CHAPTER

8

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The Harger Drunkometer was introduced in 1938 to help keep drunk drivers off the road. Drunk driving is still a problem, but methods for detecting the amount of alcohol consumed have improved greatly in the last 70 years.

Alcohols, Phenols, Ethers, and Their Sulfur Analogs

In this and the next three chapters, we'll focus on the most commonly occurring of all functional groups—those that contain *oxygen*—beginning in this chapter with a look at compounds that contain C–O single bonds. An **alcohol** is a compound that has a hydroxyl group bonded to a saturated, sp^3-hybridized carbon atom, R—OH; a **phenol** has a hydroxyl group bonded to an aromatic ring, Ar—OH; and an **ether** has an oxygen atom bonded to two organic groups, R—O—R′. The corresponding sulfur analogs are called **thiols** (R—SH), **thiophenols** (Ar—SH), and **sulfides** (R—S—R′).

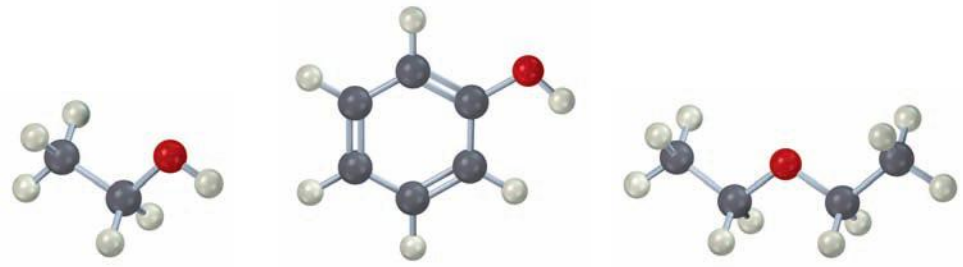
Alcohols, phenols, and ethers occur widely in nature and have many industrial, pharmaceutical, and biological applications. Ethanol, for instance, is a fuel additive, an industrial solvent, and a beverage; phenol is a general disinfectant, commonly called carbolic acid; and diethyl ether—the familiar "ether" of medical use—is frequently used as a reaction solvent and was once popular as an inhaled anesthetic.

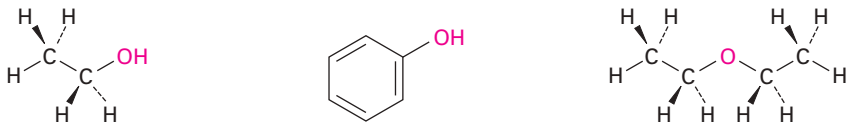
OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

WHY THIS CHAPTER?

Up to this point, we've focused on developing some general ideas of organic reactivity and on looking at the chemistry of hydrocarbons and alkyl halides. With that background, it's now time to begin a study of oxygen-containing





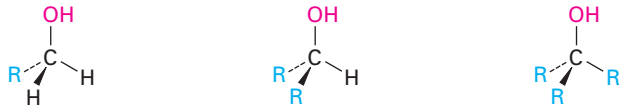
Ethanol **Phenol** **Diethyl ether**

functional groups, which lie at the heart of organic and biological chemistry. In fact, practically every one of the hundreds of thousands of different compounds in your body contains oxygen. We'll look at compounds with C–O single bonds in this chapter and then move on to carbonyl compounds in Chapters 9 to 11.

8.1 Naming Alcohols, Phenols, and Ethers

Alcohols

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



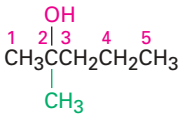
A primary (1°) alcohol **A secondary (2°) alcohol** **A tertiary (3°) alcohol**

Simple alcohols are named in the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*. As always, the locant indicating the position of the hydroxyl group in the parent chain is placed immediately before the *-ol* suffix in the newer, post-1993 naming system.

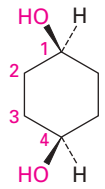
STEP 1 Select the longest carbon chain containing the hydroxyl group, and replace the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

STEP 2 Number the carbons of the parent chain beginning at the end nearer the hydroxyl group.

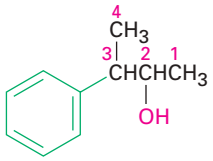
STEP 3 Number all substituents according to their position on the chain, and write the name listing the substituents in alphabetical order and identifying the position to which the –OH is bonded. Note that in naming *cis*-cyclohexane-1,4-diol, the final *-e* of cyclohexane is not deleted because the next letter (d) is not a vowel; that is, cyclohexanediol rather than cyclohexandiol.



2-Methylpentan-2-ol

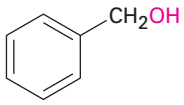


***cis*-Cyclohexane-1,4-diol**

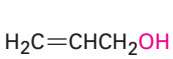


3-Phenylbutan-2-ol

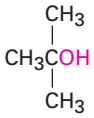
Some well-known alcohols also have common names that are accepted by IUPAC. For example:



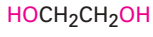
Benzyl alcohol (phenylmethanol)



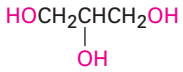
Allyl alcohol (prop-2-en-1-ol)



***tert*-Butyl alcohol (2-methylpropan-2-ol)**



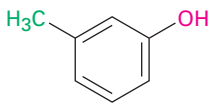
Ethylene glycol (ethane-1,2-diol)



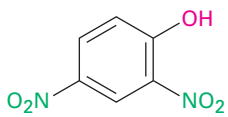
Glycerol (propane-1,2,3-triol)

Phenols

The word *phenol* is used both as the name of a specific substance (hydroxybenzene) and as the family name for all hydroxy-substituted aromatic compounds. Substituted phenols are named as described previously in Section 5.2 for aromatic compounds, with *-phenol* used as the parent name rather than *-benzene*.



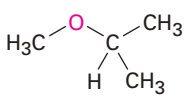
***m*-Methylphenol (*m*-cresol)**



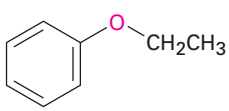
2,4-Dinitrophenol

Ethers

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

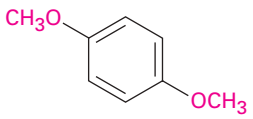


Isopropyl methyl ether

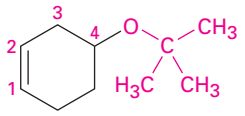


Ethyl phenyl ether

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

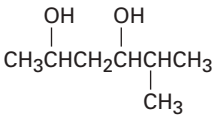


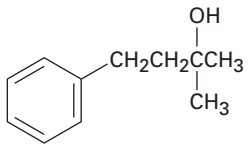
p-Dimethoxybenzene

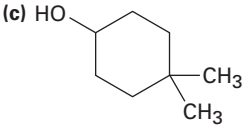


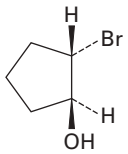
4-*tert*-Butoxycyclohex-1-ene

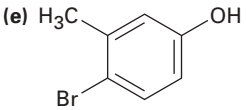
Problem 8.1 Give IUPAC names for the following compounds:

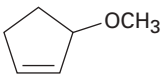
(a) 

(b) 

(c) 

(d) 

(e) 

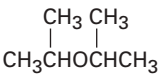
(f) 

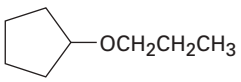
Problem 8.2 Identify the alcohols in Problem 8.1 as primary, secondary, or tertiary.

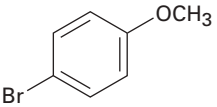
Problem 8.3 Draw structures corresponding to the following IUPAC names:

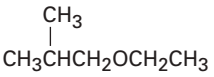
(a) 2-Methylhexan-2-ol
(b) Hexane-1,5-diol
(c) 2-Ethylbut-2-en-1-ol
(d) Cyclohex-3-en-1-ol
(e) *o*-Bromophenol
(f) 2,4,6-Trinitrophenol

Problem 8.4 Name the following ethers by IUPAC rules:

(a) 

(b) 

(c) 

(d) 

8.2 Properties of Alcohols and Phenols: Hydrogen Bonding and Acidity

Alcohols, phenols, and ethers can be thought of as organic derivatives of water in which one or both of the hydrogens have been replaced by organic parts: H—O—H becomes R—O—H, Ar —O—H, or R—O—R′. Thus, all three classes of compounds have nearly the same geometry as water. The C–O–H or C–O–C bond angles are approximately tetrahedral—109° in methanol and 112° in dimethyl ether, for instance—and the oxygen atoms are sp^3-hybridized.

Also like water, alcohols and phenols have higher boiling points than might be expected. Propan-1-ol and butane have similar molecular weights, for instance, yet propan-1-ol boils at 97.2 °C and butane boils at −0.5 °C. Similarly, phenol boils at 181.9 °C but toluene boils at 110.6 °C.

Alcohols and phenols have unusually high boiling points because, like water, they form hydrogen bonds. The positively polarized –OH hydrogen of one molecule is attracted to a lone pair of electrons on the negatively polarized oxygen of another molecule, resulting in a weak force that holds the molecules together (Figure 8.1). These forces must be overcome for a molecule to break free from the liquid and enter the vapor, so the boiling temperature is raised. Ethers, because they lack hydroxyl groups, can't form hydrogen bonds and therefore have lower boiling points.

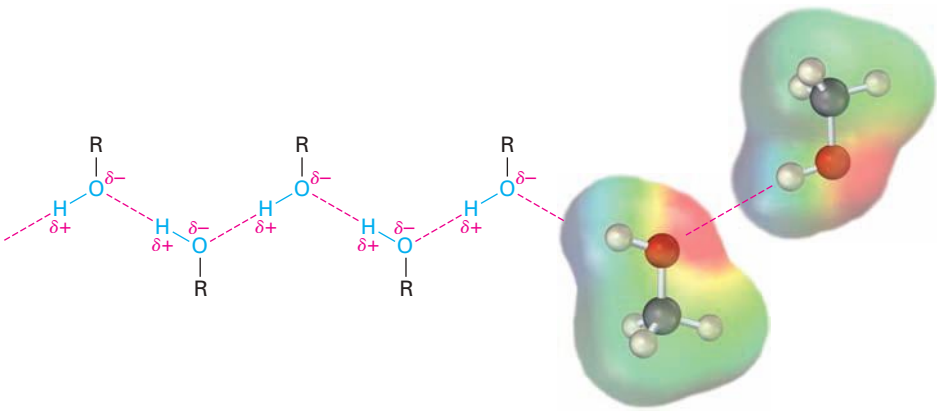
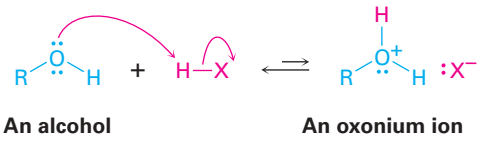
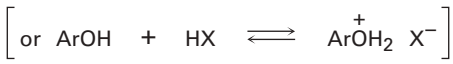


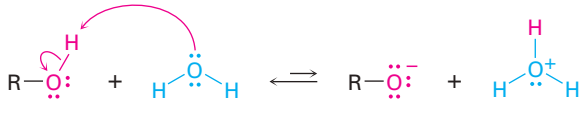
Figure 8.1 Hydrogen bonding in alcohols and phenols. The weak attraction between a positively polarized –OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the positively polarized –OH hydrogen (blue) and the negatively polarized oxygen (red).

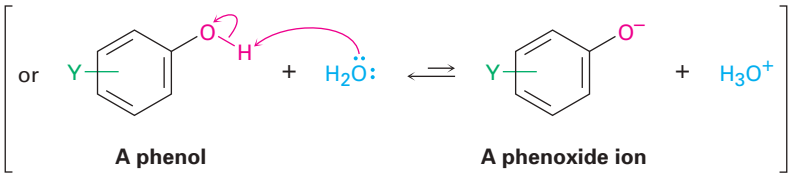
Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak Lewis bases, alcohols and phenols are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.





As weak acids, alcohols and phenols dissociate to a slight extent 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 1.10 and 1.11 that the strength of any acid HA in water can be expressed by an acidity constant, K_a.

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

Compounds with a smaller K_a and larger pK_a are less acidic, whereas compounds with a larger K_a and smaller pK_a are more acidic. Table 8.1 gives the pK_a values of some common alcohols and phenols.

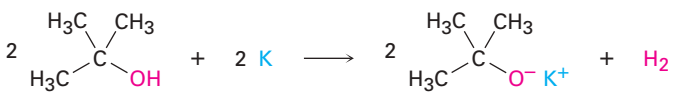
Table 8.1 Acidity of Some Alcohols and Phenols

Compound	pK_a	
$(CH_3)_3COH$	18.00	Weaker acid
CH_3CH_2OH	16.00	
H_2O	15.74	
CH_3OH	15.54	
p-Methylphenol	10.17	
Phenol	9.89	
p-Nitrophenol	7.15	Stronger acid

The data in Table 8.1 show that alcohols are about as acidic as water. Thus, they don't react with weak bases such as amines or bicarbonate ion and they react to only a limited extent with metal hydroxides, such as NaOH. They do, however, react with alkali metals to yield alkoxides that are themselves strong bases. Alkoxides are named commonly by replacing the *-ane* suffix of the corresponding alkane with *-oxide:* methane gives methoxide, for instance. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.

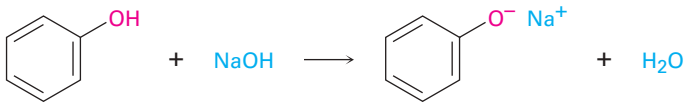
$$2\ CH_3OH + 2\ Na \longrightarrow 2\ CH_3O^-\ Na^+ + H_2$$

Methanol — **Sodium methanolate (sodium methoxide)**



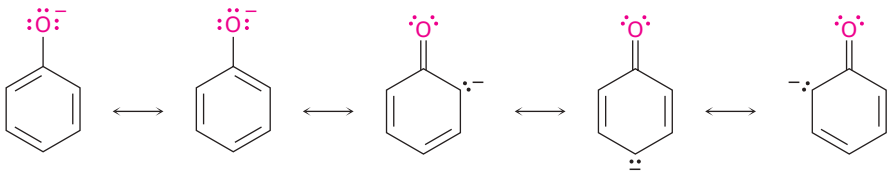
2-Methylpropan-2-ol (*tert*-butyl alcohol) — **Potassium 2-methylpropan-2-olate (potassium *tert*-butoxide)**

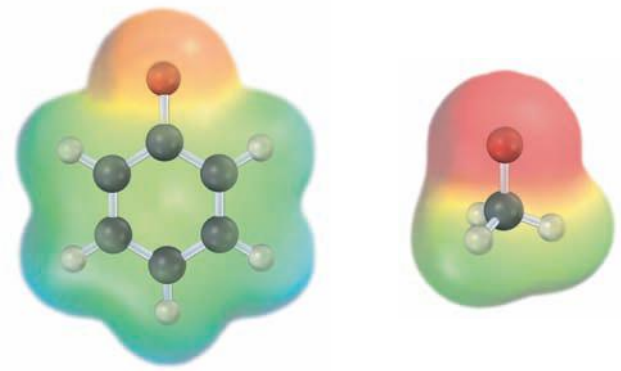
Phenols are about a million times more acidic than alcohols and are therefore soluble in dilute aqueous NaOH.



Phenol — **Sodium phenoxide (sodium phenolate)**

Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized by the aromatic ring. Sharing the negative charge over the ring increases the stability of the phenoxide anion and thus increases the tendency of the corresponding phenol to dissociate (Figure 8.2).



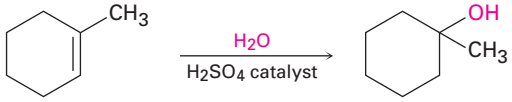


Phenoxide ion — **Methoxide ion**

Figure 8.2 A resonance-stabilized phenoxide ion is more stable than an alkoxide ion. Electrostatic potential maps show how the negative charge is more concentrated on oxygen in the methoxide ion but is less concentrated on the phenoxide oxygen.

8.3 Synthesis of Alcohols from Carbonyl Compounds

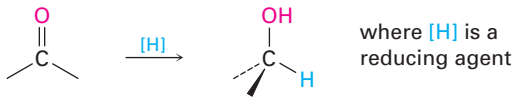
Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, aldehydes, and esters, among others), and they can be transformed into an equally wide assortment of compounds. We saw in Section 4.3, for instance, that alcohols can be prepared by hydration of alkenes.



1-Methylcyclohexene — **1-Methylcyclohexanol**

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 4.5), reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



A carbonyl compound **An alcohol**

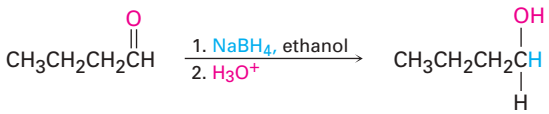
Reduction of Aldehydes and Ketones

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

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

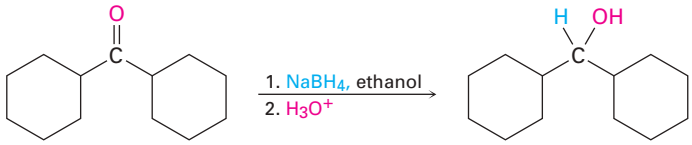
Many reducing reagents are available, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety. It is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

Aldehyde reduction



Butanal **Butan-1-ol (85%) (a 1° alcohol)**

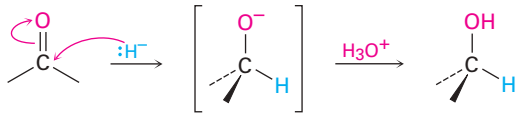
Ketone reduction



Dicyclohexyl ketone **Dicyclohexylmethanol (88%) (a 2° alcohol)**

We'll defer a discussion of the mechanisms of these reductions until Section 9.6 but might note for now that they involve the addition of a nucleophilic hydride ion ($:H^-$) to the positively polarized, electrophilic carbon atom of the

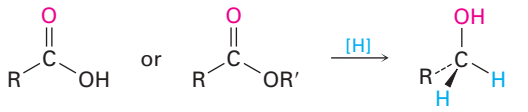
carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



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

Reduction of Carboxylic Acids and Esters

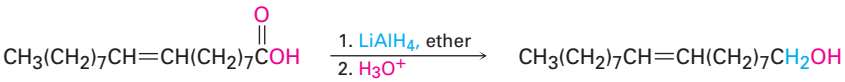
Esters and carboxylic acids are reduced to give primary alcohols.



A carboxylic acid **An ester** **A primary alcohol**

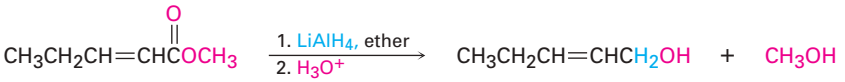
These reactions aren't as rapid as the reductions of aldehydes and ketones, so the more powerful reducing agent lithium aluminum hydride ($LiAlH_4$) is used rather than $NaBH_4$. ($LiAlH_4$ will also reduce aldehydes and ketones.) Note that only one hydrogen is added to the carbonyl carbon atom during the reduction of an aldehyde or ketone, but two hydrogens are added to the carbonyl carbon during reduction of an ester or carboxylic acid.

Carboxylic acid reduction



Octadec-9-enoic acid (oleic acid) **Octadec-9-en-1-ol (87%)**

Ester reduction

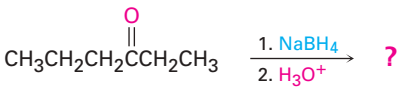


Methyl pent-2-enoate **Pent-2-en-1-ol (91%)**

Worked Example 8.1

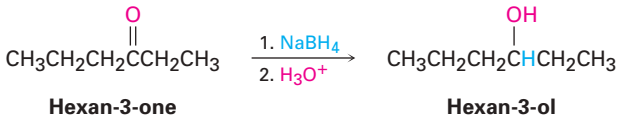
Predicting the Product of a Reduction Reaction

Predict the product of the following reaction:



Strategy Ketones are reduced by treatment with $NaBH_4$ to yield secondary alcohols. Thus, reduction of hexan-3-one yields hexan-3-ol.

Solution

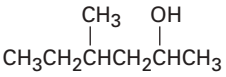


Hexan-3-one **Hexan-3-ol**

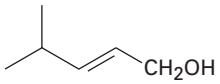
Worked Example 8.2 Synthesizing an Alcohol by Reduction of a Carbonyl Compound

What carbonyl compound(s) might you reduce to obtain the following alcohols?

(a)



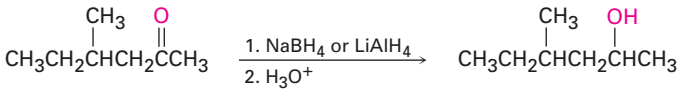
(b)



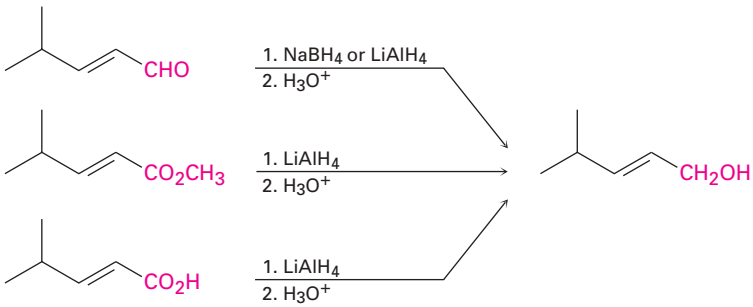
Strategy Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

Solution

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



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

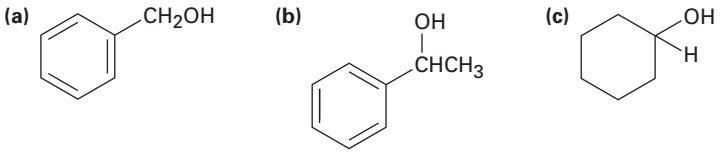


Problem 8.5 How would you carry out the following reactions?

(a)

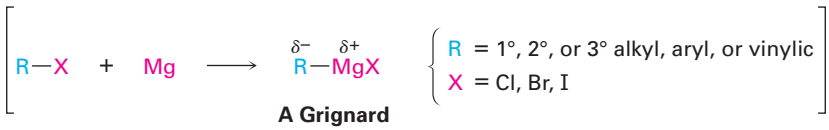
(b)

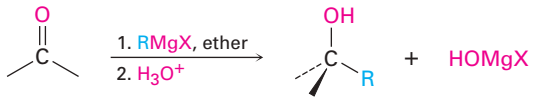
Problem 8.6 What carbonyl compounds give the following alcohols on reduction with $LiAlH_4$? Show all possibilities.



Grignard Reactions of Carbonyl Compounds

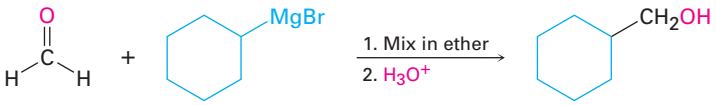
Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 7.3), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion to the C=O bond, Grignard reaction involves addition of a carbanion ($R:^-\ ^+MgX$).





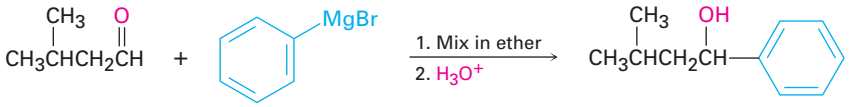
Formaldehyde, $H_2C{=}O$, reacts with Grignard reagents giving primary alcohols, aldehydes give secondary alcohols, and ketones give tertiary alcohols.

Formaldehyde reaction



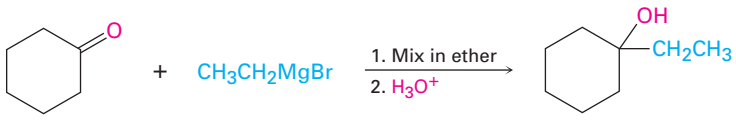
Formaldehyde — **Cyclohexylmagnesium bromide** — **Cyclohexylmethanol (65%) (a 1° alcohol)**

Aldehyde reaction



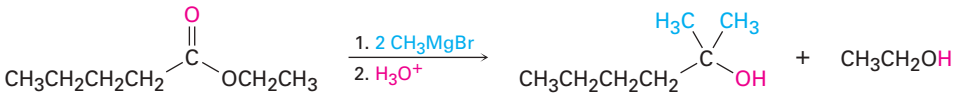
3-Methylbutanal — **Phenylmagnesium bromide** — **3-Methyl-1-phenylbutan-1-ol (73%) (a 2° alcohol)**

Ketone reaction



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

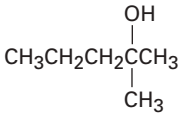
Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as esters are reduced by $LiAlH_4$ with addition of two hydrogens. As with the reduction of carbonyl compounds, we'll defer a discussion of the mechanism of Grignard additions until Section 9.6.



Ethyl pentanoate — **2-Methylhexan-2-ol (85%) (a 3° alcohol)**

Worked Example 8.3 Using a Grignard Reaction to Synthesize an Alcohol

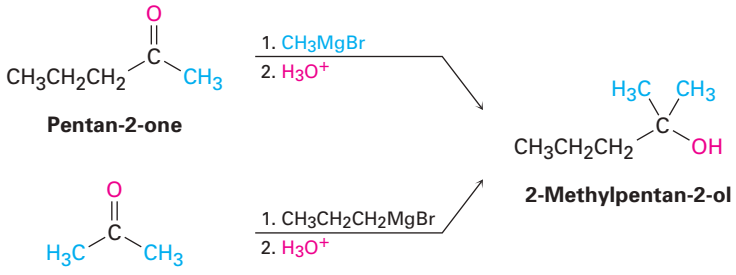
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methylpentan-2-ol?



2-Methylpentan-2-ol

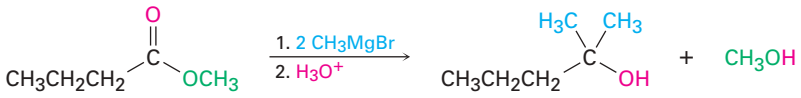
Strategy Identify the alcohol as 1°, 2°, or 3°. If the alcohol is secondary, the starting carbonyl compound must be an aldehyde. If the alcohol is tertiary and the three groups are all different, the starting carbonyl compound must be a ketone. If the alcohol is tertiary and two of the three groups are 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 pentan-2-one and addition of propylmagnesium bromide to acetone.



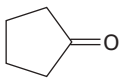
Pentan-2-one — **2-Methylpentan-2-ol** — **Acetone**

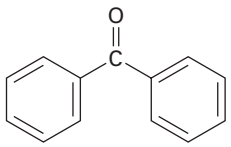
Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.

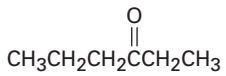


Methyl butanoate — **2-Methylpentan-2-ol**

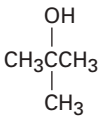
Problem 8.7 Show the products obtained from addition of CH_3MgBr to the following carbonyl compounds:

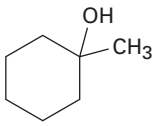
(a) 

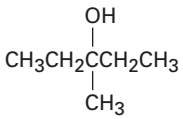
(b) 

(c) 

Problem 8.8 How might you use a Grignard reaction to prepare the following alcohols:

(a) 

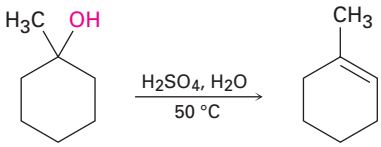
(b) 

(c) 

8.4 Reactions of Alcohols

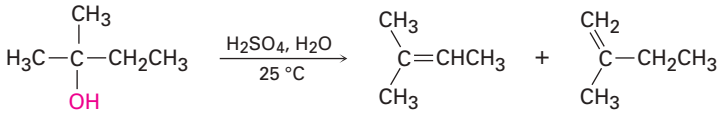
Dehydration of Alcohols

Alcohols undergo *dehydration*—the elimination of H_2O—to give alkenes. A method that works particularly well for secondary and tertiary alcohols is treatment with a strong acid. For example, when 1-methylcyclohexanol is treated with aqueous sulfuric acid, dehydration occurs to yield 1-methylcyclohexene.



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

Acid-catalyzed dehydrations usually follow Zaitsev's rule (Section 7.7) and yield the more highly substituted alkene as the major product. Thus, 2-methylbutan-2-ol gives primarily 2-methylbut-2-ene (trisubstituted) rather than 2-methylbut-1-ene (disubstituted).



2-Methylbutan-2-ol

2-Methylbut-2-ene (trisubstituted) — **Major product**

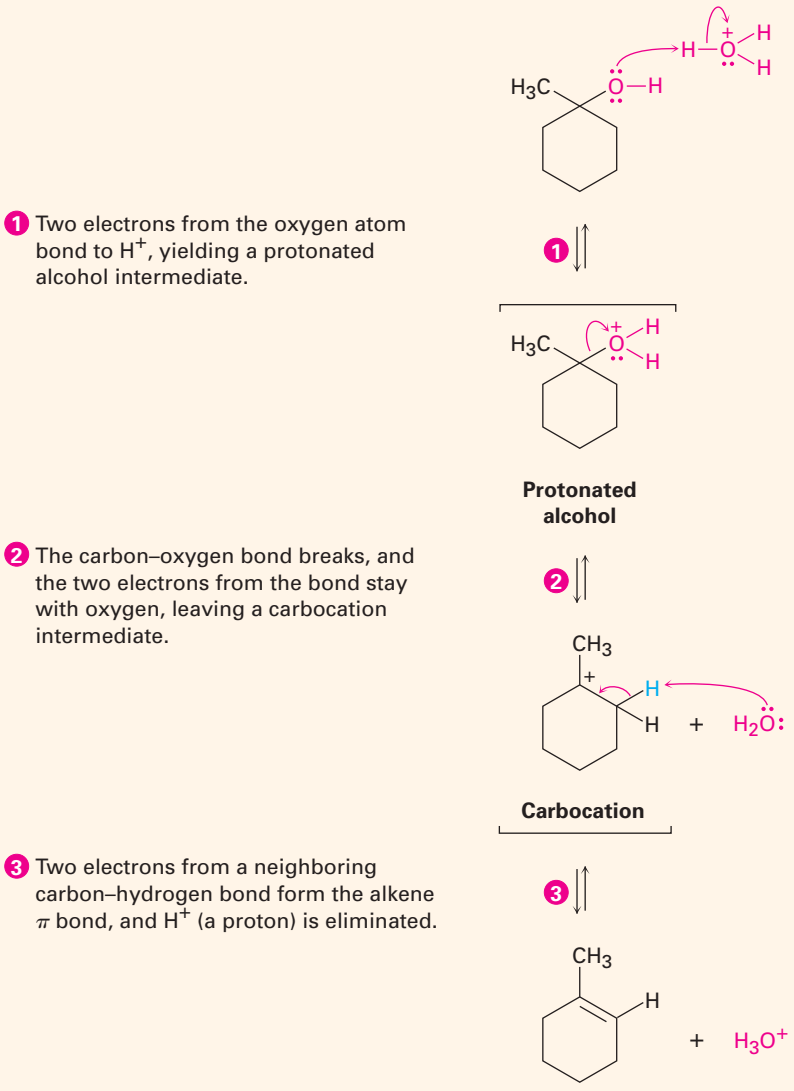
2-Methylbut-1-ene (disubstituted) — **Minor product**

The mechanism of this acid-catalyzed dehydration is an E1 process (Section 7.8). Strong acid first protonates the alcohol oxygen, the protonated

intermediate spontaneously loses water to generate a carbocation, and loss of H^+ from a neighboring carbon atom then yields the alkene product (Figure 8.3).

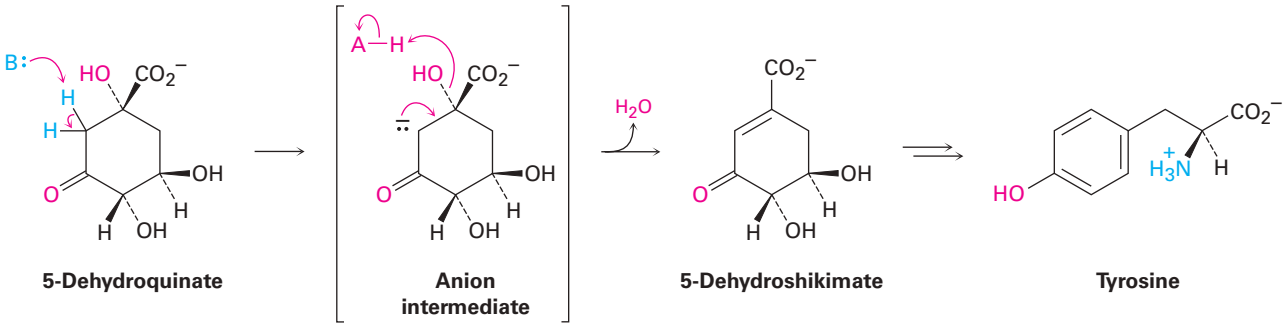
MECHANISM

Figure 8.3 Mechanism of the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.



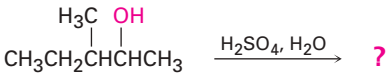
As noted previously in Section 7.10, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the –OH group is two carbons away from a carbonyl group. An example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base (:B) first abstracts a proton from the carbon adjacent to the carbonyl group, and the

anion intermediate then expels the –OH group with simultaneous protonation by an acid (HA) to form water.



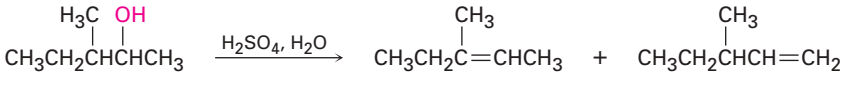
Worked Example 8.4 Predicting the Product of a Dehydration Reaction

Predict the major product of the following reaction:



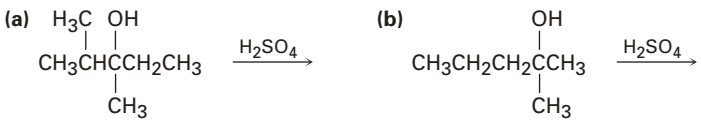
Strategy Treatment of an alcohol with H_2SO_4 leads to dehydration and formation of the more highly substituted alkene product (Zaitsev's rule). Thus, dehydration of 3-methylpentan-2-ol yields 3-methylpent-2-ene as the major product rather than 3-methylpent-1-ene.

Solution

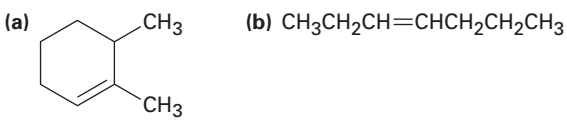


3-Methylpentan-2-ol → **3-Methylpent-2-ene** (major) + **3-Methylpent-1-ene** (minor)

Problem 8.9 Predict the products you would expect from the following reactions. Indicate the major product in each case.

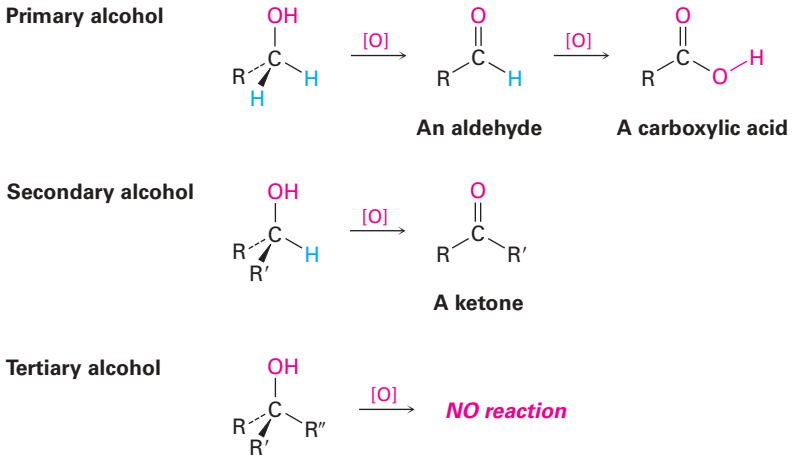


Problem 8.10 What alcohols might the following alkenes be made from?

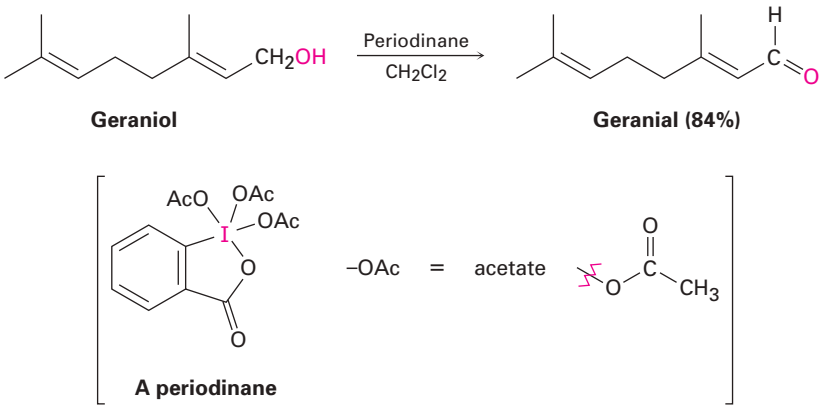


Oxidation of Alcohols

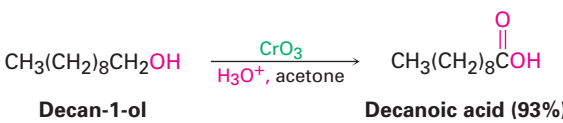
Perhaps the most valuable reaction of alcohols is their oxidation to yield carbonyl compounds—the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, and secondary alcohols yield ketones, but tertiary alcohols don't normally react with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



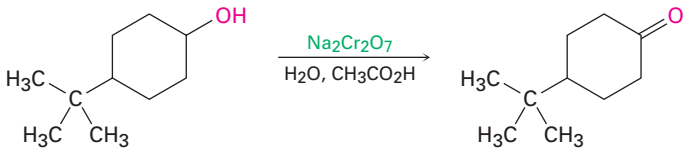
Primary alcohols are oxidized either to aldehydes or to carboxylic acids, depending on the reagent used. Older methods were often based on Cr(VI) reagents, such as CrO_3 or $Na_2Cr_2O_7$, but the most common current choice for preparing an aldehyde from a primary alcohol in the laboratory is to use a *periodinane,* which contains an iodine atom in the +5 oxidation state. This reagent is too expensive for large-scale use in industry, however.



Many oxidizing agents, such as chromium trioxide (CrO_3) and sodium dichromate ($Na_2Cr_2O_7$) in aqueous acid solution, oxidize primary alcohols to carboxylic acids. Although aldehydes are intermediates in these oxidations, they usually can't be isolated because further oxidation takes place too rapidly.



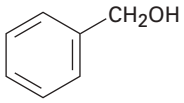
Secondary alcohols are oxidized to produce ketones. For a sensitive or costly alcohol, a periodinane is often used. For a large-scale oxidation, however, an inexpensive reagent such as CrO_3 or $Na_2Cr_2O_7$ in aqueous acetic acid is more economical.



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

Worked Example 8.5 Predicting the Product of an Alcohol Oxidation

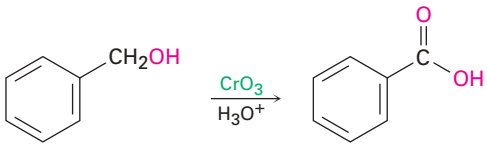
What product would you expect from reaction of benzyl alcohol with CrO_3?



Benzyl alcohol

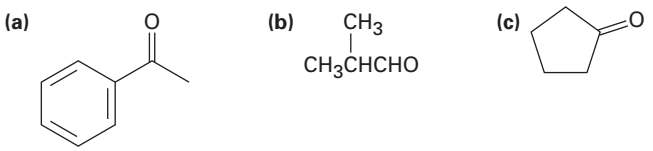
Strategy Treatment of a primary alcohol with CrO_3 yields a carboxylic acid. Thus, oxidation of benzyl alcohol yields benzoic acid.

Solution



Benzyl alcohol **Benzoic acid**

Problem 8.11 What alcohols would give the following products on oxidation?



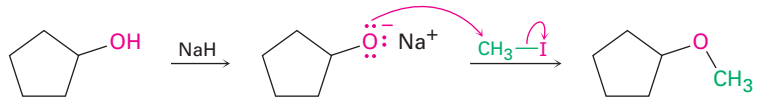
Problem 8.12 What products would you expect to obtain from oxidation of the following alcohols with CrO_3?

(a) Cyclohexanol **(b)** Hexan-1-ol **(c)** Hexan-2-ol

Problem 8.13 What products would you expect to obtain from oxidation of the alcohols in Problem 8.12 with a periodinane?

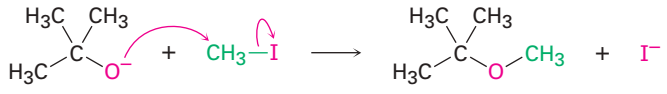
Conversion into Ethers

Alcohols are converted into ethers by formation of the corresponding alkoxide ion followed by reaction with an alkyl halide, a reaction known as the *Williamson ether synthesis*. As noted in Section 8.2, the alkoxide ion needed in the reaction can be prepared either by reaction of an alcohol with an alkali metal or by reaction with a strong base such as sodium hydride, NaH.

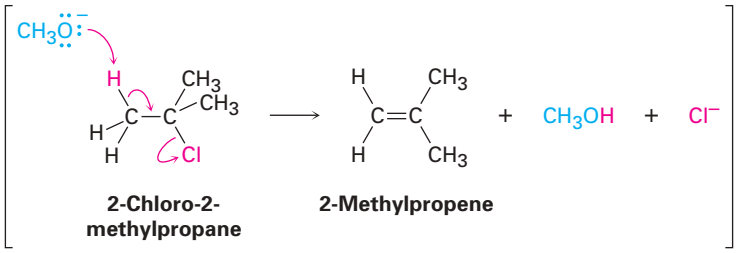


Cyclopentanol **Alkoxide ion** **Cyclopentyl methyl ether (74%)**

Mechanistically, the Williamson synthesis is an S_N2 reaction (Section 7.5) and occurs by nucleophilic substitution of halide ion by the alkoxide ion. As with all S_N2 reactions, primary alkyl halides work best because competitive E2 elimination of HX can occur with more hindered substrates. Unsymmetrical ethers are therefore best prepared by reaction of the more hindered alkoxide partner with the less hindered alkyl halide partner, rather than vice versa. *tert*-Butyl methyl ether, for example, is best prepared by reaction of *tert*-butoxide ion with iodomethane, rather than by reaction of methoxide ion with 2-chloro-2-methylpropane.



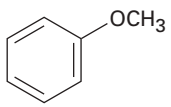
***tert*-Butoxide** **Iodomethane** ***tert*-Butyl methyl ether**



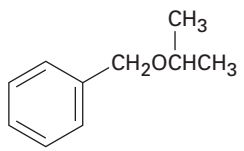
2-Chloro-2-methylpropane **2-Methylpropene**

Problem 8.14 How would you prepare the following ethers?

(a) $CH_3OCH_2CH_2CH_3$ **(b)**

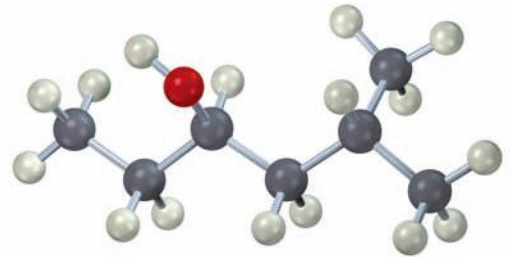


(c)



Problem 8.15 Rank the following alkyl halides in order of their expected reactivity toward an alkoxide ion in the Williamson ether synthesis: bromoethane, 2-bromopropane, chloroethane, 2-chloro-2-methylpropane.

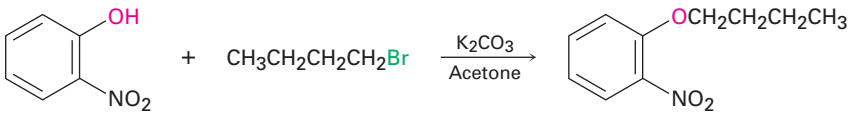
Problem 8.16 Draw the structure of the carbonyl compound(s) from which the following alcohol might have been prepared, and show the products you would obtain by treatment of the alcohol with (i) Na metal, followed by CH_3I, (ii) $SOCl_2$, and (iii) CrO_3.



8.5 Reactions of Phenols

Alcohol-Like Reactions of Phenols

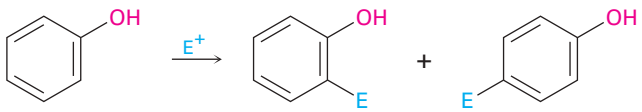
Phenols and alcohols behave very differently despite the fact that both have –OH groups. Phenols can't be dehydrated by treatment with acid and can't be converted into halides by treatment with HX. Phenols can, however, be converted into ethers by S_N2 reaction with alkyl halides in the presence of base. Williamson ether synthesis with phenols occurs easily because phenols are more acidic than alcohols and are more readily converted into their anions.



***o*-Nitrophenol** **1-Bromobutane** **Butyl *o*-nitrophenyl ether (80%)**

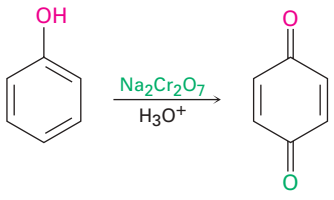
Electrophilic Aromatic Substitution Reactions of Phenols

The –OH group is an activating, ortho- and para-directing substituent in electrophilic aromatic substitution reactions (Sections 5.6 and 5.7). As a result, phenols are reactive substrates for electrophilic halogenation, nitration, and sulfonation.

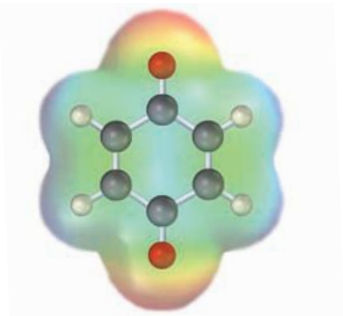


Oxidation of Phenols: Quinones

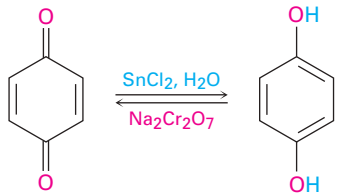
Phenols don't undergo oxidation in the same way that alcohols do because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, oxidation of a phenol with sodium dichromate yields a cyclohexa-2,5-diene-1,4-dione, or **quinone**.



Phenol **Benzoquinone (79%)**

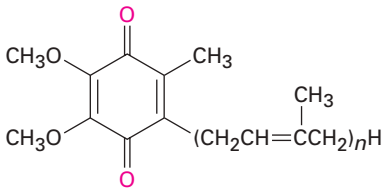


Quinones are an interesting and valuable class of compounds because of their oxidation–reduction properties. They can be easily reduced to **hydroquinones** (*p*-dihydroxybenzenes) by $NaBH_4$ or $SnCl_2$, and hydroquinones can be easily oxidized back to quinones by $Na_2Cr_2O_7$.



Benzoquinone **Hydroquinone**

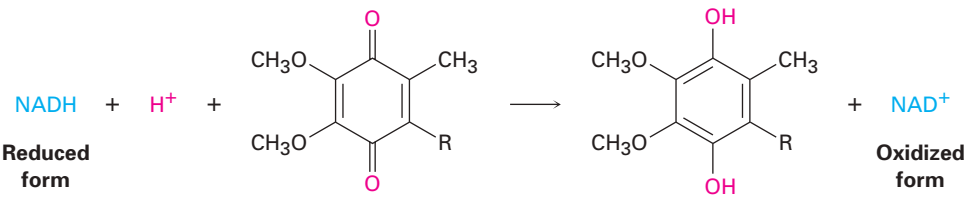
The oxidation–reduction properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q,* are components of the 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)

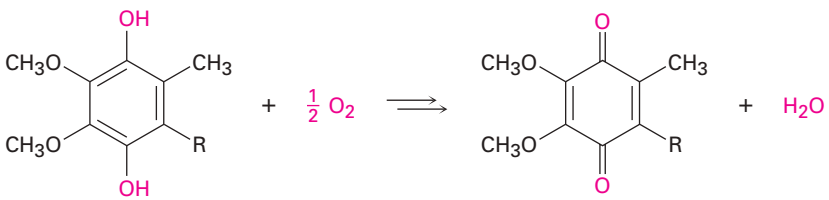
Ubiquinones function within the mitochondria of cells to mediate the respiration process in which electrons are transported from the biological reducing agent NADH to molecular oxygen. Through a complex series of steps, the ultimate result is a cycle whereby NADH is oxidized to NAD^+, O_2 is reduced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

Step 1



Reduced form **Oxidized form**

Step 2

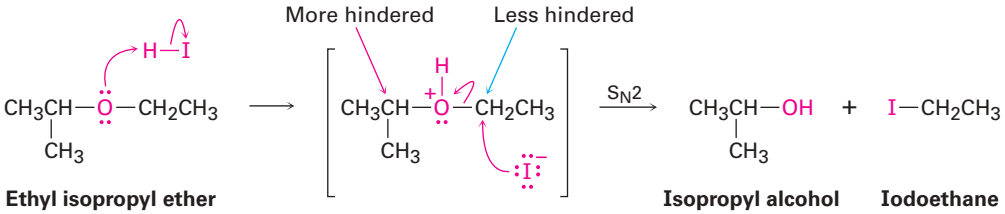


Net change: NADH + $\frac{1}{2}$ O_2 + H^+ ⟶ NAD^+ + H_2O

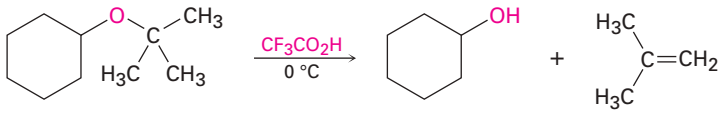
8.6 Reactions of Ethers

Ethers are unreactive to most common reagents, a property that accounts for their frequent use as reaction solvents. Halogens, mild acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one general reaction—they are cleaved by strong acids such as aqueous HI or HBr.

Acidic ether cleavages are typical nucleophilic substitution reactions, which take place by either an S_N1 or S_N2 pathway, depending on the structure of the ether. Ethers with only primary and secondary alkyl groups react by an S_N2 pathway, in which nucleophilic halide ion attacks the protonated ether at the less highly substituted site. The ether oxygen atom stays with the more hindered alkyl group, and the halide bonds to the less hindered group. For example, ethyl isopropyl ether yields isopropyl alcohol and iodoethane on cleavage by HI.



Ethers with a tertiary alkyl group cleave by an S_N1 mechanism because they can produce stable intermediate carbocations. In such reactions, the ether oxygen atom stays with the less hindered alkyl group and the halide bonds to the tertiary group. Like most S_N1 reactions, the cleavage is rapid and often takes place at room temperature or below.



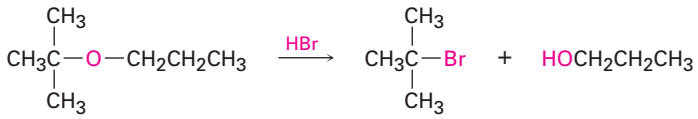
Worked Example 8.6 Predicting the Product of an Ether Cleavage

Predict the products of the reaction of *tert*-butyl propyl ether with HBr.

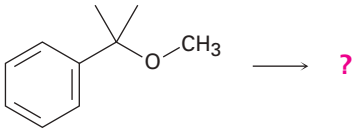
Strategy

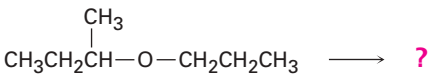
Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl groups usually undergoes cleavage by S_N2 attack of a nucleophile on the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

Solution



Problem 8.17 What products do you expect from the reaction of the following ethers with HI?

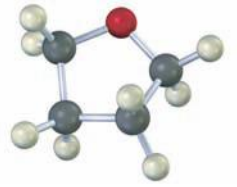
(a) 

(b) 

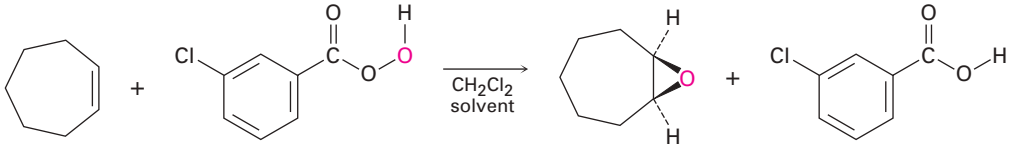
8.7 Cyclic Ethers: Epoxides

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. Thus, the cyclic ether tetrahydrofuran (THF) is often used as a solvent because of its inertness.

Tetrahydrofuran

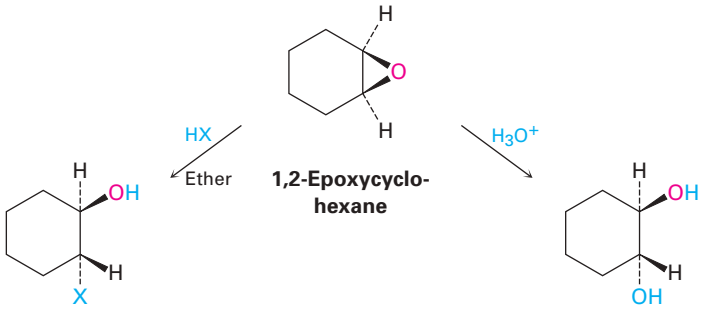


The three-membered-ring ethers, called *epoxides,* make up the one group of cyclic ethers that behave differently from open-chain ethers. The strain of the three-membered ring makes epoxides much more reactive than other ethers. As we saw in Section 4.6, epoxides are prepared by reaction of an alkene with a peroxyacid, RCO_3H, usually *m*-chloroperoxybenzoic acid.



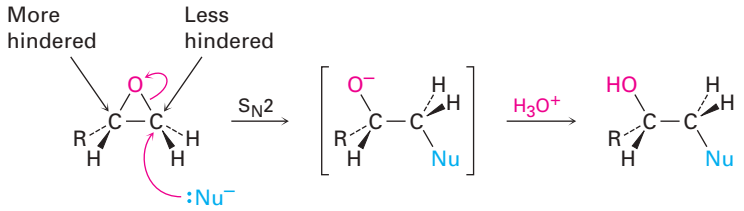
Cycloheptene | ***meta*-Chloroperoxybenzoic acid** | **1,2-Epoxycycloheptane** | ***meta*-Chlorobenzoic acid**

Epoxide rings are cleaved by treatment with acid just like other ethers, but they react under much milder conditions because of the strain of the three-membered ring. Dilute aqueous acid at room temperature converts an epoxide to a 1,2-diol (Section 4.6), and halogen acids HX convert an epoxide into a halo alcohol called a *halohydrin.* Both reactions take place by S_N2 attack of the nucleophile (H_2O or X^-) on the protonated epoxide so that the product has trans stereochemistry.

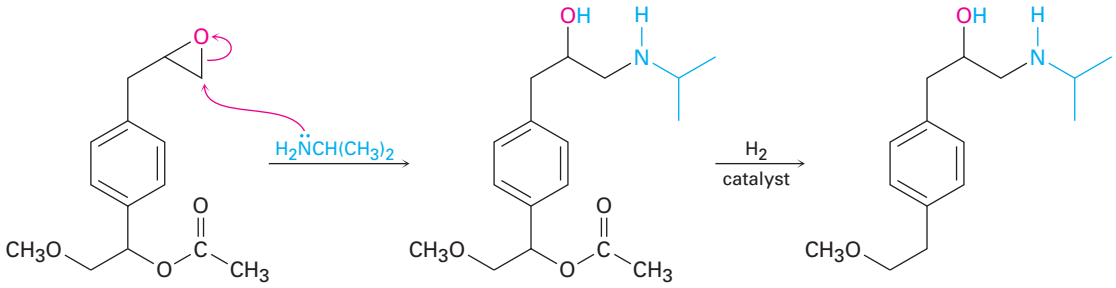


***trans*-2-Halocyclohexanol** | **1,2-Epoxycyclohexane** | ***trans*-Cyclohexane-1,2-diol**

In addition to their reaction with acids, epoxides also undergo rapid ring-opening when treated with bases and other nucleophiles. The reaction takes place by an S_N2 mechanism, with attack of the nucleophile at the less hindered epoxide carbon and simultaneous cleavage of the C–O bond.



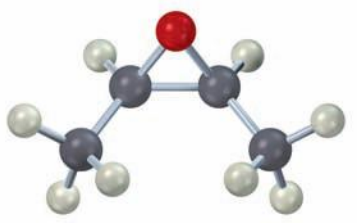
Many different nucleophiles can be used for epoxide opening, including hydroxide ion (HO^-), alkoxide ions (RO^-), amines (RNH_2 or R_2NH), and Grignard reagents (RMgX). An example occurs in the commercial synthesis of metoprolol, a so-called beta-blocker that is used for treatment of cardiac arrhythmias, hypertension, and heart attacks.



Metoprolol

You've probably also heard of "epoxy" adhesives, resins, and coatings that are used in a vast number of applications, from aircraft construction to simple home repairs. The *Interlude* at the end of this chapter tells more about them and describes how they work.

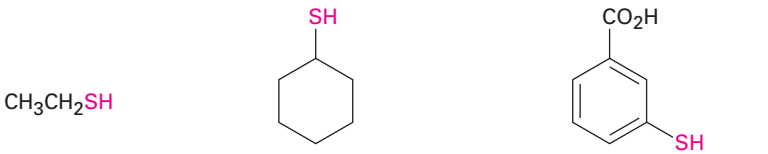
Problem 8.18 Show the structure of the product you would obtain by treatment of the following epoxide with aqueous acid. What is the stereochemistry of the product if the ring-opening takes place by normal backside S_N2 attack?



8.8 Thiols and Sulfides

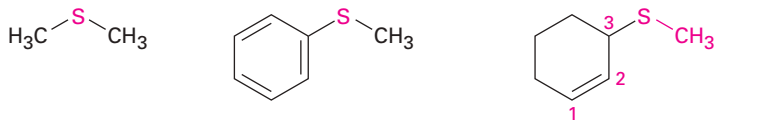
Sulfur is the element just below oxygen in the periodic table, and many oxygen-containing organic compounds have sulfur analogs. *Thiols* (R—SH) are sulfur analogs of alcohols, and sulfides (R—S—R′) are sulfur analogs of ethers. Both classes of compounds are widespread in living organisms.

Thiols are named in the same way as alcohols, with the suffix *-thiol* used in place of *-ol*. The –SH group itself is referred to as a **mercapto group**.



Ethanethiol **Cyclohexanethiol** ***m*-Mercaptobenzoic acid**

Sulfides are named in the same way as ethers, with *sulfide* used in place of *ether* for simple compounds and with *alkylthio* used in place of *alkoxy* for more complex substances.

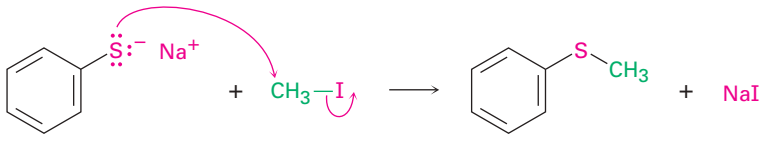


Dimethyl sulfide **Methyl phenyl sulfide** **3-(Methylthio)cyclohexene**

Thiols can be prepared from the corresponding alkyl halide by S_N2 displacement with a sulfur nucleophile such as hydrosulfide anion, SH^-.

1-Bromooctane **Octane-1-thiol (83%)**

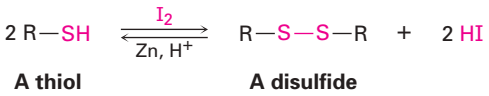
Sulfides are prepared by treating a primary or secondary alkyl halide with a *thiolate ion,* RS^-, the sulfur analog of an alkoxide ion. Reaction occurs by an S_N2 mechanism analogous to the Williamson ether synthesis (Section 8.4). Thiolate anions are among the best nucleophiles known, so these reactions usually work well.



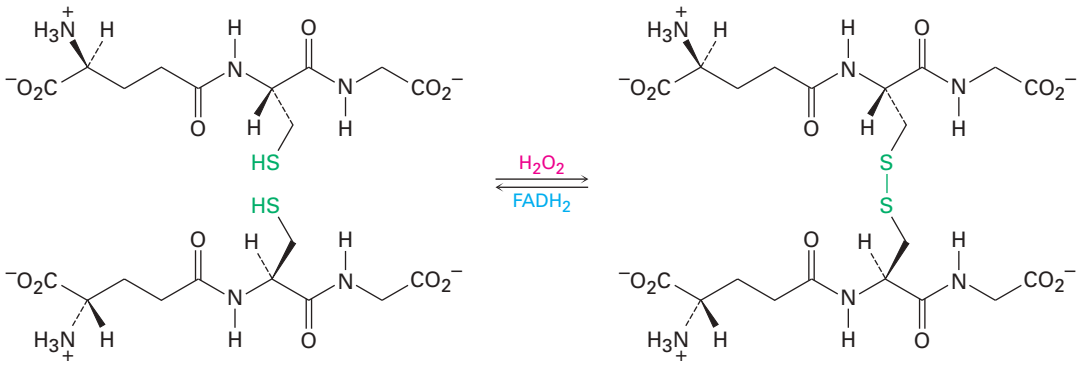
Sodium benzenethiolate **Methyl phenyl sulfide (96%)**

Physically, the most unforgettable characteristic of thiols is their appalling odor. Skunk scent, in fact, is due primarily to the simple thiols 3-methylbutane-1-thiol and but-2-ene-1-thiol. Chemically, thiols can be oxidized by mild reagents such as bromine or iodine to yield *disulfides,* R—S—S—R,

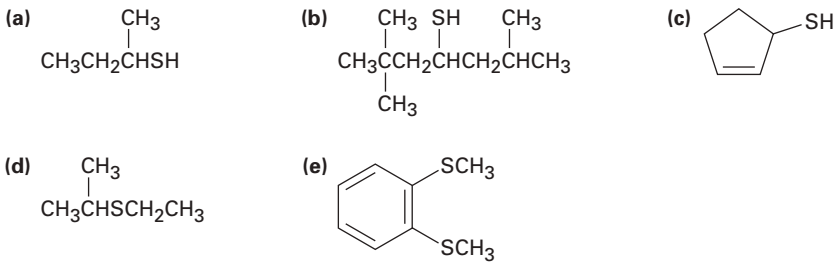
and disulfides can be reduced back to thiols by treatment with zinc metal and acetic acid.



This thiol–disulfide interconversion is a key part of numerous biological processes. We'll see in Section 15.4, 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 thiol-containing amino acids 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.



Problem 8.19 Name the following compounds:



Problem 8.20 But-2-ene-1-thiol is a component of skunk spray. How would you synthesize this substance from but-2-en-1-ol? From methyl but-2-enoate, $CH_3CH{=}CHCO_2CH_3$? More than one step is required in both instances.

INTERLUDE

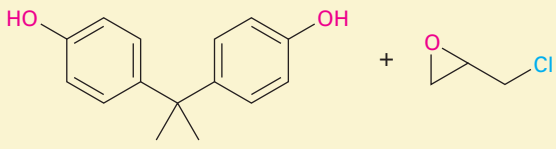
Epoxy Resins and Adhesives

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

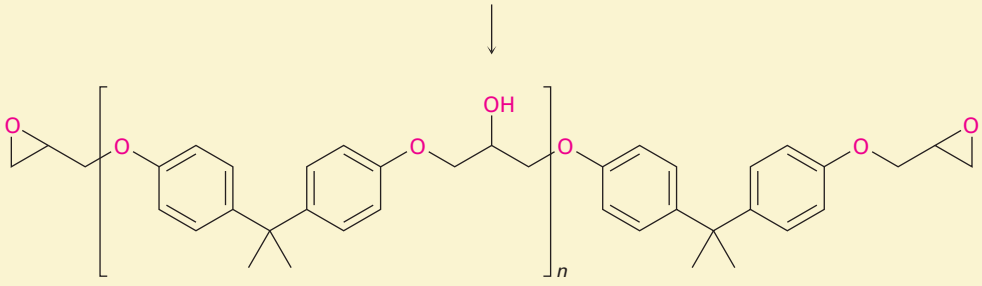
Few nonchemists know exactly what an epoxide is, but practically everyone has used an "epoxy glue" for household repairs or an epoxy resin for a protective coating. Worldwide, approximately $15 billion of epoxies are used annually for a vast number of adhesive and coating applications including many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

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

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



Bisphenol A **Epichlorohydrin**



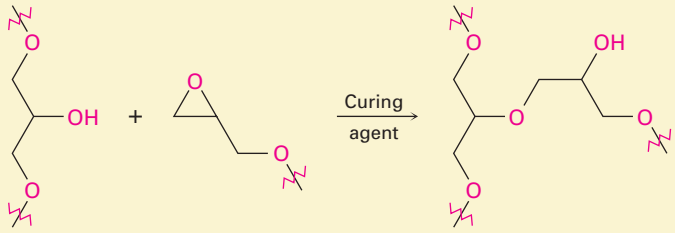
Prepolymer

When the epoxide is to be used, a basic curing agent such as a tertiary amine, R_3N, is added to cause the individual prepolymer chains to link together. This "cross-linking" of chains is simply a base-catalyzed, S_N2 epoxide ring-opening of an −OH group in the middle of one chain with

continued

INTERLUDE

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.



Middle of chain 1 **End of chain 2** **Cross-linked chains**

Summary and Key Words

alcohol 256
alkoxide ion 260
ether 256
hydroquinone 275
mercapto group 279
phenol 256
phenoxide ion 260
quinone 274
sulfide 256
thiol 256
thiophenol 256

In past chapters, we focused on developing general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides. With that accomplished, we have now begun in this chapter to study the oxygen-containing functional groups that lie at the heart of organic chemistry. To understand the chemistry of living organisms, in particular, it's necessary to understand oxygen-containing functional groups. Alcohols, phenols, and ethers are organic derivatives of water in which one or both of the water hydrogens have been replaced by organic groups.

Alcohols are compounds that have an –OH bonded to an sp^3-hybridized carbon. They can be prepared in many ways, including hydration of alkenes. The most general method of alcohol synthesis involves reduction of a carbonyl compound. Aldehydes, esters, and carboxylic acids yield primary alcohols on reduction; ketones yield secondary alcohols. In addition, Grignard reagents, prepared from an organohalide and magnesium, add to carbonyl compound to give alcohols. Formaldehyde ($H_2C{=}O$) reacts with Grignard reagents to give primary alcohols, ketones give tertiary alcohols, and esters give tertiary alcohols in which two of the substituents on the alcohol carbon are identical.

Alcohols are weak acids and can be converted into their **alkoxide anions** by treatment with a strong base or with an alkali metal. Alcohols can also be dehydrated to yield alkenes, converted into ethers by reaction of their anions with alkyl halides, and oxidized to yield carbonyl compounds. Primary alcohols give either aldehydes or carboxylic acids when oxidized, secondary alcohols give ketones, and tertiary alcohols are not oxidized.

Phenols are aromatic counterparts of alcohols. Although similar to alcohols in some respects, phenols are more acidic than alcohols because **phenoxide anions** are stabilized by resonance. Phenols undergo electrophilic aromatic substitution reactions readily and can be oxidized to yield **quinones**. Quinones, in turn, can be reduced to give *p*-dihydroxybenzenes, called **hydroquinones**.

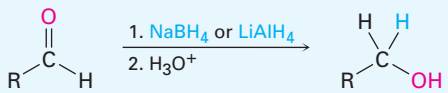
Ethers have two organic groups bonded to the same oxygen atom. They are prepared by S_N2 reaction of an alkoxide ion with a primary alkyl halide—the Williamson ether synthesis. Ethers are inert to most reagents but are cleaved

by the strong acids HBr and HI. Epoxides—cyclic ethers with an oxygen atom in a three-membered ring—differ from other ethers in their ease of cleavage. The high reactivity of the strained three-membered ether ring allows epoxides to react with aqueous acid, yielding diols and with HX yielding halohydrins. In addition, epoxides react with nucleophiles such as amines and alkoxides.

Sulfides (R—S—R′) and **thiols (R—SH)** are sulfur analogs of ethers and alcohols. Thiols are prepared by S_N2 reaction of an alkyl halide with HS^-, and sulfides are prepared by further alkylation of the thiol with an alkyl halide.

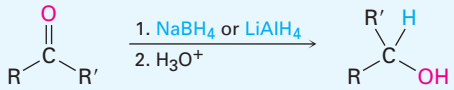
Summary of Reactions

1. Synthesis of alcohols (Section 8.3)
   (a) Reduction of carbonyl compounds
   (1) Aldehydes



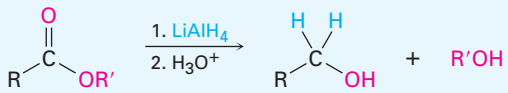
Primary alcohol

   (2) Ketones



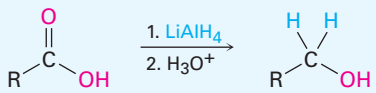
Secondary alcohol

   (3) Esters



Primary alcohol

   (4) Carboxylic acids

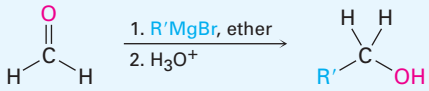


Primary alcohol

continued

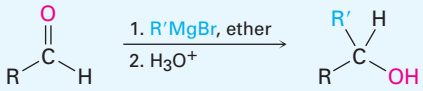
(b) Grignard reaction with carbonyl compounds

(1) Formaldehyde



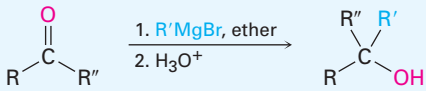
Primary alcohol

(2) Aldehydes



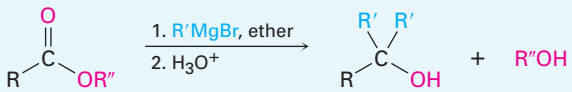
Secondary alcohol

(3) Ketones



Tertiary alcohol

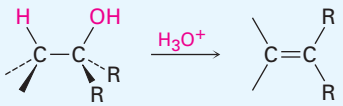
(4) Esters



Tertiary alcohol

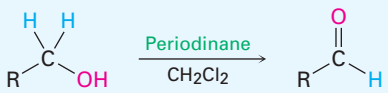
2. Reactions of alcohols (Section 8.4)

(a) Dehydration

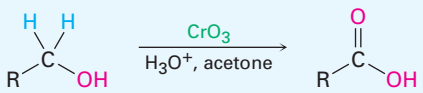


(b) Oxidation

(1) Primary alcohols

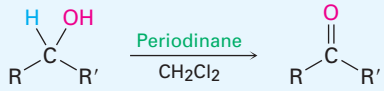


Aldehyde



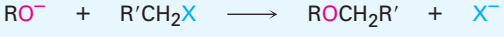
Carboxylic acid

(2) Secondary alcohols

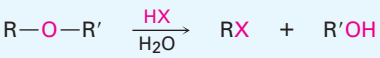


Ketone

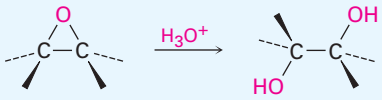
3. Synthesis of ethers (Section 8.4)
Williamson ether synthesis



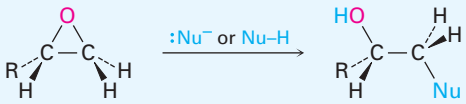
4. Reactions of ethers
(a) Acidic cleavage with HBr or HI (Section 8.6)



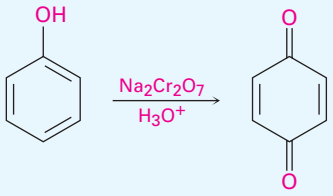
(b) Epoxide opening with aqueous acid (Section 8.7)



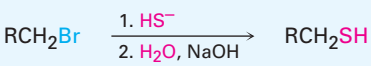
(c) Epoxide opening with nucleophiles (Section 8.7)



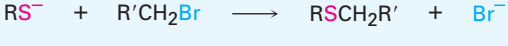
5. Reactions of phenols (Section 8.5)
Oxidation to give quinones



6. Synthesis of thiols (Section 8.8)



7. Synthesis of sulfides (Section 8.8)



Exercises

Visualizing Chemistry

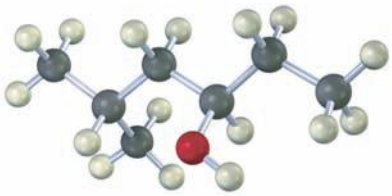
(Problems 8.1–8.20 appear within the chapter.)

OWL

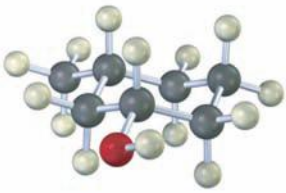
Interactive versions of these problems are assignable in OWL.

8.21 Give IUPAC names for the following compounds (red = O, blue = N, yellow = S):

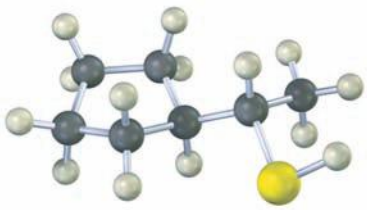
(a)



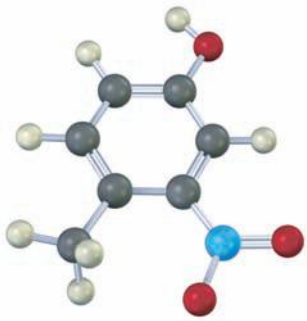
(b)



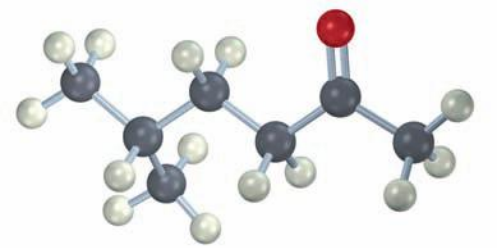
(c)



(d)

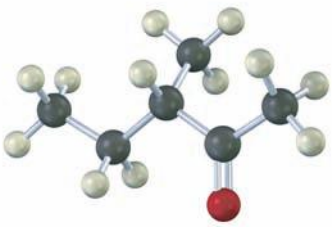


8.22 Predict the product of the following reaction (red = O):



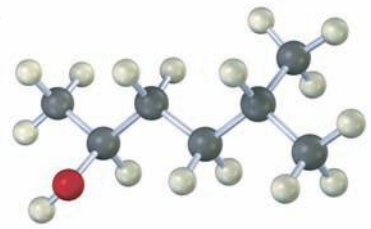
8.23 Show the product you would obtain by reaction of the following compound with:

(a) $NaBH_4$ **(b)** CH_3CH_2MgBr

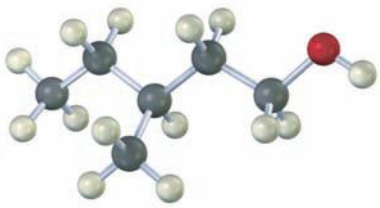


8.24 Show the structures of the carbonyl compounds that would give the following alcohols on reduction. Show also the structure of the products that would result by treating the alcohols with a periodinane and with aqueous acidic CrO_3.

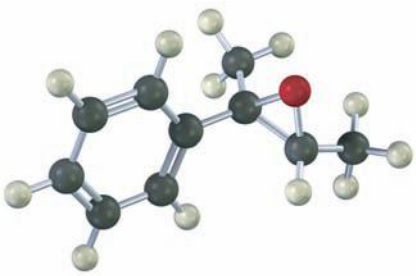
(a)



(b)



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



Additional Problems

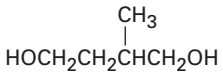
Naming Alcohols and Ethers

8.26 Draw structures corresponding to the following IUPAC names:

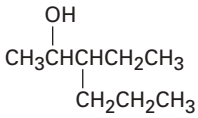
(a) Ethyl isopropyl ether
(b) 3,4-Dimethoxybenzoic acid
(c) 2-Methylheptane-2,5-diol
(d) *trans*-3-Ethylcyclohexanol
(e) 4-Allyl-2-methoxyphenol (eugenol, from oil of cloves)

8.27 Name the following compounds:

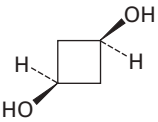
(a)



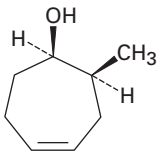
(b)



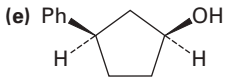
(c)



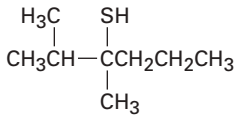
(d)



(e)



(f)



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

8.29 Which of the eight alcohols you identified in Problem 8.28 are chiral?

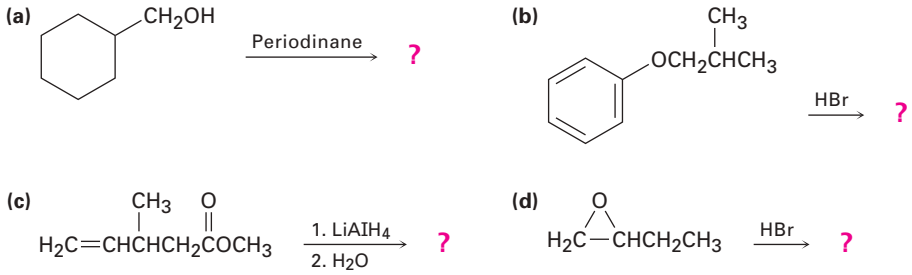
8.30 Draw and name the six ethers that are isomeric with the alcohols you drew in Problem 8.28. Which are chiral?

REACTIONS AND SYNTHESIS

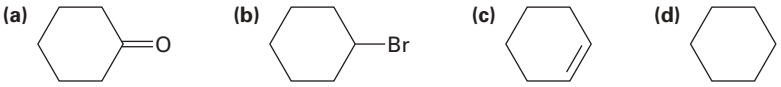
8.31 Which of the eight alcohols you identified in Problem 8.28 would react with aqueous acidic CrO_3? Show the products you would expect from each reaction.

8.32 Show the HI cleavage products of the ethers you drew in Problem 8.30.

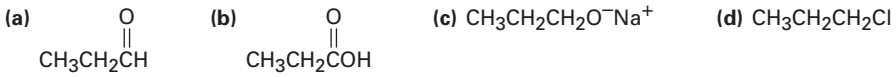
8.33 Predict the product(s) of the following transformations:



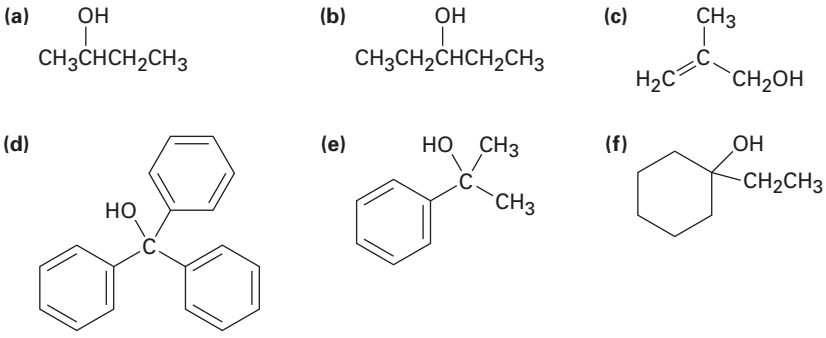
8.34 Show how you could prepare the following substances from cyclohexanol:



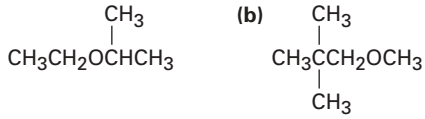
8.35 Show how you could prepare the following substances from propan-1-ol:



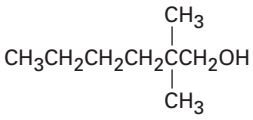
8.36 What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols?

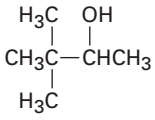


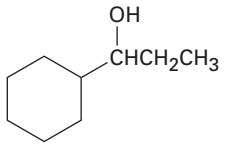
8.37 Predict the likely products of reaction of the following ethers with HI:



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

(a) 

(b) 

(c) 

8.39 How would you prepare the following compounds from 2-phenylethanol?

(a) Benzoic acid
(b) Ethylbenzene
(c) 1-Bromo-2-phenylethane
(d) Phenylacetic acid ($C_6H_5CH_2CO_2H$)
(e) Phenylacetaldehyde ($C_6H_5CH_2CHO$)

8.40 Give the structures of the major products you would obtain from reaction of phenol with the following reagents:

(a) Br_2 (1 mol) **(b)** Br_2 (3 mol)
(c) NaOH, then CH_3I **(d)** $Na_2Cr_2O_7$, H_3O^+

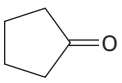
8.41 What products would you obtain from reaction of butan-1-ol with the following reagents?

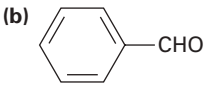
(a) PBr_3 **(b)** CrO_3, H_3O^+ **(c)** Na **(d)** A periodinane

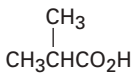
8.42 What products would you obtain from reaction of 1-methylcyclohexanol with the following reagents?

(a) HBr
(b) H_2SO_4
(c) CrO_3
(d) Na
(e) Product of part (d), then CH_3I

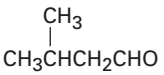
8.43 What alcohols would you oxidize to obtain the following products?

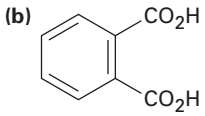
(a) 

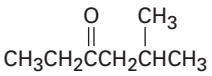
(b) 

(c) 

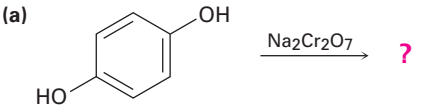
8.44 Show the alcohols you would obtain by reduction of the following carbonyl compounds:

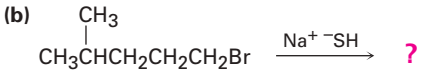
(a) 

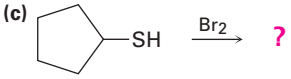
(b) 

(c) 

8.45 Predict the product(s) of the following reactions:

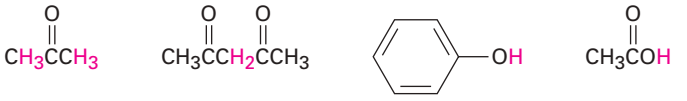
(a) 

(b) 

(c) 

Acidity

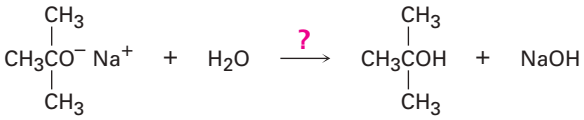
8.46 Rank the following substances in order of increasing acidity:



Acetone ($pK_a = 19$) | **Pentane-2,4-dione** ($pK_a = 9$) | **Phenol** ($pK_a = 9.9$) | **Acetic acid** ($pK_a = 4.7$)

8.47 Which, if any, of the substances in Problem 8.46 are strong enough acids to react substantially with NaOH? (The pK_a of H_2O is 15.7.)

8.48 Is *tert*-butoxide anion a strong enough base to react with water? In other words, does the following reaction take place as written? (The pK_a of *tert*-butyl alcohol is 18.)

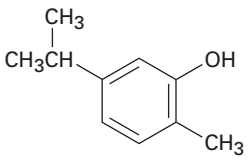


8.49 Sodium bicarbonate, $NaHCO_3$, is the sodium salt of carbonic acid (H_2CO_3), $pK_a = 6.4$. Which of the substances shown in Problem 8.46 will react with sodium bicarbonate?

8.50 Assume you have two unlabeled bottles, one that contains phenol ($pK_a = 9.9$) and one that contains acetic acid ($pK_a = 4.7$). In light of your answer to Problem 8.49, propose a simple way to tell what is in each bottle.

General Problems

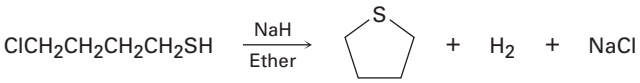
8.51 *Carvacrol* is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?



Carvacrol

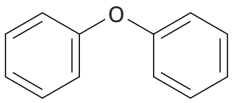
8.52 *Bombykol,* the sex pheromone secreted by the female silkworm moth, has the formula $C_{16}H_{30}O$ and the systematic name (10*E*,12*Z*)-hexadeca-10,12-dien-1-ol. Draw bombykol showing correct stereochemistry for the two double bonds.

8.53 When 4-chlorobutane-1-thiol is treated with a strong base such as sodium hydride, NaH, tetrahydrothiophene is produced. Suggest a mechanism for this reaction.



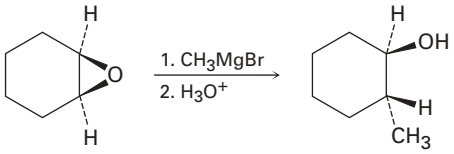
Tetrahydrothiophene

8.54 Why can't the Williamson ether synthesis be used to prepare diphenyl ether?



Diphenyl ether

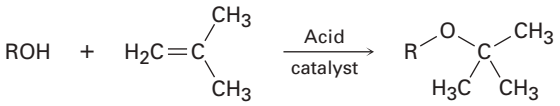
8.55 Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.



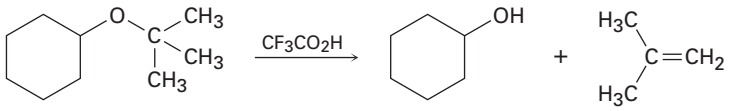
8.56 It's found experimentally that a substituted cyclohexanol with an axial –OH group reacts with aqueous CrO_3 more rapidly than its isomer with an equatorial –OH group. Draw both *cis*- and *trans*-4-*tert*-butylcyclohexanol, and predict which oxidizes faster. (The large *tert*-butyl group is equatorial in both.)

8.57 Because all hamsters look pretty much alike, pairing and mating is governed by chemical means of communication rather than by physical attraction. Investigations have shown that dimethyl disulfide, CH_3SSCH_3, is secreted by female hamsters as a sex attractant for males. How would you synthesize dimethyl disulfide in the laboratory if you wanted to trick your hamster?

8.58 *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.

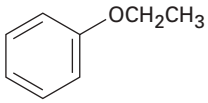


8.59 *tert*-Butyl ethers react with trifluoroacetic acid, CF_3CO_2H, to yield an alcohol and 2-methylpropene. Tell what kind of reaction is occurring, and propose a mechanism.

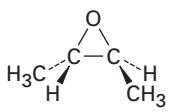


8.60 How would you prepare the following ethers?

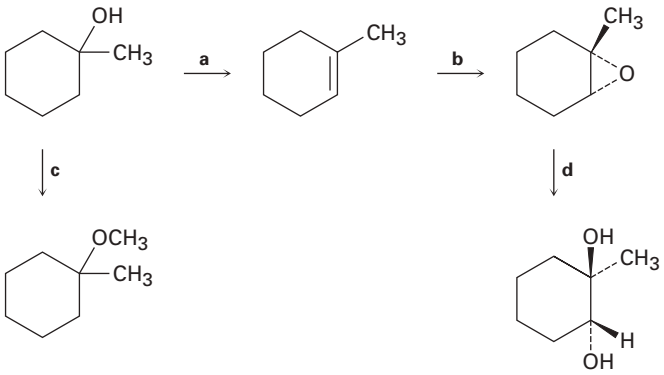
(a)



(b)



8.61 Identify the reagents **a** through **d** in the following scheme:

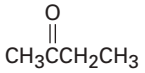


8.62 What cleavage product would you expect from reaction of tetrahydrofuran with hot aqueous HI?

Tetrahydrofuran

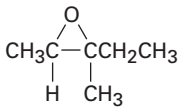
8.63 Methyl phenyl ether can be cleaved to yield iodomethane and lithium phenoxide when heated with LiI. Propose a mechanism for this reaction.

8.64 Reduction of butan-2-one with $NaBH_4$ yields butan-2-ol. Explain why the product is chiral but not optically active.



Butan-2-one

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

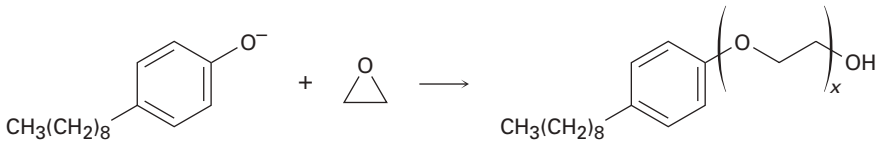


2,3-Epoxy-3-methylpentane (no stereochemistry implied)

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

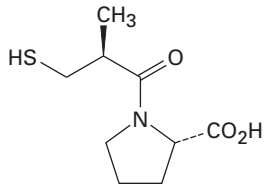
In the Medicine Cabinet

8.66 Nonoxynol 9 is a potent spermicide made by reacting ethylene oxide with *p*-nonylphenoxide. Propose a mechanism for this multistep reaction.



***p*-Nonylphenoxide** **Ethylene oxide** **Nonoxynol 9**

8.67 Captopril is a drug commonly used to treat high blood pressure and heart failure. It functions by decreasing the concentration of chemicals that constrict the blood vessels, so blood flows more smoothly and the heart can pump blood more efficiently.

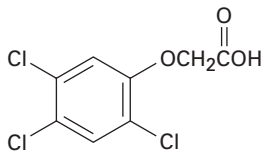


Captopril

(a) Assign *R*,*S* configuration to the two chirality centers in captopril.
(b) What three functional groups are present in captopril?
(c) Draw the disulfide that results from oxidation of captopril.

In the Field

8.68 The herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) can be prepared by heating a mixture of 2,4,5-trichlorophenol and $ClCH_2CO_2H$ with NaOH. Show the mechanism of the reaction.



2,4,5-T