute aqueous acid in a separate step yields the neutral alcohol (Figure 19.6). Unlike the nucleophilic additions of water and HCN, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

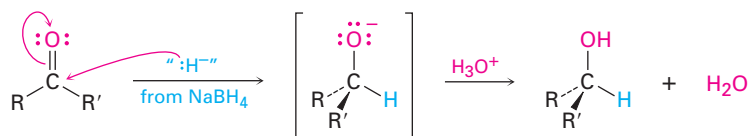
Figure 19.6 MECHANISM:

Mechanism of the Grignard reaction. Nucleophilic addition of a carbanion to an aldehyde or ketone, followed by protonation of the alkoxide intermediate, yields an alcohol.



Just as addition of a Grignard reagent to an aldehyde or ketone yields an alcohol, so does addition of hydride ion, :H^- (Section 17.4). Although the details of carbonyl-group reductions are complex, LiAlH_4 and NaBH_4 act as if they were donors of hydride ion in a nucleophilic addition reaction (Figure 19.7). Addition of water or aqueous acid after the hydride addition step protonates the tetrahedral alkoxide intermediate and gives the alcohol product.

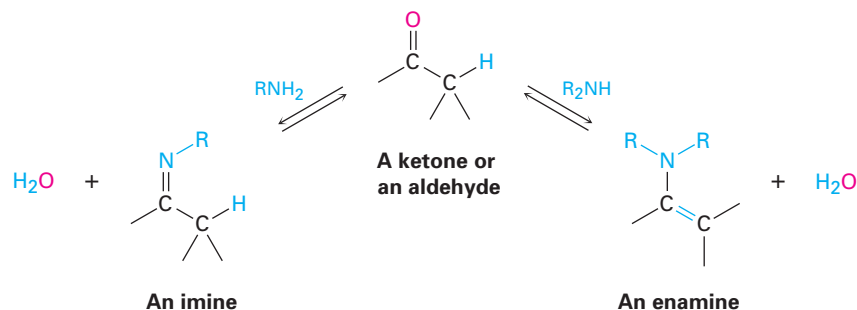
Figure 19.7 Mechanism of carbonyl-group reduction by nucleophilic addition of “hydride ion” from NaBH_4 or LiAlH_4 .



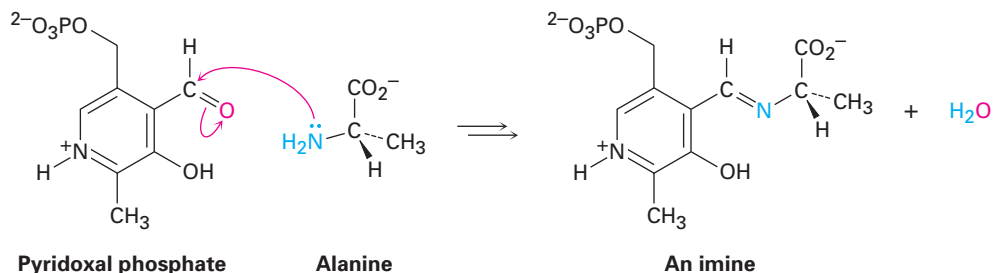
19.8 Nucleophilic Addition of Amines: Imine and Enamine Formation

ThomsonNOW Click *Organic Process* to view an animation of the addition of an amine to a carbonyl compound to form an imine.

Primary amines, RNH_2 , add to aldehydes and ketones to yield **imines**, $\text{R}_2\text{C}=\text{NR}$. Secondary amines, R_2NH , add similarly to yield **enamines**, $\text{R}_2\text{N}-\text{CR}=\text{CR}_2$ (*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.



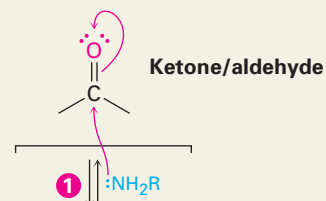
Imine formation and enamine formation appear different because one leads to a product with a $\text{C}=\text{N}$ bond and the other leads to a product with a $\text{C}=\text{C}$ bond. Actually, though, the reactions are quite similar. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new $\text{C}=\text{Nu}$ bond is formed.

Imines are formed in a reversible, acid-catalyzed process 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 $-\text{OH}$ into a better leaving group ($-\text{OH}_2^+$), 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 19.8).

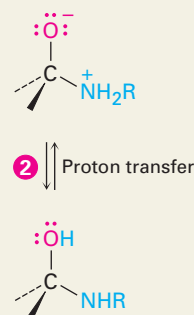
Figure 19.8 MECHANISM:

Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is nucleophilic addition to yield a carbinolamine intermediate, which then loses water to give the imine.

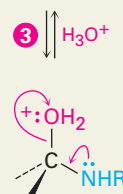
- 1 Nucleophilic attack on the ketone or aldehyde by the lone-pair electrons of an amine leads to a dipolar tetrahedral intermediate.



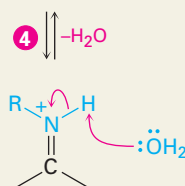
- 2 A proton is then transferred from nitrogen to oxygen, yielding a neutral carbinolamine.



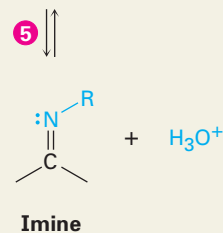
- 3 Acid catalyst protonates the hydroxyl oxygen.



- 4 The nitrogen lone-pair electrons expel water, giving an iminium ion.



- 5 Loss of H^+ from nitrogen then gives the neutral imine product.



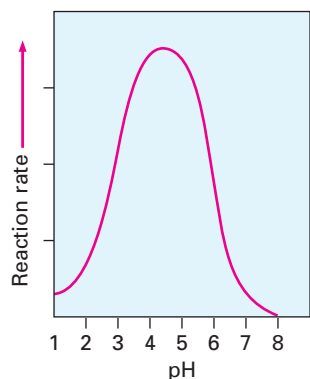


Figure 19.9 Dependence on pH of the rate of reaction between acetone and hydroxylamine: $(\text{CH}_3)_2\text{C}=\text{O} + \text{NH}_2\text{OH} \rightarrow (\text{CH}_3)_2\text{C}=\text{NOH} + \text{H}_2\text{O}$.

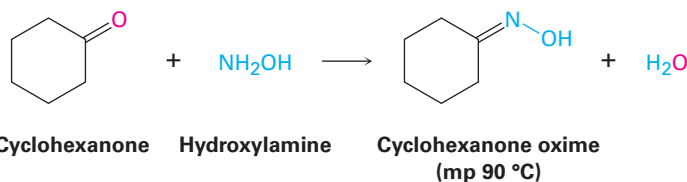
Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. For example, the profile of pH versus rate shown in Figure 19.9 for the reaction between acetone and hydroxylamine, NH_2OH , indicates that the maximum reaction rate is obtained at pH 4.5.

We can explain the observed pH dependence of imine formation by looking at the individual steps in the mechanism. As indicated in Figure 19.8, an acid catalyst is required in step 3 to protonate the intermediate carbinolamine, thereby converting the $-\text{OH}$ 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.

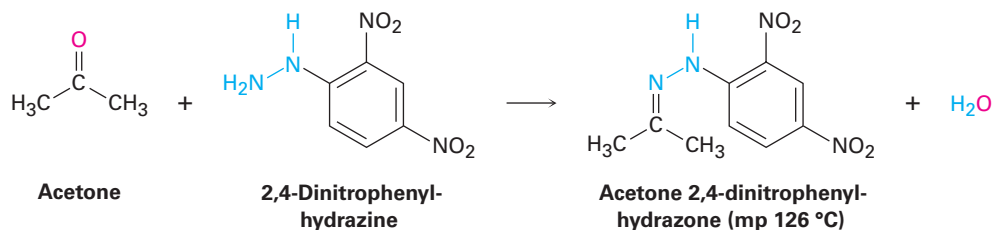
Evidently, a pH of 4.5 represents a compromise between the need for *some* acid to catalyze the rate-limiting dehydration step but *not too much* acid so as to avoid complete protonation of the amine. Each individual nucleophilic addition reaction has its own requirements, and reaction conditions must be optimized to obtain maximum reaction rates.

Imine formation from 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



2,4-Dinitrophenylhydrazone



Reaction of an aldehyde or ketone with a secondary amine, R_2NH , rather than a primary amine yields an enamine. 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 (Figure 19.10).

Figure 19.10 MECHANISM:

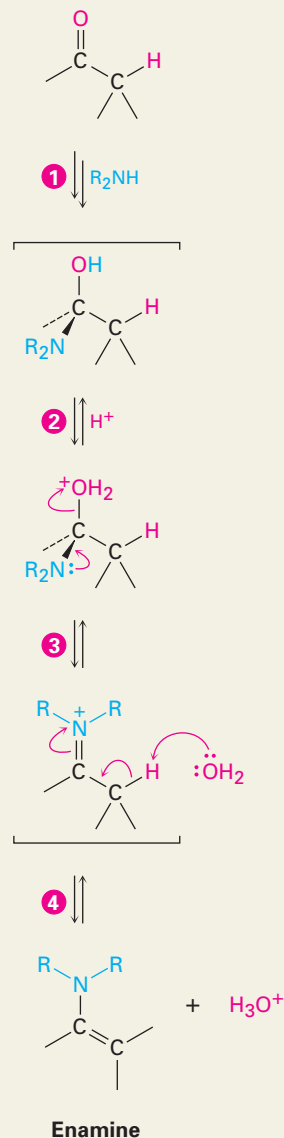
Mechanism of enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH . The iminium ion intermediate has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.

- 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.

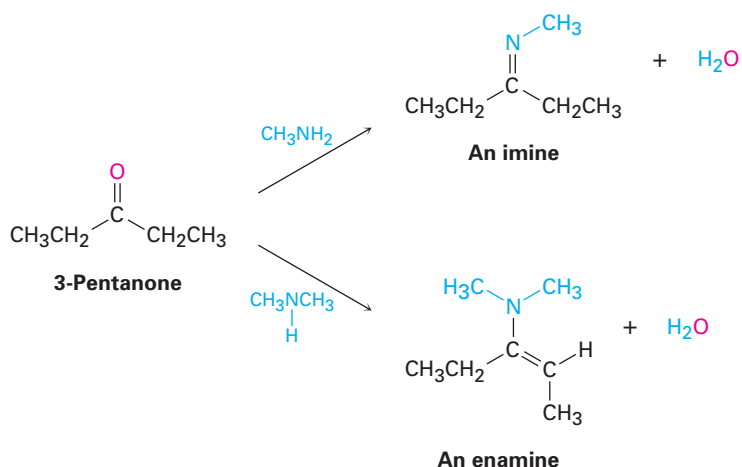
- 4 Loss of a proton from the alpha carbon atom yields the enamine product and regenerates the acid catalyst.



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, $(\text{CH}_3)_2\text{NH}$.

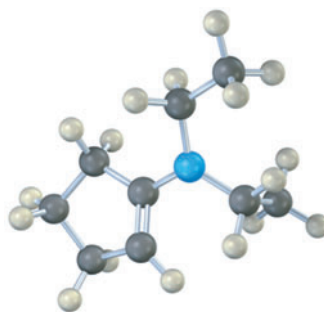
Strategy An aldehyde or ketone reacts with a primary amine, RNH_2 , to yield an imine, in which the carbonyl oxygen atom has been replaced by the $=\text{N}-\text{R}$ group of the amine. Reaction of the same aldehyde or ketone with a secondary amine, R_2NH , yields an enamine, in which the oxygen atom has been replaced by the $-\text{NR}_2$ group of the amine and the double bond has moved to a position between the former carbonyl carbon and the neighboring carbon.

Solution

Problem 19.10 Show the products you would obtain by acid-catalyzed reaction of cyclohexanone with ethylamine, $\text{CH}_3\text{CH}_2\text{NH}_2$, and with diethylamine, $(\text{CH}_3\text{CH}_2)_2\text{NH}$.

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 line-bond structure, and show how it can be prepared from a ketone and an amine.

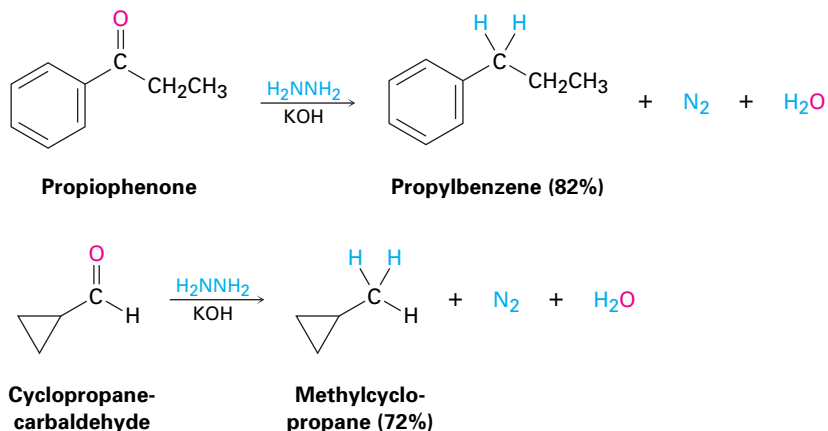


19.9 Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction

Ludwig Wolff

Ludwig Wolff (1857–1919) was born in Neustadt/Hardt, Germany, and received his Ph.D. from the University of Strasbourg working with Rudolf Fittig. He was professor of chemistry at the University of Jena.

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, $\text{R}_2\text{C}=\text{O} \rightarrow \text{R}_2\text{CH}_2$.



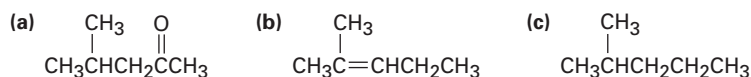
N. M. Kishner

N. M. Kishner (1867–1935) was born in Moscow and received his Ph.D. at the University of Moscow working with Vladimir Markovnikov. He became professor, first at the University of Tomsk and then at the University of Moscow.

The Wolff–Kishner reaction involves formation of a *hydrazone* intermediate, $\text{R}_2\text{C}=\text{NNH}_2$, followed by base-catalyzed double-bond migration, loss of N_2 gas, and protonation to give the alkane product (Figure 19.11). The double-bond migration takes place when base removes one of the weakly acidic NH protons 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, $(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$.



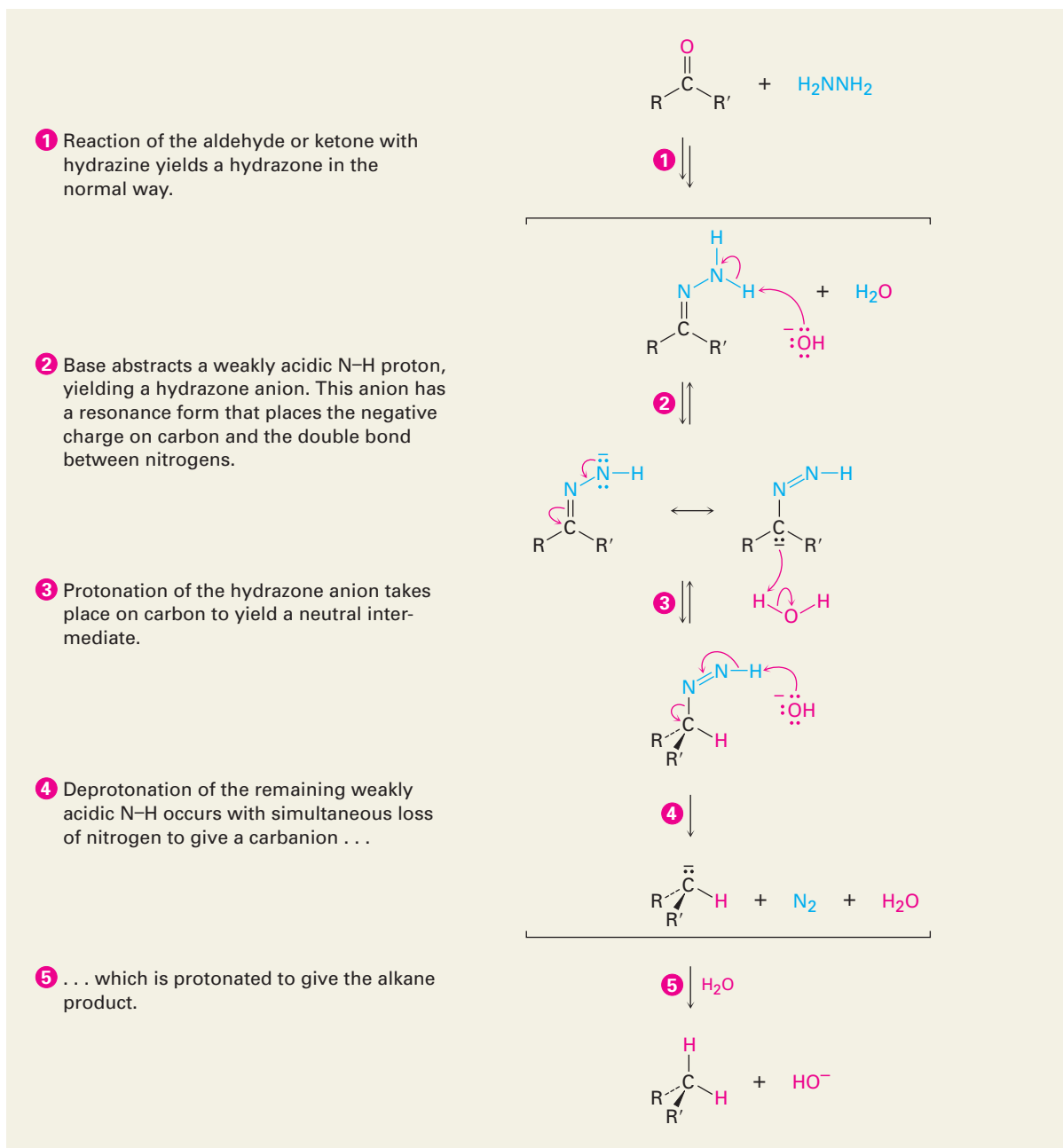
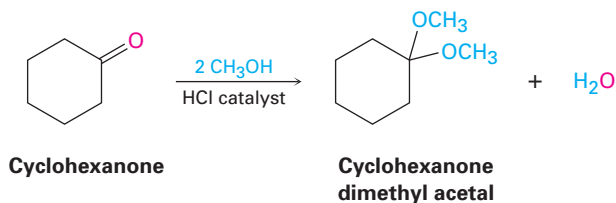


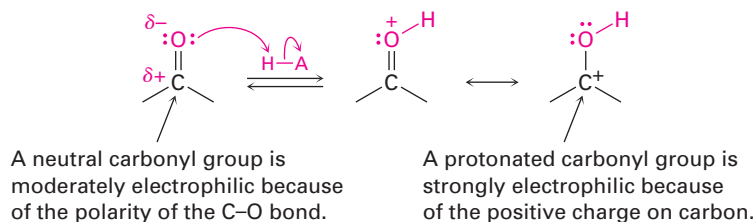
Figure 19.11 MECHANISM: Mechanism of the Wolff–Kishner reduction of an aldehyde or ketone to yield an alkane.

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**, $R_2C(OR')_2$, sometimes called *ketals* if derived from a ketone. Cyclohexanone, for instance, reacts with methanol in the presence of HCl to give the corresponding 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.



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 acetal. The mechanism is shown in Figure 19.12.

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

Figure 19.12 MECHANISM:

Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.

ThomsonNOW Click *Organic Process* to view an animation of acetal formation from an alcohol and an aldehyde.

- 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.

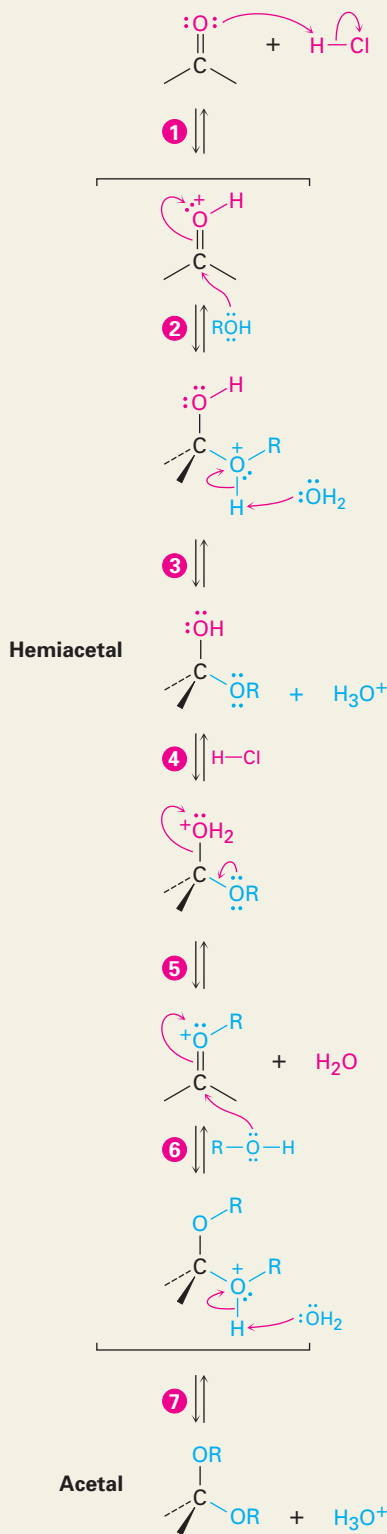
- 3 Loss of a proton yields a neutral hemiacetal tetrahedral intermediate.

- 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.

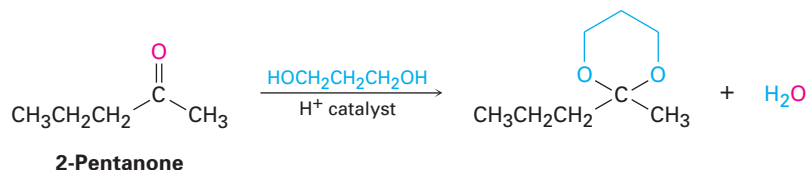


WORKED EXAMPLE 19.2

Predicting the Product of Reaction between a Ketone and an Alcohol

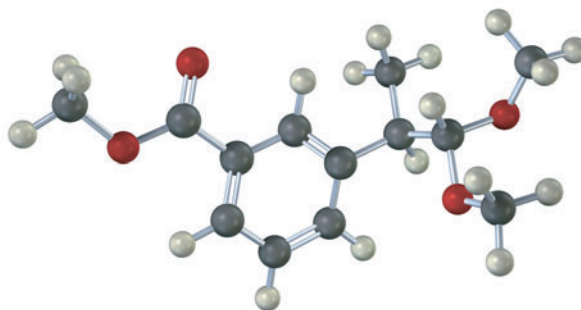
Show the structure of the acetal you would obtain by acid-catalyzed reaction of 2-pentanone with 1,3-propanediol.

Strategy Acid-catalyzed reaction of an aldehyde or ketone with 2 equivalents of a mono-alcohol 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

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

Georg F. K. Wittig

Georg F. K. Wittig (1897–1987) was born in Berlin, Germany, and received his Ph.D. at the University of Marburg in 1926, working with von Auwers. He then became professor of chemistry, first at the University of Braunschweig and later in Freiburg, Tübingen, and Heidelberg. In 1979, he received the Nobel Prize in chemistry for his work on phosphorus-containing organic compounds.

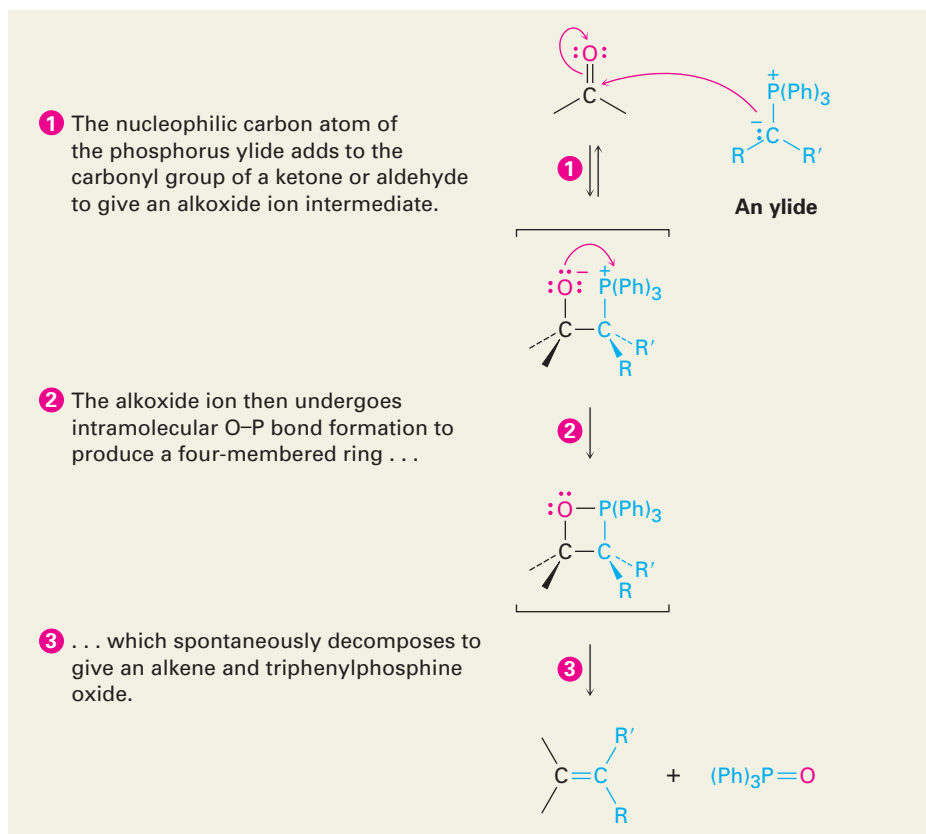
Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition called the **Wittig reaction**. The reaction has no direct biological counterpart but is important both because of its wide use in the laboratory and drug manufacture and because of its mechanistic similarity to reactions of the coenzyme thiamin diphosphate, which we'll see in Section 29.6.

In the Wittig reaction, a phosphorus *ylide*, $\text{R}_2\text{C}=\overset{\ominus}{\text{P}}(\text{C}_6\text{H}_5)_3$, also called a *phosphorane* and sometimes written in the resonance form $\text{R}_2\text{C}=\overset{\oplus}{\text{P}}(\text{C}_6\text{H}_5)_3$, adds to an aldehyde or ketone to yield a dipolar intermediate called a *betaine*. (An *ylide*—pronounced *ill-id*—is a neutral, dipolar compound with adjacent plus and minus charges. A *betaine*—pronounced *bay-ta-een*—is a neutral, dipolar compound with nonadjacent charges.)

The betaine intermediate is not isolated; rather, it spontaneously decomposes through a four-membered ring to yield alkene plus triphenylphosphine

Active Figure 19.13

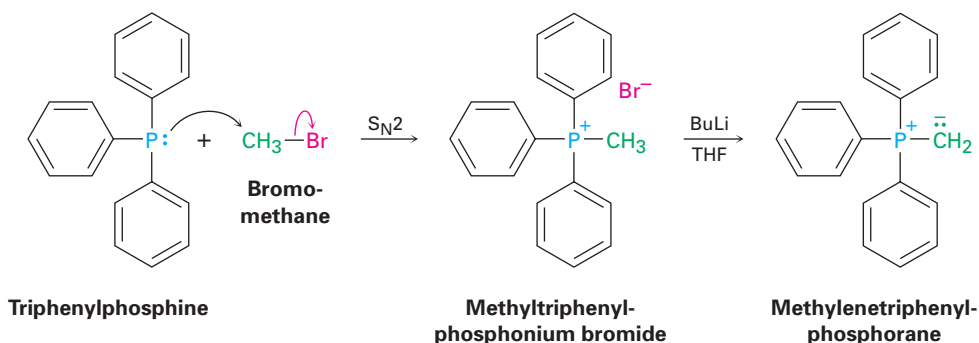
MECHANISM: The mechanism of the Wittig reaction between a phosphorus ylide and an aldehyde or ketone to yield an alkene. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.



ThomsonNOW Click *Organic Interactive* to use your problem-solving skills to design syntheses involving Wittig reactions.

oxide, $(\text{Ph})_3\text{P}=\text{O}$. The net result is replacement of the carbonyl oxygen atom by the $\text{R}_2\text{C}=\text{}$ group originally bonded to phosphorus (Figure 19.13).

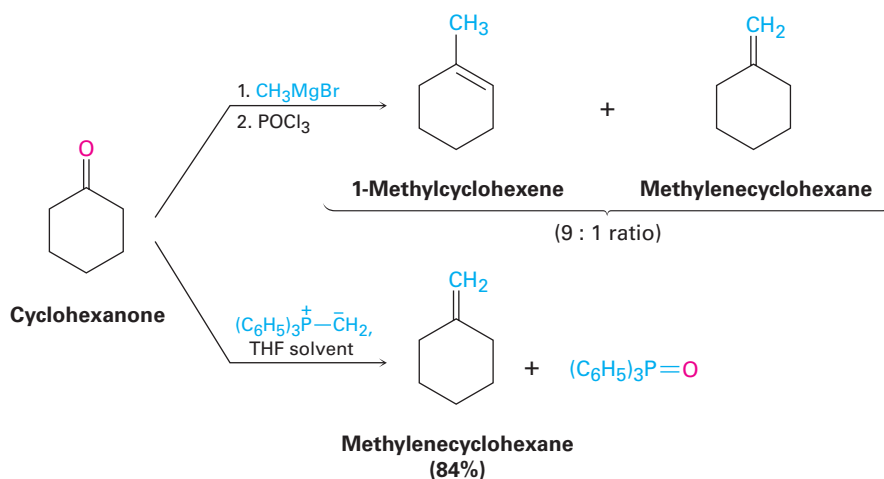
The phosphorus ylides necessary for Wittig reaction are easily prepared by $\text{S}_{\text{N}}2$ reaction of primary (and some secondary) alkyl halides with triphenylphosphine, followed by treatment with base. Triphenylphosphine, $(\text{Ph})_3\text{P}$, is a good nucleophile in $\text{S}_{\text{N}}2$ 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:



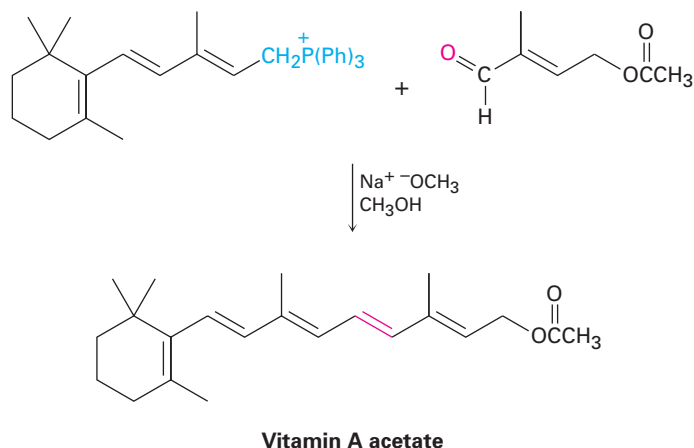
The Wittig reaction is extremely general, and a great many monosubstituted, disubstituted, and trisubstituted alkenes can be prepared from the appropriate

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 defined 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 POCl₃, 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.



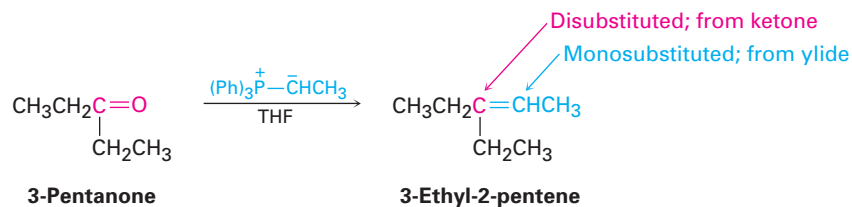
WORKED EXAMPLE 19.3

Synthesizing an Alkene Using a Wittig Reaction

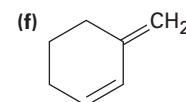
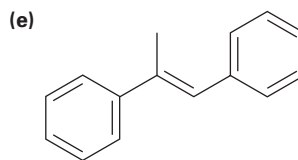
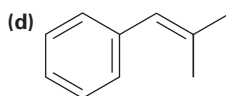
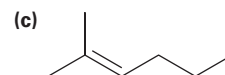
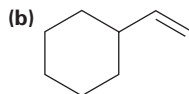
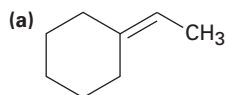
What carbonyl compound and what phosphorus ylide might you use to prepare 3-ethyl-2-pentene?

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.

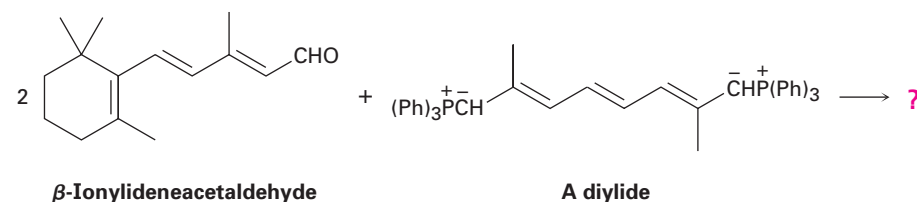
Solution



Problem 19.16 What carbonyl compound and what phosphorus ylide might you use to prepare each of the following compounds?



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.



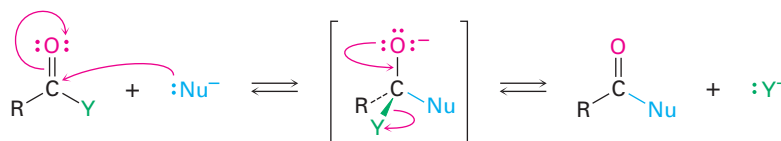
19.12 Biological Reductions

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 *A Preview of Carbonyl Compounds* and shown in Figure 19.14, 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

Stanislao Cannizzaro

Stanislao Cannizzaro (1826–1910) was born in Palermo, Sicily, the son of the chief of police. He studied at the University of Pisa under Raffaele Piria and also worked in Paris with Michel-Eugène Chevreul. As a youth, he took part in the Sicilian revolution of 1848 and was at one point condemned to death. He was professor of chemistry at the universities of Genoa, Palermo, and Rome and is best known for being the first to clarify the distinction between atoms and molecules.

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.

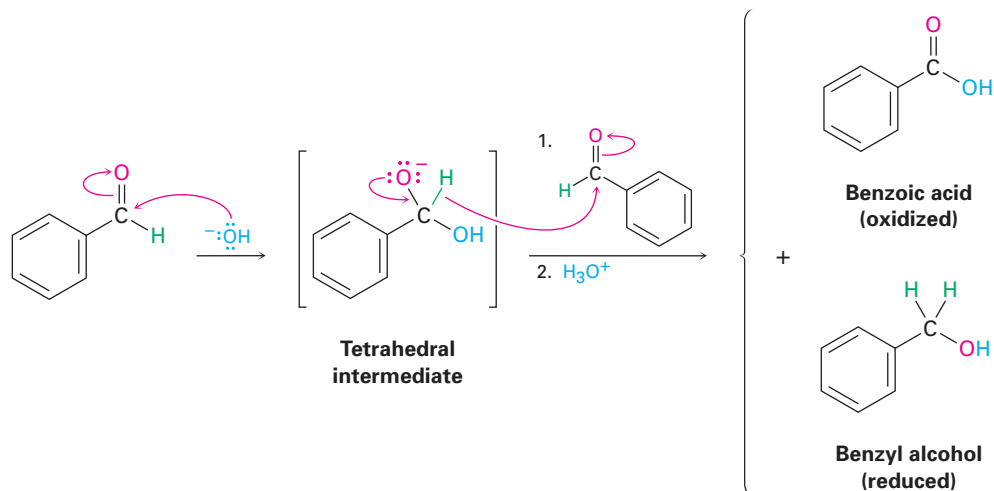


Reaction occurs when: $\text{Y} = -\text{Br}, -\text{Cl}, -\text{OR}, -\text{NR}_2$

Reaction does NOT occur when: $\text{Y} = -\text{H}, -\text{R}$

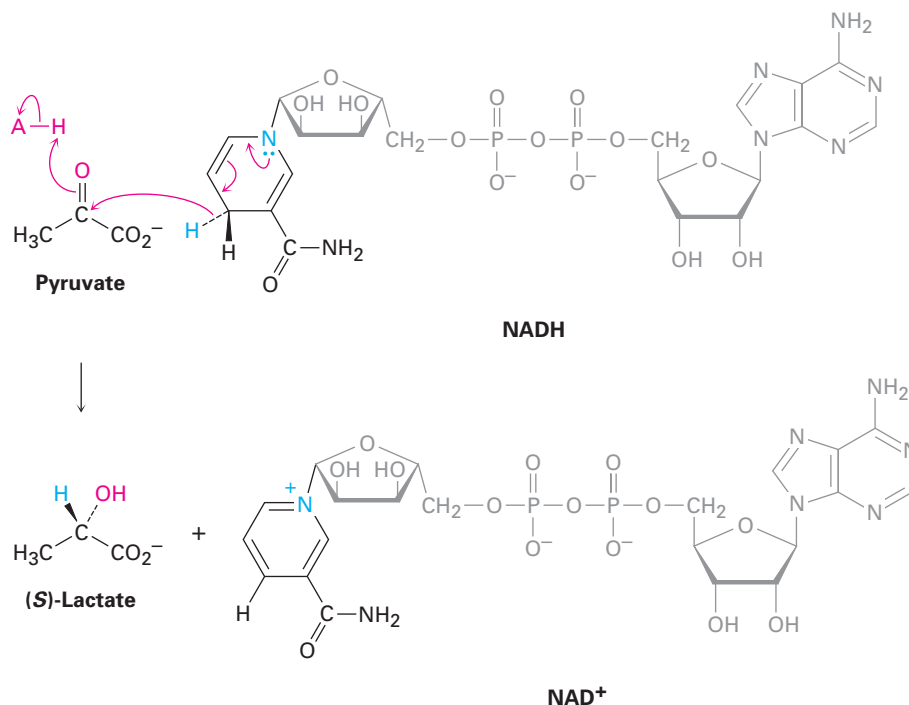
Figure 19.14 Carboxylic acid derivatives have an electronegative substituent $\text{Y} = -\text{Br}, -\text{Cl}, -\text{OR}, -\text{NR}_2$ that can be expelled as a leaving group from the tetrahedral intermediate formed by nucleophilic addition. Aldehydes and ketones have no such leaving group and thus 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 .

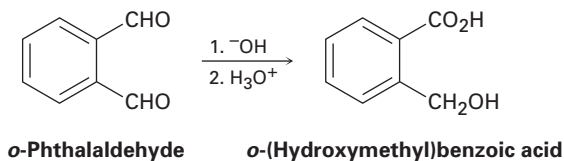


The Cannizzaro reaction has little use but is interesting mechanistically because it is a simple laboratory analogy for the primary biological pathway by which carbonyl reductions occur in living organisms. In nature, as we saw in Section 17.4, one of the most important reducing agents is NADH, reduced 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 19.15). As an example, pyruvate is converted during intense muscle activity to (*S*)-lactate, a reaction catalyzed by lactate dehydrogenase.

Figure 19.15 Mechanism of biological aldehyde and ketone reductions by the coenzyme NADH.



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 19.15? Does NADH lose its *pro-R* or *pro-S* hydrogen? Does addition occur to the *Si* face or *Re* face of pyruvate?

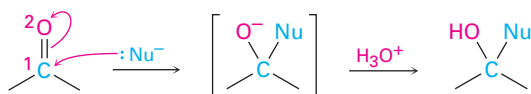
19.13 Conjugate Nucleophilic Addition to α,β -Unsaturated Aldehydes and Ketones

ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of conjugate addition reactions.

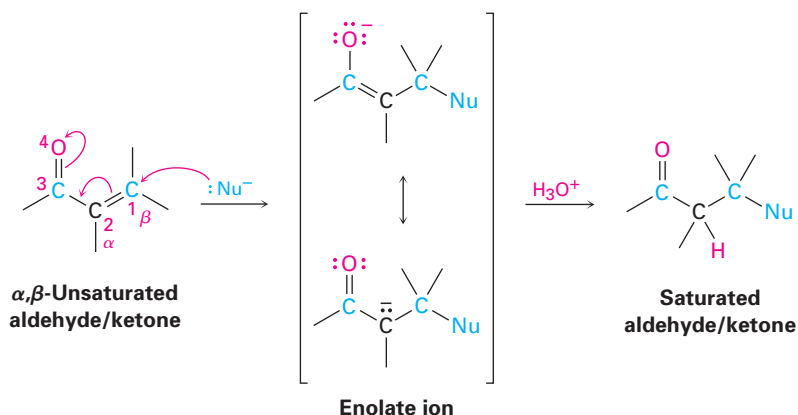
All the reactions we've been discussing to this point have involved the addition of a nucleophile directly to the carbonyl group, a so-called **1,2-addition**. Closely related to this direct addition is the **conjugate addition**, or **1,4-addition**, of a nucleophile to the $\text{C}=\text{C}$ bond 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 19.16).

Figure 19.16 A comparison of direct (1,2) and conjugate (1,4) nucleophilic addition reactions.

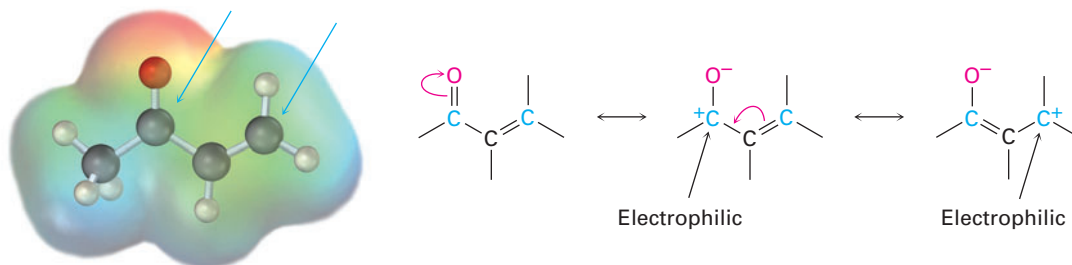
Direct (1,2) addition



Conjugate (1,4) addition

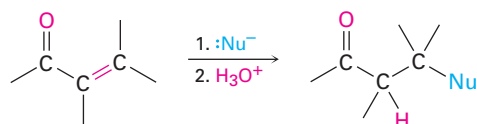


The conjugate addition of a nucleophile to an α,β -unsaturated aldehyde or ketone is caused by the same electronic factors that are responsible for direct addition. The electronegative oxygen atom of the α,β -unsaturated carbonyl compound withdraws electrons from the β carbon, thereby making it electron-poor and more electrophilic than a typical alkene carbon.

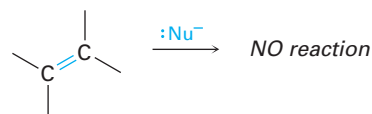


As noted previously, conjugate addition of a nucleophile to the β carbon of an α,β -unsaturated aldehyde or ketone leads to an enolate ion intermediate, which is protonated on the α carbon to give the saturated product (Figure 19.16). The net effect is addition of the nucleophile to the C=C bond, with 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.

Activated double bond

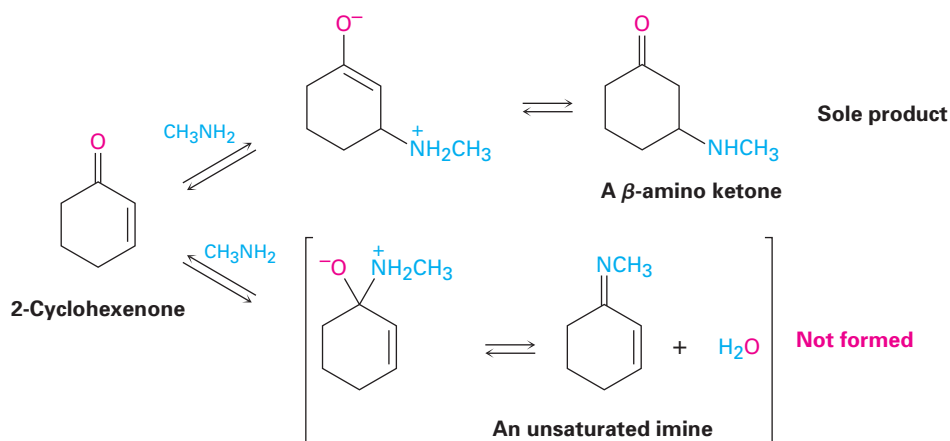


Unactivated double bond



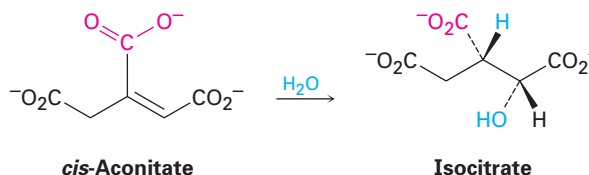
Conjugate Addition of Amines

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

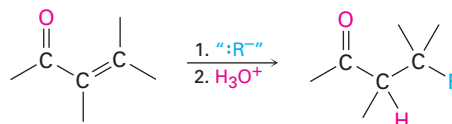
Water can add reversibly to α,β -unsaturated aldehydes and ketones to yield β -hydroxy aldehydes and ketones, although the position of the equilibrium generally favors unsaturated reactant rather than saturated adduct. A related addition to an α,β -unsaturated carboxylic acid occurs in numerous biological pathways, such as the citric acid cycle of food metabolism where *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.

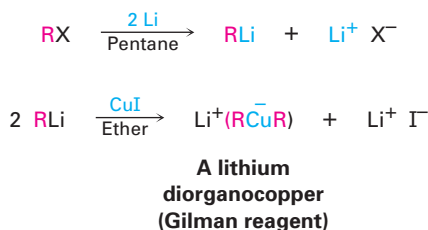
Conjugate Addition of Alkyl Groups: Organocopper Reactions

Conjugate addition of an alkyl 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.

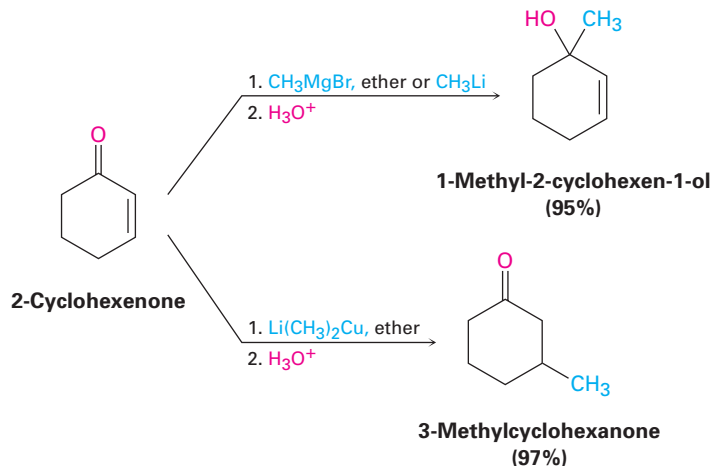


α,β -Unsaturated ketone

Conjugate addition of an alkyl group is carried out by treating the α,β -unsaturated ketone with a lithium diorganocopper reagent. As we saw in Section 10.8, diorganocopper (Gilman) reagents can be prepared by reaction between 1 equivalent of cuprous iodide and 2 equivalents of organolithium.

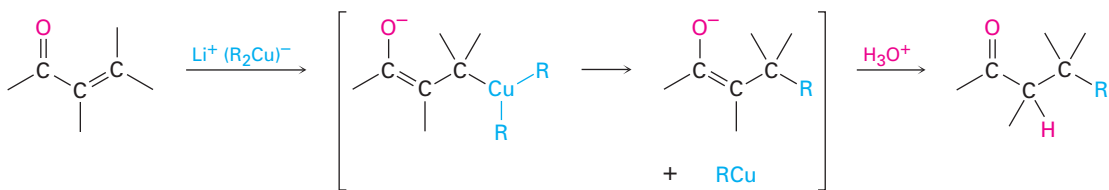


Primary, secondary, and even tertiary alkyl groups undergo the addition reaction, as do aryl and alkenyl groups. Alkynyl groups, however, react poorly in the conjugate addition process. Diorganocopper reagents are unique in their ability to give conjugate addition products. Other organometallic reagents, such as Grignard reagents and organolithiums, normally give direct carbonyl addition on reaction with α,β -unsaturated ketones.

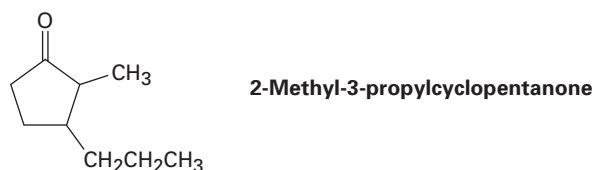


The mechanism of the reaction is thought to involve conjugate nucleophilic addition of the diorganocopper anion, R_2Cu^- , to the enone to give a

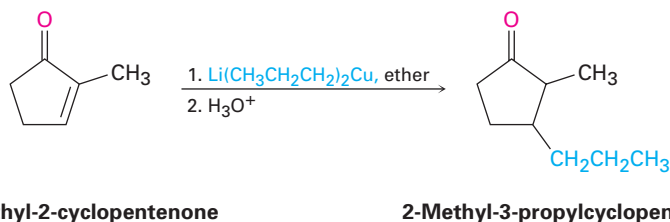
copper-containing intermediate. Transfer of an R group and elimination of a neutral organocopper species, RCu , gives the final product.

**WORKED EXAMPLE 19.4****Synthesis Using Conjugate Addition Reactions**

How might you use a conjugate addition reaction to prepare 2-methyl-3-propylcyclopentanone?

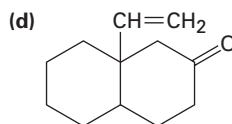
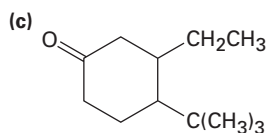
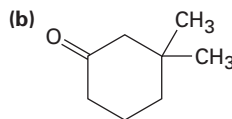
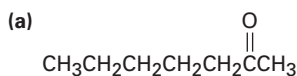


Strategy A ketone with a substituent group in its β position might be prepared by a conjugate addition of that group to an α,β -unsaturated ketone. In the present instance, the target molecule has a propyl substituent on the β carbon and might therefore be prepared from 2-methyl-2-cyclopentenone by reaction with lithium dipropylcopper.

Solution

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?



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 19.17). In addition, aldehydes show two characteristic C–H absorptions in the range 2720 to 2820 cm^{-1} .

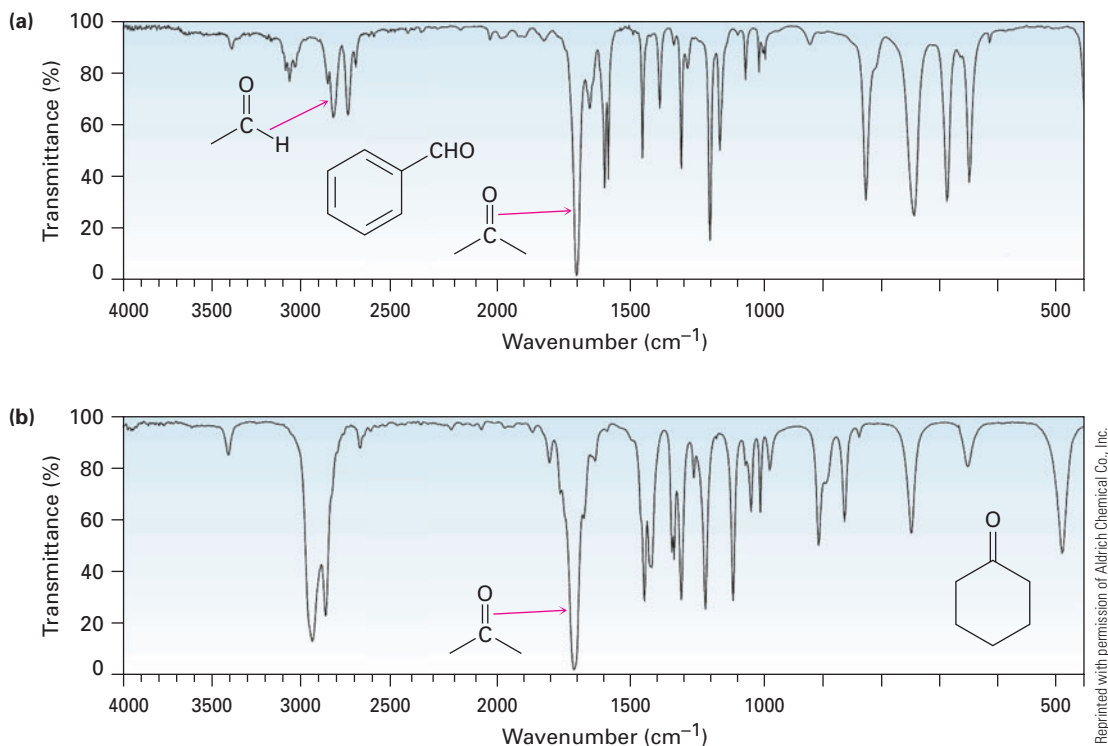


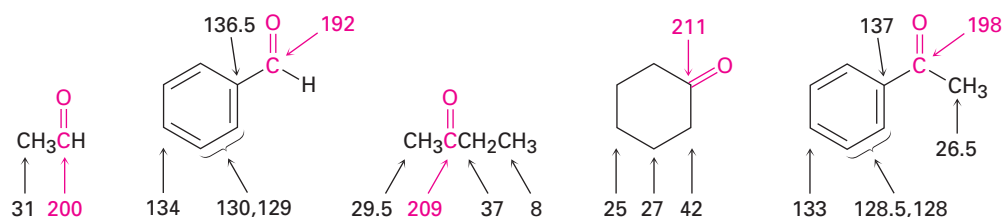
Figure 19.17 Infrared spectra of (a) benzaldehyde and (b) cyclohexanone.

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 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.

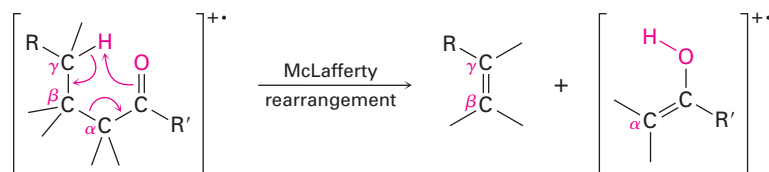
Hydrogens on the carbon next to a carbonyl group are slightly deshielded and normally absorb near 2.0 to 2.3 δ . The acetaldehyde methyl group in Figure 19.18, for instance, absorbs at 2.20 δ . Methyl ketones are particularly distinctive because they always show a sharp three-proton singlet near 2.1 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.

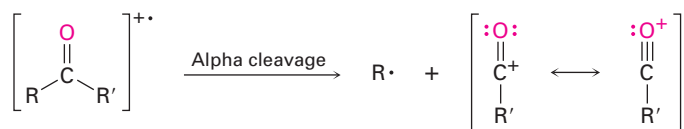


Mass Spectrometry

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, a so-called 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 19.19. 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 $[\text{CH}_3\text{CO}]^+$ fragment with $m/z = 43$.

Fred Warren McLafferty

Fred Warren McLafferty (1923–) was born in Evanston, Illinois, and received his Ph.D. in 1950 at Cornell University. He was a scientist at the Dow Chemical Company from 1950 to 1964 before becoming professor of chemistry at Purdue University. In 1968, he returned to Cornell University as professor.

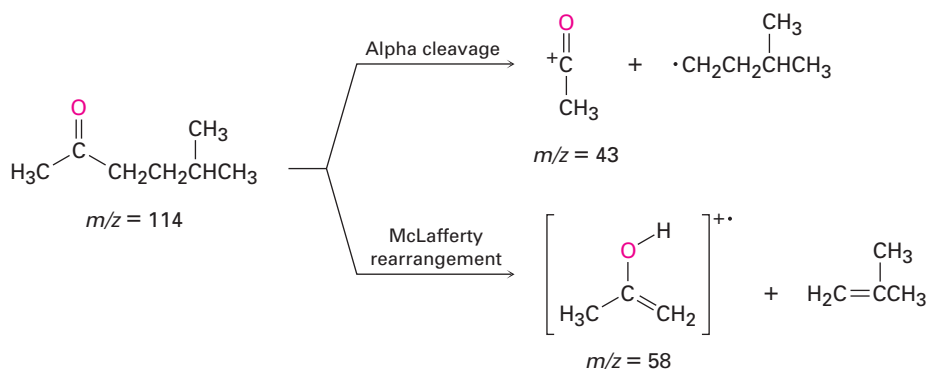
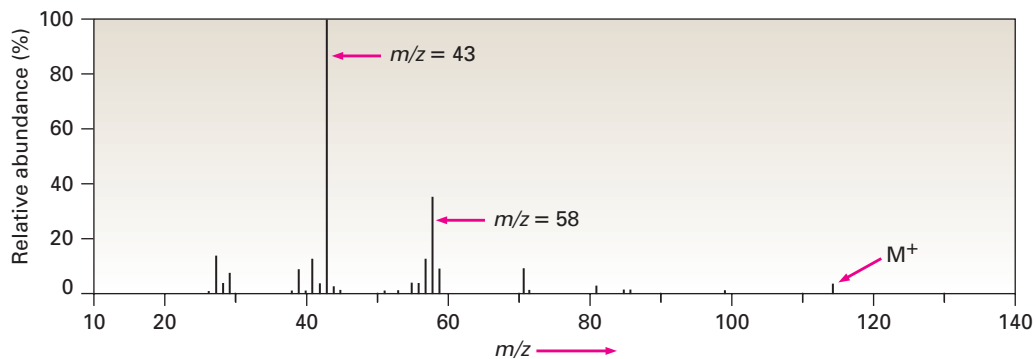
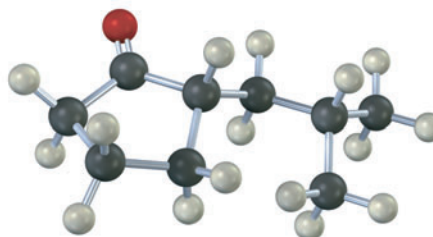


Figure 19.19 Mass spectrum of 5-methyl-2-hexanone. The peak at $m/z = 58$ is due to McLafferty rearrangement. The abundant peak at $m/z = 43$ is due to α cleavage at the more highly substituted side of the carbonyl group. Note that the peak due to the molecular ion is very small.

Problem 19.25 How might you use mass spectrometry to distinguish between the following pairs of isomers?

- 3-Methyl-2-hexanone and 4-methyl-2-hexanone
- 3-Heptanone and 4-heptanone
- 2-Methylpentanal and 3-methylpentanal

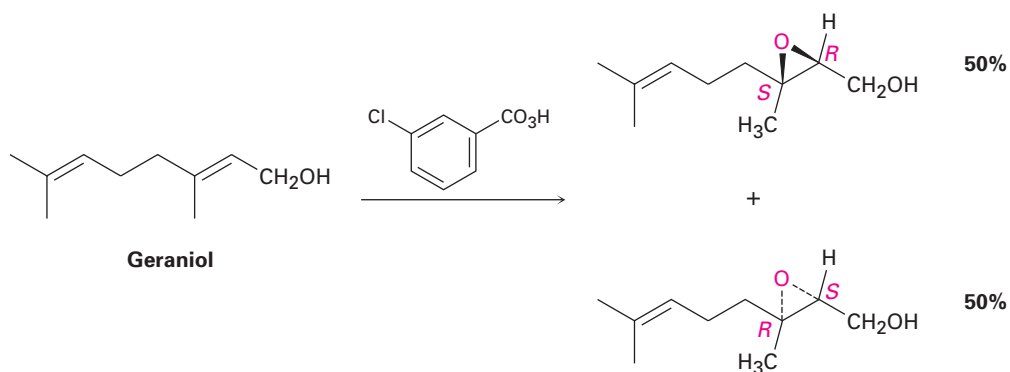
Problem 19.26 Tell the prominent IR absorptions and mass spectral peaks you would expect for the following compound:



Focus On . . .

Enantioselective Synthesis

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 a *single* 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—exactly 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

(continued)

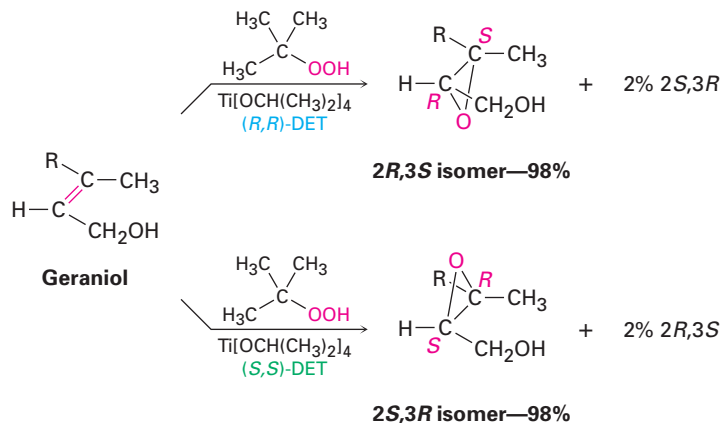
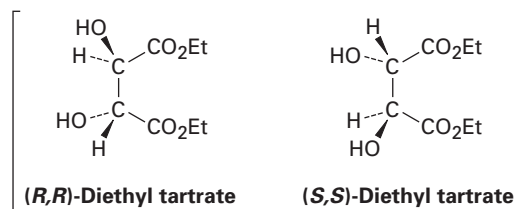


© Charles O'Rear/Corbis

A substance made from the tartaric acid found at the bottom of this wine vat catalyzes enantioselective reactions.

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.

Among the many enantioselective reactions now known, one of the most general is the so-called Sharpless epoxidation, in which an allylic alcohol, such as geraniol, is treated with *tert*-butyl hydroperoxide, $(\text{CH}_3)_3\text{C}-\text{OOH}$, in the presence of titanium tetrakisopropoxide and diethyl tartrate (DET) as a chiral auxiliary reagent. When the *(R,R)* tartrate is used, geraniol is converted into its *2R,3S* epoxide with 98% selectivity, whereas use of the *(S,S)* tartrate gives the *2S,3R* 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% *2R,3S* plus 2% *2S,3R*) 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.



acetal [R₂C(OR')₂], 717
 acyl group, 697
 1,2-addition, 725
 1,4-addition, 725
 aldehyde (RCHO), 695
 betaine, 720
 Cannizzaro reaction, 724
 carbanion, 708
 conjugate addition, 725
 cyanohydrin [RCH(OH)C≡N], 707
 enamine (R₂N—CR=CR₂), 710
 hemiacetal, 717
 imine (R₂C=NR), 710
 ketone (R₂C=O), 695
 McLafferty rearrangement, 732
 nucleophilic addition reaction, 702
 Schiff base, 710
 Wittig reaction, 720
 Wolff–Kishner reaction, 715
 ylide, 720

SUMMARY AND KEY WORDS

Aldehydes and ketones are among the most important of all compounds, both in biochemistry and in the chemical industry. 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 or by addition of diorganocopper reagents to acid chlorides.

The **nucleophilic addition reaction** is the most common reaction of aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by NaBH₄ or LiAlH₄ to yield secondary and primary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones also gives alcohols (tertiary and secondary, respectively), and addition of HCN yields **cyanohydrins**. Primary amines add to carbonyl compounds yielding **imines**, and secondary 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. Phosphoranes add to aldehydes and ketones to give alkenes (the **Wittig reaction**) in which the new C=C bond in the product is exactly where the C=O bond was in the starting material.

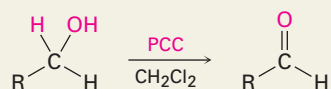
α,β -Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4-addition**. Particularly useful is the reaction with a diorganocopper reagent, which results in the addition of an alkyl, aryl, or alkenyl group to the double bond.

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. ¹³C 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**.

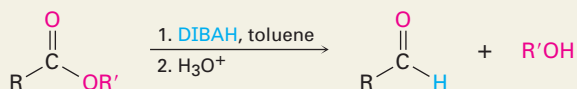
SUMMARY OF REACTIONS

1. Preparation of aldehydes (Section 19.2)

(a) Oxidation of primary alcohols (Section 17.7)

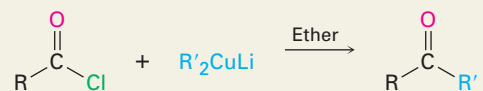


(b) Partial reduction of esters (Section 19.2)



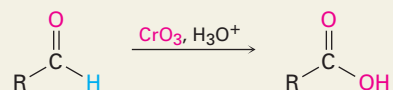
2. Preparation of ketones (Section 19.2)

Diorganocopper reaction with acid chlorides



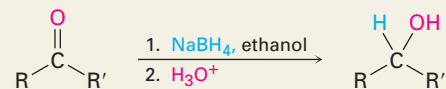
3. Reactions of aldehydes (Section 19.3)

Oxidation to give carboxylic acids

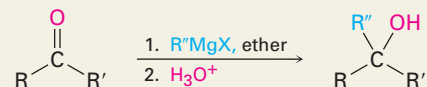


4. Nucleophilic addition reactions of aldehydes and ketones

(a) Addition of hydride: alcohols (Section 19.7)



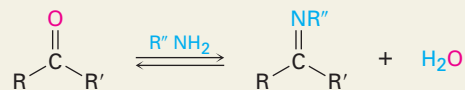
(b) Addition of Grignard reagents: alcohols (Section 19.7)



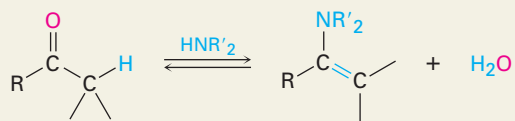
(c) Addition of HCN: cyanohydrins (Section 19.6)



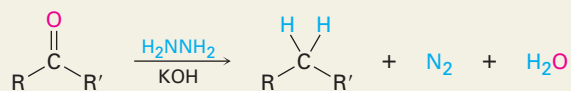
(d) Addition of primary amines: imines (Section 19.8)



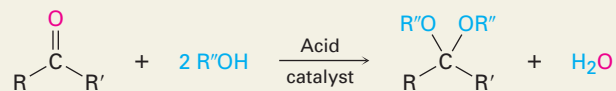
(e) Addition of secondary amines: enamines (Section 19.8)



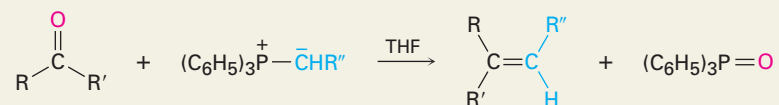
(f) Wolff–Kishner reaction (Section 19.9)



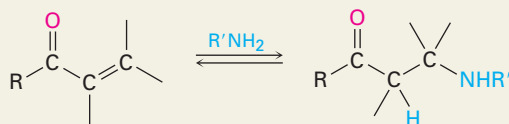
(g) Addition of alcohols: acetals (Section 19.10)



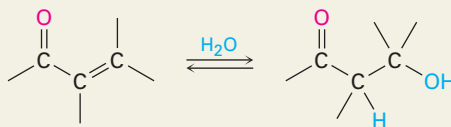
(h) Addition of phosphorus ylides: Wittig reaction (Section 19.11)

5. Conjugate additions to α,β -unsaturated aldehydes and ketones (Section 19.13)

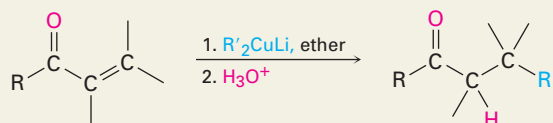
(a) Conjugate addition of amines



(b) Conjugate addition of water



(c) Conjugate addition of alkyl groups: diorganocopper reaction



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

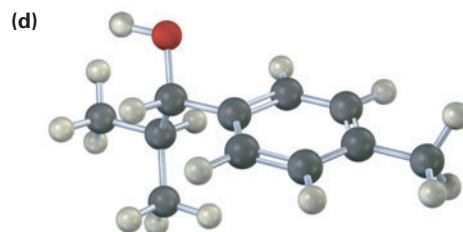
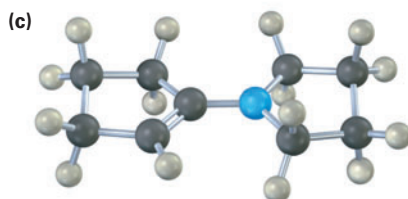
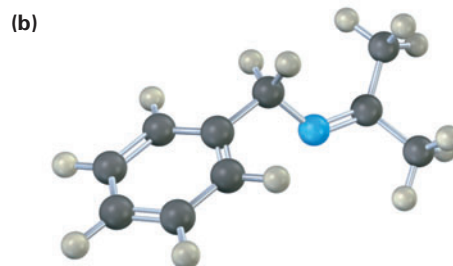
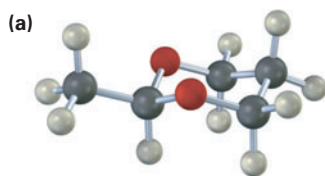
 Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

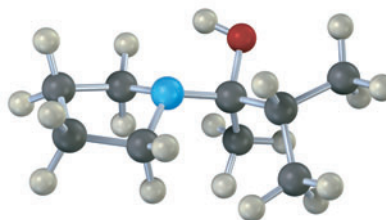
VISUALIZING CHEMISTRY

(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.

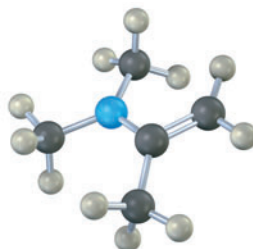


19.28 ■ The following molecular model represents a tetrahedral intermediate resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the structure of the final product when the nucleophilic addition reaction is complete.



■ Assignable in OWL

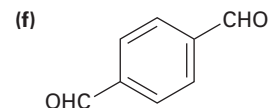
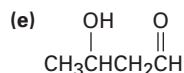
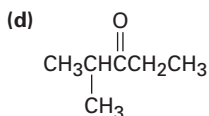
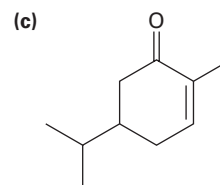
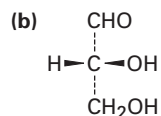
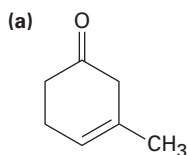
- 19.29** The enamine prepared from acetone and dimethylamine is shown here in its lowest-energy form.
- What is the geometry and hybridization of the nitrogen atom?
 - What orbital on nitrogen holds the lone pair of electrons?
 - What is the geometric relationship between the p orbitals of the double bond and the nitrogen orbital that holds the lone pair? Why do you think this geometry represents the minimum energy?



ADDITIONAL PROBLEMS

- 19.30** ■ Draw structures corresponding to the following names:
- Bromoacetone
 - (*S*)-2-Hydroxypropanal
 - 2-Methyl-3-heptanone
 - (2*S*,3*R*)-2,3,4-Trihydroxybutanal
 - 2,2,4,4-Tetramethyl-3-pentanone
 - 4-Methyl-3-penten-2-one
 - Butanedial
 - 3-Phenyl-2-propenal
 - 6,6-Dimethyl-2,4-cyclohexadienone
 - 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 structures:



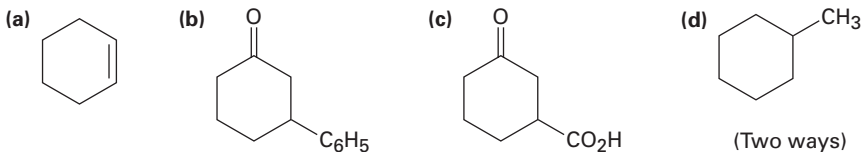
- 19.33** Give structures that fit the following descriptions:

- An α,β -unsaturated ketone, C_6H_8O
- An α -diketone
- An aromatic ketone, $C_9H_{10}O$
- A diene aldehyde, C_7H_8O

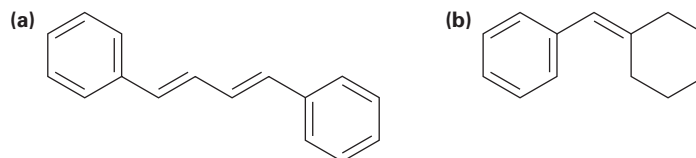
19.34 ■ Predict the products of the reaction of (i) phenylacetaldehyde and (ii) acetophenone with the following reagents:

- | | |
|--|--|
| (a) NaBH_4 , then H_3O^+ | (b) Tollens' reagent |
| (c) NH_2OH , HCl catalyst | (d) CH_3MgBr , then H_3O^+ |
| (e) 2 CH_3OH , HCl catalyst | (f) H_2NNH_2 , KOH |
| (g) $(\text{C}_6\text{H}_5)_3\text{P}=\text{CH}_2$ | (h) HCN, KCN |

19.35 ■ How would you prepare the following substances from 2-cyclohexenone? More than one step may be required.



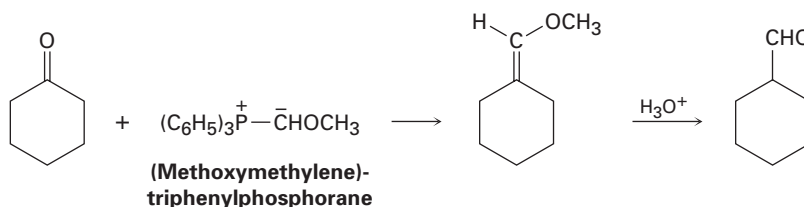
19.36 ■ Show how the Wittig reaction might be used to prepare the following alkenes. Identify the alkyl halide and the carbonyl components that would be used.



19.37 ■ How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

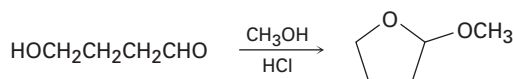
- | | |
|--------------------------|----------------------|
| (a) 2-Pentanol | (b) 1-Butanol |
| (c) 1-Phenylcyclohexanol | (d) Diphenylmethanol |

19.38 Aldehydes can be prepared by the Wittig reaction using (methoxymethylene)-triphenylphosphorane as the Wittig reagent and then hydrolyzing the product with acid. For example,

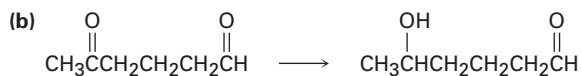


- (a) How would you prepare the necessary phosphorane?
(b) Propose a mechanism for the hydrolysis step.

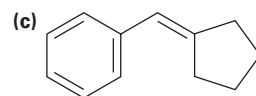
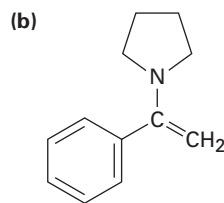
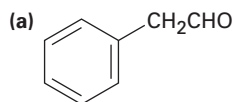
19.39 When 4-hydroxybutanal is treated with methanol in the presence of an acid catalyst, 2-methoxytetrahydrofuran is formed. Explain.



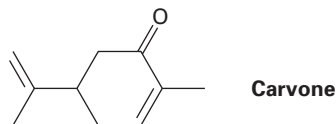
19.40 ■ How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 19.5 that aldehydes are more reactive than ketones toward nucleophilic addition.)



19.41 ■ How would you synthesize the following substances from benzaldehyde and any other reagents needed?



19.42 ■ Carvone is the major constituent of spearmint oil. What products would you expect from reaction of carvone with the following reagents?



- | | |
|--|---|
| (a) $(\text{CH}_3)_2\text{Cu}^- \text{Li}^+$, then H_3O^+ | (b) LiAlH_4 , then H_3O^+ |
| (c) CH_3NH_2 | (d) $\text{C}_6\text{H}_5\text{MgBr}$, then H_3O^+ |
| (e) H_2/Pd | (f) CrO_3 , H_3O^+ |
| (g) $(\text{C}_6\text{H}_5)_3\text{P}^+\text{CH}^-\text{CH}_3$ | (h) $\text{HOCH}_2\text{CH}_2\text{OH}$, HCl |

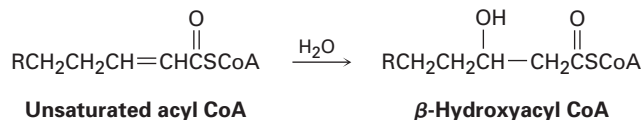
19.43 The $\text{S}_{\text{N}}2$ reaction of (dibromomethyl)benzene, $\text{C}_6\text{H}_5\text{CHBr}_2$, with NaOH yields benzaldehyde rather than (dihydroxymethyl)benzene, $\text{C}_6\text{H}_5\text{CH}(\text{OH})_2$. Explain.

19.44 Reaction of 2-butanone with HCN yields a chiral product. What stereochemistry does the product have? Is it optically active?

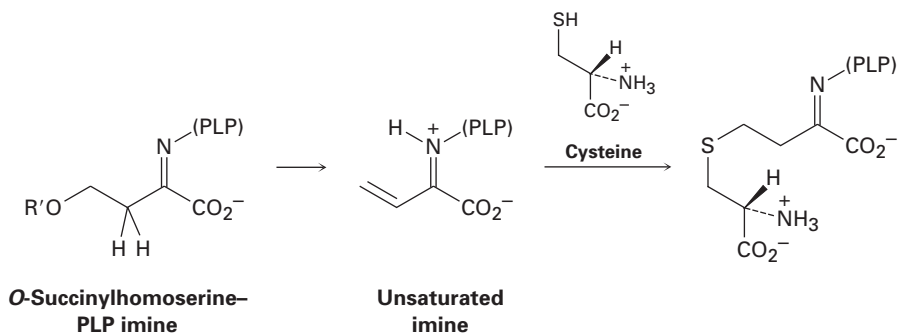
19.45 ■ How would you synthesize the following compounds from cyclohexanone?

- | | |
|-------------------------------------|------------------------------|
| (a) 1-Methylcyclohexene | (b) 2-Phenylcyclohexanone |
| (c) <i>cis</i> -1,2-Cyclohexanediol | (d) 1-Cyclohexylcyclohexanol |

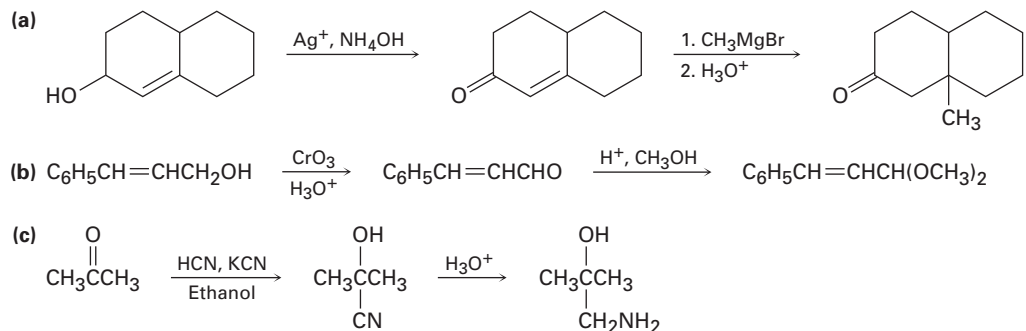
19.46 One of the steps in the metabolism of fats is the reaction of an unsaturated acyl CoA with water to give a β -hydroxyacyl CoA. Propose a mechanism.



19.47 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?



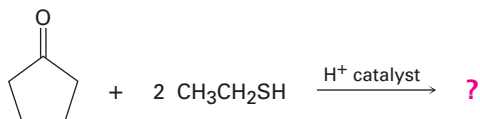
19.48 Each of the following reaction schemes contains one or more flaws. What is wrong in each case? How would you correct each scheme?



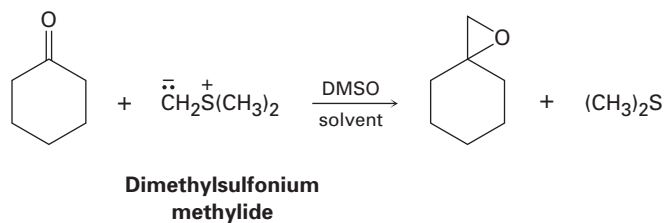
19.49 6-Methyl-5-hepten-2-one is a constituent of lemongrass oil. How could you synthesize this substance from methyl 4-oxopentanoate?



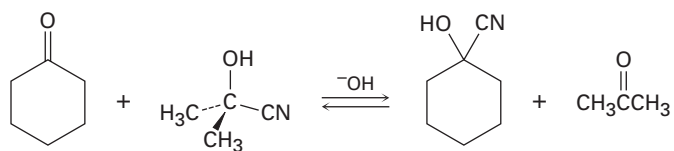
19.50 Aldehydes and ketones react with thiols to yield *thioacetals* just as they react with alcohols to yield acetals. Predict the product of the following reaction, and propose a mechanism:



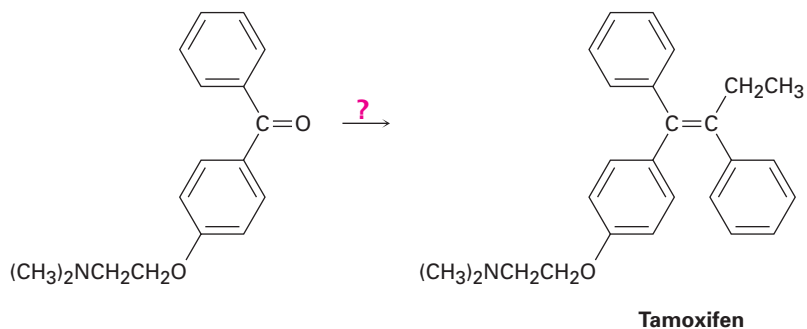
- 19.51** ■ Ketones react with dimethylsulfonium methylide to yield epoxides. Suggest a mechanism for the reaction.



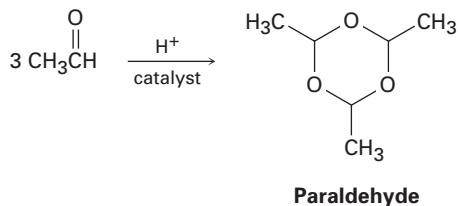
- 19.52** ■ When cyclohexanone is heated in the presence of a large amount of acetone cyanohydrin and a small amount of base, cyclohexanone cyanohydrin and acetone are formed. Propose a mechanism.



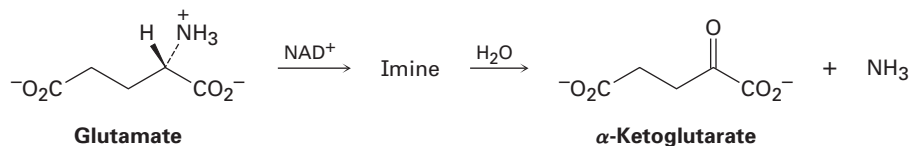
- 19.53** Tamoxifen is a drug used in the treatment of breast cancer. How would you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?



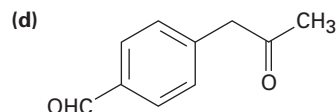
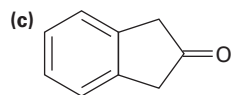
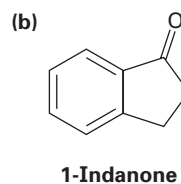
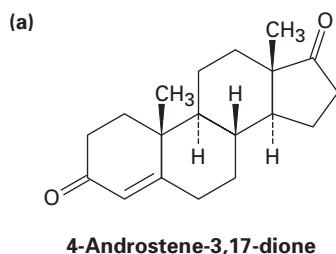
- 19.54** Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism for the reaction.



- 19.60** ■ 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.

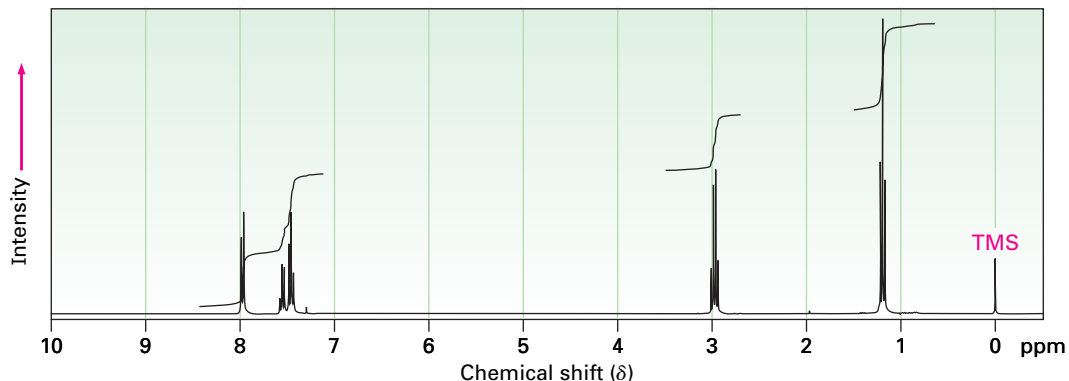


- 19.61** At what position would you expect to observe IR absorptions for the following molecules?

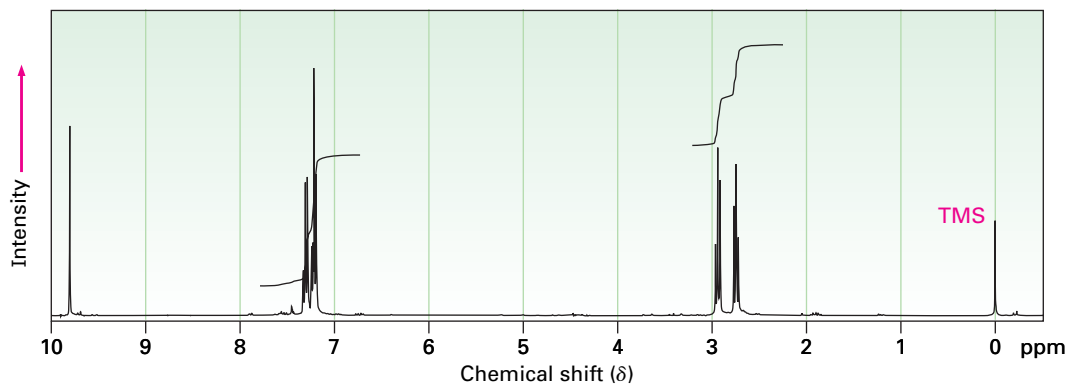


- 19.62** Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What possible structures are there for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{-1} , what is its structure?
- 19.63** ■ Compound A, MW = 86, shows an IR absorption at 1730 cm^{-1} and a very simple ^1H NMR spectrum with peaks at $9.7\ \delta$ (1 H, singlet) and $1.2\ \delta$ (9 H, singlet). Propose a structure for A.
- 19.64** ■ Compound B is isomeric with A (Problem 19.63) and shows an IR peak at 1715 cm^{-1} . The ^1H NMR spectrum of B has peaks at $2.4\ \delta$ (1 H, septet, $J = 7\text{ Hz}$), $2.1\ \delta$ (3 H, singlet), and $1.2\ \delta$ (6 H, doublet, $J = 7\text{ Hz}$). What is the structure of B?

- 19.65** ■ The ^1H NMR spectrum shown is that of a compound with formula $\text{C}_9\text{H}_{10}\text{O}$. 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?

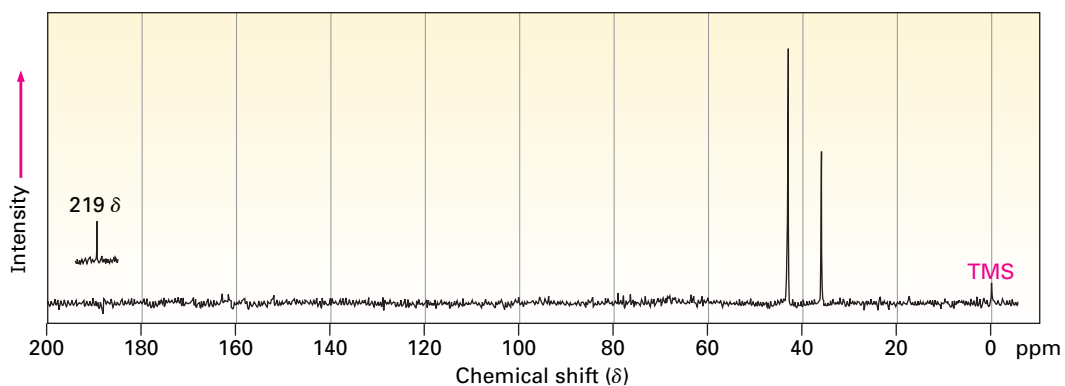


- 19.66** The ^1H NMR spectrum shown is that of a compound isomeric with the one in Problem 19.65. This isomer has an IR absorption at 1730 cm^{-1} . Propose a structure. [Note: Aldehyde protons (CHO) often show low coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]



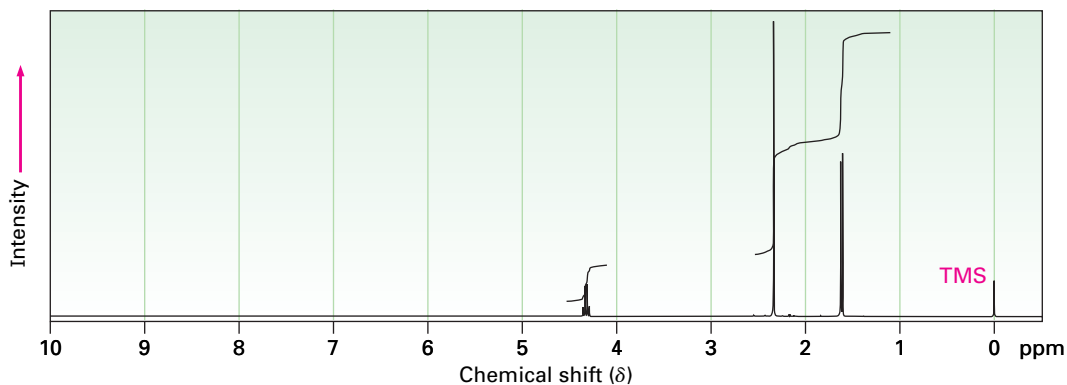
- 19.67** ■ Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1° , 2° , 3° , or 4°) have been assigned by DEPT-NMR.
- $\text{C}_6\text{H}_{12}\text{O}$; IR: 1715 cm^{-1} ; ^{13}C NMR: $8.0\ \delta$ (1°), $18.5\ \delta$ (1°), $33.5\ \delta$ (2°), $40.6\ \delta$ (3°), $214.0\ \delta$ (4°)
 - $\text{C}_5\text{H}_{10}\text{O}$; IR: 1730 cm^{-1} ; ^{13}C NMR: $22.6\ \delta$ (1°), $23.6\ \delta$ (3°), $52.8\ \delta$ (2°), $202.4\ \delta$ (3°)
 - $\text{C}_6\text{H}_8\text{O}$; IR: 1680 cm^{-1} ; ^{13}C NMR: $22.9\ \delta$ (2°), $25.8\ \delta$ (2°), $38.2\ \delta$ (2°), $129.8\ \delta$ (3°), $150.6\ \delta$ (3°), $198.7\ \delta$ (4°)

19.68 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.

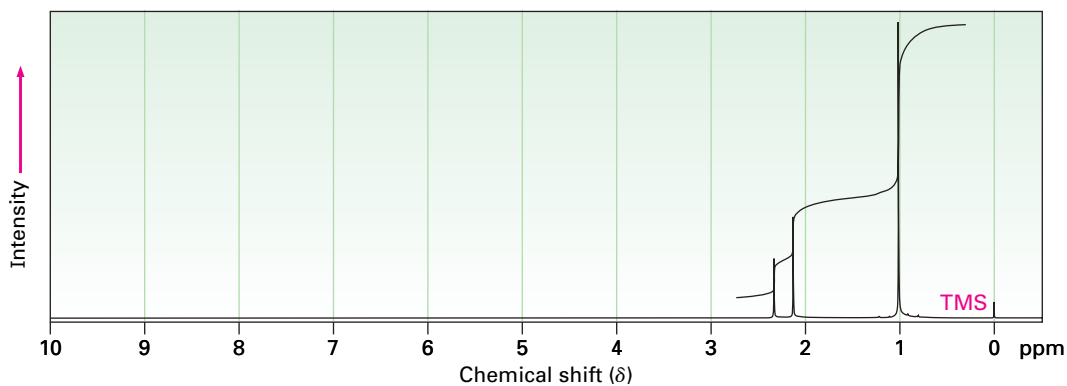


19.69 Propose structures for ketones or aldehydes that have the following 1H NMR spectra:

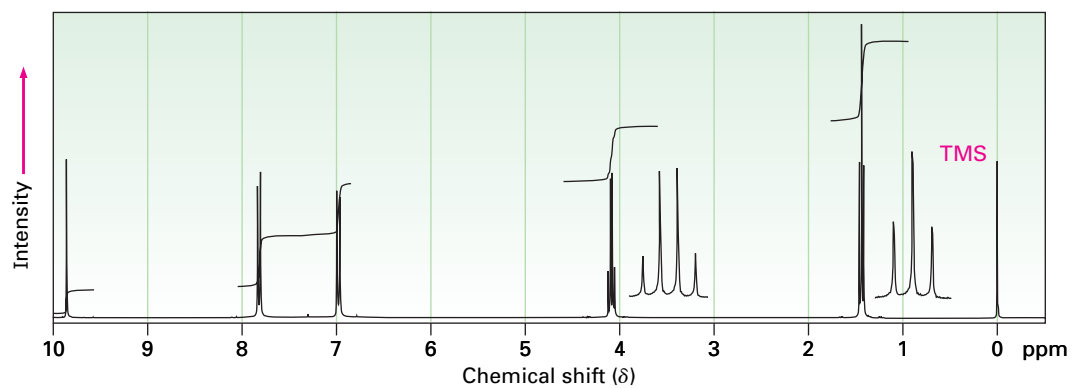
(a) C_4H_7ClO
IR: 1715 cm^{-1}



(b) $C_7H_{14}O$
IR: 1710 cm^{-1}

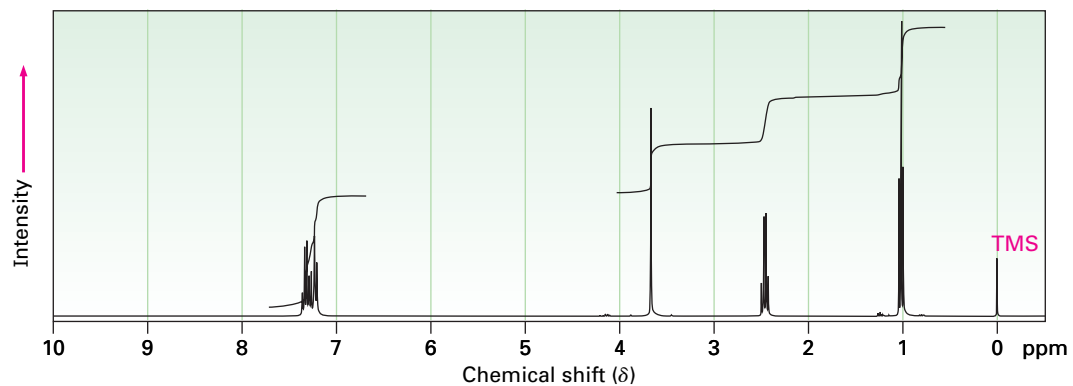


(c) $C_9H_{10}O_2$
IR: 1695 cm^{-1}

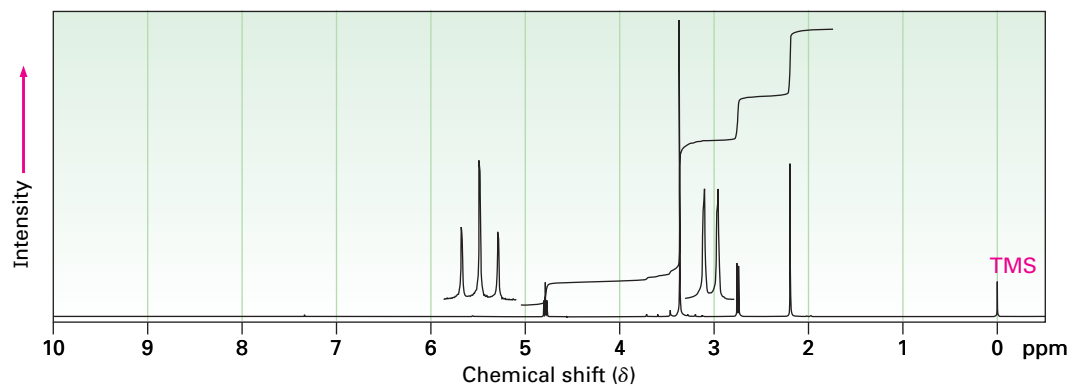


19.70 Propose structures for ketones or aldehydes that have the following 1H NMR spectra.

(a) $C_{10}H_{12}O$
IR: 1710 cm^{-1}

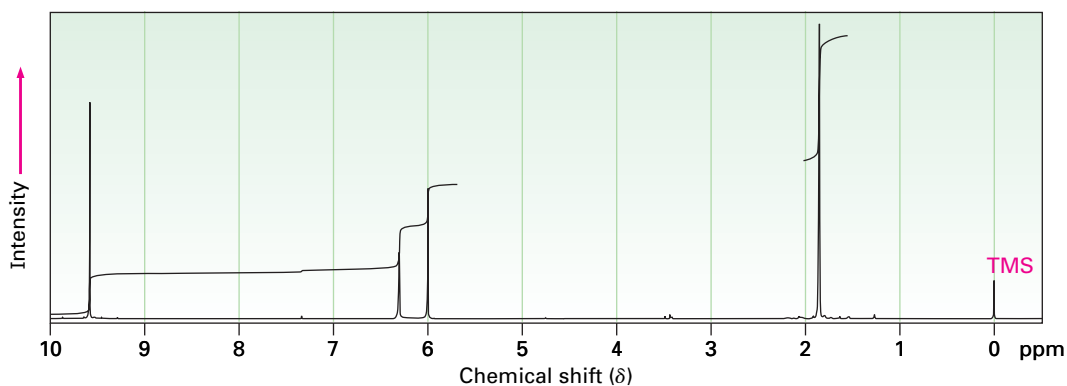


(b) $C_6H_{12}O_3$
IR: 1715 cm^{-1}

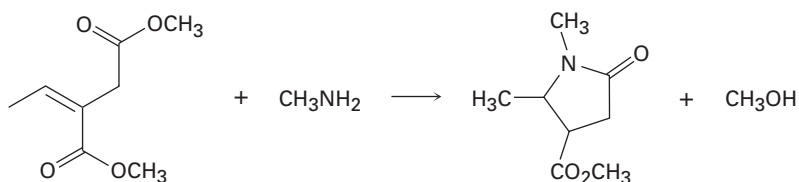


■ Assignable in OWL

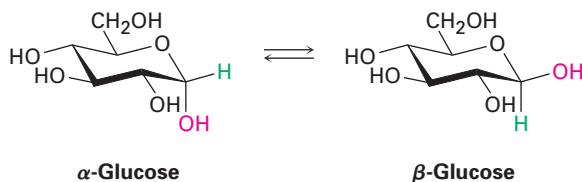
(c) C_4H_6O
IR: 1690 cm^{-1}



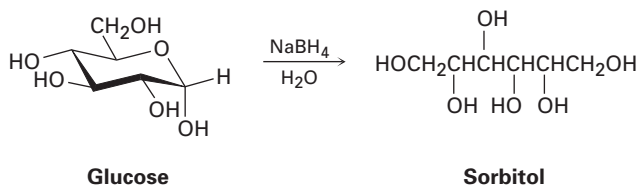
19.71 Primary amines react with esters to yield amides: $RCO_2R' + R''NH_2 \rightarrow RCONHR'' + R'OH$. Propose a mechanism for the following reaction of an α,β -unsaturated ester.



19.72 When crystals of pure α -glucose are dissolved in water, isomerization slowly occurs to produce β -glucose. Propose a mechanism for the isomerization.



19.73 When glucose (Problem 19.72) is treated with $NaBH_4$, reaction occurs to yield *sorbitol*, a polyalcohol commonly used as a food additive. Show how this reduction occurs.



20

Carboxylic Acids and Nitriles

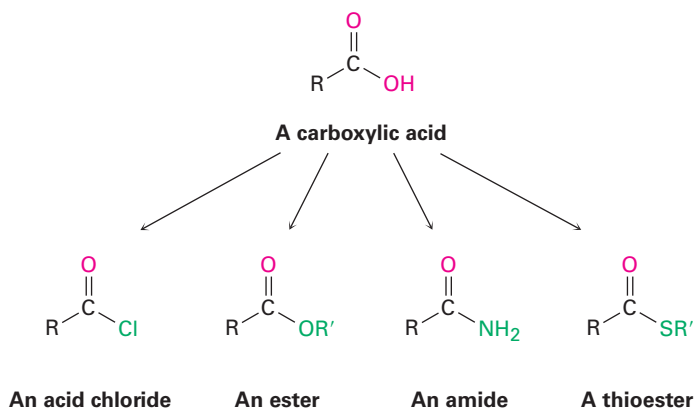
Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at www.thomsonedu.com for online self-study and interactive tutorials based on your level of understanding.

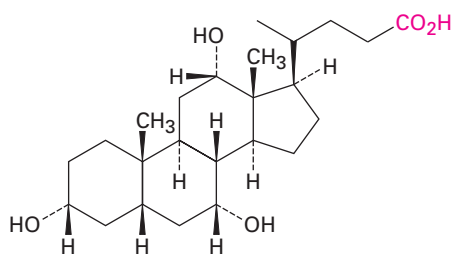


Online homework for this chapter may be assigned in Organic OWL.

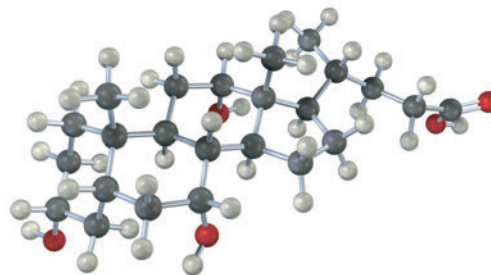
Carboxylic acids, RCO_2H , occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous *acyl derivatives* such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways. We'll look both at acids and at their close relatives, *nitriles* ($\text{RC}\equiv\text{N}$), in this chapter and at acyl derivatives in the next chapter.



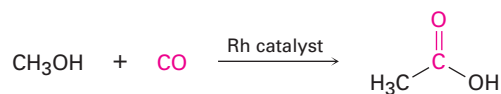
A great many carboxylic acids are found in nature: acetic acid, $\text{CH}_3\text{CO}_2\text{H}$, is the chief organic component of vinegar; butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$, 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, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, a biological precursor of fats and vegetable oils.



Cholic acid



Approximately 2.5 million tons of acetic acid is produced each year in the United States 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.



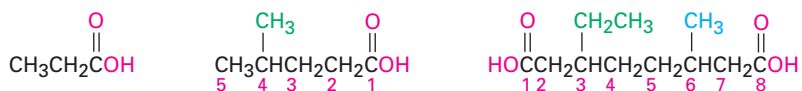
WHY THIS CHAPTER?

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. In this chapter, we'll look both at acids and at their close relatives, *nitriles* ($\text{RC}\equiv\text{N}$). In the next chapter, we'll look at acyl derivatives.

20.1 Naming Carboxylic Acids and Nitriles

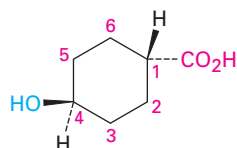
Carboxylic Acids, RCO_2H

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 $-\text{CO}_2\text{H}$ carbon atom is numbered C1.

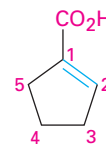


Propanoic acid 4-Methylpentanoic acid 3-Ethyl-6-methyloctanedioic acid

Compounds that have a $-\text{CO}_2\text{H}$ 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

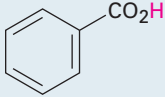
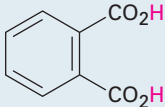


1-Cyclopentene-1-carboxylic acid

ThomsonNOW Click *Organic Interactive* to use a web-based palette to draw structures of carboxylic acids based on their IUPAC names.

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. 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 common names used for acyl groups derived from the parent acids. Except for the small handful at the top of Table 20.1, acyl groups are named by changing the *-ic acid* or *-oic acid* ending to *-oyl*.

Table 20.1 Common Names of Some Carboxylic Acids and Acyl Groups

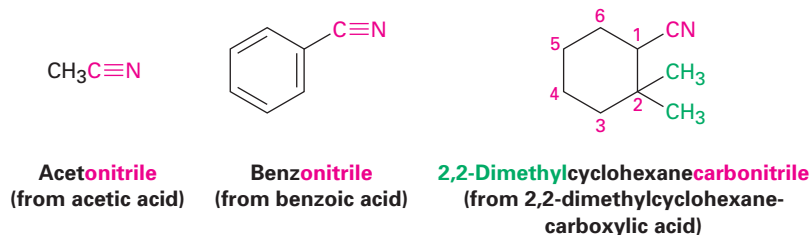
Structure	Name	Acyl group
HCO_2H	Formic	Formyl
$\text{CH}_3\text{CO}_2\text{H}$	Acetic	Acetyl
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	Propionic	Propionyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Butyric	Butyryl
$\text{HO}_2\text{CCO}_2\text{H}$	Oxalic	Oxalyl
$\text{HO}_2\text{CCH}_2\text{CO}_2\text{H}$	Malonic	Malonyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Succinic	Succinyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Glutaric	Glutaryl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Adipic	Adipoyl
$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	Acrylic	Acryloyl
$\text{HO}_2\text{CCH}=\text{CHCO}_2\text{H}$	Maleic (cis)	Maleoyl
	Fumaric (trans)	Fumaroyl
$\text{HOCH}_2\text{CO}_2\text{H}$	Glycolic	Glycoloyl
$\begin{array}{c} \text{OH} \\ \\ \text{CH}_3\text{CHCO}_2\text{H} \end{array}$	Lactic	Lactoyl
$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{CCO}_2\text{H} \end{array}$	Pyruvic	Pyruvoyl
$\begin{array}{c} \text{OH} \\ \\ \text{HOCH}_2\text{CHCO}_2\text{H} \end{array}$	Glyceric	Glyceroyl
$\begin{array}{c} \text{OH} \\ \\ \text{HO}_2\text{CCHCH}_2\text{CO}_2\text{H} \end{array}$	Malic	Maloyl
$\begin{array}{c} \text{O} \\ \\ \text{HO}_2\text{CCCH}_2\text{CO}_2\text{H} \end{array}$	Oxaloacetic	Oxaloacetyl
	Benzoic	Benzoyl
	Phthalic	Phthaloyl

Nitriles, $\text{RC}\equiv\text{N}$

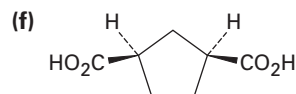
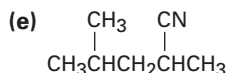
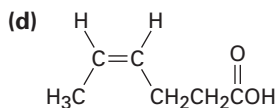
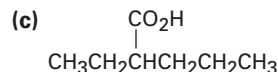
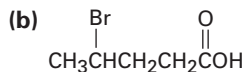
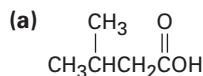
Compounds containing the $-\text{C}\equiv\text{N}$ functional group are called **nitriles** and undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.



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.



Problem 20.1 Give IUPAC names for the following compounds:



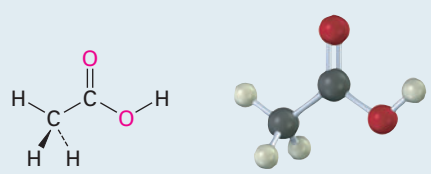
Problem 20.2 Draw structures corresponding to the following IUPAC names:

- | | |
|--|-----------------------------------|
| (a) 2,3-Dimethylhexanoic acid | (b) 4-Methylpentanoic acid |
| (c) <i>trans</i> -1,2-Cyclobutanedicarboxylic acid | (d) <i>o</i> -Hydroxybenzoic acid |
| (e) (9Z,12Z)-9,12-Octadecadienoic acid | (f) 2-Pentenenitrile |

20.2 Structure and Properties of Carboxylic Acids

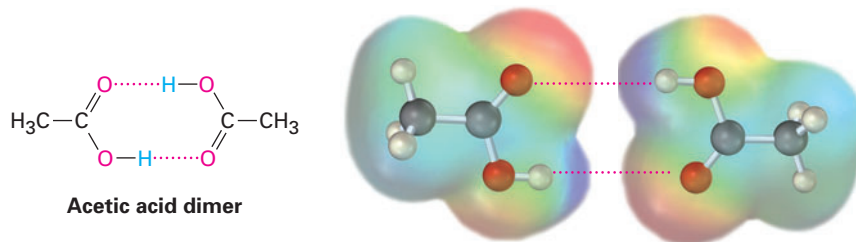
Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2 -hybridized, and carboxylic acid groups are therefore planar with $\text{C}-\text{C}=\text{O}$ and $\text{O}=\text{C}-\text{O}$ bond angles of approximately 120° (Table 20.2).

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

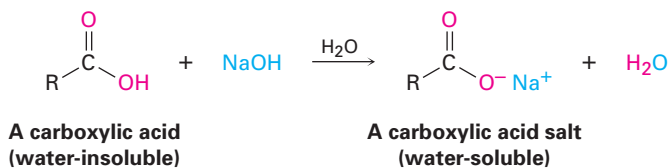
Table 20.2 Physical Parameters for Acetic Acid


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

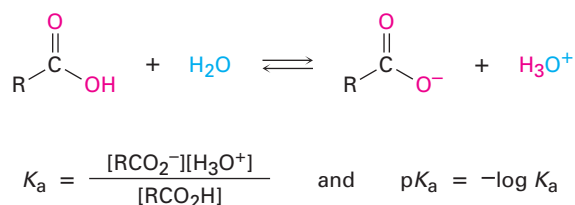
alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.



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 NaHCO₃ to give metal carboxylate salts, RCO₂[−] 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.



Like other Brønsted–Lowry acids discussed in Section 2.7, carboxylic acids dissociate slightly in dilute aqueous solution to give H₃O⁺ and the corresponding carboxylate anions, RCO₂[−]. The extent of dissociation is given by an acidity constant, K_a.

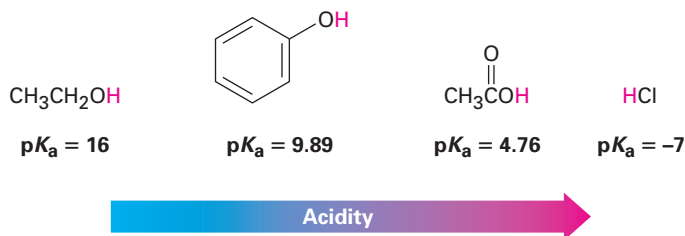


A list of K_a values for various carboxylic acids is given in Table 20.3. For most, K_a is approximately 10^{-4} to 10^{-5} . Acetic acid, for instance, has $K_a = 1.75 \times 10^{-5}$, which corresponds to a pK_a of 4.76. In practical terms, a K_a value near 10^{-5} means that only about 0.1% of the 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

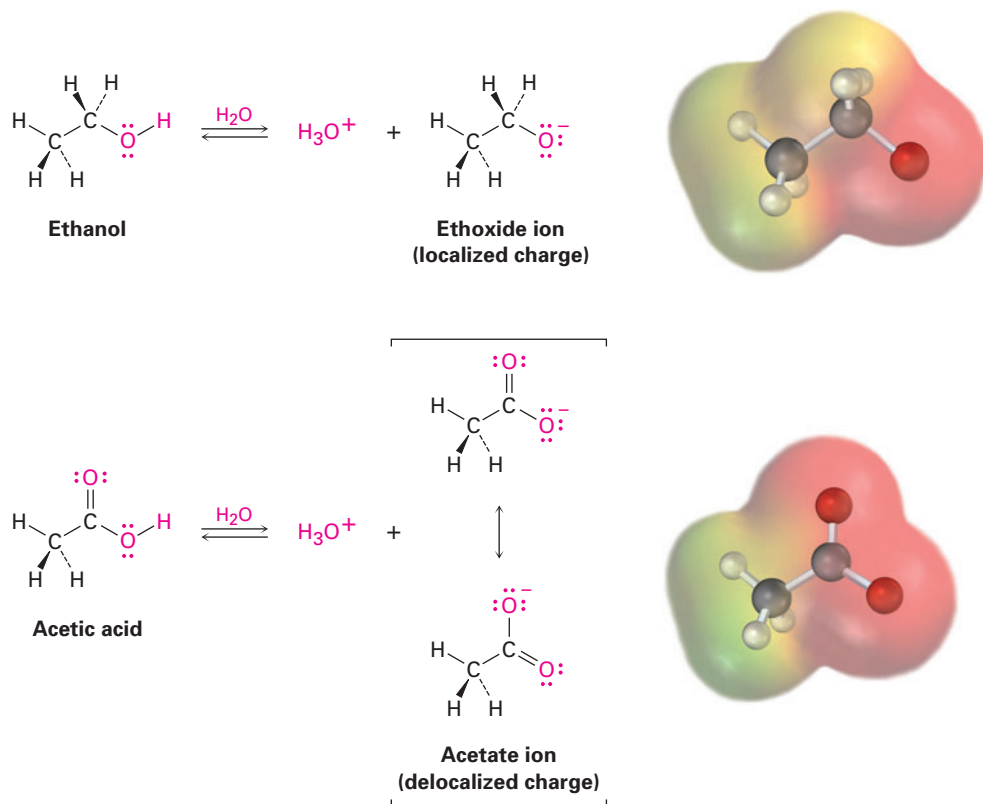
Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C=CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	
CH_3CH_2OH (ethanol)	(1.00×10^{-16})	(16.00)	

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} .



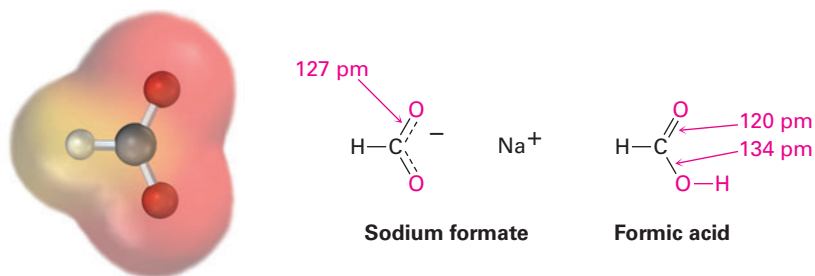
Why are carboxylic acids so much more acidic than alcohols, even though both contain $-OH$ groups? An alcohol dissociates to give an alkoxide ion, in which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge 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.



Active 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. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.

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 $\text{C}=\text{O}$ bond (120 pm) and $\text{C}-\text{O}$ bond (134 pm) of formic acid. An electrostatic potential map of the formate ion also shows how the negative charge (red) is dispersed 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 $\text{pH} = 7.3$, 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 $\text{p}K_a$ value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using what is called the **Henderson–Hasselbalch equation**.

For any acid HA, we have

$$\begin{aligned} \text{p}K_a &= -\log \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} = -\log[\text{H}_3\text{O}^+] - \log \frac{[\text{A}^-]}{[\text{HA}]} \\ &= \text{pH} - \log \frac{[\text{A}^-]}{[\text{HA}]} \end{aligned}$$

which can be rearranged to give

$$\begin{aligned} \text{pH} &= \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]} && \text{Henderson–Hasselbalch equation} \\ \text{so } \log \frac{[\text{A}^-]}{[\text{HA}]} &= \text{pH} - \text{p}K_a \end{aligned}$$

This equation says that the logarithm of the concentration of dissociated acid $[\text{A}^-]$ divided by the concentration of undissociated acid $[\text{HA}]$ is equal to the pH of the solution minus the $\text{p}K_a$ of the acid. Thus, if we know both the pH of the solution and the $\text{p}K_a$ of the acid, we can calculate the ratio of $[\text{A}^-]$ to $[\text{HA}]$. Furthermore, when $\text{pH} = \text{p}K_a$, 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 $\text{pH} = 7.3$. According to Table 20.3, the $\text{p}K_a$ of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\begin{aligned} \log \frac{[\text{A}^-]}{[\text{HA}]} &= \text{pH} - \text{p}K_a = 7.3 - 4.76 = 2.54 \\ \frac{[\text{A}^-]}{[\text{HA}]} &= \text{antilog}(2.54) = 3.5 \times 10^2 \quad \text{so} \quad [\text{A}^-] = (3.5 \times 10^2) [\text{HA}] \end{aligned}$$

In addition, we know that

$$[\text{A}^-] + [\text{HA}] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives $[A^-] = 0.0010 \text{ M}$ and $[HA] = 3 \times 10^{-6} \text{ M}$. 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:

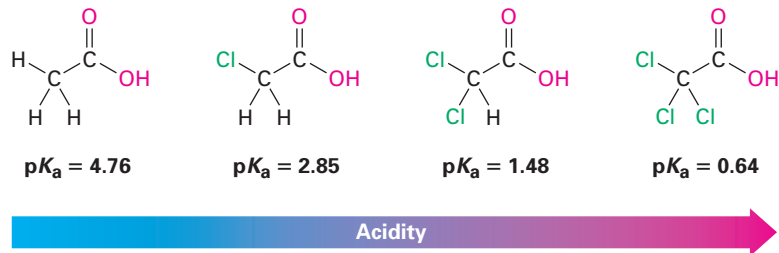
(a) 0.0010 M glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$; $\text{p}K_a = 3.83$) at $\text{pH} = 4.50$

(b) 0.0020 M propanoic acid ($\text{p}K_a = 4.87$) at $\text{pH} = 5.30$

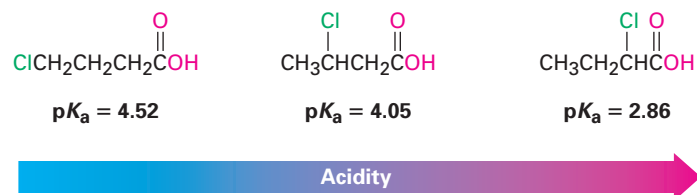
20.4 Substituent Effects on Acidity

The listing of $\text{p}K_a$ 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. An electron-withdrawing chlorine atom, for instance, makes chloroacetic acid ($K_a = 1.4 \times 10^{-3}$) approximately 80 times as strong as acetic acid; introduction of two chlorines makes dichloroacetic acid 3000 times as strong as acetic acid, and introduction of three chlorines makes trichloroacetic acid more than 12,000 times as strong.

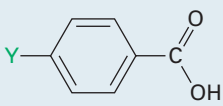



Because inductive effects operate through σ bonds and are dependent on distance, the effect of halogen substitution decreases as the substituent moves farther from the carboxyl. Thus, 2-chlorobutanoic acid has $\text{p}K_a = 2.86$, 3-chlorobutanoic acid has $\text{p}K_a = 4.05$, and 4-chlorobutanoic acid has $\text{p}K_a = 4.52$, similar to that of butanoic acid itself.

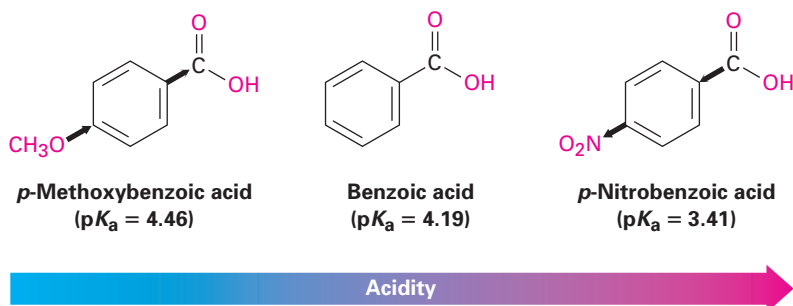


Substituent effects on acidity are also found in substituted benzoic acids. We saw during the discussion of electrophilic aromatic substitution in Section 16.4 that substituents on the aromatic ring dramatically affect reactivity. Aromatic rings with electron-donating groups are activated toward further 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).

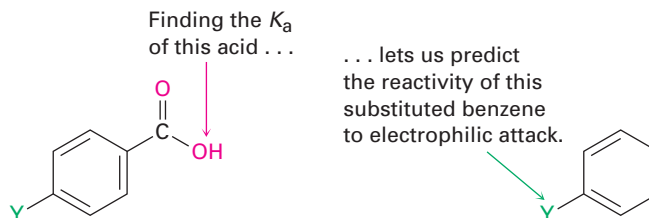
Table 20.4 Substituent Effects on Acidity of *p*-Substituted Benzoic Acids

			
	Y	$K_a \times 10^{-5}$	pK_a
 <p>Stronger acid</p>	-NO ₂	39	3.41
	-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
	-OCH ₃	3.5	4.46
	-OH	3.3	4.48
	Weaker acid		

As Table 20.4 shows, an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion, and an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion.



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 example.

**WORKED EXAMPLE 20.1**

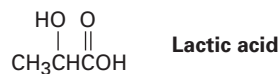
Predicting the Effect of a Substituent on the Reactivity of an Aromatic Ring toward Electrophilic Substitution

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.



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, $\text{HO}_2\text{C}-\text{CO}_2\text{H}$, the first ionization constant has $pK_{a1} = 1.2$ and the second ionization constant has $pK_{a2} = 4.2$. 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.

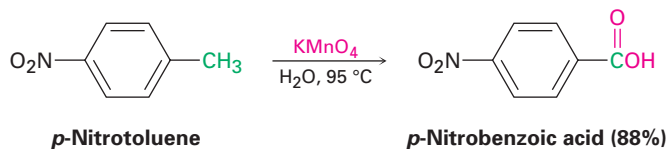
- (a) Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid
 (b) *p*-Nitrobenzoic acid, acetic acid, benzoic acid

20.5 Preparation of Carboxylic Acids

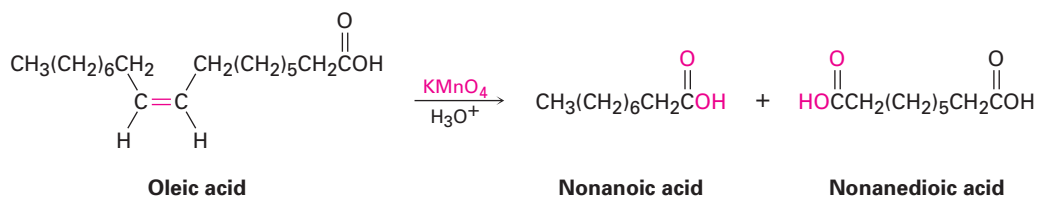
ThomsonNOW Click *Organic Interactive* to use your problem-solving skills to design syntheses of carboxylic acids.

Let's review briefly some of the methods for preparing carboxylic acids that we've seen in past chapters.

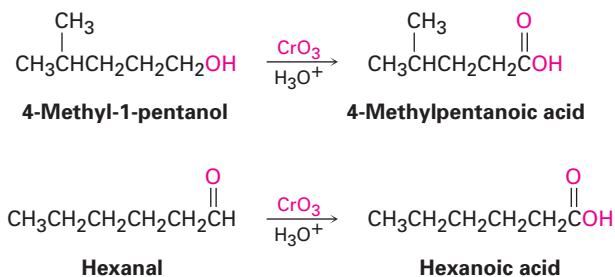
- Oxidation of a substituted alkylbenzene with KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ gives a substituted benzoic acid (Section 16.9). Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



- Oxidative cleavage of an alkene with KMnO_4 gives a carboxylic acid if the alkene has at least one vinylic hydrogen (Section 7.9).



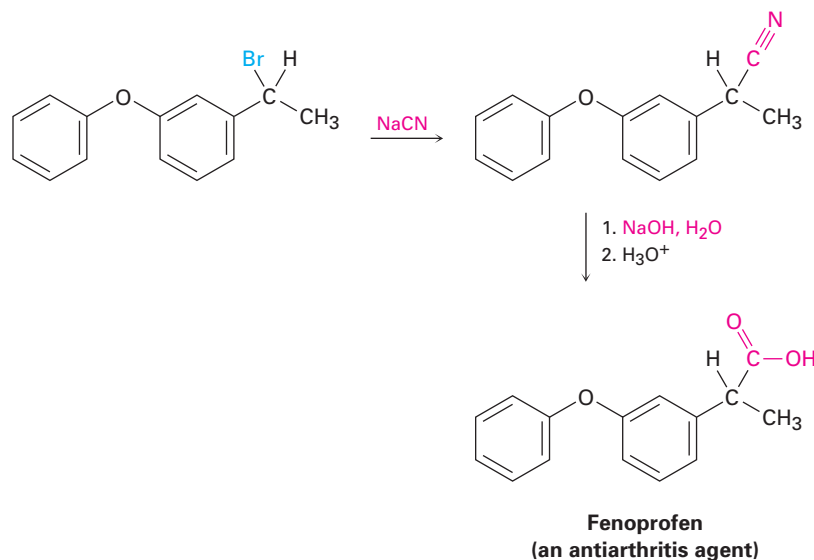
- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid (Sections 17.7 and 19.3). Primary alcohols are often oxidized with CrO_3 in aqueous acid, and aldehydes are oxidized with either acidic CrO_3 or basic silver oxide (Tollens' reagent).



Hydrolysis of Nitriles

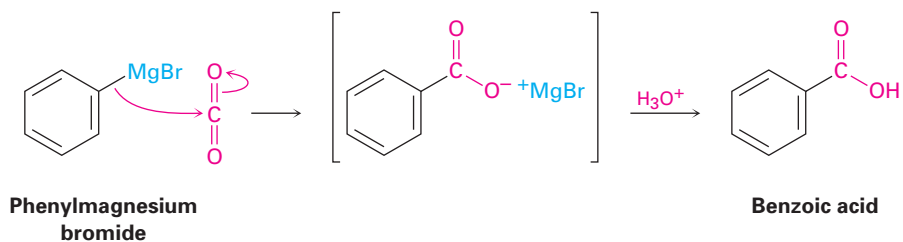
Carboxylic acids can be prepared from nitriles by reaction with hot aqueous acid or base by a mechanism that we'll see in Section 20.9. Since nitriles themselves are usually made by $\text{S}_{\text{N}}2$ reaction of a primary or secondary alkyl halide with CN^- , the two-step sequence of cyanide displacement followed by nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($\text{RBr} \rightarrow \text{RC}\equiv\text{N} \rightarrow \text{RCO}_2\text{H}$).

Note that the product acid has one more carbon than the starting alkyl halide. An example occurs in the commercial synthesis of fenopropfen, a nonsteroidal anti-inflammatory drug, or NSAID, marketed under the trade name Nalfon. (See Chapter 15 *Focus On*.)



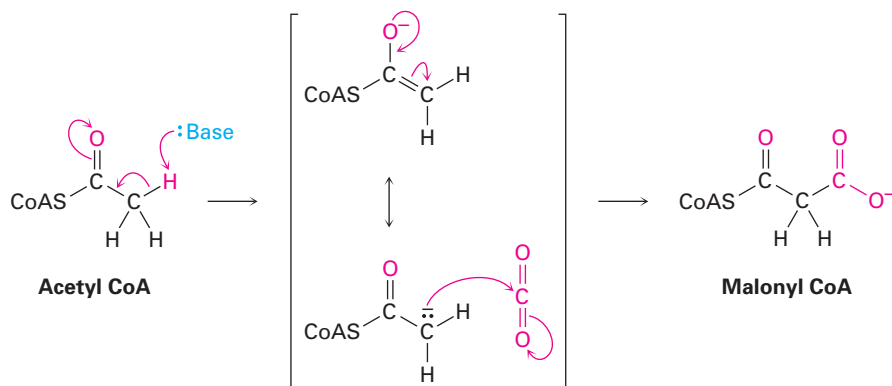
Carboxylation of Grignard Reagents

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 $\text{C}=\text{O}$ 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



There are, of course, 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.



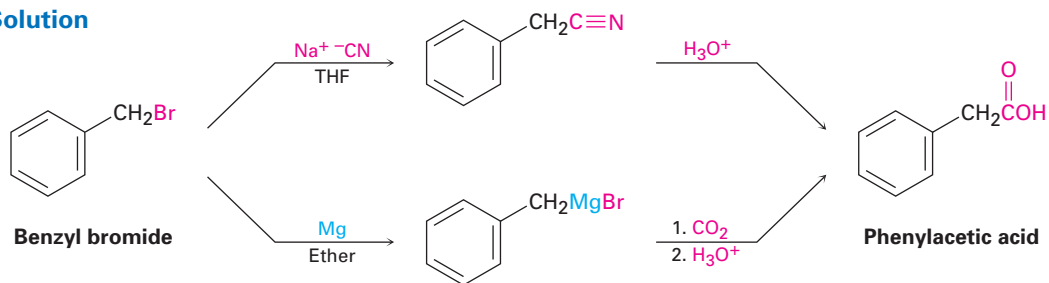
WORKED EXAMPLE 20.2

Devising a Synthesis Route for a Carboxylic Acid

How would you prepare phenylacetic acid (PhCH₂CO₂H) from benzyl bromide (PhCH₂Br)?

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?

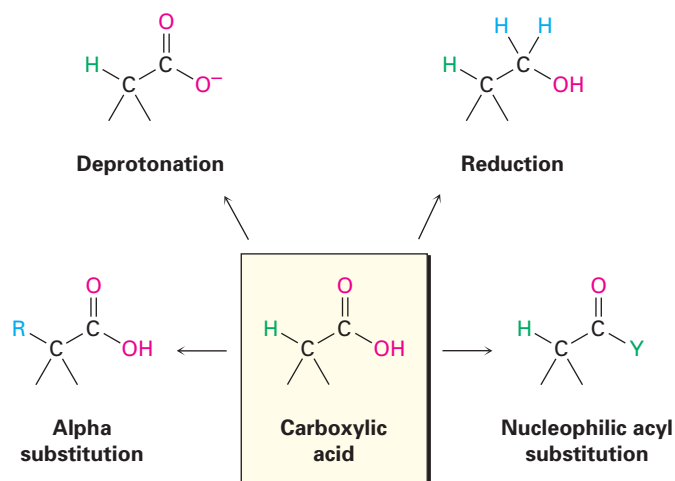
- (CH₃)₃CCO₂H from (CH₃)₃CCl
- CH₃CH₂CH₂CO₂H from CH₃CH₂CH₂Br

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,

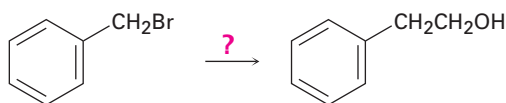
carboxylic acids undergo addition of nucleophiles to the carbonyl group. In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones. Figure 20.2 shows some of the general reactions of carboxylic acids.

Figure 20.2 Some general reactions of carboxylic acids.

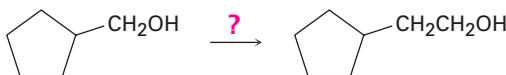


Reactions of carboxylic acids can be grouped into the four categories indicated in Figure 20.2. Of the four, we've already discussed the acidic behavior of carboxylic acids in Sections 20.2 through 20.4, and we mentioned reduction by treatment of the acid with LiAlH_4 in Section 17.4. The remaining two 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.



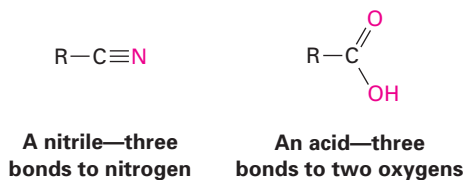
Problem 20.12 How might you carry out the following transformation? More than one step is needed.



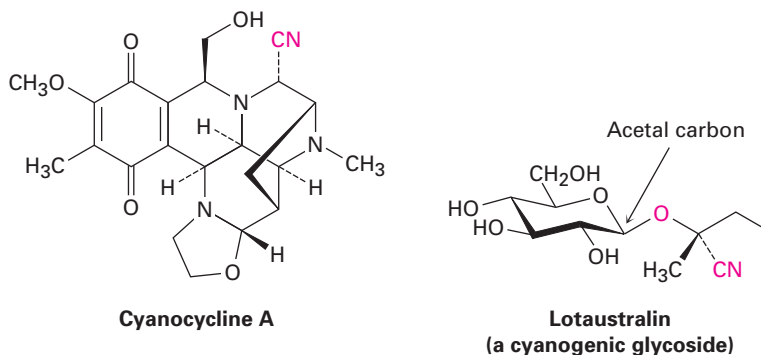
20.7 Chemistry of Nitriles

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.

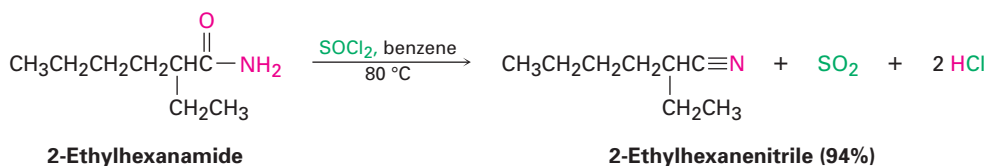


Nitriles occur infrequently in living organisms, although several hundred examples of their occurrence are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and found to have both antimicrobial and antitumor activity. In addition, more than 1000 compounds 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.

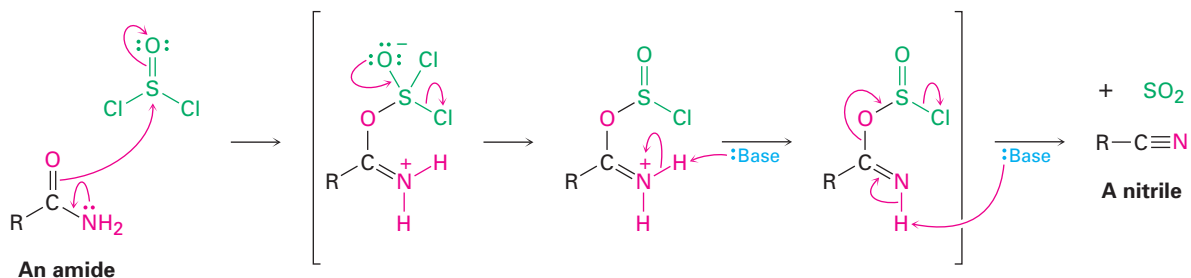


Preparation of Nitriles

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.



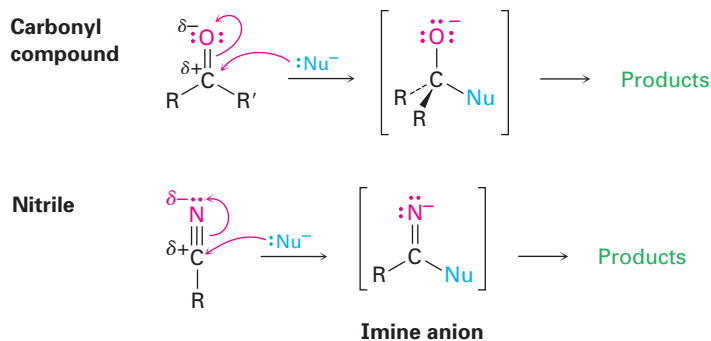
The dehydration occurs by initial reaction of SOCl_2 on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.



Both methods of nitrile synthesis— $\text{S}_{\text{N}}2$ 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.

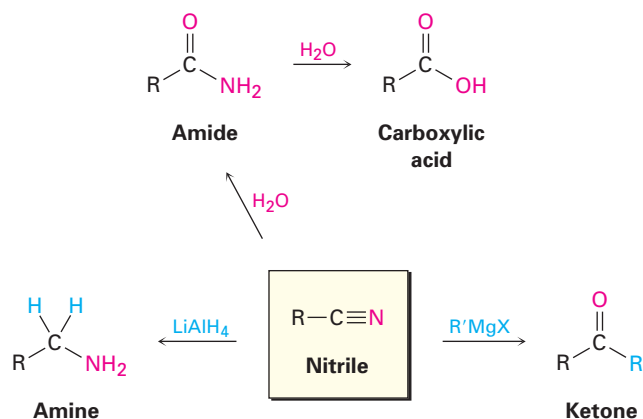
Reactions of Nitriles

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.

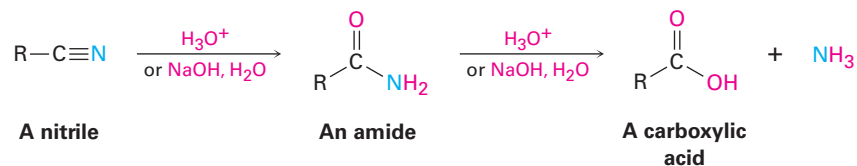


Among the most useful reactions of nitriles are hydrolysis to yield first an amide and then a carboxylic acid plus ammonia, reduction to yield an amine, and Grignard reaction to yield a ketone (Figure 20.3).

Figure 20.3 Some reactions of nitriles.

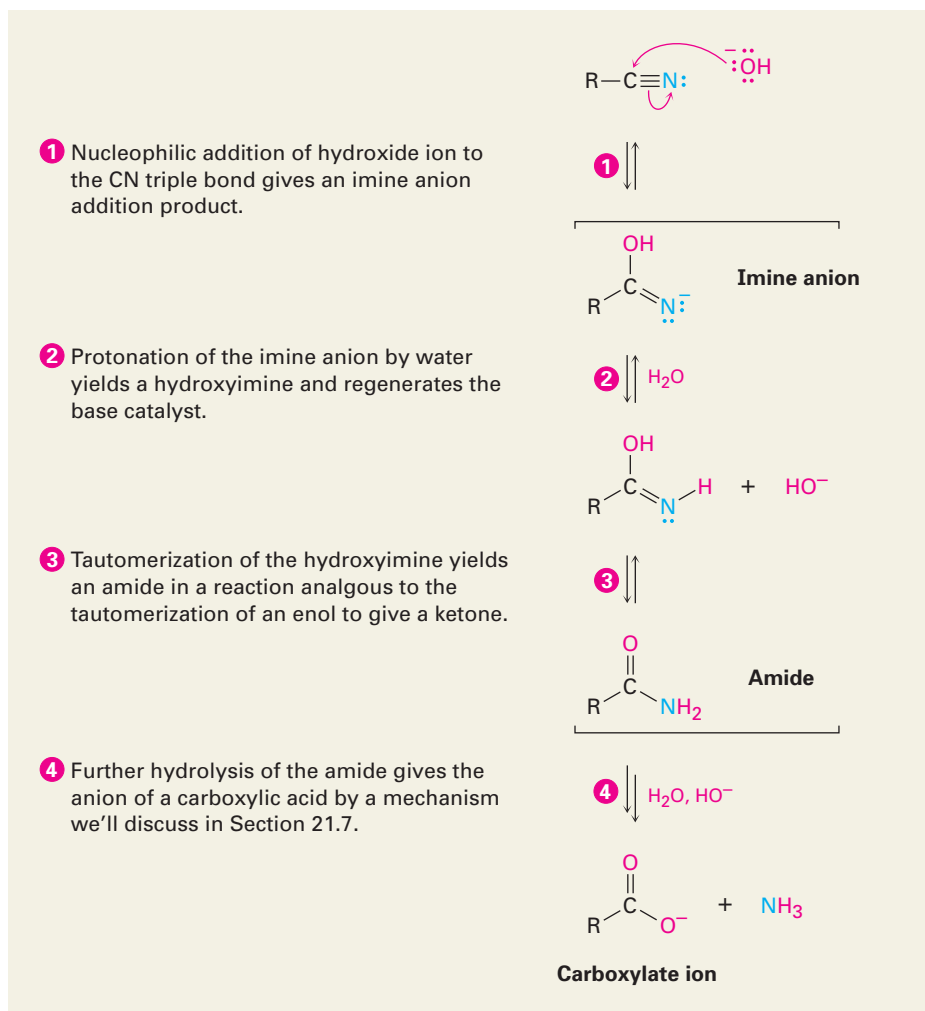


Hydrolysis: Conversion of Nitriles into Carboxylic Acids A nitrile is hydrolyzed in either basic or acidic aqueous solution to yield a carboxylic acid plus ammonia or an amine.

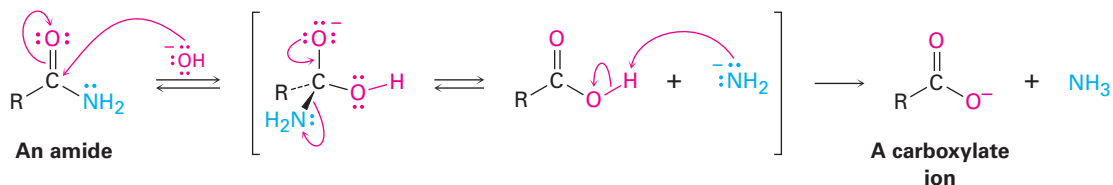


Base catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion in a process similar to nucleophilic addition to a polar C=O bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes (Section 8.4) to an amide in a step similar to the tautomerization of an enol to a ketone. The mechanism is shown in Figure 20.4.

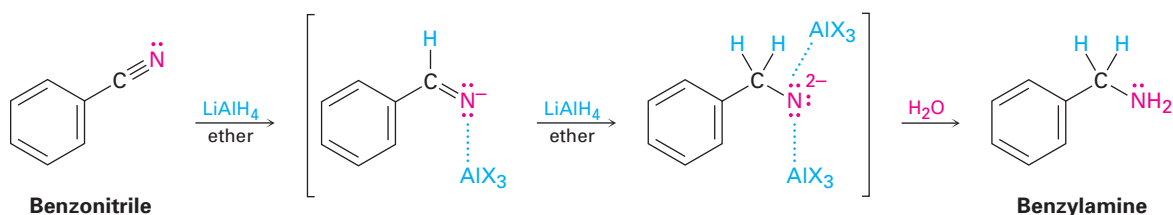
Active Figure 20.4 MECHANISM: Mechanism of the basic hydrolysis of a nitrile to yield an amide, which is subsequently hydrolyzed further to a carboxylic acid anion. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.



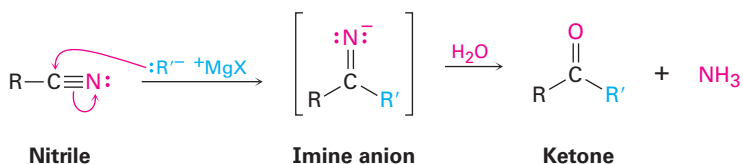
Following formation of the amide intermediate, a second nucleophilic addition of hydroxide ion to the amide carbonyl group then yields a tetrahedral alkoxide ion, which expels amide ion, NH_2^- , as leaving group and gives the carboxylate ion, thereby driving the reaction toward products. Subsequent 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 $\text{C}\equiv\text{N}$ bond, yielding an imine anion, which still contains a $\text{C}=\text{N}$ 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.

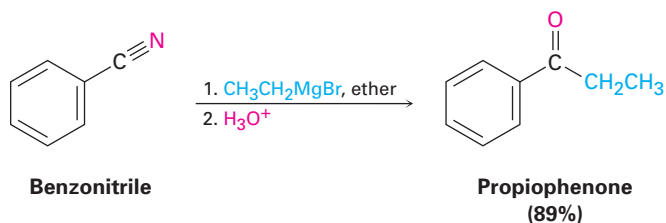


Reaction of Nitriles with Organometallic Reagents Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone.



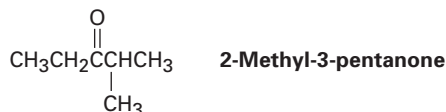
ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of reactions involving carboxylic acids and nitriles.

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:



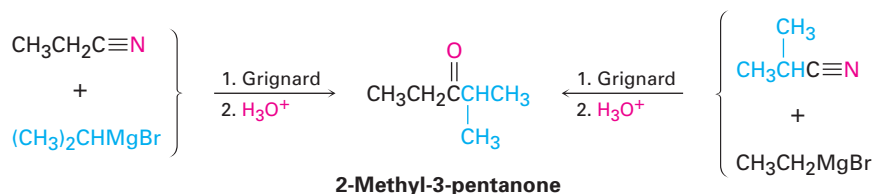
WORKED EXAMPLE 20.3**Synthesizing a Ketone from a Nitrile**

How would you prepare 2-methyl-3-pentanone from a nitrile?

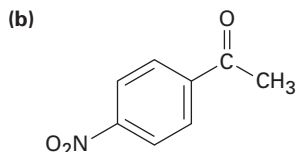
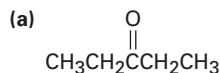


Strategy A ketone results from the reaction between a Grignard reagent and a nitrile, with the $\text{C}\equiv\text{N}$ carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent, and the other will come from the nitrile.

Solution There are two possibilities.



Problem 20.13 How would you prepare the following carbonyl compounds from a nitrile?



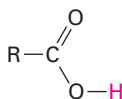
Problem 20.14 How would you prepare 1-phenyl-2-butanone, $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2\text{CH}_3$, from benzyl bromide, $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$? More than one step is required.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

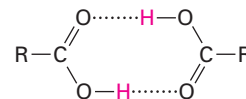
Infrared Spectroscopy

Carboxylic acids have two characteristic IR absorptions that make the $-\text{CO}_2\text{H}$ group easily identifiable. The $\text{O}-\text{H}$ bond of the carboxyl group gives rise to a very broad absorption over the range 2500 to 3300 cm^{-1} , and the $\text{C}=\text{O}$ bond shows an absorption between 1710 and 1760 cm^{-1} . The exact position of $\text{C}=\text{O}$ 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.

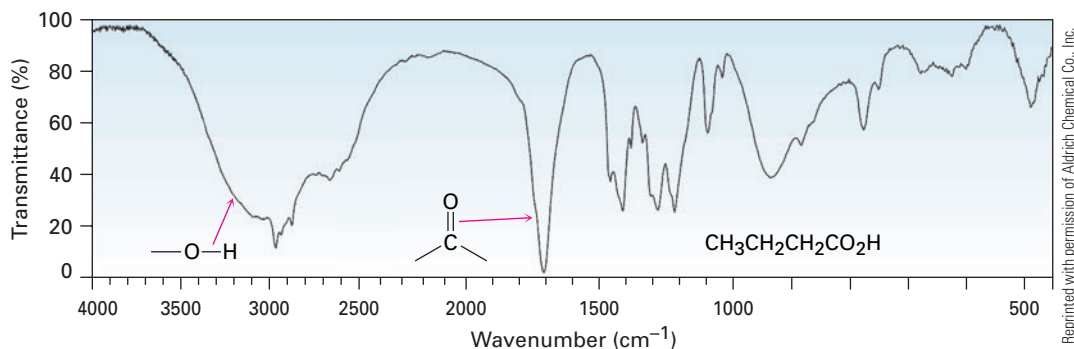


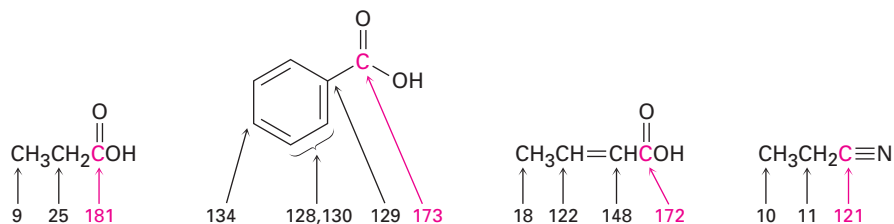
Figure 20.5 IR spectrum of butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$.

Nitriles show an intense and easily recognizable $\text{C}\equiv\text{N}$ bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules. Since few other functional groups absorb in this region, IR spectroscopy is highly diagnostic for nitriles.

Problem 20.15 Cyclopentanecarboxylic acid and 4-hydroxycyclohexanone have the same formula ($\text{C}_6\text{H}_{10}\text{O}_2$), and both contain an $-\text{OH}$ and a $\text{C}=\text{O}$ group. How could you distinguish between them by IR spectroscopy?

Nuclear Magnetic Resonance Spectroscopy

Carboxylic acid groups can be detected by both ^1H and ^{13}C NMR spectroscopy. Carboxyl carbon atoms absorb in the range 165 to $185\ \delta$ in the ^{13}C NMR spectrum, with aromatic and α,β -unsaturated acids near the upfield end of the range ($\sim 165\ \delta$) and saturated aliphatic acids near the downfield end ($\sim 185\ \delta$). Nitrile carbons absorb in the range 115 to $130\ \delta$.



In the ^1H NMR spectrum, the acidic $-\text{CO}_2\text{H}$ proton normally absorbs as a singlet near $12\ \delta$. As with alcohols (Section 17.11), the $-\text{CO}_2\text{H}$ 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 ^1H NMR spectrum of phenylacetic acid. Note that the carboxyl proton absorption occurs at $12.0\ \delta$.

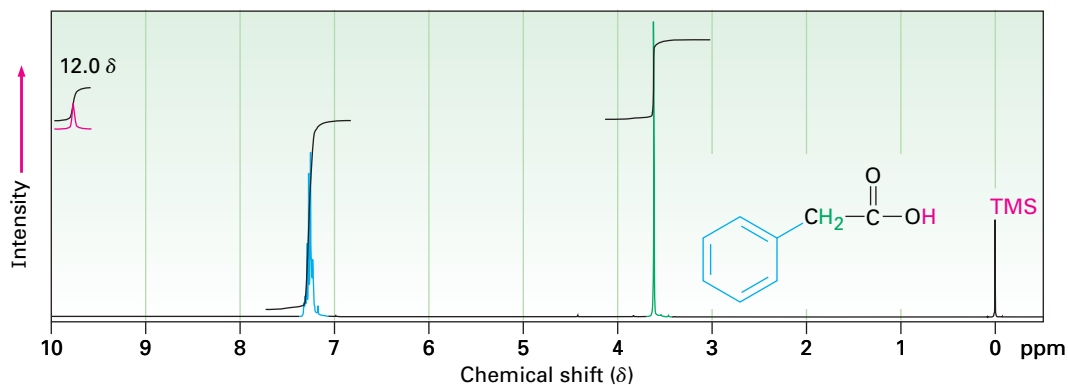


Figure 20.6 Proton NMR spectrum of phenylacetic acid, $C_6H_5CH_2CO_2H$.

Problem 20.16 | How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by 1H and ^{13}C NMR spectroscopy? (See Problem 20.14.)

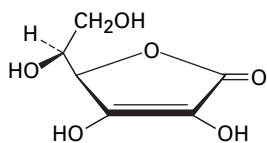
Focus On . . .

Vitamin C

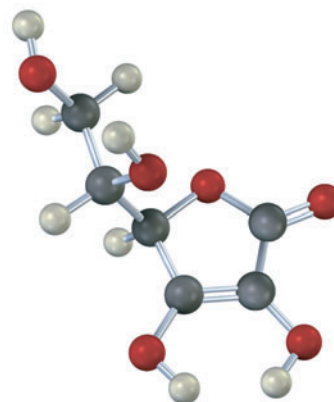


In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency.

Vitamin C, or ascorbic acid, is surely the best known of all vitamins. It was the first vitamin to be discovered (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 200 million pounds of vitamin C are now synthesized worldwide each year, more than the total amount of all other vitamins 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)



(continued)

Vitamin C is perhaps most famous 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 8%.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry. The Hoffmann-La Roche company synthesizes ascorbic acid from glucose through the five-step route shown in Figure 20.7. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which 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 protects four of the remaining hydroxyl groups in acetal linkages, and the unprotected hydroxyl group is chemically oxidized to the 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.

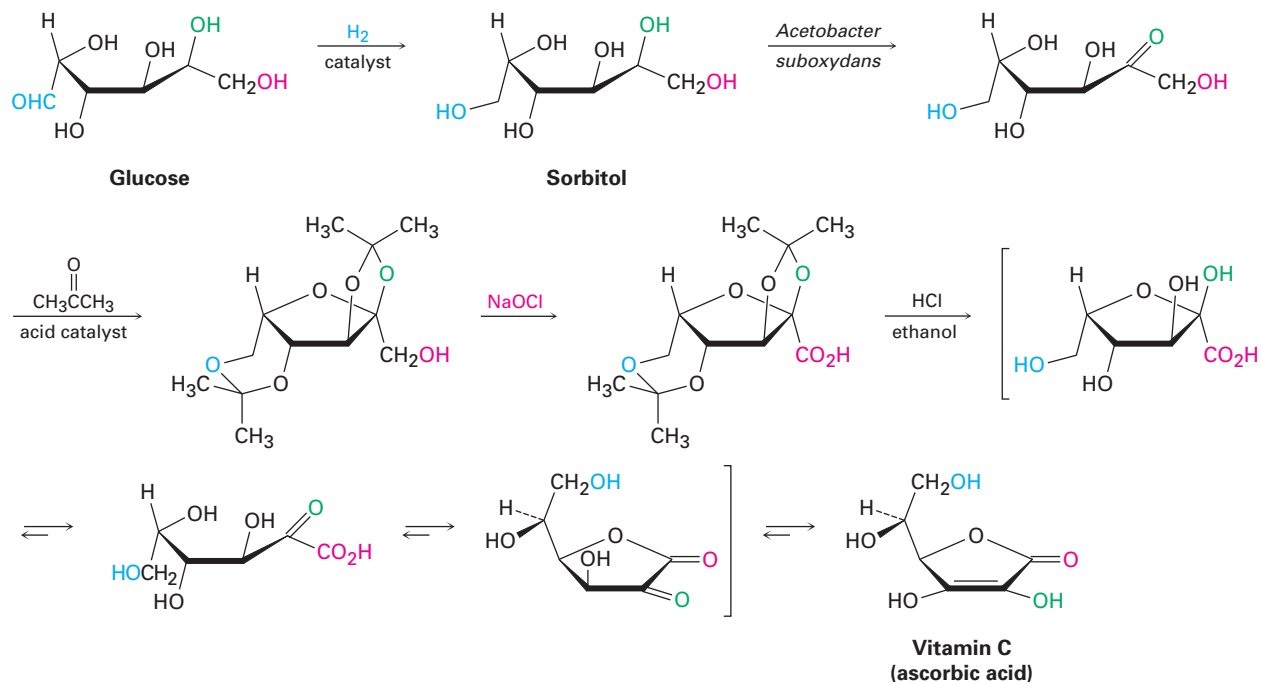


Figure 20.7 The industrial synthesis of ascorbic acid from glucose.

carboxyl group, 752
carboxylation, 763
carboxylic acid (RCO₂H), 751
Henderson–Hasselbalch equation, 758
nitrile (RC≡N), 754

SUMMARY AND KEY WORDS

Carboxylic acids are among the most useful building blocks for synthesizing other molecules, both in nature and in the chemical laboratory. They 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.

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) oxidative cleavage of alkenes, (3) oxidation of primary alcohols or aldehydes, (4) hydrolysis of nitriles, and (5) reaction of Grignard reagents with CO₂ (**carboxylation**). 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.

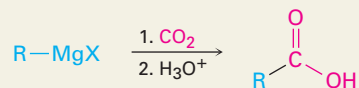
Nitriles are similar in some respects to carboxylic acids and are prepared either by S_N2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar C≡N bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with organometallic 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 and another at 1710 to 1760 cm⁻¹ due to the C=O; nitriles have an absorption at 2250 cm⁻¹. Acids also show ¹³C NMR absorptions at 165 to 185 δ and ¹H NMR absorptions near 12 δ; nitriles have a ¹³C NMR absorption in the range 115 to 130 δ.

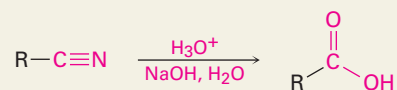
SUMMARY OF REACTIONS

1. Preparation of carboxylic acids (Section 20.5)

(a) Carboxylation of Grignard reagents

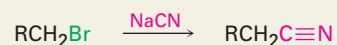


(b) Hydrolysis of nitriles

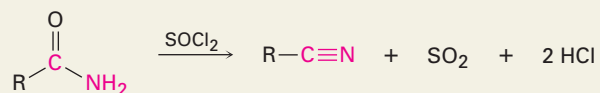


2. Preparation of nitriles (Section 20.7)

(a) S_N2 reaction of alkyl halides

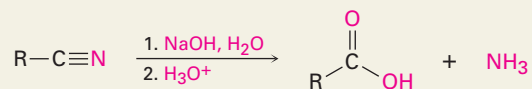


(b) Dehydration of amides

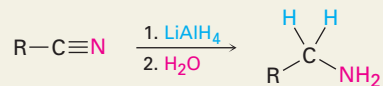


3. Reactions of nitriles (Section 20.7)

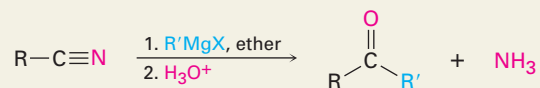
(a) Hydrolysis to yield carboxylic acids



(b) Reduction to yield primary amines




(c) Reaction with Grignard reagents to yield ketones



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

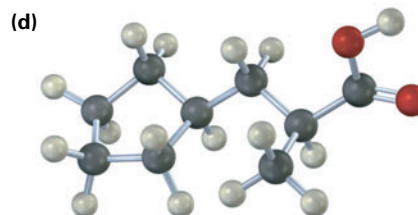
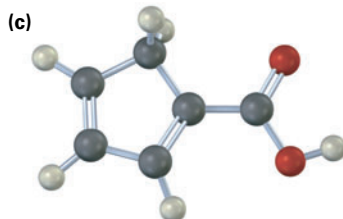
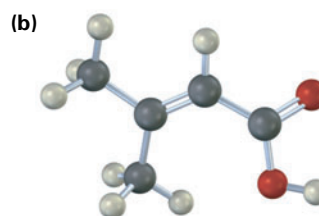
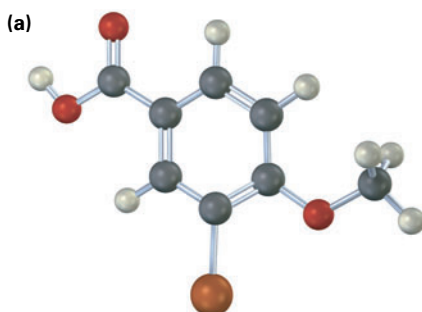
 Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

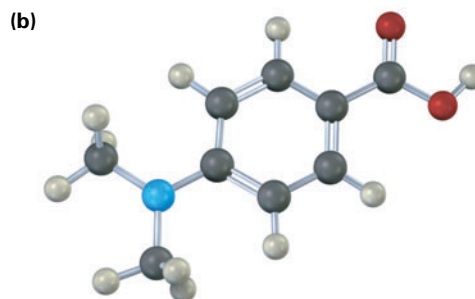
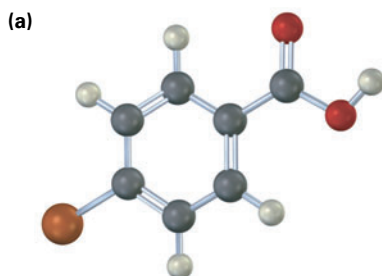
VISUALIZING CHEMISTRY

(Problems 20.1–20.16 appear within the chapter.)

20.17 ■ Give IUPAC names for the following carboxylic acids (reddish brown = Br):

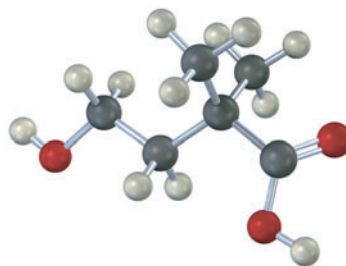


20.18 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Reddish brown = Br.)

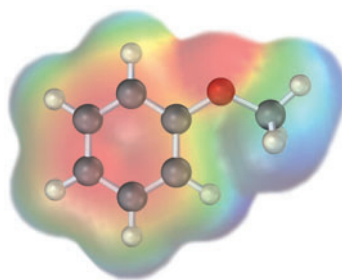
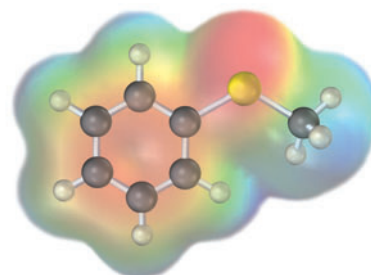


■ Assignable in OWL

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.

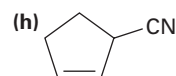
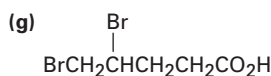
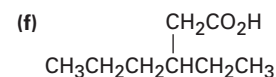
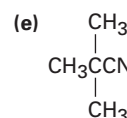
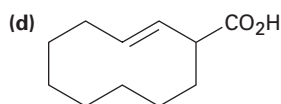
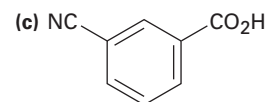
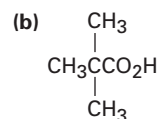
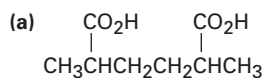


20.20 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.

Anisole (C₆H₅OCH₃)Thioanisole (C₆H₅SCH₃)

ADDITIONAL PROBLEMS

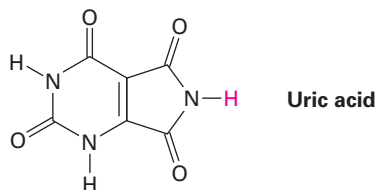
20.21 ■ Give IUPAC names for the following compounds:



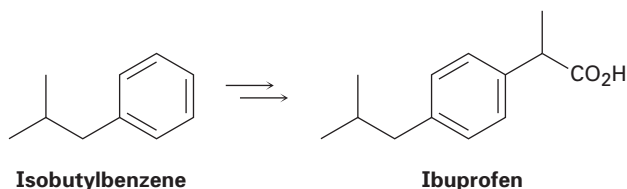
20.22 ■ Draw structures corresponding to the following IUPAC names:

- | | |
|--|-----------------------------------|
| (a) <i>cis</i> -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) <i>m</i> -Benzoylbenzonitrile |

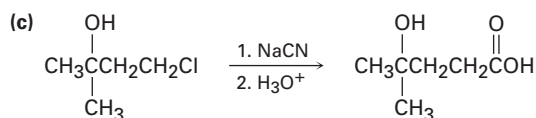
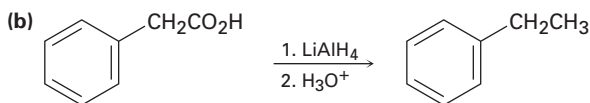
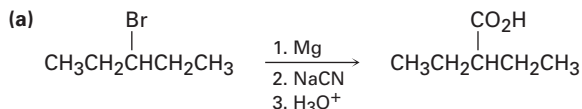
- 20.23** Draw and name the following:
 (a) The eight carboxylic acids with the formula $C_6H_{12}O_2$
 (b) Three nitriles with the formula C_5H_7N
- 20.24** Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentanedioic acid. Draw the structure.
- 20.25** ■ 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
- 20.26** ■ 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
- 20.27** ■ 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
- 20.28** ■ 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
- 20.29** ■ 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
- 20.30** ■ 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, $C_6H_5CH_2CO_2H$
- 20.31** ■ Calculate pK_a 's for the following acids:
 (a) Lactic acid, $K_a = 8.4 \times 10^{-4}$ (b) Acrylic acid, $K_a = 5.6 \times 10^{-6}$
- 20.32** ■ Calculate K_a 's for the following acids:
 (a) Citric acid, $pK_a = 3.14$ (b) Tartaric acid, $pK_a = 2.98$
- 20.33** ■ 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 $pH = 3.0$?
- 20.34** ■ 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?



- 20.42** Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.

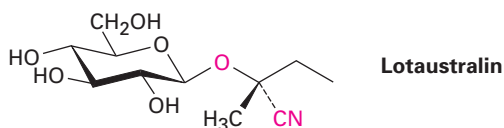


- 20.43** The following synthetic schemes all have at least one flaw in them. What is wrong with each?



- 20.44** 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.

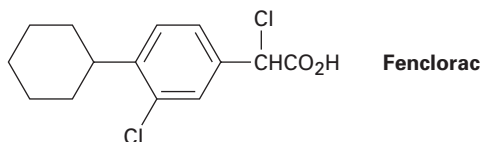
- (a) Show the mechanism of the acetal hydrolysis and the structure of the cyanohydrin that results.
 (b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.



- 20.45** 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.

- 20.46** *p*-Aminobenzoic acid (PABA) is widely used as a sunscreen agent. Propose a synthesis of PABA starting from toluene.

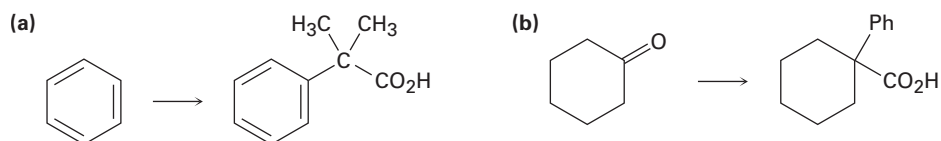
- 20.47** Propose a synthesis of the anti-inflammatory drug Fenclorac from phenylcyclohexane.



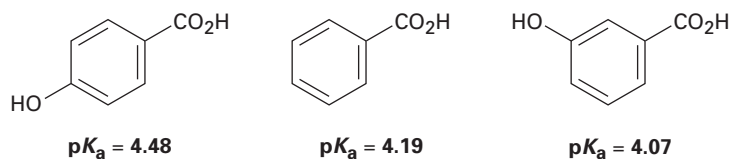
20.48 The pK_a 's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) follow. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has $pK_a = 4.19$, which of the substituents are activators and which are deactivators?

Substituent Y	pK_a of $Y-C_6H_4-CO_2H$
$-Si(CH_3)_3$	4.27
$-CH=CHC\equiv N$	4.03
$-HgCH_3$	4.10
$-OSO_2CH_3$	3.84
$-PCl_2$	3.59

20.49 How would you carry out the following transformations? More than one step is required in each case.

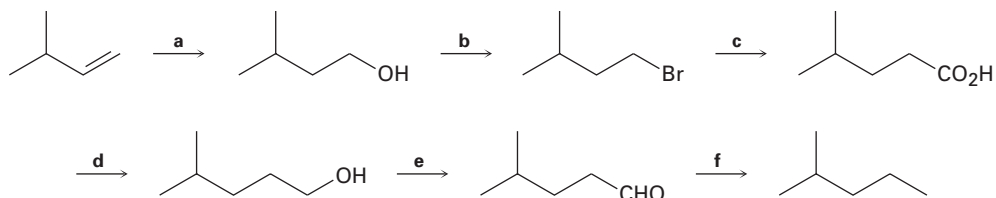


20.50 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.

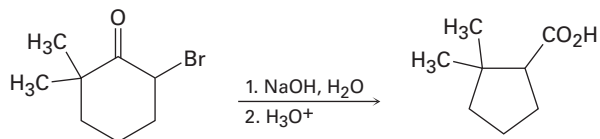


20.51 3-Methyl-2-hexenoic acid (mixture of *E* and *Z* isomers) has been identified as the substance responsible for the odor of human sweat. Synthesize the compound from starting materials having five or fewer carbons.

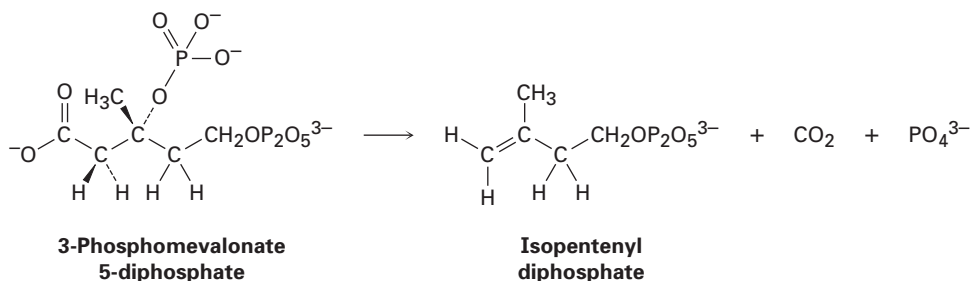
20.52 Identify the missing reagents a–f in the following scheme:



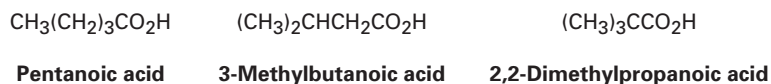
- 20.53** ■ 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentane-carboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the *Favorskii reaction*. Propose a mechanism.



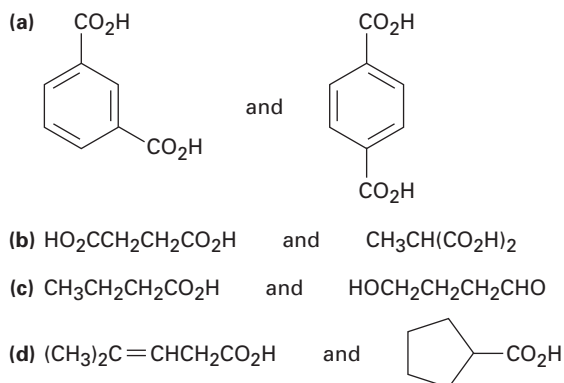
- 20.54** In plants, terpenes (see Chapter 6 *Focus On*) are biosynthesized by a pathway that involves loss of CO₂ from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.



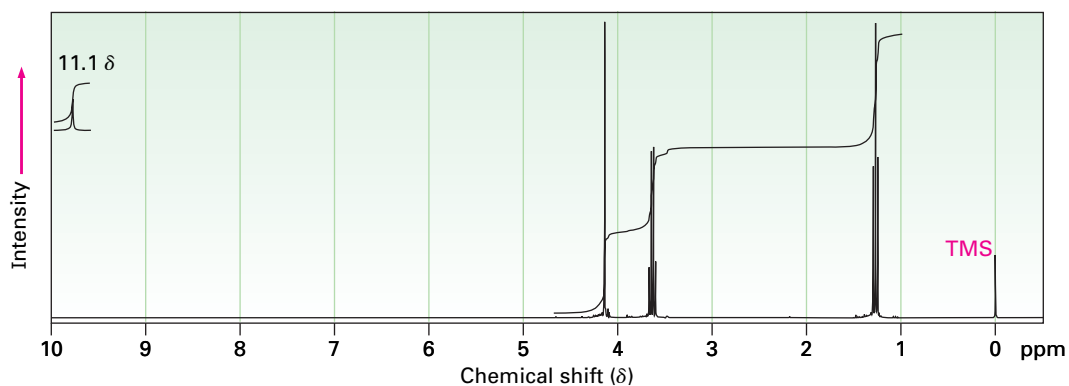
- 20.55** ■ Propose a structure for a compound C₆H₁₂O₂ that dissolves in dilute NaOH and shows the following ¹H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).
- 20.56** What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.



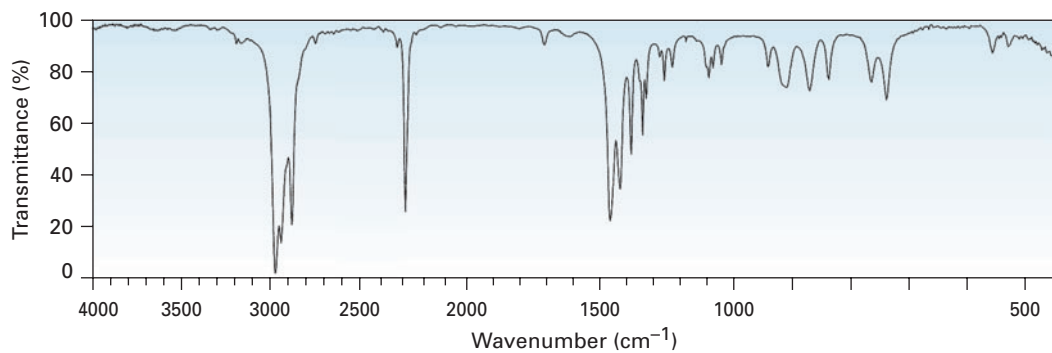
- 20.57** How would you use NMR (either ¹³C or ¹H) to distinguish between the following pairs of isomers?



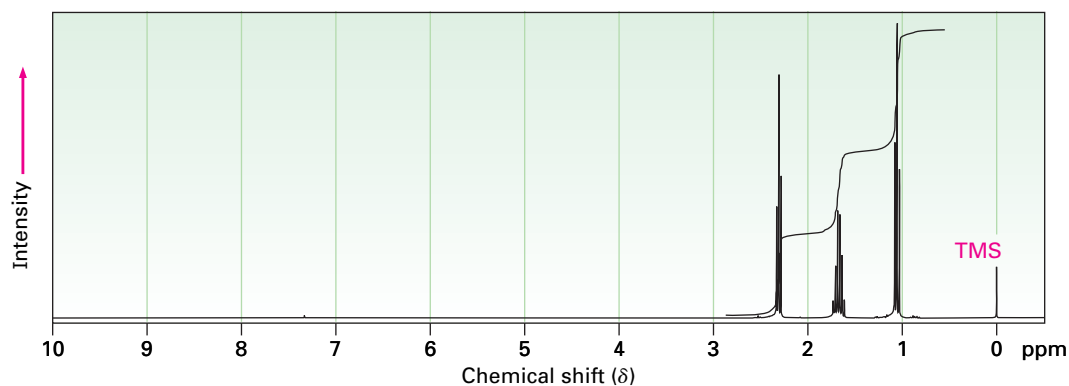
20.58 ■ Compound A, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for A.



20.59 ■ Propose a structure for a compound, C_4H_7N , that has the following IR and ^1H NMR spectra:

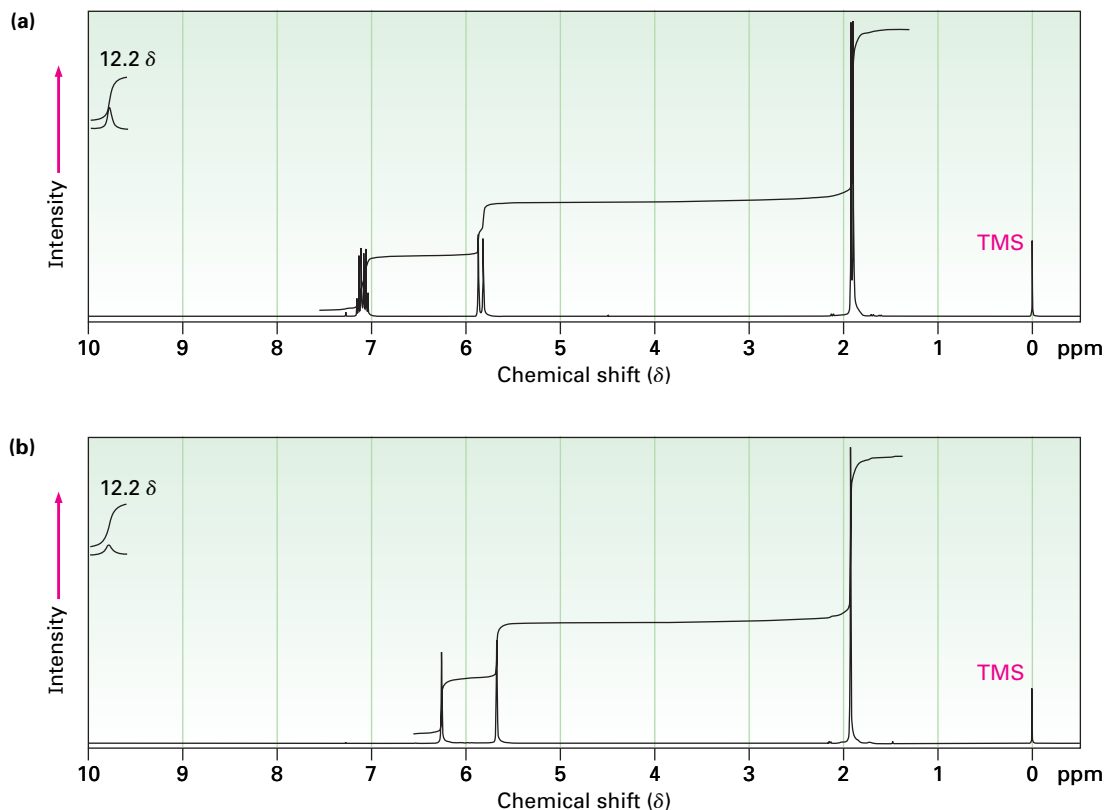


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20.60 ■ The two ^1H NMR spectra shown here belong to crotonic acid (*trans*- $\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$) and methacrylic acid [$\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$]. Which spectrum corresponds to which acid? Explain.



20.61 ■ 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) $\text{C}_7\text{H}_{12}\text{O}_2$: $25.5\ \delta$ (2°), $25.9\ \delta$ (2°), $29.0\ \delta$ (2°), $43.1\ \delta$ (3°), $183.0\ \delta$ (4°)

(b) $\text{C}_8\text{H}_8\text{O}_2$: $21.4\ \delta$ (1°), $128.3\ \delta$ (4°), $129.0\ \delta$ (3°), $129.7\ \delta$ (3°), $143.1\ \delta$ (4°), $168.2\ \delta$ (4°)

20.62 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.

